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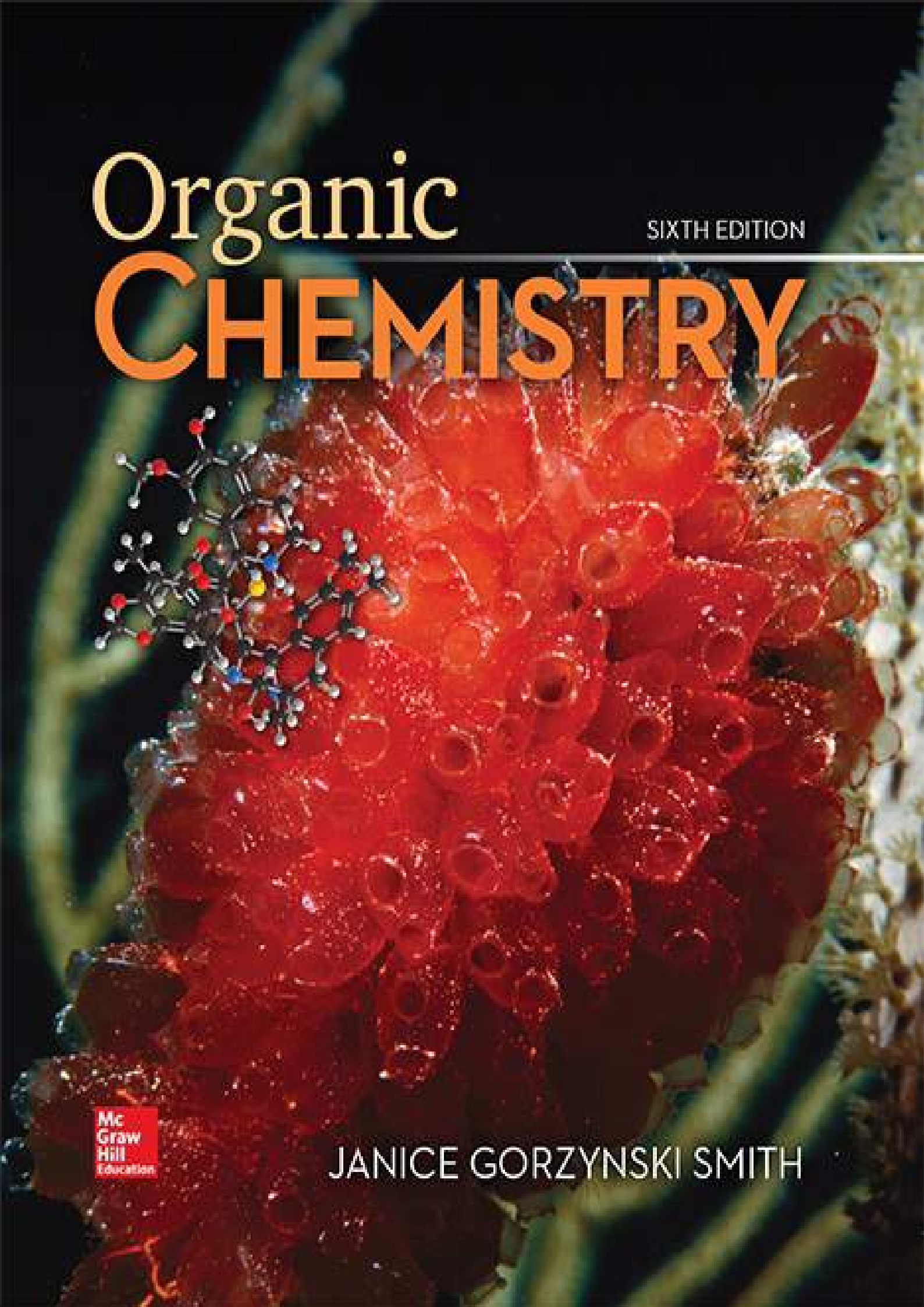

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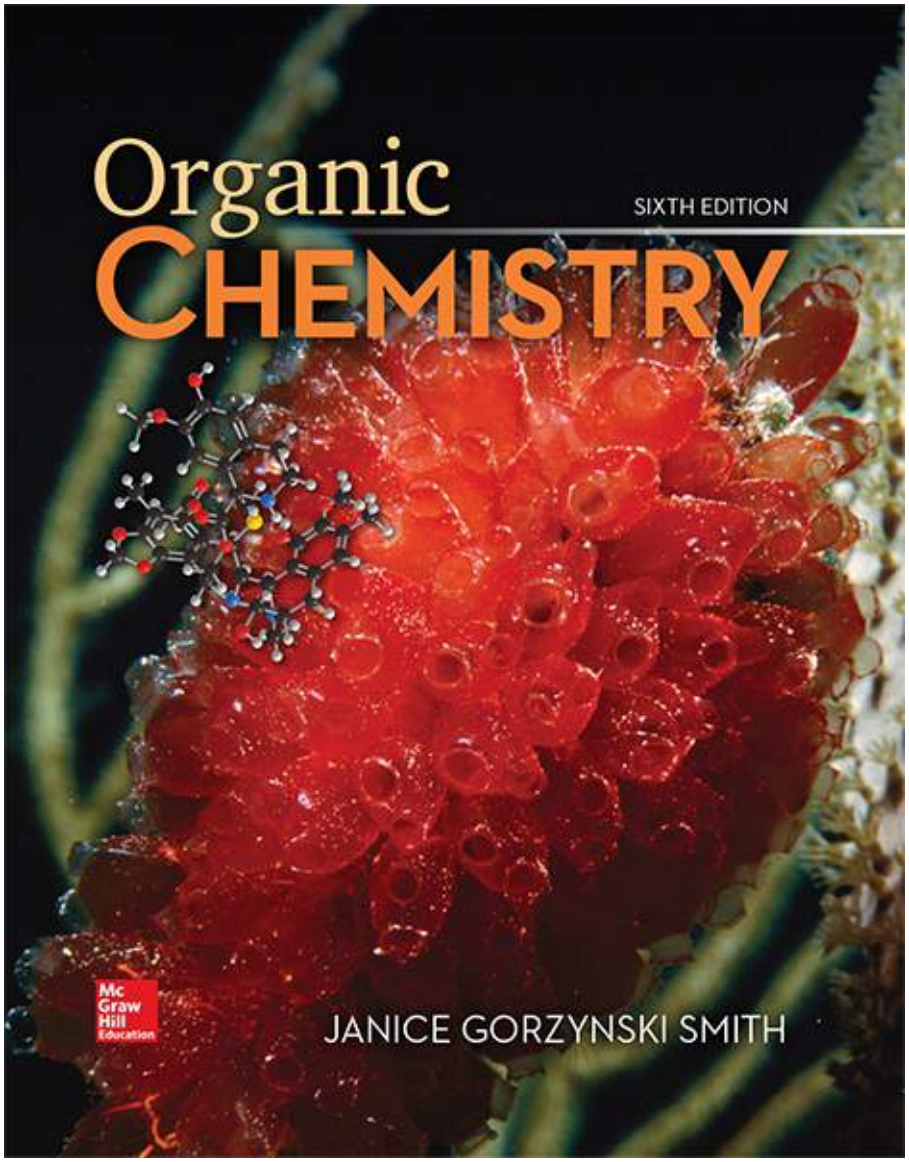
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JANICE GORZYNSKI SMITH

Organic Chemistry

Sixth Edition

Janice Gorzynski Smith

University of Hawai'i at Mānoa

ORGANIC CHEMISTRY, SIXTH EDITION

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About the Author

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Janice Gorzynski Smith was born in Schenectady, New York. She received an A.B. degree *summa cum laude* in chemistry from Cornell University, and a Ph.D. in Organic Chemistry from Harvard University under the direction of Nobel Laureate E. J. Corey. During her tenure with the Corey group, she completed the total synthesis of the plant growth hormone gibberellic acid.

Following her postdoctoral work as a National Science Foundation National Needs Postdoctoral Fellow at Harvard, Jan joined the faculty of Mount Holyoke College, where she was employed for 21 years. During this time she was active in teaching organic chemistry lecture and lab courses, conducting a research program in organic synthesis, and serving as department chair. Her organic chemistry class was named one of Mount Holyoke's “Don't-miss courses” in a survey by *Boston* magazine. After spending two sabbaticals amidst the natural beauty and diversity in Hawai'i in the 1990s, Jan and her family moved there permanently in 2000. She is a faculty member at the University of Hawai'i at Mānoa, where she teaches the two-semester organic chemistry lecture and lab courses. In 2003, she received the Chancellor's Citation for

Meritorious Teaching.

Jan resides in Hawai'i with her husband Dan, an emergency medicine physician, pictured with her in Antarctica in 2018. She has four children and six grandchildren. When not teaching, writing, or enjoying her family, Jan bikes, hikes, snorkels, and scuba dives in sunny Hawai'i, and time permitting, enjoys travel and Hawaiian quilting.

For Megan Sarah

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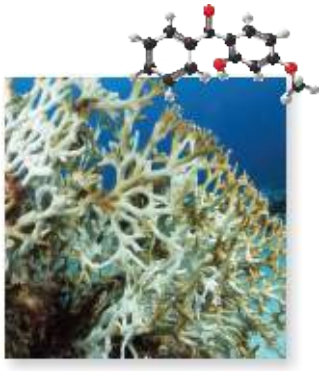

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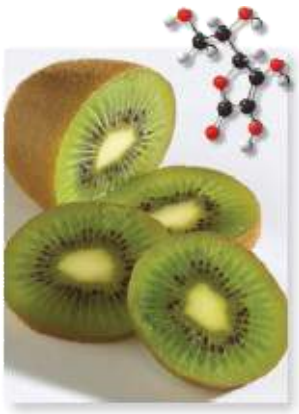

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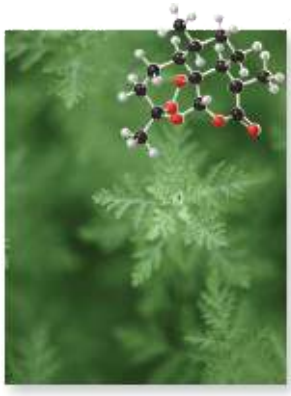

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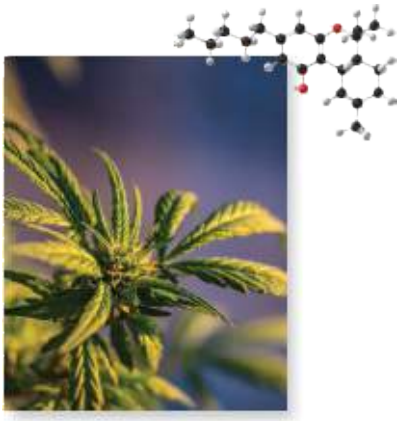

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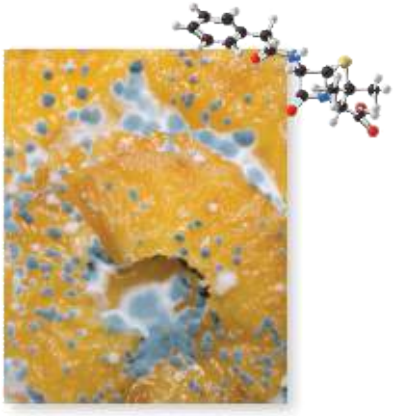

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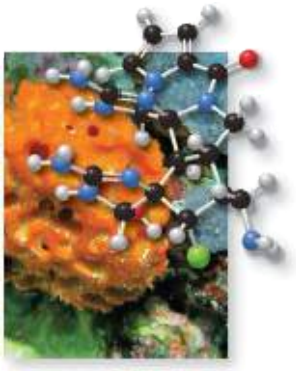

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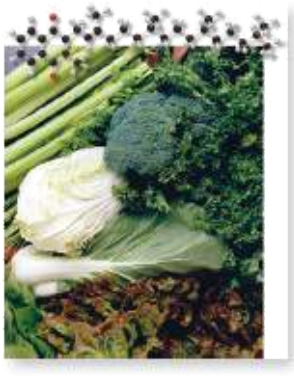

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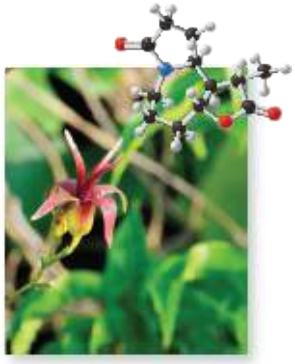

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Preface

My goal in writing *Organic Chemistry* was to create a text that showed students the beauty and logic of organic chemistry by giving them a book that they would *use*. *Organic Chemistry* is my attempt to simplify and clarify a course that intimidates many students—to make organic chemistry interesting, relevant, and accessible to *all* students, both chemistry majors and those interested in pursuing careers in biology, medicine, and other disciplines, without sacrificing the rigor they need to be successful in the future.

The Basic Features

- Style This text is different—by design. The text uses less prose and more diagrams, equations, tables, and bulleted summaries to introduce and reinforce the major concepts and themes of organic chemistry.
- Content *Organic Chemistry* accents basic themes in an effort to keep memorization at a minimum. Relevant examples from everyday life are used to illustrate concepts, and this material is integrated throughout the chapter rather than confined to a boxed reading. Each topic is broken down into small chunks of information that are more manageable and easily learned. Sample problems are used as a tool to illustrate stepwise problem solving. Exceptions to the rule and older, less useful reactions are omitted to focus attention on the basic themes.
- Organization *Organic Chemistry* uses functional groups as the framework within which chemical reactions are discussed. Similar reactions are grouped together so that parallels can be emphasized. These include acid–base reactions (Chapter 2), oxidation and reduction (Chapters 12 and 17), radical reactions (Chapter 13), and reactions of organometallic reagents (Chapter 17).

By introducing one new concept at a time, keeping the basic themes in focus, and

breaking complex problems down into small pieces, I have found that many students find organic chemistry an intense but learnable subject. Many, in fact, end the year-long course surprised that they have actually *enjoyed* their organic chemistry experience.

Organization and Presentation

For the most part, the overall order of topics in the text is consistent with the way most instructors currently teach organic chemistry. There are, however, some important differences in the way topics are presented to make the material logical and more accessible. This can especially be seen in the following areas.

- Review material Chapter 1 presents a healthy dose of review material covering Lewis structures, molecular geometry and hybridization, bond polarity, and types of bonding. Although many of these topics are covered in general chemistry courses, they are presented here from an organic chemist's perspective. I have found that giving students a firm grasp of these fundamental concepts helps tremendously in their understanding of later material.
- Acids and bases Chapter 2 on acids and bases serves two purposes. It gives students experience with curved arrow notation using some familiar proton transfer reactions. It also illustrates how some fundamental concepts in organic structure affect a reaction, in this case an acid–base reaction. Since many mechanisms involve one or more acid–base reactions, I emphasize proton transfer reactions early and come back to this topic often throughout the text.
- Functional groups Chapter 3 uses the functional groups to introduce important properties of organic chemistry. Relevant examples—PCBs, vitamins, soap, and the cell membrane— illustrate fundamental solubility concepts. In this way, practical topics that are sometimes found in the last few chapters of an organic chemistry text (and thus often omitted because instructors run out of time) are introduced early so that students can better grasp why they are studying the discipline.
- Stereochemistry Stereochemistry (the three-dimensional structure of molecules) is introduced early (Chapter 5) and reinforced often so that students have every opportunity to learn and understand a crucial concept in modern chemical research, drug design, and synthesis.
- Modern reactions While there is no shortage of new chemical reactions to present in an organic chemistry text, I have chosen to concentrate on new methods that

introduce a particular three-dimensional arrangement in a molecule, so-called asymmetric or enantioselective reactions. Examples include Sharpless epoxidation (Chapter 12), CBS reduction (Chapter 17), and enantioselective synthesis of amino acids (Chapter 27).

- Grouping reactions Because certain types of reactions have their own unique characteristics and terminology that make them different from the basic organic reactions, I have grouped these reactions together in individual chapters. These include acid–base reactions (Chapter 2), oxidation and reduction (Chapters 12 and 17), radical reactions (Chapter 13), and reactions of organometallic reagents (Chapter 17). I have found that focusing on a group of reactions that share a common theme helps students to better see their similarities.
- Synthesis Synthesis, one of the most difficult topics for a beginning organic student to master, is introduced in small doses, beginning in Chapter 7 and augmented with a detailed discussion of retrosynthetic analysis in Chapter 11. In later chapters, special attention is given to the retrosynthetic analysis of compounds prepared by carbon–carbon bond-forming reactions (for example, Sections 17.11 and 18.9C).
- Spectroscopy Because spectroscopy is such a powerful tool for structure determination, four methods are discussed over three chapters (Spectroscopy A, B, and C).
- Chapter Reviews End-of-chapter summaries succinctly summarize the main concepts and themes of the chapter, making them ideal for review prior to working the end-of-chapter problems or taking an exam.

New to this Edition

Students sometimes ask me if the facts of organic chemistry have significantly changed since the last edition. While the basic principles remain the same—carbon forms four bonds in stable compounds and oppositely charged species attract each other—organic chemistry is a dynamic subject that is continually refined as new facts are determined, and new editions reflect current understanding. Each year, novel compounds are discovered and new drugs are marketed, and these compounds replace older examples to illustrate particular concepts. Also of significance is *how* the material in the text is presented. I continue to endeavor to make this difficult subject as student-friendly as possible, by redesigning sample problems and end-of-chapter material, and rewriting sentences and paragraphs for improved clarity.

General

Expanded Problem-Solving Approach A central component of each chapter of *Organic Chemistry* has always been the Sample Problems, which illustrate how to solve key elements of the chapter. In this edition, Sample Problems are always paired with a follow-up Problem to allow students to apply what they have just learned. The Problems are followed by "More Practice," a list of end-of-chapter problems that are similar in concept. Students can find detailed solutions and verify their answers to *all* of the Problems from the book with the *Organic Chemistry* Student Study Guide/Solutions Manual.

Chapter Review The end-of-chapter summary sections have been expanded into parts: Key Concepts, Key Skills, Key Reactions, and Key Mechanism Concepts, with structures and examples to illustrate each part, providing students with a broader and more detailed overview of each chapter's important concepts and skills. Extensive cross-referencing has also been added to connect this material with relevant Sample Problems, Problems, Figures, and Tables within the body of the chapter.

Artwork and Chemical Structures The colors in artwork throughout the text were revised for emphasis, clarity, and consistency. Color has also been used in many areas to help students better understand three-dimensional structure, stereochemistry, and reactions.

Problems Over 300 new problems have been added, increasing the variety of problems for instructors and students alike.

New *How To*'s, Sample Problems, and Illustrations Much new content has also been added throughout the new edition to clarify topics and enhance the student learning experience.

Photos Roughly one-half of the chapter-opening photos have been replaced with photos emphasizing relevant material within the chapter. More marginal photos of applications have also been added.

Online Only Content The chapter on Lipids appears online and is available in customizable versions of the text in McGraw-Hill Create. A supplement covering Imine Derivatives is also available on the Online Learning Center's Instructor Resources, via the Library tab in Connect.

Chapter-Specific

Spectroscopy

The revisions to the spectroscopy coverage are designed to allow for more flexibility, making these chapters more portable to accommodate various lecture and lab arrangements. Three new spectroscopy chapters have been created for the sixth edition: Spectroscopy A Mass Spectrometry; Spectroscopy B Infrared Spectroscopy; and Spectroscopy C Nuclear Magnetic Resonance Spectroscopy. The coverage and problem sets for these chapters have also been expanded to include material previously covered in other sections of earlier editions. Extensive cross-referencing has been added so that whether spectroscopy is covered early or late in an organic chemistry course, students can readily find the material they need.

- Spectroscopy A Mass Spectrometry There has been extensive revision of the molecular ion, molecular formulas, and fragmentation coverage. A new *How To* was added on proposing molecular formulas from molecular ions. New Sample Problems on using molecular ions and degrees of unsaturation to propose molecular formulas and on determining isomer identity using fragmentation were also added. Several mass spectra have been added to the text and in problems.
- Spectroscopy B Infrared Spectroscopy A new *How To* on analyzing an IR spectrum has been added. The chapter also includes a new Sample Problem B.1 on carbonyl absorptions. Section B.3 has been expanded to include the effect of resonance on a carbonyl absorption, and a new section on IR absorptions based on functional groups also appears in the chapter. A new Table B.1 summarizes IR absorption by functional group.
- Spectroscopy C Nuclear Magnetic Resonance Spectroscopy Section C.7 on complex splitting was extensively revised to add clarity and deeper understanding for students who often struggle with this topic. There are also two new sample problems: Sample Problem C.3 on determining proton equivalency in cyclic compounds and Sample Problem C.8 on looking for points of difference in the NMR spectra of similar compounds. More complex NMRs, previously found in later chapters, were imported to expand the breadth of the problems.

Carbonyls

The coverage of nitriles has been moved to the chapter on carboxylic acids, forming Chapter 19, Carboxylic Acids and Nitriles. This chapter has been moved to follow Aldehydes and Ketones, making this coverage closer to the chemistry of acyl derivatives of carboxylic acids. These revisions also allow for the coverage of the nucleophilic addition reactions that occur with nitriles in closer proximity to the

coverage of nucleophilic additions of aldehydes and ketones.

Other New Coverage

Several sections include new material, including Section 4.7, sources of methane in the atmosphere; Section 5.5, drawing an enantiomer of a complex compound; Section 7.4, drugs that contain fluorine; Section 13.9, the latest ozone map and updated information on CFC alternatives now in use; Section 19.4, new drugs that contain nitriles; Section 26.12, human milk oligosaccharides; and Section 29.7, how isoprene units are connected.

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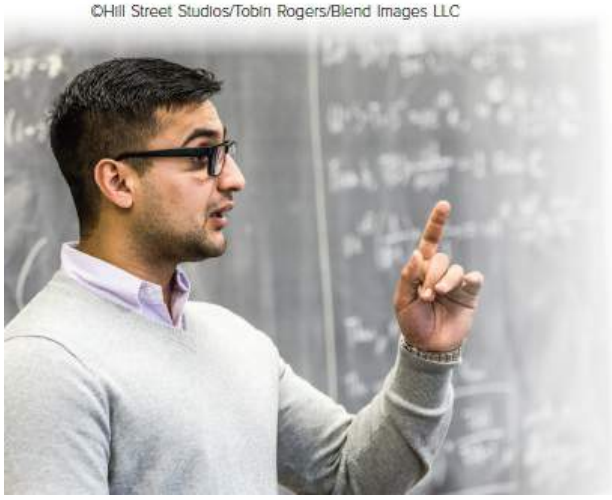

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- Jordan Cunningham,
Eastern Washington University

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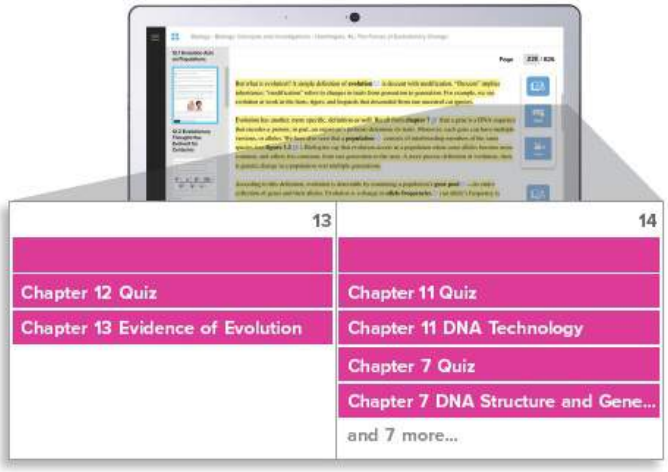

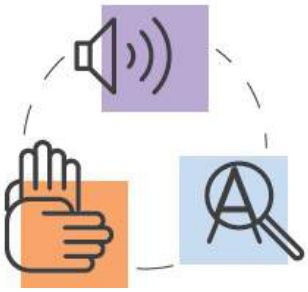

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Features of the Text to Make Learning Organic Chemistry Easier

Illustrations *Organic Chemistry* is supported by a well-developed illustration program. Besides traditional skeletal (line) structures and condensed formulas, there are numerous ball-and-stick molecular models and electrostatic potential maps to help students grasp the three-dimensional structure of molecules (including

stereochemistry) and to better understand the distribution of electronic charge.

Micro-to-Macro Illustrations Unique to *Organic Chemistry* are micro-to-macro illustrations, where line art and photos combine with chemical structures to reveal the underlying molecular structures giving rise to macroscopic properties of common phenomena. Examples include starch and cellulose (Chapter 5), adrenaline (Chapter 7), partial hydrogenation of vegetable oil (Chapter 12), and dopamine (Chapter 23).

Spectra Over 100 spectra created specifically for *Organic Chemistry* are presented mainly in the spectroscopy chapters. The spectra are color-coded by type and generously labeled. Mass spectra are green; infrared spectra are red; and proton and carbon nuclear magnetic resonance spectra are blue.

Mechanisms Curved arrow notation is used extensively to help students follow the movement of electrons in reactions.

Problem Solving

Sample Problems Sample Problems show students how to solve organic chemistry problems in a logical, stepwise manner. More than 800 follow-up problems are located throughout the chapters to test whether students understand concepts covered in the Sample Problems.

How To's *How To*'s provide students with detailed instructions on how to work through key processes.

Applications and Summaries

Chapter Reviews Succinct summary tables reinforcing important principles and concepts are provided at the end of each chapter.

Margin Notes Margin notes are placed carefully throughout the chapters, providing interesting information relating to topics covered in the text. Some margin notes are illustrated with photos to make the chemistry more relevant.

Learning Resources for Instructors and Students

The following items may accompany this text. Please consult your McGraw-Hill representative for policies, prices, and availability as some restrictions may apply.

Presentation Tools

Within the Instructor's Presentation Tools, instructors have access to editable

PowerPoint lecture outlines, which appear as ready-made presentations that combine art and lecture notes for each chapter of the text. For instructors who prefer to create their lecture notes from scratch, all illustrations and photos are pre-inserted by chapter into a separate set of PowerPoint slides. They are also available as individual .jpg files. All assets are copyrighted by McGraw-Hill Higher Education, but can be used by instructors for classroom purposes.

Student Study Guide/Solutions Manual

Written by Janice Gorzynski Smith and Erin R. Smith, the Student Study Guide/Solutions Manual provides step-by-step solutions to all in-chapter and end-of-chapter problems. Each chapter begins with an overview of key concepts and includes a short-answer practice test on the fundamental principles and new reactions.

Acknowledgments

I have been an author with McGraw-Hill for many years, and I continue to be impressed with the dedication and energy of the team of publishing professionals with which I work.

This edition would not be possible without the help of Senior Product Developer Mary Hurley, whom I rely on for both her day-to-day oversight of project details and her anticipation of larger issues that must be addressed in the future. I hope that my collaboration with Mary can continue for many ensuing projects. I am also grateful to both Peggy Selle and Sherry Kane, who skillfully managed the production of this updated text. Special thanks go out to the marketing team led by Marketing Manager Tami Hodge. The artful design that accents the key features that aid student learning is the work of Matthew Backhaus, and the beautiful photos that make the text so visually appealing are supplied by photo researcher Lorraine Buczek.

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My immediate family has experienced the day-to-day demands of living with a busy author. Thanks go to my husband Dan and my children and grandchildren, all of whom keep me grounded during the time-consuming process of writing and publishing a textbook.

Among the many others that go unnamed but who have profoundly affected this work are the thousands of students I have been lucky to teach over the last 30 years. I have learned so much from my daily interactions with them, and I hope that the wider chemistry community can benefit from this experience by the way I have presented the material in this text.

This sixth edition has evolved based on the helpful feedback of many people who reviewed the fifth edition text and digital products, class-tested the book, and attended

focus groups or symposiums. These many individuals have collectively provided constructive improvements to the project.

Listed below are the reviewers of previous editions of this text:

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Although every effort has been made to make this text and its accompanying Student Study Guide/Solutions Manual as error-free as possible, some errors undoubtedly remain. Please feel free to email me about any inaccuracies, so that subsequent editions may be further improved.

With much aloha,

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Prologue

What is organic chemistry?
Some representative organic molecules
Marine natural products

Organic chemistry. You might wonder how a discipline that conjures up images of eccentric old scientists working in basement laboratories is relevant to you, a student in the twenty-first century.

Consider for a moment the activities that occupied your past 24 hours. You likely showered with soap, drank a caffeinated beverage, ate at least one form of starch, took some medication, and traveled in a vehicle that had rubber tires and was powered at least partly by fossil fuels. If you did any *one* of these, your life was touched by organic chemistry.

What Is Organic Chemistry?

- **Organic chemistry is the chemistry of compounds that contain the element carbon.**

It is one branch in the entire field of chemistry, which encompasses many classical subdisciplines including inorganic, physical, and analytical chemistry, and newer fields such as bioinorganic chemistry, physical biochemistry, polymer chemistry, and materials science.

Organic chemistry was singled out as a separate discipline for historical reasons. Originally, it was thought that compounds in living things, termed *organic compounds*, were fundamentally different from those in nonliving things, called *inorganic compounds*. Although we have known for more than 150 years that this distinction is artificial, the name *organic* persists. Today the term refers to the study of the compounds that contain carbon, many of which, incidentally, are found in living organisms.

Some compounds that contain the element carbon are not organic compounds. Examples include carbon dioxide (CO_2), sodium carbonate (Na_2CO_3), and sodium bicarbonate ($NaHCO_3$).

It may seem odd that a whole discipline is devoted to the study of a single element in the periodic table, when more than 100 elements exist. It turns out, though, that there are far more organic compounds than any other type. Organic chemicals affect virtually every facet of our lives, and for this reason, it is important and useful to know something about them.

Clothes, foods, medicines, gasoline, refrigerants, and soaps are composed almost solely of organic compounds. Some, like cotton, wool, or silk, are *naturally occurring;* that is, they can be isolated directly from natural sources. Others, such as nylon and polyester, are *synthetic*, meaning they are produced by chemists in the laboratory. By studying the principles and concepts of organic chemistry, you can learn more about compounds such as these and how they affect the world around you.

Realize, too, what organic chemistry has done for us. Organic chemistry has made available both comforts and necessities that were previously nonexistent, or reserved for only the wealthy. We have seen an enormous increase in life span, from 47 years in 1900 to over 70 years currently. To a large extent this is due to the isolation and synthesis of new drugs to fight infections and the availability of vaccines for childhood diseases. Chemistry has also given us the tools to control insect populations that spread disease, and there is more food for all because of fertilizers, pesticides, and herbicides. Our lives would be vastly different today without the many products that result from organic chemistry (Figure 1).

Figure 1 **Products of organic chemistry used in medicine**

a. Oral contraceptives

©Comstock Images/PictureQuest

c. Antibiotics

©Julian Claxton/Alamy Stock Photo

b. Plastic syringes

©Corbis Premium/Alamy Stock Photo

d. Synthetic heart valves

©Layne Kennedy/Corbis

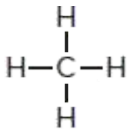
- Organic chemistry has given us contraceptives, plastics, antibiotics, and the knitted material used in synthetic heart valves.

Some Representative Organic Molecules

Perhaps the best way to appreciate the variety of organic molecules is to look at a few. Three simple organic compounds are methane, ethanol, and trichlorofluoromethane.

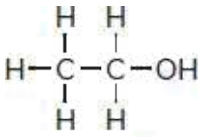
- Methane, the simplest of all organic compounds, contains one carbon atom.

Methane—the main component of natural gas—occurs widely in nature. Like other hydrocarbons—organic compounds that contain only carbon and hydrogen—methane is combustible; that is, it burns in the presence of oxygen. Methane is the product of the anaerobic (without air) decomposition of organic matter by bacteria. The natural gas we use today was formed by the decomposition of organic material millions of years ago. Hydrocarbons such as methane are discussed in Chapter 4.



methane

- Ethanol, the alcohol present in beer, wine, and other alcoholic beverages, is formed by the fermentation of sugar, possibly the oldest example of organic synthesis. Ethanol can also be made in the lab by a totally different process, but the ethanol produced in the lab is *identical* to the ethanol produced by fermentation. Alcohols including ethanol are discussed in Chapter 9.



ethanol

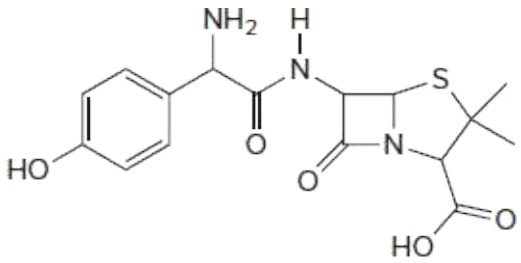
- Trichlorofluoromethane is a member of a class of molecules called chlorofluorocarbons, or CFCs, which contain one or two carbon atoms and several halogens. Trichlorofluoromethane is an unusual organic molecule in that it contains no hydrogen atoms. Because it has a low molecular weight and is easily vaporized, trichlorofluoromethane has been used as an aerosol propellant and refrigerant. It and other CFCs have been implicated in the destruction of the stratospheric ozone layer, a topic discussed in Chapter 13.

trichlorofluoromethane

Three complex organic molecules that are important medications are amoxicillin, fluoxetine, and AZT.

- Amoxicillin is one of the most widely used antibiotics in the penicillin family. The

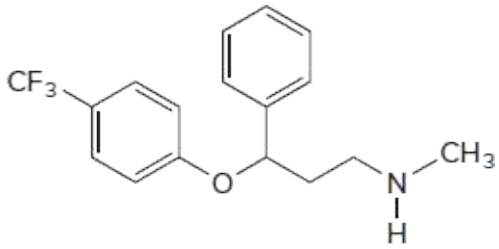
discovery and synthesis of such antibiotics in the twentieth century made routine the treatment of infections that were formerly fatal. You were likely given some amoxicillin to treat an ear infection when you were a child. The penicillin antibiotics are discussed in Chapter 20.



amoxicillin

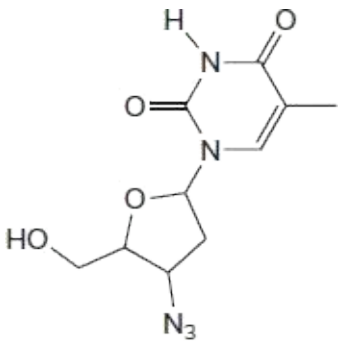
Complex organic structures are drawn with shorthand conventions described in Chapter 1.

- Fluoxetine is the generic name for the antidepressant Prozac. Prozac was designed and synthesized by chemists in the laboratory, and is now produced on a large scale in chemical factories. Because it is safe and highly effective in treating depression, Prozac is widely prescribed. Over 40 million individuals worldwide have used Prozac since 1986.



fluoxetine

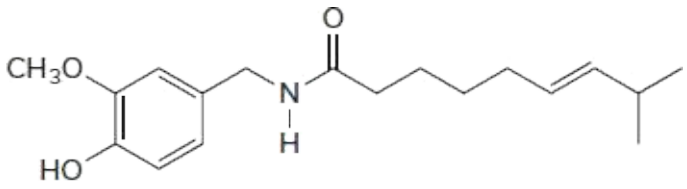
- AZT, azidodeoxythymidine, is a drug that treats human immunodeficiency virus (HIV), the virus that causes acquired immune deficiency syndrome (AIDS). Also known by its generic name zidovudine, AZT represents a chemical success to a different challenge: synthesizing agents that combat viral infections.



AZT

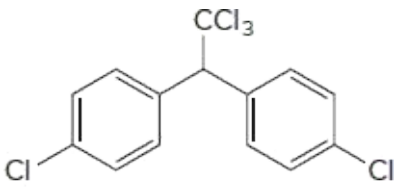
Other complex organic compounds with interesting properties are capsaicin and DDT.

- Capsaicin, one member of a group of compounds called *vanilloids*, is responsible for the characteristic spiciness of hot peppers. It is the active ingredient in pepper sprays used for personal defense and topical creams used for pain relief.



capsaicin

- DDT, dichlorodiphenyltrichloroethane, is a pesticide once called “miraculous” by Winston Churchill because of the many lives it saved by killing disease-carrying mosquitoes. DDT use is now banned in the United States and many developed countries because it is a nonspecific insecticide that persists in the environment.



DDT

What are the common features of these organic compounds?

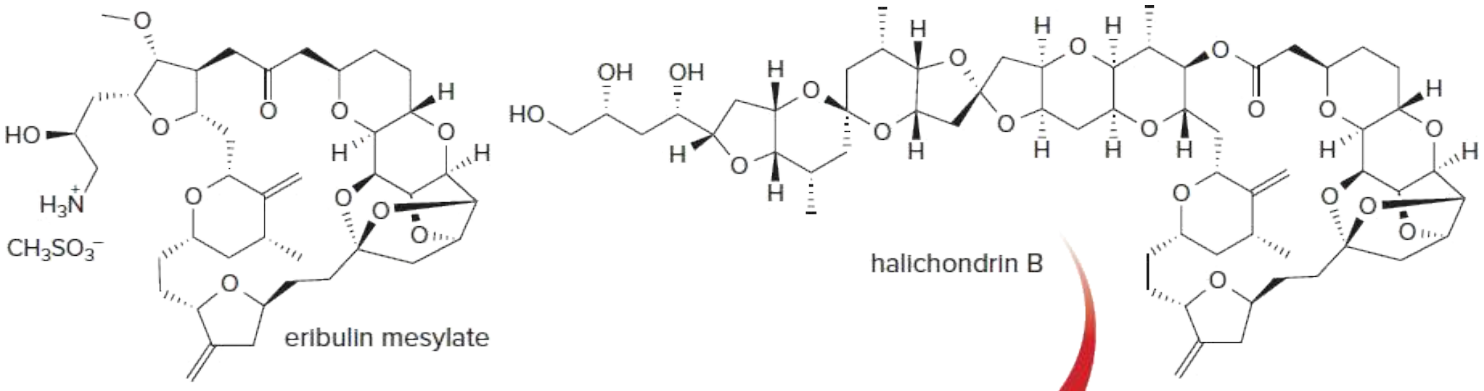
- **All organic compounds contain carbon atoms and most contain hydrogen atoms.**
- **All the carbon atoms have four bonds. A stable carbon atom is said to be *tetravalent.***
- **Other elements may also be present. Any atom that is not carbon or hydrogen is called a *heteroatom.* Common heteroatoms include N, O, S, P, and the halogens.**
- **Some compounds have chains of atoms and some compounds have rings.**

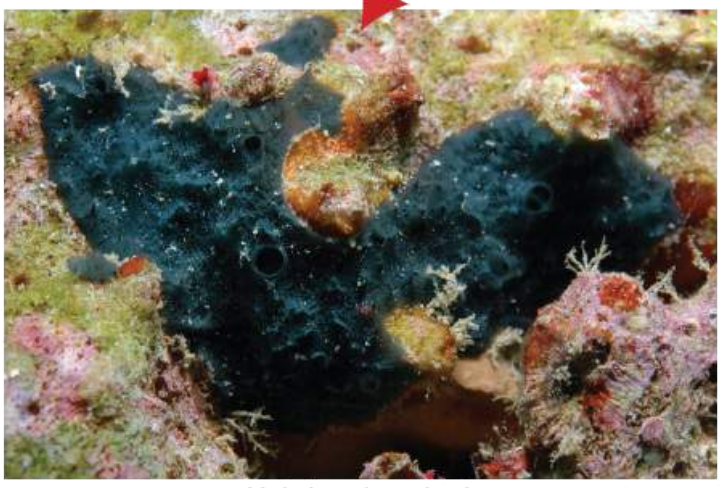
These features explain why there are so many organic compounds: Carbon forms four strong bonds with itself and other elements. Carbon atoms combine together to form rings and chains.

Marine Natural Products

Nature has generously supplied the organic chemist with a wide variety of complex compounds that have promising therapeutic potential. In the last 40 years, the largely unexplored marine environment has been recognized as a vast resource of unique compounds with novel chemical properties, but the challenges in discovering drug leads among such expansive biodiversity are many. Organisms are often found in waters offshore remote islands, and structure determination must be carried out on minute quantities of material. Even when potential targets are identified, supplying enough compound for preclinical and clinical trials often means that the compound must then be synthesized in the laboratory. Nonetheless, new compounds with useful bioactivity are routinely discovered and synthesized. Among the first available anticancer drugs with origins in the world of marine natural products are eribulin mesylate and trabectedin.

Eribulin mesylate is a synthetic analogue of the more complex natural product halichondrin B, which is isolated from the black sponge *Halichondria okadai*. Sold under the trade name Halaven, it was approved in the United States in 2010 for the treatment of metastatic breast cancer.



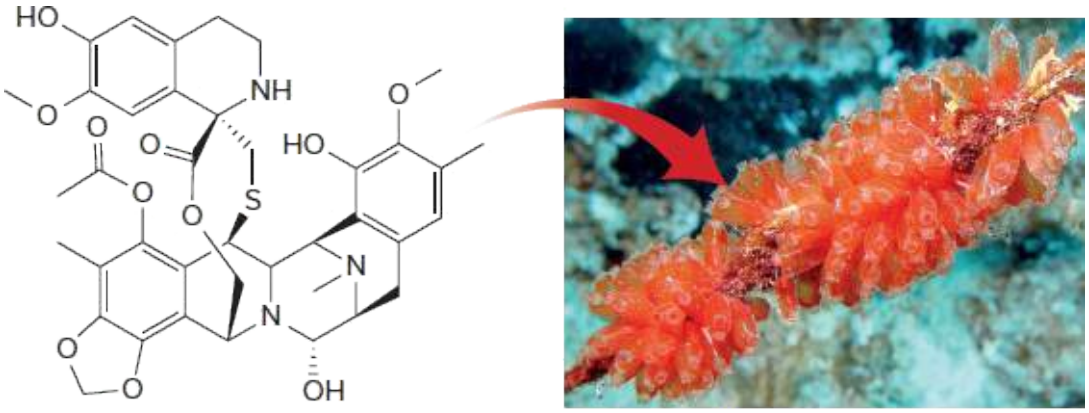


Halichondria okadai

© Guido & Philippe Poppe

Trabectedin, also known as ecteinascidin 743 or ET-743, is obtained from the sea

squirt *Ecteinascidia turbinata*. Sold under the trade name Yondelis, it was approved in the European Union in 2007 for the treatment of advanced soft tissue sarcoma. In 2015, the U.S. Food and Drug Administration approved trabectedin for the treatment of specific soft tissue cancers that cannot be removed by surgery.



trabectedin, ET-743

Ecteinascidia turbinata

© ***Florent Charpin***

Because isolation of enough trabectedin for clinical trials was not feasible—one ton of organisms yielded one gram of compound—trabectedin was synthesized in the laboratory of Nobel Laureate E. J. Corey in 1996. Now it is readily available by a shorter synthesis from a starting material obtained by a fermentation process.

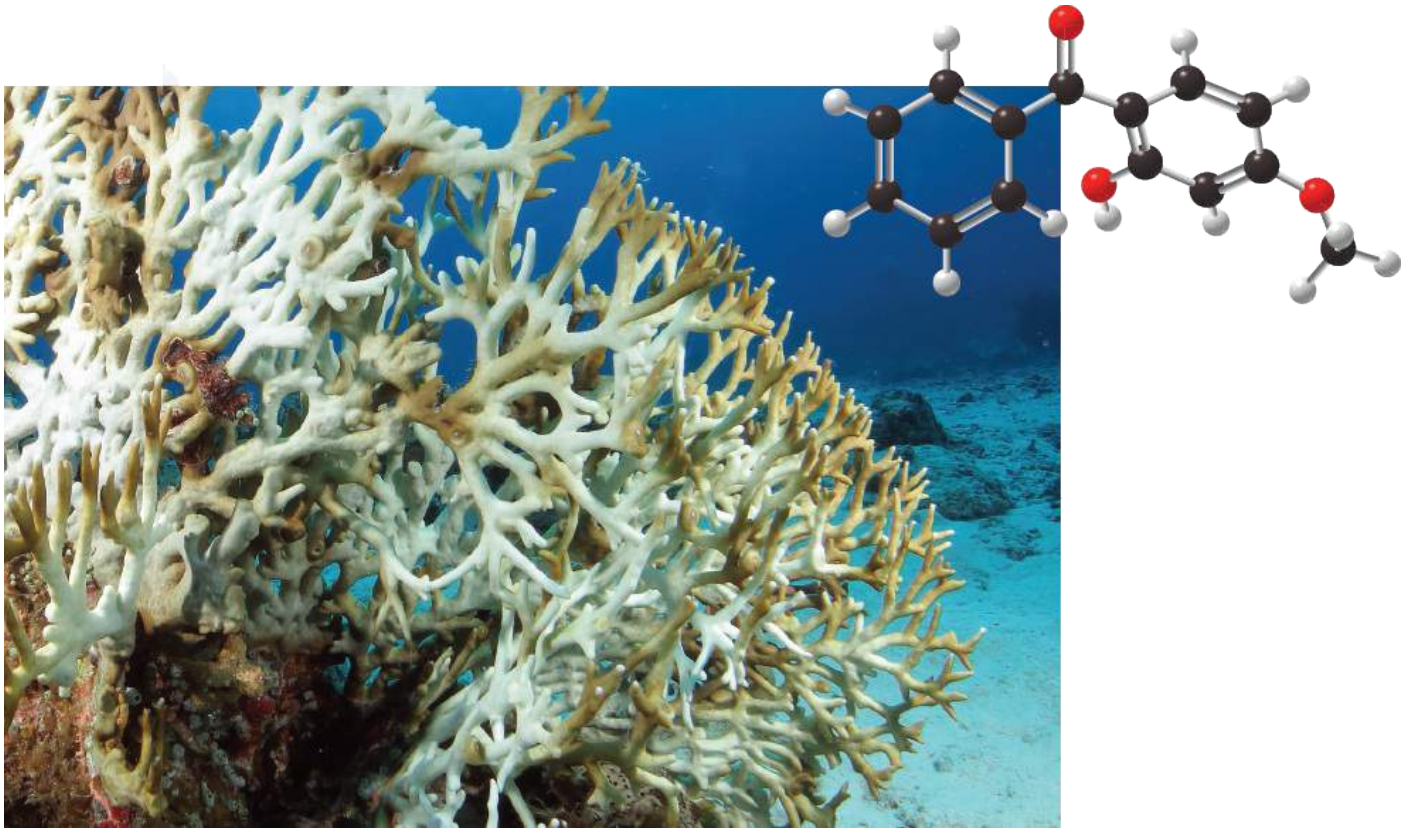
Hundreds of new biologically active marine natural products are now isolated each year, so the number of compounds in the marine drug pipeline should continue to increase in the near future.

In this introduction, we have seen a variety of molecules that have diverse structures. They represent a miniscule fraction of the organic compounds currently known and the many thousands that are newly discovered or synthesized each year. The principles you learn in organic chemistry will apply to all of these molecules, from simple ones like methane and ethanol, to complex ones like eribulin mesylate and trabectedin. It is these beautiful molecules, their properties, and their reactions that we will study in organic chemistry.

WELCOME TO THE WORLD OF ORGANIC CHEMISTRY!

Structure and Bonding

1



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1.1 The periodic table

1.2 Bonding

1.3 Lewis structures

1.4 Isomers

1.5 Exceptions to the octet rule

1.6 Resonance

1.7 Determining molecular shape

1.8 Drawing organic structures

1.9 Hybridization

1.10 Ethane, ethylene, and acetylene
1.11 Bond length and bond strength
1.12 Electronegativity and bond polarity
1.13 Polarity of molecules
1.14 Oxybenzone—A representative organic molecule

Bleaching is a phenomenon that occurs when corals expel symbiotic algae from their tissues in response to an external stress, causing the coral to turn white. Although coral bleaching is most often associated with an increase in water temperature, recent research at the University of Hawai'i suggests that minute amounts of compounds such as oxybenzone also contribute to bleaching. Oxybenzone effectively filters a broad spectrum of harmful ultraviolet light, so it is a common sunscreen component, but it can be washed off while swimming, leading to a low but potentially harmful concentration in the water. In Chapter 1, we learn about the structure, bonding, and properties of organic compounds like oxybenzone.

Why Study…

Structure and Bonding?

Before examining organic molecules in detail, we must review topics about structure and bonding learned in previous chemistry courses. We will discuss these concepts primarily from an organic chemist's perspective, and spend time on only the particulars needed to understand organic compounds.

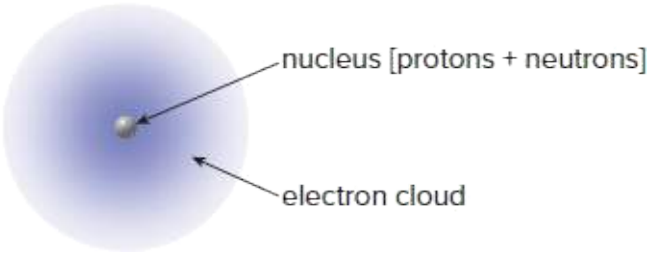
Important topics in Chapter 1 include drawing Lewis structures, predicting the shape of molecules, determining what orbitals are used to form bonds, and how electronegativity affects bond polarity. Equally important is Section 1.8 on drawing organic molecules, both shorthand methods routinely used for simple and complex compounds, and three-dimensional representations that allow us to more clearly visualize them.

1.1 The Periodic Table

All matter is composed of the same building blocks called atoms. There are two main

components of an atom.

- **The nucleus contains positively charged protons and uncharged neutrons. Most of the mass of the atom is contained in the nucleus.**
- **The electron cloud is composed of negatively charged electrons. The electron cloud comprises most of the volume of the atom.**



The charge on a proton is equal in magnitude but opposite in sign to the charge on an electron. In a neutral atom, the number of protons in the nucleus equals the number of electrons. This quantity, called the atomic number, is unique to a particular element. For example, every neutral carbon atom has an atomic number of six, meaning it has six protons in its nucleus and six electrons surrounding the nucleus.

In addition to neutral atoms, we will encounter charged ions.

- **A *cation* is positively charged and has fewer electrons than protons.**
- **An *anion* is negatively charged and has more electrons than protons.**

The number of neutrons in the nucleus of a particular element can vary. Isotopes are two atoms of the same element having a different number of neutrons. The mass number of an atom is the total number of protons and neutrons in the nucleus. Isotopes have *different* mass numbers. The atomic weight of a particular element is the weighted average of the mass of all its isotopes, reported in atomic mass units (amu).

Isotopes of carbon and hydrogen are sometimes used in organic chemistry. The most common isotope of hydrogen has one proton and no neutrons in the nucleus, but 0.02% of hydrogen atoms have one proton and one neutron. This isotope of hydrogen is called deuterium and is sometimes symbolized by the letter D.

Each atom is identified by a one- or two-letter abbreviation that is the characteristic symbol for that element. Carbon is identified by the single letter C. Sometimes the atomic number is indicated as a subscript to the left of the element symbol, and the mass number is indicated as a superscript. Using this convention, the most common isotope of carbon, which contains six protons and six neutrons, is designated as ${}^{12}_{6}\mathrm{C}$.

A row in the periodic table is also called a *period*, and a column is also called a *group.* A periodic table is located in Appendix A for your reference.

The periodic table is a schematic arrangement of the more than 100 known elements, arranged in order of increasing atomic number. The periodic table is composed of rows and columns. Each column in the periodic table is identified by a group number, an Arabic (1 to 8) or Roman (I to VIII) numeral followed by the letter A or B. Carbon is located in group 4A in the periodic table in this text.

- **Elements in the same row are similar in *size.***
- **Elements in the same column have similar *electronic and chemical properties.***

Although more than 100 elements exist, most are not common in organic compounds. Figure 1.1 contains a truncated periodic table, indicating the handful of elements that are routinely seen in this text. Most elements in organic compounds are located in the first and second rows of the periodic table.

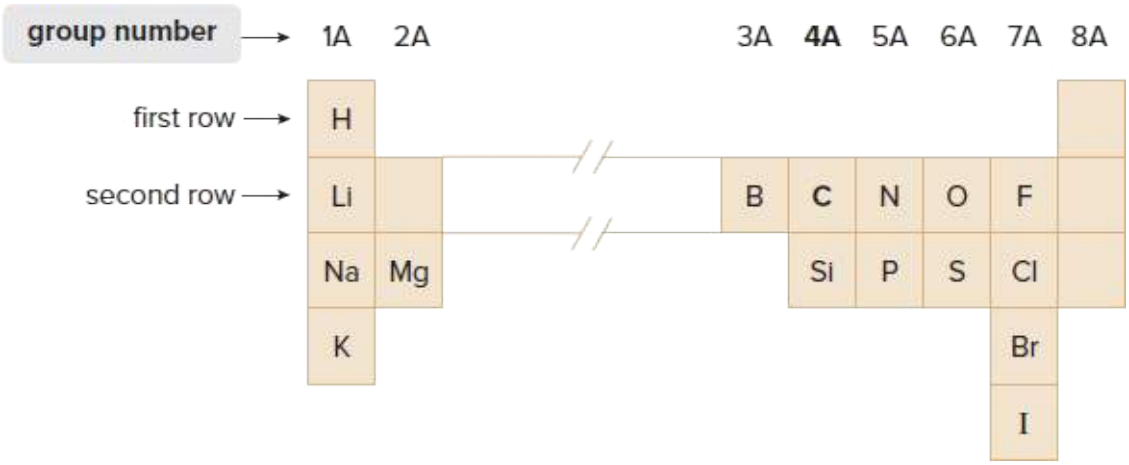
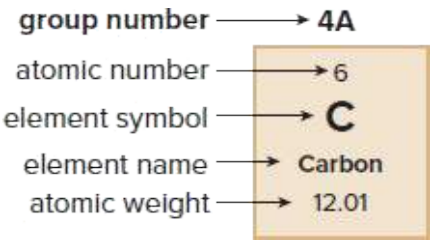


Figure 1.1 **A periodic table of the common elements seen in organic chemistry**

- **Carbon is located in the second row, group 4A.**

Carbon's entry in the periodic table:

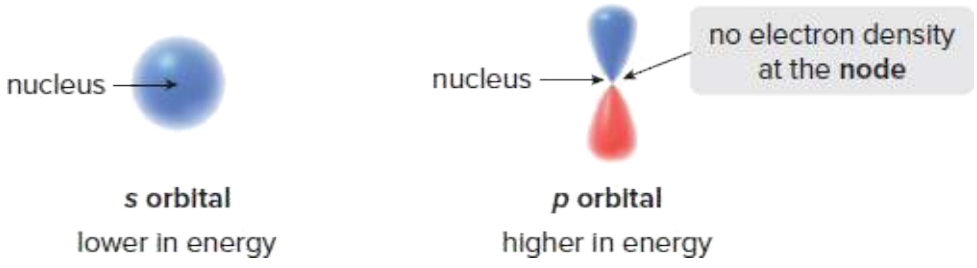


Across each row of the periodic table, electrons are added to a particular shell of orbitals around the nucleus. The shells are numbered 1, 2, 3, and so on. Adding electrons to the first shell forms the first row. Adding electrons to the second shell forms the second row. Electrons are first added to the shells closest to the nucleus.

Each shell contains a certain number of orbitals. An orbital is a region of space that is high in electron density. There are four different kinds of orbitals, called *s*, *p*, *d*, and *f*. The first shell has only one orbital, an *s* orbital. The second shell has two kinds of orbitals, *s* and *p*, and so on. Each type of orbital has a particular shape.

For the first- and second-row elements, we must consider only *s* orbitals and *p* orbitals.

- **An *s* orbital has a sphere of electron density. It is *lower in energy* than other orbitals of the same shell, because electrons are kept closer to the positively charged nucleus.**
- **A *p* orbital has a dumbbell shape. It contains a node of electron density at the nucleus. A node means there is *no* electron density in this region. A *p* orbital is *higher in energy* than an *s* orbital (in the same shell) because its electron density is farther away from the nucleus.**



An *s* orbital is filled with electrons before a *p* orbital in the same shell.

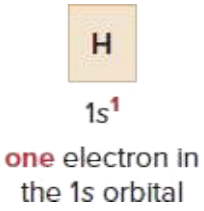
1.1A The First Row

The first row of the periodic table is formed by adding electrons to the first shell of orbitals around the nucleus. There is only one orbital in the first shell, called the 1*s*

orbital.

- **Each orbital can have a maximum of two electrons.**

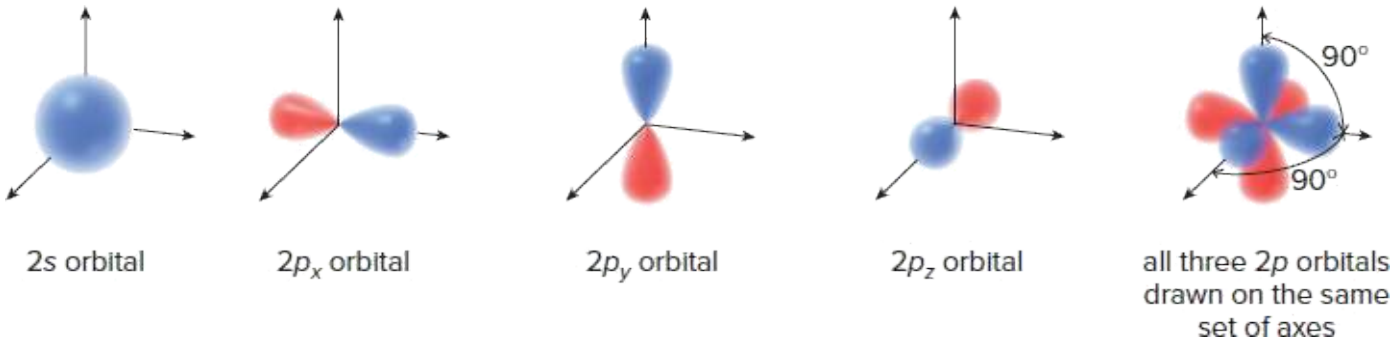
As a result, there are two elements in the first row, one having one electron added to the 1*s* orbital, and one having two. The element hydrogen (H) has what is called a $1s^1$ configuration with one electron in the 1s orbital, and helium (He) has a $1s^2$ configuration with two electrons in the 1*s* orbital.



1.1B The Second Row

Every element in the second row has a filled first shell of electrons. Thus, all second-row elements have a $1s^2$ configuration. Each element in the second row of the periodic table also has four orbitals available to accept additional electrons:

- one 2*s* orbital, the *s* orbital in the second shell
- three 2*p* orbitals, all dumbbell-shaped and perpendicular to each other along the *x*, *y*, and *z* axes



Because each of the four orbitals in the second shell can hold two electrons, there is a maximum capacity of *eight* electrons for elements in the second row. The second row of the periodic table consists of eight elements, obtained by adding electrons to the 2*s* and three 2*p* orbitals.

The outermost electrons are called valence electrons. The valence electrons are more loosely held than the electrons closer to the nucleus, and as such, they participate in chemical reactions. The group number of a second-row element reveals its number of valence electrons. For example, carbon in group 4A has four valence electrons, and oxygen in group 6A has six.

Problem 1.1

While the most common isotope of nitrogen has a mass number of 14 (nitrogen-14), a radioactive isotope of nitrogen has a mass number of 13 (nitrogen-13). Nitrogen-13 is used in PET (positron emission tomography) scans by physicians to monitor brain activity and diagnose dementia. For each isotope, give the following information: (a) the number of protons; (b) the number of neutrons; (c) the number of electrons in the neutral atom; (d) the group number; and (e) the number of valence electrons.

1.2 Bonding

Until now our discussion has centered on individual atoms, but it is more common in nature to find two or more atoms joined together.

- ***Bonding*** **is the joining of two atoms in a stable arrangement.**

Joining two or more elements forms compounds. Although only about 100 elements exist, more than 50 million compounds are known. Examples of compounds include hydrogen gas (H_2), formed by joining two hydrogen atoms, and methane (CH_4), the simplest organic compound, formed by joining a carbon atom with four hydrogen atoms.

One general rule governs the bonding process.

- **Through bonding, atoms attain a complete outer shell of valence electrons.**

Because the noble gases in group 8A of the periodic table are especially stable as atoms having a filled shell of valence electrons, the general rule can be restated.

- **Through bonding, atoms gain, lose, or share electrons to attain the electronic configuration of the noble gas closest to them in the periodic table.**

What does this mean for first- and second-row elements? A first-row element like hydrogen can accommodate *two electrons* around it. This would make it like the noble gas helium at the end of the same row. A second-row element is generally most stable with *eight valence electrons* around it like neon. Elements that behave in this manner are said to follow the octet rule.

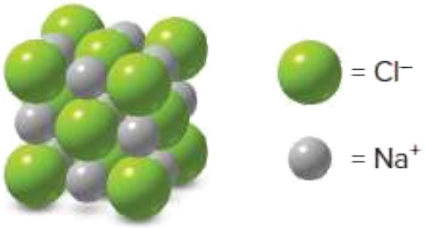
There are two different kinds of bonding: ionic bonding and covalent bonding.

- ***Ionic bonds*** **result from the** ***transfer*** **of electrons from one element to another.**
- ***Covalent bonds*** **result from the** ***sharing*** **of electrons between two nuclei.**

Atoms readily form ionic bonds when they can attain a noble gas configuration by gaining or losing just one or two electrons. NaCl and KI are ionic compounds. ©*Jill Braaten*

The type of bonding is determined by the location of an element in the periodic table. An ionic bond generally occurs when elements on the far left side of the periodic table combine with elements on the far right side, ignoring the noble gases, which form bonds only rarely. The resulting ions are held together by extremely strong electrostatic interactions. A positively charged cation formed from the element on the left side attracts a negatively charged anion formed from the element on the right side. Examples of ionic inorganic compounds include sodium chloride (NaCl), common table salt, and potassium iodide (KI), an essential nutrient added to make iodized salt.

Ionic compounds form extended crystal lattices that maximize the positive and negative electrostatic interactions. In NaCl, each positively charged Na^+ ion is surrounded by six negatively charged Cl^- ions, and each Cl^- ion is surrounded by six Na^+ ions.



NaCl

- **The transfer of electrons forms stable salts composed of cations and anions.**

A compound may have either ionic or covalent bonds. A molecule has only covalent bonds.

The second type of bonding, covalent bonding, occurs with elements like carbon in the middle of the periodic table, which would otherwise have to gain or lose several electrons to form an ion with a complete valence shell. A covalent bond is a two-electron bond, and a compound with covalent bonds is called a molecule. Covalent bonds also form between two elements from the same side of the table, such as two hydrogen atoms or two chlorine atoms. H_2, Cl_2, and CH_4 are all examples of covalent molecules.

Problem 1.2

Label each bond in the following compounds as ionic or covalent.

a. F_2

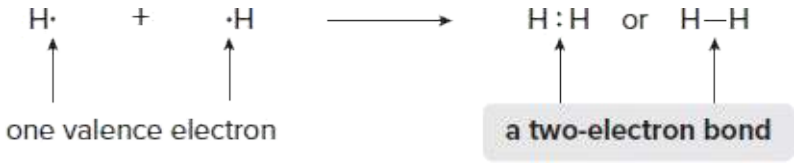
b. LiBr

c. CH_3CH_3

d. $NaNH_2$

e. $NaOCH_3$

How many covalent bonds will a particular atom typically form? As you might expect, it depends on the location of the atom in the periodic table. In the first row, hydrogen forms one covalent bond using its one valence electron. When two hydrogen atoms are joined in a bond, each has a filled valence shell of two electrons. A *solid line* indicates a two-electron bond.



Second-row elements can have no more than eight valence electrons around them. For neutral molecules, two consequences result.

- **Atoms with one, two, three, or four valence electrons form one, two, three, or four bonds, respectively, in neutral molecules.**
- **Atoms with five or more valence electrons form enough bonds to give an octet. In this case, the predicted number of bonds = 8 − the number of valence electrons.**

For example, B has three valence electrons, so it forms three bonds, as in BF_3. N has five valence electrons, so it also forms three bonds (8 − 5 = 3 bonds), as in NH_3.

Nonbonded pair of electrons = unshared pair of electrons = lone pair

These guidelines are used in Figure 1.2 to summarize the usual number of bonds formed by the common atoms in organic compounds. When second-row elements form fewer than four bonds their octets consist of both bonding (shared) electrons and nonbonding (unshared) electrons. Unshared electrons are also called lone pairs.

Problem 1.3

How many covalent bonds are predicted for each atom?

a. O

b. Al

c. Br

d. Si

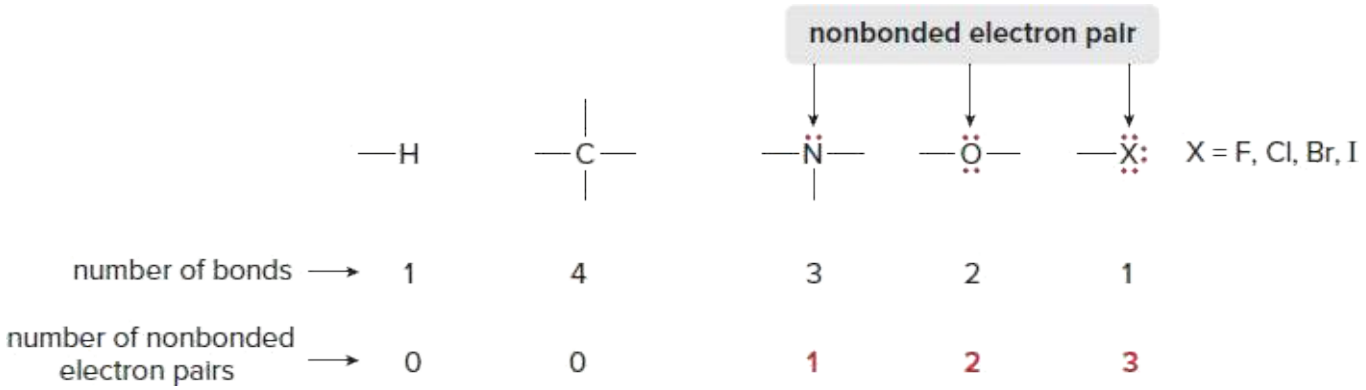


Figure 1.2 **The usual number of bonds of common neutral atoms**

1.3 Lewis Structures

Lewis structures are electron dot representations for molecules. Three rules are used for drawing Lewis structures.

1. **Draw only the valence electrons.**
2. **Give every second-row element no more than eight electrons.**
3. **Give each hydrogen two electrons.**

1.3A A Procedure for Drawing Lewis Structures

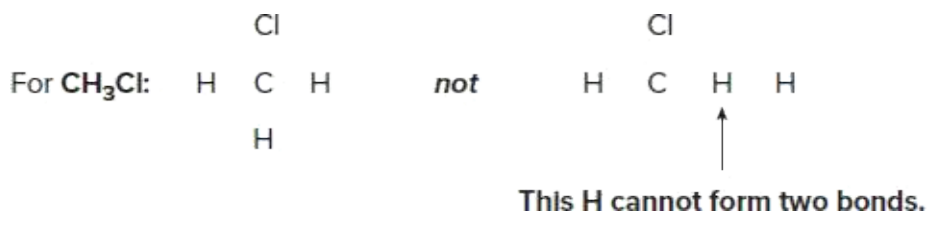
Follow a stepwise procedure to draw a Lewis structure.

How To **Draw a Lewis Structure**

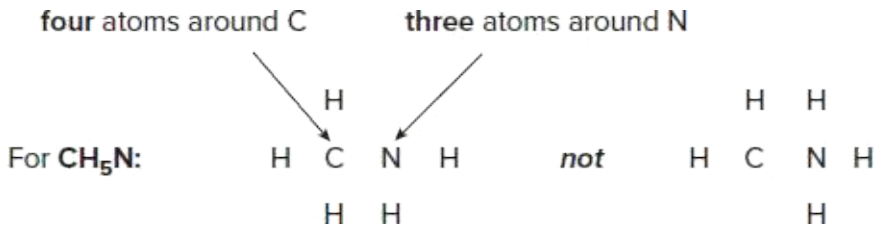
Step [1] **Arrange atoms next to each other that you think are bonded together.**

- **Always place hydrogen atoms and halogen atoms on the periphery because H and X (X = F, Cl, Br, and I) form only one bond each.**

The letter X is often used to represent one of the halogens in group 7A: F, Cl, Br, or I.



- **As a first approximation, use the common bonding patterns in Figure 1.2 to arrange the atoms.**



- **In truth, the proper arrangement of atoms may not be obvious, or more than one arrangement may be possible (Section 1.4). Even in many simple molecules, the connectivity between atoms must be determined experimentally.**

Step [2] Count the electrons.

- **Count the number of valence electrons from all atoms.**
- **Add one electron for each negative charge.**
- **Subtract one electron for each positive charge.**
- **This sum gives the total number of electrons that must be used in drawing the Lewis structure.**

Step [3] Arrange the electrons around the atoms.

- **Place a bond between every two atoms, giving two electrons to each H and no more than eight to any second-row atom.**
- **Use all remaining electrons to fill octets with lone pairs.**
- **If all valence electrons are used and an atom does not have an octet, form multiple bonds, as shown in Sample Problem 1.2.**

Step [4] Assign formal charges to all atoms.

- **Formal charges are discussed in Section 1.3C.**

Sample Problem 1.1 illustrates how to draw the Lewis structure of a simple organic molecule.

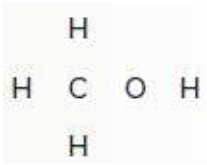
Sample Problem 1.1 Drawing a Lewis Structure for a Simple Molecule

Draw a Lewis structure for methanol, a compound with molecular formula CH_4O.

Solution

Step [1] Arrange the atoms.

- **Place the second-row elements, C and O, in the middle.**
- **Place three H's around C to surround C by four atoms.**
- **Place one H next to O to surround O by two atoms.**

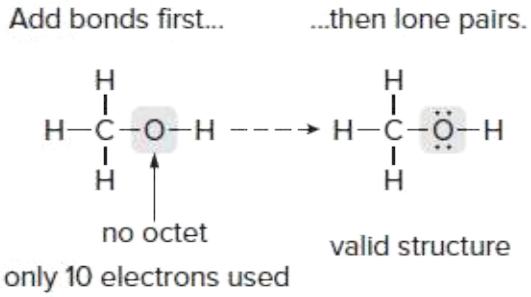


Step [2] Count the electrons.

$$\begin{aligned} 1\,C \times 4\,e^- &= 4\,e^- \\ 1\,O \times 6\,e^- &= 6\,e^- \\ 4\,H \times 1\,e^- &= 4\,e^- \\ &\overline{14\ e^-\ \text{total}} \end{aligned}$$

Step [3] Add the bonds and lone pairs.

- **Add five two-electron bonds to form the C–H, C–O, and O–H bonds, using 10 of the 14 electrons.**
- **Place two lone pairs on the O atom to use the remaining four electrons and give the O atom an octet.**



This Lewis structure is valid because it uses all 14 electrons, each H is surrounded by two electrons, and each second-row element is surrounded by no more than eight electrons.

Problem 1.4

Draw a valid Lewis structure for each species.

a. CH_3CH_3

b. CH_5N

c. C_2H_5Br

More Practice:

Try Problem 1.45a.

1.3B Multiple Bonds

Sample Problem 1.2 illustrates an example of a Lewis structure with a double bond.

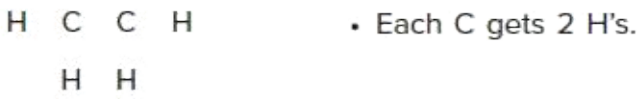
Sample Problem 1.2 Drawing a Lewis Structure with a Multiple Bond

Draw a Lewis structure for ethylene, a compound of molecular formula C_2H_4, in which each carbon is bonded to two hydrogens.

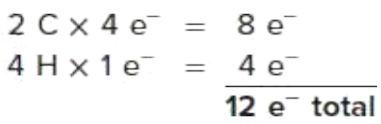
Solution

Follow Steps [1] to [3] to draw a Lewis structure.

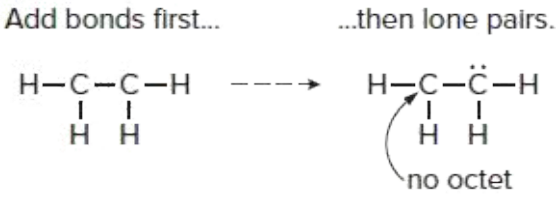
Step [1] Arrange the atoms.



Step [2] Count the electrons.



Step [3] Add the bonds and lone pairs.



After placing five bonds between the atoms and adding the two remaining electrons as a lone pair, one C still has no octet.

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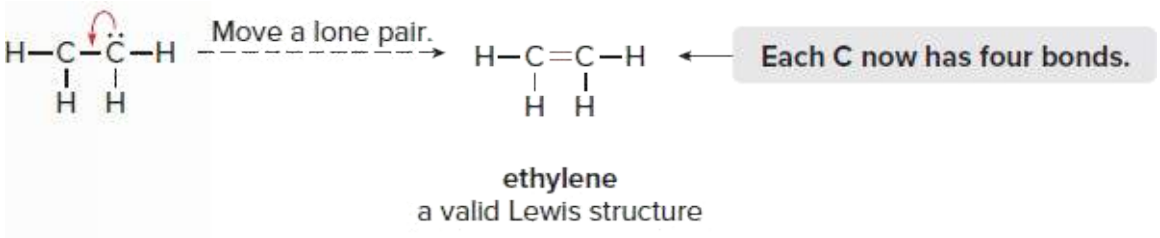
To give both C's an octet, change *one* lone pair into *one* bonding pair of electrons between the two C's, forming a double bond.



This uses all 12 electrons, each C has an octet, and each H has two

electrons. The Lewis structure is valid. Ethylene contains a carbon–carbon double bond.

Problem 1.5

Draw an acceptable Lewis structure for each compound, assuming the atoms are connected as arranged. Formaldehyde (H_2CO) is a preservative, and glycolic acid ($HOCH_2CO_2H$) is used to make dissolving sutures.

a. H_2CO H C O H

b. $HOCH_2CO_2H$ H O C C O H H

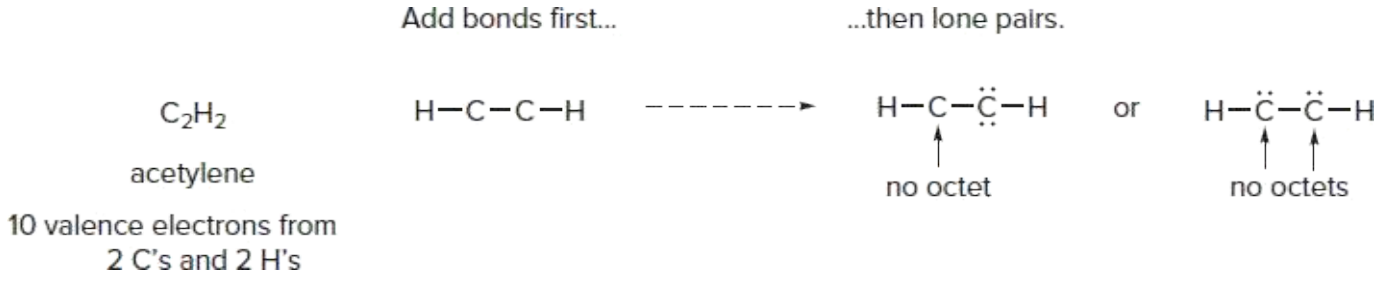
More Practice:

Try Problems 1.44, 1.45b–d.

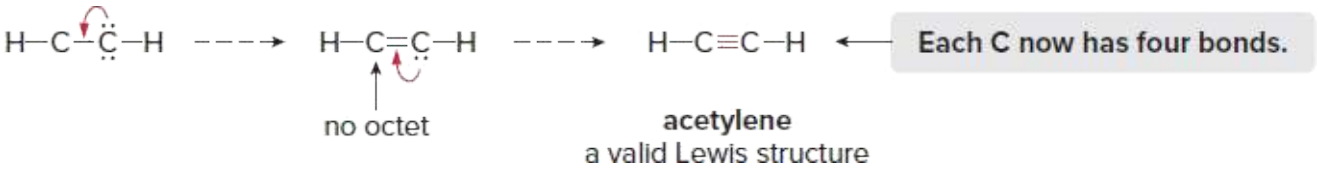
Carbon always forms four bonds in stable organic molecules. Carbon forms single, double, and triple bonds to itself and other elements.

- **After placing all electrons in bonds and lone pairs, use a lone pair to form a multiple bond if an atom does not have an octet.**

You must change *one* lone pair into *one* new bond for each *two* electrons needed to complete an octet. In acetylene, a compound with molecular formula C_2H_2, placing the 10 valence electrons gives a Lewis structure in which one or both of the C's lack an octet.



In this case, change *two* lone pairs into *two* bonding pairs of electrons, forming a triple bond.



Problem 1.6

Draw an acceptable Lewis structure for each compound, assuming the atoms are connected as arranged.

a. HCN H C N

b. C_3H_4 H C C C H
H

1.3C Formal Charge

To manage electron bookkeeping in a Lewis structure, chemists use formal charge.

- ***Formal charge*** **is the charge assigned to individual atoms in a Lewis structure.**

By calculating formal charge, we determine how the number of electrons around a particular atom compares to its number of valence electrons. Formal charge is calculated as follows:

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$$\text{formal charge} = \text{number of valence electrons} - \text{number of electrons an atom "owns"}$$

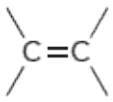
The number of electrons "owned" by an atom is determined by its number of bonds and lone pairs.

- **An atom "owns"** ***all*** **of its unshared electrons and** ***half*** **of its shared electrons.**

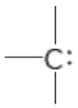
$$\text{number of electrons owned} = \text{number of unshared electrons} + \frac{1}{2}\left[\text{number of shared electrons}\right]$$

The number of electrons "owned" by different carbon atoms is indicated in the following examples:

- C shares eight electrons.
- C "owns" **four** electrons.



- Each C shares eight electrons.
- Each C "owns" **four** electrons.

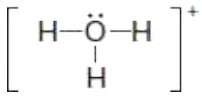


- C shares six electrons.
- C has two unshared electrons.
- C "owns" **five** electrons.

Sample Problem 1.3 illustrates how formal charge is calculated on the atoms of a polyatomic ion. The sum of the formal charges on the individual atoms equals the net charge on the molecule or ion.

Sample Problem 1.3 Determining the Formal Charge on an Atom

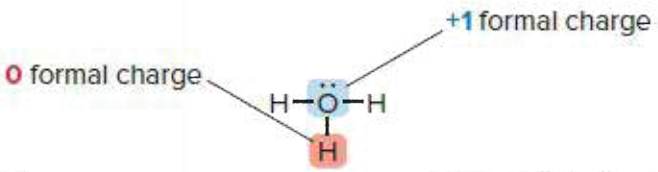
Determine the formal charge on each atom in the ion H_3O^+.



Solution

To calculate the formal charge on each atom:

- **Determine the number of valence electrons from the group number.**
- **Determine the number of electrons an atom "owns" from the number of bonding and nonbonding electrons it has.**
- **Subtract the second quantity from the first to give the formal charge.**



For the O atom (group 6A):
- number of valence electrons = 6
- number of bonding electrons = 6
- number of nonbonding electrons = 2

$$\text{formal charge} = 6 - \left[2 + \frac{1}{2}(6)\right] = +1$$

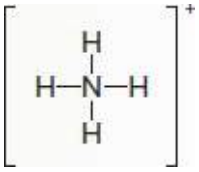
For each H atom (group 1A):
- number of valence electrons = 1
- number of bonding electrons = 2
- number of nonbonding electrons = 0

$$\text{formal charge} = 1 - \left[0 + \frac{1}{2}(2)\right] = 0$$

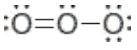
The formal charge on the O atom is +1 and the formal charge on each H is 0. The overall charge on the ion H_3O+ is the sum of all of the formal charges on the atoms: 1 + 0 + 0 + 0 = +1.

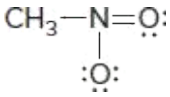
Problem 1.7

Calculate the formal charge on each second-row atom.

a. 

b. $CH_3-N\equiv C:$

c. 

d. 

More Practice:

Try Problems 1.42, 1.43.

Problem 1.8

Draw a Lewis structure for each ion.

a. CH_3O^-

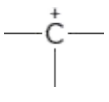
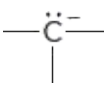
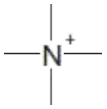
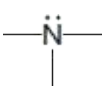
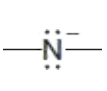
b. HC_2^-

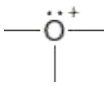
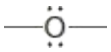
c. $(CH_3NH_3)^+$

d. $(CH_3NH)^-$

When you first add formal charges to Lewis structures, use the procedure in Sample Problem 1.3. With practice, you will notice that certain bonding patterns always result in the same formal charge. For example, any N atom with four bonds (and thus no lone pairs) has a +1 formal charge. Table 1.1 lists the bonding patterns and resulting formal charges for carbon, nitrogen, and oxygen.

Table 1.1 Formal Charge Observed with Common Bonding Patterns for C, N, and O

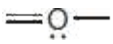
Atom	Number of valence electrons	Formal charge		
		+1	0	−1
C	4			
N	5			

O	6			

Problem 1.9

What is the formal charge on the O atom in each of the following species that contains a multiple bond to O?

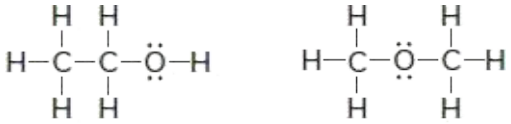
a.

b. 

c.

1.4 Isomers

Sometimes in drawing a Lewis structure, more than one arrangement of atoms is possible for a given molecular formula. For example, there are two acceptable arrangements of atoms for the molecular formula C_2H_6O.



ethanol dimethyl ether

same molecular formula
C_2H_6O

Isomers

Both are valid Lewis structures, and both molecules exist. One is called ethanol, and the other, dimethyl ether. These two compounds are called isomers.

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- ***Isomers*** **are different molecules having the same molecular formula.**

Ethanol and dimethyl ether are constitutional isomers because they have the same molecular formula, but the *connectivity of their atoms is different*. Ethanol has one C–C bond and one O–H bond, whereas dimethyl ether has two C–O bonds. A second class of isomers, called stereoisomers, is introduced in Section 4.13B.

Problem 1.10

Draw Lewis structures for each molecular formula.

a. $C_2H_4Cl_2$ **(two isomers)**

b. C_3H_8O **(three isomers)**

c. C_3H_6 (two isomers)

1.5 Exceptions to the Octet Rule

Most of the common elements in organic compounds—C, N, O, and the halogens—follow the octet rule. Hydrogen is a notable exception, because it accommodates only two electrons in bonding. Additional exceptions include boron and beryllium (second-row elements in groups 3A and 2A, respectively), and elements in the third row (particularly phosphorus and sulfur).

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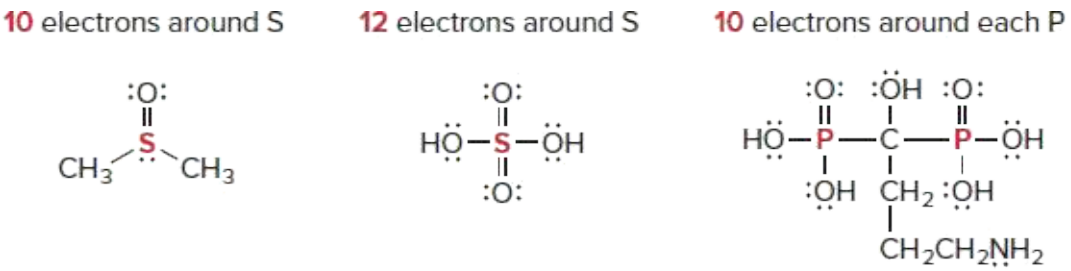
Alendronic acid, sold as a sodium salt under the trade name of Fosamax, is used to prevent osteoporosis in women. Osteoporosis decreases bone density, as shown by comparing normal bone (top) with brittle bone (bottom).

Elements in groups 2A and 3A of the periodic table, such as beryllium and boron, do not have enough valence electrons to form an octet in a neutral molecule. Lewis structures for BeH2 and BF_3 show that these atoms have only four and six electrons, respectively, around the central atom. There simply aren't enough electrons to form an octet. Because the Be and B atoms each have less than an octet of electrons, these molecules are highly reactive.

four electrons around Be six electrons around B

A second exception to the octet rule occurs with some elements located in the third row and later in the periodic table. These elements have empty *d* orbitals available to accept electrons, and thus they may have *more than eight* electrons around them. For organic chemists, the two most common elements in this category are phosphorus and sulfur, which can have 10 or even 12 electrons around them, as shown in dimethyl sulfoxide, sulfuric acid, and alendronic acid.



10 electrons around S 12 electrons around S 10 electrons around each P

dimethyl sulfoxide
DMSO sulfuric acid alendronic acid

1.6 Resonance

Some molecules can't be adequately represented by a single Lewis structure. For example, two valid Lewis structures can be drawn for the anion $(HCONH)^-$. One structure has a negatively charged N atom and a C–O double bond; the other has a negatively charged O atom and a C–N double bond. These structures are called resonance structures or resonance forms. A double-headed arrow is used to separate two resonance structures.

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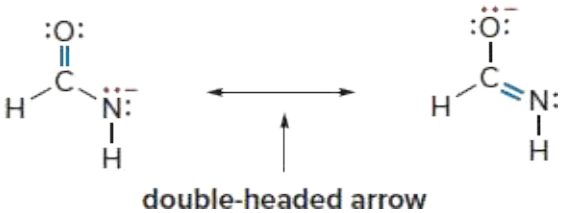


double-headed arrow

- ***Resonance structures*** **are two Lewis structures having the *same* placement of atoms but a *different* arrangement of electrons.**

Which resonance structure is an accurate representation for $(HCONH)^-$? The answer is *neither* of them. The true structure is a composite of both resonance forms, and is called a resonance hybrid. The hybrid shows characteristics of *both* resonance structures.

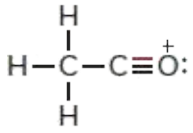
Each resonance structure implies that electron pairs are localized in bonds or on atoms. In actuality, resonance allows certain electron pairs to be *delocalized* over two or more atoms, and this delocalization of electron density adds stability. A molecule with two or more resonance structures is said to be *resonance stabilized*.

1.6A An Introduction to Resonance Theory

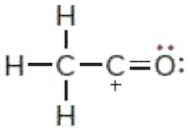
Keep in mind the following basic principles of resonance theory.

- **Resonance structures are not real. An individual resonance structure does not accurately represent the structure of a molecule or ion.**
- **Resonance structures are *not* in equilibrium with each other. There is no movement of electrons from one form to another.**
- **Resonance structures are *not* isomers. Two isomers differ in the arrangement of *both* atoms and electrons, whereas resonance structures differ *only* in the *arrangement of electrons.***

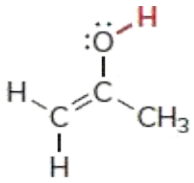
For example, ions A and B are resonance structures because the atom position is the same in both compounds, but the location of an electron pair is different. In contrast, compounds C and D are isomers because the atom placement is different; C has an O–H bond, and D has an additional C–H bond.



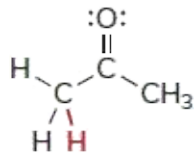
A



B



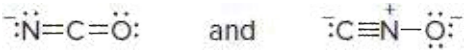
C

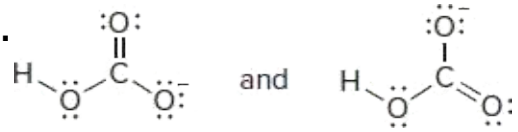


D

Problem 1.11

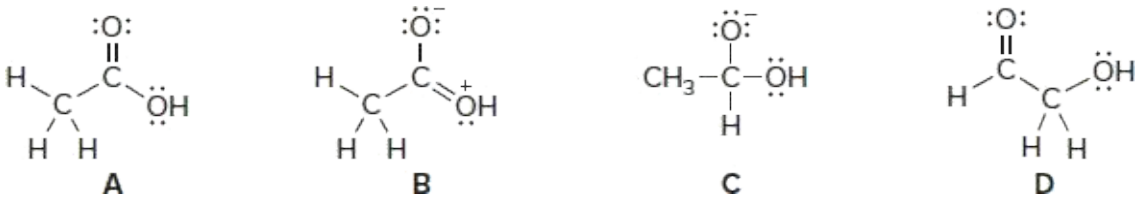
Classify each pair of compounds as isomers or resonance structures.

a. 

b. 

Problem 1.12

Considering structures A–D, classify each pair of compounds as isomers, resonance structures, or neither: (a) A and B; (b) A and C; (c) A and D; (d) B and D.



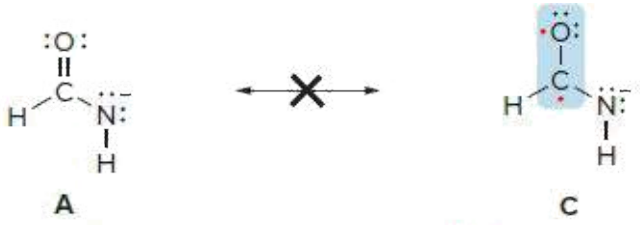
1.6B Drawing Resonance Structures

To draw resonance structures, use three criteria.

Rule [1] **Two resonance structures differ in the position of multiple bonds and nonbonded electrons. The placement of atoms and single bonds always stays the same.**

- The position of a double bond (In blue) is different.
- The position of a lone pair (In red) is different.

Rule [2] **Two resonance structures must have the same number of unpaired electrons.**

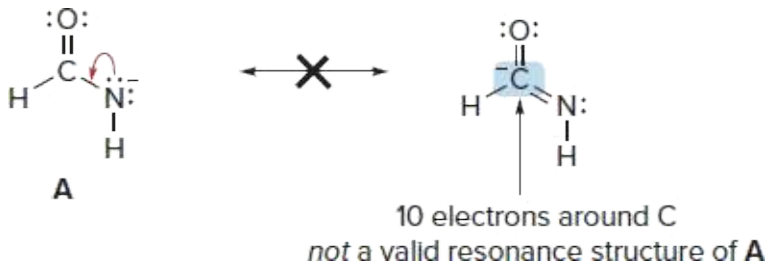


no unpaired electrons

two unpaired electrons

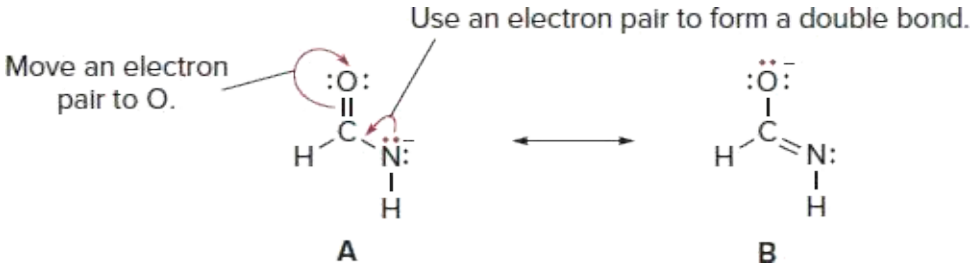
not a resonance structure of **A** (or **B**)

Rule [3] **Resonance structures must be valid Lewis structures. Hydrogen must have two electrons, and a second-row element can have no more than *eight* electrons.**



Curved arrow notation is a convention that shows how electron position differs between the two resonance forms.

- ***Curved arrow notation shows the movement of an electron pair.*** **The tail of the arrow always begins at an electron pair, in either a bond or lone pair. The head points to where the electron pair "moves."**



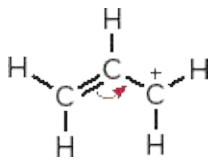
A curved arrow always begins at an electron pair. It ends at an atom or a bond.

Resonance structures A and B differ in the location of two electron pairs, so two curved arrows are needed. To convert A to B, take the lone pair on N and form a double bond between C and N. Then, move an electron pair in the C–O double bond to form a lone pair on O. Curved arrows thus show how to reposition the electrons in converting one resonance form to another. The electrons themselves do not actually move. Sample Problem 1.4 illustrates the use of curved arrows to convert one resonance structure to another.

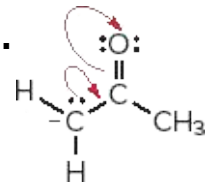
Sample Problem 1.4 Using Curved Arrows

Follow the curved arrows to draw a second resonance structure for each ion.

a.

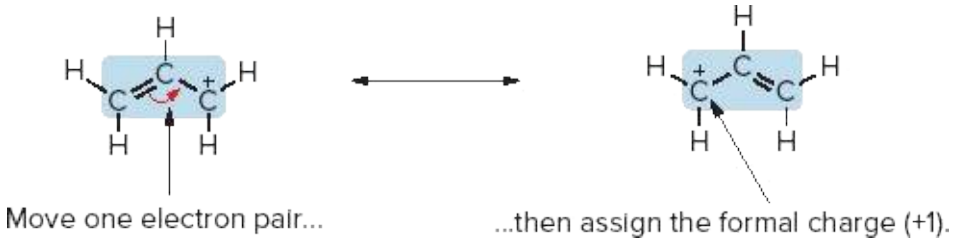


b.



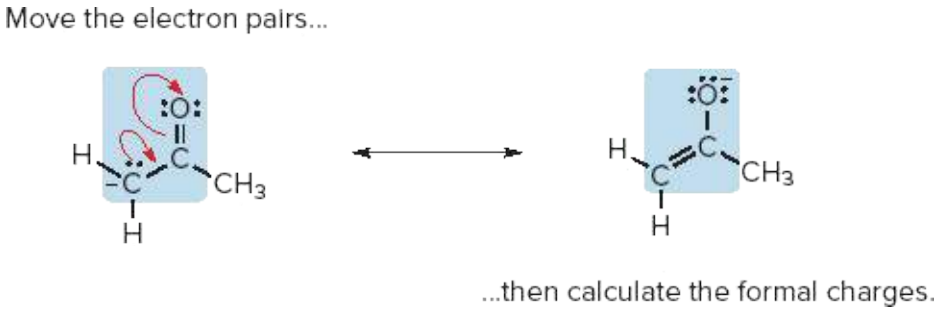
Solution

a. The curved arrow tells us to move one electron pair in the double bond to the adjacent C–C bond. Then determine the formal charge on any atom whose bonding is different.



Positively charged carbon atoms are called carbocations. Carbocations are unstable intermediates because they contain a carbon atom that is lacking an octet of electrons.

b. Two curved arrows tell us to move two electron pairs. The second resonance structure has a formal charge of (−1) on O.



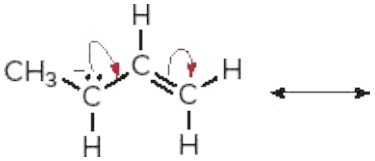
This type of resonance-stabilized anion is called an enolate anion. Enolates are important intermediates in many organic reactions, and all of Chapters 21 and 22 is devoted to their preparation and reactions.

Problem 1.13

Follow the curved arrows to draw a second resonance structure for each species.

a.

b.



More Practice:

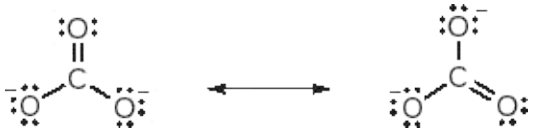
Try Problems 1.52, 1.53.

Problem 1.14

Use curved arrow notation to show how the first resonance structure can be converted to the second.

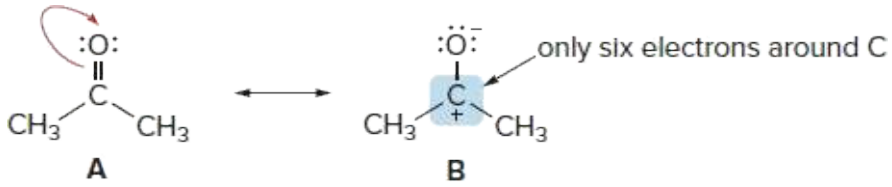
a.

b.



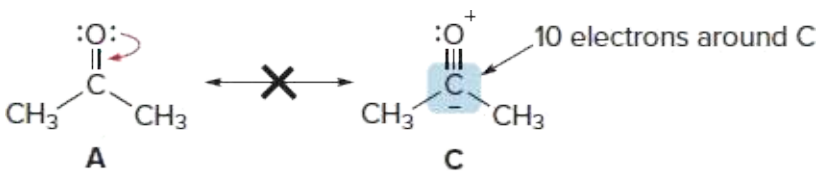
Two resonance structures can have exactly the same kinds of bonds, as they do in the carbocation in Sample Problem 1.4a, or they may have different types of bonds, as they do in the enolate in Sample Problem 1.4b. Either possibility is fine as long as the individual resonance structures are valid Lewis structures.

A resonance structure can have an atom with *fewer* than eight electrons around it. B is a resonance structure of A even though the carbon atom is surrounded by only six electrons.



valid resonance structure

In contrast, a resonance structure can *never* have a second-row element with more than eight electrons. C is *not* a resonance structure of A because the carbon atom is now surrounded by 10 electrons.

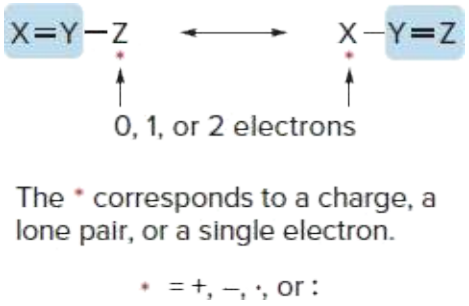


not a valid resonance structure

We will learn much more about resonance in Chapter 14.

The ability to draw and manipulate resonance structures is a necessary skill that will be used throughout your study of organic chemistry. With practice, you will begin to recognize certain common bonding patterns for which more than one Lewis structure can be drawn. For instance, both the carbocation in Sample Problem 1.4a and the enolate anion in Sample Problem 1.4b are specific examples of one general type of resonance observed in certain three-atom systems.

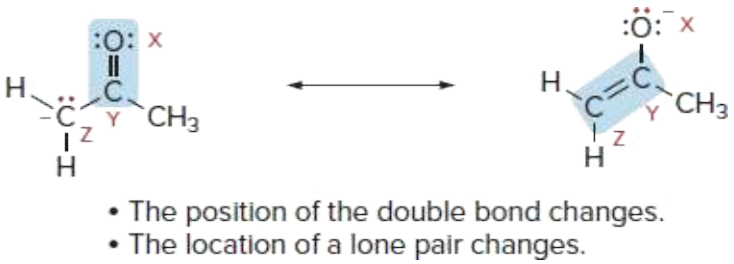
- **In a group of three atoms having a multiple bond X=Y joined to an atom Z having a *p* orbital with zero, one, or two electrons, two resonance structures can be drawn.**



Recall from the Prologue that a *heteroatom* is an atom other than carbon or hydrogen.

X, Y, and Z may all be carbon atoms or they may be heteroatoms such as nitrogen or oxygen. The atom Z can be charged (positive or negative) or neutral (with a lone pair or a single electron), corresponding to the [*] in the general structure X=Y–Z*. The two resonance structures differ in the location of the multiple bond and the [*].

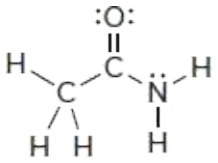
In the enolate anion in Sample Problem 1.4b, X corresponds to oxygen and [*] is a lone pair, which gives carbon a net negative charge. Moving the double bond and the lone pair and readjusting charges gives the second resonance structure.



In Chapter 14, we will learn more about the orbitals involved in this type of resonance.

Sample Problem 1.5 Drawing Resonance Structures

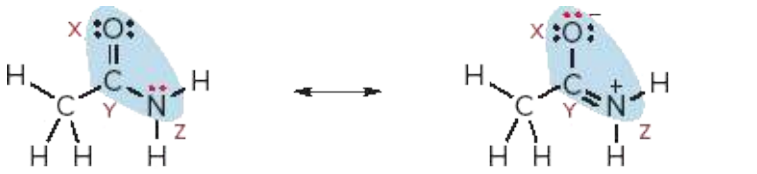
Draw a second resonance structure for acetamide.



acetamide

Solution

Always look for a three-atom system that contains a multiple bond joined to an atom Z with zero, one, or two nonbonded electrons. Move the double bond (from X=Y to Y=Z) and move the [*] from Z to X. Recalculate formal charges on X and Z.



acetamide
- C=O
- lone pair on N

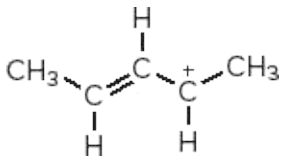
second resonance structure
- C=N
- additional lone pair on O

In this example, the three-atom system for resonance (X=Y–Z*) is O=C–N with a lone pair on N. After moving the double bond and the lone pair, the formal charges on O and N are −1 and +1, respectively, calculated using the procedure for determining formal charges.

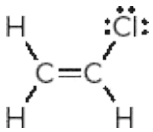
Problem 1.15

Draw a second resonance structure for each species in parts (a), (b), and (c). Draw two additional resonance structures for the ion in part (d).

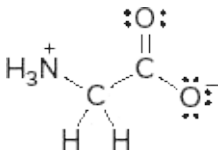
a.



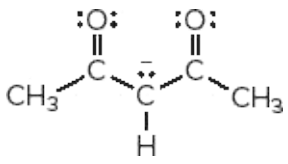
b.



c.



d.



More Practice:

Try Problems 1.54, 1.55.

1.6C The Resonance Hybrid

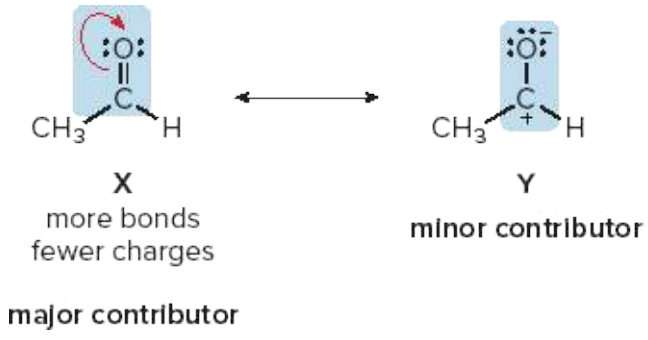
The resonance hybrid is the composite of all possible resonance structures. In the resonance hybrid, the electron pairs drawn in different locations in individual resonance structures are *delocalized*.

- **The resonance hybrid is more stable than any resonance structure because it delocalizes electron density over a larger volume.**

What does the hybrid look like? When all resonance forms are identical, as they were in the carbocation in Sample Problem 1.4a, each resonance form contributes equally to the hybrid.

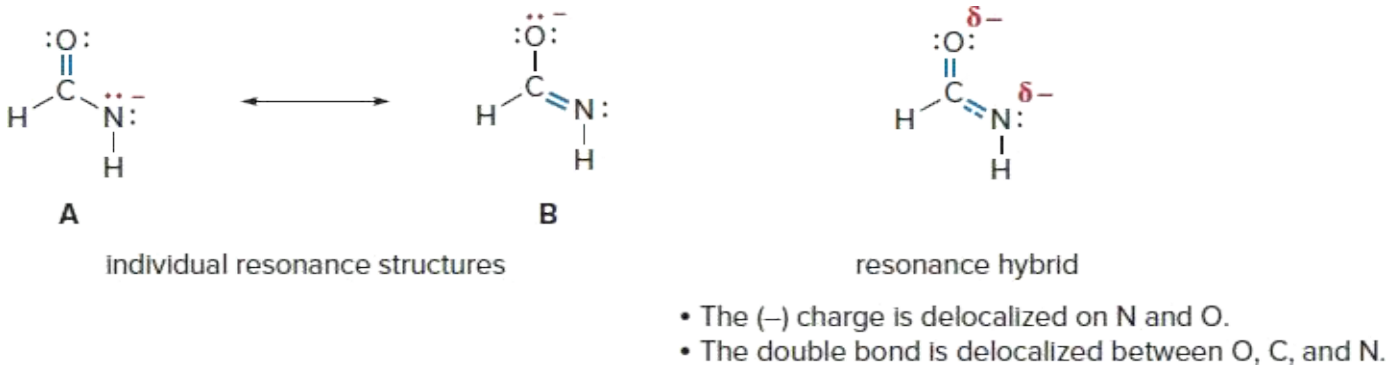
When two resonance structures are different, the hybrid looks more like the "better" resonance structure. The "better" resonance structure is called the major contributor to the hybrid, and all others are minor contributors. The hybrid is the weighted average of the contributing resonance structures. What makes one resonance structure "better" than another? There are many factors, but for now, we will learn one fact.

- **A "better" resonance structure is one that has *more bonds* and *fewer charges.***



Comparing resonance structures X and Y, X is the major contributor because it has more bonds and fewer charges. Thus, the hybrid looks more like X than Y.

How can we draw a hybrid, which has delocalized electron density? First, we must determine what is different in the resonance structures. Two differences commonly seen are the position of a multiple bond and the site of a charge. The anion $(HCONH)^-$ illustrates two conventions for drawing resonance hybrids.



Common symbols and conventions used in organic chemistry are summarized in Appendix B.

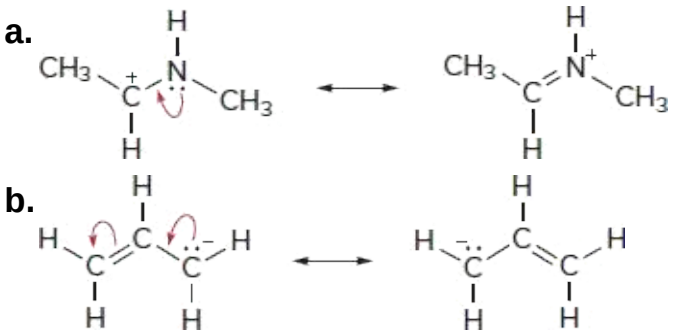
- **Double bond position. Use a dashed line for a bond that is single in one resonance structure and double in another.**
- **Location of charge. Use a δ− (partial negative charge) or δ+ (partial positive charge) for an atom that is neutral in one resonance structure and charged in another.**

The hybrid for $(HCONH)^-$ shows two dashed bonds, indicating that both the C–O and C–N bonds have partial double bond character. Both the O and N atoms bear a partial negative charge (δ–) because these atoms are neutral in one resonance structure and negatively charged in the other.

This discussion of resonance is meant to serve as an introduction only. You will learn many more facets of resonance theory in later chapters. In Chapter 2, for example, the enormous effect of resonance on acidity is discussed.

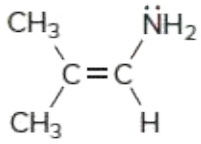
Problem 1.16

Label the resonance structures in each pair as major, minor, or equal contributors to the hybrid. Then draw the hybrid.

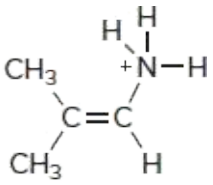


Problem 1.17

(a) Draw a second resonance structure for A. (b) Why can't a second resonance structure be drawn for B?



A



B

1.7 Determining Molecular Shape

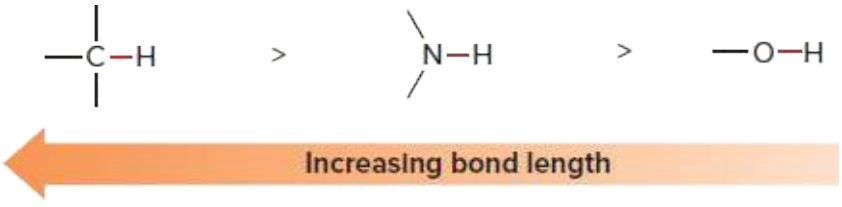
Consider the H_2O molecule. The Lewis structure tells us which atoms are connected to each other, but it implies nothing about the geometry. What does the overall molecule look like? Is H_2O a bent or linear molecule? Two variables define a molecule's structure: bond length and bond angle.

Although the SI unit for bond length is the picometer (pm), the angstrom (Å) is still widely used in the chemical literature; 1 Å = 10^{-10} m. As a result, 1 pm = 10^{-2} Å, and 95.8 pm = 0.958 Å.

1.7A Bond Length

Bond length is the average distance between the centers of two bonded nuclei. Bond lengths are typically reported in picometers (pm), where 1 pm = 10^{-12} m. For example, the O–H bond length in H_2O is 95.8 pm. Average bond lengths for common bonds are listed in Table 1.2.

- **Bond length *decreases* across a row of the periodic table as the size of the atom *decreases.***



- **Bond length *increases* down a column of the periodic table as the size of an atom *increases.***

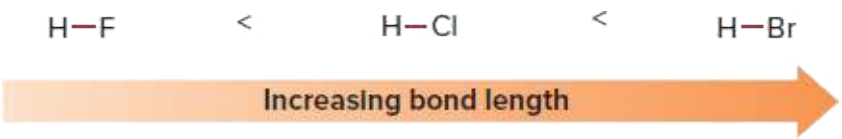


Table 1.2 Average Bond Lengths

Bond	Length (pm)	Bond	Length (pm)	Bond	Length (pm)
H–H	74	H–F	92	C–F	133
C–H	109	H–Cl	127	C–Cl	177
N–H	101	H–Br	141	C–Br	194
O–H	96	H–I	161	C–I	213

1.7B Bond Angle

Bond angle determines the shape around any atom bonded to two other atoms. To determine the bond angle and shape around a given atom, first count how many groups surround the atom. A group is either an atom or a lone pair of electrons. Then use the valence shell electron pair repulsion (VSEPR) theory to determine the shape. VSEPR is based on the fact that electron pairs repel each other; thus:

- **The most stable arrangement keeps the groups around an atom as far away from each other as possible.**

A second-row element has only three possible arrangements, defined by the number of groups surrounding it.

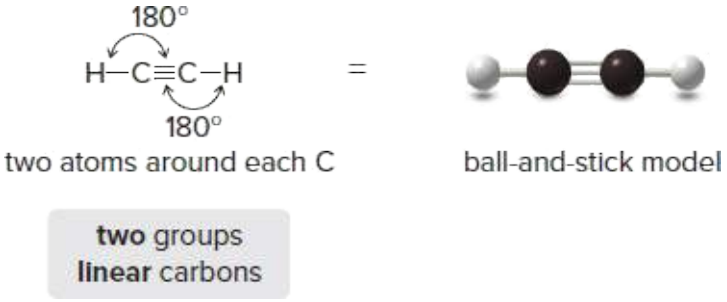
To determine geometry: [1] Draw a valid Lewis structure; [2] count groups around a given atom.

Number of groups	Geometry	Bond angle
• two groups	linear	180°
• three groups	trigonal planar	120°
• four groups	tetrahedral	109.5°

Let's examine several molecules to illustrate this phenomenon. We first need a valid Lewis structure, and then we count groups around a given atom to predict its geometry.

Two Groups Around an Atom

Any atom surrounded by only two groups is linear and has a bond angle of 180°. For example, each carbon atom in HC≡CH (acetylene) is surrounded by two atoms and no lone pairs, so each H–C–C bond angle in acetylene is 180°. Therefore all four atoms in HC≡CH are linear.



Most students in organic chemistry find that building models helps them visualize the shape of molecules. Invest in a set of models *now.*

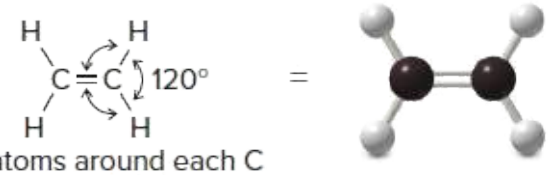
Common element colors are also shown in Appendix B.

Acetylene illustrates an important feature: *ignore multiple bonds in predicting geometry*. Count only atoms and lone pairs.

We will represent molecules with models having balls for atoms and sticks for bonds, as in the ball-and-stick model of acetylene just shown. These representations are analogous to a set of molecular models. Balls are color-coded using accepted conventions: carbon (black), hydrogen (white or gray), oxygen (red), and so forth, as shown.

Three Groups Around an Atom

Any atom surrounded by three groups is trigonal planar and has bond angles of 120°. For example, each carbon atom in CH_2=CH_2 (ethylene) is surrounded by three atoms and no lone pairs, making *each* H–C–C bond angle 120°. All six atoms of CH_2=CH_2 lie in one plane.



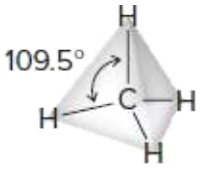
three atoms around each C

ethylene

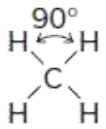
three groups
trigonal planar carbons

Four Groups Around an Atom

Any atom surrounded by four groups is tetrahedral and has bond angles of approximately 109.5°. The simple organic compound methane, CH_4, has a central carbon atom with bonds to four hydrogen atoms, each pointing to a corner of a tetrahedron. This arrangement keeps four groups farther apart than a square planar arrangement in which all bond angles would be only 90°.



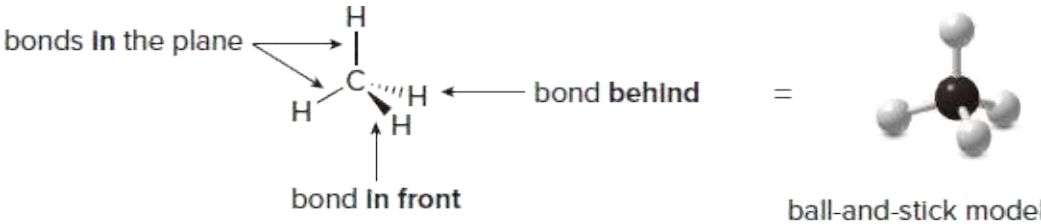
preferred geometry
larger H–C–H bond angle



square planar arrangement
This geometry does ***not*** occur.

How can we represent the three-dimensional geometry of a tetrahedron on a two-dimensional piece of paper? Place two of the bonds in the plane of the paper, one bond in front and one bond behind, using the following conventions:

- **A *solid line* is used for a bond *in* the plane.**
- **A *wedge* is used for a bond *in front* of the plane.**
- **A *dashed wedge* is used for a bond *behind* the plane.**

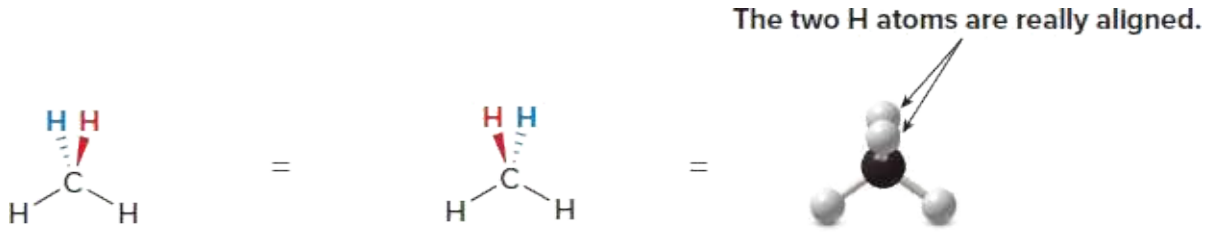


ball-and-stick model of CH_4

This is just one way to draw a tetrahedron for CH_4. We can turn the molecule in many different ways, generating many equivalent representations. All of the following are acceptable drawings for CH_4, because each drawing has two solid lines, one wedge, and one dashed wedge.

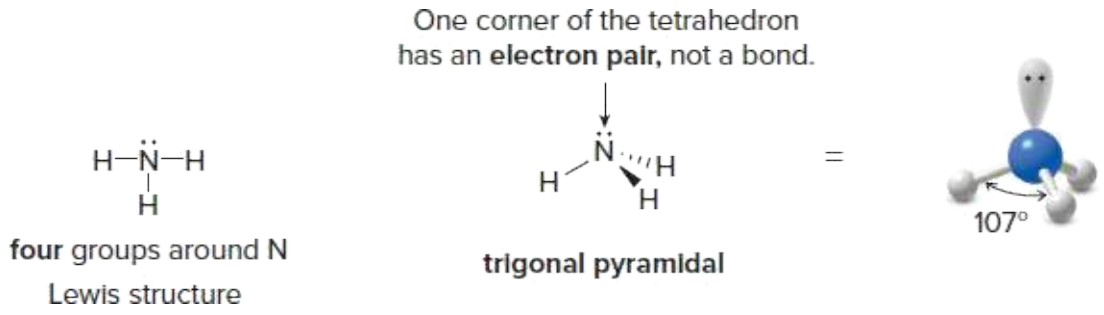
Finally, wedges and dashed wedges are used for groups that are really *aligned one behind another*. It does not matter in the following two drawings whether the wedge or dashed wedge is skewed to the left or right, because the two H atoms are really aligned as shown in the three-dimensional model.

All carbons in stable molecules are *tetravalent*, but the geometry varies with the number of groups around the particular carbon.

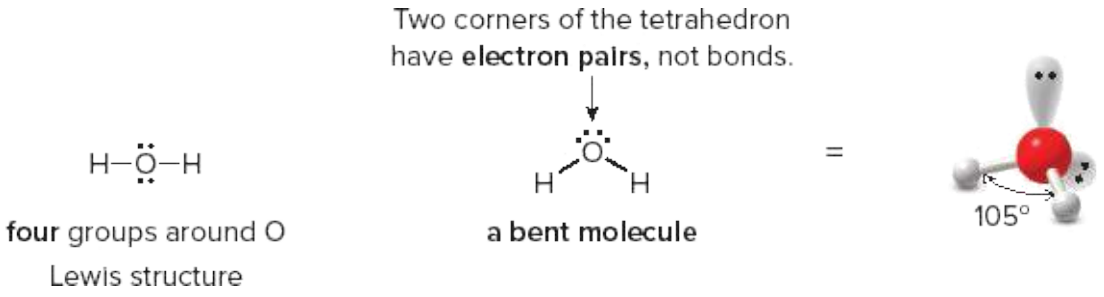


- **These representations are equivalent.**
- **The wedge can be skewed to the left or the right of the dashed wedge.**

Ammonia (NH_3) and water (H_2O) both have atoms surrounded by four groups, some of which are lone pairs. In NH_3, the three H atoms and one lone pair around N point to the corners of a tetrahedron. The H–N–H bond angle of 107° is close to the theoretical tetrahedral bond angle of 109.5°. This molecular shape is referred to as trigonal pyramidal, because one of the groups around the N is a nonbonded electron pair, not another atom.



In H_2O, the two H atoms and two lone pairs around O point to the corners of a tetrahedron. The H–O–H bond angle of 105° is close to the theoretical tetrahedral bond angle of 109.5°. Water has a bent molecular shape, because two of the groups around oxygen are lone pairs of electrons.



In both NH_3 and H_2O, the bond angle is somewhat smaller than the theoretical tetrahedral bond angle because of repulsion of the lone pairs of electrons. The bonded atoms are compressed into a smaller space with a smaller bond angle.

Predicting geometry based on counting groups is summarized in Table 1.3.

Table 1.3 Summary: Determining Geometry Based on the Number of Groups

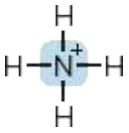
Number of groups around an atom	Geometry	Bond angle	Examples
2	linear	180°	HC≡CH
3	trigonal planar	120°	CH_2=CH_2
4	tetrahedral	109.5°	CH_4, NH_3, H_2O

Sample Problem 1.6 Determining the Geometry Around a Second-Row Atom

Determine the geometry around the highlighted atom in each species.

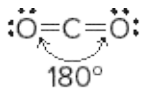
a. :O=C=O:

b.



Solution

a.

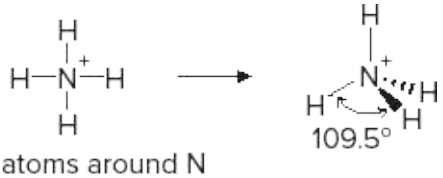


two atoms around C
no lone pairs

two groups

linear

b.



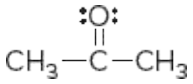
four atoms around N
no lone pairs

four groups ⟶ tetrahedral

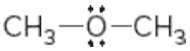
Problem 1.18

Determine the geometry around all second-row elements in each compound drawn as a Lewis structure with no implied geometry.

a.

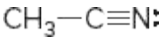


b.



c.

d.



More Practice:

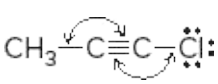
Try Problems 1.60, 1.61, 1.77c, 1.79b.

Water hemlock, which grows in wet marshy areas in the western part of North America, is the source of cicutoxin (Problem 1.20), a convulsant toxic to both livestock and humans. ©*Jeff Holcombe/123RF*

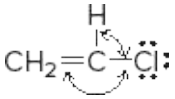
Problem 1.19

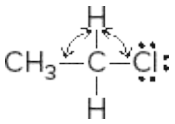
Predict the indicated bond angles in each compound drawn as a Lewis structure with no implied geometry.

a.



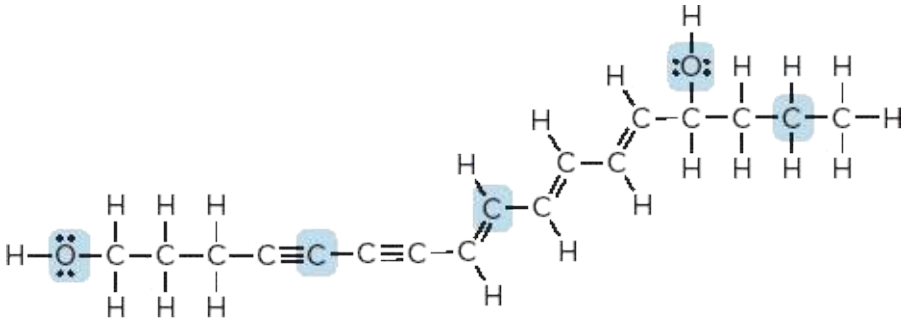
b.



c. 

Problem 1.20

Using the principles of VSEPR theory, you can predict the geometry around any atom in any molecule, no matter how complex. Cicutoxin is a poisonous compound isolated from water hemlock, a highly toxic plant that grows in temperate regions in North America. Predict the geometry around the highlighted atoms in cicutoxin.



cicutoxin

1.8 Drawing Organic Structures

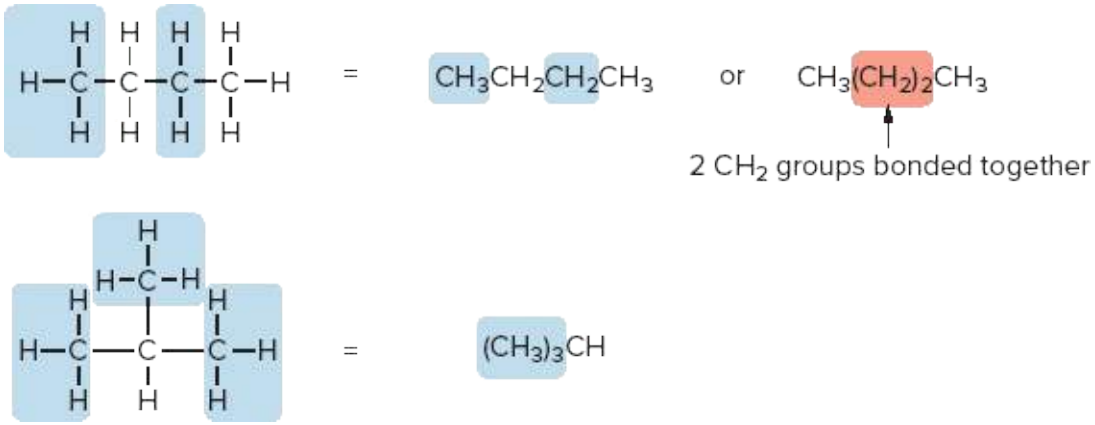
Drawing organic molecules presents a special challenge. Because they often contain many atoms, we need shorthand methods to simplify their structures. The two main types of shorthand representations used for organic compounds are condensed structures and skeletal structures.

1.8A Condensed Structures

Condensed structures can be used for compounds having a chain of atoms bonded together. The following conventions are used:

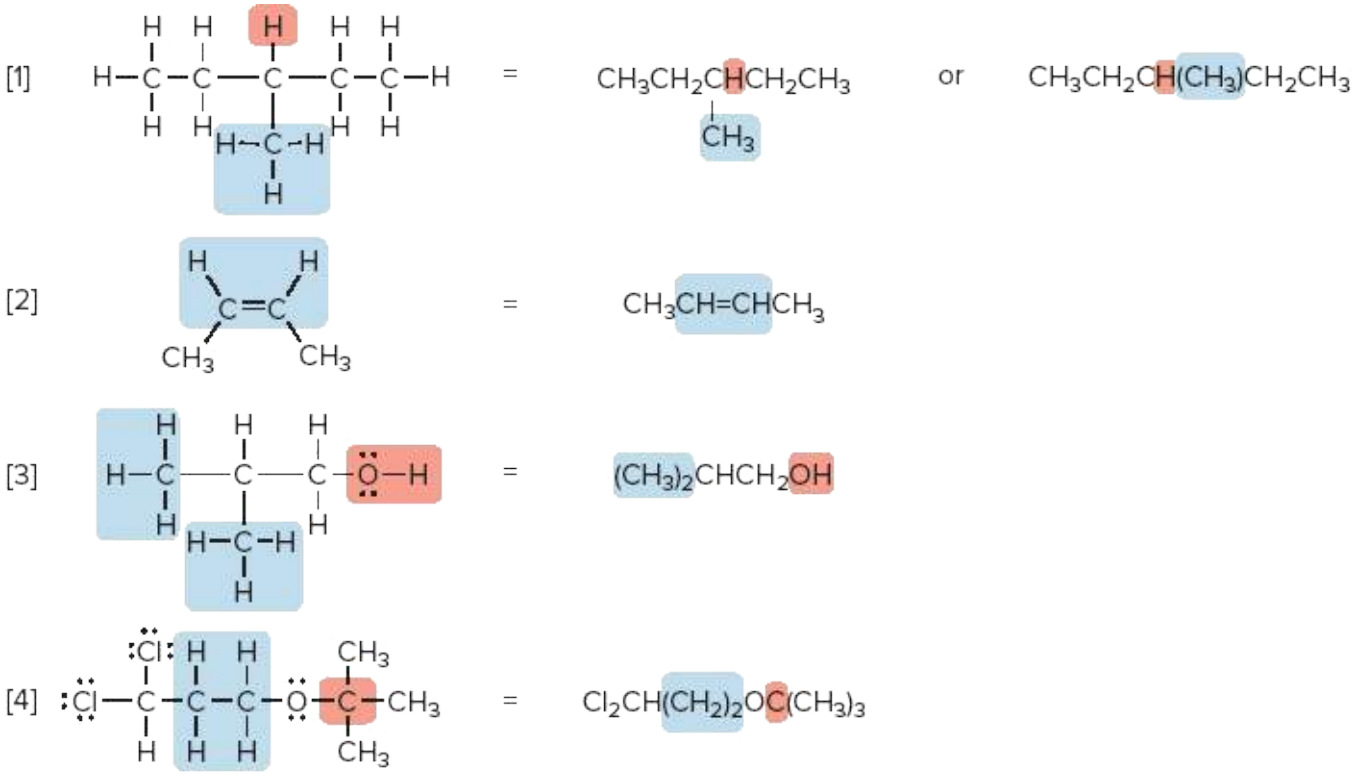
- **All of the atoms are drawn in, but the two-electron bond lines are generally omitted.**
- **Atoms are usually drawn next to the atoms to which they are bonded.**
- **Parentheses are used around similar groups bonded to the same atom.**
- **Lone pairs are omitted.**

To interpret a condensed formula, it is usually best to start at the *left side* of the molecule and remember that the *carbon atoms must be tetravalent*. A carbon bonded to three H atoms becomes CH_3; a carbon bonded to two H atoms becomes CH_2; and a carbon bonded to one H atom becomes CH.



Other examples of condensed structures with heteroatoms and carbon–carbon multiple bonds are given in Figure 1.3.

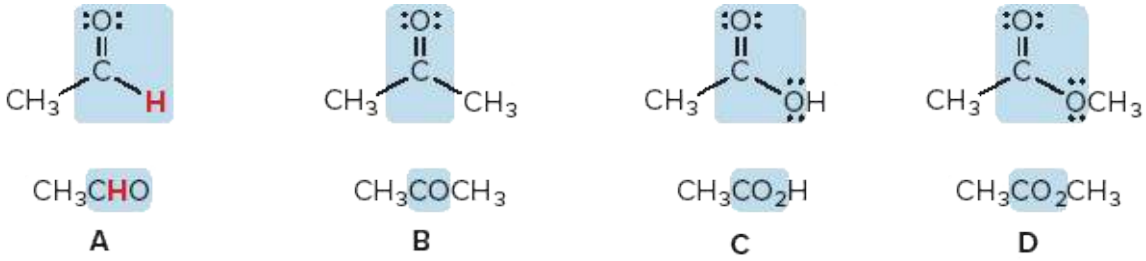
Page 30



- Entry [1]: Draw the H atom next to the C to which it is bonded, and use parentheses around CH_3 to show it is bonded to the carbon chain.
- Entry [2]: Keep the carbon–carbon double bond and draw the H atoms after each C to which they are bonded.
- Entry [3]: Omit the lone pairs on the O atom in the condensed structure.
- Entry [4]: Omit the lone pairs on Cl and O and draw the two CH_2 groups as $(CH_2)_2$.

Figure 1.3 **Examples of condensed structures**

Translating some condensed formulas is not obvious, and it will come only with practice. This is especially true for compounds containing a carbon–oxygen double bond. Some noteworthy examples in this category are given in Figure 1.4. While carbon–carbon double bonds are generally drawn in condensed structures, carbon–oxygen double bonds are usually omitted.



A B C D

- In **A**, the **H** atom is bonded to C, *not* O.
- In **B**, each CH_3 group is bonded to C, *not* O.
- In **C** and **D**, the C atom is doubly bonded to one O and singly bonded to the other O.

Figure 1.4 **Condensed structures containing a C–O double bond**

Sample Problem 1.7 Converting a Condensed Structure to a Lewis Structure

Convert each condensed formula to a Lewis structure.

a. $(CH_3)_2CHOCH_2CH_2CH_2OH$

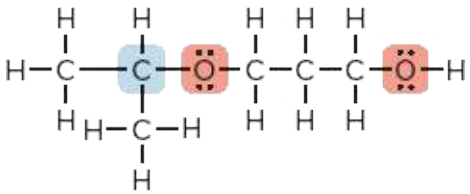
b. $CH_3(CH_2)_2CO_2C(CH_3)_3$

Solution

Page 31

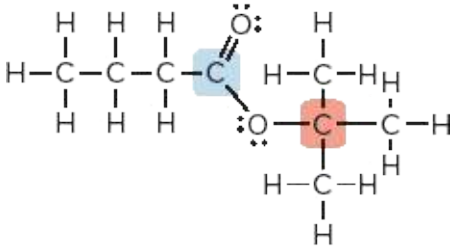
Start at the left and proceed to the right, making sure that each carbon has four bonds. Give each O atom two lone pairs to have an octet.

a. $(CH_3)_2CHOCH_2CH_2CH_2OH$



One C atom (labeled in blue) is bonded to 2 CH_3's, 1 H, and 1 O.

b. $CH_3(CH_2)_2CO_2C(CH_3)_3$



One C atom (labeled in blue) is bonded to both O's.

In part (a), the O atom is singly bonded to two C's, whereas in part (b), a C=O

is needed to give each C and O an octet.

Problem 1.21

Convert each condensed formula to a Lewis structure.

a. $CH_3(CH_2)4CH(CH_3)_2$

b. $(CH_3)_3CCH(OH)CH_2CH_3$

c. $(CH_3)_2CHCHO$

d. $(HOCH_2)_2CH(CH_2)_3C(CH_3)_2CH_2CH_3$

More Practice:

Try Problems 1.64a–c, 1.65.

Problem 1.22

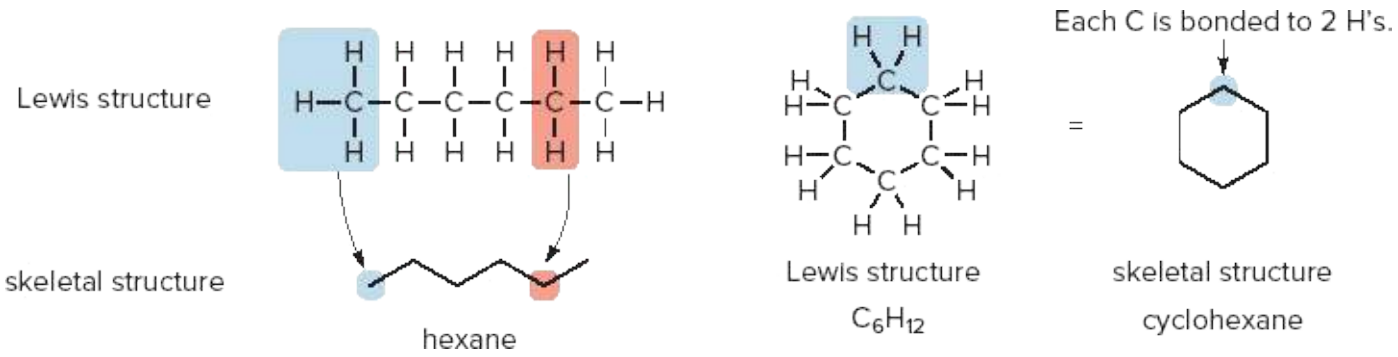
During periods of strenuous exercise, the buildup of lactic acid [$CH_3CH(OH)CO_2H$] causes the aching feeling in sore muscles. Convert this condensed structure to a Lewis structure of lactic acid.

1.8B Skeletal Structures

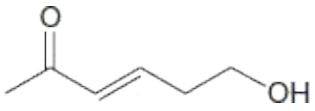
Skeletal structures are used for organic compounds containing both rings and chains of atoms. Three rules are used to draw them.

- **Assume a carbon atom is located at the junction of any two lines or at the end of any line.**
- **Assume each carbon has enough hydrogens to make it tetravalent.**
- **Draw in all heteroatoms and the hydrogens directly bonded to them.**

Carbon chains are drawn in a zigzag fashion, and rings are drawn as polygons, as shown for hexane and cyclohexane.



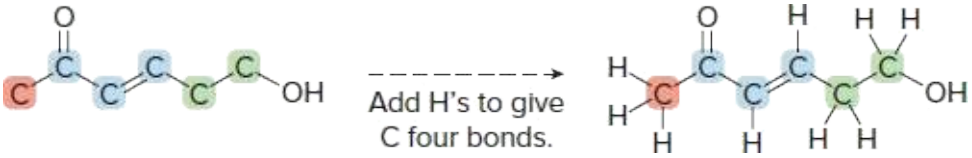
Example Draw in all C atoms, H atoms, and lone pairs in the following molecule:



Step [1] **Place a C atom at the intersection of any two lines and at the end of any line.**

- **This molecule has six carbons, including the C labeled in red at the left end of the chain.**
- **There are two C's (labeled in green) between the C=C and the OH group.**

Step [2] **Add enough H's to make each C tetravalent.**



- **The end C labeled in red needs three H's to be tetravalent.**
- **Each C on the C=C has three bonds already, so only one H must be drawn.**
- **There are two CH_2 groups between the C=C and the OH group.**

Step [3] **Add lone pairs to give each heteroatom an octet.**

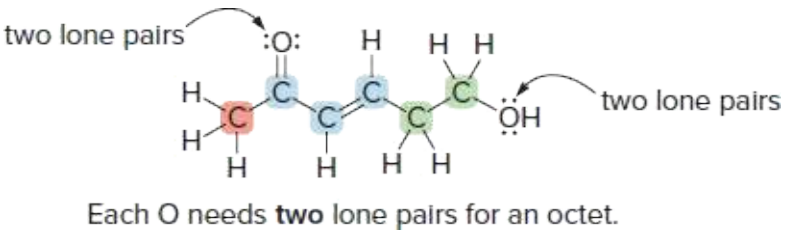


Figure 1.5 shows other examples of skeletal structures, and Sample Problem 1.8 illustrates how to interpret the skeletal structure for a more complex cyclic compound.

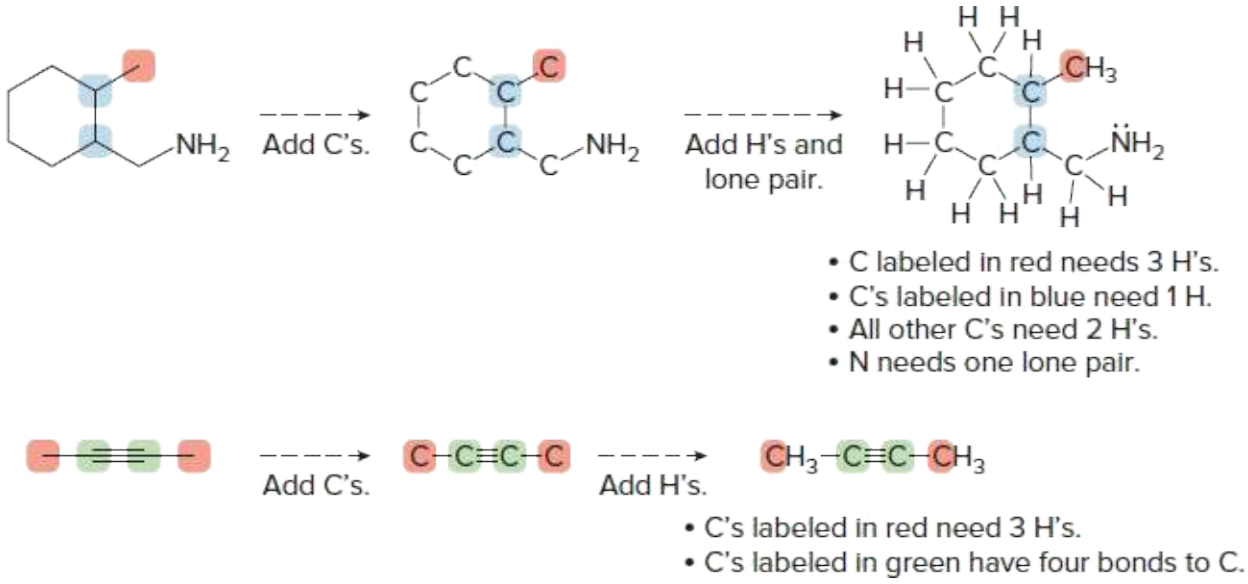
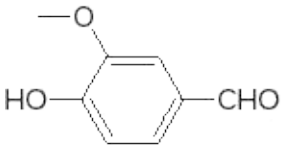


Figure 1.5 **Interpreting skeletal structures**

Sample Problem 1.8 Converting a Skeletal Structure to a Lewis Structure

Draw a complete structure for vanillin showing all C atoms, H atoms, and lone pairs, and give the molecular formula. Vanillin is the principal component of the extract of the vanilla bean.

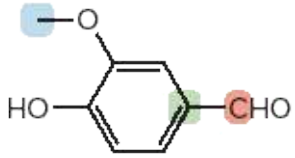


vanillin

vanilla bean

Solution

- **Skeletal structures have a C atom at the junction of any two lines and at the end of any line.**
- **Each C must have enough H's to make it tetravalent.**
- **Each O atom needs two lone pairs to have a complete octet.**



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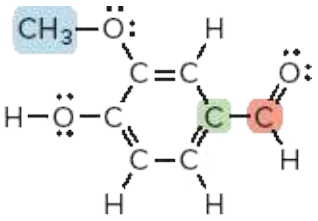


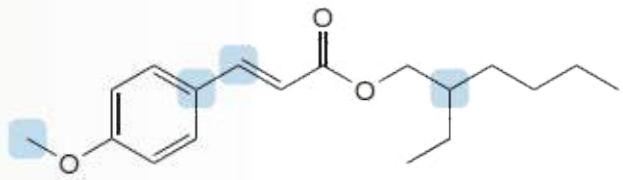
- C in blue has three H's.
- C in green has four bonds to other C's.
- C in red is doubly bonded to O.

$C_8H_8O_3$

Problem 1.23

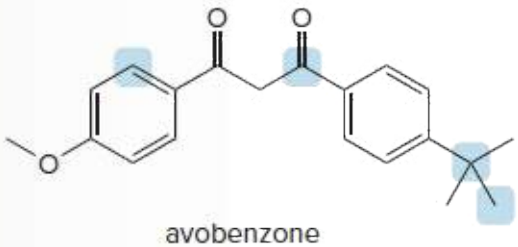
How many hydrogen atoms are present around each highlighted carbon atom in the following molecules? What is the molecular formula for each molecule? Both compounds are active ingredients in some common sunscreens.

a.



octinoxate
(2-ethylhexyl 4-methoxycinnamate)

b.



avobenzone

©McGraw-Hill Education/Elite Images

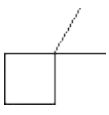
More Practice:

Try Problems 1.62, 1.63, 1.80a.

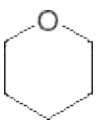
Problem 1.24

Convert each skeletal structure to a complete structure with all C's, H's, and lone pairs drawn in.

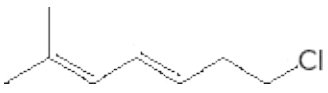
a.



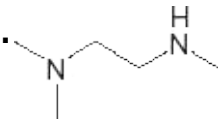
b.



c.



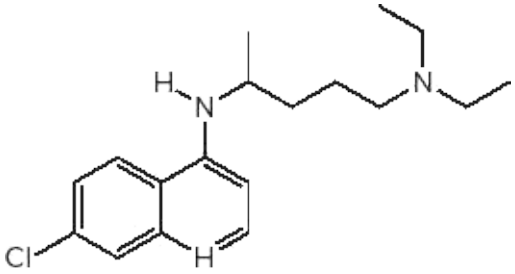
d.



Problem 1.25

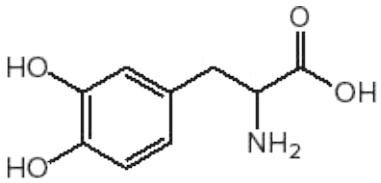
What is the molecular formula of each drug?

a.



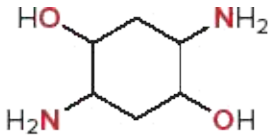
chloroquine
(antimalarial medication)

b.

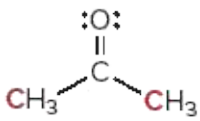


L-dopa
(drug used for Parkinson's disease)

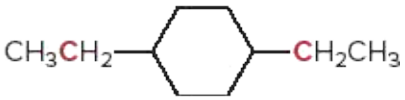
When heteroatoms are bonded to a carbon skeleton, the heteroatom is joined *directly* to the carbon to which it is bonded, with no H atoms in between. Thus, an OH group is drawn as OH or HO depending on where the OH is located. In contrast, when carbon appendages are bonded to a carbon skeleton, the H atoms will be drawn to the *right* of the carbon to which they are bonded regardless of the location.



Place the O and N atoms *directly* joined to the ring.



Two C atoms in red are bonded to the middle C.



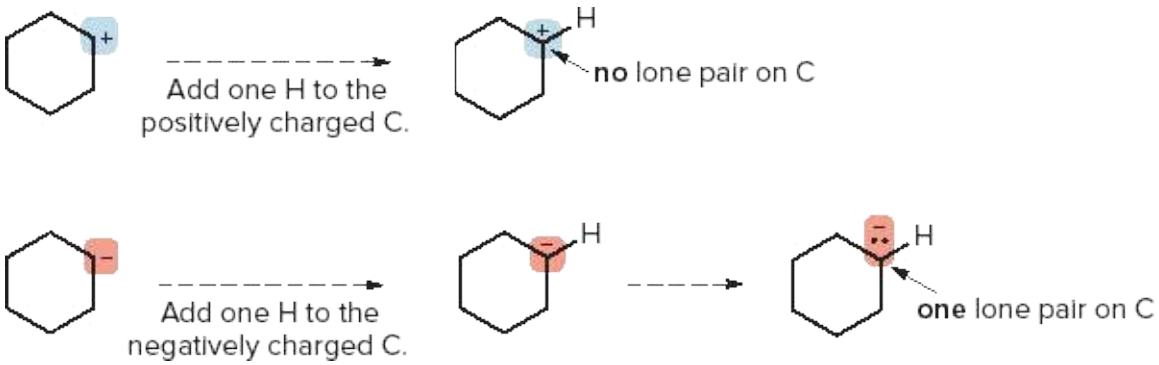
Two C atoms in red are bonded to the ring.

1.8C Skeletal Structures with Charged Atoms

Take care in interpreting skeletal structures for positively and negatively charged carbon atoms, because *both* the hydrogen atoms *and* the lone pairs are omitted. Keep in mind the following:

- **A charge on a carbon atom takes the place of one hydrogen atom.**
- **The charge determines the number of lone pairs. Negatively charged carbon atoms have one lone pair and positively charged carbon atoms**

have none.

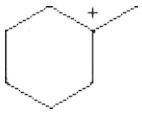


Skeletal structures often leave out lone pairs on heteroatoms, but *don't forget about them*. Use the formal charge on an atom to determine the number of lone pairs. For example, a neutral O atom with two bonds needs two additional lone pairs, and a positively charged O atom with three bonds needs only one lone pair.

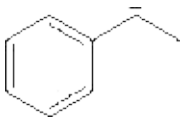
Problem 1.26

Draw in all hydrogens and lone pairs on the charged carbons in each ion.

a.

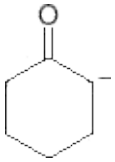


b.

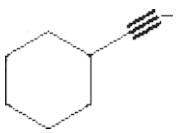


c.

d.

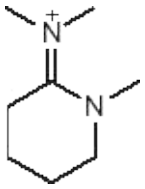


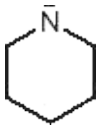
e.

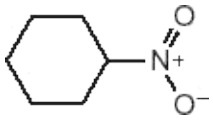


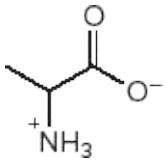
Problem 1.27

Use the formal charge to draw in the lone pairs on each N or O atom in the following compounds.

a. 

b. 

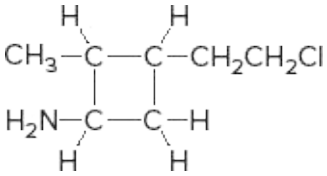
c. 

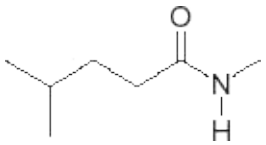
d. 

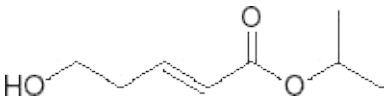
Problem 1.28

Draw a skeletal structure for the molecules in parts (a) and (b), and a condensed structure for the molecules in parts (c) and (d).

a. $CH_3O(CH_2)_2COCH = C(CH_3)_2$

b. 

c. 

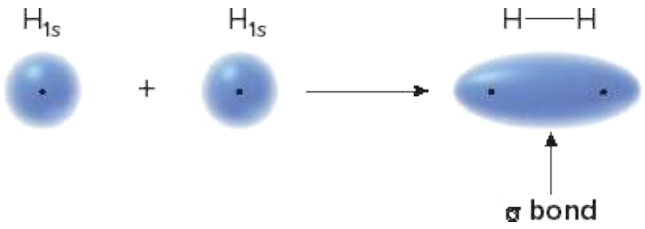
d. 

1.9 Hybridization

What orbitals do the first- and second-row atoms use to form bonds?

1.9A Hydrogen

Recall from Section 1.2 that two hydrogen atoms share each of their electrons to form H2. Thus, the 1*s* orbital on one H overlaps with the 1*s* orbital on the other H to form a bond that concentrates electron density between the two nuclei. This type of bond, called a σ (sigma) bond, is cylindrically symmetrical because the electrons forming the bond are distributed symmetrically about an imaginary line connecting the two nuclei.

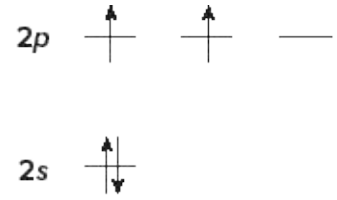


- **A σ bond concentrates electron density on the axis that joins two nuclei. All single bonds are σ bonds.**

1.9B Bonding in Methane

To account for the bonding patterns observed in more complex molecules, we must take a closer look at the 2s and 2*p* orbitals of atoms of the second row. Let's illustrate this with methane, CH_4.

Carbon has four valence electrons. To fill atomic orbitals in the most stable arrangement, electrons are placed in the orbitals of lowest energy. For carbon, this places two electrons in the 2*s* orbital and one each in two 2*p* orbitals.



ground state for
carbon's four valence electrons

- **This lowest energy arrangement of electrons for an atom is called its ground state.**

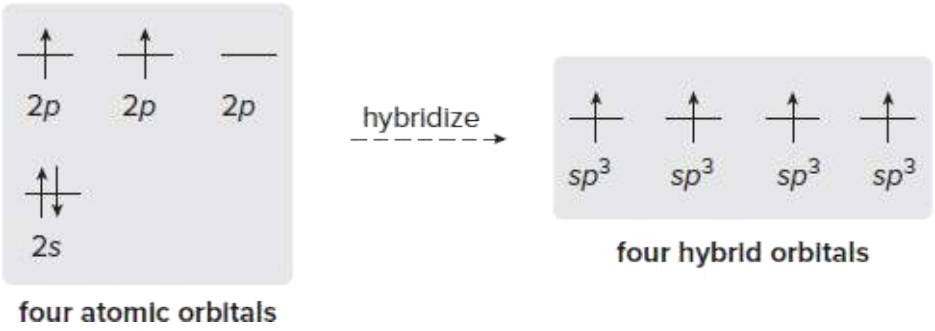
In this description, carbon should form *only two bonds* because it has only two unpaired valence electrons, and CH_2 should be a stable molecule. In reality, however, CH_2 is a highly reactive species because carbon does not have an octet of electrons.

Because the carbon atom in CH_4 forms four bonds to hydrogen and all C–H bonds are *identical*, chemists have proposed that atoms like carbon do *not* use pure *s* and pure *p* orbitals in forming bonds. Instead, atoms use a set of new orbitals called hybrid orbitals. The mathematical process by which these orbitals are formed is called hybridization.

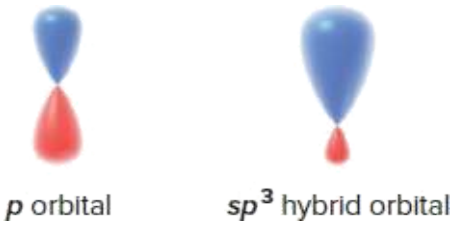
- ***Hybridization* is the combination of two or more atomic orbitals to form the same number of hybrid orbitals, each having the same shape and**

energy.

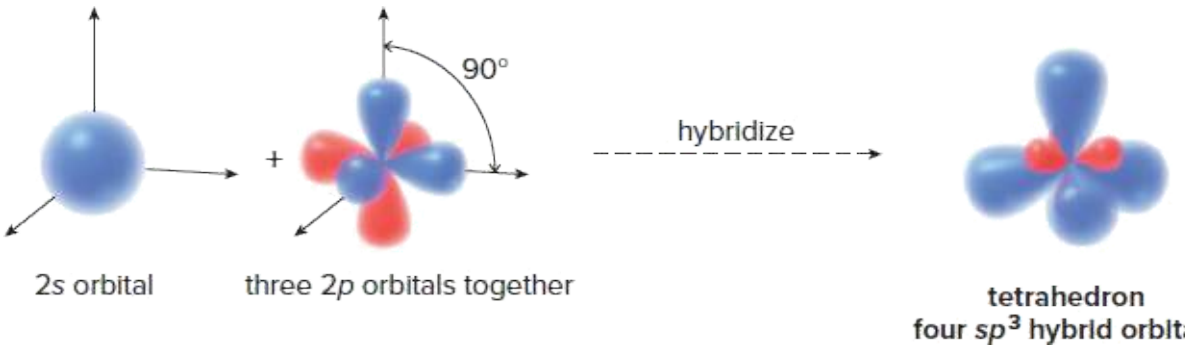
Hybridization of one 2*s* orbital and three 2*p* orbitals for carbon forms four hybrid orbitals, each with one electron. These new hybrid orbitals are intermediate in energy between the 2*s* and 2*p* orbitals.



- **These hybrid orbitals are called *sp*^{3} *hybrids* because they are formed from *one s* orbital and *three p* orbitals.**



What do these new hybrid orbitals look like? Mixing a spherical 2*s* orbital and three dumbbell-shaped 2*p* orbitals together produces four orbitals having one large lobe and one small lobe, oriented toward the corners of a tetrahedron. Each large lobe concentrates electron density in the bonding direction between two nuclei. Bonds formed from hybrid orbitals are *stronger* than bonds formed from pure *p* orbitals.



The four hybrid orbitals form four equivalent bonds. We can now explain the observed bonding in CH_4.

- **Each bond in CH_4 is formed by overlap of an *sp*^{3} hybrid orbital of carbon with a 1*s* orbital of hydrogen. These four bonds point to the**

corners of a tetrahedron.

All four C–H bonds in methane are σ bonds, because the electron density is concentrated on the axis joining C and H. An orbital picture of the bonding in CH_4 is given in Figure 1.6.

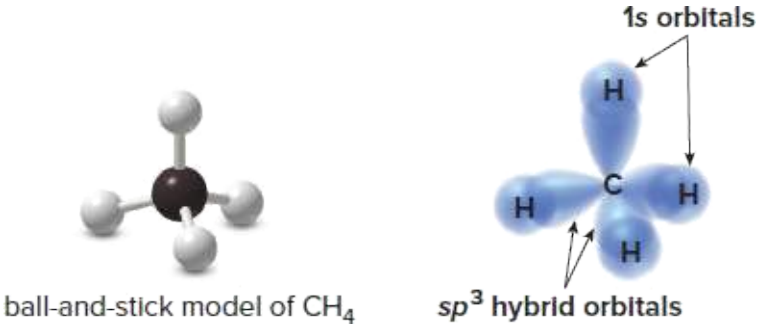


Figure 1.6 **Bonding in CH_4 using sp^3 hybrid orbitals**

- **All four C–H bonds are σ bonds. Each is formed by overlap of an sp^3 hybrid orbital on carbon and a 1*s* orbital on hydrogen.**

Problem 1.29

What orbitals are used to form each of the C–C and C–H bonds in $CH_3CH_2CH_3$ (propane)? How many σ bonds are present in this molecule?

- **Any atom surrounded by four groups (atoms and lone pairs) is sp^3 hybridized.**

The N atom in NH_3 and the O atom in H_2O are both surrounded by four groups, making them sp^3 hybridized. Each N–H and O–H bond in these molecules is formed by overlap of an sp^3 hybrid orbital with a 1*s* orbital from H. The lone pairs of electrons on N and O also occupy sp^3 hybrid orbitals, as shown in Figure 1.7.

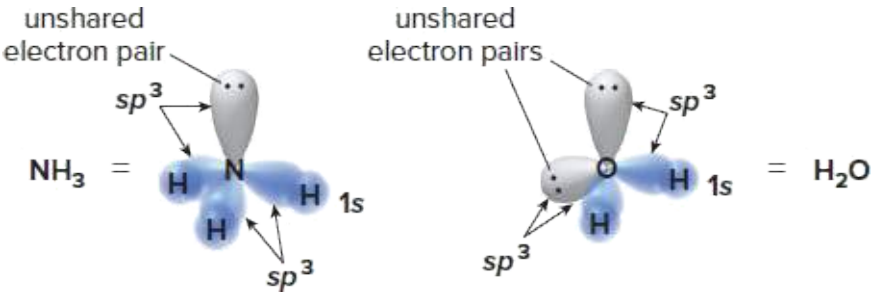


Figure 1.7 **Hybrid orbitals of NH_3 and H_2O**

1.9C Other Hybridization Patterns—*sp* and sp^2 Hybrid Orbitals

Forming sp^3 hybrid orbitals is just one way that 2s and 2p orbitals can hybridize. Three common modes of hybridization are seen in organic molecules. The number of orbitals is always conserved in hybridization; that is, a given number of atomic orbitals hybridizes to form an equivalent number of hybrid orbitals.

- ***One* 2*s* orbital and *three* 2*p* orbitals form *four* sp^3 hybrid orbitals.**
- ***One* 2*s* orbital and *two* 2*p* orbitals form *three* sp^2 hybrid orbitals.**
- ***One* 2*s* orbital and *one* 2*p* orbital form *two* *sp* hybrid orbitals.**

We have already seen pictorially how four sp^3 hybrid orbitals are formed from one 2*s* and three 2*p* orbitals. Figures 1.8 and 1.9 illustrate the same process for *sp* and sp^2 hybrids. Each *sp* and sp^2 hybrid orbital has one large and one small lobe, much like an sp^3 hybrid orbital. Note, however, that both sp^2 and *sp* hybridization leave one and two 2*p* orbitals *unhybridized*, respectively, on each atom.

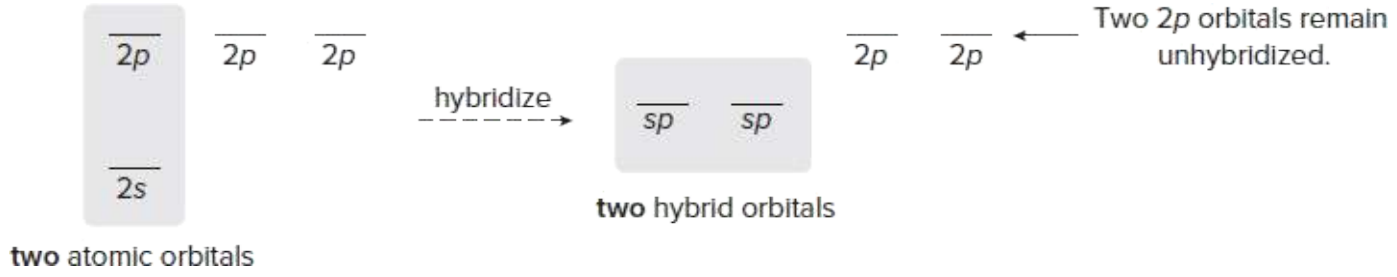


Figure 1.8 **Forming two *sp* hybrid orbitals**

- **Forming two *sp* hybrid orbitals uses one 2s and one 2p orbital, leaving two 2p orbitals *unhybridized.***

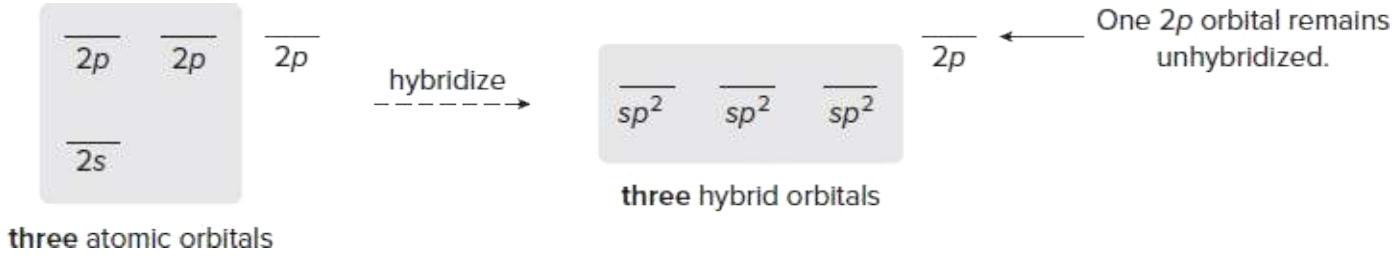
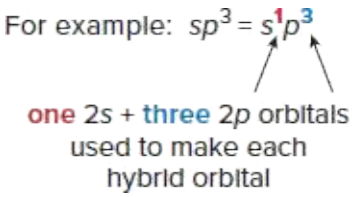


Figure 1.9 **Forming three sp^2 hybrid orbitals**

- **Forming three sp^2 hybrid orbitals uses one 2*s* and two 2*p* orbitals, leaving one 2*p* orbital *unhybridized.***

The superscripts for hybrid orbitals correspond to the number of atomic orbitals used to form them. The number "1" is understood.



To determine the hybridization of an atom in a molecule, we count groups (atoms and lone pairs) around the atom, just as we did in determining geometry.

- **The number of groups around an atom equals the number of atomic orbitals that are hybridized to form hybrid orbitals (Table 1.4).**

Table 1.4 Three Types of Hybrid Orbitals

Number of groups	Number of orbitals used	Type of hybrid orbital
2	2	two *sp* hybrid orbitals
3	3	three sp^2 hybrid orbitals
4	4	four sp^3 hybrid orbitals

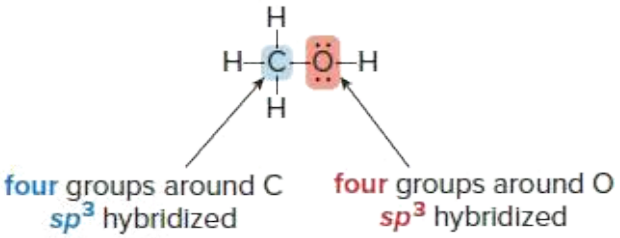
Hybridization in various carbon compounds is presented in Section 1.10.

Sample Problem 1.9 Determining the Hybridization of an Atom

What orbitals are used to form each bond in methanol, CH_3OH?

Solution

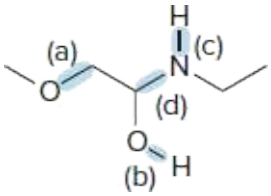
To solve this problem, draw a valid Lewis structure and count groups around each atom. Then, use the rule to determine hybridization: two groups = *sp*, three groups = sp^2, and four groups = sp^3.



- **All C–H bonds are formed from C_{sp3}–H_{1s}.**
- **The C–O bond is formed from C_{sp3}–O_{sp3}.**
- **The O–H bond is formed from O_{sp3}–H_{1s}.**

Problem 1.30

What orbitals are used to form each highlighted bond in the following molecule? In what type of orbital do the lone pairs on each O and N reside?

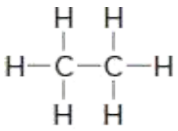


More Practice:

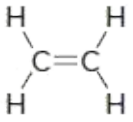
Try Problems 1.67a–c, 1.68.

1.10 Ethane, Ethylene, and Acetylene

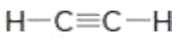
The principles of hybridization determine the type of bonds in ethane, ethylene, and acetylene.



ethane



ethylene

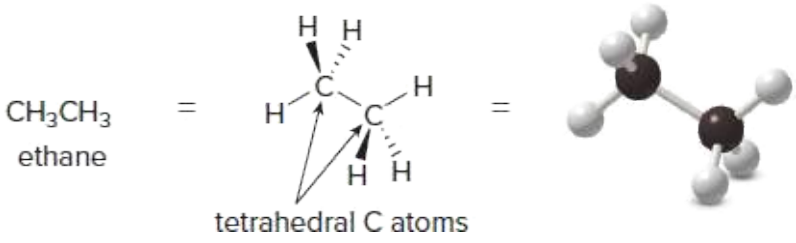


acetylene

1.10A Ethane—CH_3CH_3

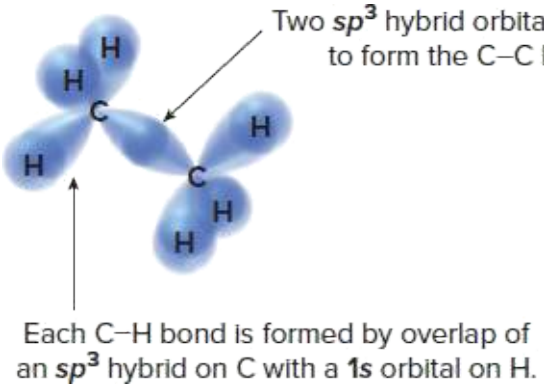
According to the Lewis structure for ethane, CH_3CH_3, each carbon atom is singly bonded to four other atoms. As a result:

- **Each carbon is tetrahedral.**
- **Each carbon is sp^3 hybridized.**

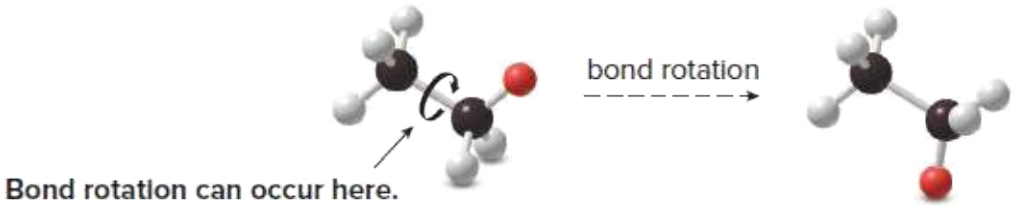


All of the bonds in ethane are σ bonds. The C–H bonds are formed from the overlap of one of the three sp^3 hybrid orbitals on each carbon atom with the 1s orbital on hydrogen. The C–C bond is formed from the overlap of an sp^3 hybrid orbital on each carbon atom.

Ethane is a constituent of natural gas. ©Steve *Allen/Brand X Pictures/Alamy Stock Photo*



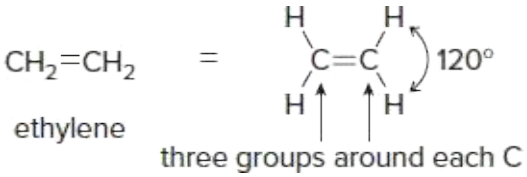
A model of ethane shows that rotation can occur around the central C–C σ bond. The relative position of the H atoms on the adjacent CH_3 groups changes with bond rotation, as seen in the location of the labeled red H atom before and after rotation. This process is discussed in greater detail in Chapter 4.



1.10B Ethylene—C_2H_4

Based on the Lewis structure of ethylene, $CH_2{=}CH_2$, each carbon atom is singly bonded to two H atoms and doubly bonded to the other C atom, so each C is surrounded by three groups. As a result:

- **Each carbon is trigonal planar (Section 1.7B).**
- **Each carbon is sp^2 hybridized.**



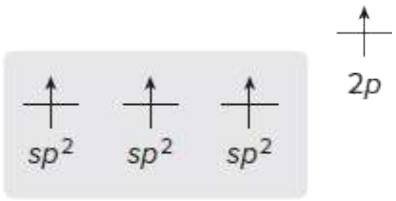
What orbitals are used to form the two bonds of the C–C double bond? Recall from Section 1.9 that sp^2 hybrid orbitals are formed from one 2*s* and two 2*p* orbitals, leaving one 2*p* orbital unhybridized. Because carbon has four valence electrons, each of these orbitals has one electron that can be used to form a bond.

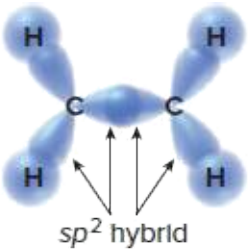
Ethylene is an important starting material in the preparation of the plastic polyethylene.

©Arthur Tilley/Getty Images

Each C–H bond results from the end-on overlap of an sp^2 hybrid orbital on carbon and the 1*s* orbital on hydrogen. Similarly, one of the C–C bonds results from the end-on overlap of an *sp* hybrid orbital on each carbon atom. Each of these bonds is a σ bond. All five σ bonds lie in the same plane, viewed from above in the following representation, and from the side in Figure 1.10a.

An sp^2 hybridized C in $CH_2=CH_2$ has three sp^2 hybrid orbitals and one higher-energy, unhybridized *p* orbital:

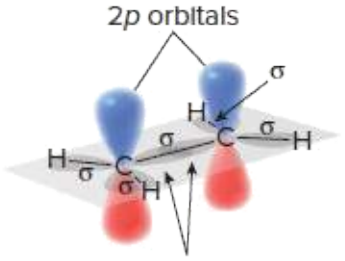




- Each C has three sp^2 hybrid orbitals.
- The C–H bonds and the C–C bond are σ bonds.

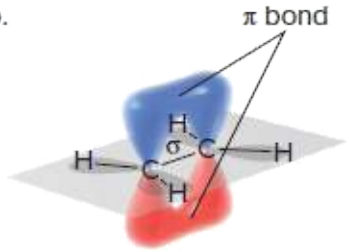
The second C–C bond results from the side-by-side overlap of the 2*p* orbitals on each carbon. Because the unhybridized 2*p* orbitals are located perpendicular to the plane of the molecule, side-by-side overlap creates an area of electron density above and below the plane containing the sp^2 hybrid orbitals (that is, the plane containing the six atoms in the σ bonding system), as shown in Figure 1.10b.

a.



- Overlap of the two sp^2 hybrid orbitals forms the C–C σ bond.

b.



- Overlap of the two 2*p* orbitals forms the C–C π bond.
- The π bond extends **above and below the plane** of the molecule.

Figure 1.10 **The σ and π bonds in ethylene**

In this second bond, the electron density is *not* concentrated on the axis joining the two nuclei. This new type of bond is called a π bond. Because the electron density in a π bond is farther from the two nuclei, π bonds are usually weaker and therefore more easily broken than σ bonds.

Thus, a carbon–carbon double bond has two components:

- **a σ bond, formed by end-on overlap of two sp^2 hybrid orbitals;**
- **a π bond, formed by side-by-side overlap of two 2*p* orbitals.**

Unlike the C–C single bond in ethane, rotation about the C–C double bond in ethylene is restricted. It can occur only if the π bond first breaks and then re-forms, a process that requires considerable energy.

All double bonds are composed of one σ and one π bond.

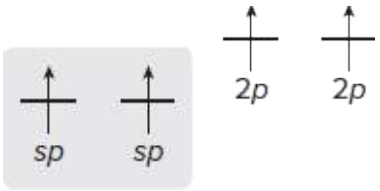
Rotation around a C=C bond does *not* occur.

1.10C Acetylene—C_2H_2

Because acetylene produces a very hot flame on burning, it is often used in welding torches. The fire is very bright, too, so it was once used in the lamps worn by spelunkers—people who study and explore caves.

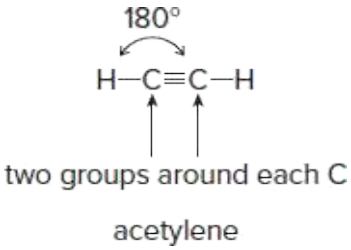
©Phillip Spears/Getty Images

An *sp* hybridized C in HC≡CH has two *sp* hybrid orbitals and two higher-energy, unhybridized *p* orbitals:



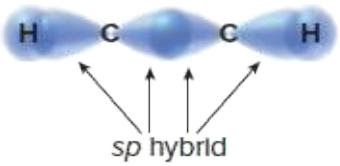
Based on the Lewis structure of acetylene, HC≡CH, each carbon atom is singly bonded to one hydrogen atom and triply bonded to the other carbon atom, so each carbon atom is surrounded by two groups. As a result:

- **Each carbon is linear (Section 1.7B).**
- **Each carbon is *sp* hybridized.**



What orbitals are used to form the bonds of the C–C triple bond? Recall from Section 1.9 that *sp* hybrid orbitals are formed from one 2*s* and one 2*p* orbital, leaving two 2*p* orbitals unhybridized. Because carbon has four valence electrons, each of these orbitals has one electron that can be used to form a bond.

Each C–H bond results from the end-on overlap of an *sp* hybrid orbital on carbon and the 1*s* orbital on hydrogen. Similarly, one of the C–C bonds results from the end-on overlap of an *sp* hybrid orbital on each carbon atom. Each of these bonds is a σ bond.



- Each C has two *sp* hybrid orbitals.
- The C–H bonds and C–C bond are σ bonds.

Each carbon atom also has two unhybridized 2*p* orbitals that are perpendicular to each other and to the *sp* hybrid orbitals (Figure 1.11a). Side-by-side overlap between the two 2*p* orbitals on one carbon with the two 2*p* orbitals on the other carbon creates the second and third bonds of the C–C triple bond (Figure 1.11b). The electron density from one of these two bonds is above and below the axis joining the two nuclei, and the electron density from the second of these two bonds is in front of and behind the axis,

so both of these bonds are π bonds.

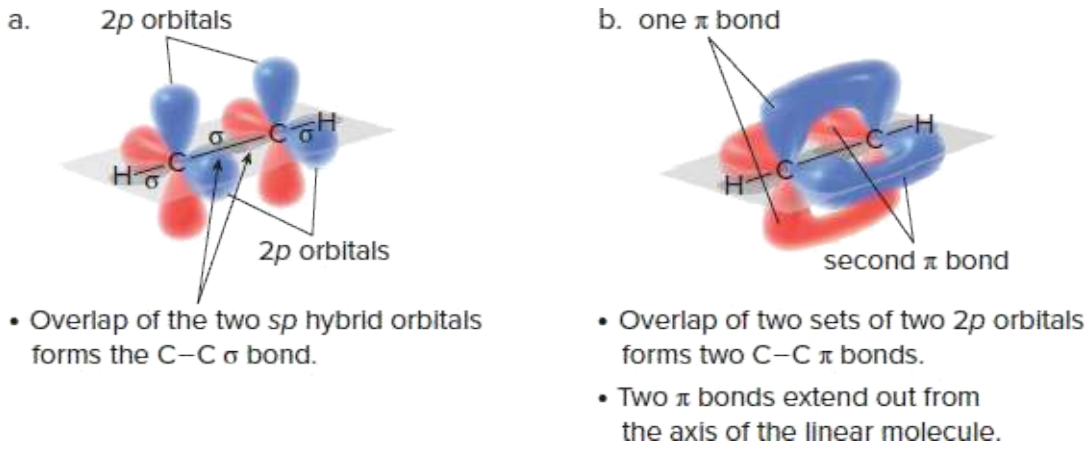


Figure 1.11 **The σ and π bonds in acetylene**

The side-by-side overlap of two *p* orbitals always forms a π bond.

All triple bonds are composed of one σ and two π bonds.

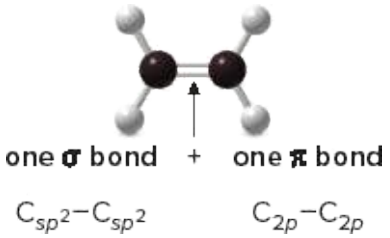
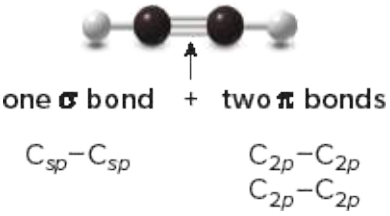
Thus, a carbon–carbon triple bond has three components:

- **a σ bond, formed by end-on overlap of two *sp* hybrid orbitals;**
- **two π bonds, formed by side-by-side overlap of two sets of 2*p* orbitals.**

Table 1.5 summarizes the three possible types of bonding in carbon compounds. Page 42

Table 1.5 **A Summary of Covalent Bonding Seen in Carbon Compounds**

Number of groups bonded to C	Hybridization	Bond angle	Example	Observed bonding
4	sp^3	109.5°	CH_3CH_3 ethane	one σ bond C_{sp^3}–C_{sp^3}

3	sp^2	120°	$CH_2{=}CH_2$ ethylene	
2	sp	180°	HC=CH acetylene	

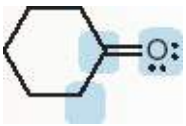
Sample Problem 1.10 Determining Hybridization

Answer each question for cyclohexanone.

a. Determine the hybridization of the highlighted atoms.

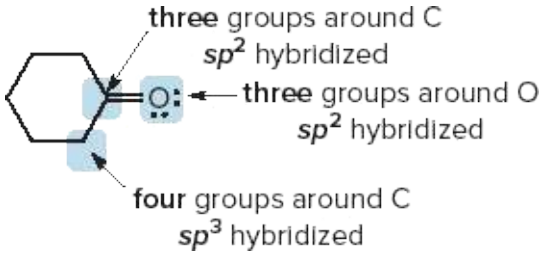
b. What orbitals are used to form the C–O double bond?

c. In what type of orbital does each lone pair reside?



Solution

a.



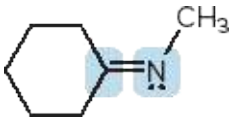
b.
- **The σ bond is formed from the end-on overlap of $C_{sp}2–O_{sp}2$.**
- **The π bond is formed from the side-by-side overlap of $C_{2p}–O_{2p}$.**

c. The O atom has three sp^2 hybrid orbitals.
- **One is used for the σ bond of the double bond.**
- **The remaining two sp^2 hybrids are occupied by the lone pairs.**

Problem 1.31

Determine the hybridization around the highlighted atoms in each molecule.

a. $CH_3–C{\equiv}CH$

b. 

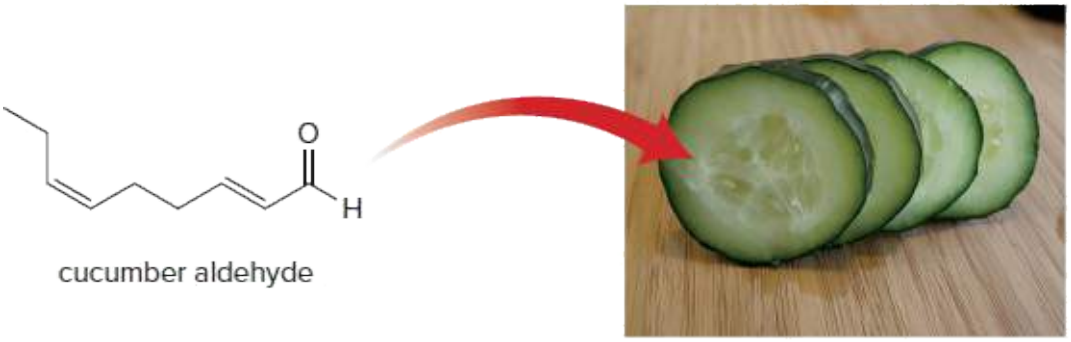
c. $CH_2=C=CH_2$

More Practice:

Try Problems 1.40d, e; 1.41d, e; 1.67d, e; 1.69; 1.76a–c.

Problem 1.32

The unmistakable odor of a freshly cut cucumber is largely due to cucumber aldehyde. (a) How many *sp*^{2} hybridized carbon atoms does cucumber aldehyde contain? (b) What is the hybridization of the O atom? (c) What orbitals are used to form the carbon–oxygen double bond? (d) How many σ bonds does cucumber aldehyde contain? (e) How many π bonds does it contain?



cucumber aldehyde

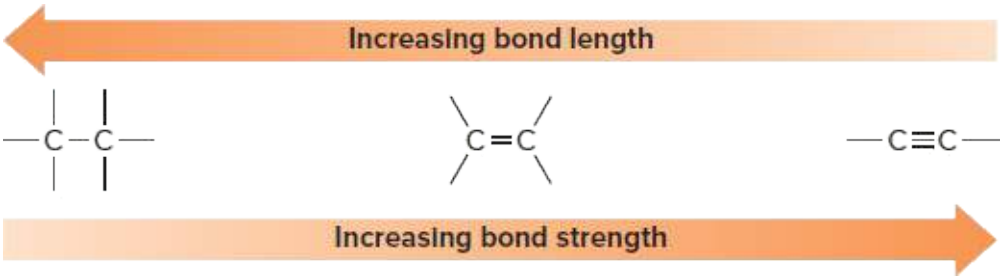
1.11 Bond Length and Bond Strength

Let's now examine the relative bond length and bond strength of the C–C and C–H bonds in ethane, ethylene, and acetylene.

1.11A A Comparison of Carbon–Carbon Bonds

While the SI unit of energy is the joule (J), organic chemists often report energy values in calories (cal). For this reason, energy values in the tables in this text are reported in joules, followed by the number of calories in parentheses. 1 cal = 4.18 J

An inverse relationship exists between bond length and bond strength. The shorter the bond, the closer the electron density is kept to the nucleus, and the harder the bond is to break. *Shorter* bonds are *stronger* bonds.



- **As the number of electrons between two nuclei *increases*, bonds become shorter and stronger.**
- **Triple bonds are shorter and stronger than double bonds, which are shorter and stronger than single bonds.**

Values for bond lengths and bond strengths for CH_3CH_3, $CH_2{=}CH_2$, and HC≡CH are listed in Table 1.6. Be careful not to confuse two related but different principles regarding multiple bonds such as C–C double bonds. Double bonds, consisting of both a σ and a π bond, are *strong*. The π component of the double bond, however, is usually much *weaker* than the σ component. This is a particularly important consideration when studying alkenes in Chapter 10.

Table 1.6 Bond Lengths and Bond Strengths for Ethane, Ethylene, and Acetylene

Compound	C–C bond length (pm)	Bond strength kJ/mol (kcal/mol)
CH_3-CH_3	153	368 (88)
$CH_2=CH_2$	134	635 (152)
HC≡CH	121	837 (200)

Increasing bond length ↑ Increasing bond strength ↓

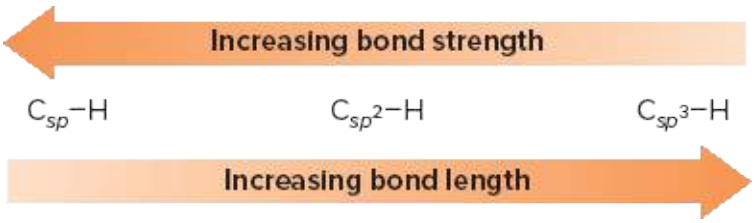
Compound	C–H bond length (pm)	Bond strength kJ/mol (kcal/mol)
CH_3CH_2-H	111	410 (98)
$CH_2=CH-H$	110	435 (104)
HC≡C–H	109	523 (125)

Increasing bond length ↑ Increasing bond strength ↓

1.11B A Comparison of Carbon–Hydrogen Bonds

The length and strength of a C–H bond vary slightly depending on the hybridization of

the carbon atom.



To understand why this is so, we must look at the atomic orbitals used to form each type of hybrid orbital. A single 2*s* orbital is always used, but the number of 2*p* orbitals varies with the type of hybridization. The percent *s*-character indicates the fraction of a hybrid orbital due to the 2*s* orbital used to form it.

***sp* hybrid**	$\frac{\text{one 2}s\text{ orbital}}{\textbf{two}\text{ hybrid orbitals}}$	**= 50% *s*-character**
sp^2 hybrid	$\frac{\text{one 2}s\text{ orbital}}{\textbf{three}\text{ hybrid orbitals}}$	**= 33% *s*-character**
sp^3 hybrid	$\frac{\text{one 2}s\text{ orbital}}{\textbf{four}\text{ hybrid orbitals}}$	**= 25% *s*-character**

Why should the percent *s*-character of a hybrid orbital affect the length of a C–H bond? A 2*s* orbital keeps electron density closer to a nucleus compared to a 2*p* orbital. As the percent *s*-character *increases*, a hybrid orbital holds its electrons closer to the nucleus, and the bond becomes *shorter* and *stronger*.

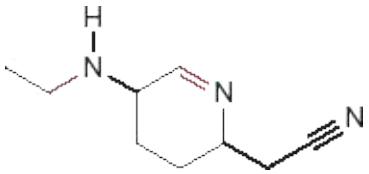
- **Increased percent *s*-character ⇢ Increased bond strength ⇢ Decreased bond length**

Problem 1.33

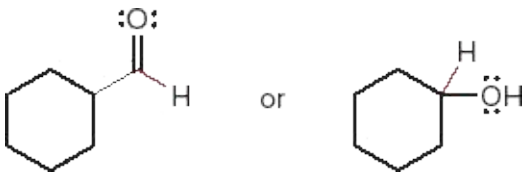
Which of the bonds shown in red in each compound or pair of compounds is shorter?

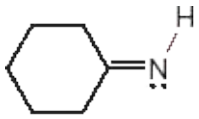
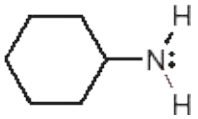
a.

b.



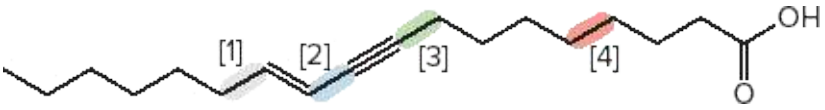
c.



d.  or 

Problem 1.34

Rank the labeled bonds in santalbic acid, a fatty acid obtained from the seeds of the sandalwood tree used in cosmetics, in order of increasing bond length.



The seeds of some types of sandalwood are rich in santalbic acid (Problem 1.34), an unusual fatty acid that contains a carbon–carbon triple bond.

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1.12 Electronegativity and Bond Polarity

Electronegativity is a measure of an atom's attraction for electrons in a bond. Electronegativity indicates how much a particular atom "*wants*" electrons.

- **Electronegativity *increases* across a row of the periodic table as the nuclear charge increases (excluding the noble gases).**
- **Electronegativity *decreases* down a column of the periodic table as the atomic radius increases, pushing the valence electrons farther from the nucleus.**

As a result, the *most* electronegative elements are located at the upper right-hand corner of the periodic table, and the *least* electronegative elements in the lower left-hand corner. A scale has been established to represent electronegativity values arbitrarily, from 0 to 4, as shown in Figure 1.12.

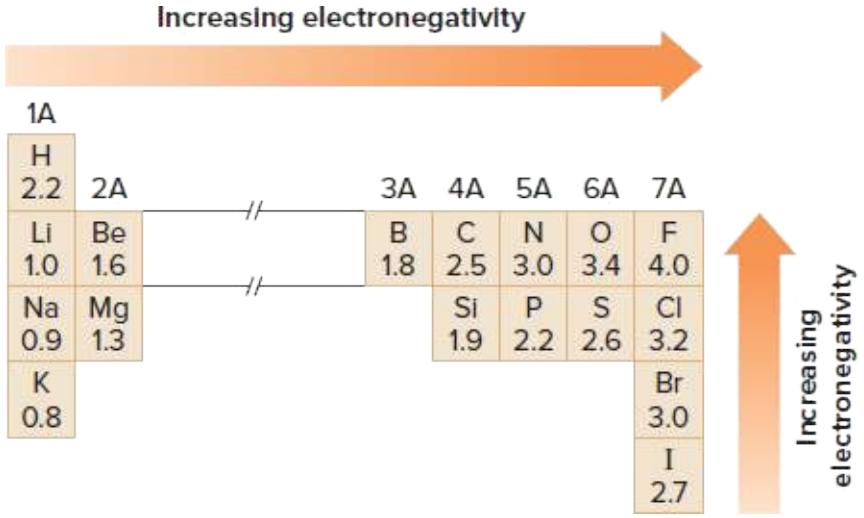


Figure 1.12 **Electronegativity values for some common elements**

Electronegativity values are relative, so they can be used for comparison purposes only. When comparing two different elements, one is more electronegative than the other if it attracts electron density toward itself. One is less electronegative—more electro*positive*—if it gives up electron density to the other element.

Problem 1.35

Rank the following atoms in order of increasing electronegativity. Label the most electronegative and most electropositive atom in each group.

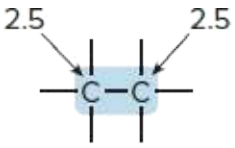
a. Se, O, S

b. P, Na, Cl

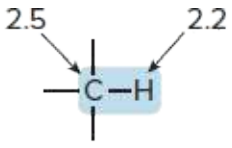
c. Cl, S, F

d. O, P, N

Electronegativity values are used as a guideline to indicate whether the electrons in a bond are equally shared or unequally shared between two atoms. Whenever two identical atoms are bonded together, each atom attracts the electrons in the bond to the same extent. The electrons are equally shared, and the bond is *nonpolar.* Thus, a carbon–carbon bond is nonpolar. Whenever two different atoms having similar electronegativities are bonded together, the bond is also nonpolar. C–H bonds are considered to be nonpolar, because the electronegativity difference between C (2.5) and H (2.2) is small.



nonpolar bond

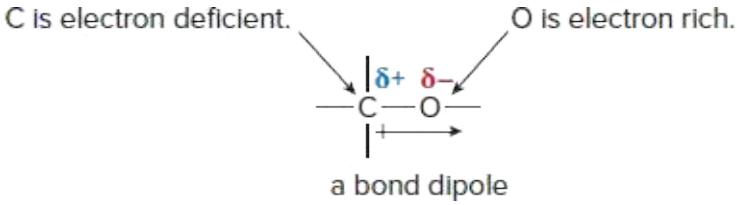


nonpolar bond

The small electronegativity difference between C and H is ignored.

Bonding between atoms of different electronegativity values results in the unequal sharing of electrons. In a C–O bond, the electrons are pulled away from C (2.5) toward O (3.4), the element of higher electronegativity. The bond is *polar*, or *polar covalent*. The bond is said to have a dipole; that is, a partial separation of charge.

A C–O bond is a polar bond.



a bond dipole

The direction of polarity in a bond is often indicated by an arrow, with the head of the arrow pointing toward the more electronegative element. The tail of the arrow, with a perpendicular line drawn through it, is positioned at the less electronegative element. Alternatively, the symbols δ+ and δ– indicate this unequal sharing of electron density.

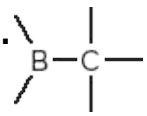
- **δ+ means an atom is electron deficient (has a partial positive charge).**
- **δ– means an atom is electron rich (has a partial negative charge).**

Problem 1.36

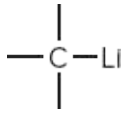
Show the direction of the dipole in each bond. Label the atoms with δ+ and δ–.

a. H–F

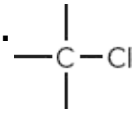
b.



c.



d.



Students often wonder how large an electronegativity difference must be to consider a bond polar. That's hard to say. We will set an arbitrary value for this difference and use it as an *approximation*. Usually, a polar bond will be one in which the electronegativity difference between two atoms is ≥ 0.5 unit.

The distribution of electron density in a molecule can be shown using an electrostatic potential map. These maps are color coded to illustrate areas of high and low electron density. Electron-rich regions are indicated in red, and electron-deficient sites are indicated in blue. Regions of intermediate electron density are shown in orange, yellow, and green.

An electrostatic potential map of CH_3Cl indicates the polar nature of the C–Cl bond (Figure 1.13). The more electronegative Cl atom pulls electron density toward it, making it electron rich. This is indicated by the red around the Cl in the plot. The carbon is electron deficient, and this is shown with blue. When comparing two maps, the comparison is useful only if they are plotted *using the same scale* of color gradation. For this reason, whenever we compare two plots in this text, they will be drawn side by side using the same scale.

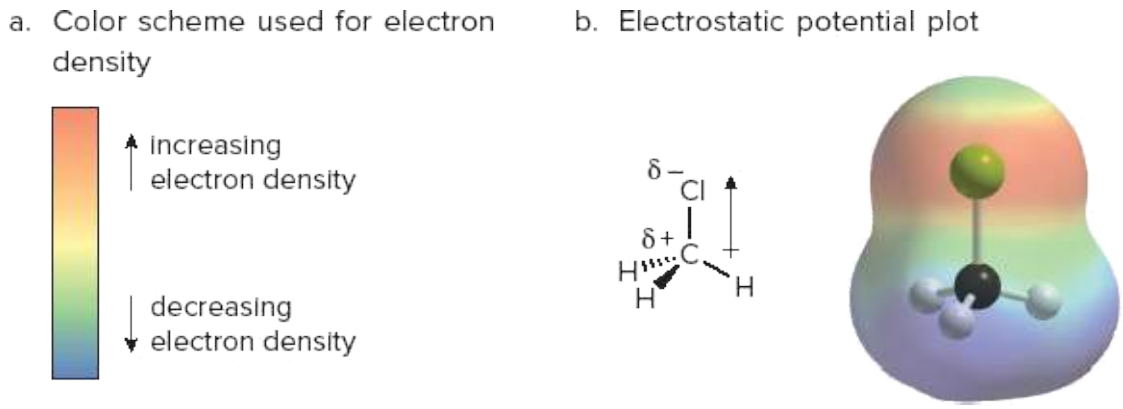


Figure 1.13 **Electrostatic potential plot of CH_3Cl**

A polar molecule has either one polar bond, or two or more bond dipoles that reinforce. A nonpolar molecule has either no polar bonds, or two or more bond dipoles that cancel.

1.13 Polarity of Molecules

Thus far, we have been concerned with the polarity of one bond. To determine whether a molecule has a net dipole, use the following two-step procedure:

[1] Use electronegativity differences to identify all of the polar bonds and the

directions of the bond dipoles.

[2] Determine the geometry around individual atoms by counting groups, and decide if individual dipoles cancel or reinforce each other in space.

The two molecules H_2O and CO_2 illustrate different outcomes of this process. In H_2O, each O–H bond is polar because the electronegativity difference between O (3.4) and H (2.2) is large. Because H2O is a bent molecule, the two dipoles reinforce (both point *up*). Thus, H_2O has a net dipole, making it a polar molecule. CO_2 also has polar C–O bonds because the electronegativity difference between O (3.4) and C (2.5) is large. However, CO_2 is a linear molecule, so the two dipoles, which are equal and opposite in direction, cancel. Thus, CO_2 is a nonpolar molecule with no net dipole.

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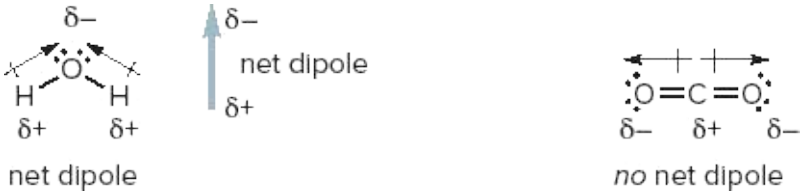
Whenever C or H is bonded to N, O, and all halogens, the bond is *polar.* Thus, the C–I bond is considered polar even though the electronegativity difference between C and I is small. Remember, electronegativity is just an approximation.



net dipole *no* net dipole

Electrostatic potential plots for H_2O and CO_2 appear in Figure 1.14. Additional examples of polar and nonpolar molecules are given in Figure 1.15.

Problem 1.37

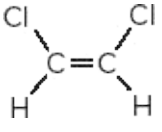
Indicate which of the following molecules is polar because it possesses a net dipole. Show the direction of the net dipole if one exists.

a. CH_3Br

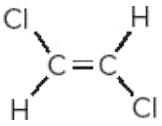
b. CH_2Br_2

c. CF_4

d.

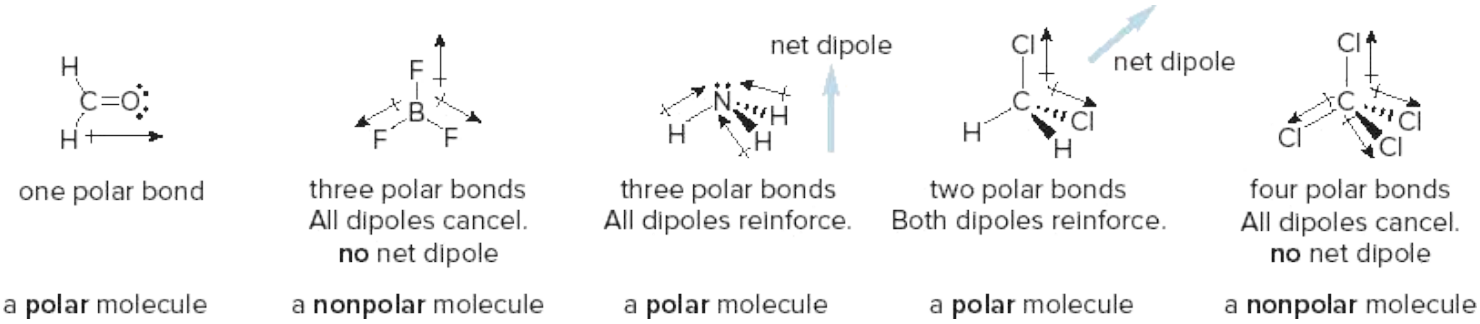


e.



- The electron-rich (red) region is concentrated on the more electronegative O atom. Both H atoms are electron deficient (blue-green).
- Both electronegative O atoms are electron rich (red), and the central C atom is electron deficient (blue).

Figure 1.14 **Electrostatic potential plots for H_2O and CO_2**



one polar bond — a **polar** molecule

three polar bonds
All dipoles cancel.
no net dipole — a **nonpolar** molecule

three polar bonds
All dipoles reinforce. — a **polar** molecule

two polar bonds
Both dipoles reinforce. — a **polar** molecule

four polar bonds
All dipoles cancel.
no net dipole — a **nonpolar** molecule

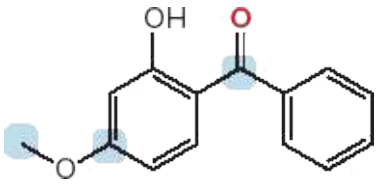
Figure 1.15 **Examples of polar and nonpolar molecules**

1.14 Oxybenzone—A Representative Organic Molecule

The principles learned in this chapter apply to all organic molecules regardless of size or complexity. We now know a great deal about the structure of the chapter-opening molecule, oxybenzene.

Sample Problem 1.11 Applying the Principles of Bonding, Geometry, and Polarity to a Representative Organic Molecule

Answer each question about oxybenzone, the popular sunscreen component described in the chapter opener.



a. How many lone pairs does oxybenzone contain?

b. What is the molecular formula of oxybenzone?

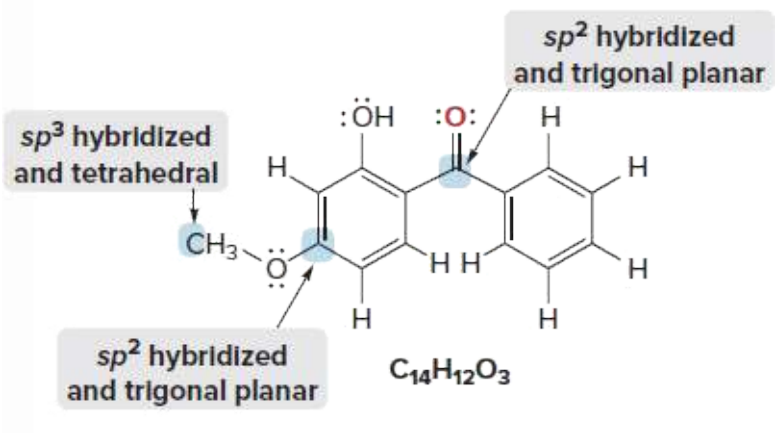
c. What is the hybridization and geometry around each atom labeled in blue?

d. In what type of orbital(s) are any lone pairs on the O atom in red located?

e. Label all polar bonds.

Solution

a, b. **Each O atom needs two lone pairs for an octet, so oxybenzone has six lone pairs. In determining the molecular formula from the skeletal structure, assume there is a C atom at the end of any line and at the intersection of two lines, and that each C has enough H's to make it tetravalent; molecular formula = $C_{14}H_{12}O_3$.**

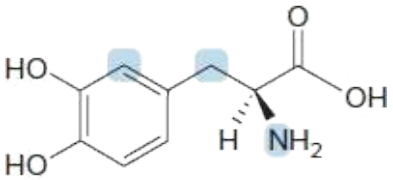


c, d. **Count groups to determine hybridization and geometry; with four groups an atom is *sp*^{3} hybridized and tetrahedral; with three groups an atom is *sp*^{2} hybridized and trigonal planar. The O atom in red is surrounded by three groups—one atom and two lone pairs—so it is *sp*^{2} hybridized and its lone pairs occupy *sp*^{2} hybrid orbitals.**

e. **All C–O and O–H bonds are polar because of the large electronegativity difference between the atoms.**

Problem 1.38

Answer each question about L-dopa, a drug used since 1967 to treat Parkinson's disease.



L-dopa

a. Convert the skeletal structure to a Lewis structure.

b. What is the hybridization and geometry around each labeled atom?

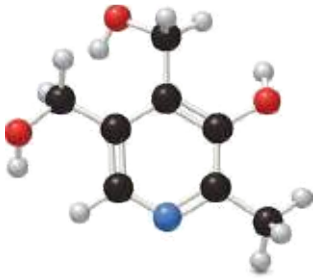
c. Label three polar bonds.

More Practice:

Try Problems 1.75, 1.77, 1.79, 1.80.

Sample Problem 1.12 illustrates how to derive structural information from a ball-and-stick model.

Sample Problem 1.12 **Use the ball-and-stick model of vitamin B_6 to answer each question.**



vitamin B_6

a. Draw a skeletal structure of vitamin B_6.

b. How many sp^2 hybridized carbons are present?

c. What is the hybridization of the N atom in the ring?

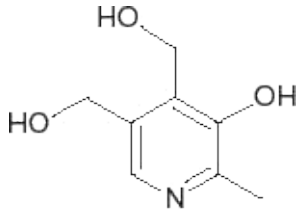
Sinemet, the trade name of a drug used to treat Parkinson's disease, contains a combination of L-dopa (Problem 1.38) and carbidopa (Problem 1.39). Carbidopa increases the

effectiveness of L-dopa by inhibiting its metabolism prior to crossing the blood–brain barrier and entering the brain.
©Cristina Pedrazzini/Science Source

Solution

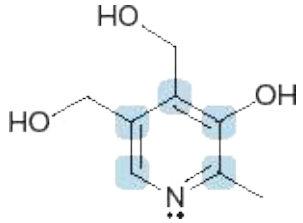
Use the element colors shown in Section 1.7B to convert the 3-D model to a skeletal structure [black (C), gray (H), red (O), blue (N)]. H atoms on carbon are omitted, but H atoms on heteroatoms are drawn. Count groups to determine hybridization. Each O atom needs two lone pairs and each N needs one to give an octet of electrons.

a.



skeletal structure of vitamin B_6

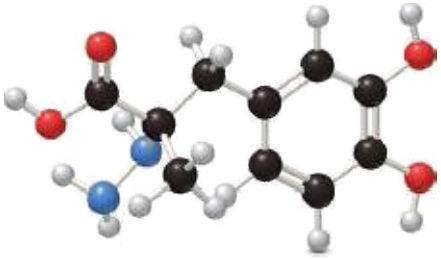
b,c.



- **Each C labeled in blue is sp^2 hybridized.**
- **The N atom is surrounded by three groups (two atoms and one lone pair), making it sp^2 hybridized.**

Problem 1.39

Use the ball-and-stick model to answer each question about carbidopa, a drug used in combination with L-dopa to treat Parkinson's disease.



a. Draw a skeletal structure of carbidopa.

b. Determine the hybridization around each carbon atom.

c. What is the hybridization and geometry around each N atom?

d. How many polar bonds are present?

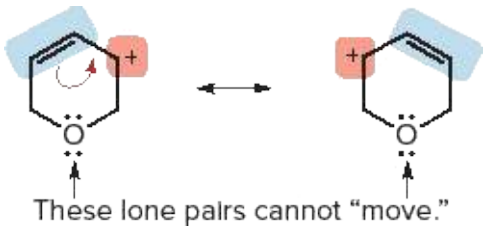
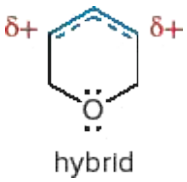
More Practice:

Try Problems 1.40, 1.41.

Chapter 1 REVIEW

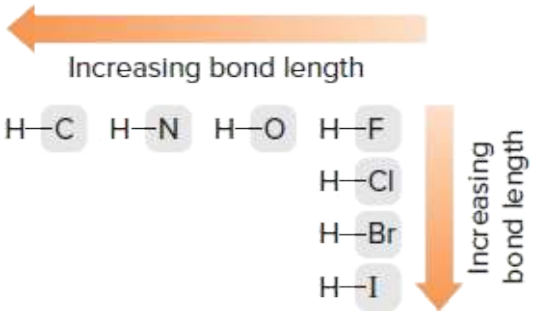
KEY CONCEPTS

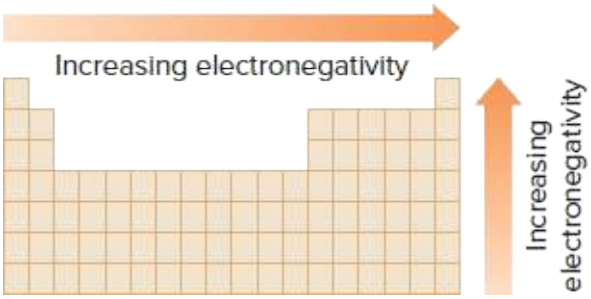
Resonance (1.6)

1 Drawing resonance structures	2 Drawing the resonance hybrid
• Look for lone pairs and multiple bonds. • Atoms and σ bonds do not change location.  See Sample Problem 1.5. Try Problems 1.46b, 1.54, 1.55, 1.75d, 1.78b, 1.79e.	• Draw σ bonds and lone pairs that do not move. • Use a dashed line for a bond that is single in one resonance structure and multiple in another. • Use a δ+ (or δ−) for an atom that is neutral in one structure and charged in another.  Try Problems 1.54, 1.57, 1.78c.

Periodic Trends

1 Bond length of H–Z bonds (1.7A)	2 Electronegativity (1.12)



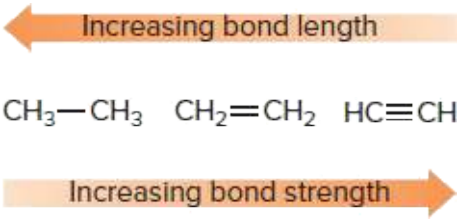


Try Problems 1.35, 1.36, 1.73.

Bond Length and Bond Strength (1.11)

1 Bond length and bond strength of C-C bonds(1.11A)

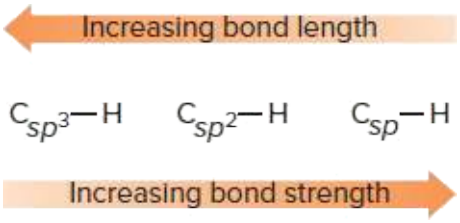
- **Bonds become shorter and stronger as the number of electrons between two nuclei increases.**



Try Problem 1.71.

2 Bond length and bond strength of C-H bonds (1.11B)

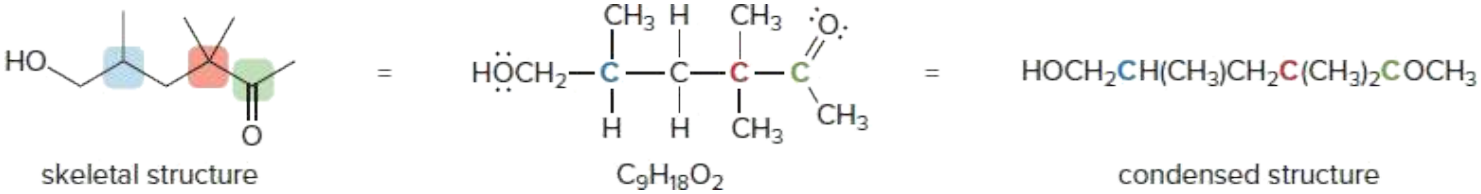
- **Bonds become shorter and stronger as the percent s character increases.**



See Table 1.6. Try Problem 1.70.

Drawing Organic Structures (1.8)

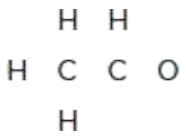
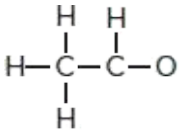
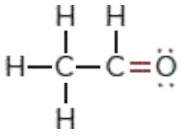
Abbreviate the structure of complex molecules with skeletal structures or condensed structures.



See Figures 1.3, 1.4, 1.5, Sample Problems 1.7, 1.8. Try Problems 1.62–1.65.

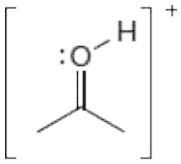
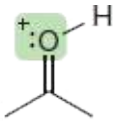
KEY SKILLS

[1] Drawing a valid Lewis structure (1.3); example: CH_3CHO

1 Arrange the atoms with H's on the periphery.	2 Count valence electrons.	3 Add single bonds.	4 Complete octets with multiple bonds and lone pairs.
	2 C's x 4 e⁻ = 8 4 H's x 1 e⁻ = 4 1 O x 6 e⁻ = 6 total e⁻ = 18	 12 e⁻ used.	

See Sample Problems 1.1, 1.2. Try Problems 1.44, 1.45.

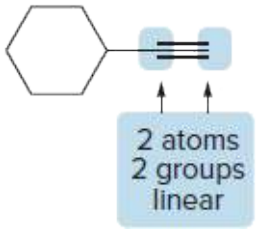
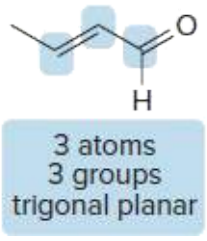
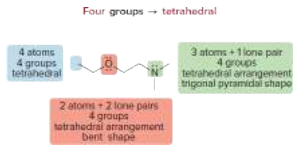
[2] Calculating formal charge (1.3C)

1 Use the group number to determine the number of valence electrons for each atom in the structure.	2 Subtract the number of electrons owned by each atom from the group number to give the formal charge.
 C: 4 e⁻ H: 1 e⁻ O: 6 e⁻	 C: 4 e⁻ – 4 e⁻ = 0 H: 1 e⁻ – 1 e⁻ = 0 O: 6 e⁻ – 5 e⁻ = +1

See Sample Problem 1.3. Try Problems 1.42, 1.43.

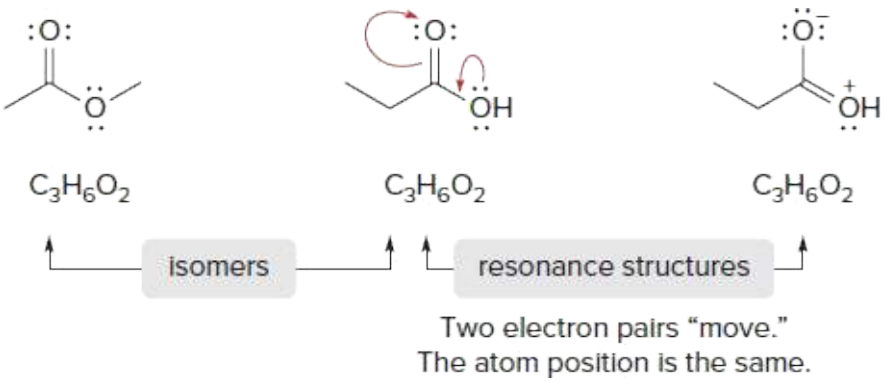
[3] Predicting geometry from a valid Lewis structure (1.7)

1 Count groups	2 Use the following rules:	

on each atom.			
A group = an atom or a lone pair of electrons.	Two groups → linear  • Don't forget about the H's when you are counting groups.	Three groups → trigonal planar  	

See Sample Problem 1.6. Try Problems 1.60, 1.61, 1.77c, 1.79b.

[4] Identifying isomers and resonance structures (1.4, 1.6)

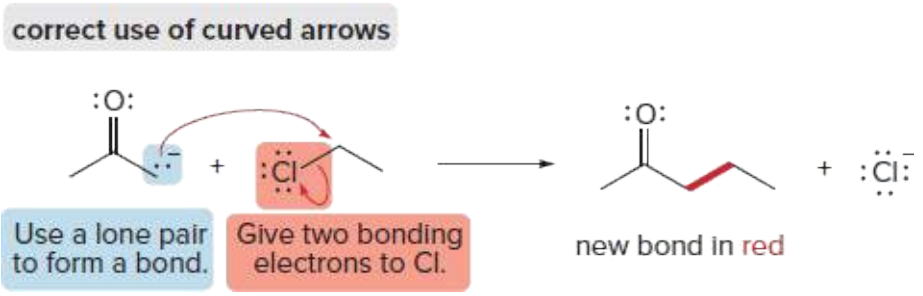
1 Check the molecular formula.	2 Check the position of the atoms and electrons.
• Isomers and resonance structures both have the *same* molecular formulas.	• Two isomers differ in the arrangement of *both* atoms and electrons. • Two resonance structures differ *only* in the arrangement of electrons. 

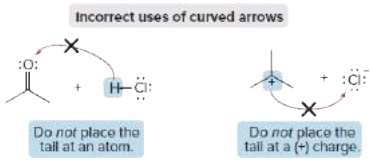
Try Problems 1.49–1.51.

[5] Using curved arrows (1.6B)

1 **Always draw the tail of the arrow from a bond or lone pair.**

2 **Never draw the tail of the arrow from an atom or positive charge.**





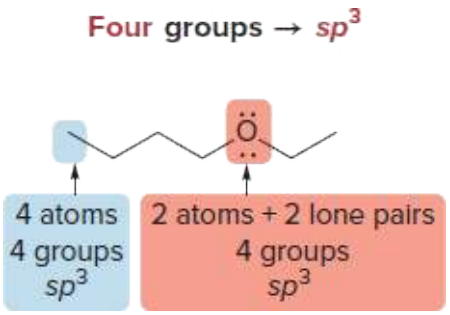
See Sample Problem 1.4. Try Problems 1.52, 1.53.

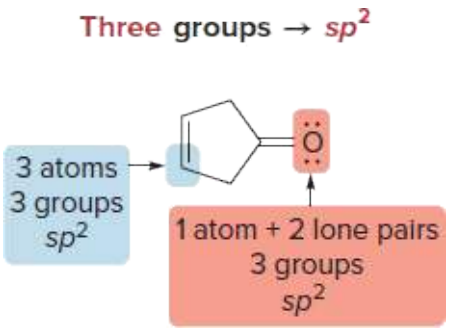
[6] Predicting hybridization from a valid Lewis structure (1.9)

1 **Count groups on each atom.**

2 **Use the following rules:**

A group = an atom or a lone pair of electrons.

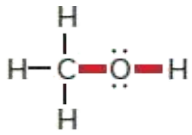
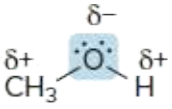
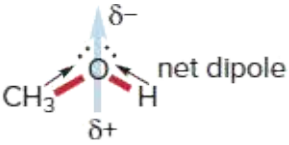




- **Don't forget about the H's when you are counting groups.**

See Sample Problem 1.10. Try Problems 1.67–1.69, 1.75c, 1.77a, 1.79a.

[7] Determining if a molecule has a net dipole from a valid Lewis structure (1.13); example: CH_3OH

1 Label polar bonds based on electronegativity differences.	2 Determine the geometry by counting groups.	3 If there is more than one polar bond, check if bond dipoles cancel or reinforce.
 Two polar bonds in red connect atoms with different electronegativities.	 four groups around O with two lone pairs **bent shape**	 Dipoles reinforce.

Try Problem 1.74.

PROBLEMS

Problems Using Three-Dimensional Models

1.40 **Citric acid is responsible for the tartness of citrus fruits, especially lemons and limes.**

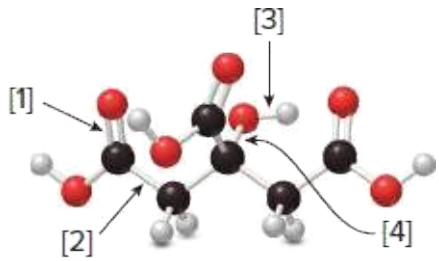
a. What is the molecular formula for citric acid?

b. How many lone pairs are present?

c. Draw a skeletal structure.

d. How many sp^2 hybridized carbons are present?

e. What orbitals are used to form each indicated bond ([1]–[4])?



citric acid

1.41 Zingerone gives ginger its pungent taste.

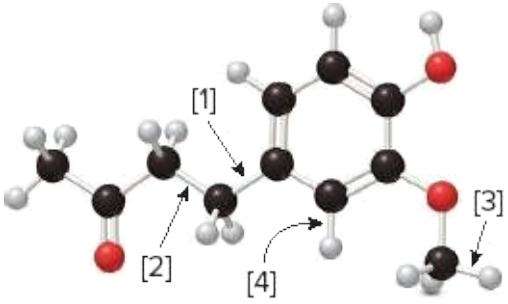
a. What is the molecular formula for zingerone?

b. How many lone pairs are present?

c. Draw a skeletal structure.

d. How many sp^2 hybridized carbons are present?

e. What orbitals are used to form each indicated bond ([1]–[4])?

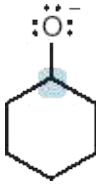


zingerone

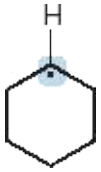
Lewis Structures and Formal Charge

1.42 Give the formal charge on the highlighted carbon in each species. All H's and electrons on the highlighted carbon are drawn in.

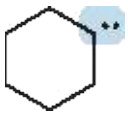
a.



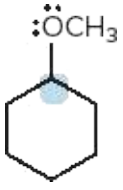
b.

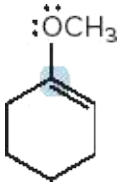


c.



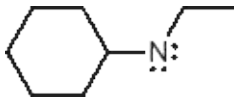
d.

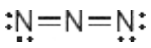


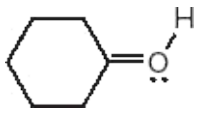
e. 

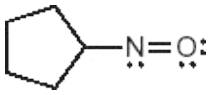
f.

1.43 **Assign formal charges to each N and O atom in the given molecules. All lone pairs have been drawn in.**

a. 

b. 

c. 

d. 

1.44 **Draw one valid Lewis structure for each compound. Assume the atoms are arranged as drawn.**

a. CH_2N_2 H C N N H

b. CH_3NO_2 H C N O H O H

c. CH_3CNO H C C N O H

d. $(CH_2CN)^-$ H C C N H

1.45 **Draw an acceptable Lewis structure from each condensed structure, such that all atoms have zero formal charge.**

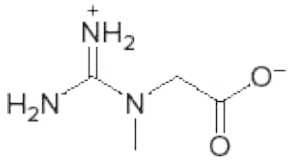
a. **diethyl ether, $(CH_3CH_2)_2O$, the first general anesthetic used in medical procedures**

b. **acrylonitrile, CH_2CHCN, starting material used to manufacture synthetic Orlon fibers**

c. **dihydroxyacetone, $(HOCH_2)_2CO$, an ingredient in sunless tanning products**

d. **acetic anhydride, $(CH_3CO)_2O$, a reagent used to synthesize aspirin**

1.46 **Creatine is a dietary supplement used by some athletes to boost their athletic performance. (a) Draw in all lone pairs in creatine. (b) Draw two additional resonance structures showing all lone pairs and formal charges.**



creatine

1.47 **Draw all possible isomers for each molecular formula.**

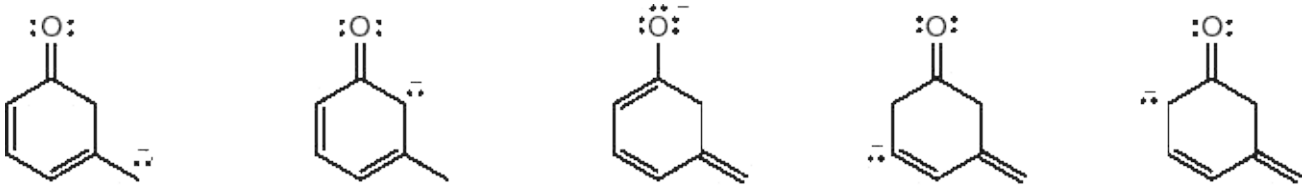
a. C_3H_7Cl (two isomers)

b. C_2H_4O (three isomers)

c. C_3H_9N (four isomers)

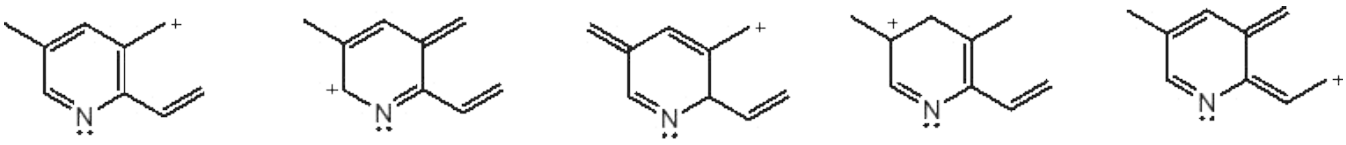
1.48 **Draw Lewis structures for the nine isomers having molecular formula C_3H_6O, with all atoms having a zero formal charge.**

1.49 **With reference to anion A, label compounds B–E as an isomer or resonance structure of A. For each isomer, indicate what bonds differ from A.**



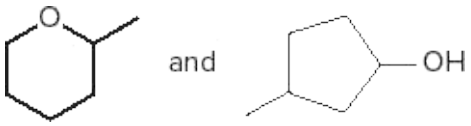
A B C D E

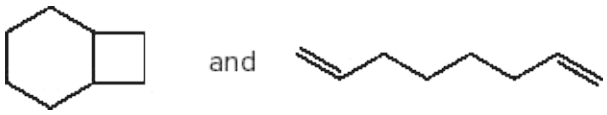
1.50 **Which of the following species is a valid resonance structure of A? Use curved arrows to show how A is converted to any valid resonance structure. When a compound is not a valid resonance structure of A, explain why not.**

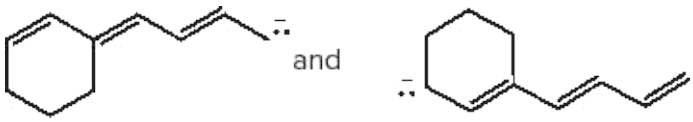


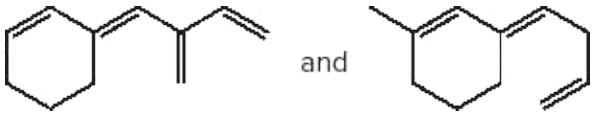
A B C D E

1.51 **How are the molecules or ions in each pair related? Classify them as resonance structures, isomers, or neither.**

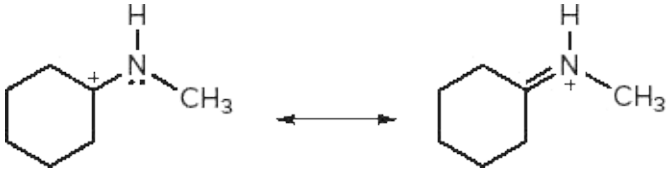
a. 

b. 

c. 

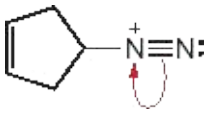
d. 

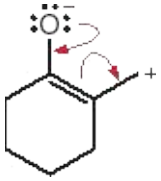
1.52 Add curved arrows to show how the first resonance structure can be converted to the second.

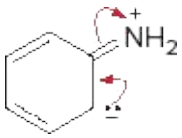
a. 

b.

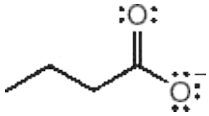
1.53 Follow the curved arrows to draw a second resonance structure for each species.

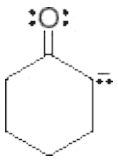
a. 

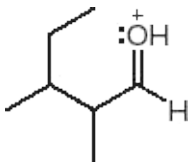
b. 

c. 

1.54 Draw a second resonance structure for each ion. Then, draw the resonance hybrid.

a. 

b. 

c. 

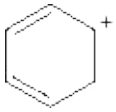
1.55 **Draw all reasonable resonance structures for each species.**

a. O_3

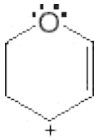
b. NO_3^- **(a central N atom)**

c. NO_3^-

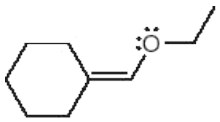
d.



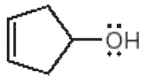
e.



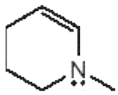
1.56 **Consider compounds A–D, which contain both a heteroatom and a double bond. (a) For which compounds are no additional Lewis structures possible? (b) When two or more Lewis structures can be drawn, draw all additional resonance structures.**



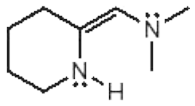
A



B

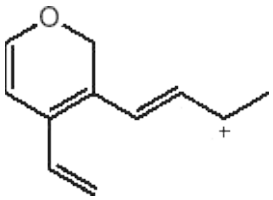


C

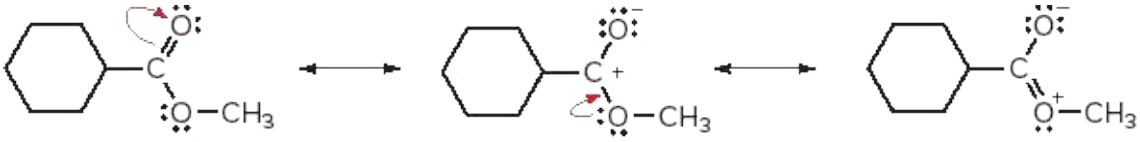


D

1.57 **Draw all reasonable resonance structures for the following cation. Then draw the resonance hybrid.**



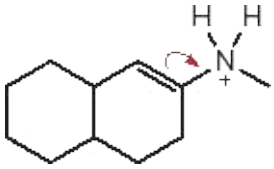
1.58 **Which of the given resonance structures (A, B, or C) contributes most to the resonance hybrid? Which contributes least?**

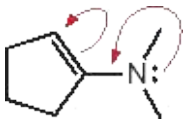


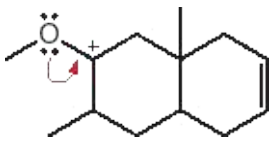
A B C

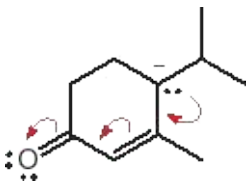
1.59 **Consider the compounds and ions with curved arrows drawn below. When the curved arrows give a second valid resonance structure, draw the resonance structure. When the curved arrows generate an invalid Lewis structure, explain why the structure is unacceptable.**

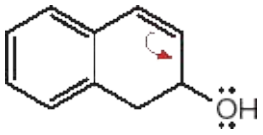
a.

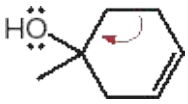


b. 

c. 

d. 

e. 

f. 

Geometry

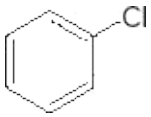
1.60 **Predict all bond angles in each compound.**

a. CH_3Cl

b. NH_2OH

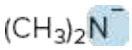
c. $CH_2{=}NCH_3$

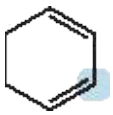
d. $HC{\equiv}CCH_2OH$

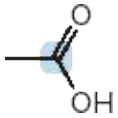
e. 

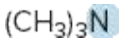
1.61 **Predict the geometry around each highlighted atom.**

a.

b. 

c. 

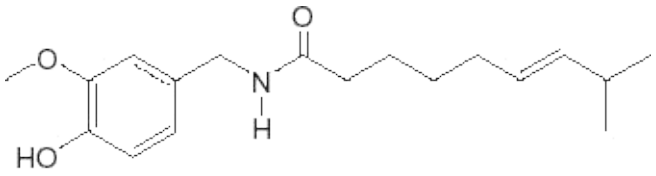
d. 

e. 

Drawing Organic Molecules

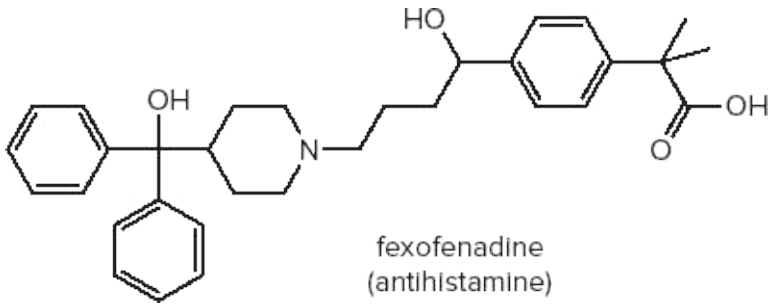
1.62 **How many hydrogens are present around each carbon atom in the following molecules?**

a.



capsaicin
(spicy component of hot peppers)

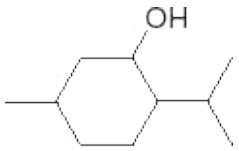
b.



fexofenadine
(antihistamine)

1.63 Draw in all the carbon and hydrogen atoms in each molecule.

a.

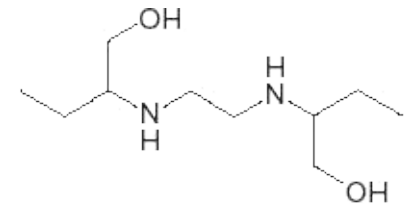


menthol
(isolated from
peppermint oil)

b.

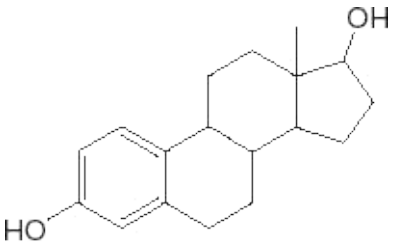
myrcene
(isolated from bayberry)

c.



ethambutol
(drug used to treat tuberculosis)

d.



estradiol
(a female sex hormone)

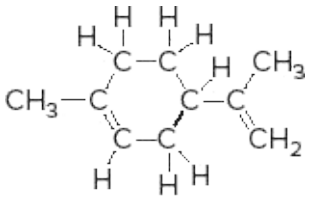
1.64 Convert each molecule to a skeletal structure.

a. $(CH_3)_2CHCH_2CH_2CH(CH_3)_2$

b. $CH_3CH(Cl)CH(OH)CH_3$

c. $CH_3(CH_2)_2C(CH_3)_2CH(CH_3)CH(CH_3)CH(Br)CH_3$

d.



limonene
(oil of lemon)

1.65 Convert the following condensed formulas into skeletal structures.

a. $CH_3CONHCH_3$

b. CH_3COCH_2Br

c. $(CH_3)_3COH$

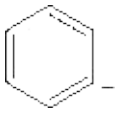
d. CH_3COCl

e. $CH_3COCH_2CO_2H$

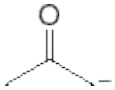
f. $HO_2CCH(OH)CO_2H$

1.66 Draw in all the hydrogen atoms and nonbonded electron pairs in each ion.

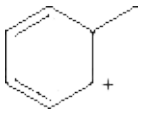
a.



b.



c.



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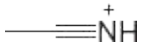
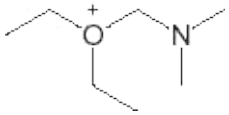


e.

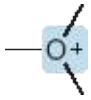


Hybridization

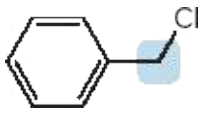
1.67 Predict the hybridization and geometry around each highlighted atom.

a.

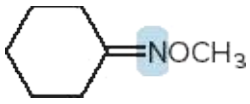
b.



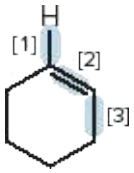
c.

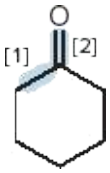


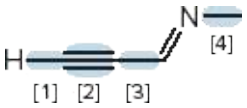
d.

e. 

1.68 What orbitals are used to form each highlighted bond? For multiple bonds, indicate the orbitals used in individual bonds.

a. 

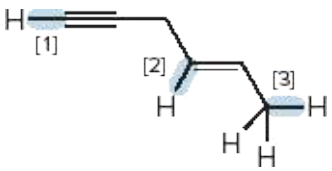
b. 

c. 

1.69 Ketene, $CH_2=C=O$, is an unusual organic molecule that has a single carbon atom doubly bonded to two different atoms. Determine the hybridization of both C atoms and the O in ketene. Then, draw a diagram showing what orbitals are used to form each bond (similar to Figures 1.10 and 1.11).

Bond Length and Strength

1.70 Rank the following bonds in order of *increasing* bond length.



1.71 Answer the following questions about compound A.

a. Label the shortest C–C single bond.

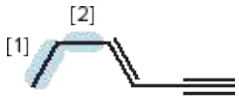
b. Label the longest C–C single bond.

c. Considering all the bonds, label the shortest C–C bond.

d. Label the weakest C–C bond.

e. Label the strongest C–H bond.

f. Explain why bond [1] and bond [2] are different in length, even though they are both C–C single bonds.



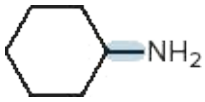
A

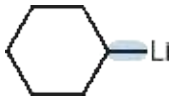
1.72 **Two useful organic compounds that contain Cl atoms are vinyl chloride (CH_2=CHCl) and chloroethane (CH_3CH_2Cl). Vinyl chloride is the starting material used to prepare poly(vinyl chloride), a plastic in insulation, pipes, and bottles. Chloroethane (ethyl chloride) is a local anesthetic. Why is the C–Cl bond in vinyl chloride stronger than the C–Cl bond in chloroethane?**

Bond Polarity

1.73 **Use the symbols δ+ and δ- to indicate the polarity of the highlighted bonds.**

a.

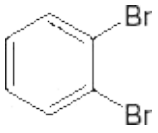
b. 

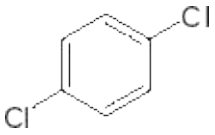
c. 

1.74 **Label the polar bonds in each molecule. Indicate the direction of the net dipole (if there is one).**

a. **$CHBr_3$**

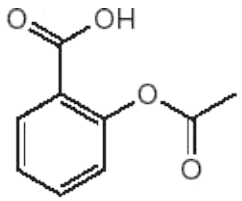
b. **$CH_3CH_2OCH_2CH_3$**

c. 

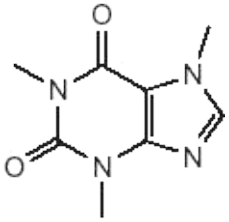
d. 

General Problems

1.75 **Anacin is an over-the-counter pain reliever that contains aspirin and caffeine. Answer the following questions about each compound.**



aspirin
(acetylsalicylic acid)



caffeine

a. What is the molecular formula?

b. How many lone pairs are present on heteroatoms?

c. Label the hybridization state of each carbon.

d. Draw three additional resonance structures.

1.76 Answer the following questions about acetonitrile ($CH_3C{\equiv}N$:).

a. Determine the hybridization of both C atoms and the N atom.

b. Label all bonds as σ or π.

c. In what type of orbital does the lone pair on N reside?

d. Label all bonds as polar or nonpolar.

1.77 Answer the following questions about octocrylene, a common sunscreen component.

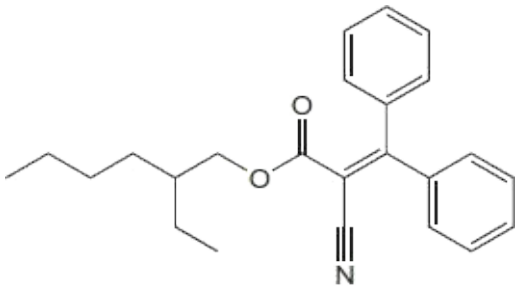
a. What is the hybridization of each C atom?

b. How many lone pairs does octocrylene contain?

c. What is the geometry around each C atom?

d. Draw two additional resonance structures.

e. Label all polar bonds.



octocrylene

1.78 (a) Add curved arrows to show how the starting material A is converted to the product B. (b) Draw all reasonable resonance structures for B. (c) Draw the resonance hybrid for B.

A B

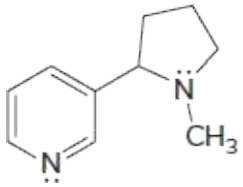
1.79 **a. What is the hybridization of each N atom in nicotine?**

b. What is the geometry around each N atom?

c. In what type of orbital does the lone pair on each N atom reside?

d. Draw a constitutional isomer of nicotine.

e. Draw a resonance structure of nicotine.



1.80 **Stalevo is the trade name for a medication used for Parkinson's disease, which contains L-dopa, carbidopa, and entacapone.**

a. Draw a Lewis structure for entacapone.

b. Which C–C bond in entacapone is the longest?

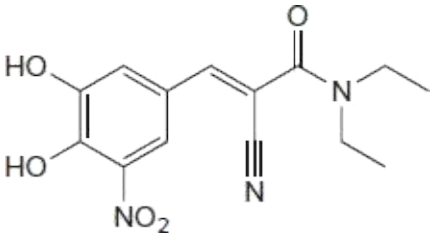
c. Which C–C single bond is the shortest?

d. Which C–N bond is the longest?

e. Which C–N bond is the shortest?

f. Use curved arrows to draw a resonance structure that is an equal contributor to the resonance hybrid.

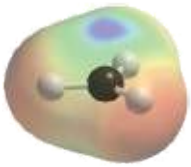
g. Use curved arrows to draw a resonance structure that is a minor contributor to the resonance hybrid.



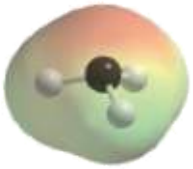
1.81 **CH_3^+ and CH_3^- are two highly reactive carbon species.**

a. What is the predicted hybridization and geometry around each carbon atom?

b. Two electrostatic potential plots are drawn for these species. Which ion corresponds to which diagram and why?



A

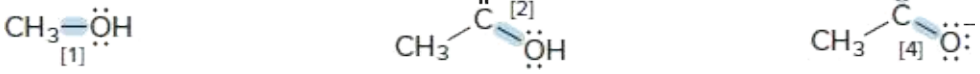


B

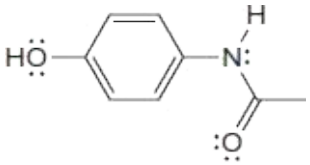
Challenge Problems

1.82 The N atom in CH_3CONH_2 (acetamide) is sp^2 hybridized, even though it is surrounded by four groups. Using this information, draw a diagram that shows the orbitals used by the atoms in the $–CONH_2$ portion of acetamide, and offer an explanation as to the observed hybridization.

1.83 Use the observed bond lengths to answer each question. (a) Why is bond [1] longer than bond [2] (143 pm versus 136 pm)? (b) Why are bonds [3] and [4] equal in length (127 pm), and shorter than bond [2]?



1.84 Draw at least 10 more resonance structures for acetaminophen, the active pain reliever in Tylenol.



acetaminophen

1.85 When two carbons having different hybridization are bonded together, the C–C bond contains a slight dipole. In a $C_{sp}2–C_{sp}3$ bond, what is the direction of the dipole? Which carbon is considered more electronegative?

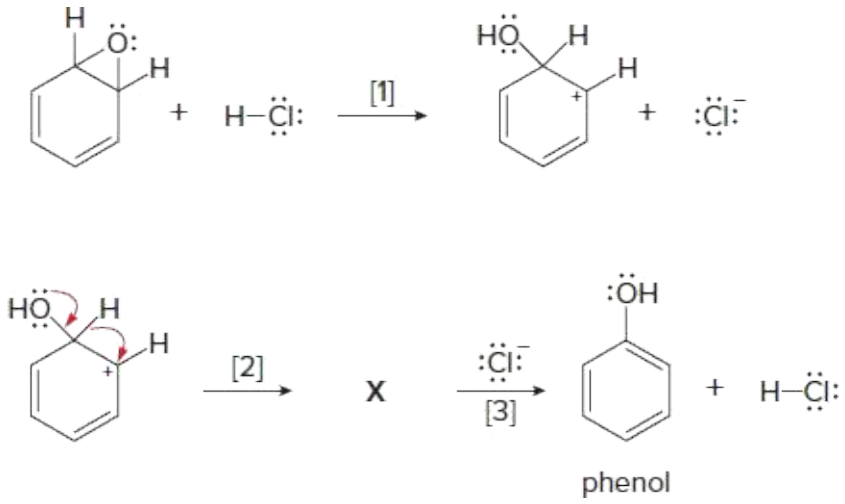
1.86 Draw all possible isomers having molecular formula C_4H_8 that contain one π bond.

1.87 Use the principles of resonance theory to explain why carbocation A is more stable than carbocation B.

A B

1.88 The curved arrow notation introduced in Section 1.6B is a powerful method used by organic chemists to show the movement of electrons not only in resonance structures, but also in chemical reactions.

Because each curved arrow shows the movement of two electrons, following the curved arrows illustrates what bonds are broken and formed in a reaction. Consider the following three-step process. (a) Add curved arrows in Step [1] to show the movement of electrons. (b) Use the curved arrows drawn in Step [2] to identify the structure of X. X is converted in Step [3] to phenol and HCl.



2 Acids and Bases

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2.1 Brønsted–Lowry acids and bases

2.2 Reactions of Brønsted–Lowry acids and bases

2.3 Acid strength and pK_a

2.4 Predicting the outcome of acid~~base reactions

2.5 Factors that determine acid strength

2.6 Common acids and bases

2.7 Aspirin

2.8 Lewis acids and bases

The rich flavor and aroma of a freshly brewed cup of coffee results from a myriad of organic compounds. The mild acidity of coffee made from the beans of plants grown at higher altitudes or in volcanic soil is in part due to quinic acid, an organic acid present in low concentration in green coffee beans. Quinic acid concentration increases during processing, as more-complex compounds are degraded by the heat of roasting, and it contributes to the increase in the perceived acidity of coffee that has been warmed for a long time on a hot surface. In Chapter 2, we learn about acidity and acid–base reactions.

Why Study…

Acids and Bases?

Chemical terms such as *anion* and *cation* may be unfamiliar to most nonscientists, but *acid* has found a place in everyday language. Commercials advertise the latest remedy for the heartburn caused by excess stomach *acid*. The nightly news may report the latest environmental impact of *acid* rain. Wine lovers know that wine sours because its alcohol has turned to *acid*. *Acid* comes from the Latin word *acidus*, meaning "sour," because when tasting compounds was a routine method of identification, these compounds were sour.

In Chapter 2, we concentrate on two definitions of acids and bases: the Brønsted–Lowry definition, which describes acids as proton donors and bases as proton acceptors, and the Lewis definition, which describes acids as electron pair acceptors and bases as electron pair donors.

The general words "acid" and "base" usually mean a *Brønsted–Lowry* acid and *Brønsted–Lowry* base.

H^+ = proton.

HA = Brønsted–Lowry acid.

B: = Brønsted–Lowry base.

2.1 Brønsted–Lowry Acids and Bases

The Brønsted–Lowry definition describes acidity in terms of protons: positively charged hydrogen ions, H^+.

- **A Brønsted–Lowry acid is a *proton donor.***
- **A Brønsted–Lowry base is a *proton acceptor.***

A Brønsted–Lowry acid must contain a *hydrogen* atom. This definition of an acid is often familiar to students, because many inorganic acids in general chemistry are Brønsted–Lowry acids. The symbol HA is used for a general Brønsted–Lowry acid.

A Brønsted–Lowry base must be able to form a bond to a proton. Because a proton has no electrons, a base must contain an "available" electron pair that can be easily donated to form a new bond. These include lone pairs or electron pairs in π bonds. The symbol B: is used for a general Brønsted–Lowry base. Examples of Brønsted–Lowry acids and bases are given in Figure 2.1.

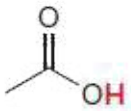
Charged species such as ^-OH and $^-NH_2$ are used as salts, with cations such as Li^+, Na^+, or K^+ to balance the negative charge. These cations are called counterions or spectator ions, and their identity is usually inconsequential. For this reason, the counterion is often omitted.

NaOH	=	Na^+	^-OH
KOH	=	K^+	^-OH
salt		counterion	base

Compounds like H_2O and CH_3OH that contain both hydrogen atoms and lone pairs may be either an acid or a base, depending on the particular reaction. These fundamental principles are true no matter how complex the compound. For example, the addictive pain reliever morphine is a Brønsted–Lowry acid because it contains many hydrogen atoms. It is also a Brønsted–Lowry base because it has lone pairs on O and N, and four π bonds.

a. **Brønsted–Lowry acids (HA)**

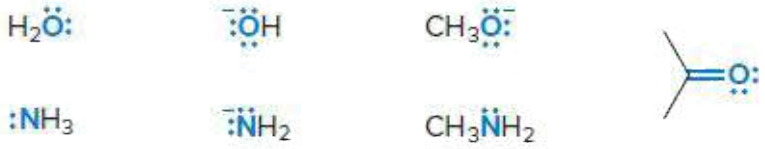
HCl
H_2SO_4
HSO_4^-
H_2O
H_3O^+



acetic acid

- **All Brønsted–Lowry acids contain a proton.**
- The net charge may be zero, (+), or (–).

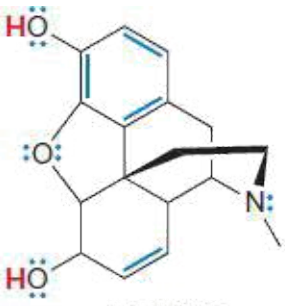
b. **Brønsted–Lowry bases (B:)**



- **All Brønsted–Lowry bases contain a lone pair of electrons or a π bond.**
- The net charge may be zero or (–).

Figure 2.1 **Examples of Brønsted–Lowry acids and bases**

Morphine is obtained from the opium poppy. ***©mafoto/Getty Images***



morphine

- H atoms on O make morphine an acid.
- Lone pairs and π bonds (in blue) make morphine a base.

Problem 2.1

a. Which compounds are Brønsted–Lowry acids: HBr, NH_3, CCl_4?

b. Which compounds are Brønsted–Lowry bases: CH_3CH_3, $(CH_3)_3CO^-$, HC≡CH?

c. Classify each compound as an acid, a base, or both: CH_3CH_2OH, $CH_3CH_2CH_2CH_3$, $CH_3CO_2CH_3$.

2.2 Reactions of Brønsted–Lowry Acids and Bases

A Brønsted–Lowry acid–base reaction results in transfer of a proton from an acid to a base. These acid–base reactions, also called *proton transfer reactions*, are fundamental to the study of organic chemistry.

Consider, for example, the reaction of the acid HA with the base :B. In an acid–base reaction, one bond is broken and one is formed.

- The electron pair of the base B: forms a new bond to the proton of the acid.
- The acid HA loses a proton, leaving the electron pair in the HA bond on A.

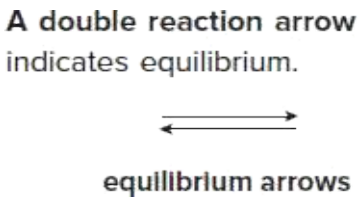
Recall from Section 1.6 that a curved arrow shows the movement of an electron pair. The tail of the arrow always begins at an electron pair, and the head points to where that electron pair "moves."

This "movement" of electrons in reactions can be illustrated using curved arrow notation. Because two electron pairs are involved in this reaction, two curved arrows are needed. Two products are formed.

- **Loss of a proton from an acid forms its *conjugate base*.**
- **Gain of a proton by a base forms its *conjugate acid*.**

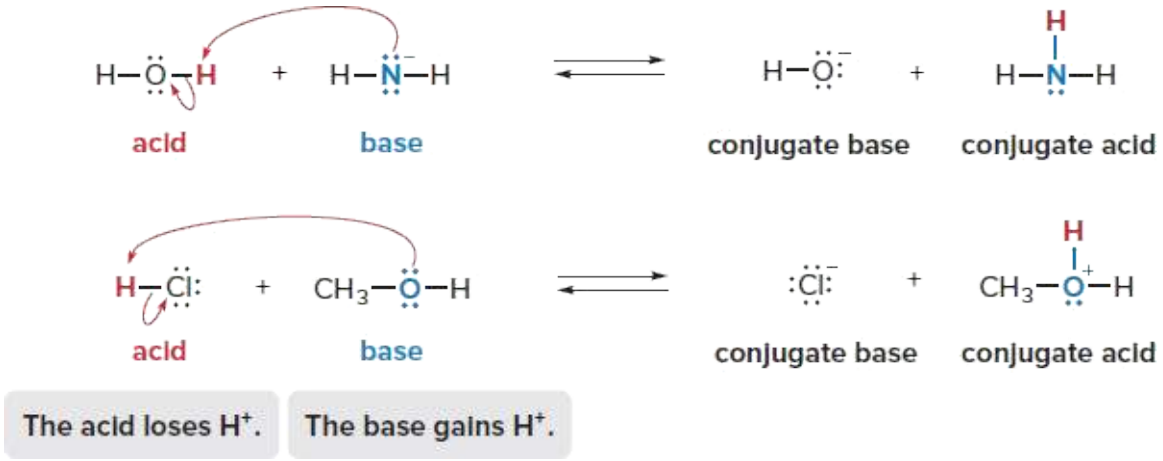
The net charge must be the same on both sides of any equation. In this example, the net charge on each side is zero. Individual charges can be calculated using formal charges. A double reaction arrow is used between starting materials and products to indicate that the reaction can proceed in the forward and reverse directions. These are equilibrium arrows.

A double reaction arrow indicates equilibrium.



Remove H^+ from an acid to form its conjugate base. Add H^+ to a base to form its conjugate acid.

Two examples of proton transfer reactions are drawn here with curved arrow notation.



- **Brønsted–Lowry acid–base reactions always result in the transfer of a proton from an acid to a base.**

The ability to identify and draw a conjugate acid or base from a given starting material is illustrated in Sample Problems 2.1 and 2.2.

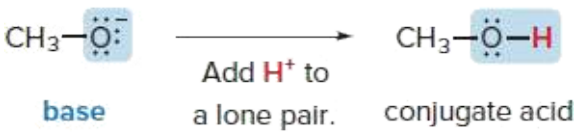
Sample Problem 2.1 Drawing a Conjugate Acid and a Conjugate Base

a. What is the conjugate acid of CH_3O^-?

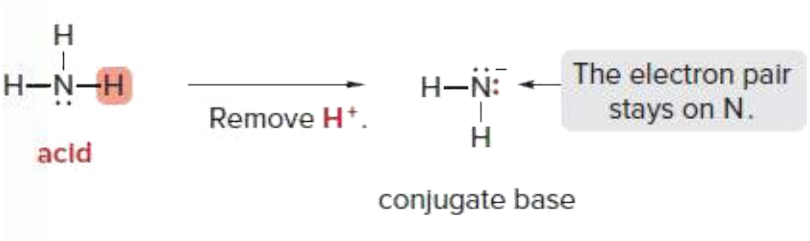
b. What is the conjugate base of NH_3?

Solution

a. Add H^+ to CH_3O^- to form its conjugate acid.



b. Remove H^+ from NH_3 to form its conjugate base.



Problem 2.2

a. Draw the conjugate acid of each base: NH_3, Cl^-, $(CH_3)_2C{=}O$.

b. Draw the conjugate base of each acid: HBr, HSO_4^-, CH_3OH.

More Practice:

Try Problems 2.38, 2.39.

Problem 2.3

Label each statement as True or False.

a. $CH_3CH_2^+$ is the conjugate acid of $CH_2{=}CH_2$.

b. $CH_3CH_2^-$ is the conjugate base of $CH_3CH_2^+$.

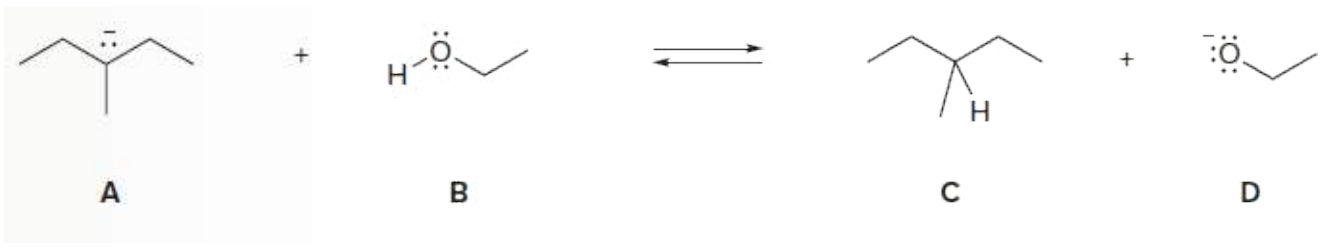
c. $CH_2{=}CH_2$ is the conjugate base of $CH_3CH_2^-$.

d. $CH_2{=}CH^-$ is the conjugate base of $CH_2{=}CH_2$.

e. CH_3CH_3 is the conjugate acid of $CH_3CH_2^-$.

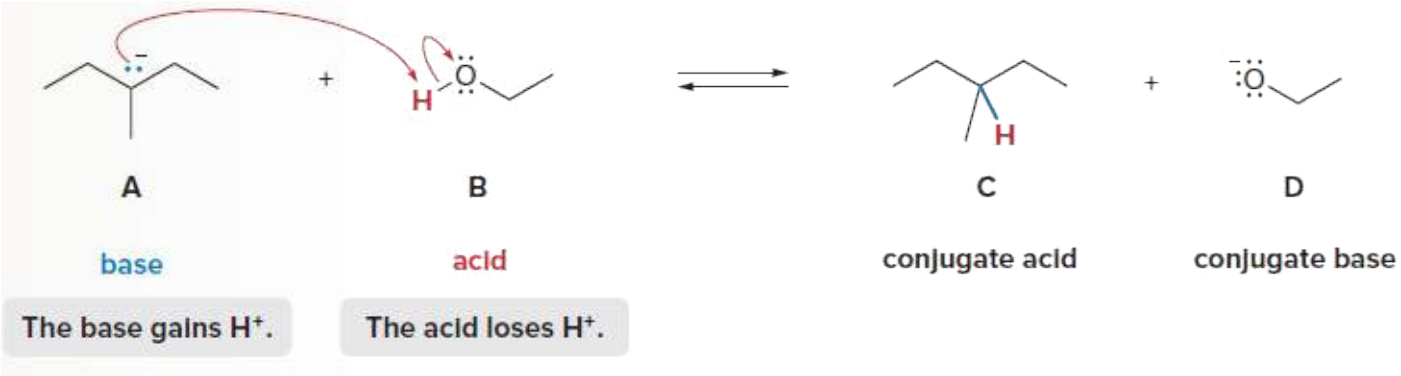
Sample Problem 2.2 Determining the Acid, Base, Conjugate Acid, and Conjugate Base in a Reaction

Label the acid and base, and the conjugate acid and base, in the following reaction. Use curved arrow notation to show the movement of electron pairs.



Solution

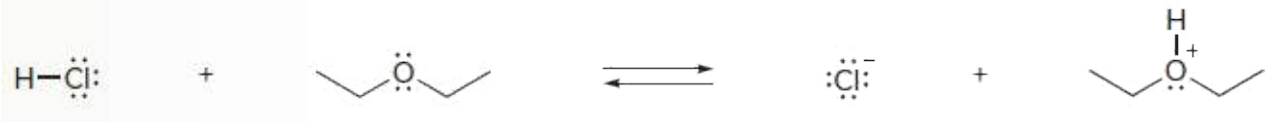
A is the base because it accepts a proton, forming its conjugate acid, C. B is the acid because it donates a proton, forming its conjugate base, D. Two curved arrows are needed because two electron pairs are involved. One shows that the lone pair on A bonds to a proton of B, and the second shows that the electron pair in the O–H bond remains on O.



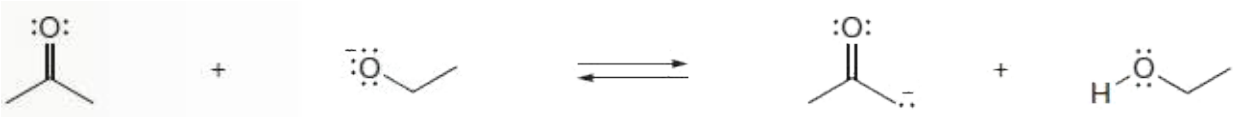
Problem 2.4

Label the acid and base, and the conjugate acid and base, in the following reactions. Use curved arrows to show the movement of electron pairs.

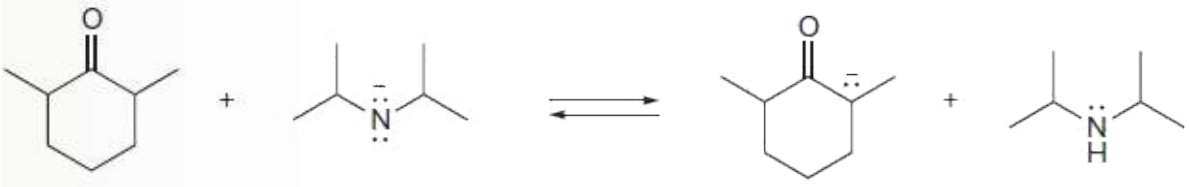
a.



b.



c.



More Practice:

Try Problem 2.40.

In all proton transfer reactions, the electron-rich base donates an electron pair to the acid, which usually has a polar HA bond. The H of the acid bears a partial positive charge, making it electron deficient. This is the first example of a general pattern of reactivity.

- **Electron-rich species react with electron-deficient ones.**

Given two starting materials, how do you know which is the acid and which is the base

in a proton transfer reaction? Use the following generalizations:

[1] Common acids and bases introduced in general chemistry are used in the same way in organic reactions. HCl and H_2SO_4 are strong acids, and ^-OH is a strong base.

[2] When only one starting material contains a hydrogen, it must be the acid. If only one starting material has a lone pair or a π bond, it must be the base.

[3] A starting material with a net positive charge is usually the acid. A starting material with a negative charge is usually the base.

Figure 2.2 shows how to use these generalizations to identify the acid and base with pairs of compounds.

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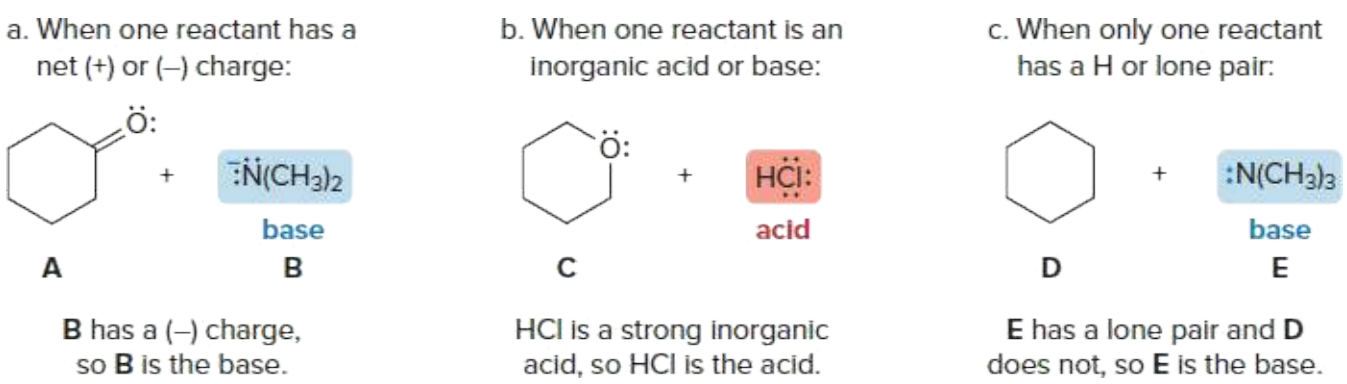
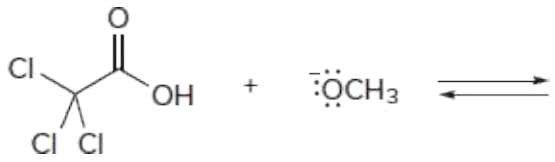


Figure 2.2 **Identifying the acid and the base in a proton transfer reaction**

Problem 2.5

Decide which compound is the acid and which is the base, and draw the products of each proton transfer reaction.

a.



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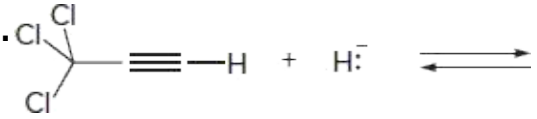

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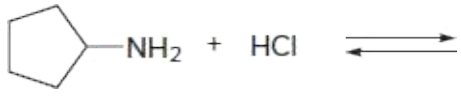

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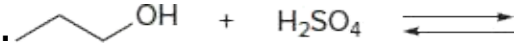
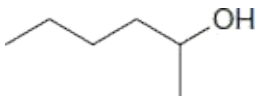
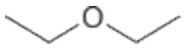
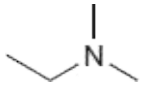


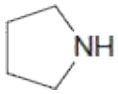
Problem 2.6

Draw the products formed from the acid–base reaction of HCl with each compound.

a. 

b. 

c. 

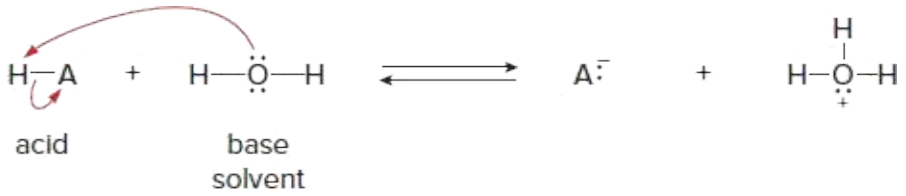
d. 

2.3 Acid Strength and pK_a

Acid strength is the tendency of an acid to donate a proton.

- **The more readily a compound donates a proton, the *stronger* the acid.**

Acidity is measured by an equilibrium constant. When a Brønsted–Lowry acid HA is dissolved in water, an acid–base reaction occurs, and an equilibrium constant K_{eq} can be written for the reaction.



$$K_{eq} = \frac{[\text{products}]}{[\text{starting materials}]} = \frac{[H_3O^+][A:^-]}{[HA][H_2O]}$$

Because the concentration of the solvent H_2O is essentially constant, the equation can be re-arranged and a new equilibrium constant, called the acidity constant, K_a, can be defined.

$$K_a = [H_2O]K_{eq} = \frac{[H_3O^+][A:^-]}{[HA]}$$

How is the magnitude of K_a related to acid strength?

- **The *stronger the acid*, the further the equilibrium lies to the right and the *larger the* K_a.**

For most organic compounds, K_a is small, typically 10^{-5} to 10^{-50}. This contrasts with the K_a values for many inorganic acids, which range from 10^0

to 10^{10}. Because using exponents can be cumbersome, it is often more convenient to use pK_a values instead of K_a values.

$$pK_a = -\log K_a$$

How does pK_a relate to acid strength?

Recall that a log is an exponent; for example, log 10^{-5} = −5.

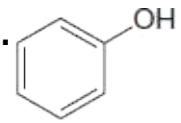
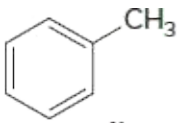
K_a values of typical organic acids		pK_a values of typical organic acids	
10^{-5} →	10^{-50}	+5 →	+50
larger number stronger acid	smaller number weaker acid	smaller number stronger acid	larger number weaker acid

- **The *smaller* the *pK_a*, the *stronger* the acid.**

Problem 2.7

Which compound in each pair is the stronger acid?

a. $CH_3CH_2CH_3$ ($pK_a = 50$) or CH_3CH_2OH ($pK_a = 16$)

b.  ($K_a = 10^{-10}$) or  ($K_a = 10^{-41}$)

Problem 2.8

Use a calculator when necessary to answer the following questions.

a. What is the pK_a for each K_a: 10^{-10}, 10^{-21}, and 5.2×10^{-5}?

b. What is the K_a for each pK_a: 7, 11, and 3.2?

An inverse relationship exists between acidity and basicity.

- **A *strong acid* readily donates a proton, forming a *weak conjugate base.***
- **A *strong base* readily accepts a proton, forming a *weak conjugate acid.***

Table 2.1 is a brief list of pK_a values for some common compounds, ranked in order of

increasing pK_a and therefore *decreasing* acidity. Because strong acids form weak conjugate bases, this list also ranks their conjugate bases, in order of *increasing* basicity. CH_4 is the weakest acid in the list, because it has the highest pK_a (50). Its conjugate base, CH_3^-, is therefore the strongest conjugate base. An extensive pK_a table is located in Appendix C.

Table 2.1 Selected pK_a Values

Acid	pK_a	Conjugate base
H–Cl	–7	Cl^-
CH_3CO_2–H	4.8	$CH_3CO_2^-$
HO–H	15.7	HO^-
CH_3CH_2O–H	16	$CH_3CH_2O^-$
HC≡CH	25	$HC{\equiv}C^-$
H–H	35	H^-
H_2N–H	38	H_2N^-
CH_2=CH_2	44	$CH_2{=}\bar{C}H$
CH_3–H	50	CH_3^-

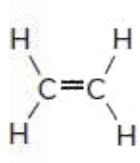
Increasing acidity ↑ (top to bottom)

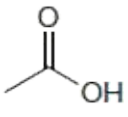
Increasing basicity ↓ (top to bottom)

Comparing pK_a values tells us the relative acidity of two acids, and the relative basicity of their conjugate bases, as shown in Sample Problem 2.3.

Sample Problem 2.3 Using pK_a Values to Determine Relative Acidity and Basicity

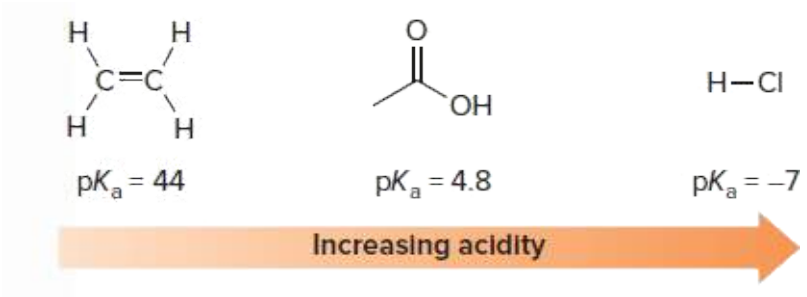
Rank the following compounds in order of increasing acidity, and then rank their conjugate bases in order of increasing basicity.



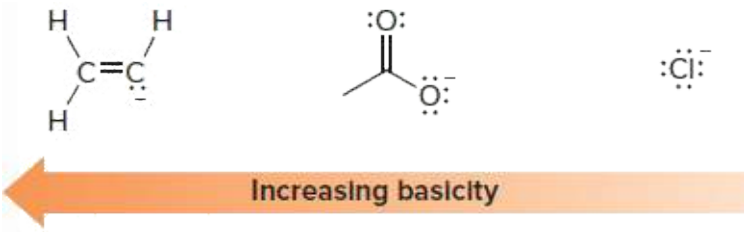


Solution

Use the pK_a values in Table 2.1 and the rule: the lower the pK_a, the stronger the acid.



Remove a proton to draw the conjugate bases. Because strong acids form weak conjugate bases, the basicity of conjugate bases increases with increasing pK_a of their acids.



Problem 2.9

Rank the conjugate bases of each group of acids in order of increasing basicity.

a. NH_3, H_2O, CH_4

b. CH_2=CH_2, HC≡CH, CH_4

More Practice:

Try Problem 2.54b.

Problem 2.10

Consider two acids: HCO_2H (formic acid, pK_a = 3.8) and pivalic acid [$(CH_3)_3CCO_2H$, pK_a = 5.0]. (a) Which acid has the larger K_a? (b) Which acid is the stronger acid? (c) Which acid forms the stronger conjugate base? (d) When each acid is dissolved in water, for which acid does the equilibrium lie further to the right?

The pK_a values in Table 2.1 span a large range (−7 to 50). The pK_a scale is logarithmic, so a small difference in pK_a translates into a large numerical difference. The difference between the pK_a values of NH_3 (38) and CH_2=CH_2 (44) is six pK_a units, so NH_3 is 10^6 or *one million times more acidic* than CH_2=CH_2.

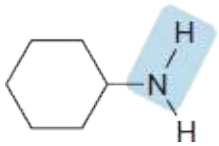
Although Table 2.1 is abbreviated, it is a useful tool for *estimating* the pK_a of a compound similar though not identical to one in the table. Suppose you are asked to

estimate the pK_a of the N—H bond of CH_3NH_2. Although CH_3NH_2 is not listed in the table, we have enough information to *approximate* its pK_a. Because the pK_a of the N—H bond of NH_3 is 38, we can estimate the pK_a of the N—H bond of CH_3NH_2 to be 38. Its actual pK_a is 40, so this is a good first approximation.

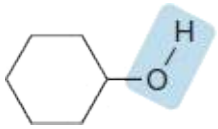
Problem 2.11

Estimate the pK_a of each of the indicated bonds.

a.



b.



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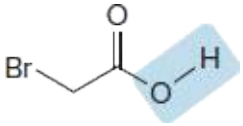
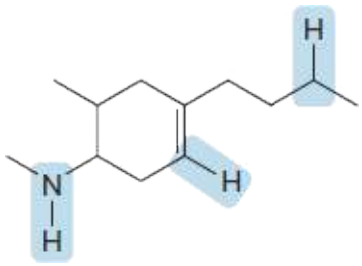


d.



2.4 Predicting the Outcome of Acid–Base Reactions

In a proton transfer reaction, the stronger acid reacts with the stronger base to form the weaker acid and the weaker base.

A proton transfer reaction represents an equilibrium. Because an acid donates a proton to a base, forming a conjugate acid and conjugate base, there are always two acids and two bases in the reaction mixture. Which pair of acids and bases is favored at equilibrium? The position of the equilibrium depends on the relative strengths of the acids and bases.

- **Equilibrium always favors formation of the *weaker* acid and base.**

Because a strong acid readily donates a proton and a strong base readily accepts one,

these two species react to form a weaker conjugate acid and base that do not donate or accept a proton as readily. Comparing pK_a values allows us to determine the position of equilibrium, as illustrated in Sample Problem 2.4.

Sample Problem 2.4 Using pK_a Values to Predict the Direction of Equilibrium

Determine the direction of equilibrium when acetylene (HC≡CH) reacts with $^-NH_2$ in a proton transfer reaction.

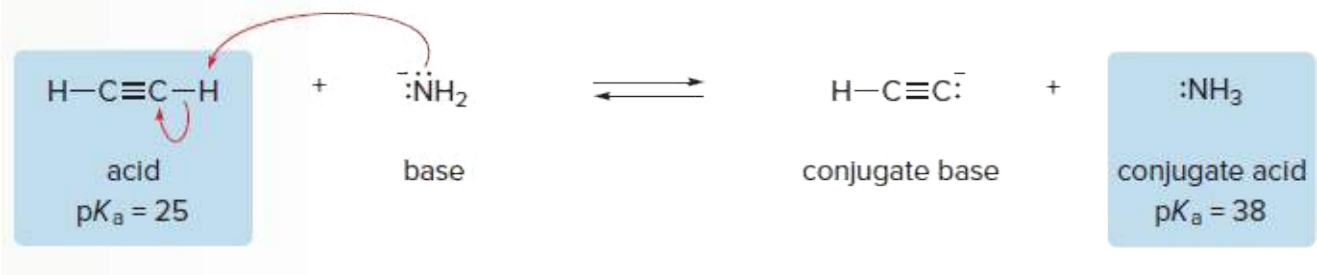
Solution

Follow three steps to determine the position of equilibrium:

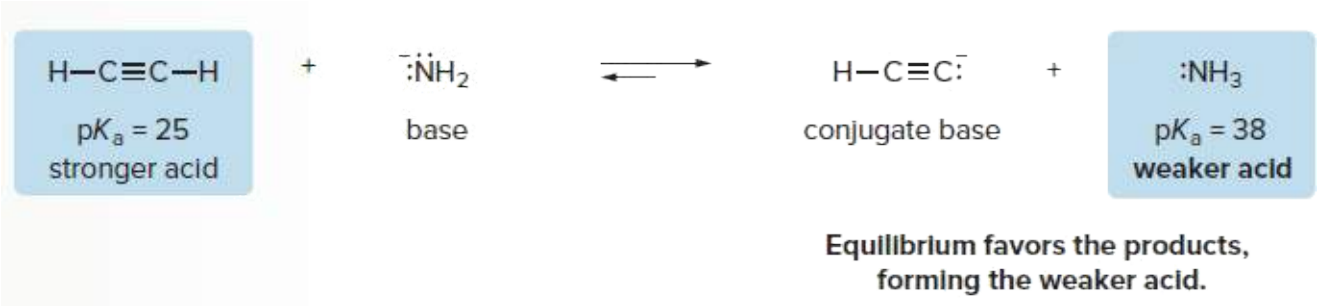
Step [1] Identify the acid and base in the starting materials.

- **$^-NH_2$ is the base because it bears a net negative charge, so HC≡CH is the acid.**

Step [2] Draw the products of proton transfer and identify the conjugate acid and base in the products.



Step [3] Compare the pK_a values of the acid and the conjugate acid. Equilibrium favors formation of the *weaker* acid with the *higher* pK_a.

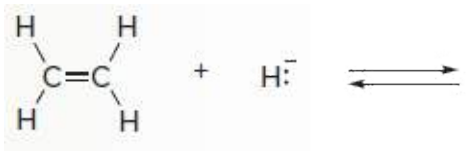


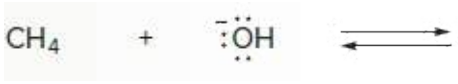
- **Because the pK_a of the starting acid (25) is *lower* than the pK_a of the conjugate acid (38), HC≡CH is a *stronger* acid and equilibrium favors the products.**

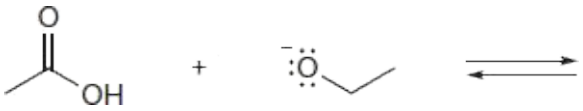
Use unequal equilibrium arrows (⇌ or ⇋) for a reversible reaction in which products or reactants are favored at equilibrium.

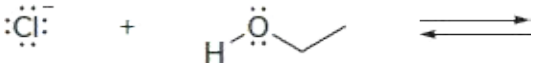
Problem 2.12

Draw the products of each reaction and determine the direction of equilibrium.

a. 

b. 

c. 

d. 

More Practice:

Try Problems 2.49, 2.50.

How can we know if a particular base is strong enough to deprotonate a given acid, so that the equilibrium lies to the right? The pK_a table readily gives us this information, as shown in Sample Problem 2.5.

Sample Problem 2.5 Determining if a Base Is Strong Enough to Deprotonate an Acid

Which of the following bases is strong enough to deprotonate *N*,*N*-dimethylacetamide [$CH_3CON(CH_3)_2$, pK_a = 30], so that equilibrium favors the products: (a) $NaNH_2$; (b) NaOH?

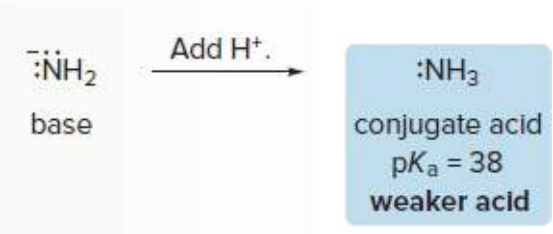
Solution

- **Draw the structure of the conjugate acid of each base, and determine its pK_a from Table 2.1 or Appendix C. Equilibrium favors the side with the weaker acid that has the higher pK_a.**
- **Compare the pK_a values of the starting acid and the conjugate acid. If the conjugate acid has a *higher* pK_a than the starting acid, the conjugate acid is the *weaker* acid and equilibrium favors the *products.***

The base is strong enough to deprotonate the acid.

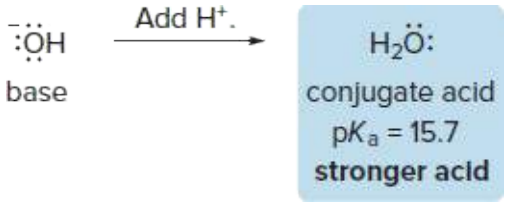
- **If the conjugate acid has a *lower* pK_a than the starting acid, the conjugate acid is the *stronger* acid and equilibrium favors the *starting materials.* The base is *not* strong enough to deprotonate the acid.**

a. Na^+ is a counterion and NH_2 is the base in $NaNH_2$.



The conjugate acid (NH_3) of the base is a *weaker* acid than $CH_3CON(CH_3)_2$ (pK_a = 30), so the base *is* strong enough to deprotonate the acid, and equilibrium favors the products.

b. Na^+ is a counterion and OH is the base in NaOH.



The conjugate acid (H_2O) of the base is a *stronger* acid than $CH_3CON(CH_3)_2$ (pK_a = 30), so the base is *not* strong enough to deprotonate the acid, and equilibrium favors the starting materials.

Problem 2.13

Using the data in Appendix C, determine which of the following bases is strong enough to deprotonate acetonitrile (CH_3CN), so that equilibrium favors the products: (a) NaH; (b) Na_2CO_3; (c) NaOH; (d) $NaNH_2$; (e) $NaHCO_3$.

More Practice:

Try Problems 2.47, 2.48.

Because Table 2.1 is arranged from low to high pK_a, an acid can be deprotonated by the conjugate base of any acid below it in the table.

Sample Problem 2.5 illustrates a fundamental principle in acid–base reactions.

- **An acid can be deprotonated by the conjugate base of any acid having a *higher* pK_a.**

2.5 Factors That Determine Acid Strength

The wide range of pK_a values in Table 2.1 illustrates that a tremendous difference in acidity exists among compounds. HCl (pK_a < 0) is an extremely strong acid, water (pK_a = 15.7) is moderate in acidity, and CH_4 (pK_a = 50) is an extremely weak acid. How are these differences explained? One general rule governs acid strength.

- **Anything that stabilizes a conjugate base $A:^-$ makes the starting acid HA more acidic.**

Four factors affect the acidity of HA:

[1] Element effects

[2] Inductive effects

[3] Resonance effects

[4] Hybridization effects

No matter which factor is discussed, follow the same procedure. To compare the acidity of any two acids:

- **Draw the conjugate bases.**
- **Determine which conjugate base is more stable.**
- **The *more stable* the conjugate base, the *more acidic* the acid.**

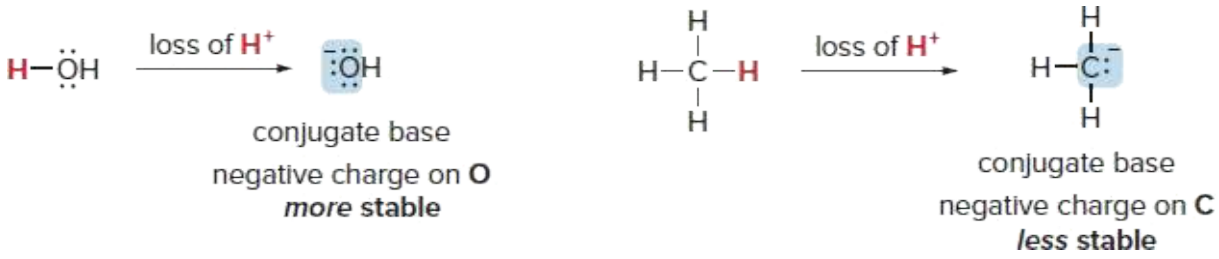
2.5A Element Effects—Trends in the Periodic Table

The most important factor determining the acidity of HA is the location of A in the periodic table.

Comparing Elements in the Same Row of the Periodic Table

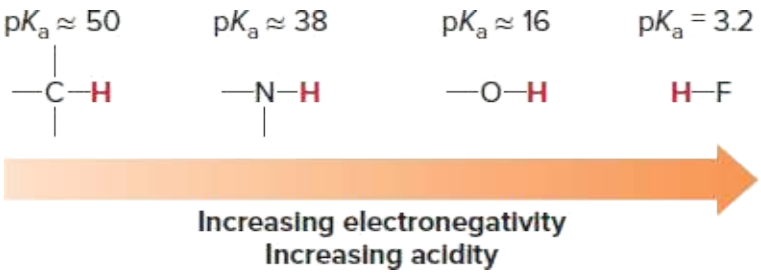
To examine acidity trends across a row of the periodic table, we compare CH_4 and H_2O, two compounds having H atoms bonded to a second-row element. We know from Table 2.1 that H_2O has a much *lower* pK_a and therefore is much *more acidic* than CH_4, but why is this the case?

To answer this question, first draw both conjugate bases and then determine which is more stable. Each conjugate base has a net negative charge, but the negative charge in ^{-}OH is on oxygen and in CH_3^- it is on carbon.



Because the oxygen atom is much more electronegative than carbon, oxygen more readily accepts a negative charge, making ^{-}OH much more stable than CH_3^-. H_2O is a stronger acid than CH_4 because ^{-}OH is a more stable conjugate base than CH_3^-. This is a specific example of a general trend.

- **Across a row of the periodic table, the acidity of HA *increases* as the electronegativity of A increases.**



The enormity of this effect is evident by comparing the pK_a values for these bonds. A C—H bond is approximately 10^{47} times *less acidic* than H—F.

Comparing Elements Down a Column of the Periodic Table

To examine acidity trends down a column of the periodic table, we compare H—F and H—Br. Draw both conjugate bases and then determine which is more stable. In this case, removal of a proton forms F^- and Br^-.

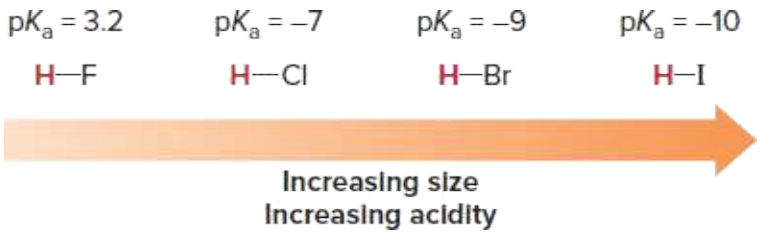
There are two important differences between F^- and Br^-—electronegativity and size. In this case, size is more important than electronegativity. The size of an atom or ion increases down a column of the periodic table, so Br^- is much larger than F^-, and this stabilizes the negative charge.

- **Positive or negative charge is stabilized when it is spread over a larger volume.**

Because Br^- is larger than F^-, Br^- is more stable than F^-, and H—Br is a stronger acid than H—F.

This again is a specific example of a general trend.

- **Down a column of the periodic table, the acidity of HA *increases* as the size of A increases.**



Because of carbon's position in the periodic table (in the second row and to the left of O, N, and the halogens), C—H bonds are usually the *least acidic* bonds in a molecule.

This is *opposite* to what would be expected on the basis of electronegativity differences between F and Br, because F is more electronegative than Br. Size and *not* electronegativity determines acidity down a column. Combining both trends together:

- **The acidity of HA *increases* both left-to-right across a row and down a column of the periodic table.**

Sample Problem 2.6 Using the Identity of X in HX to Determine Relative Acidity

Without reference to a pK_a table, decide which compound in each pair is the stronger acid:

a. H_2O or HF

b. H_2S or H_2O

Solution

a. H_2O and HF both have H atoms bonded to a second-row element. Because the acidity of HA *increases across a row* of the periodic table, the H—F bond is more acidic than the H—O bond. HF is a stronger acid than H_2O.

b. H_2O and H_2S both have H atoms bonded to elements in the same column. Because the acidity of HA *increases down a column* of the periodic table, the H—S bond is more acidic than the H—O bond. H_2S is a stronger acid than H_2O.

Problem 2.14

Without reference to a pK_a table, decide which compound in each pair is the stronger acid.

a. or H_2O

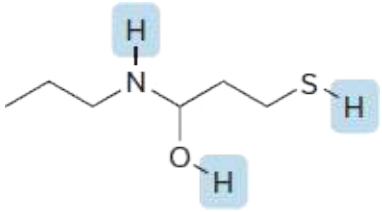
b. or H_2S

More Practice:

Try Problems 2.51a, b; 2.54a; 2.58.

Problem 2.15

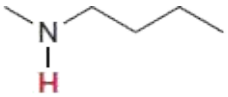
Rank the labeled H atoms in the following compound in order of increasing acidity.



Because the pseudoephedrine (Problem 2.17) in Sudafed can be readily converted to the illegal, addictive drug methamphetamine, products that contain pseudoephedrine are now stocked behind the pharmacy counter so that their sale can be more closely monitored. Sudafed PE is a related product that contains a decongestant less easily converted to methamphetamine. ©*McGraw-Hill Education/Jill Braaten, photographer*

When discussing acidity, the most acidic proton in a compound is the one removed first by a base. Although four factors determine the overall acidity of a particular hydrogen atom, the element effect—the identity of A—is the single most important factor in determining the acidity of the HA bond.

To decide which hydrogen is most acidic, first determine what element each hydrogen is bonded to and then decide its acidity based on periodic trends. For example, $CH_3NHCH_2CH_2CH_2CH_3$ contains only C—H and N—H bonds. Because the acidity of HA increases across a row of the periodic table, the single H on N is the most acidic H in this compound.

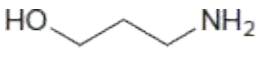


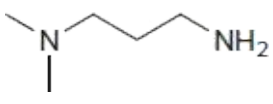
most acidic H shown in red

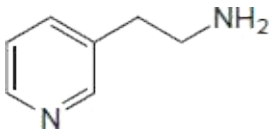
Problem 2.16

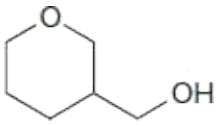
Which hydrogen in each molecule is most acidic?

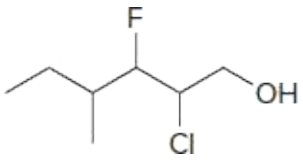
a.

b. 

c. 

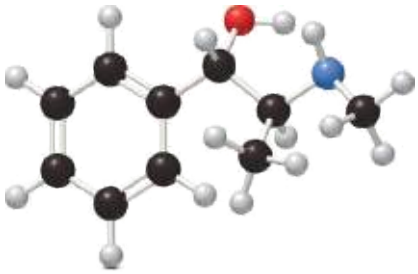
d. 

e. 

f. 

Problem 2.17

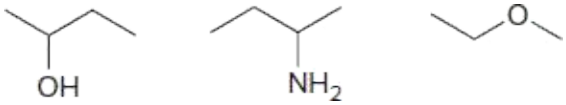
Which hydrogen in pseudoephedrine, the nasal decongestant in the commercial medication Sudafed, is most acidic?

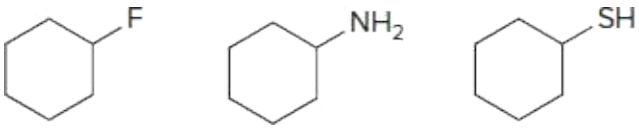


pseudoephedrine

Problem 2.18

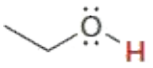
Rank the compounds in each group in order of increasing acidity.

a. 

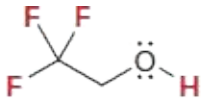
b. 

2.5b Inductive Effects

A second factor affecting the acidity of HA is the presence of atoms more electronegative than carbon. To illustrate this phenomenon, compare ethanol (CH_3CH_2OH) and 2,2,2-trifluoroethanol (CF_3CH_2OH), two compounds containing O—H bonds. The pK_a table in Appendix C indicates that CF_3CH_2OH is a stronger acid than CH_3CH_2OH. We are comparing the acidity of the O—H bond in both compounds, so what causes the difference?



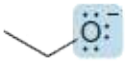
ethanol
$pK_a = 16$



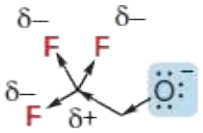
2,2,2-trifluoroethanol
$pK_a = 12.4$

stronger acid

Draw both conjugate bases and then determine which is more stable. Both bases have a negative charge on an electronegative oxygen, but the second anion has three very electronegative fluorine atoms. These fluorine atoms withdraw electron density from the carbon to which they are bonded, making it electron deficient. Furthermore, this electron-deficient carbon pulls electron density through a bonds from the negatively charged oxygen atom, stabilizing the negative charge. This is called an inductive effect.



No additional electronegative atoms stabilize the conjugate base.



CF_3 withdraws electron density, stabilizing the conjugate base.

- **An *inductive effect* is the pull of electron density through σ bonds caused by electronegativity differences of atoms.**

In this case, the electron density is pulled away from the negative charge through a bonds by the very electronegative fluorine atoms, so it is called an electron-*withdrawing* inductive effect. Thus, the three very electronegative fluorine atoms stabilize the negatively charged conjugate base $CF_3CH_2O^-$, making CF_3CH_2OH a stronger acid than CH_3CH_2OH. We have learned two important principles from this discussion:

- **More electronegative atoms stabilize regions of high electron density by an *electron-withdrawing* inductive effect.**
- **The acidity of HA *increases* with the presence of electron-withdrawing groups in A.**

Inductive effects result because an electronegative atom stabilizes the negative charge of the conjugate base. The *more electronegative* the atom and the *closer* it is to the site of the negative charge, the greater the effect. This effect is discussed in greater detail in Chapter 19.

Electrostatic potential plots in Figure 2.3 compare the electron density around the

oxygen atoms in $CH_3CH_2O^-$ and $CF_3CH_2O^-$. The darker red region around the O atom of $CH_3CH_2O^-$ indicates a higher concentration of electron density compared to the O atom of $CF_3CH_2O^-$.

$CH_3CH_2O^-$
The dark red of the O atom indicates a region of high electron density.

$CF_3CH_2O^-$
The O atom is yellow, indicating it is less electron rich.

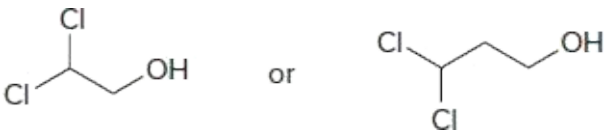
Figure 2.3 **Electrostatic potential plots of $CH_3CH_2O^-$ and $CF_3CH_2O^-$**

Problem 2.19

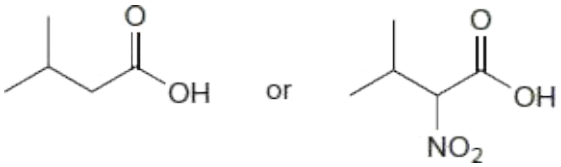
Which compound in each pair is the stronger acid?

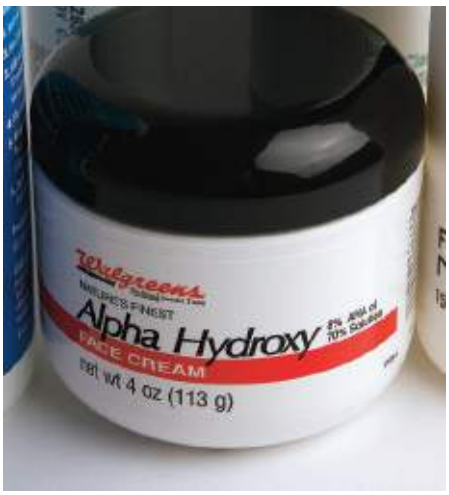
a.

b.



c.





α-Hydroxy acids (Problem 2.20) are used in skin care products that purportedly smooth fine lines and improve skin texture by

reacting with the outer layer of skin cells, causing them to loosen and flake off. ***©McGraw-Hill Education/Jill Braaten, photographer***

Resonance structures are two Lewis structures having the same placement of atoms but a different arrangement of electrons.

Problem 2.20

Glycolic acid, $HOCH_2CO_2H$, is the simplest member of a group of compounds called α-hydroxy acids, ingredients in skin care products that have an OH group on the carbon adjacent to a CO_2H group. Would you expect $HOCH_2CO_2H$ to be a stronger or weaker acid than acetic acid, CH_3CO_2H?

Problem 2.21

Explain the apparent paradox: HBr is a stronger acid than HCl, but HOCl is a stronger acid than HOBr.

2.5c Resonance Effects

A third factor that determines acidity is resonance. Recall from Section 1.6 that resonance occurs whenever two or more different Lewis structures can be drawn for the same arrangement of atoms. To illustrate this phenomenon, compare ethanol (CH_3CH_2OH) and acetic acid (CH_3CO_2H), two compounds containing O—H bonds. Based on Table 2.1, CH_3CO_2H is a stronger acid than CH_3CH_2OH.

ethanol
$pK_a = 16$

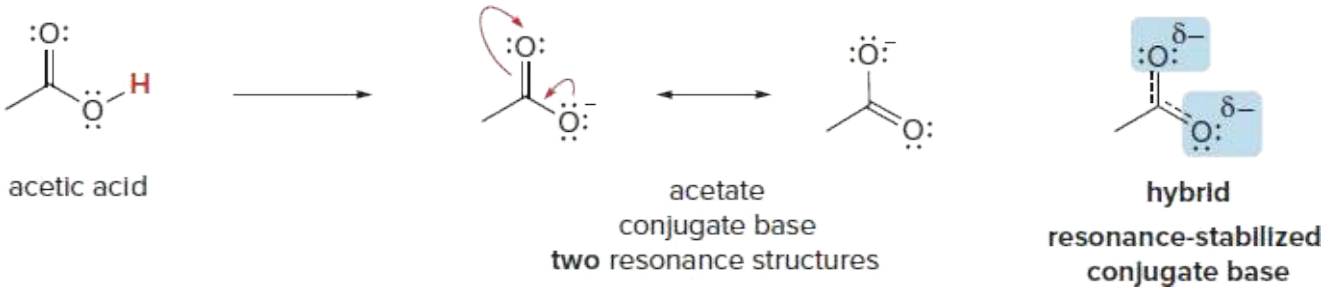
acetic acid
$pK_a = 4.8$
stronger acid

Draw the conjugate bases of these acids to illustrate the importance of resonance. For ethoxide ($CH_3CH_2O^-$), the conjugate base of ethanol, only one Lewis structure can be drawn. The negative charge of this conjugate base is *localized* on the O atom.

ethanol
acid

ethoxide
conjugate base
only **one** Lewis structure

With acetate ($CH_3CO_2^-$), however, two resonance structures can be drawn.



These two resonance structures differ in the position of a π bond and a lone pair. Although each resonance structure of acetate implies that the negative charge is localized on an O atom, in actuality, charge is *delocalized* over both O atoms. Delocalization of electron density stabilizes acetate, making it a weaker base.

Resonance delocalization often produces a larger effect on pK_a than the inductive effects discussed in Section 2.5B. Resonance makes CH_3CO_2H (pK_a = 4.8) a much stronger acid than CH_3CH_2OH (pK_a = 16), whereas the inductive effects due to three electronegative F atoms make CF_3CH_2OH (pK_a = 12.4) a somewhat stronger acid than CH_3CH_2OH.

Remember that neither resonance form adequately represents acetate. The true structure is a hybrid of both structures. In the hybrid, the electron pairs drawn in different locations in individual resonance structures are *delocalized*. With acetate, a dashed line is used to show that each C—O bond has partial double bond character. The symbol δ– (partial negative) indicates that the charge is delocalized on both O atoms in the hybrid.

Thus, resonance delocalization makes $CH_3CO_2^-$ more stable than $CH_3CH2_O^-$, so CH_3CO_2H is a stronger acid than CH_3CH_2OH. This is another example of a general rule.

- **The acidity of HA *increases* when the conjugate base $A:^-$ is resonance stabilized.**

Electrostatic potential plots of $CH_3CH_2O^-$ and $CH_3CO_2^-$ in Figure 2.4 indicate that the negative charge is concentrated on a single O in $CH_3CH_2O^-$, but delocalized over the O atoms in $CH_3CO_2^-$.

$CH_3CH_2O^-$
The negative charge is concentrated on the single oxygen atom, making this anion *less stable*.

$CH_3CO_2^-$
The negative charge is delocalized over both oxygen atoms, making this anion *more stable*.

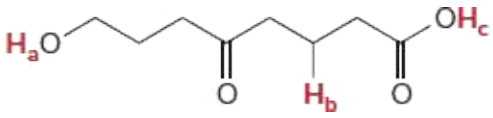
Figure 2.4 **Electrostatic potential plots of $CH_3CH_2O^-$ and $CH_3CO_2^-$**

Problem 2.22

The C—H bond in acetone, $(CH_3)_2C{=}O$, has a pK_a of 19.2. Draw two resonance structures for its conjugate base. Then, explain why acetone is much more acidic than propane, $CH_3CH_2CH_3$ (pK_a = 50).

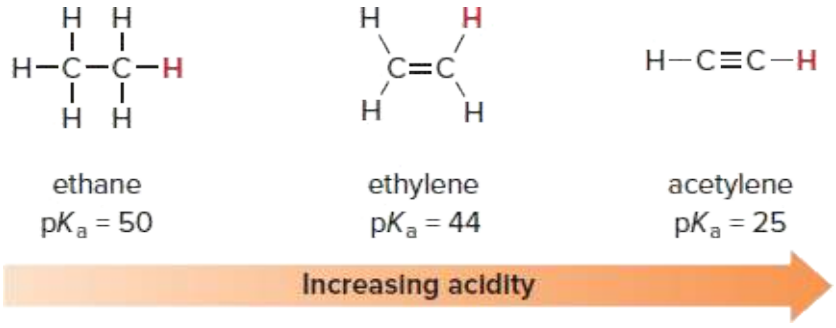
Problem 2.23

Rank the labeled protons in the following molecule in order of increasing pK_a.

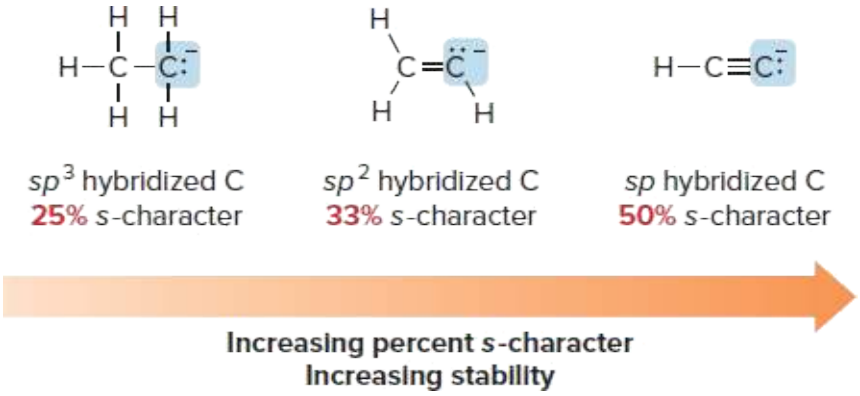


2.5D Hybridization Effects

The final factor affecting the acidity of HA is the hybridization of A. To illustrate this phenomenon, compare ethane (CH_3CH_3), ethylene ($CH_2{=}CH_2$), and acetylene (HC=CH). Appendix C indicates that there is a considerable difference in the pK_a values of these compounds.



The conjugate bases formed by removing a proton from ethane, ethylene, and acetylene are carbanions—species with a negative charge on carbon.



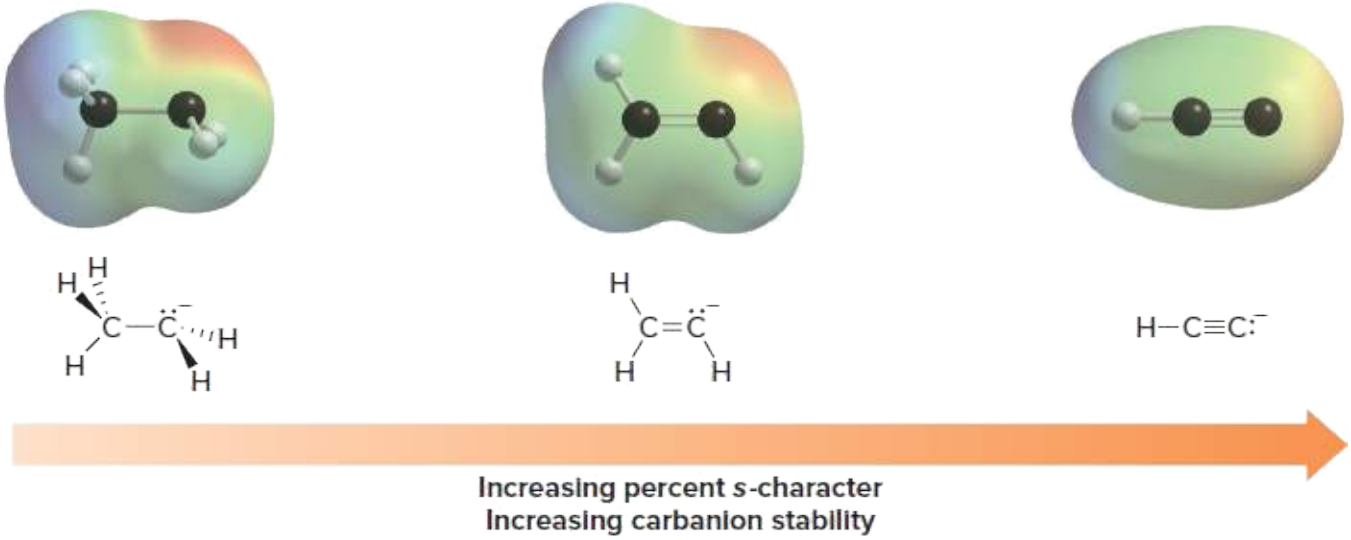
The hybridization of the carbon bearing the negative charge is different in each anion, so the lone pair of electrons occupies an orbital with a different percent *s*-character in each case. A higher percent *s*-character means a hybrid orbital has a larger fraction of the lower-energy *s* orbital.

- **The *higher* the percent *s*-character of the hybrid orbital, the more stable the conjugate base.**

Thus, acidity increases from CH_3CH_3 to $CH_2{=}CH_2$ to HC≡CH as the negative charge of the conjugate base is stabilized by increasing percent *s*-character. Once again this is a specific example of a general trend.

- **The acidity of HA *increases* as the percent *s*-character of $A:^-$ increases.**

Electrostatic potential plots of these carbanions appear in Figure 2.5.



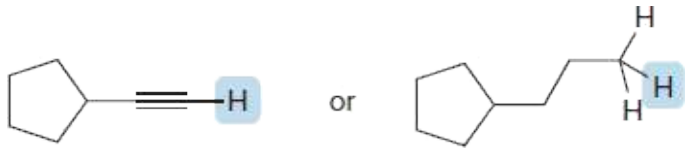
- As the lone pair of electrons is pulled closer to the nucleus, the negatively charged carbon appears less intensely red.

Figure 2.5 **Electrostatic potential plots of three carbanions**

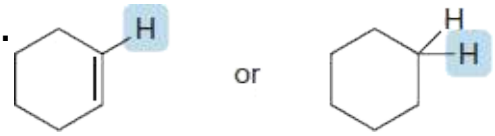
Problem 2.24

For each pair of compounds: [1] Which indicated H is more acidic? [2] Draw the conjugate base of each acid. [3] Which conjugate base is stronger?

a.



b.



2.5E Summary of Factors Determining Acid Strength

The ability to recognize the most acidic site in a molecule will be important throughout the study of organic chemistry. All the factors that determine acidity are therefore summarized in Figure 2.6. The following two-step procedure shows how these four factors can be used to determine the relative acidity of protons.

Figure 2.6 **Summary of the factors that determine acidity**

Factor	Example		
1. Element effects: The acidity of HA increases both left-to-right across a row and down a column of the periodic table.	CH_4	and	H_2O more acidic
2. Inductive effects: The acidity of HA increases with the presence of electron-withdrawing groups in A.	$CH_3CH_2O—H$	and	$CF_3CH_2O—H$ more acidic
3. Resonance effects: The acidity of HA increases when the conjugate base $A:^-$ is resonance stabilized.	$CH_3CH_2O—H$	and	$CH_3CO_2—H$ more acidic
4. Hybridization effects: The acidity of HA increases as the percent *s*-character of $A:^-$ increases.	$CH_2=CH_2$	and	$H—C\equiv C—H$ more acidic

How To Determine the Relative Acidity of Protons

Step [1] **Identify the atoms bonded to hydrogen, and use periodic trends to assign relative acidity.**

- **The most common HA bonds in organic compounds are C—H, N—H, and O—H. Because acidity increases left-to-right across a row, the relative acidity of these bonds is C—H < N—H < O—H. Therefore, H atoms bonded to C atoms are usually *less acidic* than H atoms bonded to any heteroatom.**

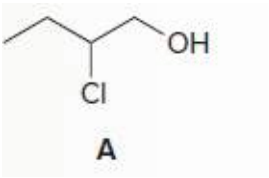
Step [2] **If the two H atoms in question are bonded to the same element, draw the conjugate bases and look for other points of difference. Ask three questions:**

- **Do electron-withdrawing groups stabilize the conjugate base?**
- **Is the conjugate base resonance stabilized?**
- **How is the conjugate base hybridized?**

Sample Problem 2.7 shows how to apply this procedure to actual compounds.

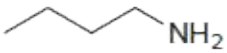
Sample Problem 2.7 Determining the Relative Acidity of Compounds

Rank the following compounds in order of increasing acidity of their most acidic hydrogen atom.



A

B

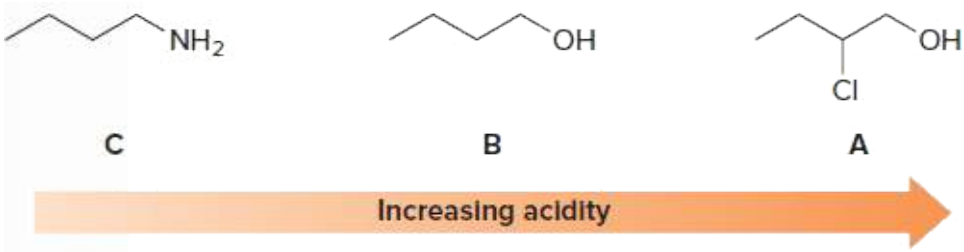


C

Solution

[1] **Compounds A, B, and C contain C—H, N—H, and O—H bonds. Because acidity increases left-to-right across a row of the periodic table, the O—H bonds are most acidic. Compound C is thus the least acidic because it has *no* O—H bonds.**

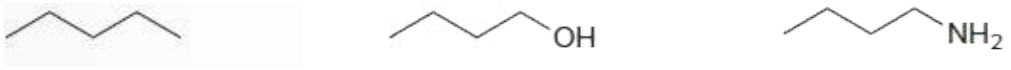
[2] **The only difference between compounds A and B is the presence of an electronegative Cl in A. The Cl atom stabilizes the conjugate base of A, making it more acidic than B. Thus,**



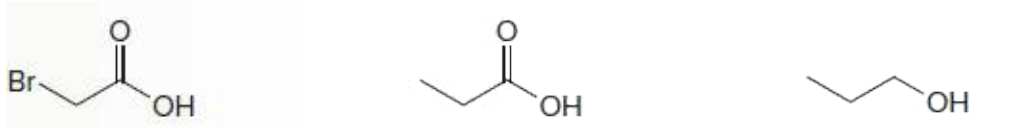
Problem 2.25

Rank the compounds in each group in order of increasing acidity.

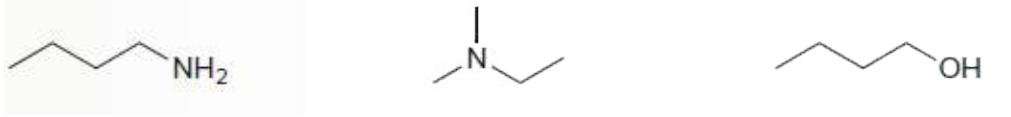
a.



b.



c.



More Practice:

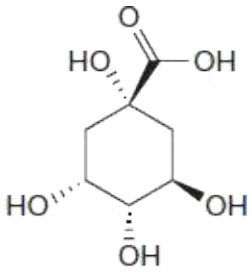
Try Problems 2.51c, d; 2.53; 2.54c, d.

Problem 2.26

Which anion (A or B) is the stronger base?

Sample Problem 2.8 Determining the Most Acidic Proton in a More Complex Molecule

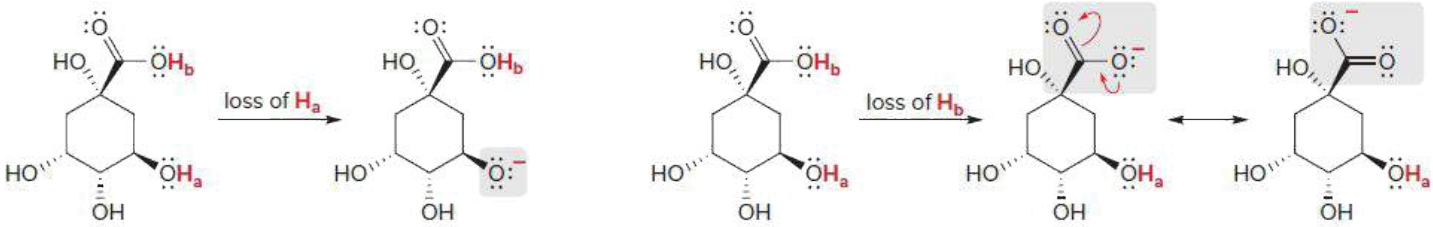
Which proton in quinic acid, the chapter-opening compound present in a brewed cup of coffee, is most acidic?



quinic acid

Solution

Because acidity increases left-to-right across a row of the periodic table, concentrate on the O—H bonds, which are more acidic than the C—H bonds. By drawing the conjugate bases formed by removal of the O—H protons, we can see that the OH groups bonded to the six-membered ring are different from the OH group bonded to the C=O.



conjugate base
only **one** Lewis structure

two resonance structures
resonance-stabilized conjugate base

Removal of H_a (or any of the protons on the OH groups bonded to the six-membered ring) forms a conjugate base for which only *one* Lewis structure can be drawn, so the negative charge is *localized* on one O atom. Removal of Hb forms a conjugate base for which *two* resonance structures can be drawn, so the negative charge is *delocalized* on two O atoms. Delocalization makes this conjugate base more stable, so Hb is the most acidic proton in quinic acid.

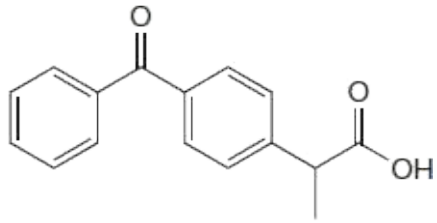
Problem 2.27

Which proton in each of the following drugs is most acidic? THC is the active component in marijuana, and ketoprofen is an anti-inflammatory agent.

a.

THC
tetrahydrocannabinol

b.



ketoprofen

More Practice:

Try Problems 2.36a, 2.37a, 2.43, 2.44, 2.61a, 2.64, 2.65.

2.6 Common Acids and Bases

Many strong or moderately strong acids and bases are used as reagents in organic reactions.

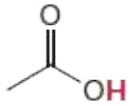
Sulfuric acid is the most widely produced industrial chemical. It is also formed when sulfur oxides, emitted into the atmosphere by burning fossil fuels high in sulfur content, dissolve in water. This makes rainwater acidic, forming acid rain, which has destroyed acres of forests worldwide.

©Mary Terriberry/Shutterstock

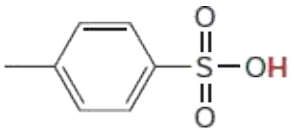
2.6A Common Acids

Several organic reactions are carried out in the presence of strong inorganic acids, most commonly HCl and H_2SO_4. These strong acids, with pK_a values ≤ 0, should be familiar from previous chemistry courses.

Two organic acids are also commonly used, namely acetic acid and *p*-toluenesulfonic acid (usually abbreviated as TsOH). Although acetic acid has a higher pK_a than the inorganic acids, making it a weaker acid, it is more acidic than most organic compounds. *p*-Toluenesulfonic acid is similar in acidity to the strong inorganic acids. Because it is a solid, small quantities can be easily weighed on a balance and then added to a reaction mixture.



acetic acid
$pK_a = 4.8$



p-toluenesulfonic acid
$pK_a = -7$

2.6B Common Bases

Three common kinds of strong bases include:

[1] Negatively charged oxygen bases: ^-OH (hydroxide) and its organic derivatives

[2] Negatively charged nitrogen bases: $^-NH_2$ (amide) and its organic derivatives

[3] Hydride (H^-)

Figure 2.7 gives examples of these strong bases. Each negatively charged base is used as a salt with a spectator ion (usually Li^+, Na^+, or K^+) that serves to balance charge.

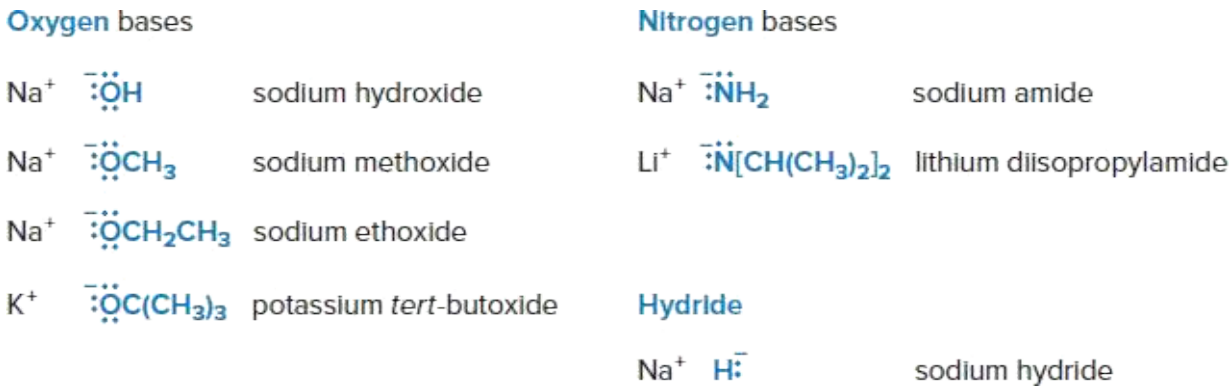
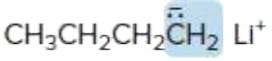


Figure 2.7 **Some common negatively charged bases**

- **Strong bases have weak conjugate acids with high pK_a values, usually > 12.**

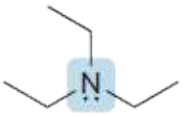
Strong bases have a net negative charge, but not all negatively charged species are strong bases. For example, none of the halides, F^-, Cl^-, Br^-, or I^-, is a strong base. These anions have very strong conjugate acids and have little affinity for donating their electron pairs to a proton.

Carbanions, negatively charged carbon atoms discussed in Section 2.5D, are especially strong bases. Perhaps the most common example is butyllithium. Butyllithium and related compounds are discussed in greater detail in Chapter 17.

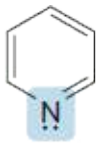


butyllithium

Two other weaker organic bases are triethylamine and pyridine. These compounds have a lone pair on nitrogen, making them basic, but they are considerably weaker than the amide bases because they are neutral, not negatively charged.



triethylamine



pyridine

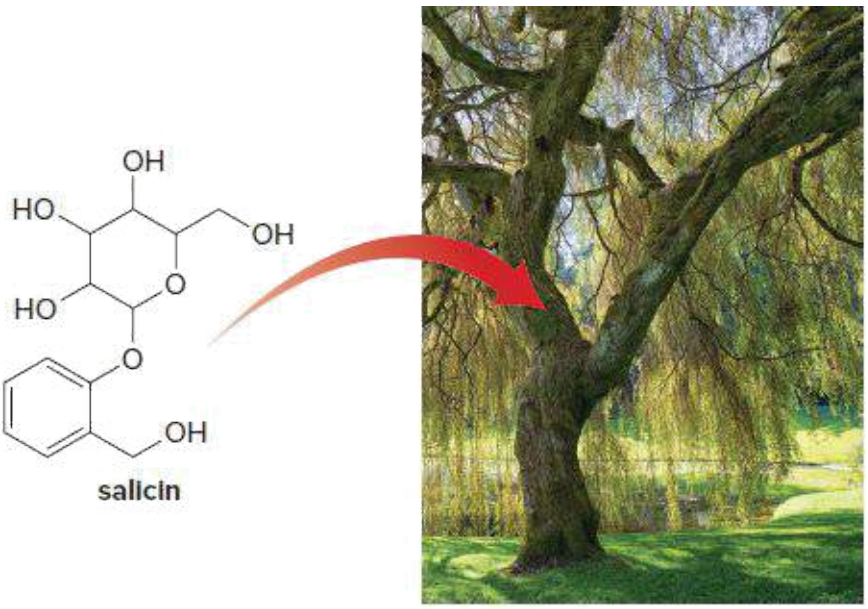
Problem 2.28

Draw the products formed when propan-2-ol [$(CH_3)_2CHOH$], the main ingredient in rubbing alcohol, is treated with each acid or base: (a) NaH; (b) H_2SO_4; (c) $Li^+ {}^-N[CH(CH_3)_2]_2$; (d) CH_3CO_2H.

2.7 Aspirin

Aspirin is one of the most widely used over-the-counter drugs. Whether you purchase Anacin, Bufferin, Bayer, or a generic, the active ingredient is the same—acetylsalicylic acid.

Aspirin is the most well known member of a group of compounds called salicylates. Although aspirin was first used in medicine for its analgesic (pain-relieving), antipyretic (fever-reducing), and anti-inflammatory properties, today it is commonly used as an antiplatelet agent in the treatment and prevention of heart attacks and strokes. Aspirin is a synthetic compound; it does not occur in nature, although some related salicylates are found in willow bark and meadowsweet blossoms (Figure 2.8).



willow tree

©july7th/iStock/Getty Images

- The modern history of aspirin dates back to 1763 when Reverend Edmund Stone reported on the analgesic effect of chewing on the bark of the willow tree. Willow bark is now known to contain *salicin,* which is structurally related to aspirin.

Figure 2.8 **Salicin, an analgesic in willow bark**

Like many drugs, aspirin undergoes a proton transfer reaction. Its most acidic proton is the H bonded to O, and in the presence of base, this H is readily removed.

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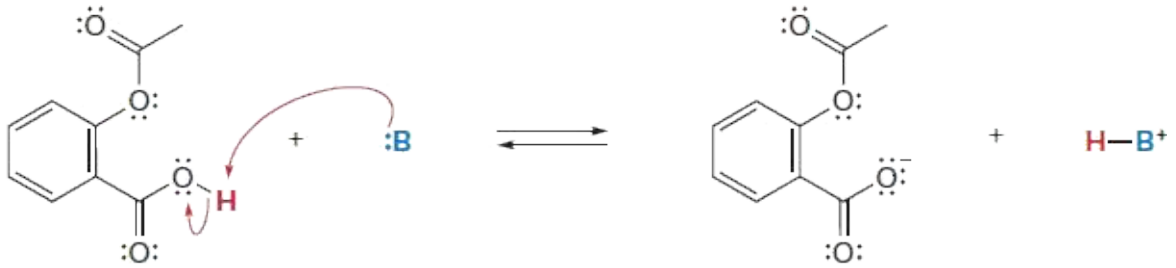


aspirin
acetylsalicylic acid
neutral form

This form exists in the **stomach.**

conjugate base
ionic form

This form exists in the **intestines.**

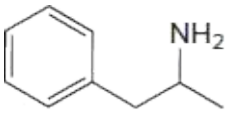
Why is this acid–base reaction important? After ingestion, aspirin first travels into the stomach and then the intestines. In the acidic environment of the stomach, aspirin remains in its neutral form, but in the basic environment of the small intestine, aspirin is deprotonated to form its conjugate base, an ion. Likewise, in the slightly basic environment of the blood, aspirin exists primarily as its ionic conjugate base.

We will learn more about solubility and the cell membrane in

Section 3.7.

Whether aspirin is a neutral acid or an ionic conjugate base affects its transport throughout the body and its ability to pass through a cell membrane. In its ionic form, aspirin is readily soluble in the aqueous environment of the blood, so it is transported in the bloodstream to tissues. Once aspirin has reached its target location, however, its conjugate base must be re-protonated to form the neutral acid that can pass through the nonpolar interior of a cell membrane where it inhibits prostaglandin synthesis, as we will learn in Chapter 19. Thus, in the body, aspirin undergoes acid–base reactions and these reactions are crucial in determining its properties and action.

Problem 2.29



amphetamine

Compounds like amphetamine that contain nitrogen atoms are protonated by the HCl in the gastric juices of the stomach, and the resulting salt is then deprotonated in the basic environment of the intestines to regenerate the neutral form. Write proton transfer reactions for both of these processes. In which form will amphetamine pass through a cell membrane?

2.8 Lewis Acids and Bases

The Lewis definition of acids and bases is more general than the Brønsted–Lowry definition.

All Brønsted–Lowry bases are Lewis bases.

- **A Lewis acid is an *electron pair acceptor.***
- **A Lewis base is an *electron pair donor.***

Lewis bases are structurally the same as Brønsted–Lowry bases. Both have an available electron pair—a lone pair or an electron pair in a π bond. A Brønsted–Lowry base always donates this electron pair to a proton, but a Lewis base donates this electron pair to anything that is electron deficient. Simple Lewis bases are shown in Figure 2.9.

A Lewis acid must be able to accept an electron pair, but there are many ways for this to occur. All Brønsted–Lowry acids are also Lewis acids, but the reverse is not

necessarily true. Any species that is electron deficient and capable of accepting an electron pair is also a Lewis acid, as shown in Figure 2.9.

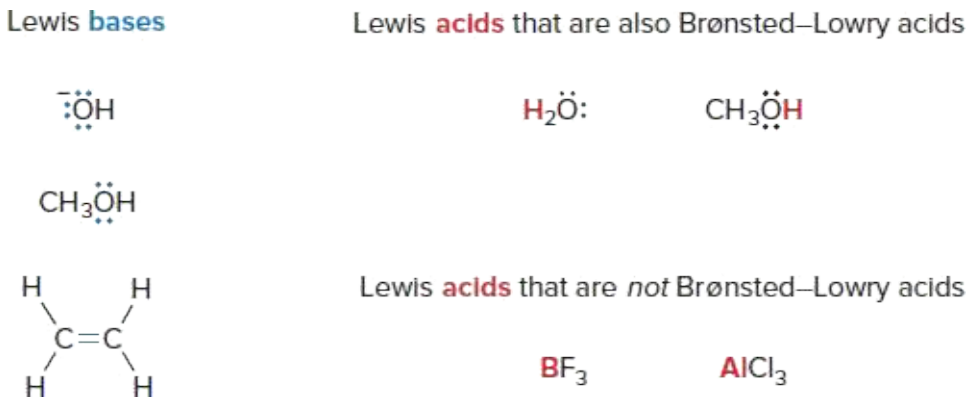
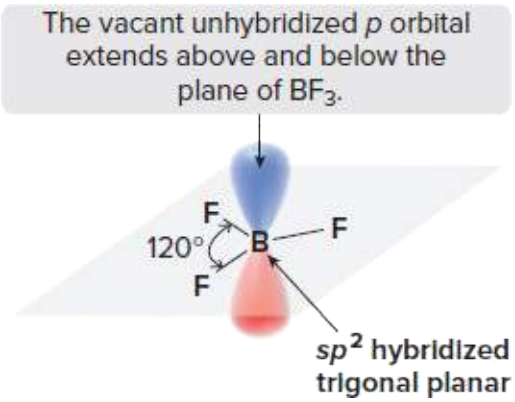


Figure 2.9 **Simple Lewis acids and bases**



Common examples of Lewis acids (which are not Brønsted–Lowry acids) include BF_3 and $AlCl_3$. These compounds contain elements in group 3A of the periodic table that can accept an electron pair because they do not have filled valence shells of electrons. For example, BF_3 contains an sp^2 hybridized, trigonal planar B atom with a vacant unhybridized *p* orbital that can accept two electrons.

Problem 2.30

Which species are Lewis bases?

a. NH_3

b. $CH_3CH_2CH_3$

c. H^-

d. H—C≡C—H

Problem 2.31

Which species are Lewis acids?

a. BBr_3

b. CH_3CH_2OH

c. $(CH_3)_3C^+$

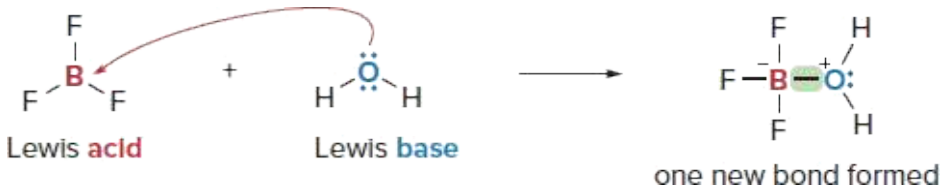
d. Br^-

Any reaction in which one species donates an electron pair to another species is a Lewis acid–base reaction.

In a Lewis acid–base reaction, a Lewis base donates an electron pair to a Lewis acid. Most reactions in organic chemistry involving movement of electron pairs can be classified as Lewis acid–base reactions. Lewis acid–base reactions illustrate a general pattern of reactivity.

- **Electron-rich species react with electron-poor species.**

In the simplest Lewis acid–base reaction, one bond is formed and no bonds are broken. This is illustrated with the reaction of BF_3 with H_2O. BF_3 has only six electrons around B, so it is the electron-deficient Lewis acid. H_2O has two lone pairs on O, so it is the electron-rich Lewis base.



H_2O donates an electron pair to BF_3 to form one new bond. The electron pair in the new B—O bond comes from the oxygen atom, and a single product, a Lewis acid–base complex, is formed. Both B and O bear formal charges in the product, but the overall product is neutral.

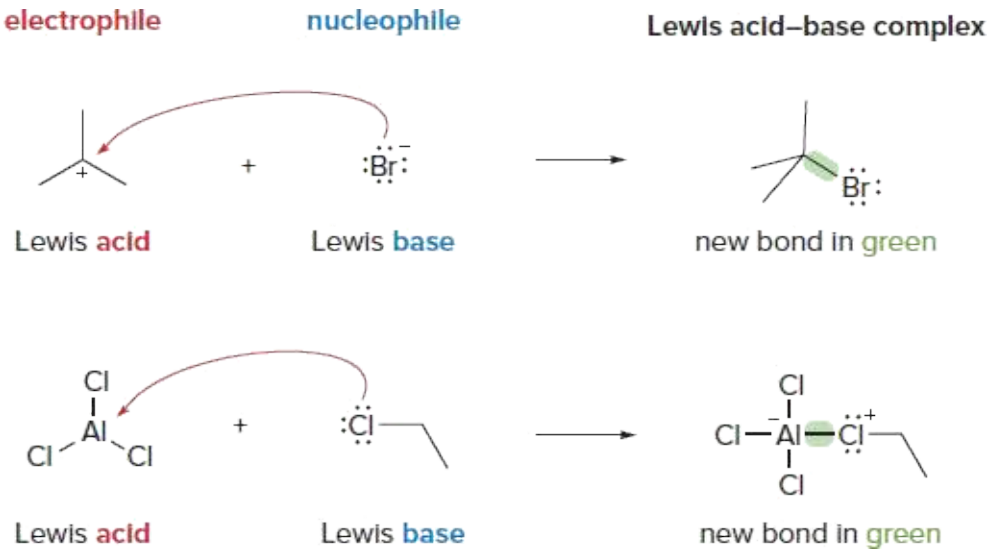
Nucleophile = nucleus loving.

Electrophile = electron loving.

- **A Lewis acid is called an *electrophile*.**
- **When a Lewis base reacts with an electrophile other than a proton, the Lewis base is called a *nucleophile*.**

In this Lewis acid–base reaction, BF3 is the electrophile and H2O is the nucleophile.

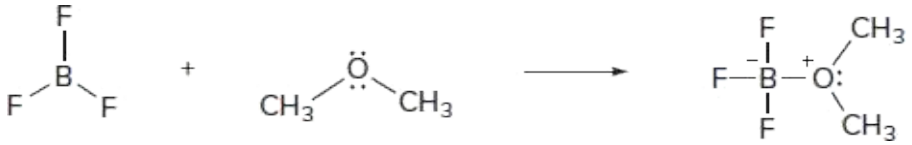
Two other examples are drawn. In each reaction the electron pair is not removed from the Lewis base; instead, the electron pair is donated to an atom of the Lewis acid, and one new covalent bond is formed.



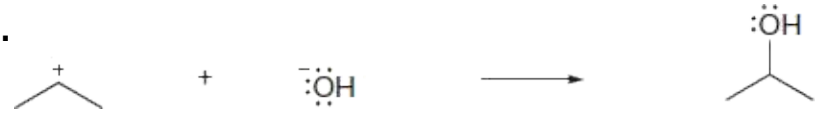
Problem 2.32

For each reaction, label the Lewis acid and base. Use curved arrow notation to show the movement of electron pairs.

a.



b.



Problem 2.33

Draw the products of each reaction, and label the nucleophile and electrophile.

a.

b.

Problem 2.34

Draw the product formed when $(CH_3CH_2)_3N$:, a Lewis base, reacts with each Lewis acid: (a) $B(CH_3)_3$; (b) $(CH3)3C^+$; (c) AlCl3.

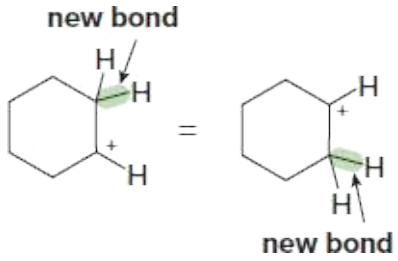
In some Lewis acid–base reactions, one bond is formed and one bond is broken. To draw the products of these reactions, keep the following steps in mind.

[1] Always identify the Lewis acid and base first.

[2] Draw a curved arrow from the electron pair of the base to the electron-deficient atom of the acid.

[3] Count electron pairs and break a bond when needed to keep the correct number of valence electrons.

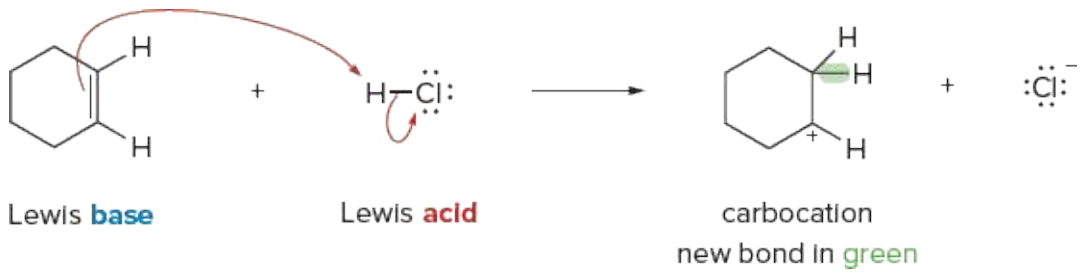
Recall from Section 1.6B that a positively charged carbon atom is called a carbocation.



In the reaction of cyclohexene with HCl, the new bond to H could form at either carbon of the double bond, because the same carbocation results.

For example, draw the Lewis acid–base reaction between cyclohexene and H—Cl. The Brønsted–Lowry acid HCl is also a Lewis acid, and cyclohexene, having a π bond, is the Lewis base.

To draw the product of this reaction, the electron pair in the π bond of the Lewis base forms a new bond to the proton of the Lewis acid, forming a carbocation. The H—Cl bond must break, giving its two electrons to Cl, forming Cl^-. Because two electron pairs are involved, two curved arrows are needed.



The Lewis acid–base reaction of cyclohexene with HCl is a specific example of a

fundamental reaction of compounds containing C—C double bonds, as discussed in Chapter 10.

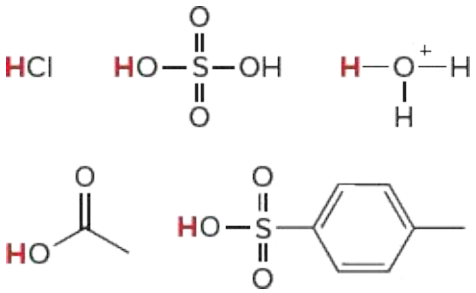
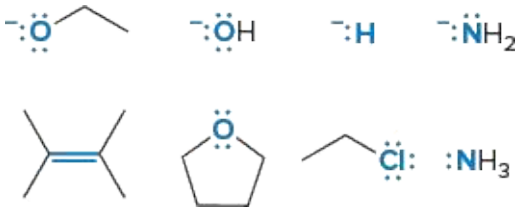
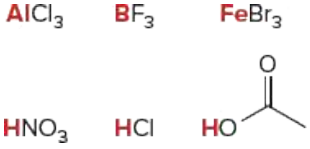
Problem 2.35

Label the Lewis acid and base. Use curved arrow notation to show the movement of electron pairs.

Chapter 2 REVIEW

KEY CONCEPTS

Brønsted–Lowry and Lewis Acids and Bases (2.1, 2.8)

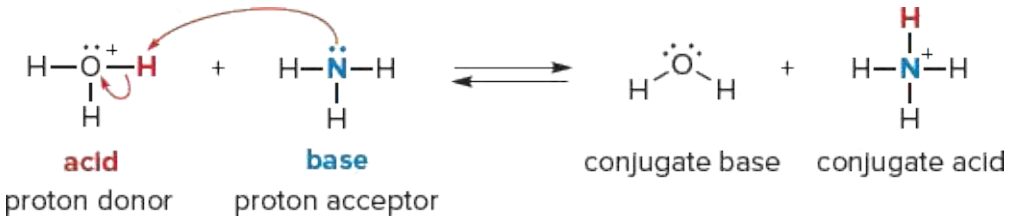
1 Brønsted–Lowry acids	2 Brønsted–Lowry bases and Lewis bases	3 Lewis acids
• A Brønsted–Lowry acid is a proton donor. 	• A Brønsted–Lowry base is a proton acceptor. • A Lewis base is an electron pair donor. 	• A Lewis acid is an electron pair acceptor. 

See Figures 2.1, 2.9. Try Problems 2.67, 2.68.

Acid–Base Reactions

1 Drawing the products of a Brønsted–Lowry acid–base reaction (2.2)

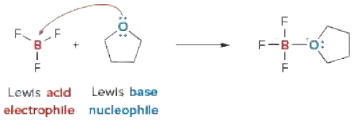
- **A Brønsted–Lowry acid donates a proton to a Brønsted–Lowry base.**



See Sample Problems 2.1, 2.2, Figure 2.2. Try Problems 2.40–2.42, 2.49.

2 Drawing the products of a Lewis acid–base reaction (2.8)

- **A Lewis base donates an electron pair to a Lewis acid.**

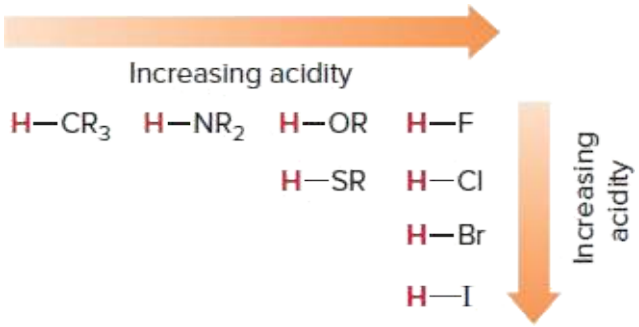


- **Electron-rich species react with electron-poor ones.**
- **Nucleophiles react with electrophiles.**

Try Problems 2.69–2.71.

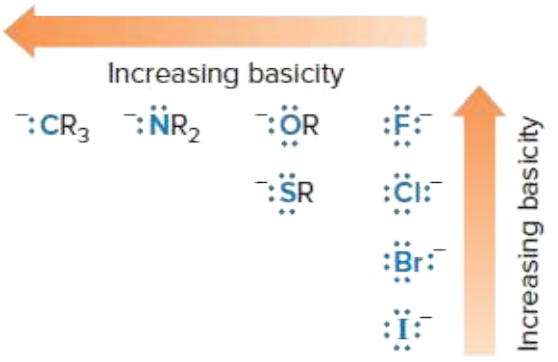
Periodic Trends (2.5A)

1 Trends in acidity



Try Problem 2.51a, b.

2 Trends in basicity

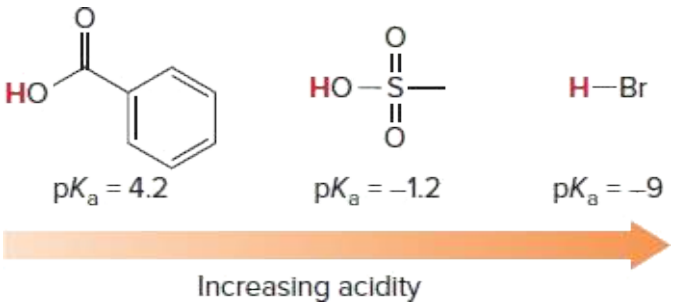


Try Problem 2.54a, b.

Acid and Base Strength and pK_a (2.3)

1 Acidity and pK_a

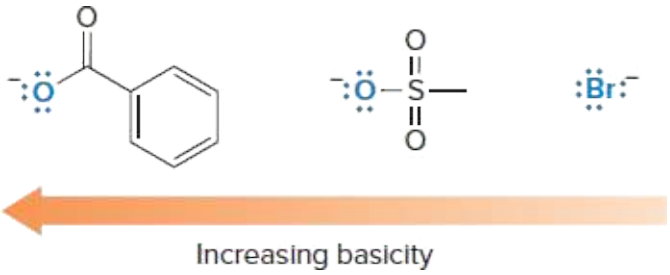
- pK_a = −log K_a
- The lower the pK_a, the stronger the acid.



See Table 2.1, Sample Problem 2.3. Try Problem 2.51a, b.

2 Basicity and pK_a

- As the pK_a of an acid increases, the basicity of its conjugate base increases.
- A strong acid has a weak conjugate base.

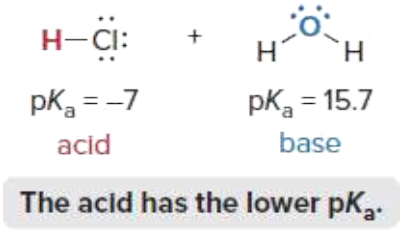


Try Problems 2.54a, b; 2.57.

KEY SKILLS

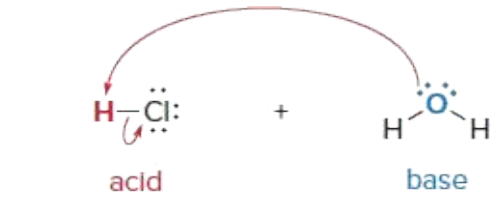
[1] Drawing the products of a Brønsted–Lowry acid–base reaction (2.2)

1 Identify the acid and the base.



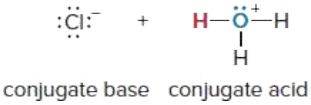
The acid has the lower pK_a.

2 Draw curved arrows to move a proton from the acid to the base.



The acid loses H^+. The base gains H^+.

3 Draw the products of proton transfer.

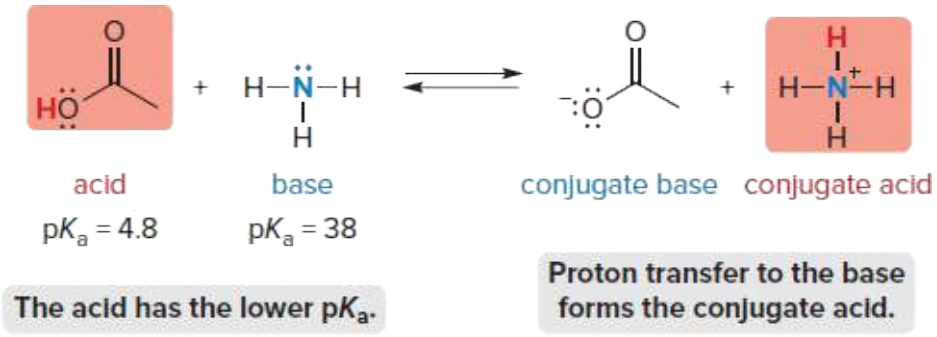
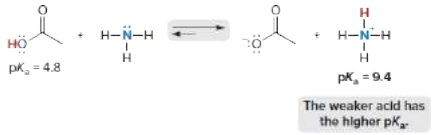


- Loss of H^+ from the acid forms its conjugate base.
- Gain of H^+ by the

		base forms its conjugate acid.

Try Problems 2.41–2.43.

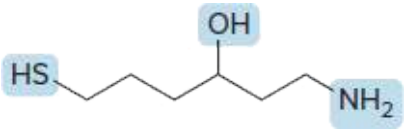
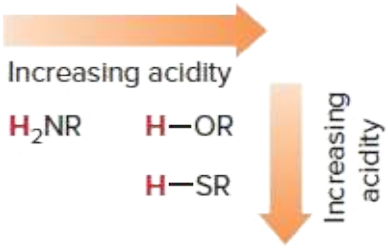
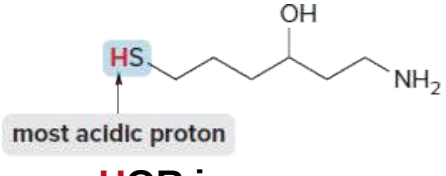
[2] Determining the direction of equilibrium using pK_a (2.4)

1 Identify the acids on each side of the arrows.	**2** Compare the pK_a values of the acids.
	 • Equilibrium favors the side of the weaker acid (higher pK_a), so the products are favored.

See Sample Problems 2.4, 2.5. Try Problem 2.49.

Page 85

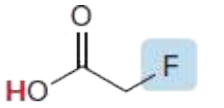
[3] Determining acidity using trends in the periodic table (2.5A)

1 Identify the element attached to each proton in the acid.	**2** Compare the electronegativities and sizes of these elements.	**3** Determine the most acidic proton.
		 • HOR is more acidic than H_2NR

	Across a row of the periodic table, the acidity of HA increases as the electronegativity of A increases. Down a column of the periodic table, the acidity of HA increases as the size of A increases.	because O is more electronegative than N. HSR is more acidic than HOR because S is larger than O.

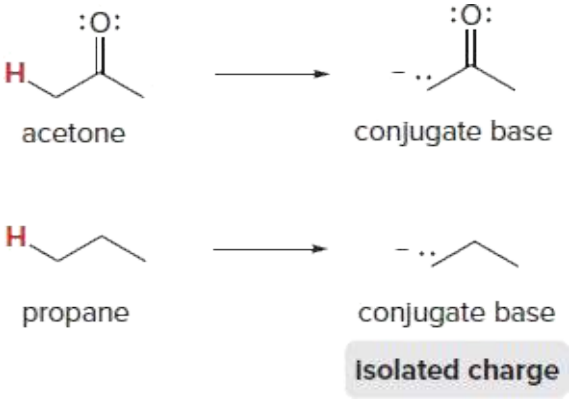
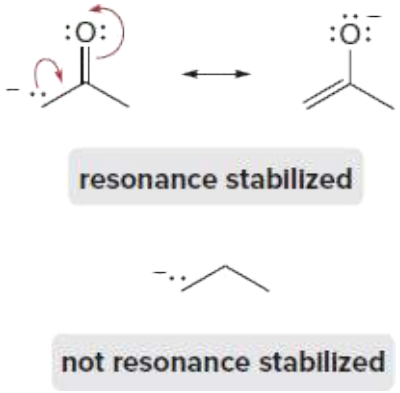
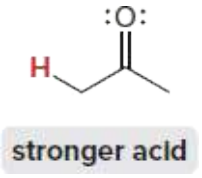
See Sample Problem 2.6. Try Problems 2.51a, b; 2.54a, b.

[4] Determining acidity using inductive effects (2.5B)

1 Identify the electron-withdrawing or donating group(s) in each acid, and compare the effect(s) of these groups.	2 Determine the stronger acid.
 2-fluoroacetic acid 2-chloroacetic acid • The acidity of HA increases as the electronegativity of electron-withdrawing groups in close proximity to HA increases.	 2-fluoroacetic acid stronger acid • Fluorine is more electronegative than chlorine, so it has a greater electron-withdrawing inductive effect.

See Figure 2.3. Try Problems 2.51c, 2.53, 2.55.

[5] Determining acidity using resonance effects (2.5C)

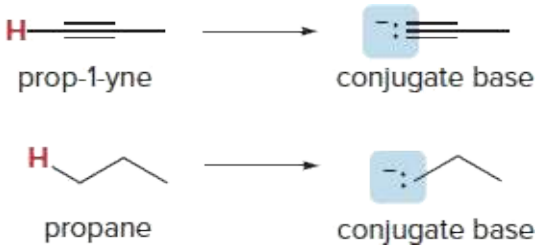
1 Draw the conjugate bases of the acids.	2 Draw all reasonable resonance structures.	3 Determine the stronger acid.
		 • The acidity of HA increases when the conjugate base $A:^-$ is resonance stabilized. • The conjugate base of acetone is resonance stabilized, and the conjugate base of propane is not.

See Figure 2.4. Try Problems 2.54c, 2.57.

[6] Determining acidity using hybridization effects (2.5D)

1 Draw the conjugate bases of the following compounds.	2 Identify the hybridization of the carbanions.	3 Dete the stror

acid.



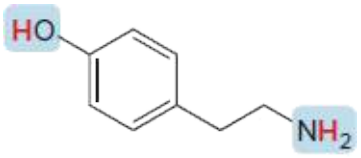
- The higher the percent *s*-character of the hybrid orbital, the more stable the conjugate base.

- The acic HA incr as t perc cha of A incr

See Figure 2.5. Try Problems 2.51d, 2.54d.

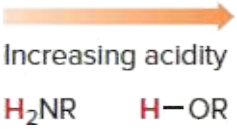
[7] Determining the most acidic proton (2.5E)

1 Identify the atoms bonded to hydrogen, and use periodic trends to assign acidity.

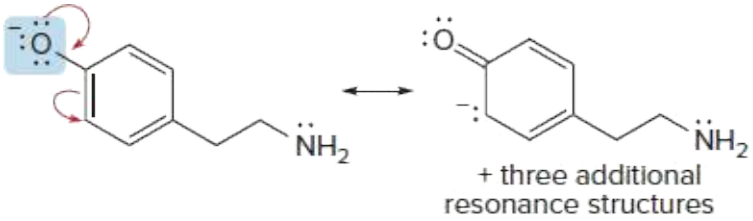


tyramine

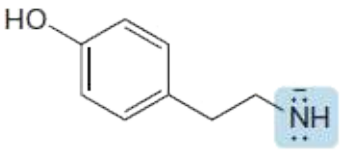
- HOR is more acidic than H_2NR based on electronegativity.



2 Draw conjugate bases and resonance structures.



The oxygen anion is resonance stabilized.



The nitrogen anion is not resonance stabilized.

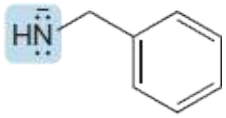
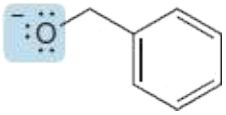
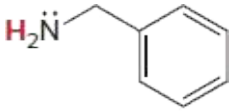
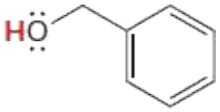
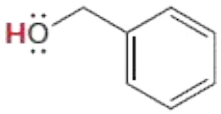
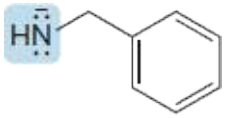
3 D n p

-

See *How To* (p. 76), Figure 2.6, Sample Problems 2.7, 2.8. Try Problems 2.43,

2.44, 2.52, 2.64.

[8] Identifying the most basic electron pair (2.6B)

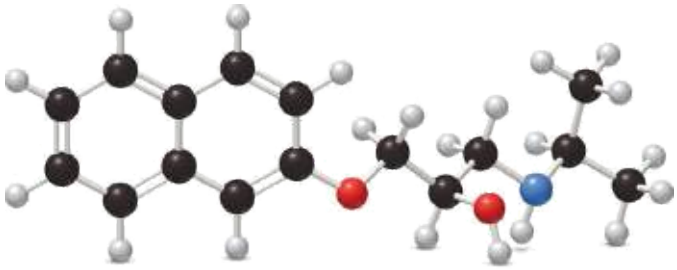
1 Identify the basic electron pairs.	2 Draw the conjugate acids.	3 Identify the stronger acid.	4 Determine the more basic electron pair.
 	 	• HOR is more acidic than H_2NR based on electronegativity.  stronger acid • The stronger acid has the weaker conjugate base.	 stronger base • The stronger base has the weaker conjugate acid.

Try Problems 2.36c, 2.37c, 2.54, 2.61b.

PROBLEMS

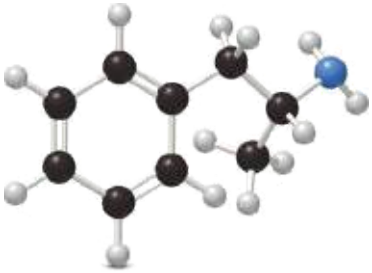
Problems Using Three-Dimensional Models

2.36 Propranolol is an antihypertensive agent—that is, it lowers blood pressure. (a) Which proton in propranolol is most acidic? (b) What products are formed when propranolol is treated with NaH? (c) Which atom is most basic? (d) What products are formed when propranolol is treated with HCl?



propranolol

2.37 **Amphetamine is a powerful stimulant of the central nervous system. (a) Which proton in amphetamine is most acidic? (b) What products are formed when amphetamine is treated with NaH? (c) What products are formed when amphetamine is treated**

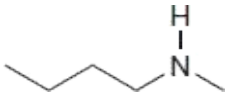


amphetamine

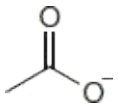
Brønsted–Lowry Acids and Bases

2.38 **What is the conjugate acid of each base?**

a. HCO_3^-

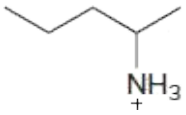
b. 

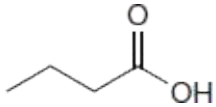
c.

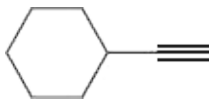
d. 

2.39 **What is the conjugate base of each acid?**

a. HCO_3^-

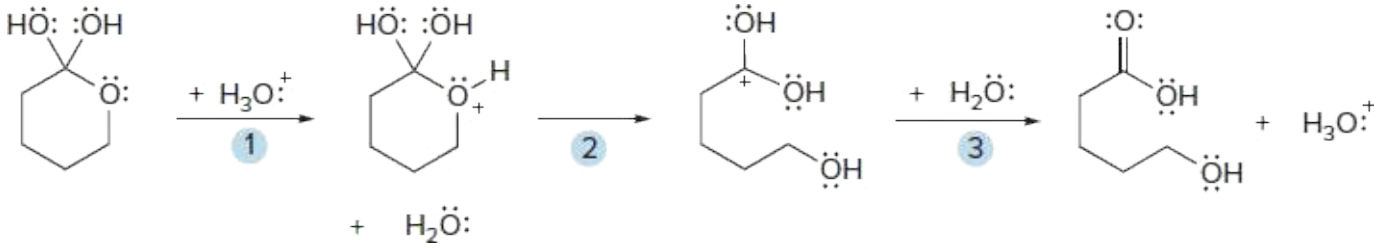
b. 

c. 

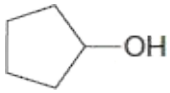
d. 

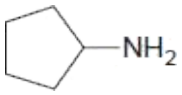
Reactions of Brønsted–Lowry Acids and Bases

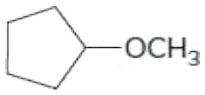
2.40 **As we will see in later chapters, many steps in key reaction sequences involve acid–base reactions. (a) Draw curved arrows to illustrate the flow of electrons in steps [1]–[3]. (b) Identify the base and its conjugate acid in step [1]. (c) Identify the acid and its conjugate base in step [3].**

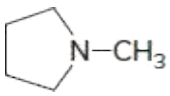


2.41 **Draw the products formed from the acid–base reaction of H_2SO_4 with each compound.**

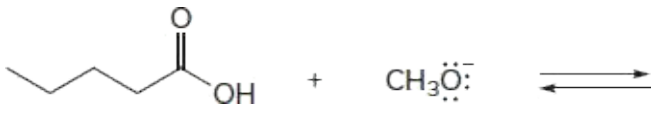
a. 

b. 

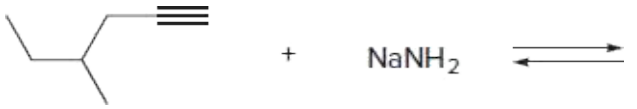
c. 

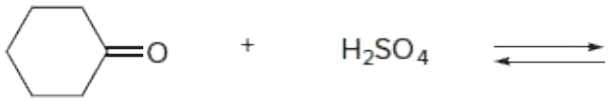
d. 

2.42 **Draw the products of each proton transfer reaction. Label the acid and base in the starting materials, and the conjugate acid and base in the products.**

a. 

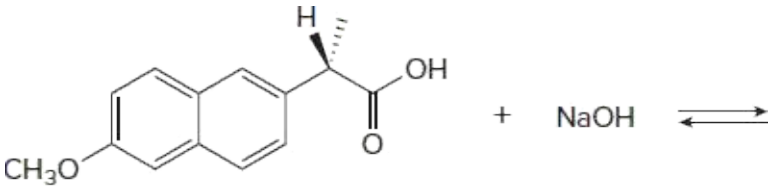
b.

c. 

d. 

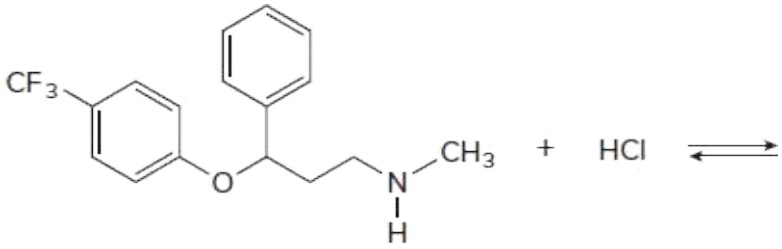
2.43 **Draw the products of each acid–base reaction.**

a.



naproxen
anti-inflammatory agent

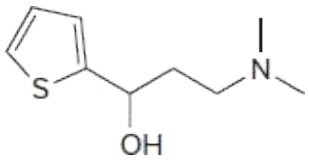
b.



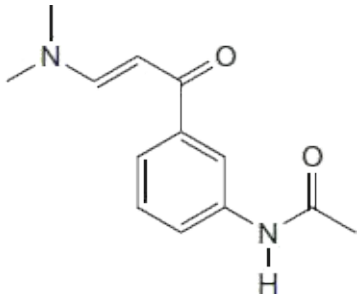
fluoxetine
antidepressant

2.44 What product is formed when each compound is treated with NaH? Each of these acid–base reactions was a step in a synthesis of a commercially available drug.

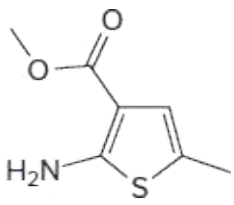
a.



b.



c.



pK_a, K_a, and the Direction of Equilibrium

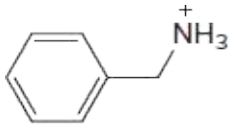
2.45 What is the K_a for each compound? Use a calculator when necessary.

a. H_2S
$pK_a = 7.0$

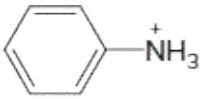
b. $ClCH_2COOH$
$pK_a = 2.8$

c. HCN
$pK_a = 9.1$

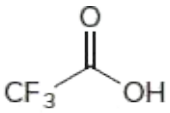
2.46 **What is the pK_a for each compound?**

a. 

$K_a = 4.7 \times 10^{-10}$

b. 

$K_a = 2.3 \times 10^{-5}$

c. 

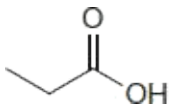
$K_a = 5.9 \times 10^{-1}$

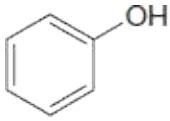
2.47 **Which of the following bases are strong enough to deprotonate $CH_3CH_2CH_2C{\equiv}CH$ (pK_a = 25) so that equilibrium favors the products: (a) H_2O; (b) NaOH; (c) $NaNH_2$; (d) NH_3; (e) NaH; (f) CH_3Li?**

2.48 **Which of the following bases are strong enough to deprotonate C_6H_5OH (pK_a = 10) so that equilibrium favors the products:**
(a) H_2O; (b) NaOH; (c) $NaNH_2$; (d) CH_3NH_2; (e) $NaHCO_3$; (f) NaSH; (g) NaH?

2.49 **Draw the products of each reaction. Use the pK_a table in Appendix C to decide if the equilibrium favors the starting materials or products.**

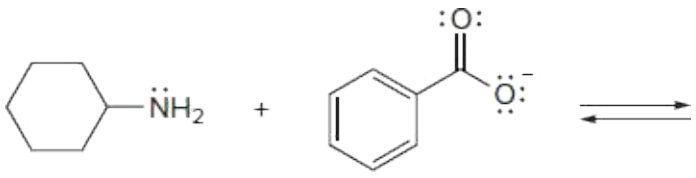
a. $CH_3NH_2 + H_2SO_4 \rightleftharpoons$

b.  $+ \quad NaCl \rightleftharpoons$

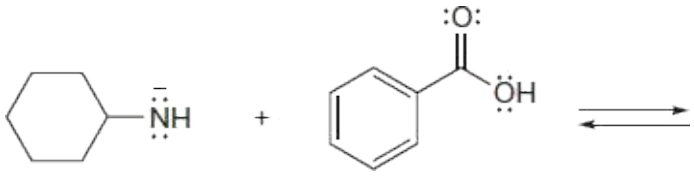
c.  $+ \quad NaHCO_3 \rightleftharpoons$

d. $H{-}C{\equiv}C{-}H + CH_3CH_2{}^-Li^+ \rightleftharpoons$

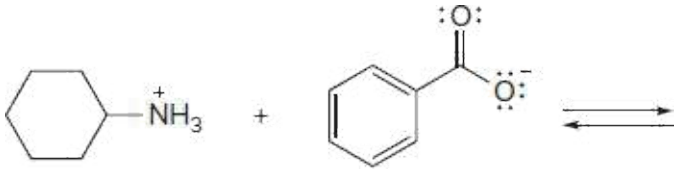
2.50 **Draw the products of each reaction and decide if equilibrium favors the starting materials or the products.**

a. 

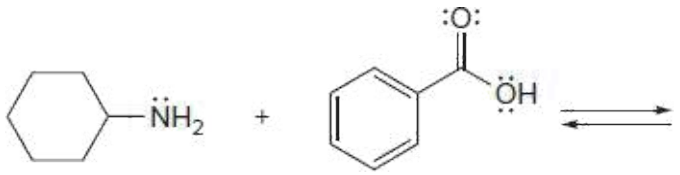
b.



c.



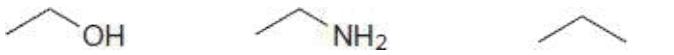
d.



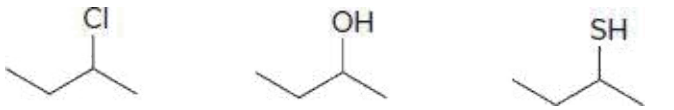
Relative Acid Strength

2.51 **Rank the following compounds in order of increasing acidity.**

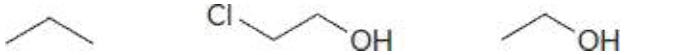
a.



b.

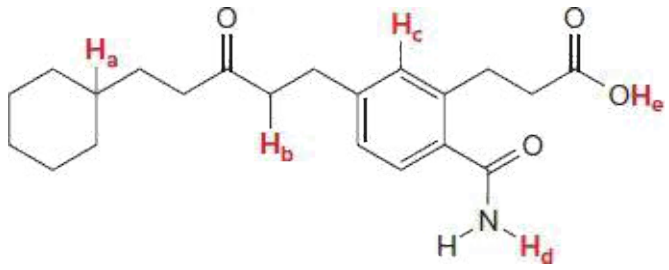


c.

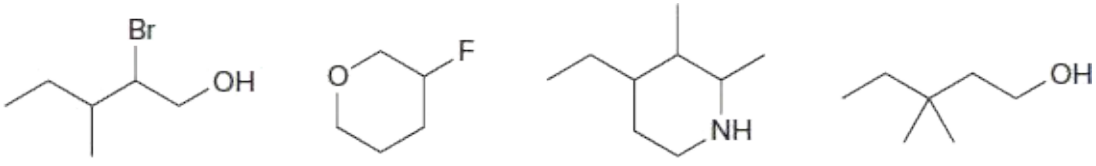


d.

2.52 **Rank the labeled protons in the following molecule in order of increasing pK_a.**



2.53 **Rank the following Brønsted–Lowry acids in order of increasing acidity. Which compound forms the strongest conjugate base?**



A **B** **C** **D**

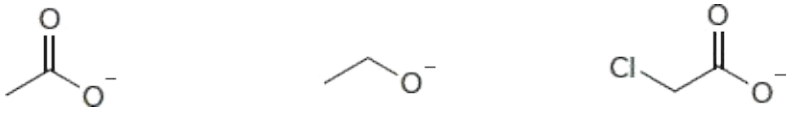
2.54 **Rank the following ions in order of increasing basicity.**

$CH_3\bar{C}H_2$, CH_3O^-, $CH_3\bar{N}H$

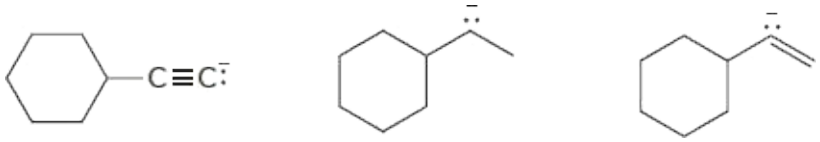
a.

b. CH_3^-, HO^-, Br^-

c.

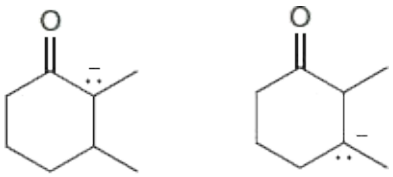


d.



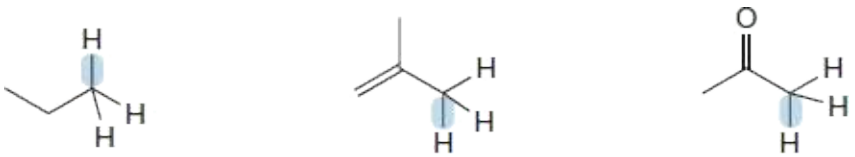
2.55 **The pK_a values of the two ammonium cations drawn below are 8.33 and 11.1. Which pK_a corresponds to which cation? Explain your choice.**

2.56 **Which of the following anions is the stronger base? Explain your choice.**



X **Y**

2.57 **The pK_a of three CH bonds is given below.**



pK_a = 50 pK_a = 43 pK_a = 19.2

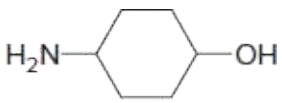
a. For each compound, draw the conjugate base, including all possible resonance structures.

b. Explain the observed trend in pK_a.

2.58

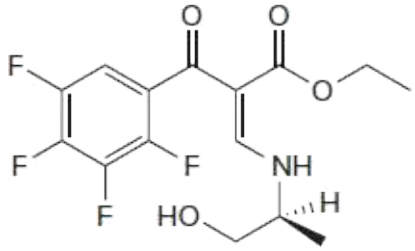
a. What is the conjugate acid of A?

b. What is the conjugate base of A?

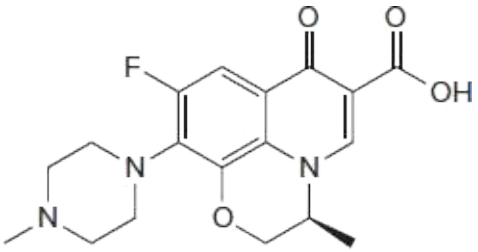


A

2.59 **Explain why the N—H proton in X is more acidic than the O—H proton. X was a key intermediate in the synthesis of the antibiotic levofloxacin.**



X



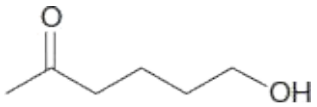
levofloxacin

2.60 **Draw the structure of a constitutional isomer of compound B that fits each description.**

a. an isomer that is at least 10^5 times more acidic than B

b. an isomer that is at least 10^5 times less acidic than B

c. an isomer that is comparable in acidity to B

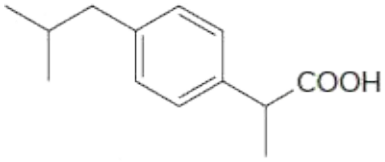


B

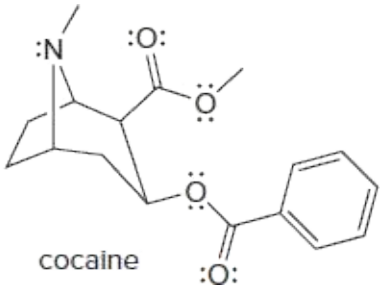
2.61 **Many drugs are Brønsted–Lowry acids or bases.**

a. What is the most acidic proton in the analgesic ibuprofen? Draw the conjugate base.

b. What is the most basic electron pair in cocaine? Draw the conjugate acid.



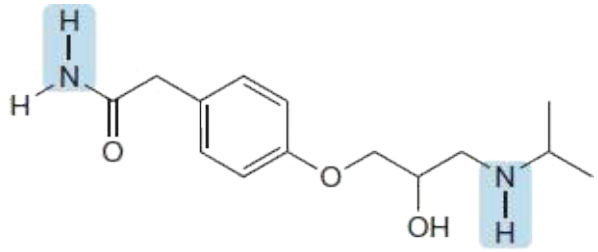
ibuprofen



cocaine

2.62 **Dimethyl ether (CH_3OCH_3) and ethanol (CH_3CH_2OH) are isomers, but CH_3OCH_3 has a pK_a of 40 and CH_3CH_2OH has a pK_a of 16. Why are these pK_a values so different?**

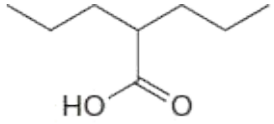
2.63 **Atenolol is a β (beta) blocker, a drug used to treat high blood pressure. Which of the indicated N—H bonds is more acidic? Explain your reasoning.**



atenolol

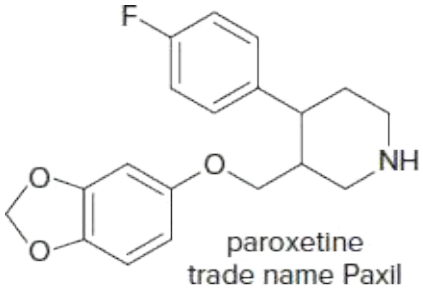
2.64 **Use the principles in Section 2.5 to label the most acidic hydrogen in each drug. Explain your choice.**

a.



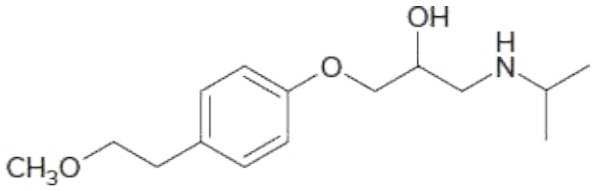
valproic acid
(used to treat epilepsy)

b.



paroxetine
trade name Paxil
(used to treat depression)

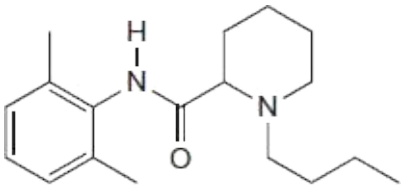
c.



metoprolol
(used to treat high blood pressure)

2.65 **Label the three most acidic hydrogen atoms in lactic acid, $CH_3CH(OH)CO_2H$, and rank them in order of decreasing acidity. Explain your reasoning.**

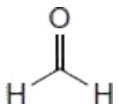
2.66 **Bupivacaine (trade name Marcaine) is a quick-acting anesthetic often used during labor and delivery. Which nitrogen atom in bupivacaine is more basic? Explain your reasoning.**

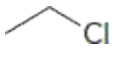


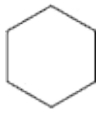
bupivacaine

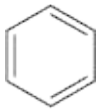
Lewis Acids and Bases

2.67 **Classify each compound as a Lewis base, a Brønsted–Lowry base, both, or neither.**

a. 

b. 

c. 

d. 

2.68 **Classify each species as a Lewis acid, a Brønsted–Lowry acid, both, or neither.**

a. H_3O^+

b. Cl_3C^+

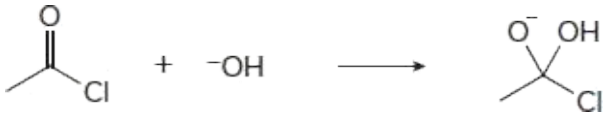
c. BCl_3

d. BF_4^-

Lewis Acid–Base Reactions

2.69 **Label the Lewis acid and Lewis base in each reaction. Use curved arrows to show the movement of electron pairs.**

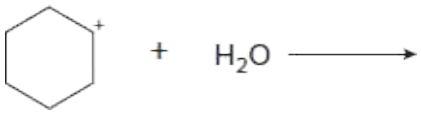
a.

b. 

2.70 **Draw the products of each Lewis acid–base reaction. Label the electrophile and nucleophile.**

a.

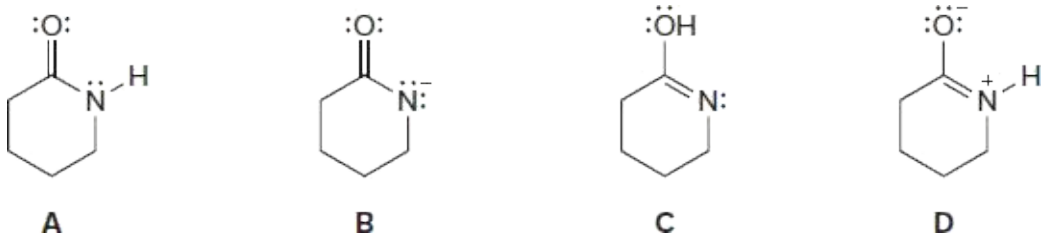
b.

c. 

2.71 Draw the product formed when the Lewis acid $(CH_3CH_2)_3C^+$ reacts with each Lewis base: (a) CH_3OH; (b) $(CH_3)_2O$; (c) $(CH_3)_2NH$.

General Problems

2.72 Answer the following questions about the four species A–D.

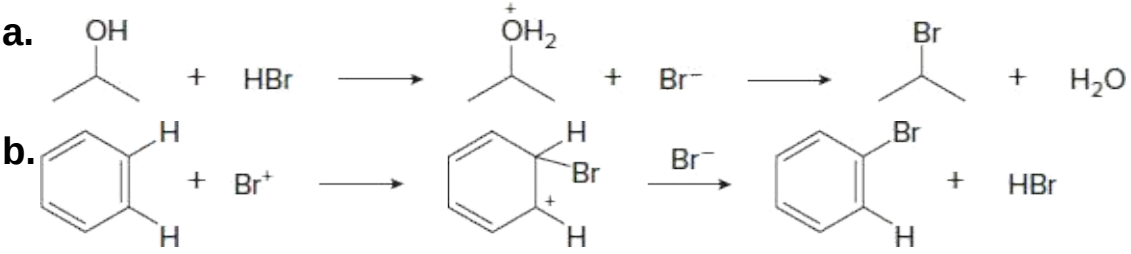


a. Which two species represent a conjugate acid–base pair?

b. Which two species represent resonance structures?

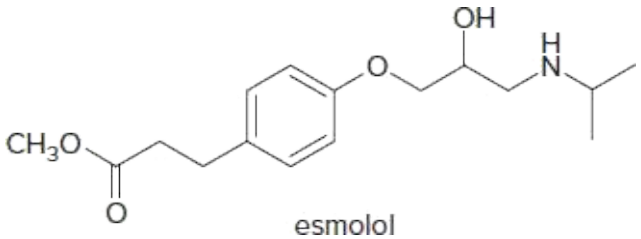
c. Which two species represent constitutional isomers?

2.73 Classify each reaction as either a proton transfer reaction, or a reaction of a nucleophile with an electrophile. Use curved arrows to show how the electron pairs move.



2.74 Hydroxide (^-OH) can react as a Brønsted–Lowry base (and remove a proton) or as a Lewis base (and attack a carbon atom). (a) What organic product is formed when ^-OH reacts with the carbocation $(CH_3)_3C+$ as a Brønsted–Lowry base? (b) What organic product is formed when ^-OH reacts with $(CH_3)_3C^+$ as a Lewis base?

2.75 Answer the following questions about esmolol, a drug used to treat high blood pressure sold under the trade name Brevibloc.



esmolol

a. Label the most acidic hydrogen atom in esmolol.

b. What products are formed when esmolol is treated with NaH?

c. What products are formed when esmolol is treated with HCl?

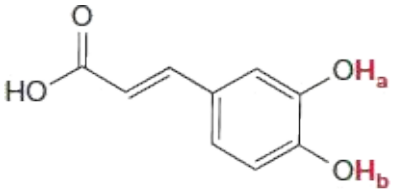
d. Label all sp^2 hybridized C atoms.

e. Label the only trigonal pyramidal atom.

f. Label all C's that bear a δ_+ charge.

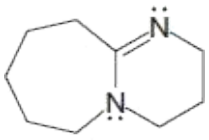
Challenge Problems

2.76 Caffeic acid is an organic acid isolated from coffee beans. Predict which labeled hydrogen (H_a or H_b) is more acidic and explain your choice.



caffeic acid

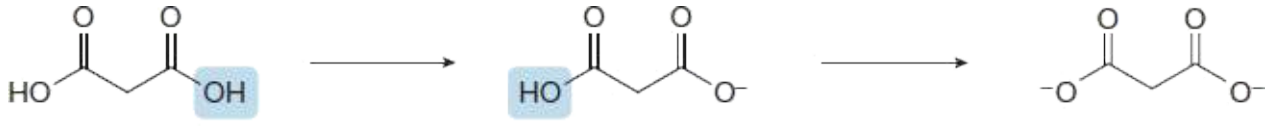
2.77 DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene, is a base we will encounter in elimination reactions in Chapter 8. Which N atom is more basic in DBU? Explain your choice.



DBU

2.78 Molecules like acetamide (CH_3CONH_2) can be protonated on either their O or N atoms when treated with a strong acid like HCl. Which site is more readily protonated and why?

2.79 Two pK_a values are reported for malonic acid, a compound with two COOH groups. Explain why one pK_a is lower and one pK_a is higher than the pK_a of acetic acid (CH_3COOH, pK_a = 4.8).



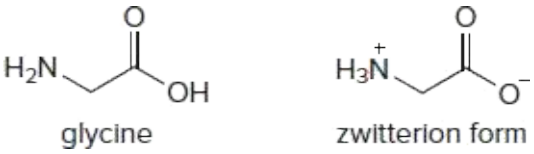
malonic acid

pK_a = 2.86

pK_a = 5.70

2.80 Amino acids such as glycine are the building blocks of large molecules

called proteins that give structure to muscle, tendon, hair, and nails.



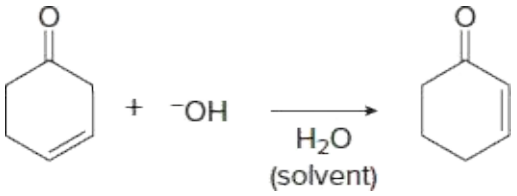
glycine zwitterion form

a. **Explain why glycine does not actually exist in the form with all atoms uncharged, but actually exists as a salt called a zwitterion.**

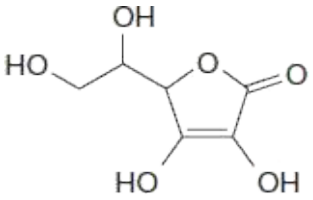
b. **What product is formed when glycine is treated with concentrated HCl?**

c. **What product is formed when glycine is treated with NaOH?**

2.81 **Write a stepwise reaction sequence using proton transfer reactions to show how the following reaction occurs. (Hint: As a first step, use $^-$OH to remove a proton from the CH_2 group between the C=O and C=C.)**



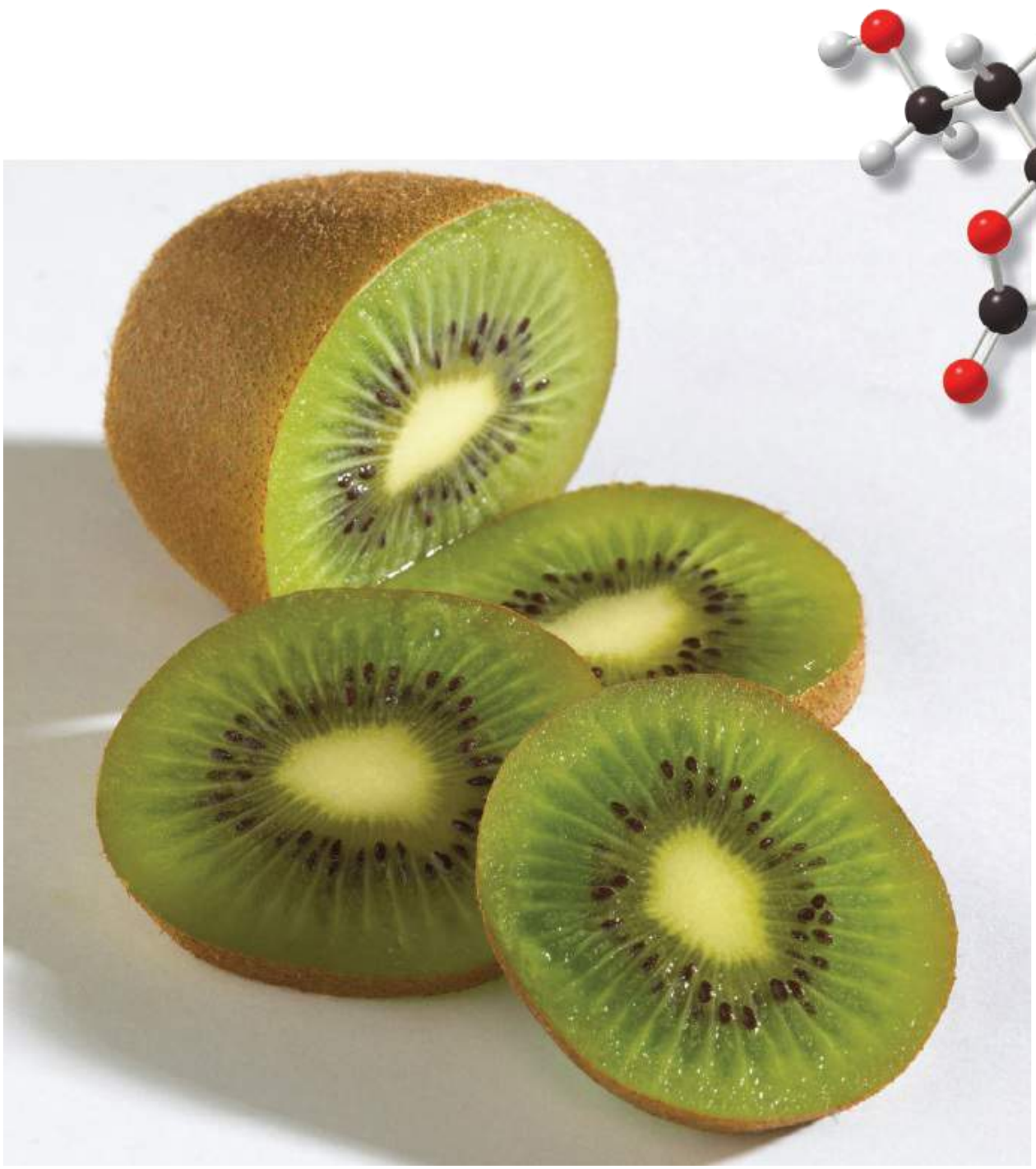
2.82 **Which H atom in vitamin C (ascorbic acid) is most acidic?**



vitamin C
ascorbic acid

Introduction to Organic Molecules and Functional Groups

3



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3.1 Functional groups

3.2 An overview of functional groups
3.3 Intermolecular forces
3.4 Physical properties
3.5 Application: Vitamins
3.6 Application of solubility: Soap
3.7 Application: The cell membrane
3.8 Functional groups and reactivity
3.9 Biomolecules

Vitamin C, or ascorbic acid, is important in the formation of collagen, a protein that holds together the connective tissues of skin, muscle, and blood vessels. In addition to oranges and grapefruit, kiwi is an excellent source of vitamin C. Grown commercially in Italy, New Zealand, and several other countries, kiwi fruit has a unique sweet flavor, sometimes reminiscent of strawberries. A deficiency of vitamin C causes scurvy, a common disease of sailors in the 1600s when they had no access to fresh fruits on long voyages. In Chapter 3, we learn why some vitamins like vitamin A can be stored in the fat cells in the body, whereas others like vitamin C are excreted in urine.

Why Study…

Functional Groups?

Having learned some basic concepts about structure, bonding, and acid–base chemistry in Chapters 1 and 2, we will now concentrate on organic molecules.

- What are the characteristic features of an organic compound?
- What determines the properties of an organic compound?

After these questions are answered, we can understand some common phenomena. For example, why do we store some vitamins in the body and readily excrete others? How does soap clean away dirt? We will also use the properties of organic molecules to explain some basic biological phenomena, such as the structure of cell membranes and the transport of species across these membranes.

3.1 Functional Groups

What are the characteristic features of an organic compound? Most organic molecules have C–C and C–H σ bonds. These bonds are strong, nonpolar, and not readily broken. Organic molecules may have these structural features as well:

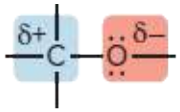
- Heteroatoms—atoms other than carbon or hydrogen. Common heteroatoms are nitrogen, oxygen, sulfur, phosphorus, and the halogens.
- π Bonds. The most common π bonds occur in C–C and C–O double bonds.

These structural features distinguish one organic molecule from another. They determine a molecule's geometry, physical properties, and reactivity, and comprise what is called a functional group.

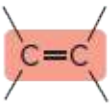
- **A *functional group* is an atom or a group of atoms with characteristic chemical and physical properties. It is the *reactive part* of the molecule.**

Why do heteroatoms and π bonds confer reactivity on a particular molecule?

- **Heteroatoms have lone pairs and create electron-deficient sites on carbon.**
- **π Bonds are easily broken in chemical reactions. A π bond makes a molecule a base and a nucleophile.**



- Lone pairs make O a base and a nucleophile.
- The C atom is electron deficient, making it an electrophile.



- The π bond is easily broken.
- The π bond makes a compound a base and a nucleophile.

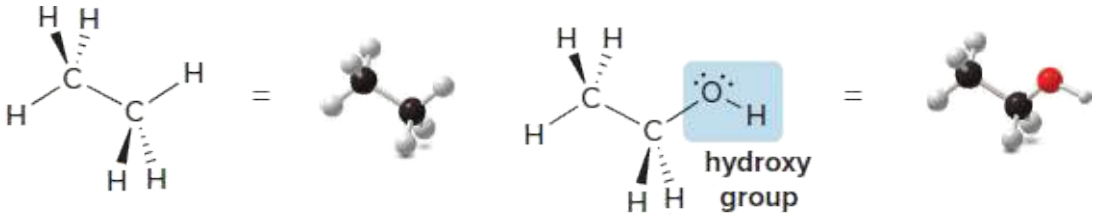
Don't think, though, that the C–C and C–H σ bonds are unimportant. They form the carbon backbone or skeleton to which the functional groups are bonded. A functional group usually behaves the same whether it is bonded to a carbon skeleton having as few as two or as many as 20 carbons. For this reason, we often abbreviate the carbon and hydrogen portion of the molecule by a capital letter R, and draw the R bonded to a particular functional group.

Ethane, for example, has only C–C and C–H σ bonds, so it has *no* functional group.

Ethane has no polar bonds, no lone pairs, and no π bonds, so it has no reactive sites. Because of this, ethane and molecules like it are very unreactive.

Ethanol, on the other hand, has two carbons and five hydrogens in its carbon backbone, as well as an OH group, a functional group called a hydroxy group. Ethanol has lone pairs and polar bonds that make it reactive with a variety of reagents, including the acids and bases discussed in Chapter 2. The hydroxy group makes the properties of ethanol very different from the properties of ethane. Moreover, any organic molecule containing a hydroxy group has properties similar to ethanol.

Page 95



ethane

- all C–C and C–H σ bonds
- no functional group

ethanol

- polar C–O and O–H bonds
- two lone pairs

Most organic compounds can be grouped into a relatively small number of categories, based on the structure of their functional group. Ethane, for example, is an alkane, whereas ethanol is a simple alcohol.

Problem 3.1

What reaction occurs when CH_3CH_2OH is treated with (a) H_2SO_4? (b) NaH? What happens when CH_3CH_3 is treated with these same reagents?

3.2 An Overview of Functional Groups

We can subdivide the most common functional groups into three types.

- Hydrocarbons
- Compounds containing a C–Z σ bond where Z = an electronegative element
- Compounds containing a C=O group

3.2A Hydrocarbons

To review the structure and bonding of the simple aliphatic hydrocarbons, return to Section 1.10.

The word *aliphatic* is derived from the Greek word *aleiphas* meaning "fat." Aliphatic compounds have physical

properties similar to fats.

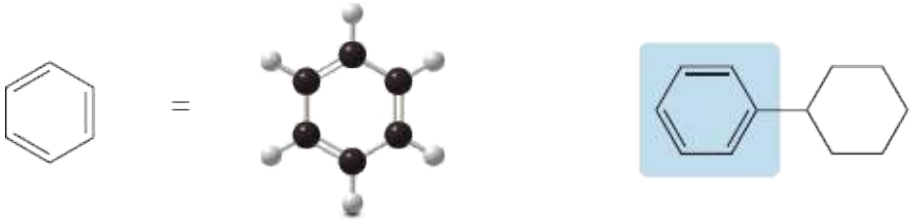
Hydrocarbons **are compounds made up of only the elements carbon and hydrogen. They may be aliphatic or aromatic.**

[1] Aliphatic hydrocarbons. Aliphatic hydrocarbons can be divided into three subgroups.

- **Alkanes have only C–C σ bonds and no functional group. Ethane, CH_3CH_3, is a simple alkane.**
- **Alkenes have a C–C double bond as a functional group. Ethylene, $CH_2=CH_2$, is a simple alkene.**
- **Alkynes have a C–C triple bond as a functional group. Acetylene, HC≡CH, is a simple alkyne.**

[2] Aromatic hydrocarbons. This class of hydrocarbons was so named because many of the earliest known aromatic compounds had strong, characteristic odors.

The simplest aromatic hydrocarbon is benzene. The six-membered ring and three π bonds of benzene comprise a *single* functional group. Benzene is a component of the BTX mixture (B for benzene) added to gasoline to boost octane ratings.



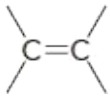
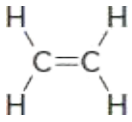
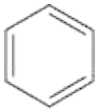
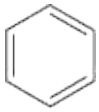
benzene
molecular formula C_6H_6

phenyl group
C_6H_5–
phenylcyclohexane

When a benzene ring is bonded to another group, it is called a phenyl group. Page 96 In phenylcyclohexane, for example, a phenyl group is bonded to the six-membered cyclohexane ring. Table 3.1 summarizes the four different types of hydrocarbons.

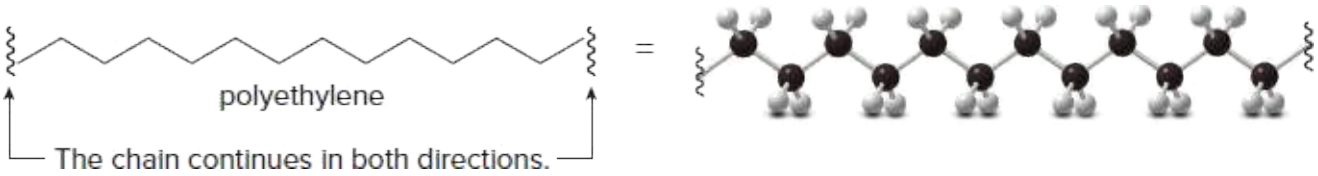
Table 3.1 Hydrocarbons

Type of compound	General structure	Example	Functional group
Alkane	R–H	CH_3CH_3	–

Alkene			**double bond**
Alkyne	**–C≡C–**	**H–C≡C–H**	**triple bond**
Aromatic compound			**phenyl group**

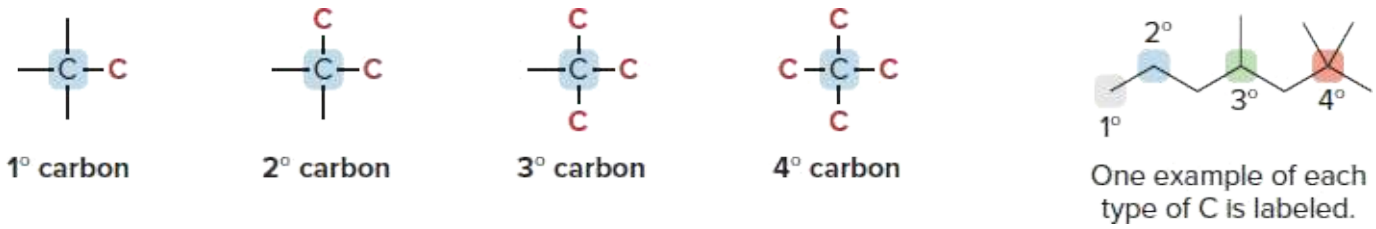
Polyethylene is a synthetic plastic first produced in the 1930s, and initially used as insulating material for radar during World War II. It is now a plastic used in milk containers, sandwich bags, and plastic wrapping. Over 100 billion pounds of polyethylene are manufactured each year.

Alkanes, which have no functional groups, are notoriously unreactive except under very drastic conditions. For example, polyethylene is a synthetic plastic and high-molecular-weight alkane, consisting of chains of $–CH_2–$ groups bonded together, hundreds or even thousands of atoms long. Because it is an alkane with no reactive sites, it is a very stable compound that does not readily degrade and thus persists for years in landfills.



Carbon atoms in alkanes and other organic compounds are classified by the number of other carbons directly bonded to them.

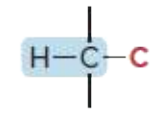
- **A *primary carbon* (1° carbon) is bonded to *one* other C atom.**
- **A *secondary carbon* (2° carbon) is bonded to *two* other C atoms.**
- **A *tertiary carbon* (3° carbon) is bonded to *three* other C atoms.**
- **A *quaternary carbon* (4° carbon) is bonded to *four* other C atoms.**



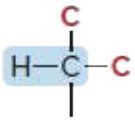
Hydrogen atoms are classified as primary (1°), secondary (2°), or tertiary (3°)

depending on the type of carbon atom to which they are bonded.

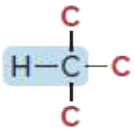
- **A *primary hydrogen* (1° H) is on a C bonded to one other C atom.**
- **A *secondary hydrogen* (2° H) is on a C bonded to two other C atoms.**
- **A *tertiary hydrogen* (3° H) is on a C bonded to three other C atoms.**



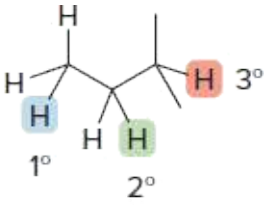
1° hydrogen



2° hydrogen



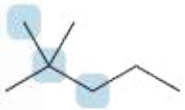
3° hydrogen



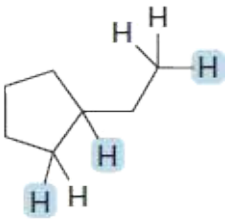
One example of each type of H is labeled.

Sample Problem 3.1 Classifying the Carbons and Hydrogens in a Molecule

Classify the designated carbon atoms in A as 1°, 2°, 3°, or 4°. Classify the designated hydrogen atoms in B as 1°, 2°, or 3°.



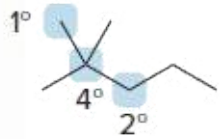
A



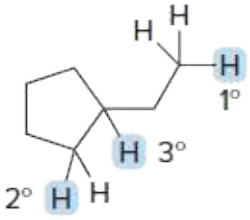
B

Solution

- **Classify C's by the number of other C's bonded to them.**
- **Classify H's by the type of C to which they are bonded; a 1° H is bonded to a 1° C, etc.**



A



B

Problem 3.2

(a) Classify the carbon atoms in each compound as 1°, 2°, 3°, or 4°. (b) Classify the

hydrogen atoms in each compound as 1°, 2°, or 3°.

More Practice:

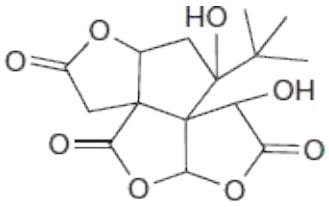
Try Problems 3.33, 3.61d.

Bilobalide (Problem 3.3) is obtained from *Ginkgo biloba*, the oldest seed-producing plant that currently lives on earth. Extracts from the leaves, roots, bark, and seeds of the ginkgo tree have been used in traditional Chinese medicine and currently comprise a widely used herbal supplement.
©Michael Pettigrew/Getty Images

Chloroethane, CH_3CH_2Cl, is a local anesthetic. *Courtesy of Gebauer Company, Cleveland, Ohio*

Problem 3.3

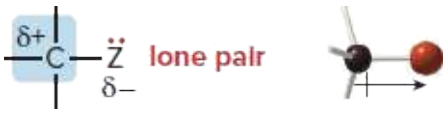
Classifying a carbon atom by the number of carbons to which it is bonded can also be done in more-complex molecules that contain heteroatoms. Classify each sp^3 hybridized carbon atom in bilobalide, a compound isolated from *Ginkgo biloba* extracts, as 1°, 2°, 3°, or 4°.



bilobalide

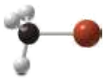
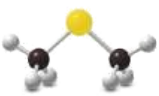
3.2B Compounds Containing C–Z σ Bonds

Functional groups that contain C–Z σ bonds include alkyl halides, alcohols, ethers, amines, thiols, and sulfides (Table 3.2). The electronegative heteroatom Z creates a polar bond, making carbon electron deficient. The lone pairs on Z are available for reaction with protons and other electrophiles, especially when Z = N or O.



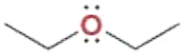
Several simple compounds in this category are widely used. As an example, chloroethane (CH_3CH_2Cl, commonly called ethyl chloride) is an alkyl halide used as a local anesthetic. Chloroethane quickly evaporates when sprayed on a wound, causing a cooling sensation that numbs the site of an injury.

Table 3.2 Compounds Containing C–Z σ Bonds

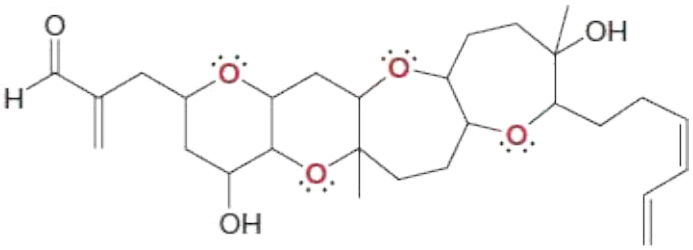
Type of compound	General structure	Example	3-D structure	Functional group
Alkyl halide	R—X: (X = F, Cl, Br, I)	CH_3—Br:		–X halo group
Alcohol	R—OH	CH_3—O—H		–OH hydroxy group
Ether	R—O—R	CH_3—O—CH_3		–OR alkoxy group
Amine	R—NH_2 or R_2NH or R_3N	CH_3—N(H)—H		–NH_2 amino group
Thiol	R—SH	CH_3—S—H		–SH mercapto group
Sulfide	R—S—R	CH_3—S—CH_3		–SR alkylthio group

Molecules containing these functional groups may be simple or very complex. Diethyl ether, the first common general anesthetic, is a simple ether because it contains a single O atom, depicted in red, bonded to two C atoms. Hemibrevetoxin B, on the other hand, contains four ether groups, in addition to other functional groups.

Hemibrevetoxin B is a neurotoxin produced by algal blooms referred to as "red tides," because of the color often seen in shallow ocean waters when these algae proliferate.

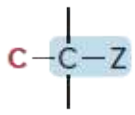


diethyl ether



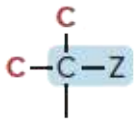
hemibrevetoxin B

Alkyl halides and alcohols are classified as primary (1°), secondary (2°), or tertiary (3°) based on the number of carbon atoms bonded to the carbon bearing the halogen or OH group.

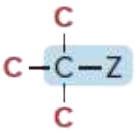


Z = X
Z = OH

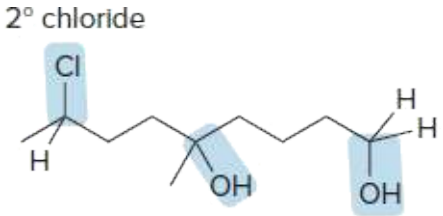
1° alkyl halide
1° alcohol



2° alkyl halide
2° alcohol



3° alkyl halide
3° alcohol

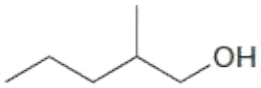


3° alcohol
1° alcohol

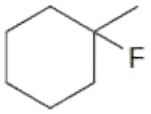
Problem 3.4

Classify each alkyl halide and alcohol as 1°, 2°, or 3°.

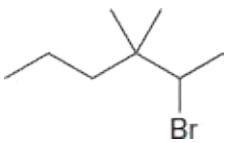
a.



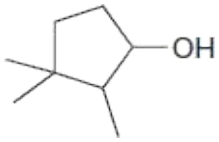
b.



c.

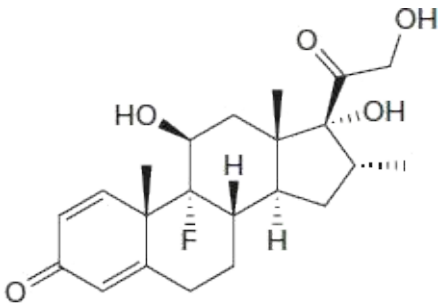


d.



Problem 3.5

Classify each OH group and halogen in dexamethasone, a synthetic steroid, as 1°, 2°, or 3°.

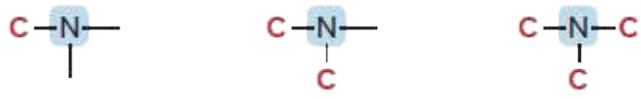


dexamethasone

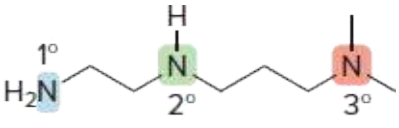
Dexamethasone (Problem 3.5) relieves inflammation and is used to treat some forms of arthritis, skin conditions, and asthma.

©Jill Braaten

Amines are classified as primary (1°), secondary (2°), or tertiary (3°) based on the number of carbon atoms bonded to the *nitrogen* atom.



1° amine 2° amine 3° amine

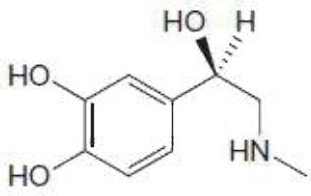


Classifying amines is different from classifying alcohols and alkyl halides as primary (1°), secondary (2°), or tertiary (3°). Amines are classified by the number of carbon–*nitrogen* bonds, whereas alkyl halides and alcohols are classified by the type of *carbon* bonded to the halogen or hydroxy group.

Problem 3.6

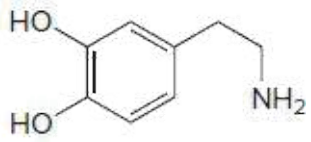
Classify each amine in the following compounds as 1°, 2°, or 3°.

a.



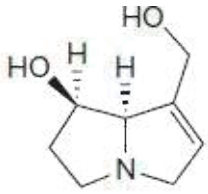
adrenaline
(hormone)

b.



dopamine
(neurotransmitter)

c.



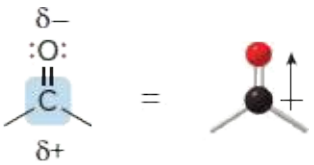
retronecine
(plant natural product)

Problem 3.7

Draw the structure of a compound of molecular formula $C_4H_{11}NO$ that fits each description: (a) a compound that contains a 1° amine and a 3° alcohol; (b) a compound that contains a 3° amine and a 1° alcohol.

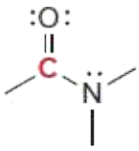
3.2C Compounds Containing a C=O Group

Many different types of functional groups possess a C–O double bond (a carbonyl group), including aldehydes, ketones, carboxylic acids, esters, amides, and acid chlorides (Table 3.3). The polar C–O bond makes the carbonyl carbon an electrophile, while the lone pairs on O allow it to react as a nucleophile and base. The carbonyl group also contains a π bond that is more easily broken than a C–O σ bond.

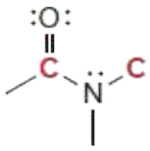


carbonyl group

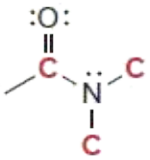
Amides, compounds that contain a nitrogen atom bonded directly to the carbonyl carbon, are classified as primary (1°), secondary (2°), or tertiary (3°) based on the number of carbon atoms bonded to the nitrogen atom.



1° amide



2° amide



3° amide

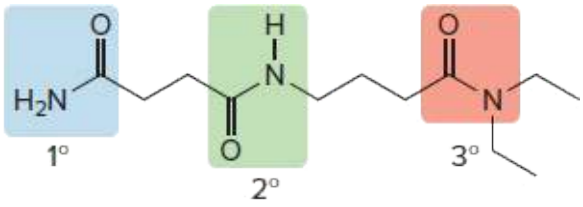
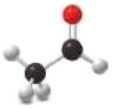
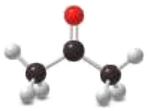
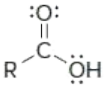
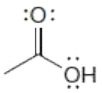
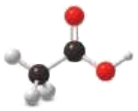
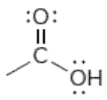
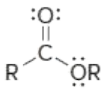
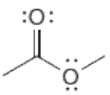
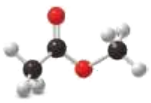
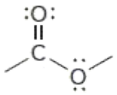
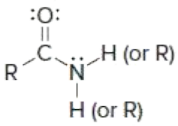
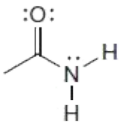
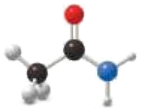
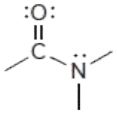
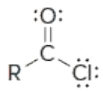
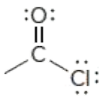
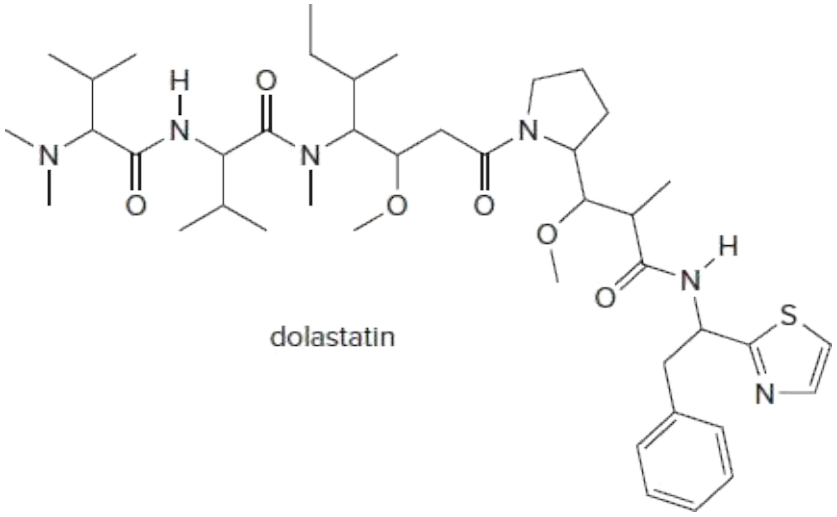


Table 3.3 Compounds Containing a C=O Group

Type of compound	General structure	Example	Condensed structure	3-D structure	Functional group
Aldehyde			CH_3CHO		
Ketone			$(CH_3)_2CO$		carbonyl group
Carboxylic acid			CH_3CO_2H		 carboxy group
Ester			$CH_3CO_2CH_3$		
Amide			CH_3CONH_2		
Acid chloride			CH_3COCl		

Problem 3.8

Classify the amides in dolastatin, an anticancer compound isolated from the Indian seahare *Dolabella auricularia*, as 1°, 2°, or 3°.

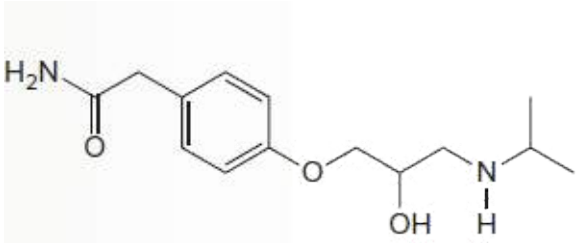


dolastatin

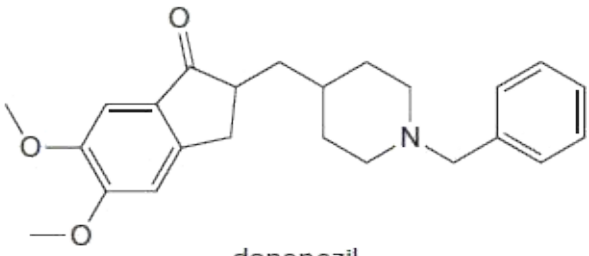
The importance of a functional group cannot be overstated. A functional group determines a molecule's bonding and shape, type and strength of intermolecular forces, physical properties, nomenclature, and chemical reactivity.

Sample Problem 3.2 Identifying Functional Groups in a Complex Molecule

Identify the functional groups in two drugs, atenolol and donepezil. Atenolol is a β (beta) blocker, a drug used to treat hypertension (high blood pressure), and donepezil (trade name Aricept) is used to treat mild to moderate dementia associated with Alzheimer's disease.



atenolol
(used to treat high blood pressure)

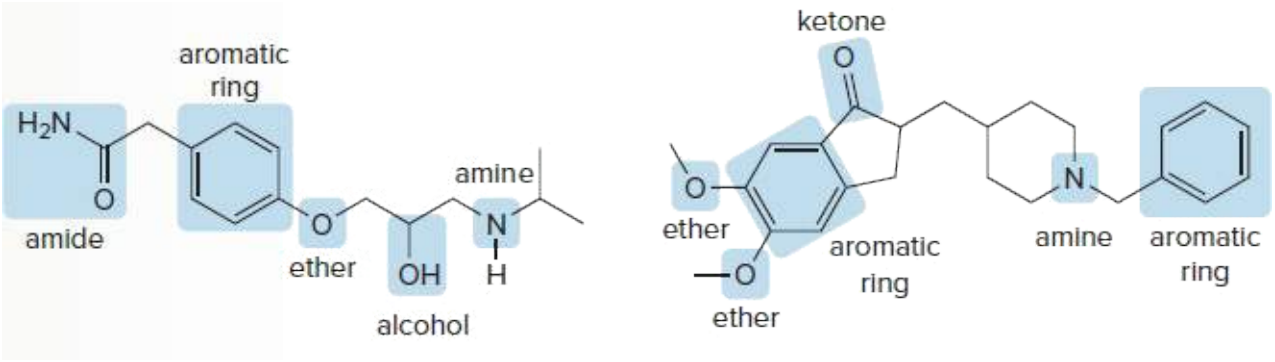


donepezil
(used to treat Alzheimer's disease)

Tamiflu (Problem 3.9) is the trade name for oseltamivir, an antiviral drug used to treat influenza. ***©Jill Braaten***

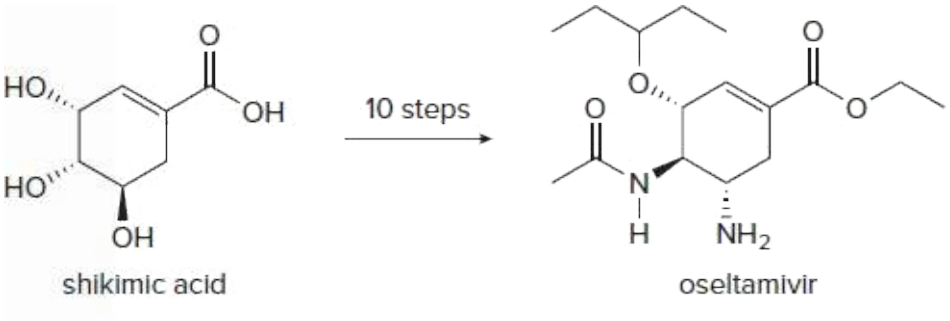
Solution

Concentrate on the heteroatoms and π bonds. With carbonyl groups, pay attention to what is bonded to the carbonyl carbon—hydrogen, carbon, or a heteroatom.



Problem 3.9

Oseltamivir can be prepared in 10 steps from shikimic acid. Identify the functional groups in oseltamivir and shikimic acid.



More Practice:

Try Problems 3.31a; 3.32a; 3.34–3.36; 3.62a, b; 3.63a, b; 3.64a, b; 3.66a.

Problem 3.10

Draw the structure of a compound fitting each description:

a. an aldehyde with molecular formula C_4H_8O

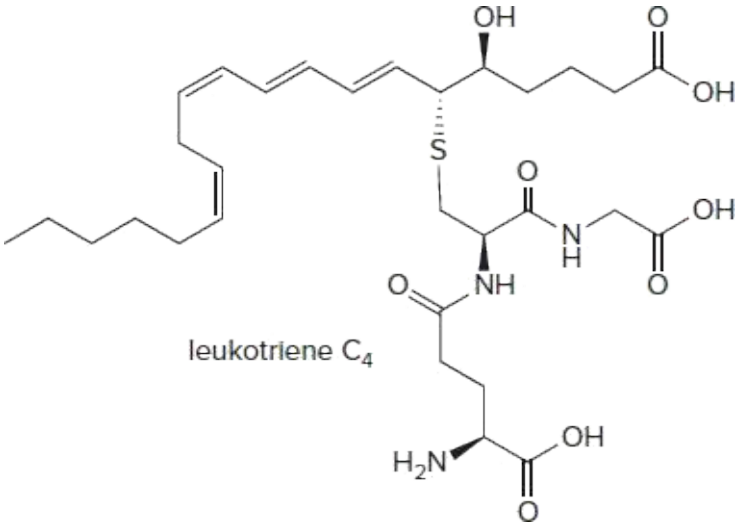
b. a ketone with molecular formula C_4H_8O

c. a carboxylic acid with molecular formula $C_4H_8O_2$

d. an ester with molecular formula $C_4H_8O_2$

Problem 3.11

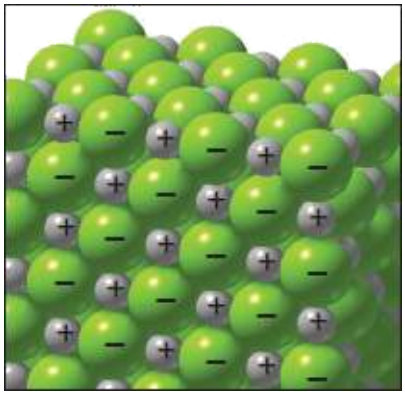
Identify the functional groups in leukotriene C_4, a major contributor to the inflammation associated with asthma.



3.3 Intermolecular Forces

Intermolecular forces are the interactions that exist *between* molecules. A functional group determines the type and strength of these interactions.

Intermolecular forces are also referred to as noncovalent interactions or nonbonded interactions.



strong electrostatic interaction between Na^+ and Cl^-

3.3A Ionic Compounds

Ionic compounds, such as NaCl, contain oppositely charged particles held together by extremely strong electrostatic interactions. These ionic interactions are much *stronger* than the intermolecular forces present between covalent molecules, so it takes a great deal of energy to separate oppositely charged ions from each other.

3.3B Covalent Compounds

Covalent compounds are composed of discrete molecules. The nature of the forces

between the molecules depends on the functional group present. There are three different types of interactions, presented here in order of *increasing strength:*

- van der Waals forces
- dipole–dipole interactions
- hydrogen bonding

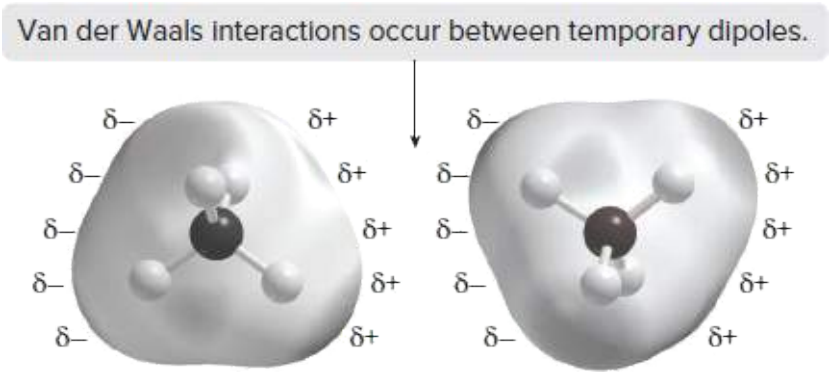
Van der Waals Forces

Van der Waals forces, also called London forces, are very weak interactions caused by the momentary changes in electron density in a molecule. Van der Waals forces are the only attractive forces present in nonpolar compounds.

For example, although a nonpolar CH_4 molecule has no net dipole, at any one instant its electron density may not be completely symmetrical, creating a *temporary* dipole. This can induce a temporary dipole in another CH4 molecule, with the partial positive and negative charges arranged close to each other. The weak interaction of these temporary dipoles constitutes van der Waals forces. All compounds exhibit van der Waals forces.

Although any single van der Waals interaction is weak, a large number of van der Waals interactions creates a strong force. For example, geckos stick to walls and ceilings by van der Waals interactions of the surfaces with the 500,000 tiny hairs on each foot.

(top): ©Don Mennig/Alamy Stock Photo; (bottom): ©wrangel/iStockphoto/Getty Images



The surface area of a molecule determines the strength of the van der Waals interactions. The *larger* the surface area, the *larger* the attractive force between two molecules, and the *stronger* the intermolecular forces. Long, sausage-shaped molecules such as $CH_3CH_2CH_2CH_2CH_3$ (pentane) have stronger van der Waals interactions than compact, spherical ones like $C(CH_3)_4$ (2,2-dimethylpropane), as shown in Figure 3.1.

Another factor affecting the strength of van der Waals forces is polarizability.

- ***Polarizability*** **is a measure of how the electron cloud around an atom responds to changes in its electronic environment.**

Larger atoms like iodine, which have more loosely held valence electrons, are more polarizable than smaller atoms like fluorine, which have more tightly held electrons. Because larger atoms have more easily induced dipoles, compounds containing them possess stronger intermolecular interactions.

Two F_2 molecules have little force of attraction between them, because the electrons are held very tightly and temporary dipoles are difficult to induce. On the other hand, two I_2 molecules exhibit a much stronger force of attraction, because the electrons are held much more loosely and temporary dipoles are easily induced.

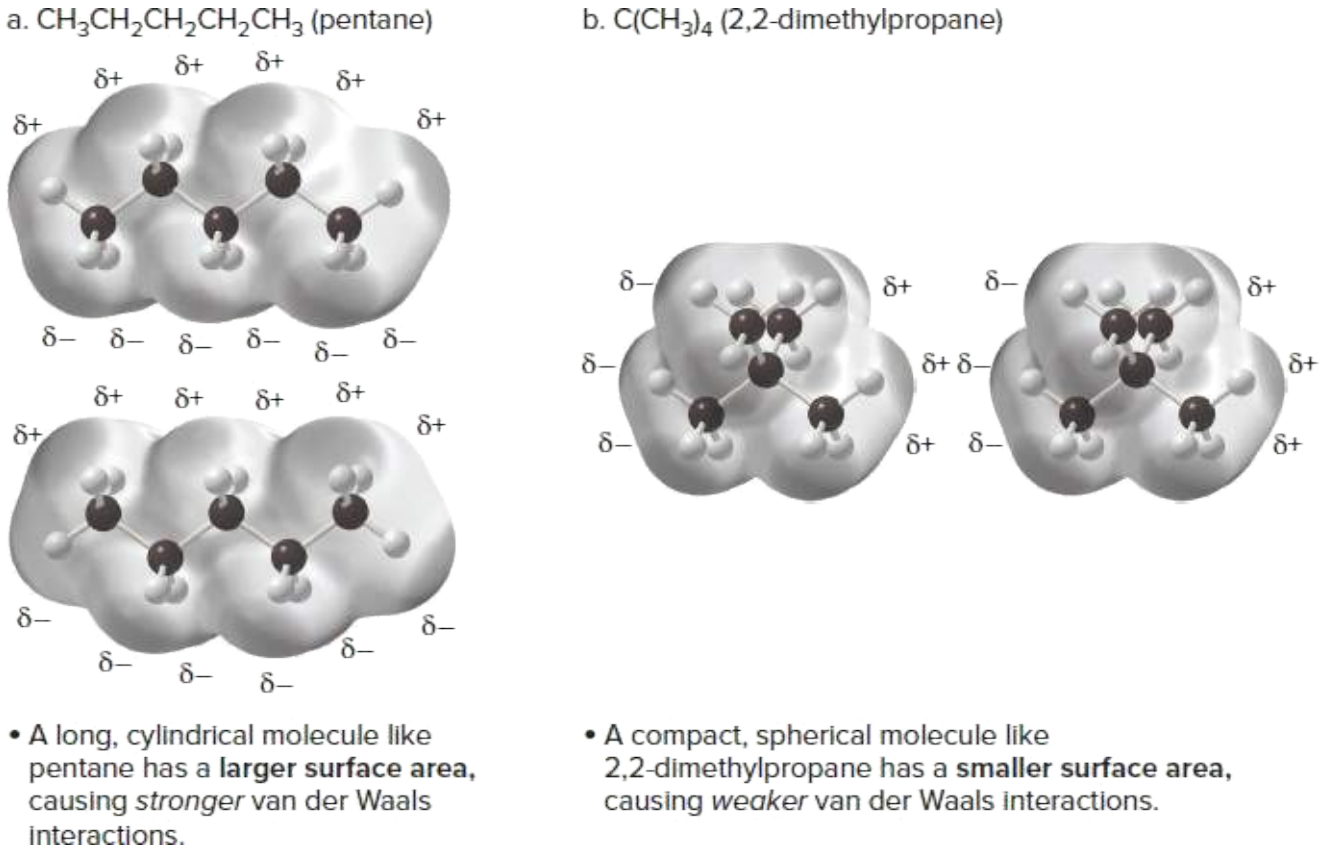
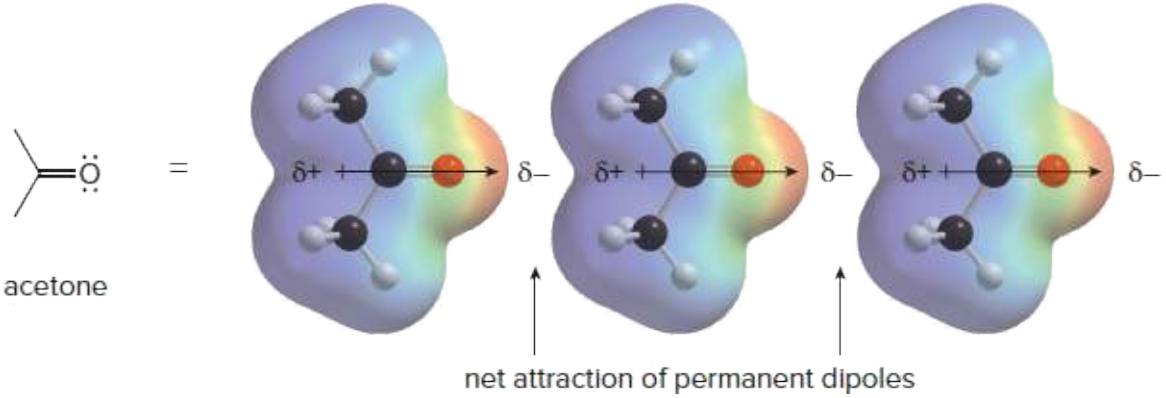


Figure 3.1 **Surface area and van der Waals forces**

- **Compounds with large, polarizable atoms have stronger intermolecular forces than compounds with small, less polarizable atoms.**

Dipole–Dipole Interactions

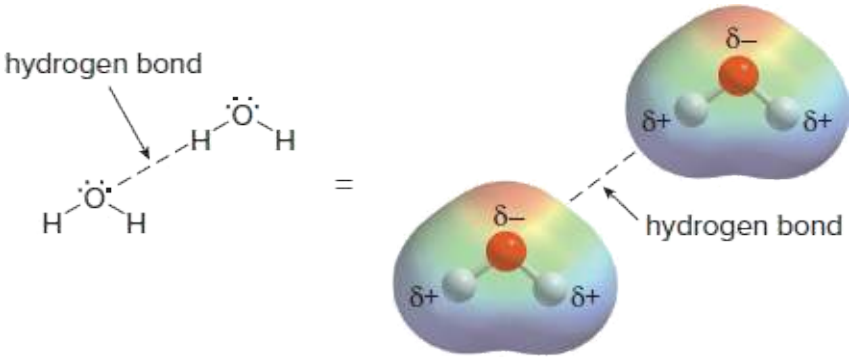
Dipole–dipole interactions are the attractive forces between the permanent dipoles of two polar molecules. In acetone, $(CH_3)_2C{=}O$, for example, the dipoles in adjacent molecules align so that the partial positive and partial negative charges are in close proximity. These attractive forces caused by permanent dipoles are much stronger than weak van der Waals forces.



Hydrogen bonding helps determine the three-dimensional shape of large biomolecules such as carbohydrates and proteins. See Chapters 26 and 27 for details.

Hydrogen Bonding

Hydrogen bonding typically occurs when a hydrogen atom bonded to O, N, or F is electrostatically attracted to a lone pair of electrons on an O, N, or F atom in another molecule. Thus, H2O molecules can hydrogen bond to each other. When they do, a H atom covalently bonded to O in one water molecule is attracted to a lone pair of electrons on the O in another water molecule. Hydrogen bonds are the *strongest* of the three types of intermolecular forces, though they are still much weaker than any covalent bond.



Sample Problem 3.3 illustrates how to determine the relative strength of intermolecular forces for a group of compounds. Table 3.4 summarizes the four types of interactions that affect the properties of all compounds.

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Table 3.4 Summary of Types of Intermolecular Forces

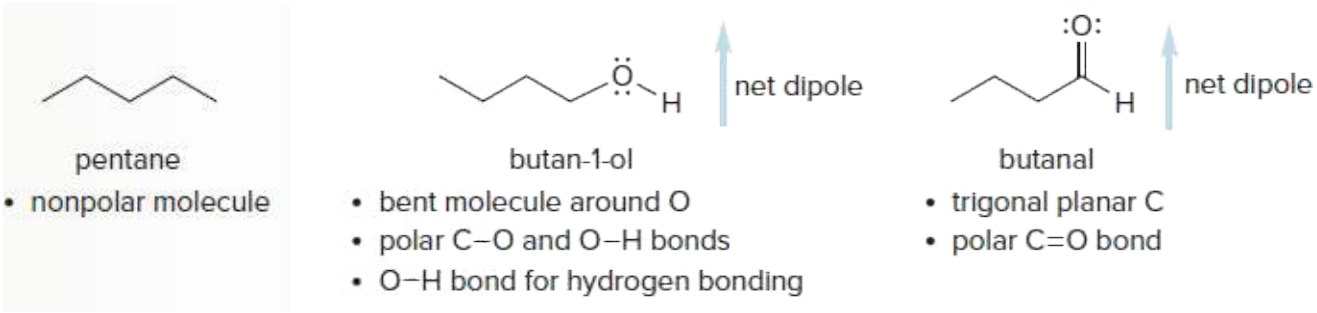
Type of force	Relative strength	Exhibited by	Example
van der Waals	**weak**	**all molecules**	$CH_3CH_2CH_2CH_2CH_3$ $CH_3CH_2CH_2CHO$ $CH_3CH_2CH_2CH_2OH$
dipole–dipole	**moderate**	**molecules with a net dipole**	$CH_3CH_2CH_2CHO$ $CH_3CH_2CH_2CH_2OH$
hydrogen bonding	**strong**	**molecules with an O–H, N–H,**	**$CH_3CH_2CH_2CH_2OH$**

		or H–F bond	
ion–ion	very strong	ionic compounds	NaCl, LiF

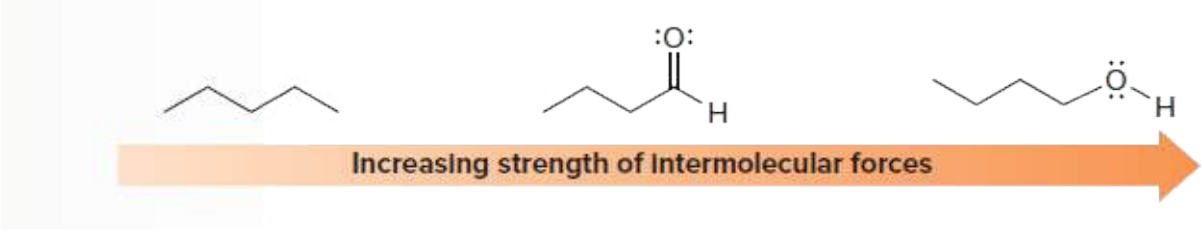
Sample Problem 3.3 Determining Intermolecular Forces in Organic Compounds

Rank the following compounds in order of increasing strength of intermolecular forces: $CH_3CH_2CH_2CH_2CH_3$ (pentane), $CH_3CH_2CH_2CH_2OH$ (butan-1-ol), and $CH_3CH_2CH_2CHO$ (butanal).

Solution

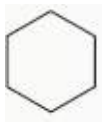


- **Pentane has only nonpolar C–C and C–H bonds, so its molecules are held together by only van der Waals forces.**
- **Butan-1-ol is a polar bent molecule, so it can have dipole–dipole interactions in addition to van der Waals forces. Because it has an O–H bond, butan-1-ol molecules are held together by intermolecular hydrogen bonds as well.**
- **Butanal has a trigonal planar carbon with a polar C=O bond, so it exhibits dipole–dipole interactions in addition to van der Waals forces. There is *no* H atom bonded to O, so two butanal molecules *cannot* hydrogen bond to each other.**

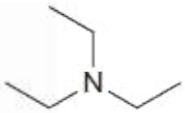


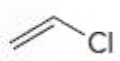
Problem 3.12

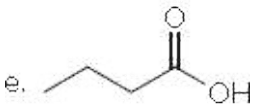
What types of intermolecular forces are present in each compound?

a. 

b.

c. 

d. 

e. 

f.

More Practice:

Try Problems 3.38, 3.41.

3.4 Physical Properties

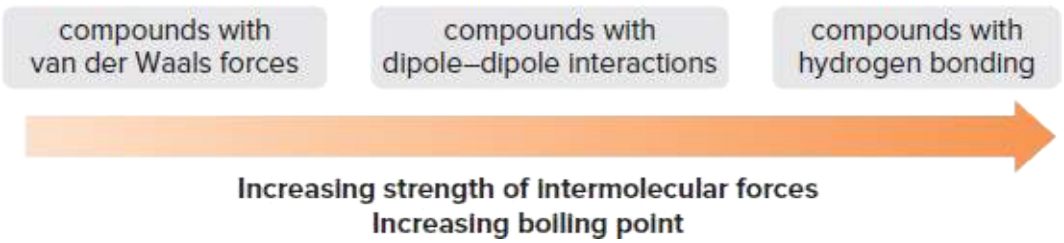
The strength of a compound's intermolecular forces determines many of its physical properties, including its boiling point, melting point, and solubility.

3.4A Boiling Point (bp)

The *boiling point* of a compound is the temperature at which a liquid is converted to a gas. In boiling, energy is needed to overcome the attractive forces in the more ordered liquid state.

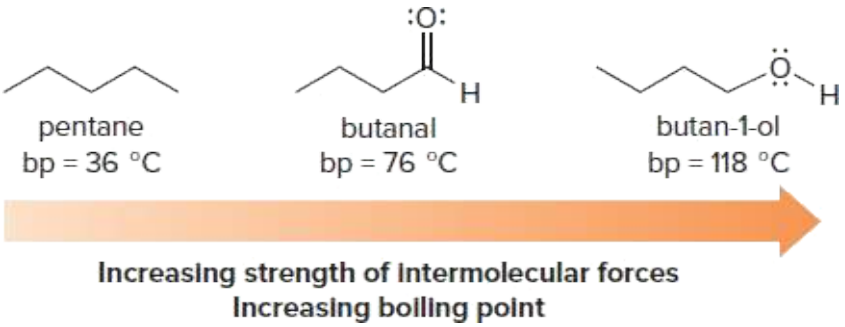
- **The *stronger* the intermolecular forces, the *higher* the boiling point.**

Because ionic compounds are held together by extremely strong interactions, they have very high boiling points. The boiling point of NaCl, for example, is 1413 °C. With covalent molecules, the boiling point depends on the identity of the functional group. For compounds of approximately the same molecular weight:



Recall from Sample Problem 3.3, for example, that the relative strength of the

intermolecular forces increases from pentane to butanal to butan-1-ol. The boiling points of these compounds increase in the same order.



Because surface area and polarizability affect the strength of intermolecular forces, they also affect the boiling point. For two compounds with similar functional groups:

- **The *larger* the surface area, the *higher* the boiling point.**
- **The *more polarizable* the atoms, the *higher* the boiling point.**

Examples of each phenomenon are illustrated in Figure 3.2. In comparing two ketones that differ in size, pentan-3-one has a higher boiling point than acetone because it has a greater molecular weight and *larger surface area*. In comparing two alkyl halides having the same number of carbon atoms, CH_3I has a higher boiling point than CH_3F because I is *more polarizable* than F.

- **In comparing two compounds, the lower-boiling compound is said to be *more volatile* and the higher-boiling compound is said to be *less volatile.***

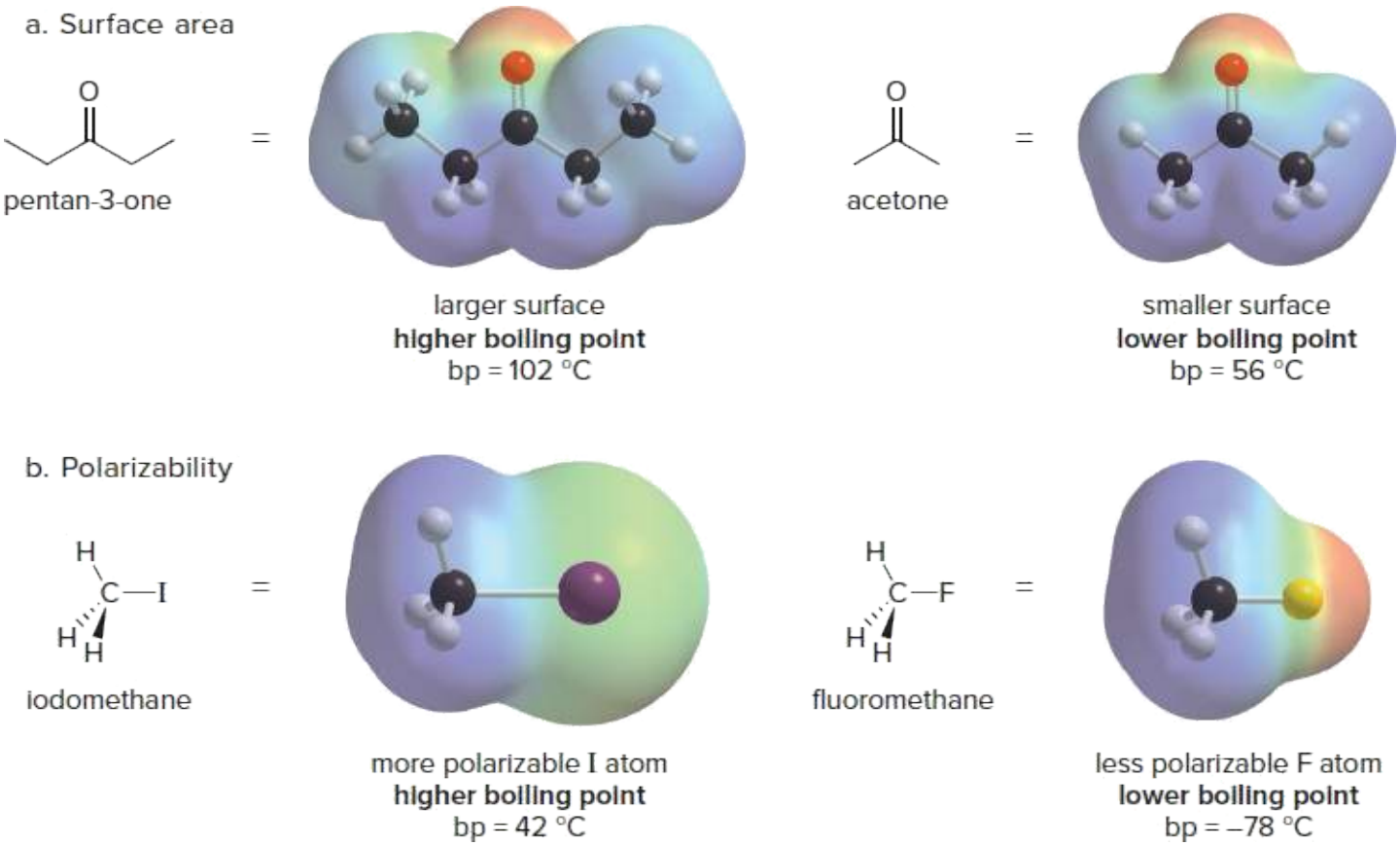
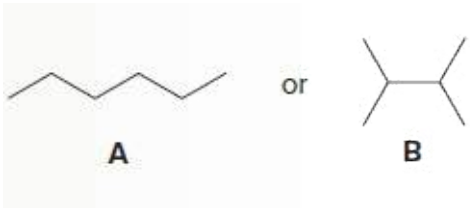


Figure 3.2 **Effect of surface area and polarizability on boiling point**

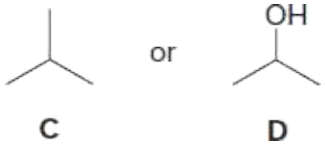
Sample Problem 3.4 Determining Relative Boiling Points

Which compound in each pair has the higher boiling point? Which compound in each pair is more volatile?

a.



b.



Solution

a. Isomers A and B have only nonpolar C–C and C–H bonds, so they exhibit only van der Waals forces. Because B is more compact, it has less surface area and a lower boiling point. The lower-boiling compound is more volatile, so B is more volatile than A.

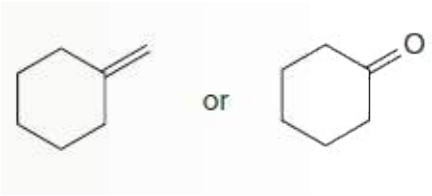
b. Compounds C and D have approximately the same molecular weight but different functional groups. C is a nonpolar alkane, exhibiting only van der

Waals forces. D is an alcohol with an O–H group available for hydrogen bonding, so it has stronger intermolecular forces and a higher boiling point. C is more volatile than D.

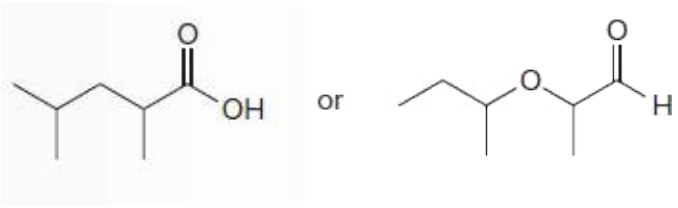
Problem 3.13

Which compound in each pair has the higher boiling point?

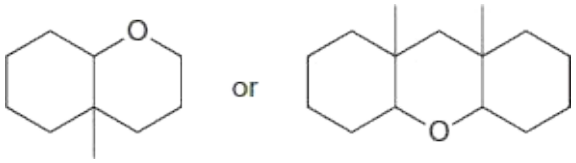
a.



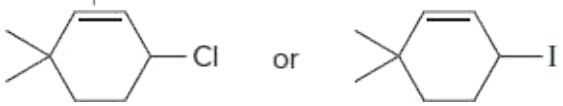
b.



c.



d.



More Practice:

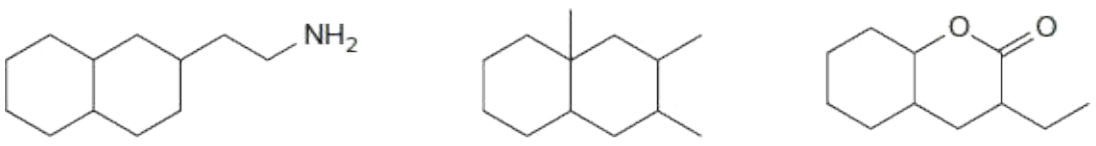
Try Problems 3.43, 3.44.

Problem 3.14

Explain why the boiling point of propanamide, $CH_3CH_2CONH_2$, is considerably higher than the boiling point of *N,N*-dimethylformamide, $HCON(CH_3)_2$ (213 °C vs. 153 °C), even though both compounds are isomeric amides.

Problem 3.15

Rank the following compounds in order of increasing boiling point.



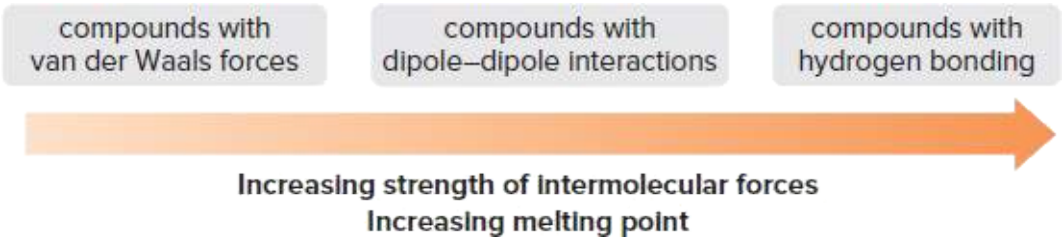
A B C

3.4B Melting Point (mp)

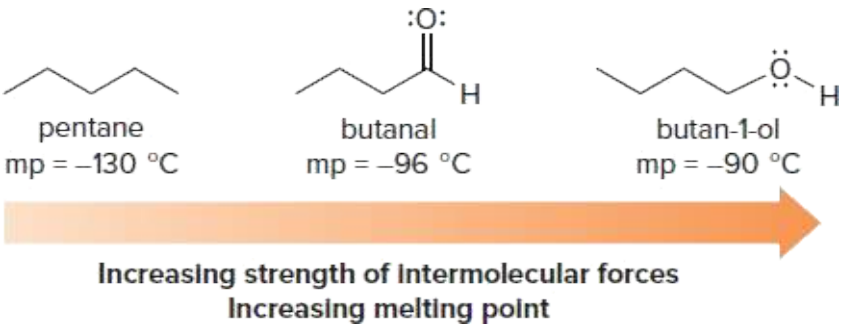
The *melting point* is the temperature at which a solid is converted to a liquid. In melting, energy is needed to overcome the attractive forces in the more ordered crystalline solid. Two factors determine the melting point of a compound.

- **The *stronger* the intermolecular forces, the *higher* the melting point.**
- **Given the same functional group, the *more symmetrical* the compound, the *higher* the melting point.**

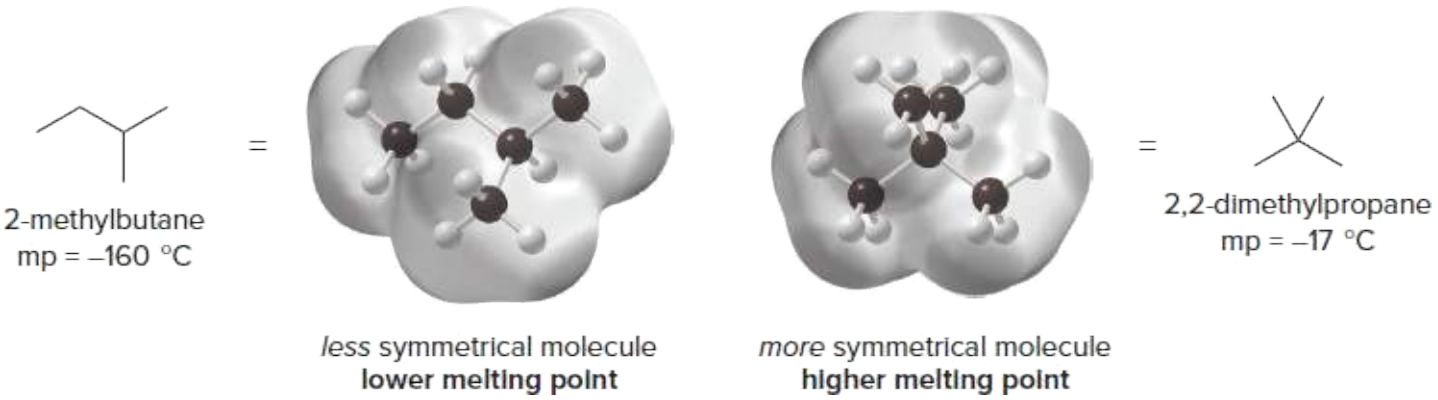
Because ionic compounds are held together by extremely strong interactions, they have very high melting points. For example, the melting point of NaCl is 801 °C. With covalent molecules, the melting point once again depends on the identity of the functional group. For compounds of approximately the same molecular weight:



The trend in the melting points of pentane, butanal, and butan-1-ol parallels the trend observed in their boiling points.

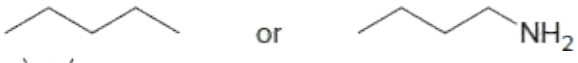


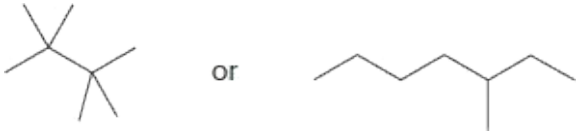
Symmetry also plays a role in determining the melting points of compounds having the same functional group and similar molecular weights, but very different shapes. A compact symmetrical molecule like 2,2-dimethylpropane packs well into a crystalline lattice whereas 2-methylbutane, which has a CH_3 group dangling from a four-carbon chain, does not. Thus, 2,2-dimethylpropane has a much higher melting point.



Problem 3.16

Predict which compound in each pair has the higher melting point.

a. 

b. 

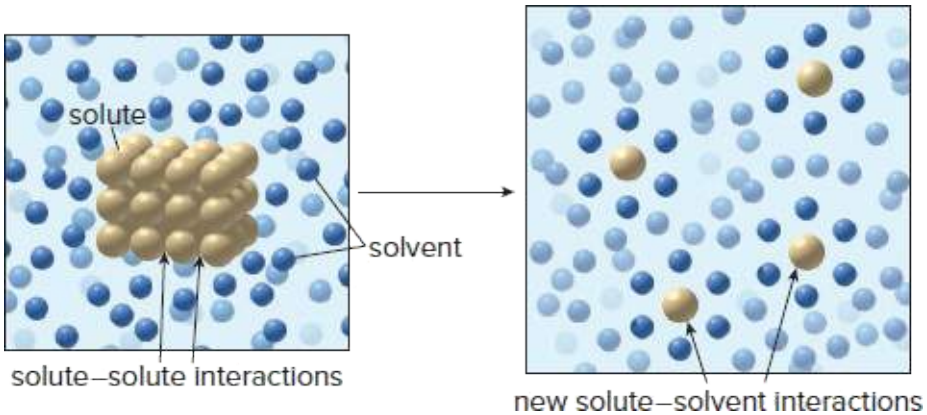
Problem 3.17

Consider acetic acid (CH_3CO_2H) and its conjugate base, sodium acetate (CH_3CO_2Na). (a) What intermolecular forces are present in each compound? (b) Explain why the melting point of sodium acetate (324 °C) is considerably higher than the melting point of acetic acid (17 °C).

3.4C Solubility

Solubility is the extent to which a compound, called the *solute*, dissolves in a liquid, called the *solvent*. In dissolving a compound, the energy needed to break up the interactions between the molecules or ions of the solute comes from new interactions between the solute and the solvent.

Quantitatively, a compound may be considered soluble when 3 g of solute dissolves in 100 mL of solvent.

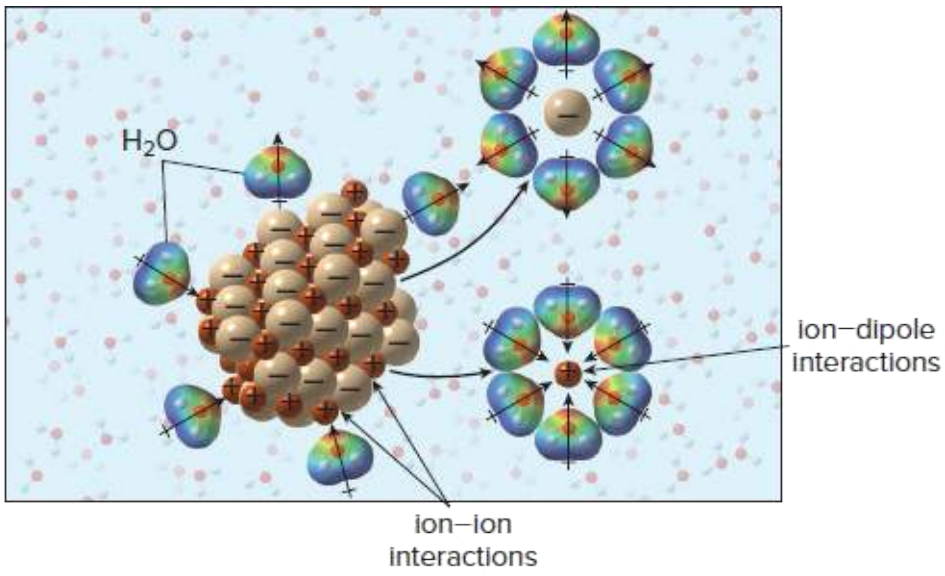


Compounds dissolve in solvents having similar kinds of intermolecular forces.

- **"Like dissolves like."**
- **Polar compounds dissolve in polar solvents. Nonpolar or weakly polar compounds dissolve in nonpolar or weakly polar solvents.**

Water and organic liquids are two different kinds of solvents. Water is very polar because it is capable of hydrogen bonding with a solute. Many organic solvents are either nonpolar, like carbon tetrachloride (CCl_4) and hexane [$CH_3(CH_2)_4CH_3$], or weakly polar like diethyl ether ($CH_3CH_2OCH_2CH_3$).

Ionic compounds are held together by strong electrostatic forces, so they need very polar solvents to dissolve. Most ionic compounds are soluble in water, but are insoluble in organic solvents. To dissolve an ionic compound, the strong ion–ion interactions must be replaced by many weaker ion–dipole interactions, as illustrated in Figure 3.3.

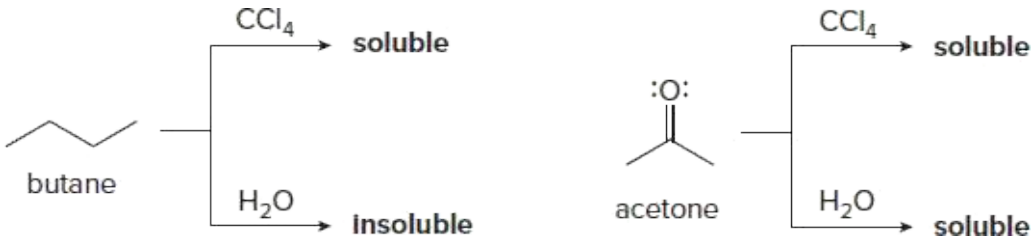


- When an ionic solid is dissolved in H_2O, the ion–ion interactions are replaced by ion–dipole interactions. Though these forces are weaker, there are so many of them that they compensate for the stronger ionic bonds.

Figure 3.3 **Dissolving an ionic compound in H_2O**

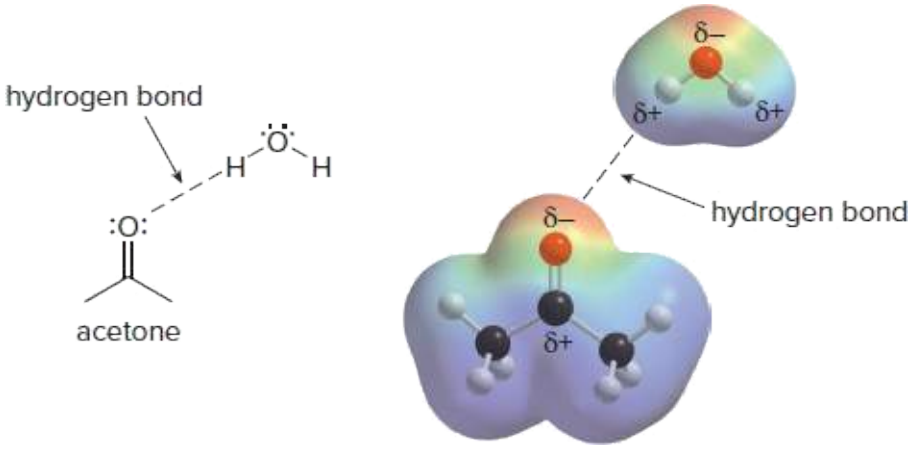
Most organic compounds are soluble in organic solvents (remember, *like dissolves like*). An organic compound is water soluble only if it contains one polar functional group capable of hydrogen bonding with the solvent for every five C atoms it contains. In other words, a water-soluble organic compound has an O- or N-containing functional group that solubilizes its nonpolar carbon backbone.

Compare, for example, the solubility of butane and acetone in H_2O and CCl_4.



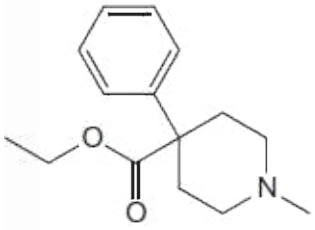
Because butane and acetone are both organic compounds having a C–C and C–H backbone, they are soluble in the organic solvent CCl_4. Butane, a nonpolar molecule, is insoluble in the polar solvent H_2O. Acetone, however, is H_2O soluble because it contains only three C atoms and its O atom can hydrogen bond with one H atom of H_2O. In fact, acetone is so soluble in water that acetone and water are miscible—they form solutions in all proportions with each other.

$(CH_3)_2C{=}O$ molecules cannot hydrogen bond to each other because they have no OH group. However, $(CH_3)_2C{=}O$ can hydrogen bond to H_2O because its O atom can hydrogen bond to one of the H atoms of H_2O.

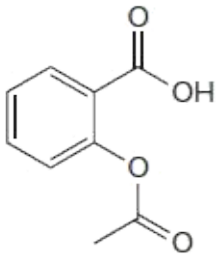


Sample Problem 3.5 Determining Hydrogen Bonding

(a) Which of the following compounds can hydrogen bond to another molecule like itself? (b) Which of the following compounds can hydrogen bond to water?



meperidine
(a narcotic)
trade name Demerol



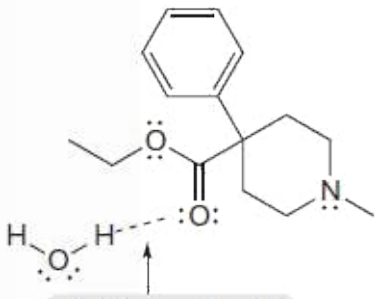
acetylsalicylic acid
(aspirin)

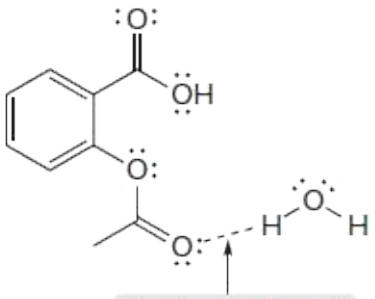
Solution

- **To hydrogen bond to another molecule like itself, a compound needs an O–H or N–H bond.**
- **To hydrogen bond with water, a compound needs an O or N atom.**

a. Only acetylsalicylic acid has an O–H bond for intermolecular hydrogen bonding, so two molecules of acetylsalicylic acid can hydrogen bond to each other, but two molecules of meperidine cannot.

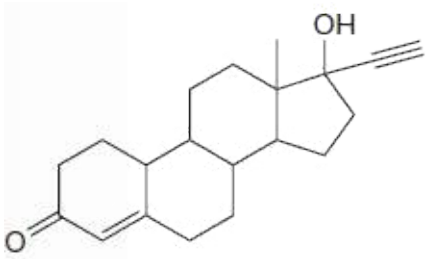
b. Both meperidine and acetylsalicylic acid have electronegative O atoms and meperidine has an electronegative N atom, so both compounds can hydrogen bond to water. One possibility for each compound:





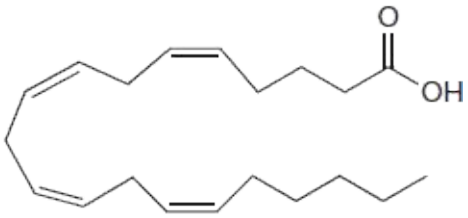
Problem 3.18

(a) At which sites can C hydrogen bond to another molecule like itself? (b) At which sites can D hydrogen bond to water?



C

norethindrone
(oral contraceptive component)



D

arachidonic acid
(fatty acid)

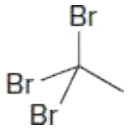
More Practice:

Try Problems 3.39; 3.40; 3.61a, b; 3.62c; 3.63c, d.

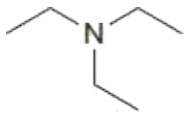
Problem 3.19

Which of the following molecules can hydrogen bond to another molecule like itself? Which can hydrogen bond to water?

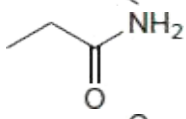
a.



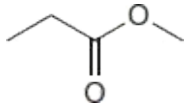
b.



c.

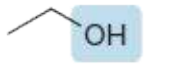


d.



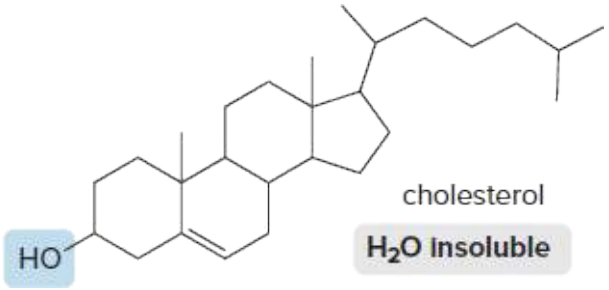
For an organic compound with one functional group, a compound is water soluble only if it has ≤ five C atoms and contains an O or N atom.

The size of an organic molecule with a polar functional group determines its water solubility. A low-molecular-weight alcohol like ethanol is water soluble because it has a small carbon skeleton (≤ five C atoms) compared to the size of its polar OH group. Cholesterol, on the other hand, has 27 carbon atoms and only one OH group. Its carbon skeleton is too large for the OH group to solubilize by hydrogen bonding, so cholesterol is insoluble in water.



ethanol

H_2O soluble



cholesterol

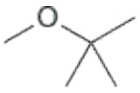
H_2O insoluble

Hydrophobic = afraid of H_2O.

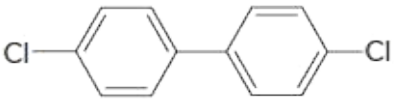
Hydrophilic = H_2O loving.

- **The nonpolar part of a molecule that is not attracted to H_2O is said to be *hydrophobic.***
- **The polar part of a molecule that can hydrogen bond to H_2O is said to be *hydrophilic.***

In cholesterol, for example, the hydroxy group is hydrophilic, whereas the carbon skeleton is hydrophobic.



MTBE
tert-butyl methyl ether



4,4'-dichlorobiphenyl
(a polychlorinated biphenyl, PCB)

MTBE (*tert*-butyl methyl ether) and 4,4′-dichlorobiphenyl (a polychlorinated biphenyl, abbreviated as PCB) demonstrate that solubility properties can help determine the fate of organic compounds in the environment.

Using MTBE as a high-octane additive in unleaded gasoline has had a negative environmental impact. Although MTBE is not toxic or carcinogenic, it has a distinctive, nauseating odor, and it is water soluble. Small amounts of MTBE have contaminated the drinking water in several communities, making it unfit for consumption. For this reason, the use of MTBE as a gasoline additive has steadily declined in the United States since 1999.

4,4′-Dichlorobiphenyl is a polychlorinated biphenyl (PCB), a compound that contains two benzene rings joined by a C–C bond, and substituted by one or more chlorine

atoms on each ring. PCBs have been used as plasticizers in polystyrene coffee cups and coolants in transformers. They have been released into the environment during production, use, storage, and disposal, making them one of the most widespread organic pollutants. PCBs are insoluble in H_2O, but very soluble in organic media, so they are soluble in fatty tissue, including that found in all types of fish and birds around the world. Although PCBs are not acutely toxic, frequently ingesting large quantities of fish contaminated with PCBs has been shown to retard growth and memory retention in children.

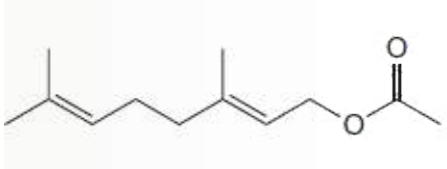
Solubility properties of some representative compounds are summarized in Table 3.5.

Table 3.5 Summary of Solubility

Type of compound	Solubility in H_2O	Solubility in organic solvents (such as CCl_4)
Ionic		
NaCl	**soluble**	**insoluble**
Covalent		
$CH_3CH_2CH_2CH_3$	**insoluble (no N or O atom to hydrogen bond to H_2O)**	**soluble**
$CH_3CH_2CH_2OH$	**soluble (≤ 5 C's and an O atom for hydrogen bonding to H_2O)**	**soluble**
$CH_3(CH_2)_{10}OH$	**insoluble (> 5 C's; too large to be soluble even though it has an O atom for hydrogen bonding to H_2O)**	**soluble**

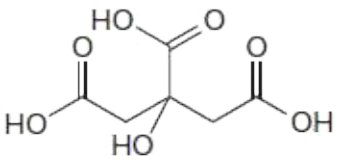
Sample Problem 3.6 Predicting the Water Solubility of a Compound

Which compounds are water soluble?



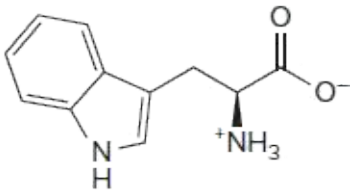
geranyl acetate
(from lily of the valley)

A



citric acid
(tart acid from citrus fruits)

B



tryptophan
(an amino acid)

C

Solution

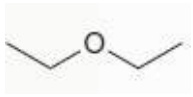
Water-soluble compounds are ionic or contain a functional group with an O or N atom that can hydrogen bond to water for every 5 C's.

- **A has 12 C's and only one oxygen-containing functional group (an ester), so A is water insoluble.**
- **B has 6 C's and many OH and C=O's that can hydrogen bond to water, so B is water soluble.**
- **C is ionic, so C is water soluble.**

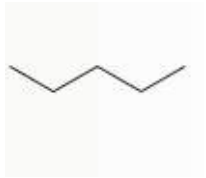
Problem 3.20

Which compounds are water soluble?

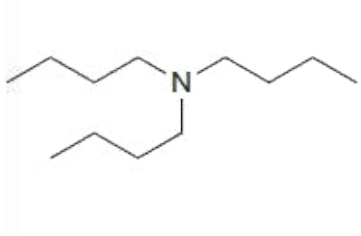
a.



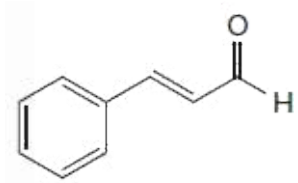
b.



c.

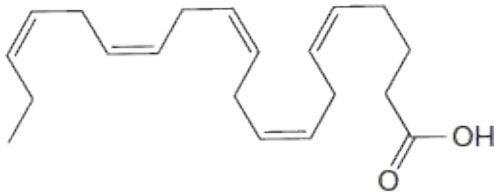


d.



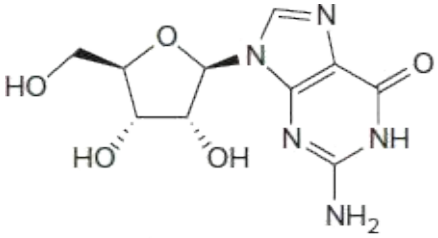
cinnamaldehyde
(odor of cinnamon)

e.



eicosapentaenoic acid
(fatty acid from fish oil)

f.



guanosine
(DNA component)

More Practice:

Try Problems 3.48, 3.50, 3.51.

3.5 Application: Vitamins

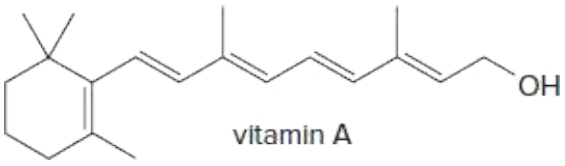
Vitamins are organic compounds needed in small amounts for normal cell function. Our bodies cannot synthesize these compounds, so they must be obtained in the diet. Most vitamins are identified by a letter, such as A, C, D, E, and K. There are several different B vitamins, though, so a subscript is added to distinguish them: for example, B_1, B_2, and B_{12}.

Whether a vitamin is fat soluble (it dissolves in organic media) or water soluble can be determined by applying the solubility principles discussed in Section 3.4C. Vitamins A and C illustrate the differences between fat-soluble and water-soluble vitamins.

3.5A Vitamin A

Vitamin A, or retinol, is an essential component of the vision receptors in the eyes. It also helps to maintain the health of mucous membranes and the skin, so many anti-aging creams contain vitamin A. A deficiency of this vitamin leads to a loss of night vision.

Vitamin A is synthesized from β-carotene, the orange pigment in carrots. ©*Purestock/SuperStock*

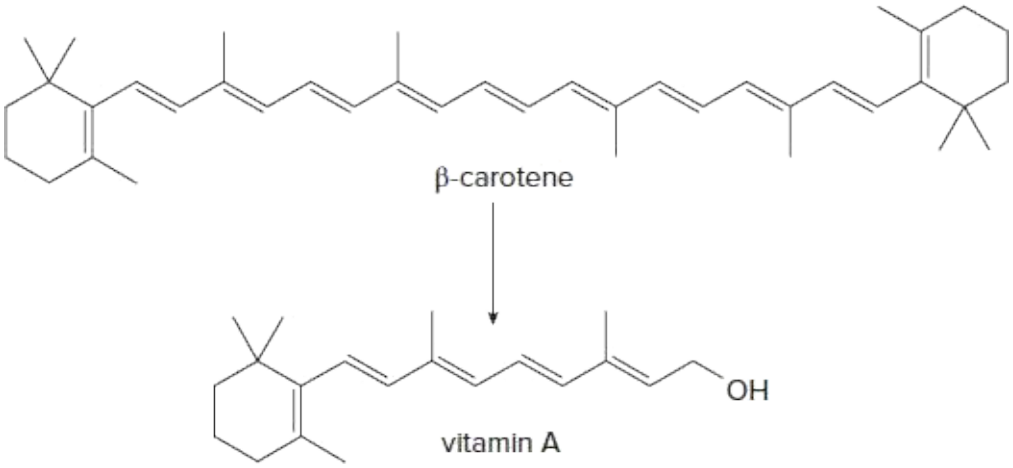


vitamin A

Vitamin A contains 20 carbons and a single OH group, making it water insoluble. Because it is organic, it is soluble in any organic medium. To understand the consequences of these solubility characteristics, we must learn about the chemical environment of the body.

About 70% of the body is composed of water. Fluids such as blood, gastric juices in the stomach, and urine are largely water with dissolved ions such as Na^+ and K^+. Vitamin A is insoluble in these fluids. There are also fat cells composed of organic compounds having C–C and C–H bonds. Vitamin A is soluble in this organic environment, and thus it is readily stored in these fat cells, particularly in the liver.

Vitamin A may be obtained directly from the diet. In addition, β-carotene, the orange pigment found in many plants including carrots, is readily converted to vitamin A in our bodies.



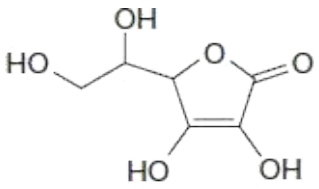
Eating too many carrots does not result in an excess of stored vitamin A. If you consume more β-carotene than you need, your body stores this precursor until it needs more vitamin A. Some β-carotene reaches the surface tissues of the skin and eyes, giving them an orange color. This phenomenon may look odd, but it is harmless and reversible. When stored β-carotene is converted to vitamin A and is no longer in excess, these tissues will return to their normal hue.

3.5B Vitamin C

Although most animal species can synthesize vitamin C, humans, guinea pigs, the Indian fruit bat, and the bulbul bird must obtain this vitamin from dietary sources. Citrus fruits, strawberries, kiwi, tomatoes, and sweet potatoes are all excellent sources of vitamin C.

Vitamin C is obtained by eating citrus fruits and a wide variety of other fruits and vegetables. Individuals can also obtain the recommended daily dose of vitamin C by taking tablets that contain vitamin C prepared in the laboratory. Both the "natural" vitamin C in oranges and the "synthetic" vitamin C in vitamin supplements are identical.

©McGraw-Hill Education/Mary Reeg, photographer



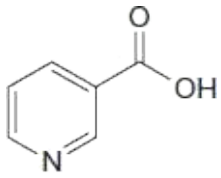
vitamin C
(ascorbic acid)

Vitamin C has six carbon atoms, each bonded to an oxygen atom that is capable of hydrogen bonding, making it water soluble. Vitamin C thus dissolves in urine. Although it has been acclaimed as a deterrent for all kinds of diseases, from the common cold to cancer, the consequences of taking large amounts of vitamin C are not really known, because any excess of the minimum daily requirement is excreted in the urine.

Problem 3.21

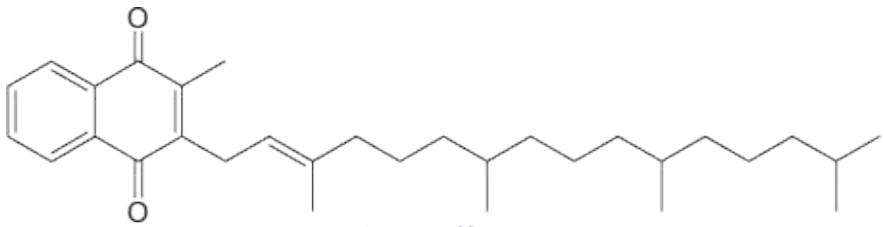
Predict the water solubility of each vitamin.

a.



vitamin B_3
(niacin)

b.

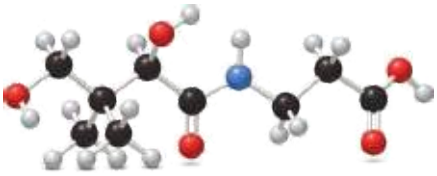


vitamin K_1
(phylloquinone)

Avocados are an excellent dietary source of pantothenic acid, vitamin B5. ©*Pixtal/age fotostock*

Problem 3.22

(a) Identify the functional groups in the ball-and-stick model of pantothenic acid, vitamin B_5. (b) At which sites can pantothenic acid hydrogen bond to water? (c) Predict the water solubility of pantothenic acid.



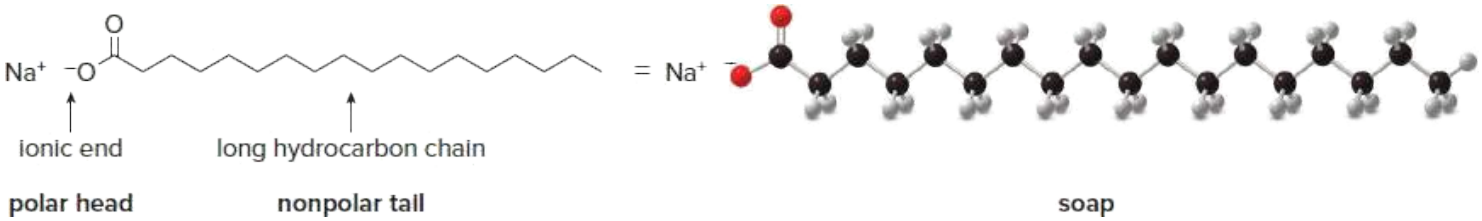
pantothenic acid
vitamin B_5

3.6 Application of Solubility: Soap

Soap has been used by humankind for some 2000 years. Historical records describe its manufacture in the first century and document the presence of a soap factory in Pompeii. Before this time clothes were cleaned by rubbing them on rocks in water, or by forming soapy lathers from the roots, bark, and leaves of certain plants. These plants produced natural materials called *saponins*, which act in much the same way as modern soaps.

On a molecular level, soap has two distinct parts:

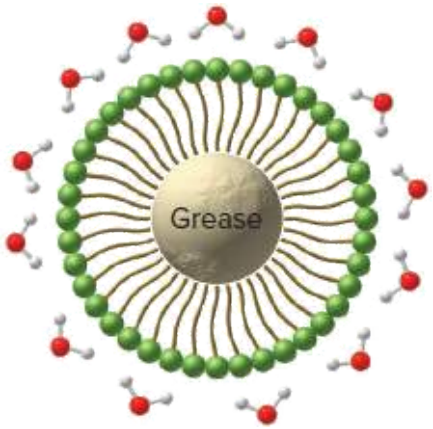
- a hydrophilic portion composed of ions, called the *polar head*
- a hydrophobic carbon chain of nonpolar C–C and C–H bonds, called the *nonpolar tail*



Dissolving soap in water forms *micelles*, spherical droplets having the ionic heads on the surface and the nonpolar tails packed together in the interior, as shown in Figure 3.4. In this arrangement, the ionic heads are solvated by the polar solvent water, thus solubilizing the nonpolar, "greasy" hydrocarbon portion of the soap.

- When soap is dissolved in H_2O, it forms micelles with the nonpolar tails in the interior and the polar heads on the surface. The polar heads are solvated by ion–dipole interactions with H_2O molecules.

Figure 3.4 **Dissolving soap in water**



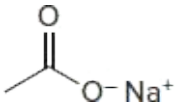
Cross-section of a soap micelle with a grease particle dissolved in the interior

How does soap dissolve grease and oil? Water alone cannot dissolve dirt, which is composed largely of nonpolar hydrocarbons. When soap is mixed with water, however, the nonpolar hydrocarbon tails dissolve the dirt in the interior of the micelle. The polar head of the soap remains on the surface of the micelle to interact with water. The nonpolar tails of the soap are so well sealed off from the water by the polar head groups that the micelles are water soluble, allowing them to separate from the fibers of our clothes and be washed down the drain with water. In this way, soaps do a seemingly impossible task: they remove nonpolar hydrocarbon material from skin and clothes, by solubilizing it in the polar solvent water.

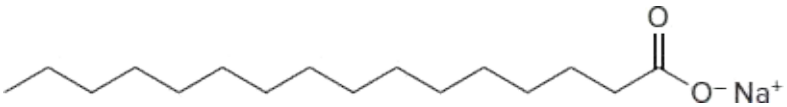
Problem 3.23

Which of the following structures represent soaps? Explain your answers.

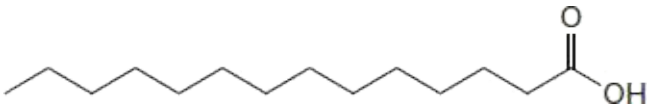
a.



b.

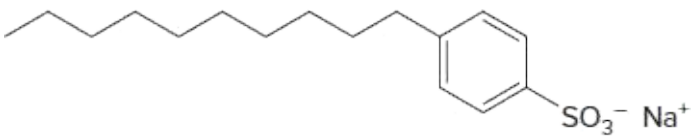


c.



Problem 3.24

Today, synthetic detergents like the compound drawn here, not soaps, are used to clean clothes. Explain how this detergent cleans away dirt.



a detergent

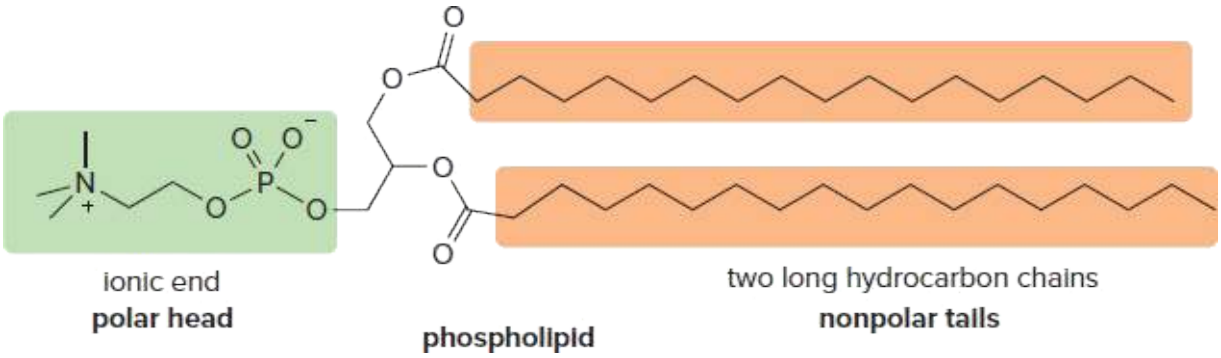
3.7 Application: The Cell Membrane

The cell membrane is a beautifully complex example of how the principles of organic chemistry come into play in a biological system.

3.7A Structure of the Cell Membrane

The basic unit of living organisms is the cell. The cytoplasm is the aqueous medium inside the cell, separated from water outside the cell by the cell membrane. The cell membrane acts as a barrier to the passage of ions, water, and other molecules into and out of the cell, and it is also selectively permeable, letting nutrients in and waste out.

A major component of the cell membrane is a group of organic compounds called phospholipids. Like soap, they contain a hydrophilic ionic portion and a hydrophobic hydrocarbon portion, in this case two long carbon chains composed of C–C and C–H bonds. Phospholipids thus contain a polar head and *two* nonpolar tails.

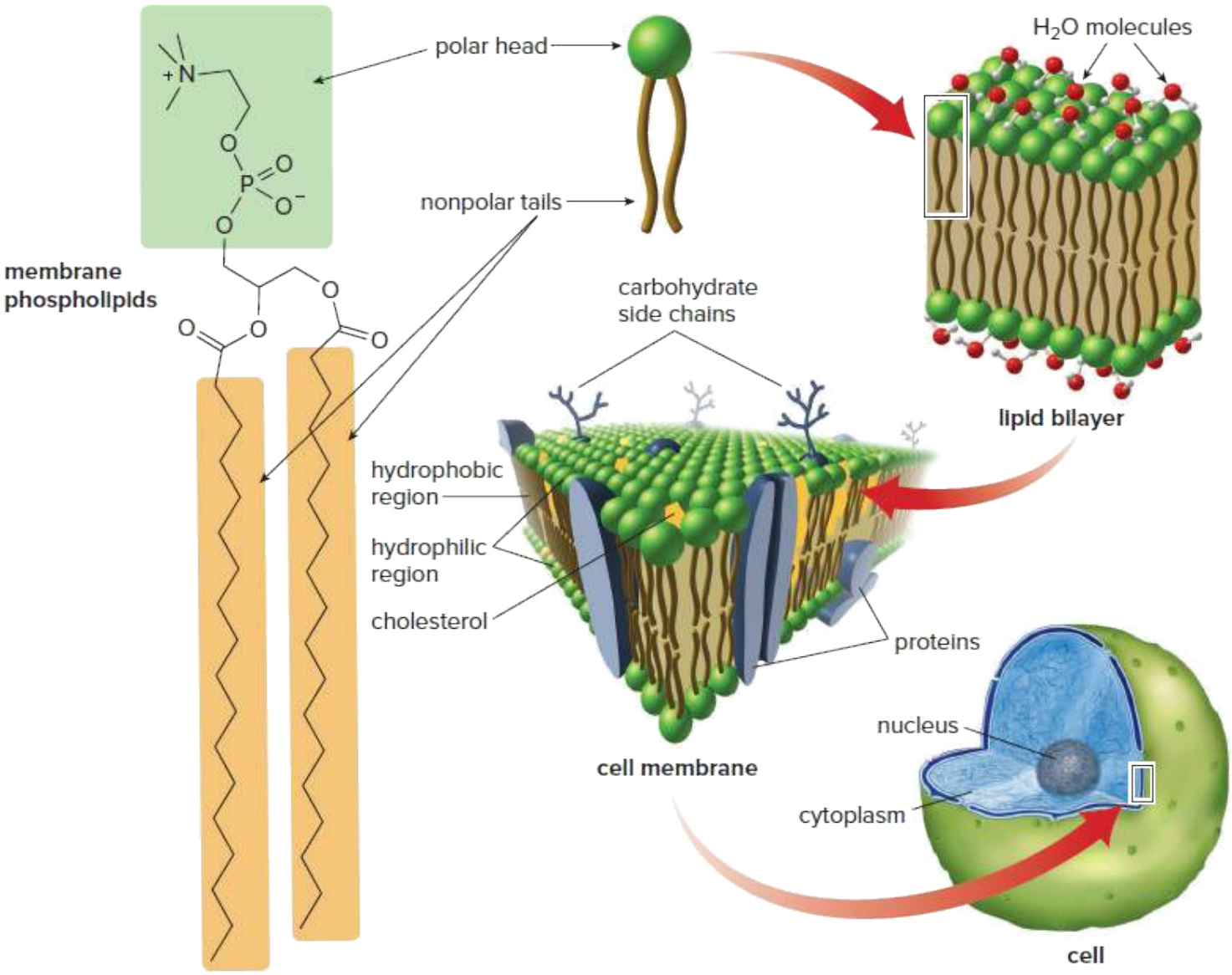


When phospholipids are mixed with water, they assemble in an arrangement called a lipid bilayer, with the ionic heads oriented on the outside and the nonpolar tails on the inside. The polar heads electrostatically interact with the polar solvent H_2O, while the nonpolar tails are held in close proximity by numerous van der Waals interactions. This is schematically illustrated in Figure 3.5.

Cell membranes are composed of these lipid bilayers. The charged heads of the phospholipids are oriented toward the aqueous interior and exterior of the cell. The nonpolar tails form the hydrophobic interior of the membrane, thus serving as an insoluble barrier that protects the cell from the outside.

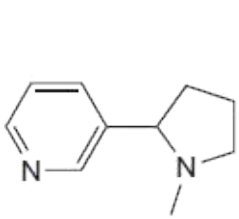
The nonpolar interior of the cell membrane is especially important in protecting the human brain from fluctuation in the concentration of compounds in the blood, as well as the passage of unwanted substances into the brain. The blood–brain barrier consists of a tight layer of cells in the blood capillaries of the brain, and all substances must pass through the cell membrane of these capillaries to enter the brain. Because ions are not soluble in the nonpolar interior of the cell membrane, the blood–brain barrier is

only slightly permeable to ions. On the other hand, uncharged organic molecules like nicotine, caffeine, and heroin are very soluble in the interior of the cell membrane, so they readily pass into the brain.

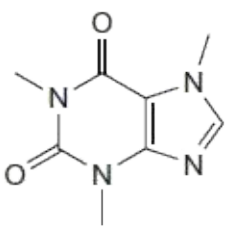


- Phospholipids contain an ionic or polar head, and two long nonpolar hydrocarbon tails. In an aqueous environment, phospholipids form a lipid bilayer, with the polar heads oriented toward the aqueous exterior and the nonpolar tails forming a hydrophobic interior. Cell membranes are composed largely of this lipid bilayer.

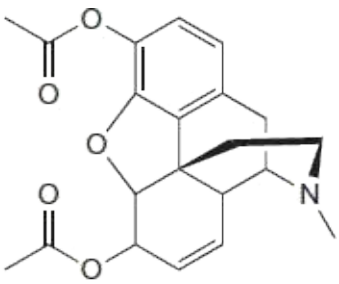
Figure 3.5 **The cell membrane**



nicotine



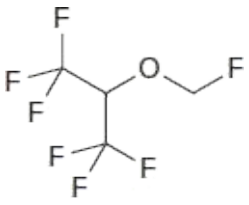
caffeine



heroin

General anesthetics such as sevoflurane are also weakly polar compounds that can

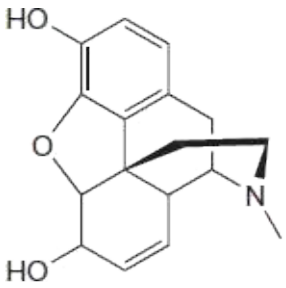
penetrate the blood–brain barrier because they are soluble in the lipid bilayer of the blood capillaries.



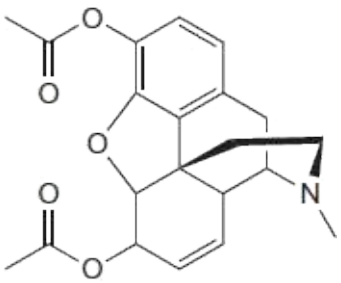
sevoflurane

Problem 3.25

(a) What types of intermolecular forces do morphine and heroin each possess? (b) Which compound can cross the blood–brain barrier more readily, and therefore serve as the more potent pain reliever?



morphine



heroin

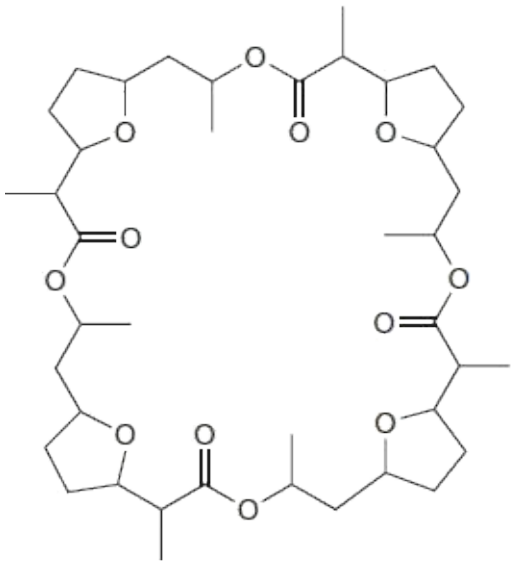
Problem 3.26

Explain why the noble gas xenon is a general anesthetic.

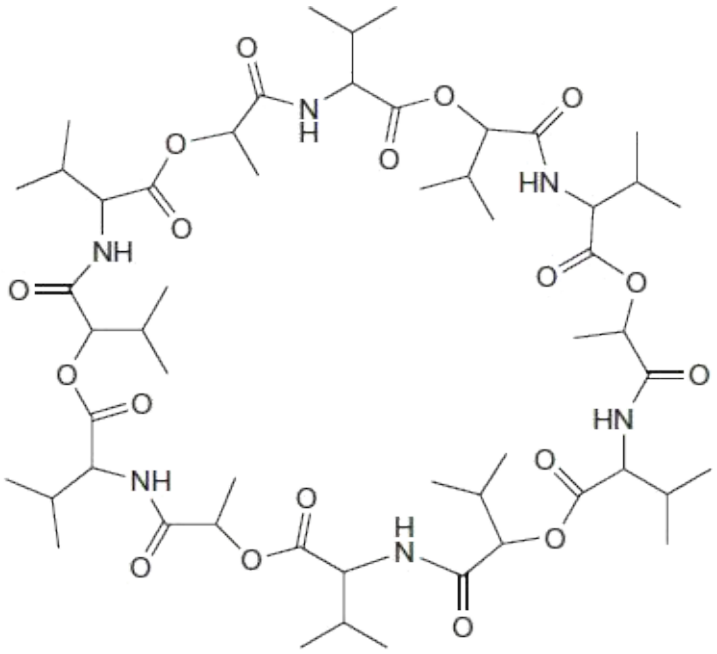
3.7B Transport Across a Cell Membrane

How does a polar molecule or ion in the water outside a cell pass through the nonpolar interior of the cell membrane and enter the cell? Some nonpolar molecules like O_2 are small enough to enter and exit the cell by diffusion. Polar molecules and ions, on the other hand, may be too large or too polar to diffuse efficiently. Some ions are transported across the membrane with the help of molecules called ionophores.

Ionophores are organic molecules that complex cations. They have a hydrophobic exterior that makes them soluble in the nonpolar interior of the cell membrane, and a central cavity with several oxygen atoms whose lone pairs complex with a given ion. The size of the cavity determines the identity of the cation with which the ionophore complexes. Two naturally occurring antibiotics that act as ionophores are nonactin and valinomycin.

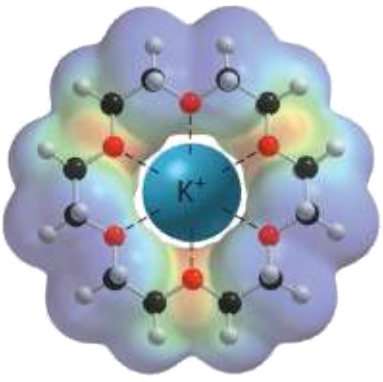


nonactin

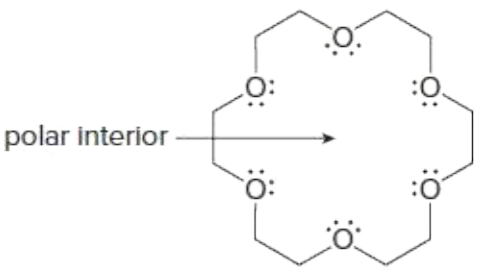


valinomycin

Several synthetic ionophores have also been prepared, including one group called crown ethers. *Crown ethers* are cyclic ethers containing several oxygen atoms that bind specific cations depending on the size of their cavity. Crown ethers are named according to the general format *x*-crown-*y*, where *x* is the total number of atoms in the ring and *y* is the number of oxygen atoms. For example, 18-crown-6 contains 18 atoms in the ring, including 6 O atoms. This crown ether binds potassium ions. Sodium ions are too small to form a tight complex with the O atoms, and larger cations do not fit in the cavity.



complex with K^+



18-crown-6

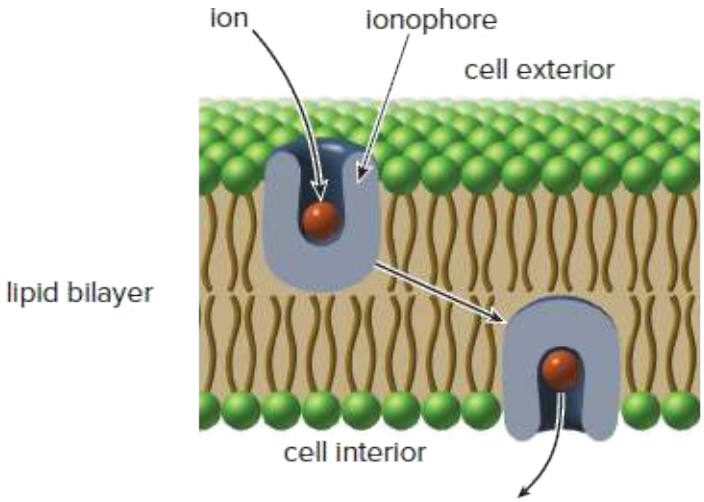
How does an ionophore transfer an ion across a membrane? The ionophore binds the

ion on one side of the membrane in its polar interior. It can then move across the membrane because its hydrophobic exterior interacts with the hydrophobic tails of the phospholipid. The ionophore then releases the ion on the other side of the membrane. This ion-transfer role is essential for normal cell function. This process is illustrated in Figure 3.6.

In this manner, antibiotic ionophores like nonactin transport ions across a cell membrane of bacteria. This disrupts the normal ionic balance in the cell, thus interfering with cell function and causing the bacteria to die.

Problem 3.27

Now that you have learned about solubility, explain why aspirin (Section 2.7) crosses a cell membrane as a neutral carboxylic acid rather than an ionic conjugate base.



- By binding an ion on one side of a lipid bilayer (where the concentration of the ion is high) and releasing it on the other side of the bilayer (where the concentration of the ion is low), an ionophore transports an ion across a cell membrane.

Figure 3.6 **Transport of ions across a cell membrane**

3.8 Functional Groups and Reactivity

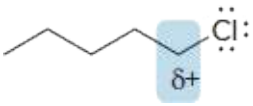
Much of Chapter 3 has been devoted to how a functional group determines the strength of intermolecular forces and, consequently, the physical properties of molecules. A functional group also determines reactivity. What type of reaction does a particular kind of organic compound undergo? Begin by recalling two fundamental concepts:

- **Functional groups create reactive sites in molecules.**

- **Electron-rich sites react with electron-poor sites.**

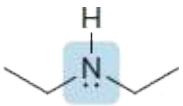
All functional groups contain a heteroatom, a π bond, or both, and these features make electron-deficient (or electrophilic) sites and electron-rich (or nucleophilic) sites in a molecule. To predict reactivity, first locate the functional group and then determine the resulting electron-rich or electron-deficient sites it creates. Keep three guidelines in mind:

- **An electronegative heteroatom like N, O, or X makes a carbon atom *electrophilic.***



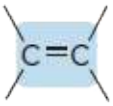
- **A lone pair on a heteroatom makes it *basic* and *nucleophilic.***

base
nucleophile



base
nucleophile

- **π Bonds create *nucleophilic* sites and are more easily broken than σ bonds.**



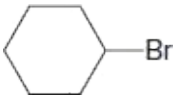
one easily broken
π bond

two easily broken
π bonds

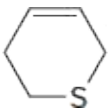
Problem 3.28

Label the electrophilic and nucleophilic sites in each molecule.

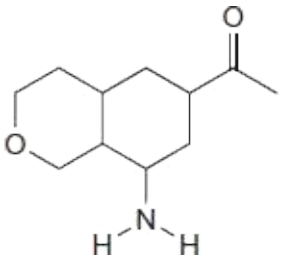
a.



b.



c.



:Nu$^-$ = a nucleophile;

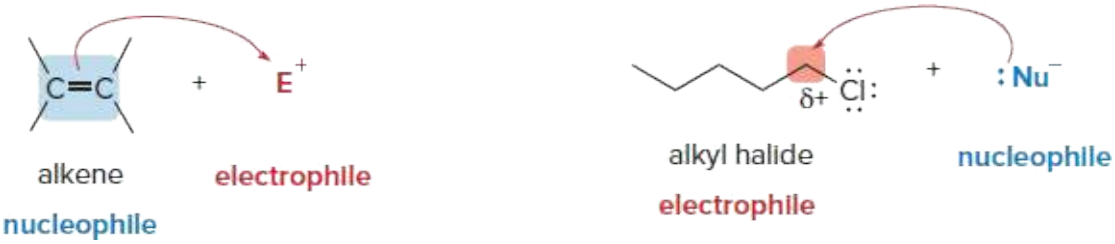
E$^+$ = an electrophile.

By identifying the nucleophilic and electrophilic sites in a compound you can begin to understand how it will react. In general, electron-rich sites react with electron-deficient sites:

- **An electron-deficient carbon atom reacts with a nucleophile, symbolized as: Nu$^-$.**
- **An electron-rich carbon reacts with an electrophile, symbolized as E$^+$.**

At this point we don't know enough organic chemistry to draw the products of many reactions with confidence. We do know enough, however, to begin to predict if two compounds might react together based solely on electron density arguments, and at what atoms that reaction is most likely to occur.

For example, alkenes contain an electron-rich C–C double bond, so they react with electrophiles, E$^+$. On the other hand, alkyl halides possess an electrophilic carbon atom, so they react with electron-rich nucleophiles.

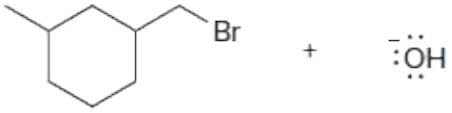


You don't need to worry about the products of these reactions. At this point you should only be able to find reactive sites in molecules and begin to understand why a reaction might occur at these sites. After you learn more about the structure of organic molecules in Chapters 4 and 5s, we will begin a detailed discussion of organic reactions in Chapter 6.

Problem 3.29

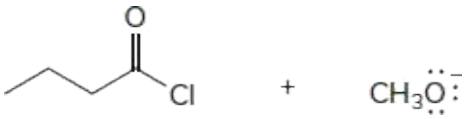
Considering only electron density, state whether the following reactions will occur.

a.

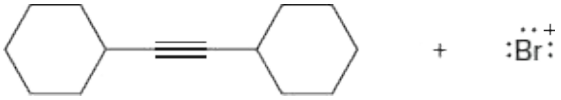


b.

c.

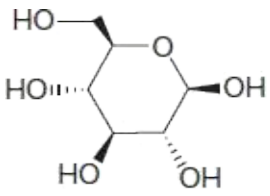


d.

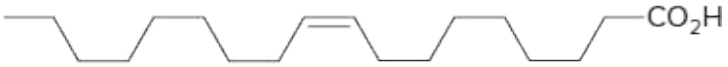


3.9 Biomolecules

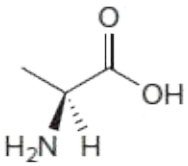
Biomolecules are organic compounds found in biological systems. Many are relatively small, with molecular weights of less than 1000 g/mol. There are four main families of these small molecules—simple sugars, amino acids, lipids, and nucleotides. Many simple biomolecules are used to synthesize larger compounds that have important cellular functions.



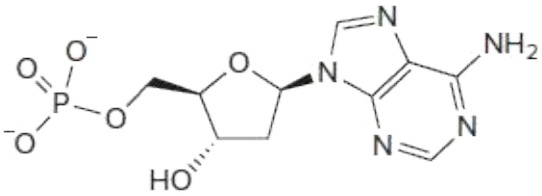
glucose
a simple sugar



oleic acid
a fatty acid



alanine
an amino acid



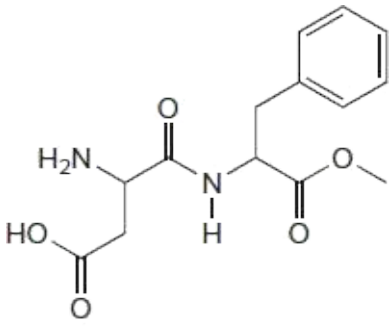
deoxyadenosine 5'-monophosphate
a nucleotide

Simple sugars such as glucose combine to form the complex carbohydrates starch and cellulose, as described in Chapter 26. Alanine is an amino acid used to synthesize proteins, the subject of Chapter 27. Fatty acids such as oleic acid react with alcohols to form triacylglycerols, the most prevalent lipids, first mentioned in Chapter 10, and discussed in more detail in Chapters 18 and 29. While these biomolecules all contain more than one functional group, their properties and reactions are explained by the principles of basic organic chemistry.

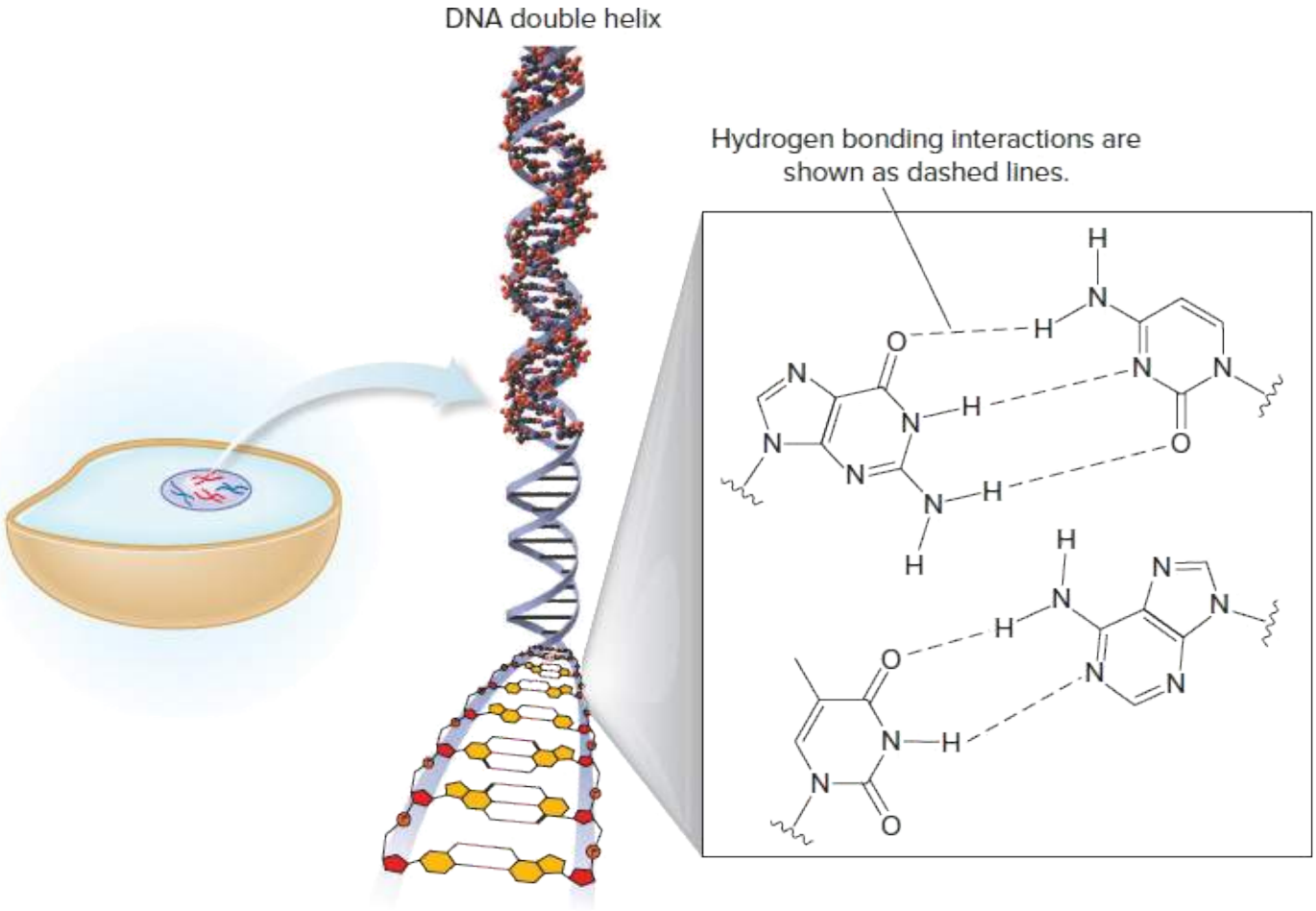
Finally, deoxyadenosine 5′-monophosphate is a nucleotide that combines with thousands of other nucleotides to form DNA, deoxyribonucleic acid, the high-molecular-weight polynucleotide that stores the genetic information of an organism. DNA consists of two polynucleotide chains that wind together in a double helix. Figure 3.7 illustrates the importance of hydrogen bonding in the structure of DNA. The two polynucleotide chains are held together by an extensive network of hydrogen bonds in which the N–H groups on one chain intermolecularly hydrogen bond to an oxygen or nitrogen atom on the adjacent chain.

Problem 3.30

The fact that sweet-tasting carbohydrates like table sugar are also high in calories has prompted the development of sweet, low-calorie alternatives. (a) Identify the functional groups in aspartame, the artificial sweetener in Equal. (b) Label all of the sites that can hydrogen bond to the oxygen atom of water. (c) Label all of the sites that can hydrogen bond to a hydrogen atom of water.



aspartame



- DNA, which is contained in the chromosomes of the nucleus of a cell, stores all of the genetic information in an organism. DNA consists of two long strands of polynucleotides held together by hydrogen bonding.

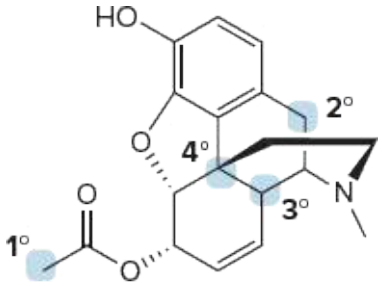
Figure 3.7 **The double helix of DNA**

Chapter 3 REVIEW

KEY CONCEPTS

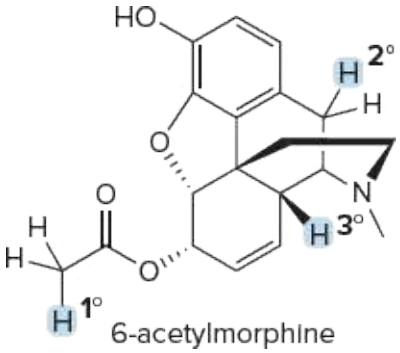
[1] Classifying atoms and functional groups (3.2)

1 Carbon atoms	2 Hydrogen atoms	3 Alcohols and alkyl halides



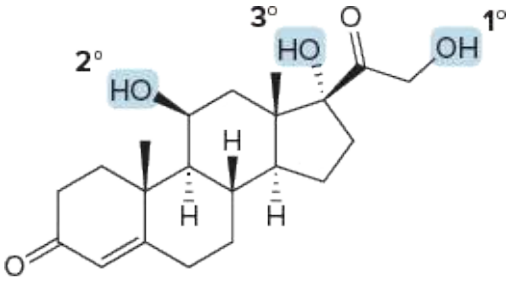
6-acetylmorphine

- **Carbon atoms are classified by the number of carbon atoms bonded to them; a 1° carbon is bonded to one other carbon, and so forth.**



6-acetylmorphine

- **Hydrogen atoms are classified by the type of carbon to which they are bonded; a 1° hydrogen is bonded to a 1° carbon, and so forth.**

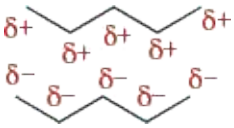
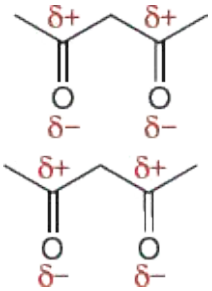
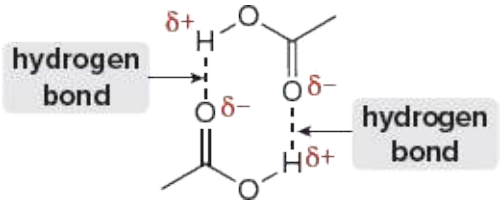


cortisol

- **Alcohols and alkyl halides are classified by the type of carbon to which they are bonded; a 1° alcohol has an OH group bonded to a 1° carbon, and so forth.**

See Sample Problem 3.1. Try Problems 3.33, 3.34, 3.36b, 3.61d, 3.62b, 3.63b, 3.64b.

[2] Types of intermolecular forces (3.3)

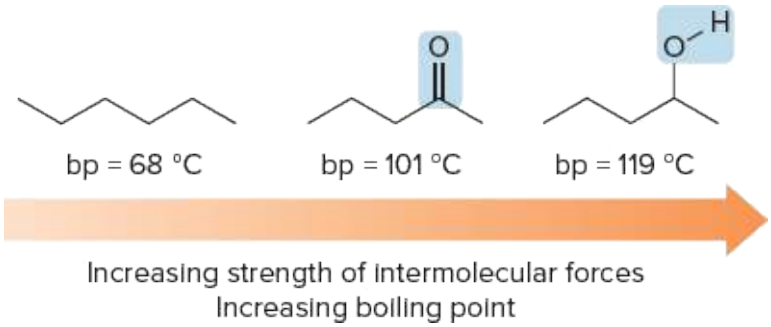
1 Van der Waals	2 Dipole–dipole	3 Hydrogen bonding	4 I
			
• weakest force • caused by the interaction of temporary	• caused by the interaction of permanent	• strongest force in covalent compounds • caused by the electrostatic interaction of a H atom in an O–H, N–H,	•

dipoles See Figure 3.1.	dipoles	or H–F bond with the lone pair of another N, O, or F atom	

See Table 3.4, Sample Problem 3.3. Try Problems 3.38, 3.41, 3.66d.

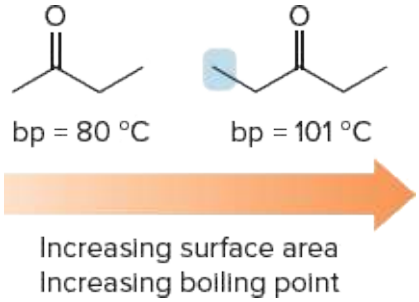
[3] Factors that determine boiling point (3.4A)

1 Intermolecular forces



- **For compounds of comparable molecular weight, the stronger the intermolecular forces, the higher the boiling point.**

2 Surface area



- **For compounds with similar functional groups, the larger the surface area, the higher the boiling point.**

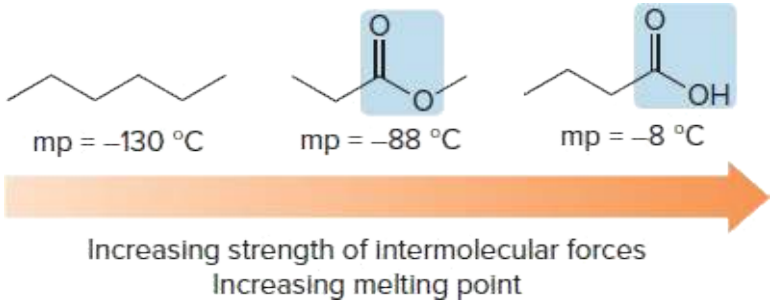
3 P

- I

See Figure 3.2, Sample Problem 3.4. Try Problems 3.43, 3.44.

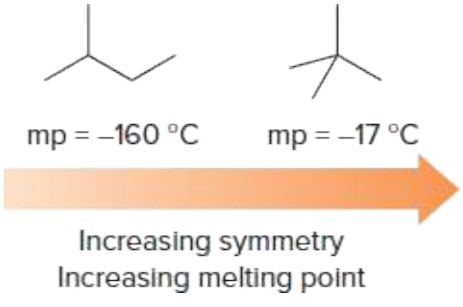
[4] Factors that determine melting point (3.4B)

1 Intermolecular forces



- **For compounds of comparable molecular weight, the stronger the intermolecular forces, the higher the melting point.**

2 Symmetry

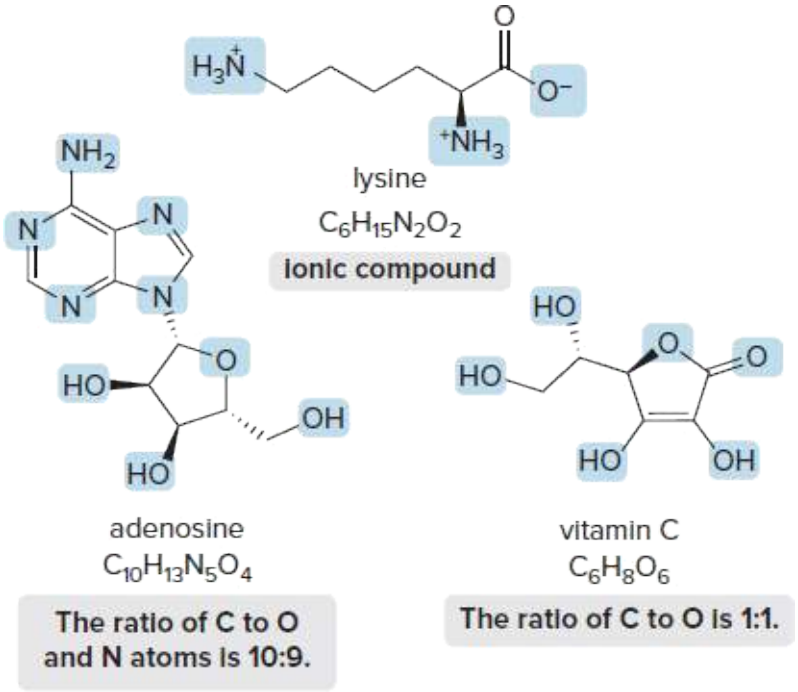
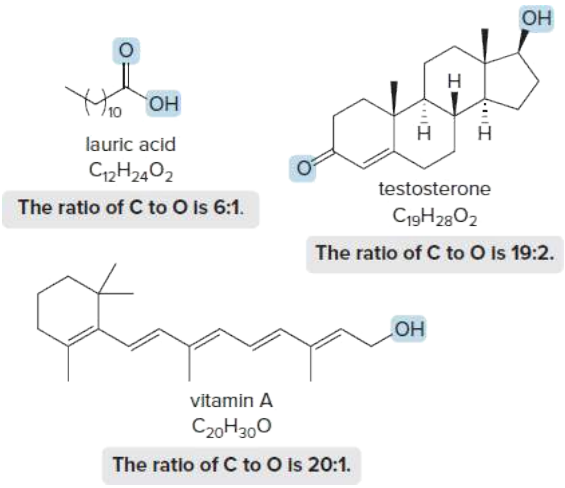


- **For compounds with similar functional groups, the more symmetrical, the higher**

	the melting point.

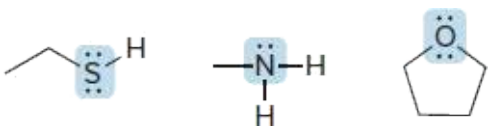
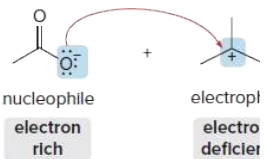
Try Problems 3.45, 3.46.

[5] Factors that determine solubility (3.4C, 3.5)

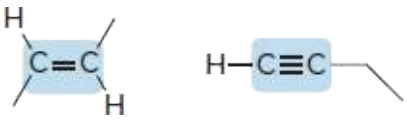
1 Water-soluble compounds	2 Water-insoluble compounds
	
• Ionic compounds are water soluble. • Organic compounds that have a ratio of ≤ five C atoms per O or N atom are water soluble.	• Compounds that have a ratio of > five C atoms per O or N atom are water insoluble.

See Figure 3.3, Table 3.5. Try Problems 3.48, 3.50, 3.51.

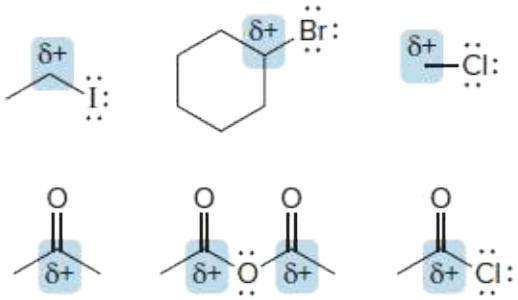
[6] Reactivity of functional groups (3.8)

1 Nucleophiles	2 Electrophiles	3 The reactio of nucleophile with electrophile
		
• A lone pair on a heteroatom makes it		• The

basic and nucleophilic.



- π Bonds create nucleophilic sites and are more easily broken than σ bonds.



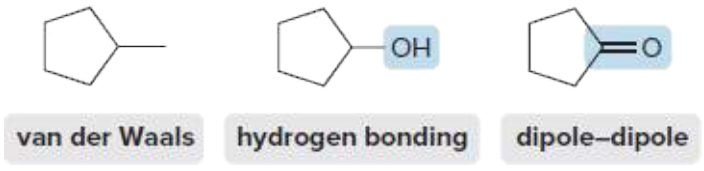
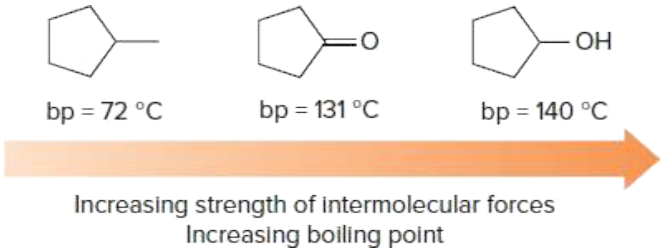
- An electronegative heteroatom like N, O, or X makes a carbon atom electrophilic.

electron-rich nucleophil reacts with the electron-deficient electrophil

Try Problems 3.31c; 3.32c; 3.57; 3.58; 3.62d, e; 3.66g.

KEY SKILLS

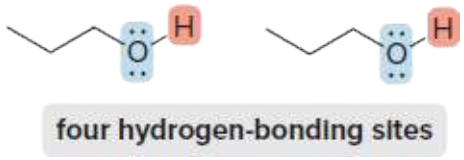
[1] Predicting boiling points (3.4A)

1 Identify the intermolecular forces that differ.	2 Rank the compounds in order of increasing strength of intermolecular forces.
	

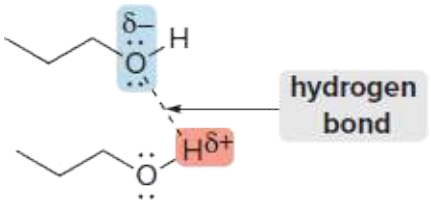
See Sample Problem 3.3. Try Problems 3.43, 3.44.

[2] Determining sites of hydrogen bonding between two identical molecules (3.4C)

1 Identify the hydrogen bonding sites.	2 Draw the hydrogen bond between the two molecules.



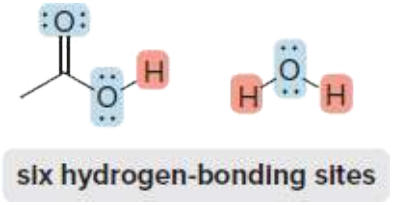
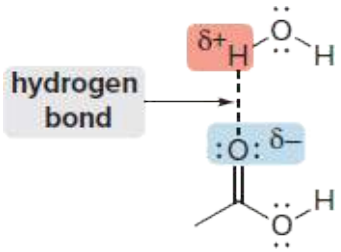
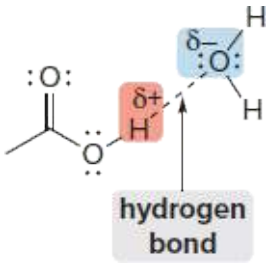
- O atoms are electrostatically attracted to H atoms bonded to O.



- An O atom hydrogen bonds with a H atom.

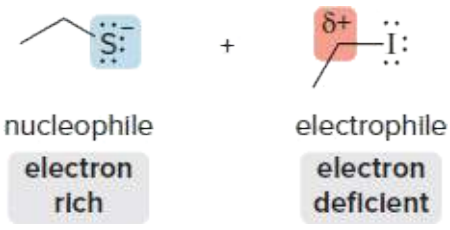
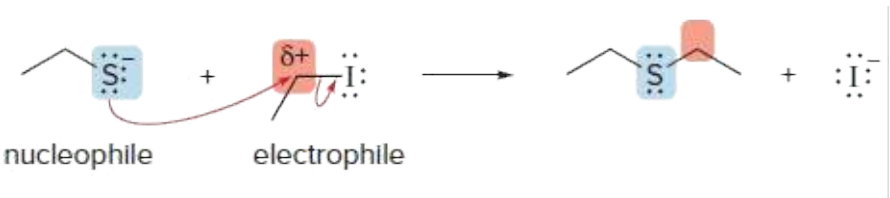
See Sample Problem 3.5. Try Problems 3.39a, 3.40a, 3.61a, 3.62c.

[3] Determining sites of hydrogen bonding between an organic molecule and H_2O (3.4C)

1 Identify the hydrogen-bonding sites.	2 Draw an example of a hydrogen bond involving a H atom of H_2O.	3 Draw an example of a hydrogen bond involving an O atom of H_2O.
		

Try Problems 3.39b, 3.40b, 3.61b, 3.63c, 3.66f.

[4] Drawing curved arrows to show the reaction between a nucleophile and an electrophile (3.8)

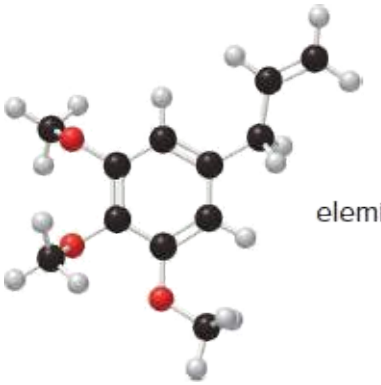
1 Identify the nucleophile and electrophile.	2 Draw a curved arrow from the nucleophile to the electrophile.
	

- As the electron pair of the nucleophile attacks the electrophile, the C–I bond breaks to give the products.

PROBLEMS

Problems with Three-Dimensional Models

3.31



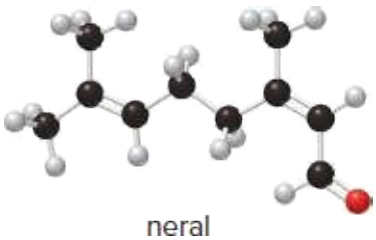
elemicin

a. Identify the functional groups in the ball-and-stick model of elemicin, a compound partly responsible for the flavor and fragrance of nutmeg.

b. Draw a skeletal structure of a constitutional isomer of elemicin that should have a higher boiling point and melting point.

c. Label all electrophilic carbon atoms.

3.32



neral

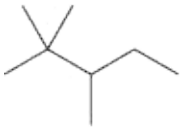
a. Identify the functional groups in the ball-and-stick model of neral, a compound with a lemony odor isolated from lemongrass.

b. Draw a skeletal structure of a constitutional isomer of neral that should be more water soluble.

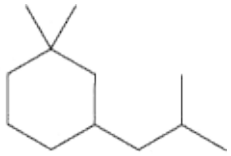
c. Label the most electrophillic carbon atom.

Functional Groups

3.33 For each alkane: (a) classify each carbon atom as 1°, 2°, 3°, or 4°; (b) classify each hydrogen atom as 1°, 2°, or 3°.



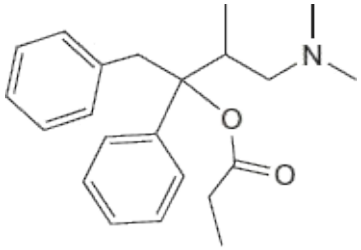
A



B

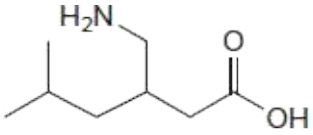
3.34 Identify the functional groups in each molecule. Classify each alcohol, alkyl halide, amide, and amine as 1°, 2°, or 3°.

a.



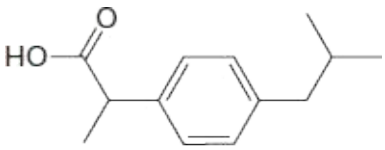
Darvon
(analgesic)

b.



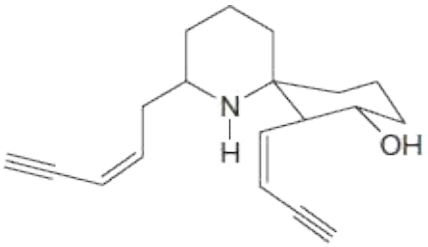
pregabalin
trade name Lyrica
(used in treating chronic pain)

c.



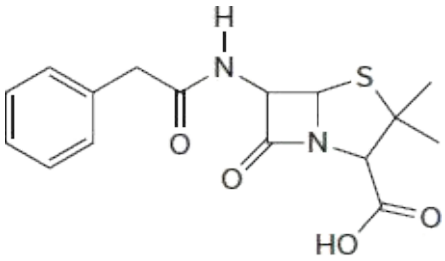
ibuprofen
(analgesic)

d.



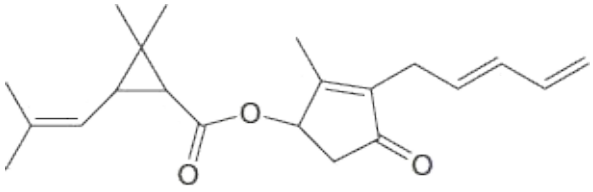
histrionicotoxin
(poison secreted by a
South American frog)

e.



penicillin G
(an antibiotic)

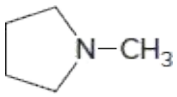
f.



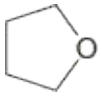
pyrethrin I
(potent insecticide
from chrysanthemums)

3.35 **Identify each functional group located in the following rings. Which structure represents a lactone—a cyclic ester—and which represents a lactam—a cyclic amide?**

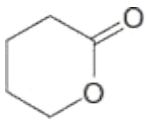
a.



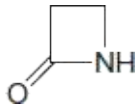
b.



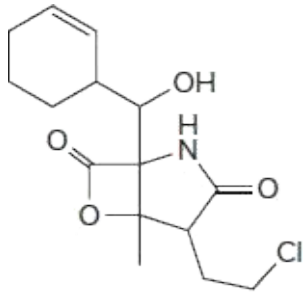
c.



d.



3.36 **(a) Identify the functional groups in salinosporamide A, an anticancer agent isolated from marine sediment. (b) Classify each alcohol, alkyl halide, amide, and amine as 1°, 2°, or 3°.**



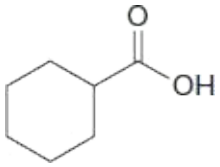
salinosporamide A

3.37 **Draw seven constitutional isomers with molecular formula $C_3H_6O_2$ that contain a carbonyl group. Identify the functional group(s) in each isomer.**

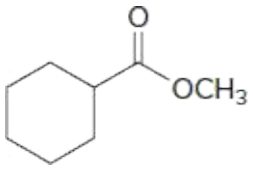
Intermolecular Forces

3.38 **What types of intermolecular forces are exhibited by each compound?**

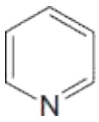
a.



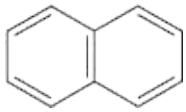
b.



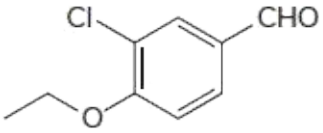
c.



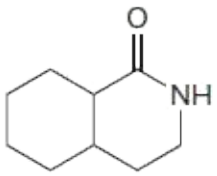
d.



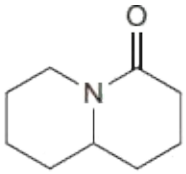
3.39 **(a) Which of the following molecules can hydrogen bond to another molecule like itself? (b) Which of the following molecules can hydrogen bond to water?**



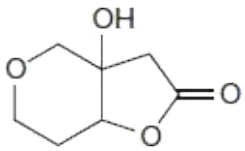
A



B

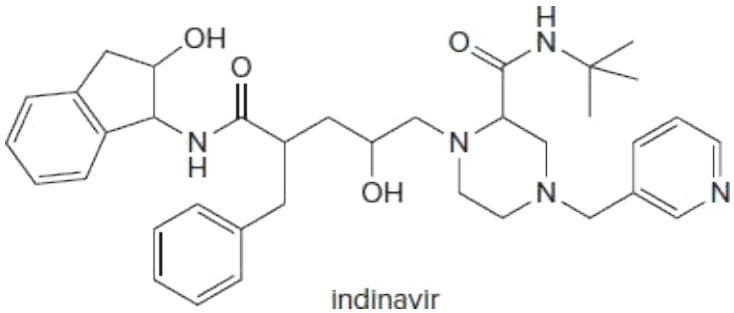


C



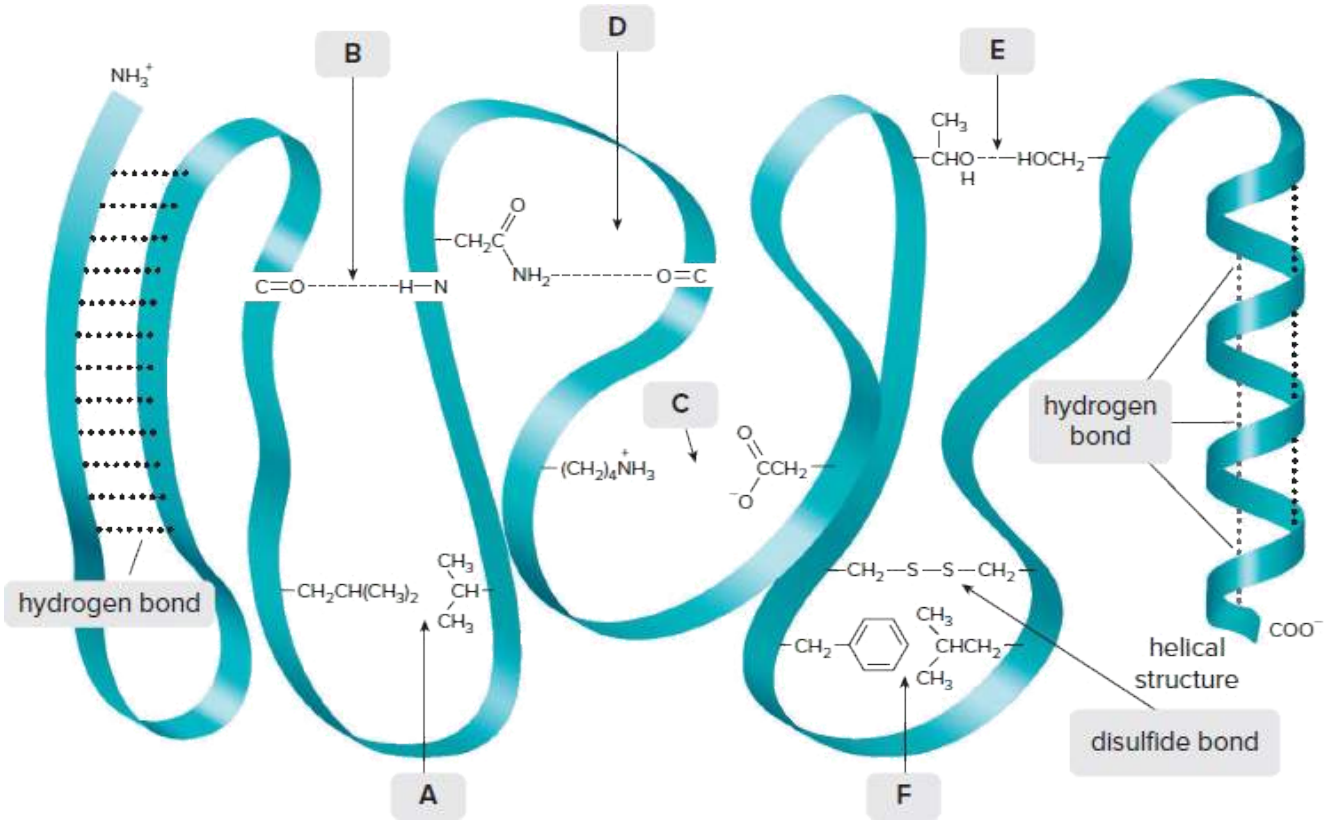
D

3.40 **Indinavir (trade name Crixivan) is a drug used to treat HIV. (a) At which sites can indinavir hydrogen bond to another molecule like itself? (b) At which sites can indinavir hydrogen bond to water?**



indinavir

3.41 **Intramolecular forces of attraction are often important in holding large molecules together. For example, some proteins fold into compact shapes, held together by attractive forces between nearby functional groups. A schematic of a folded protein is drawn here, with the protein backbone indicated by a blue-green ribbon, and various appendages drawn dangling from the chain. What types of intramolecular forces occur at each labeled site (A–F)?**



Physical Properties

3.42 **(a) Draw four compounds with molecular formula $C_6H_{12}O$, each containing at least one different functional group. (b) Predict which compound has the highest boiling point, and explain your reasoning.**

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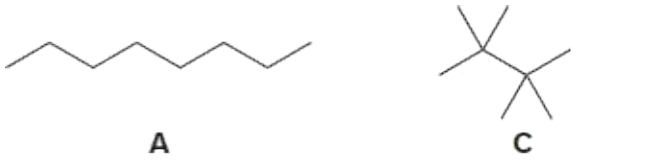
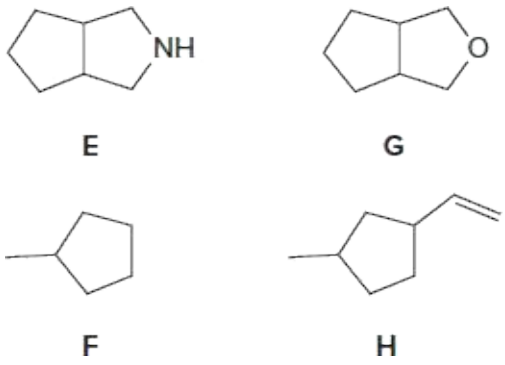
3.43 **Rank the compounds in each group in order of increasing boiling point.**

a.

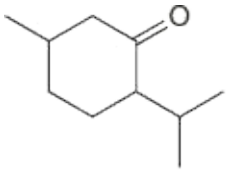


b.

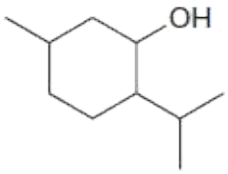


3.44 **Explain why $CH_3CH_2NHCH_3$ has a higher boiling point than $(CH_3)_3N$, even though they have the same molecular weight.**

3.45 **Menthone and menthol are both isolated from mint. Explain why menthol is a solid at room temperature but menthone is a liquid.**

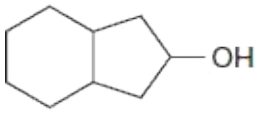


menthone

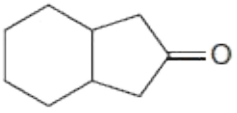


menthol

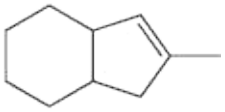
3.46 **Rank A–C in order of increasing melting point.**



A

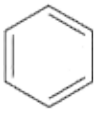


B

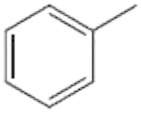


C

3.47 **Explain why benzene has a lower boiling point but much higher melting point than toluene.**

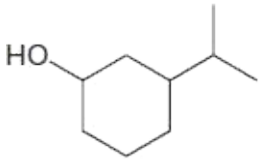


benzene
bp = 80 °C
mp = 5 °C

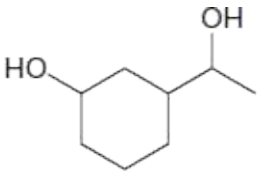


toluene
bp = 111 °C
mp = –93 °C

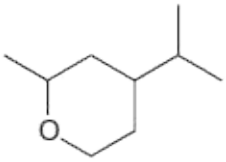
3.48 **Rank the following compounds in order of increasing water solubility.**



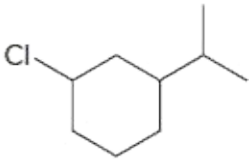
A



B



C

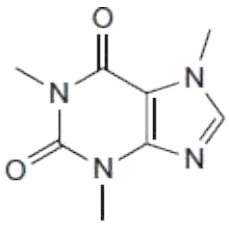


D

3.49 **Explain why diethyl ether ($CH_3CH_2OCH_2CH_3$) and butan-1-ol ($CH_3CH_2CH_2CH_2OH$) have similar solubility properties in water, but butan-1-ol has a much higher boiling point.**

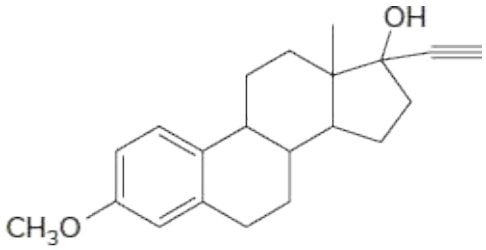
3.50 **Predict the water solubility of each of the following organic molecules.**

a.



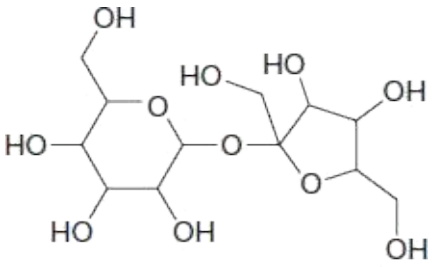
caffeine
(stimulant in coffee, tea, and many soft drinks)

b.



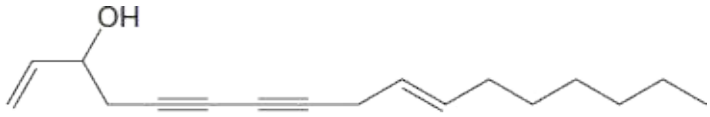
mestranol
(component in oral contraceptives)

c.



sucrose
(table sugar)

d.

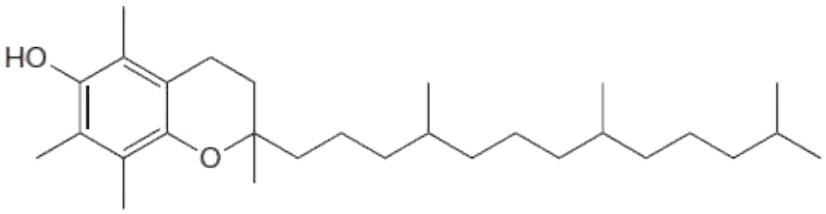


carotatoxin
(neurotoxin isolated from carrots)

Applications

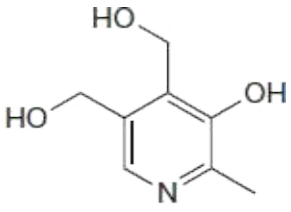
3.51 Predict the solubility of each of the following vitamins in water and in organic solvents.

a.



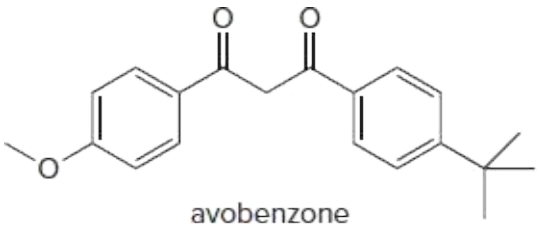
vitamin E

b.

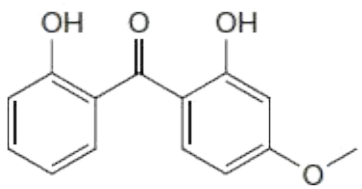


pyridoxine
vitamin B_6

3.52 Avobenzone and dioxybenzone are two commercial sunscreens. Using the principles of solubility, predict which sunscreen is more readily washed off when an individual goes swimming. Explain your choice.

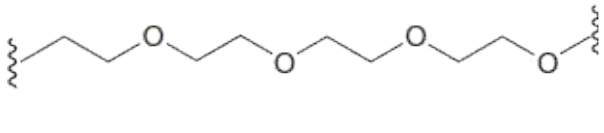


avobenzone

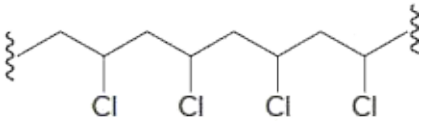


dioxybenzone

3.53 **Poly(ethylene glycol) (PEG) and poly(vinyl chloride) (PVC) are examples of polymers, large organic molecules composed of repeating smaller units covalently bonded together. Polymers have very different properties depending (in part) on their functional groups. Discuss the water solubility of each polymer and suggest why PEG is used in shampoos, whereas PVC is used to make garden hoses and pipes. Synthetic polymers are discussed in detail in Chapters 13 and 28.**

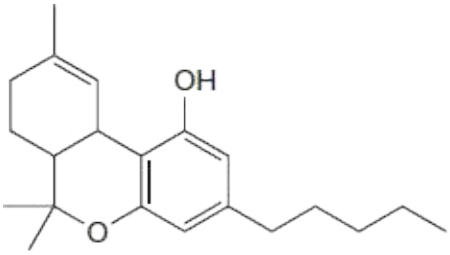


poly(ethylene glycol)
PEG

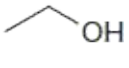


poly(vinyl chloride)
PVC

3.54 **THC is the active component in marijuana, and ethanol is the alcohol in alcoholic beverages. Explain why drug screenings are able to detect the presence of THC but not ethanol weeks after these substances have been introduced into the body.**

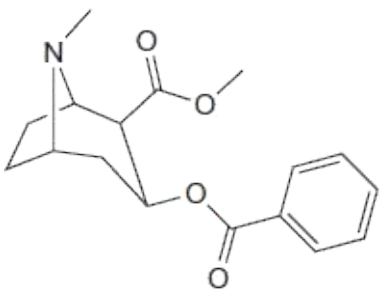


tetrahydrocannabinol
THC

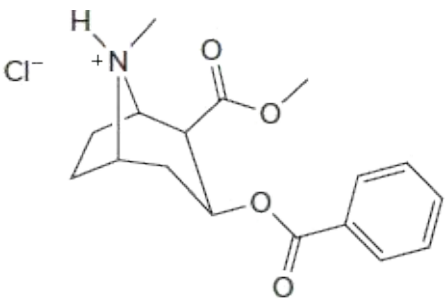


ethanol

3.55 **Cocaine is a widely abused, addicting drug. Cocaine is usually obtained as its hydrochloride salt (cocaine hydrochloride) but can be converted to crack (the neutral organic molecule) by treatment with base. Which of the two compounds here has a higher boiling point? Which is more soluble in water? How does the relative solubility explain why crack is usually smoked but cocaine hydrochloride is injected directly into the bloodstream?**

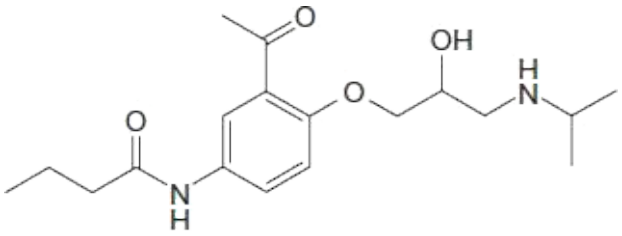


cocaine (crack)
neutral organic molecule



cocaine hydrochloride
a salt

3.56 **Many drugs are sold as their hydrochloride salts ($R_2NH_2^+$ Cl^-), formed by reaction of an amine (R_2NH) with HCl.**



acebutolol

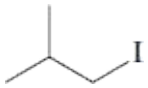
a. **Draw the product (a hydrochloride salt) formed by reaction of acebutolol with HCl. Acebutolol is a β blocker used to treat high blood pressure.**

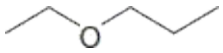
b. **Discuss the solubility of acebutolol and its hydrochloride salt in water.**

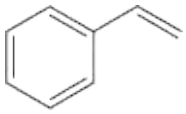
c. **Offer a reason as to why the drug is marketed as a hydrochloride salt rather than a neutral amine.**

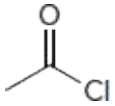
Reactivity of Organic Molecules

3.57 **Label the electrophilic and nucleophilic sites in each molecule.**

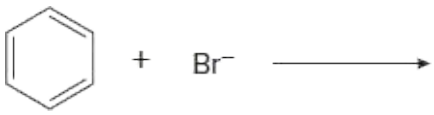
a. 

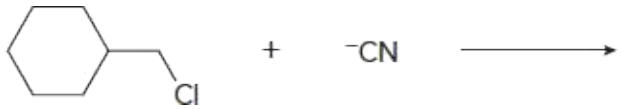
b. 

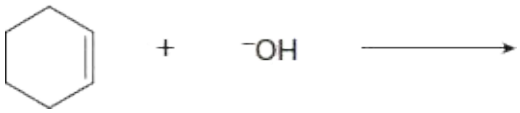
c. 

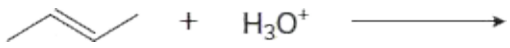
d. 

3.58 **By using only electron density arguments, determine whether the following reactions will occur.**

a. 

b. 

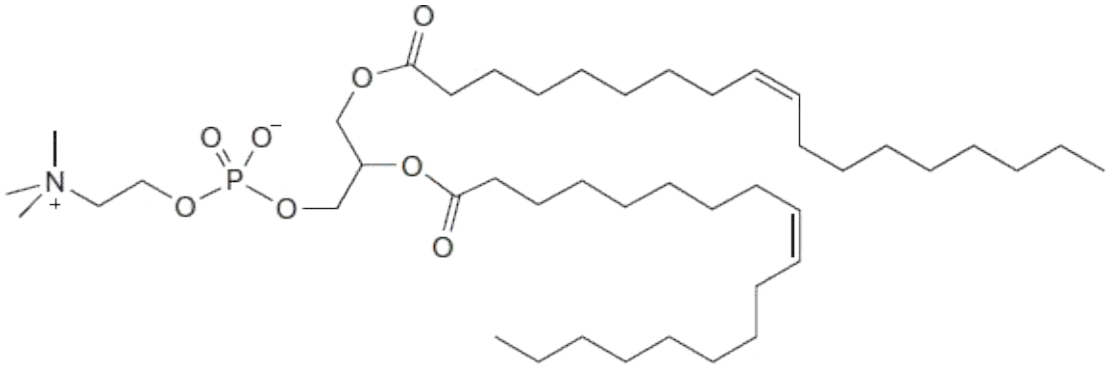
c. 

d. 

Cell Membrane

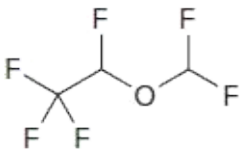
3.59 **The composition of a cell membrane is not uniform for all types of cells. Some cell membranes are more rigid than others. Rigidity is determined by a variety of factors, one of which is the structure of the carbon chains**

in the phospholipids that comprise the membrane. One example of a phospholipid was drawn in Section 3.7A, and another, having C–C double bonds in its carbon chains, is drawn here. Which phospholipid would be present in the more rigid cell membrane and why?

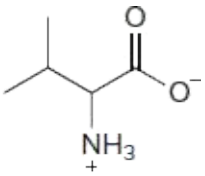


phospholipid

3.60 Which compound is more likely to be a general anesthetic? Explain your choice.



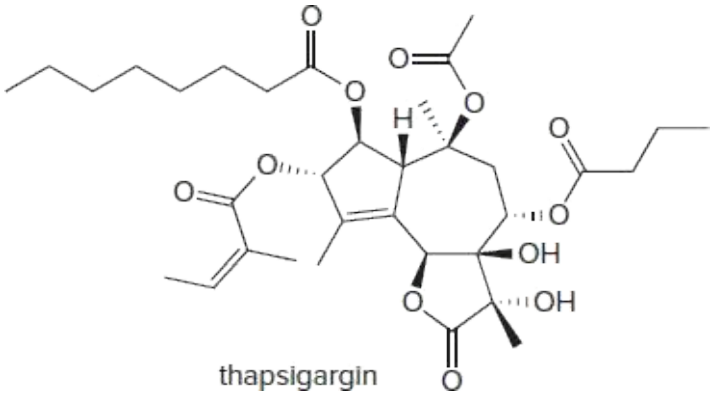
A



B

General Problems

3.61 Thapsigargin is a natural product with promising anticancer properties.



thapsigargin

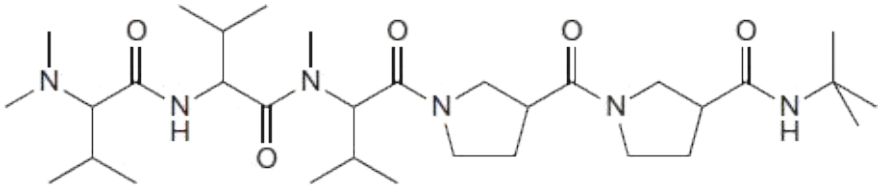
a. At which sites can thapsigargin hydrogen bond to another molecule like itself?

b. At which sites can thapsigargin hydrogen bond to water?

c. How many sp^2 hybridized C's are present?

d. How many sp^3 hybridized 3° C's are present?

3.62 Synthadotin is a promising anticancer drug in clinical trials.



synthadotin

a. **Identify the functional groups.**

b. **Classify any amine or amide as 1°, 2°, or 3°.**

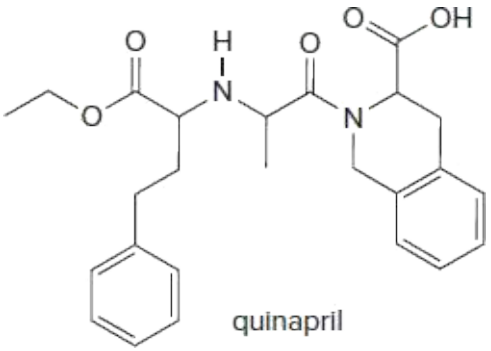
c. **At which sites can synthadotin hydrogen bond to another molecule like itself?**

d. **Label two nucleophilic sites.**

e. **Label two electrophilic sites.**

f. **What product is formed when synthadotin is treated with HCl?**

3.63 Quinapril (trade name Accupril) is a drug used to treat hypertension and congestive heart failure.



quinapril

a. **Identify the functional groups in quinapril.**

b. **Classify any alcohol, amide, or amine as 1°, 2°, or 3°.**

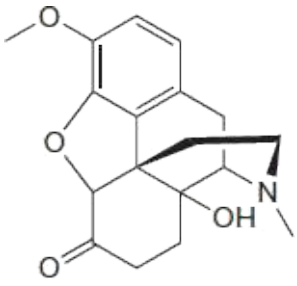
c. **At which sites can quinapril hydrogen bond to water?**

d. **At which sites can quinapril hydrogen bond to acetone [$(CH_3)_2CO$]?**

e. **Label the most acidic hydrogen atom.**

f. **Which site is most basic?**

3.64 Answer each question about oxycodone, a narcotic analgesic used for severe pain.



oxycodone

a. Identify the functional groups in oxycodone.

b. Classify any alcohol, amide, or amine as 1°, 2°, or 3°.

c. Which proton is most acidic?

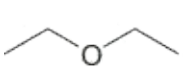
d. Which site is most basic?

e. What is the hybridization of the N atom?

f. How many sp^2 hybridized C atoms does oxycodone contain?

Challenge Problems

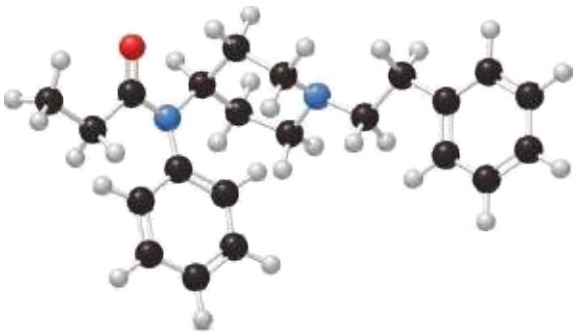
3.65 **Although diethyl ether and tetrahydrofuran are both four-carbon ethers, one compound is much more water soluble than the other. Predict which compound has higher water solubility and offer an explanation.**



diethyl ether

tetrahydrofuran

3.66 **Answer the following questions by referring to the ball-and-stick model of fentanyl, a potent narcotic analgesic used in surgical procedures.**



fentanyl

a. Identify the functional groups.

b. Label the most acidic proton.

c. Label the most basic atom.

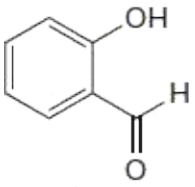
d. What types of intermolecular forces are present between two molecules of fentanyl?

e. Draw an isomer predicted to have a higher boiling point.

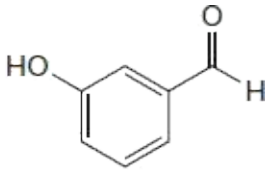
f. Which sites in the molecule can hydrogen bond to water?

g. Label all electrophilic carbons.

3.67 Explain why A is less water soluble than B, even though both compounds have the same functional groups.

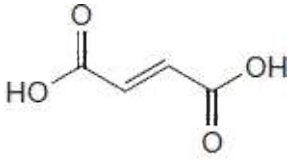


A



B

3.68 Recall from Section 1.10B that there is restricted rotation around carbon-carbon double bonds. Maleic acid and fumaric acid are two isomers with vastly different physical properties and pK_a values for loss of both protons. Explain why each of these differences occurs.



fumaric acid

maleic acid

	fumaric acid	maleic acid
mp (°C)	130	286
solubility (g/L) in H_2O at 25 °C	788	7
pK_{a1}	1.9	3.0
pK_{a2}	6.5	4.5

Alkanes

4

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4.1 Alkanes—An introduction

4.2 Cycloalkanes

4.3 An introduction to nomenclature

4.4 Naming alkanes

4.5 Naming cycloalkanes

4.6 Common names

4.7 Natural occurrence of alkanes

4.8 Properties of alkanes

4.9 Conformations of acyclic alkanes—Ethane
4.10 Conformations of butane
4.11 An introduction to cycloalkanes
4.12 Cyclohexane
4.13 Substituted cycloalkanes
4.14 Oxidation of alkanes
4.15 Lipids—Part 1

Alkanes, the simplest hydrocarbons, are found in all shapes and sizes and occur widely in nature. They are the major constituents of petroleum, a complex mixture of compounds that includes hydrocarbons such as hexane and decane. Crude petroleum spilled into the sea from a ruptured oil tanker or offshore oil well creates an insoluble oil slick on the surface. Petroleum is refined to produce gasoline, diesel fuel, home heating oil, and a myriad of other useful compounds. In Chapter 4, we learn about the properties of alkanes, how to name them (nomenclature), and oxidation—one of their important reactions.

Why Study…

Alkanes?

In **Chapter 4**, we apply the principles of bonding, shape, and reactivity discussed in Chapters 1–3 to our first family of organic compounds, the alkanes. Because alkanes have no functional group, they are much less reactive than other organic compounds, and for this reason, much of Chapter 4 is devoted to learning how to name and draw them, as well as to understanding what happens when rotation occurs about their carbon–carbon single bonds.

Studying alkanes also provides an opportunity to learn about lipids, a group of biomolecules similar to alkanes, in that they are composed mainly of nonpolar carbon–carbon and carbon–hydrogen σ bonds. Section 4.15 serves as a brief introduction only, so we will return to lipids in Chapters 10 and 29 (online).

4.1 Alkanes—An Introduction

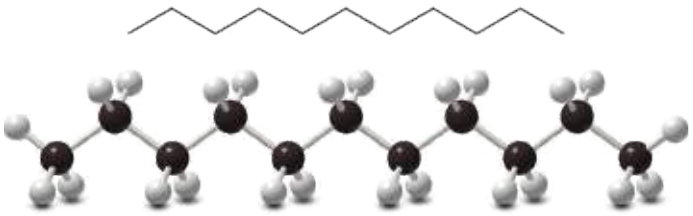
Secretion of undecane by a cockroach causes other members of the species to aggregate. Undecane is a *pheromone*, a chemical substance used for communication in an animal species, most commonly an insect population. ©*God of Insects*

Cyclohexane is one component of the mango, the most widely consumed fruit in the world.
©Pixtal/age fotostock

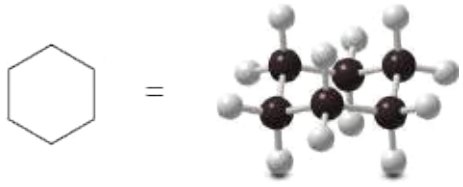
Recall from Section 3.2 that alkanes are aliphatic hydrocarbons having only C—C and C—H σ bonds. Because their carbon atoms can be joined together in chains or rings, they can be categorized as acyclic or cyclic.

- **Acyclic alkanes have the molecular formula C_nH_{2n+2} (where n = an integer) and contain only linear and branched chains of carbon atoms. Acyclic alkanes are also called saturated hydrocarbons because they have the maximum number of hydrogen atoms per carbon.**
- **Cycloalkanes contain carbons joined in one or more rings. Because their general formula is C_nH_{2n}, they have two fewer H atoms than an acyclic alkane with the same number of carbons.**

Undecane, an acyclic alkane, and cyclohexane, a cycloalkane, are two naturally occurring alkanes.



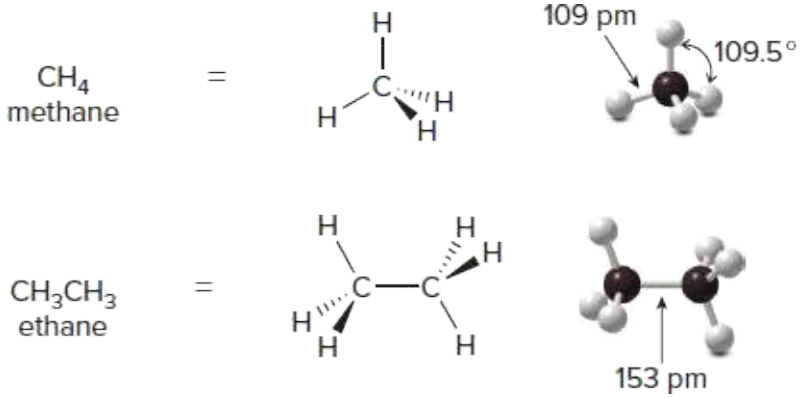
undecane
$C_{11}H_{24}$



cyclohexane
C_6H_{12}

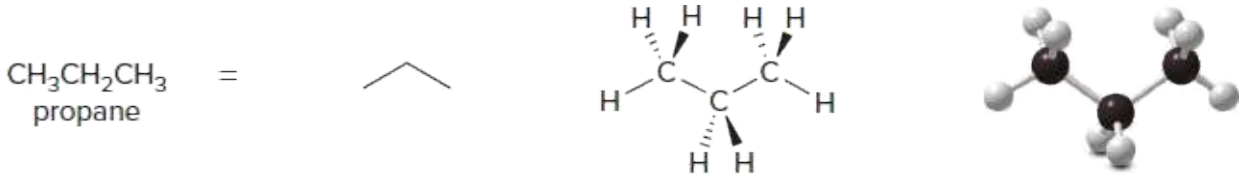
4.1A Acyclic Alkanes Having One to Five C Atoms

Structures for the two simplest acyclic alkanes were given in Chapter 1. Methane, CH_4, has a single carbon atom, and ethane, CH_3CH_3, has two. All C atoms in an alkane are surrounded by four groups, making them sp^3 hybridized and tetrahedral, and all bond angles are 109.5°.



To draw the structure of an alkane, join the carbon atoms together with single bonds, and add enough H atoms to make each C tetravalent.

The three-carbon alkane $CH_3CH_2CH_3$, propane, has molecular formula C_3H_8. Each carbon in the three-dimensional drawing has two bonds in the plane (solid lines), one bond in front (on a wedge), and one bond behind the plane (on a dashed wedge).



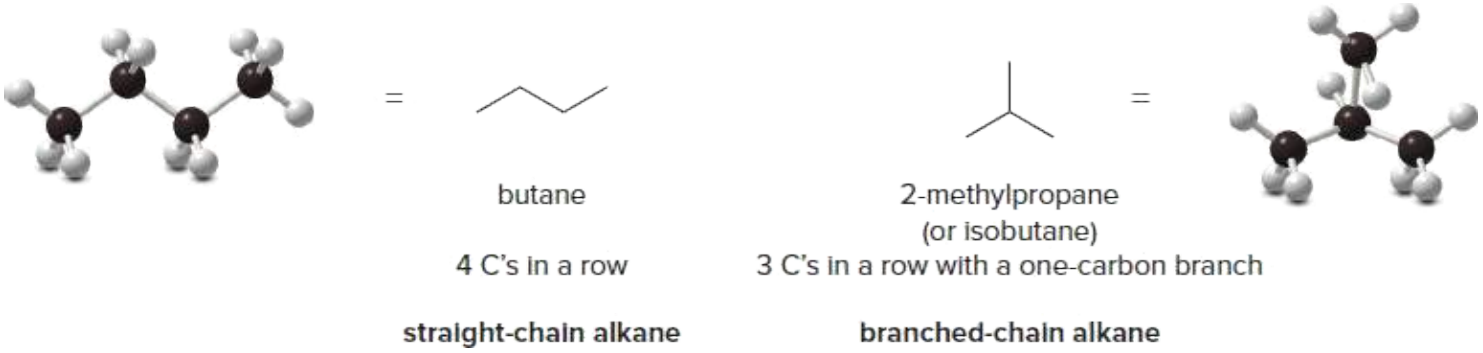
Problem 4.1

Both olives and the leaves of olive trees contain alkanes with long carbon chains. A predominant alkane in olives has 27 carbons, whereas a major alkane component in olive leaves has 31 carbons. What is the molecular formula of each of these alkanes?

The alkane content of olives and olive leaves is somewhat different (Problem 4.1), so it is possible to use alkane identity to determine the presence of leaf material in olive oil.

©Flickr Open/Getty Images

There are two different ways to arrange four carbons, giving two compounds with molecular formula C_4H_{10}, named butane and 2-methylpropane (or isobutane).



Butane and 2-methylpropane are *isomers*, two different compounds with the same molecular formula (Section 1.4). They belong to one of the two major classes of isomers called constitutional or structural isomers. We will learn about the second major class of isomers, called stereoisomers, in Section 4.13B.

- ***Constitutional isomers*** **differ in the way the atoms are connected to each other.**

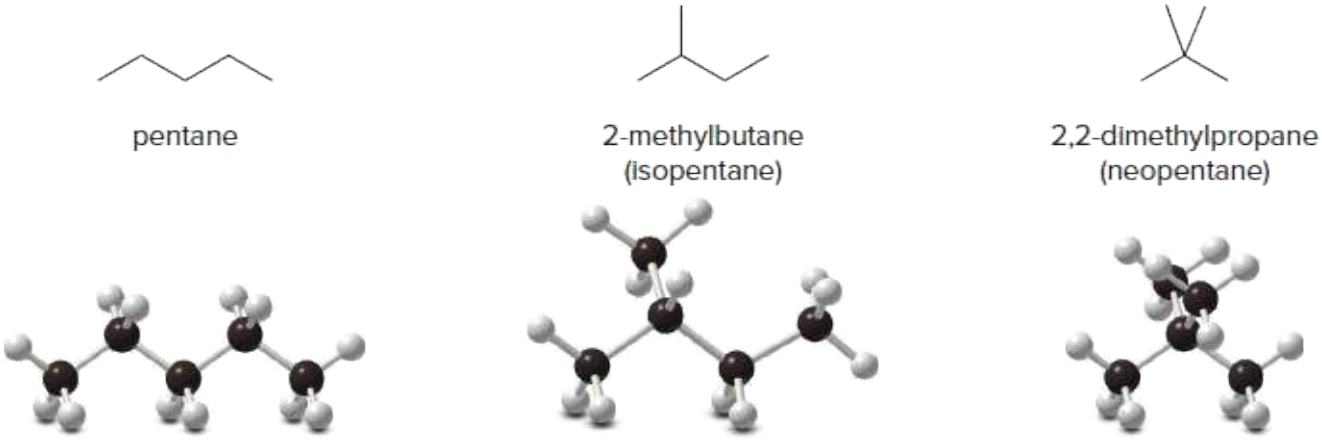
The molecular formulas for methane, ethane, and propane fit into the general molecular formula for an alkane, C_nH_{2n+2}.

- **Methane = CH_4 = $C_1H_{2(1)+2}$**
- **Ethane = C_2H_6 = $C_2H_{2(2)+2}$**
- **Propane = C_3H_8 = $C_3H_{2(3)+2}$**

Butane, which has four carbons in a row, is a straight-chain or normal alkane (an *n*-

alkane). 2-Methylpropane, on the other hand, is a branched-chain alkane.

With alkanes having more than four carbons, the names of the straight-chain isomers are systematic and derive from Greek roots: *pent*ane for five C atoms, *hex*ane for six, and so on. There are three constitutional isomers for the five-carbon alkane, each having molecular formula C_5H_{12}: pentane, 2-methylbutane (or isopentane), and 2,2-dimethylpropane (or neopentane).

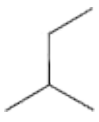


Take care in interpreting skeletal structures. Although pentane is typically drawn using a zigzag structure, the carbon skeleton can be drawn in a variety of ways, and still represent the same compound. Each of the following representations has five carbon atoms in a row, so each represents pentane, not an isomer of pentane.

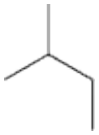
Problem 4.2

Which of the following is *not* another representation for 2-methylbutane?

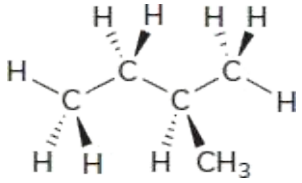
a.

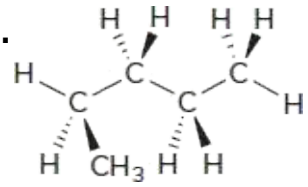


b.



c.



d. 

4.1B Acyclic Alkanes Having More Than Five C Atoms

The maximum number of possible constitutional isomers increases dramatically as the number of carbon atoms in the alkane increases, as shown in Table 4.1. For example, there are 75 possible isomers for an alkane having 10 carbon atoms, and 366,319 possible isomers for one having 20 carbons.

Each entry in Table 4.1 is formed from the preceding entry by adding a CH_2 group. A CH_2 group is called a *methylene group*. A group of compounds that differ by only a CH_2 group is called a *homologous series*. The names of all alkanes end in the suffix -*ane*, and the syllables preceding the suffix identify the number of carbon atoms in the chain.

Table 4.1 **Summary: Straight-Chain Alkanes**

Number of C atoms	Molecular formula	Name (*n*-alkane)	Number of constitutional isomers
1	CH_4	methane	—
2	C_2H_6	ethane	—
3	C_3H_8	propane	—
4	C_4H_{10}	butane	2
5	C_5H_{12}	pentane	3
6	C_6H_{14}	hexane	5
7	C_7H_{16}	heptane	9
8	C_8H_{18}	octane	18
9	C_9H_{20}	nonane	35
10	$C_{10}H_{22}$	decane	75
11	$C_{11}H_{24}$	undecane	159

12	$C_{12}H_{26}$	dodecane	355
13	$C_{13}H_{28}$	tridecane	802
14	$C_{14}H_{30}$	tetradecane	1858
15	$C_{15}H_{32}$	pentadecane	4347
20	$C_{20}H_{42}$	icosane	366,319

Problem 4.3

Draw the five constitutional isomers having molecular formula C_6H_{14}.

Problem 4.4

Review classifying carbons and hydrogens in Section 3.2, and draw the structure of an alkane with molecular formula C_7H_{16} that contains (a) one 4° carbon; (b) only 1° and 2° carbons; (c) 1°, 2°, and 3° hydrogens.

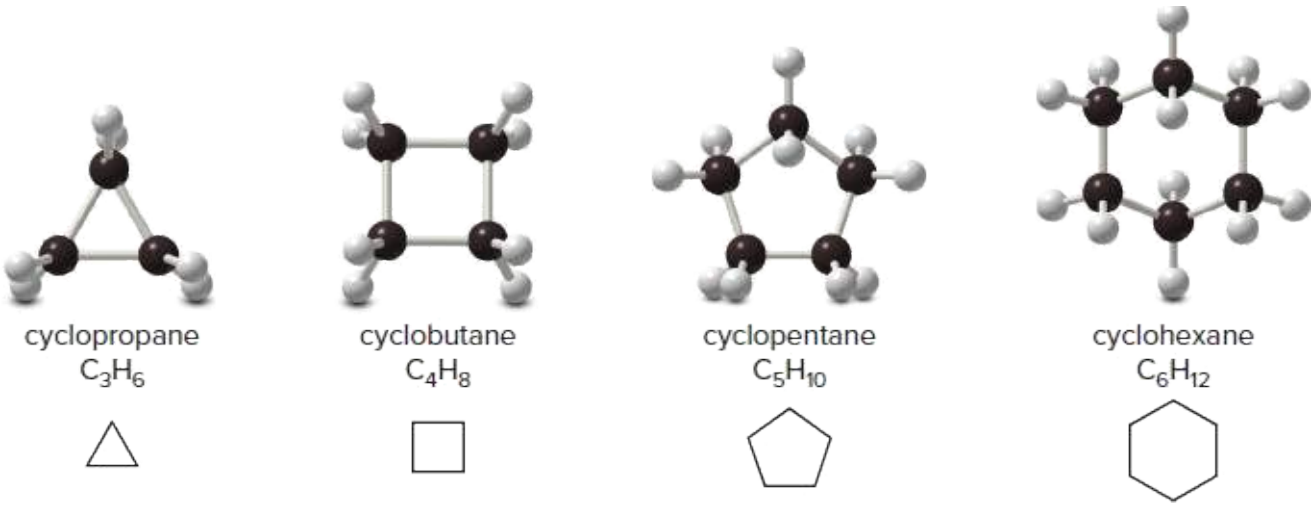
Problem 4.5

(a) Which compounds (B–F) are identical to A? (b) Which compounds (B–F) represent an isomer of A?

4.2 Cycloalkanes

Cycloalkanes have molecular formula C_nH_{2n} and contain carbon atoms arranged in a ring. Think of a cycloalkane as being formed by removing two H atoms from the end carbons of a chain, and then bonding the two carbons together. Simple cycloalkanes are named by adding the prefix *cyclo-* to the name of the acyclic alkane having the same number of carbons.

Cycloalkanes with three to six carbon atoms are shown.



Problem 4.6

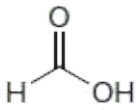
Draw the five constitutional isomers that have molecular formula C_5H_{10} and contain one ring.

4.3 An Introduction to Nomenclature

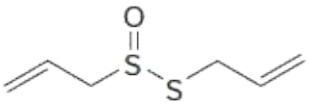
Garlic has been used in Chinese herbal medicine for more than 4000 years, as a form of currency in Siberia, and as a repellent for witches by the Saxons. Today it is used as a dietary supplement because of its reported health benefits. Allicin, the molecule largely responsible for garlic's odor, is not stored in the garlic bulb, but instead is produced by the action of enzymes when the bulb is crushed or bruised.
©Pixtal/age Fotostock

How are organic compounds named? Long ago, the name of a compound was often based on the plant or animal source from which it was obtained. For example, the name for formic acid, a caustic compound isolated from certain ants, comes from the Latin word *formica*, meaning “ant;” and allicin, the pungent principle of garlic, is derived from the botanical name for garlic, *Allium sativum*. Other compounds were named by their discoverer for personal reasons. Adolf von Baeyer supposedly named barbituric acid after a woman named Barbara, although speculation continues on

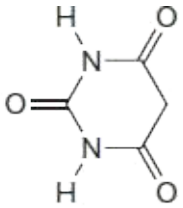
Barbara's identity—a lover, a Munich waitress, or even St. Barbara.



formic acid
(obtained from certain ants)



allicin
(odor of garlic)



barbituric acid
(named for Barbara?)

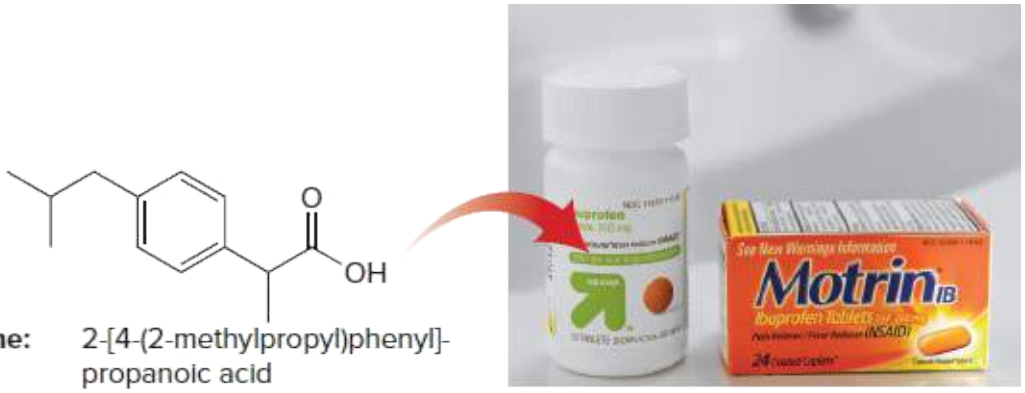
With the isolation and preparation of thousands of new organic compounds it became clear that each organic compound must have an unambiguous name, derived from a set of easily remembered rules. A systematic method of naming compounds was developed by the *I*nternational *U*nion of *P*ure and *A*pplied *C*hemistry. It is referred to as the IUPAC system of nomenclature; how it can be used to name alkanes and cycloalkanes is explained in Sections 4.4 and 4.5.

The IUPAC system of nomenclature has been regularly revised since it was first adopted in 1892. Revisions in 1979 and 1993 and extensive recommendations in 2004 have given chemists a variety of acceptable names for compounds. Many changes are minor. For example, the 1979 nomenclature rules assign the name 1-butene to CH_2=$CHCH_2CH_3$, whereas the 1993 rules assign the name but-1-ene; that is, only the position of the number differs. In this text, more recent IUPAC conventions will be used, and often a margin note will be added to mention the differences between past and recent recommendations.

Naming organic compounds has become big business for drug companies. The IUPAC name of an organic compound can be long and complex, and may be comprehensible only to a chemist. As a result, most drugs have three names:

- Systematic: The systematic name follows the accepted rules of nomenclature and indicates the compound's chemical structure; this is the IUPAC name.
- Generic: The generic name is the official, internationally approved name for the drug.
- Trade: The trade name for a drug is assigned by the company that manufactures it. Trade names are often “catchy” and easy to remember. Companies hope that the public will continue to purchase a drug with an easily recalled trade name long after a cheaper generic version becomes available.

In the world of over-the-counter anti-inflammatory agents, the compound a chemist calls 2-[4-(2-methylpropyl)phenyl]propanoic acid has the generic name ibuprofen. It is marketed under a variety of trade names including Motrin and Advil.



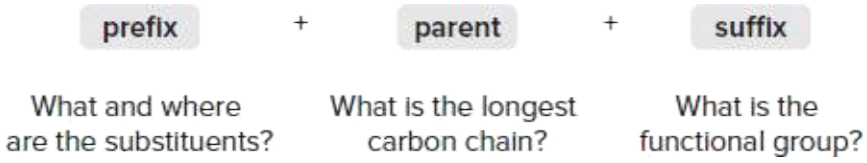
Systematic name: 2-[4-(2-methylpropyl)phenyl]-propanoic acid
Generic name: ibuprofen
Trade names: Motrin and Advil

©Jill Braaten

4.4 Naming Alkanes

The name of every organic molecule has three parts:

- The parent name indicates the number of carbons in the longest continuous carbon chain in the molecule.
- The suffix indicates what functional group is present.
- The prefix reveals the identity, location, and number of substituents attached to the carbon chain.



The names listed in Table 4.1 of Section 4.1B for the simple *n*-alkanes consist of the parent name, which indicates the number of carbon atoms in the longest carbon chain, and the suffix *-ane*, which indicates that the compounds are alkanes. The parent name for one carbon is *meth-*, for two carbons is *eth-*, and so on. Thus, we are already familiar with two parts of the name of an organic compound.

To determine the third part of a name, the prefix, we must learn how to name the carbon groups or *substituents* that are bonded to the longest carbon chain.

4.4A Naming Substituents

Carbon substituents bonded to a long carbon chain are called alkyl groups.

- **An *alkyl group* is formed by removing one hydrogen from an alkane.**

An alkyl group is a part of a molecule that is now able to bond to another atom or a functional group. To name an alkyl group, change the *-ane* ending of the parent alkane to *-yl*. Thus, methane (CH_4) becomes methyl (CH_3—) and ethane (CH_3CH_3) becomes

ethyl (CH_3CH_2—). As we learned in Section 3.1, R denotes a general carbon group bonded to a functional group. R thus denotes any alkyl group.

Naming three- and four-carbon alkyl groups is more complicated because the parent hydrocarbons have more than one type of hydrogen atom. Propane has both 1° and 2° H atoms, and removal of each of these H atoms forms a different alkyl group, propyl or isopropyl.

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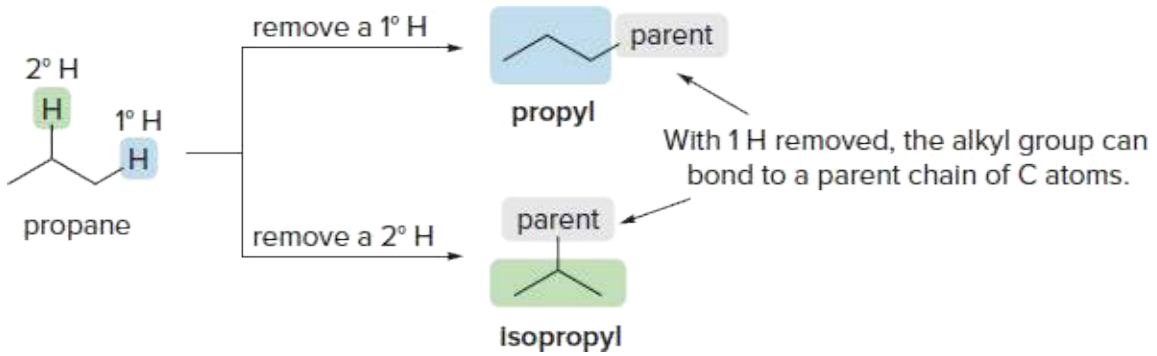
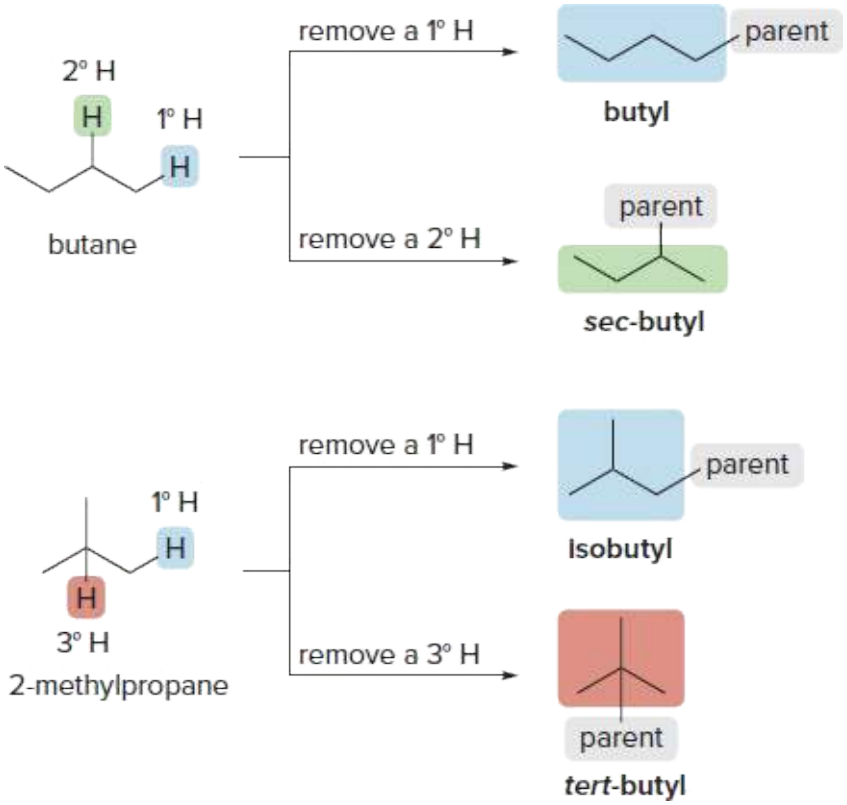


The prefix *iso*- is part of the words *propyl* and *butyl*, forming a single word: isopropyl and isobutyl. The prefixes *sec*- and *tert*- are separated from the word *butyl* by a hyphen: *sec*-butyl and *tert*-butyl.

The prefix *sec*- is short for *secondary* A sec-butyl group is formed by removal of a 2° H. The prefix *tert*- is short for *tertiary.* A *tert*-butyl group is formed by removal of a 3° H.

Because there are two different butane isomers to begin with, each with two different kinds of H atoms, there are four possible alkyl groups containing four carbon atoms: butyl, *sec*-butyl, isobutyl, and *tert*-butyl.



Abbreviations are sometimes used for certain common alkyl groups.

- **methyl (Me)**
- **ethyl (Et)**
- **butyl (Bu)**
- ***tert*-butyl (*t*-Bu)**

The names isopropyl, *sec*-butyl, isobutyl, and *tert*-butyl are recognized as acceptable substituent names in both the 1979 and 1993 revisions of IUPAC nomenclature. A general method to name these substituents, as well as alkyl groups that contain five or more carbon atoms, is described in Appendix D.

4.4B Naming an Acyclic Alkane

Four steps are needed to name an alkane.

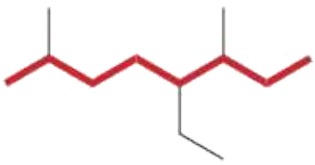
How To Name an Alkane Using the IUPAC System

Step [1] Find the parent carbon chain and add the suffix.

- **Find the *longest continuous* carbon chain, and name the molecule by using the parent name for that number of carbons, given in Table 4.1. To the name of the parent, add the suffix *-ane* for an alkane. Each functional group has its own characteristic**

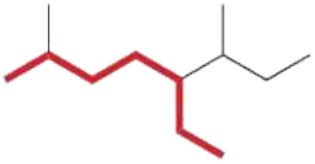
suffix.

Correct



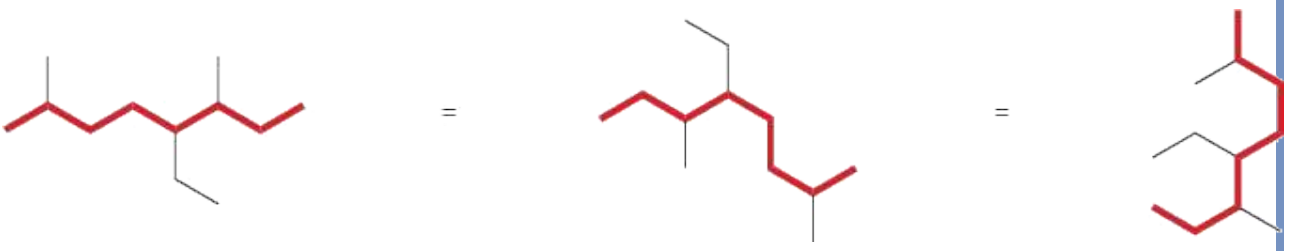
8 C's in the longest chain
8 C's ----→ **octane**

Incorrect



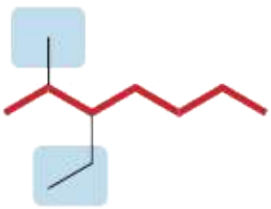
7 C's in the longest chain

- **Finding the longest chain is a matter of trial and error. Place your pencil on one end of the chain, go to the other end without picking it up, and count carbons. Repeat this procedure until you have found the chain with the largest number of carbons.**
- **It does not matter if the chain is *straight* or has *bends.* All of the following representations are equivalent, and each longest chain has eight carbons.**



- **If there are two chains of equal length, pick the chain with *more* substituents. In the following example, two different chains in the same alkane contain 7 C's, but the compound on the left has two alkyl groups attached to its long chain, whereas the compound to the right has only one.**

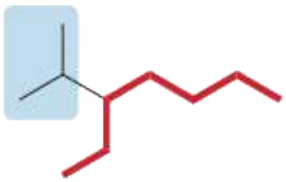
Correct



7 atoms in the longest chain
2 substituents

***more* substituents**

Incorrect



7 atoms in the longest chain
only 1 substituent

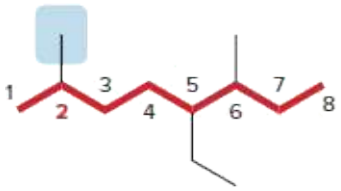
***fewer* substituents**

Step [2] Number the atoms in the carbon chain.

- **Number the longest chain to give the *first* substituent the lower**

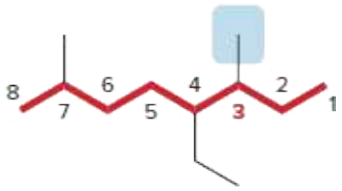
number.

Correct



first substituent at C2

Incorrect



first substituent at C3

- **If the first substituent is the same distance from both ends, number the chain to give the *second* substituent the lower number. Always look for the first point of difference in numbering from each end of the longest chain.**

Correct

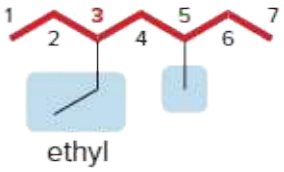
CH_3 groups at C2, C3, and C5
The second CH_3 group has the *lower* number (C3).

Incorrect

CH_3 groups at C2, C4, and C5
The second CH_3 group has the *higher* number (C4).

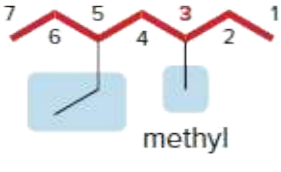
- **When numbering a carbon chain results in the *same* numbers from either end of the chain, assign the lower number *alphabetically* to the first substituent.**

Correct



- ethyl at C3
- methyl at C5

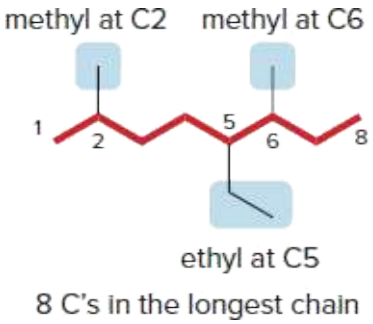
Incorrect



- methyl at C3
- ethyl at C5

Earlier letter ⟶ *lower* number

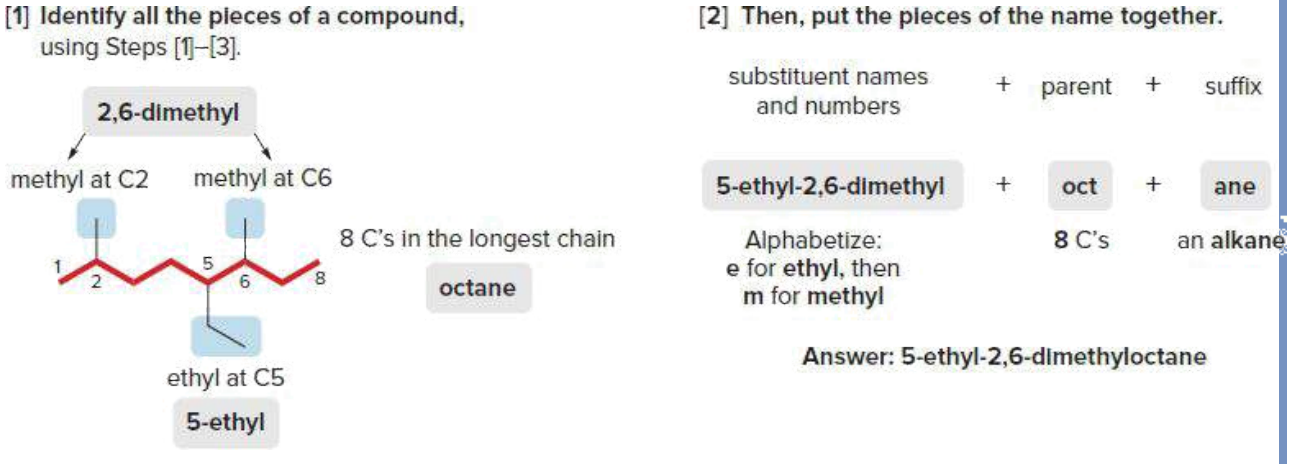
Step [3] Name and number the substituents.



- **Name the substituents as alkyl groups, and use the numbers from Step [2] to designate their location.**
- **Every carbon belongs to *either* the longest chain or a substituent, but *not both.***
- **Each substituent needs its *own* number.**
- **If two or more identical substituents are bonded to the longest chain, use prefixes to indicate how many: *di-* for two groups, *tri-* for three groups, *tetra-* for four groups, and so forth. This molecule has two methyl substituents, so its name contains the prefix *di-* before the word methyl → *di*methyl.**

Step [4] Combine substituent names and numbers + parent + suffix.

- **Precede the name of the parent by the names of the substituents.**
- **Alphabetize the names of the substituents, ignoring all prefixes except *iso-*, as in isopropyl and isobutyl.**
- **Precede the name of each substituent by the number that indicates its location. There must be one number for each substituent.**
- **Separate numbers by commas and separate numbers from letters by hyphens. The name of an alkane is a single word, with no spaces after hyphens or commas.**



Several additional examples of alkane nomenclature are given in Figure 4.1.

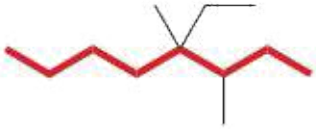
Figure 4.1 **Examples of alkane nomenclature**

2,3-dimethylpentane

Number to give the 1st methyl group the lower number.

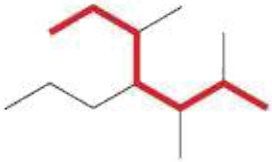
4-ethyl-5-methyloctane

Assign the lower number to the 1st substituent alphabetically: the **e** of ethyl before the **m** of methyl.



4-ethyl-3,4-dimethyloctane

Alphabetize the **e** of ethyl before the **m** of methyl.



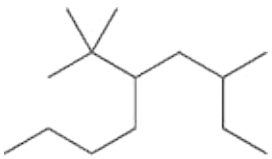
2,3,5-trimethyl-4-propylheptane

Pick the long chain with more substituents.

- The carbon atoms of each long chain are drawn in red.

Sample Problem 4.1 Naming an Alkane

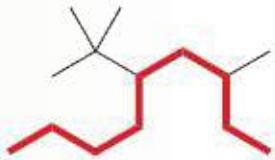
Give the IUPAC name for the following compound.



Solution

To help identify which carbons belong to the longest chain and which are substituents, box in or highlight the atoms of the long chain. Every other carbon atom then becomes a substituent that needs its own name as an alkyl group.

Step 1: Name the parent.



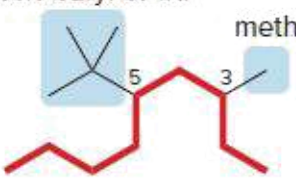
9 C's in the longest chain

nonane

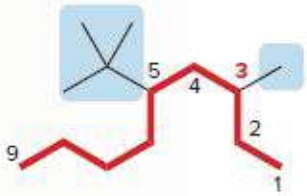
Step 3: Name and number the substituents.

tert-butyl at C5

methyl at C3



Step 2: Number the chain.



first substituent at C3

Step 4: Combine the parts.

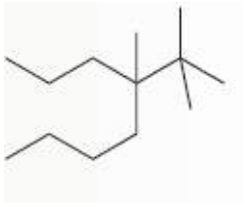
- Alphabetize: the **b** of **butyl** before the **m** of **methyl**

Answer: 5-*tert*-butyl-3-methylnonane

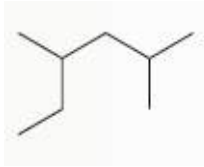
Problem 4.7

Give the IUPAC name for each compound.

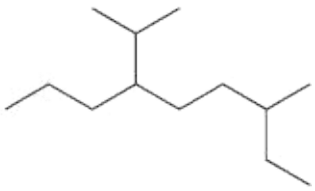
a.



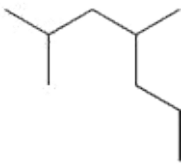
b.



c.



d.



More Practice:

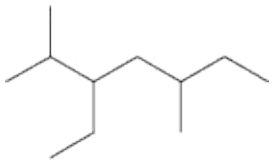
Try Problems 4.34a; 4.38a, b, c, d, h, j.

Problem 4.8

Give the IUPAC name for each compound.

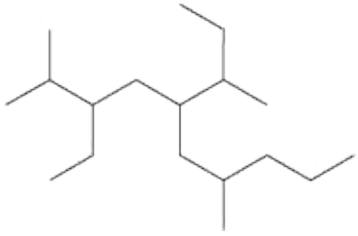
a. $(CH_3)_3CCH_2CH(CH_2CH_3)_2$

b.



c. $CH_3(CH_2)_3CH(CH_2CH_2CH_3)CH(CH_3)_2$

d.



You must also know how to derive a structure from a given name. Sample Problem 4.2 illustrates a stepwise method.

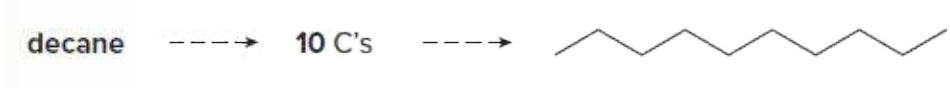
Sample Problem 4.2 Deriving a Structure from a Name

Give the structure corresponding to the following IUPAC name: 6-isopropyl-3,3,7-trimethyldecane.

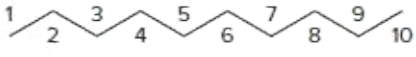
Solution

Follow three steps to derive a structure from a name.

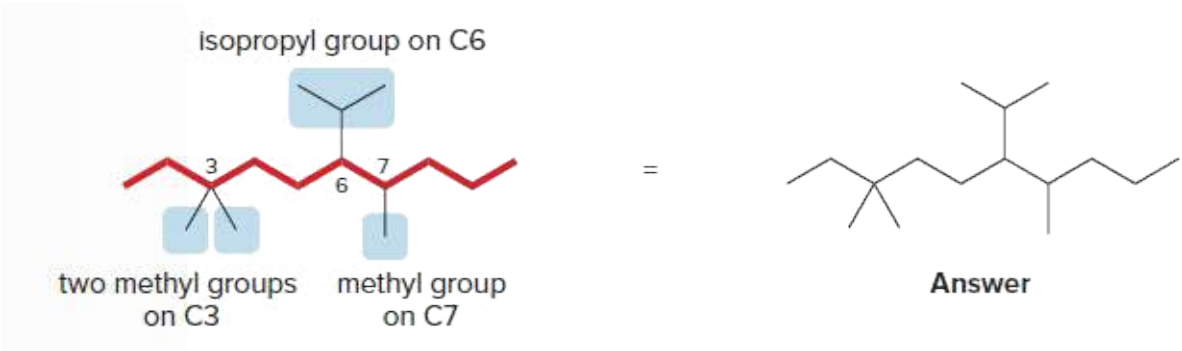
Step [1] **Identify the parent name and functional group found at the *end* of the name.**



Step [2] **Number the carbon skeleton in *either* direction.**



Step [3] **Add the substituents at the appropriate carbons.**



Problem 4.9

Give the structure corresponding to each IUPAC name.

a. 3-methylhexane

b. 3,3-dimethylpentane

c. 3,5,5-trimethyloctane

d. 3-ethyl-4-methylhexane

e. 3-ethyl-5-isobutylnonane

More Practice:

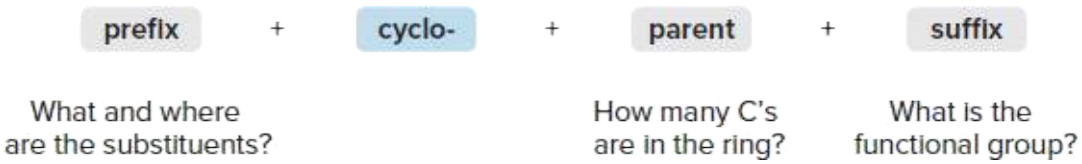
Try Problem 4.39a, c, g, h.

Problem 4.10

Give the IUPAC name for each of the five constitutional isomers of molecular formula C_6H_{14} in Problem 4.3.

4.5 Naming Cycloalkanes

Cycloalkanes are named by using similar rules, but the prefix *cyclo-* immediately precedes the name of the parent.

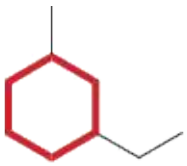


How To Name a Cycloalkane Using the IUPAC System

Step [1] Find the parent cycloalkane.

- **Count the number of carbon atoms in the ring and use the parent name for that number of carbons. Add the prefix *cyclo-***

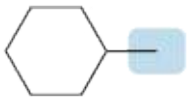
and the suffix *-ane* to the parent name.



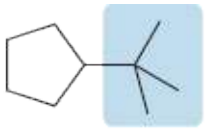
6 C's in the ring
cyclohexane

Step [2] Name and number the substituents.

- **No number is needed to indicate the location of a single substituent.**

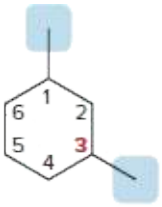


methylcyclohexane



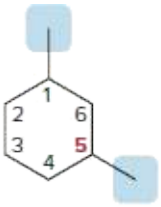
tert-butylcyclopentane

- **For rings with more than one substituent, begin numbering at one substituent and proceed around the ring clockwise or counterclockwise to give the second substituent the *lower* number.**



CH_3 groups at C1 and C3
The 2nd substituent has a lower number.

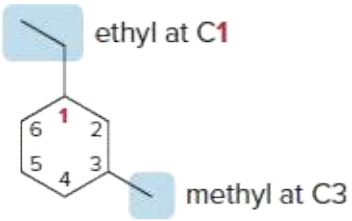
Correct: 1,3-dimethylcyclohexane



CH_3 groups at C1 and C5

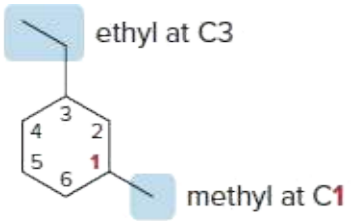
Incorrect: 1,5-dimethylcyclohexane

- **With two different substituents, number the ring to assign the *lower* number to the substituents *alphabetically*.**



earlier letter → *lower* number

Correct: 1-ethyl-3-methylcyclohexane



Incorrect: 3-ethyl-1-methylcyclohexane

When an alkane is composed of both a ring and a long chain, what determines whether

a compound is named as an acyclic alkane or a cycloalkane? If the number of carbons in the ring is greater than or equal to the number of carbons in the longest chain, the compound is named as a cycloalkane, as shown in Figure 4.2. Several examples of cycloalkane nomenclature are given in Figure 4.3.

Figure 4.2 **Naming compounds containing both a ring and a chain of carbon atoms**

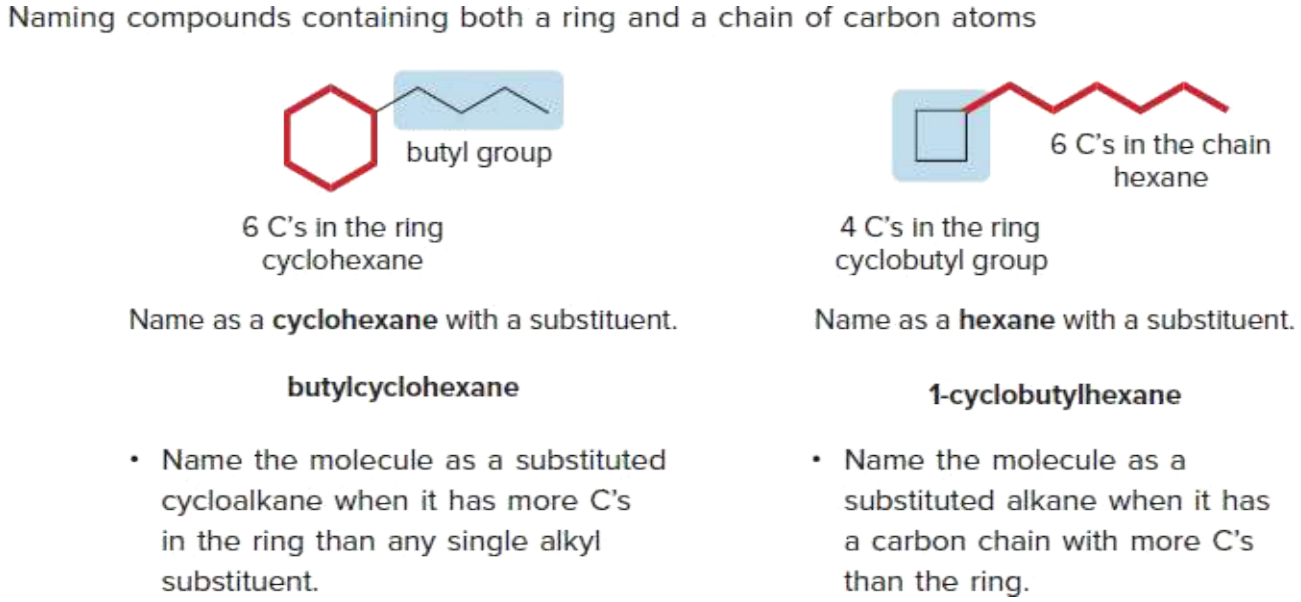
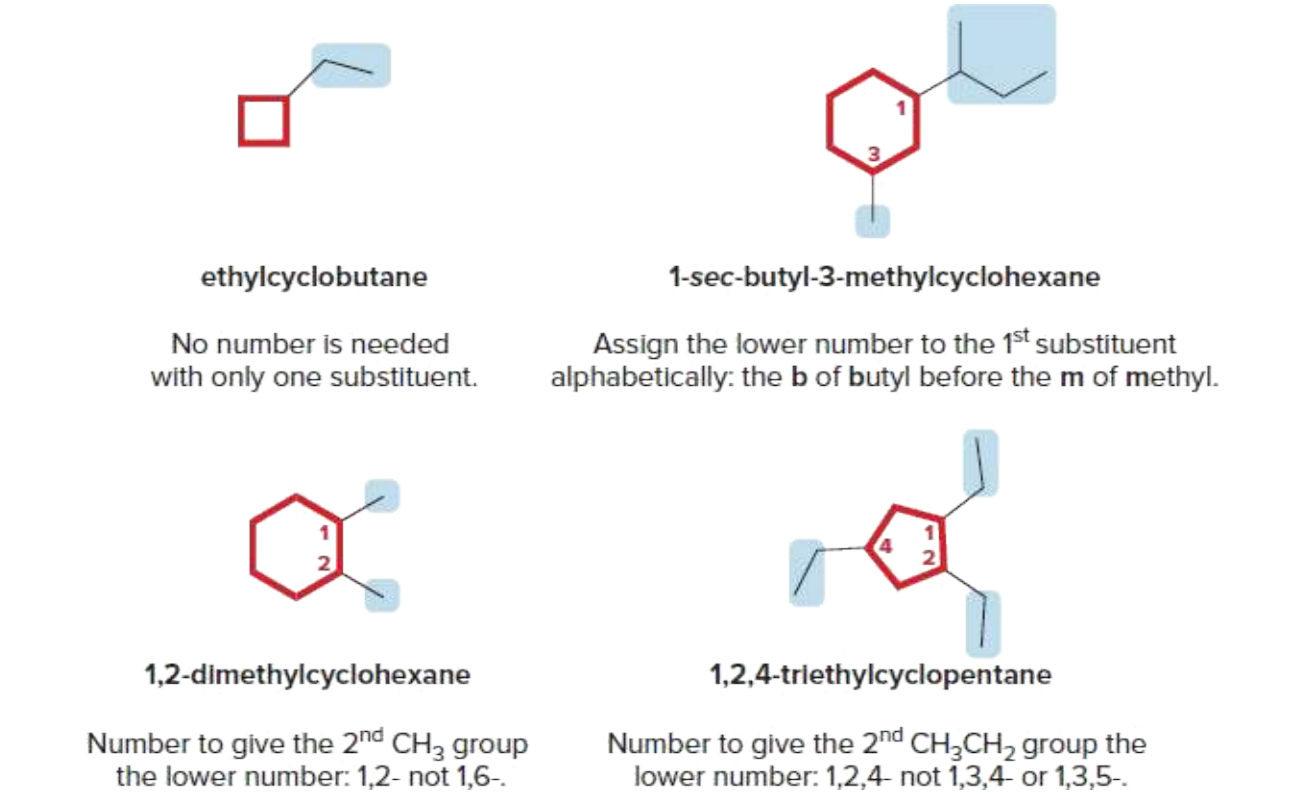
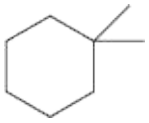


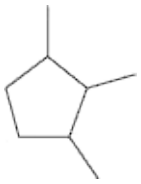
Figure 4.3 **Examples of cycloalkane nomenclature**

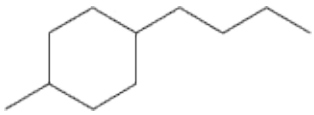


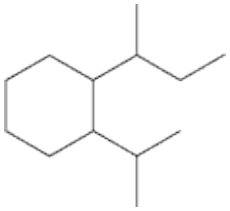
Problem 4.11

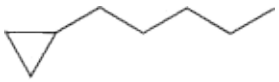
Give the IUPAC name for each compound.

a. 

b. 

c. 

d. 

e. 

f.

Problem 4.12

Give the structure corresponding to each IUPAC name.

a. 1,2-dimethylcyclobutane

b. 1,1,2-trimethylcyclopropane

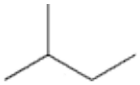
c. 4-ethyl-1,2-dimethylcyclohexane

d. 1-*sec*-butyl-3-isopropylcyclopentane

e. 1,1,2,3,4-pentamethylcycloheptane

4.6 Common Names

Some organic compounds are identified using common names that do not follow the IUPAC system of nomenclature. Many of these names were given to molecules long ago, before the IUPAC system was adopted. These names are still widely used. For example, isopentane, an older name for 2-methylbutane, is still allowed by IUPAC rules. We will follow the IUPAC system except in cases in which a common name is widely accepted.



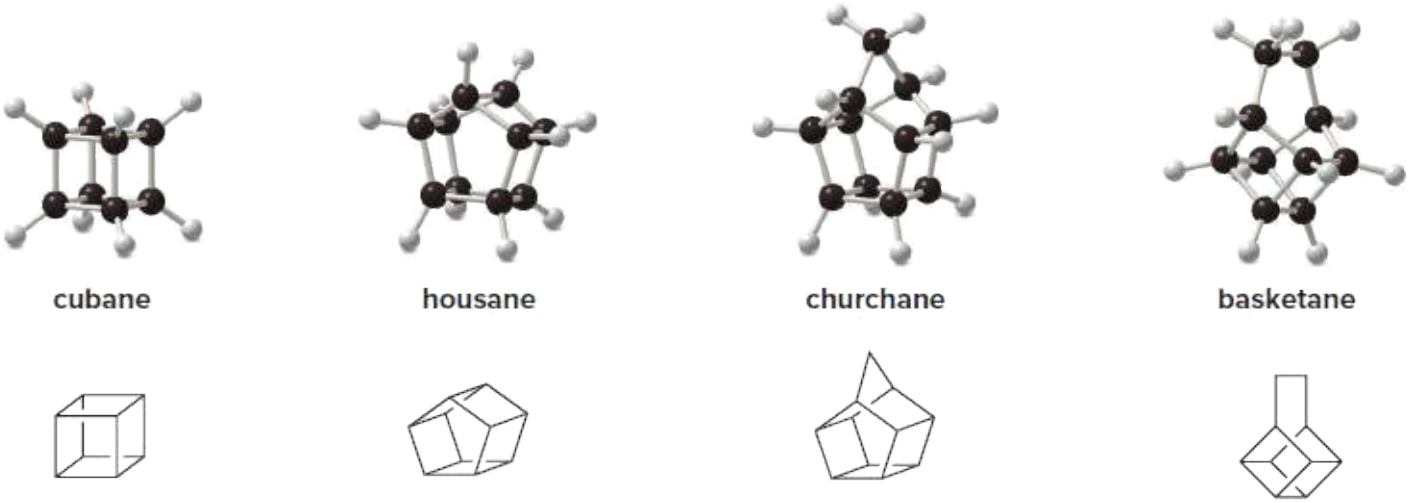
isopentane or 2-methylbutane

In the past several years, organic chemists have attempted to synthesize some unusual cycloalkanes not found in nature. Dodecahedrane, a beautifully symmetrical compound composed of 12 five-membered rings, is one such molecule. It was first prepared at The Ohio State University in 1982. The IUPAC name for dodecahedrane is undecacyclo[9.9.0.$0^{2,9}$.$0^{3,7}$.$0^{4,20}$.$0^{5,18}$.$0^{6,16}$.$0^{8,15}$.$0^{10,14}$.$0^{12,19}$.$0^{13,17}$]-icosane, a name so complex that few trained organic chemists would be able to identify its structure.

dodecahedrane

Because these systematic names are so unwieldy, organic chemists often assign a name to a polycyclic compound that is more descriptive of its shape and structure. Dodecahedrane is named because its 12 five-membered rings resemble a dodecahedron. Figure 4.4 shows the names and structures of several other cycloalkanes whose names were inspired by the shape of their carbon skeletons. All the names end in the suffix *-ane*, indicating that they refer to alkanes.

Figure 4.4 **Common names for some polycyclic alkanes**



cubane housane churchane basketane

- For a comprehensive list of unusual polycyclic alkanes (including windowpane, davidane, catenane, propellane, and many others), see *Organic Chemistry: The Name Game* by Alex Nickon and Ernest Silversmith, Pergamon Press, 1987.

A significant source of atmospheric methane comes from flooded rice fields. Methane, a greenhouse gas like CO_2 (Section 4.14), is produced by the decomposition of organic matter under anaerobic conditions by soil bacteria.
©Daniel C. Smith

4.7 Natural Occurrence of Alkanes

Many alkanes occur in nature, primarily in natural gas and petroleum. Both of these fossil fuels serve as energy sources, formed from the degradation of organic material long ago.

Natural gas is composed largely of methane (60% to 80% depending on its source), with lesser amounts of ethane, propane, and butane. These organic compounds burn in the presence of oxygen, releasing energy for cooking and heating.

Methane in the atmosphere comes from natural and man-made sources. As global temperatures increase, methane trapped in permafrost and glaciers is released with melting. Microorganisms in the gut of ruminant animals produce methane that is released during defecation and belching. The microorganisms in wetlands and flooded rice fields decompose organic material to form methane when no oxygen is present. Although methane does not persist in the atmosphere as long as carbon dioxide (Section 4.14), methane is a greenhouse gas with significant global warming potential, and its concentration has increased significantly in the last 200 years.

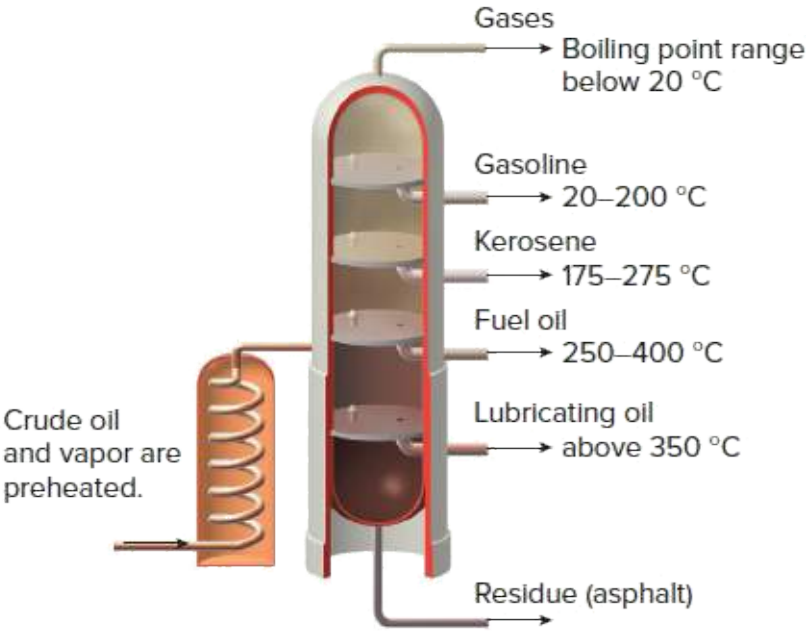
Petroleum is a complex mixture of compounds, most of which are hydrocarbons containing 1–40 carbon atoms. Distilling crude petroleum, a process called refining, separates it into usable fractions that differ in boiling point (Figure 4.5). Most products

of petroleum refining provide fuel for home heating, automobiles, diesel engines, and airplanes. Each fuel type has a different composition of hydrocarbons: gasoline (C_5H_{12}—$C_{12}H_{26}$), kerosene ($C_{12}H_{26}$—$C_{16}H_{34}$), and diesel fuel ($C_{15}H_{32}$—$C_{18}H_{38}$).

Figure 4.5 **Refining crude petroleum into usable fuel and other petroleum products**

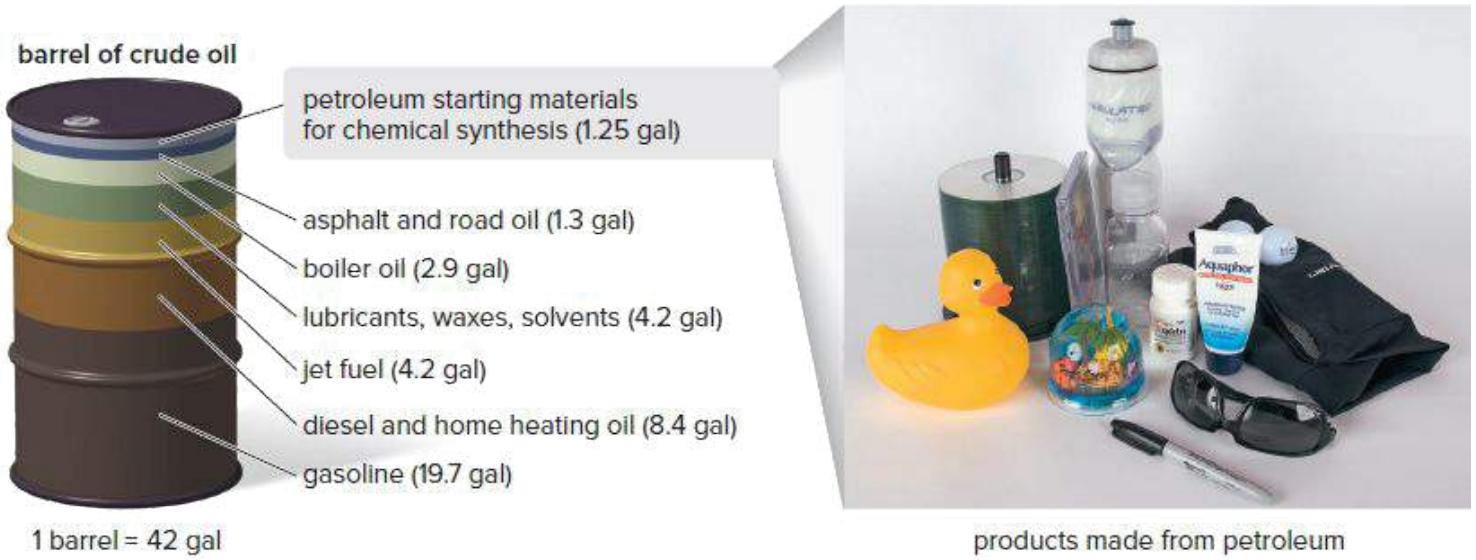
©Glow Images

- **An oil refinery.** At an oil refinery, crude petroleum is separated into fractions of similar boiling point by the process of **distillation.**



- **Schematic of a refinery tower.** As crude petroleum is heated, the lower boiling, more volatile components distill first, followed by fractions of progressively higher boiling point.

Petroleum provides more than fuel. About 3% of crude oil is used to make plastics and other synthetic compounds including drugs, fabrics, dyes, and pesticides. These products are responsible for many of the comforts we now take for granted in industrialized countries. Imagine what life would be like without air conditioning, refrigeration, anesthetics, and pain relievers, all products of the petroleum industry.



©McGraw-Hill Education/Jill Braaten, photographer

Energy from petroleum is *nonrenewable*, and the remaining known oil reserves are limited. Given our dependence on petroleum, not only for fuel, but also for the many necessities of modern society, it becomes clear that we must both conserve what we have and find alternate energy sources.

4.8 Properties of Alkanes

4.8A Physical Properties

Alkanes contain only nonpolar C—C and C—H bonds, and as a result they exhibit only weak van der Waals forces. Table 4.2 summarizes how these intermolecular forces affect the physical properties of alkanes.

The gasoline industry exploits the dependence of boiling point and melting point on alkane size by seasonally changing the composition of gasoline in locations where it gets very hot in the summer and very cold in the winter. Gasoline is refined to contain a larger fraction of higher-boiling hydrocarbons in warmer weather, so it evaporates less readily. In colder weather, it is refined to contain more lower-boiling hydrocarbons, so it freezes less readily.

Because nonpolar alkanes are not water soluble, crude petroleum that leaks into the sea from an oil tanker or offshore oil well creates an insoluble oil slick on the surface. The insoluble hydrocarbon oil poses a special threat to birds whose feathers are coated with natural nonpolar oils for insulation. Because these hydrophobic oils dissolve in the crude petroleum, birds lose their layer of natural protection and many die.

The mutual insolubility of nonpolar oil and very polar water

leads to the common expression “Oil and water don't mix.”

Problem 4.13

Arrange the following compounds in order of increasing boiling point.

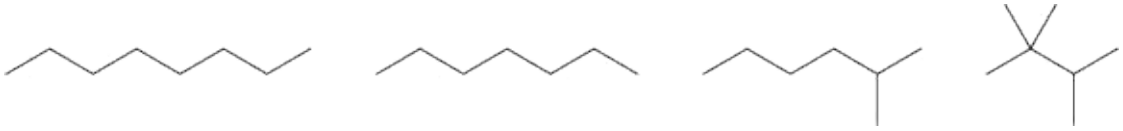
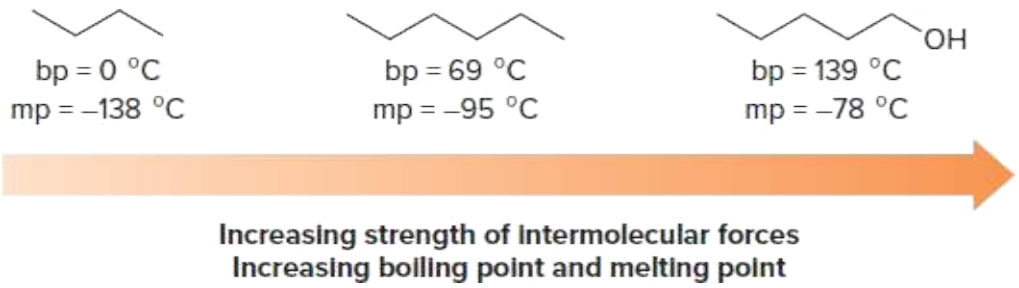
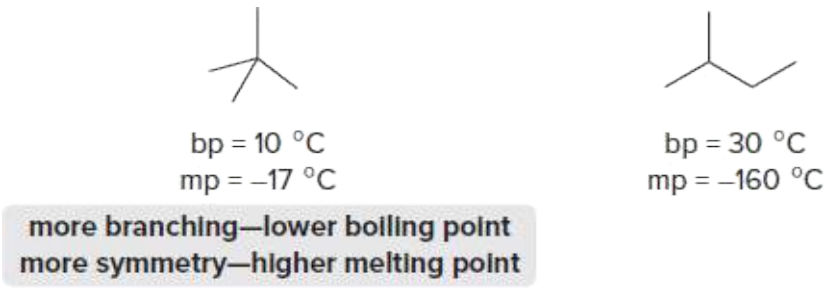


Table 4.2 Physical Properties of Alkanes

Property	Observation
Boiling point and melting point	• Alkanes have low bp's and mp's compared to more polar compounds of comparable size. • Bp and mp increase as the number of carbons increases because of increased surface area. 
	• The bp of isomers decreases with branching because of decreased surface area. • Mp increases with increased symmetry. 
Solubility	• Alkanes are soluble in organic solvents. • Alkanes are insoluble in water.

Key: bp = boiling point; mp = melting point

4.8B Spectroscopic Properties

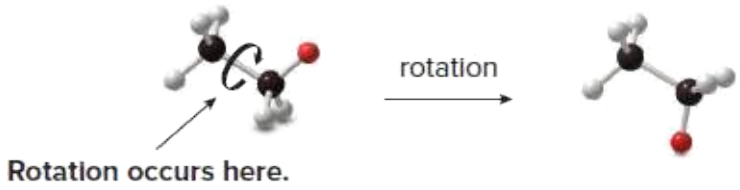
Students who would like to learn about the spectroscopic properties of alkanes are referred to the following sections in later chapters:

- Mass spectrometry: Sections A.1A and A.3, especially Figure A.5 and Sample Problem A.6
- Infrared spectroscopy: Section B.4A and Table B.2

4.9 Conformations of Acyclic Alkanes—Ethane

Let's now take a closer look at the three-dimensional structure of alkanes. The three-dimensional structure of molecules is called stereochemistry. In Chapter 4, we examine the effect of rotation around single bonds. In Chapter 5, we will learn about other aspects of stereochemistry.

Recall from Section 1.10A that rotation occurs around carbon–carbon σ bonds. Thus, the two CH_3 groups of ethane rotate, allowing the hydrogens on one carbon to adopt different orientations relative to the hydrogens on the other carbon. These arrangements are called conformations.

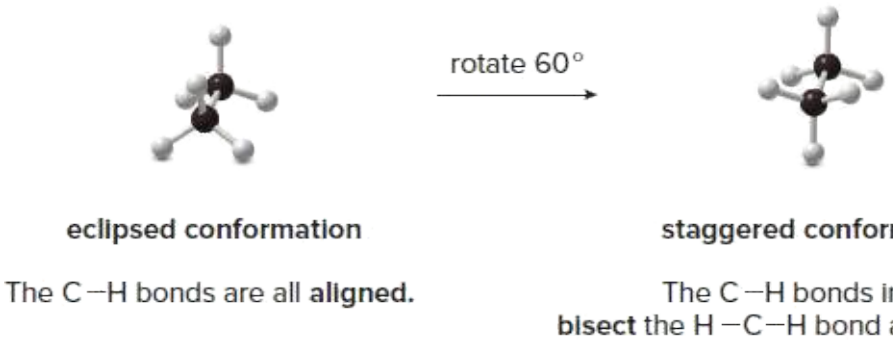


two different conformations

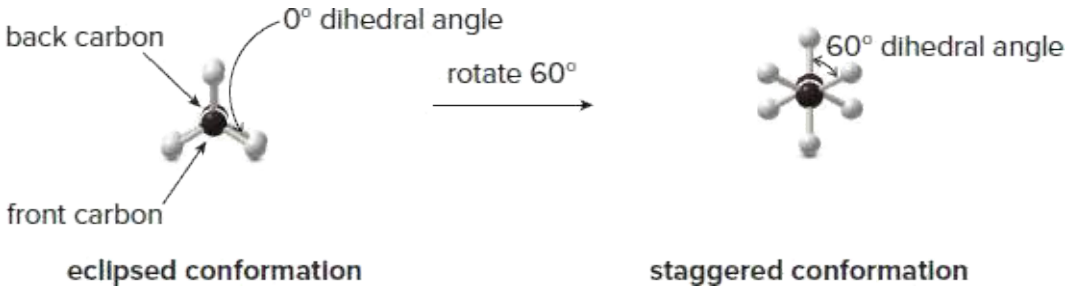
- ***Conformations*** **are different arrangements of atoms that are interconverted by rotation around single bonds.**

Two different arrangements are the eclipsed conformation and the staggered conformation.

- **In the *eclipsed conformation*, the C—H bonds on one carbon are directly aligned with the C—H bonds on the adjacent carbon.**
- **In the *staggered conformation*, the C—H bonds on one carbon bisect the H—C—H bond angle on the adjacent carbon.**



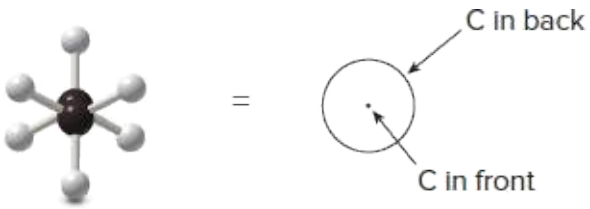
Rotating the atoms on one carbon by 60° converts an eclipsed conformation into a staggered conformation, and vice versa. These conformations are often viewed end-on —that is, looking directly down the carbon–carbon bond. The angle that separates a bond on one atom from a bond on an adjacent atom is called a dihedral angle. For ethane in the staggered conformation, the dihedral angle for the C—H bonds is 60°. For eclipsed ethane, it is 0°.



End-on representations for conformations are commonly drawn using a convention called a Newman projection. A Newman projection is a graphic that shows the three groups bonded to each carbon atom in a particular C—C bond, as well as the dihedral angle that separates them.

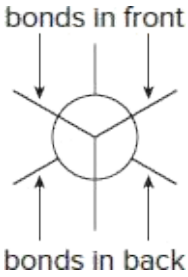
How To Draw a Newman Projection

Step [1] **Look directly down the C—C bond (end-on), and draw a circle with a dot in the center to represent the carbons of the C—C bond.**



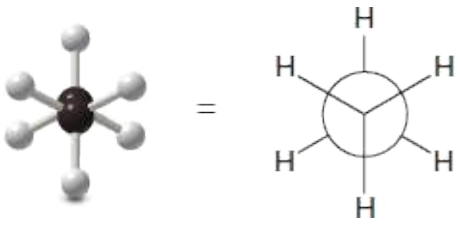
- **The circle represents the back carbon and the dot represents the front carbon.**

Step [2] **Draw in the bonds.**



- **Draw the bonds on the front C as three lines meeting at the center of the circle.**
- **Draw the bonds on the back C as three lines coming out of the edge of the circle.**

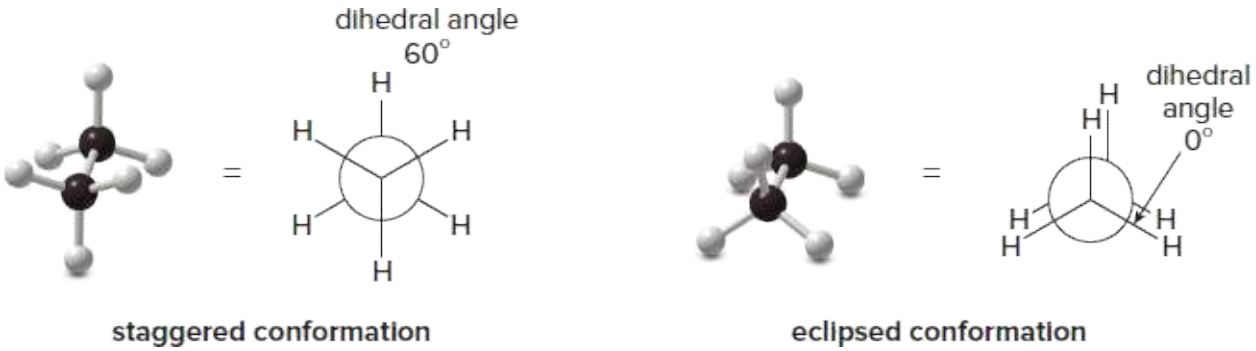
Step [3] Add the atoms on each bond.



- **Each C has 3 H's in ethane.**

[Figure 4.6](#) illustrates the Newman projections for both the staggered and eclipsed conformations for ethane. Page 148

Figure 4.6 **Newman projections for the staggered and eclipsed conformations of ethane**

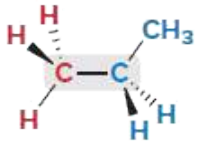


Follow this procedure for any C—C bond. With a Newman projection, always consider *one* C—C bond only and draw the atoms bonded to the carbon atoms, *not* the carbon atoms in the bond itself. Newman projections for the staggered and eclipsed conformations of propane are drawn in [Figure 4.7](#).

Figure 4.7 **Newman projections for the staggered and eclipsed conformations**

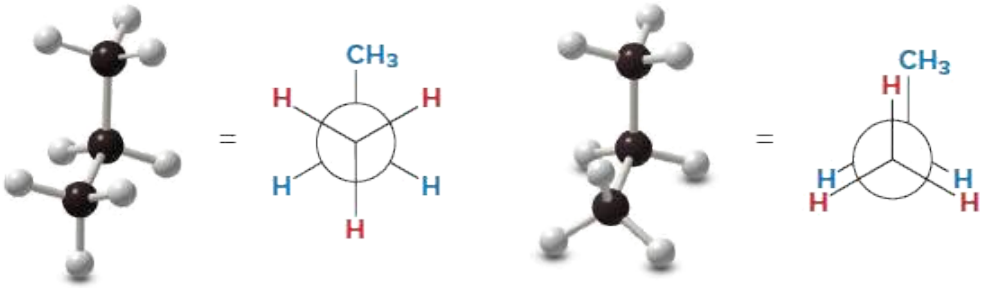
of propane

Consider one C–C bond only.



propane

- Arbitrarily pick one C to be in front and one C to be in back.
- 3 H's on one C
- 2 H's and 1 CH_3 on the other C



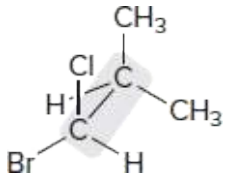
staggered conformation

eclipsed conformation

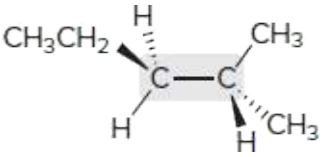
Problem 4.14

Convert each representation to a Newman projection around the indicated bond.

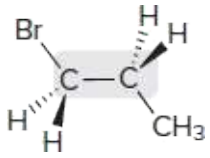
a.



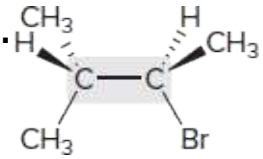
b.



c.

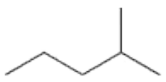


d.

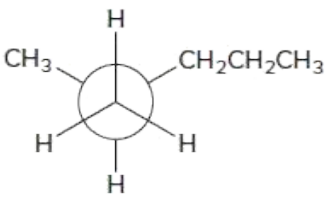


Problem 4.15

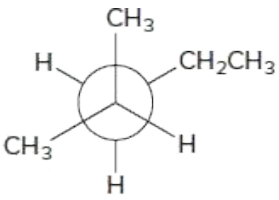
Which of the following is (are) possible Newman projections for 2-methylpentane?



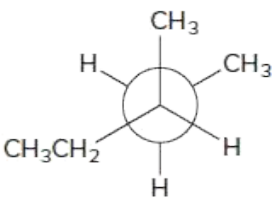
2-methylpentane



A



B



C

The staggered and eclipsed conformations of ethane interconvert at room temperature, but each conformation is *not* equally stable.

- **The staggered conformations are more stable (lower in energy) than the eclipsed conformations.**

The cause of this stability difference is the subject of some debate in the chemical literature. A contributing factor may be increased electron–electron repulsion between the bonds in the eclipsed conformation compared to the staggered conformation, where the bonding electrons are farther apart. The difference in energy between the staggered and eclipsed conformations is 12 kJ/mol (2.9 kcal/mol), a small enough difference that the rotation is still very rapid at room temperature, and the conformations cannot be separated. Because three eclipsed C—H bonds increase the energy of a conformation by 12 kJ/mol, each eclipsed C—H bond results in an increase in energy of 4.0 kJ/mol (1.0 kcal/mol). The energy difference between the staggered and eclipsed conformations is called torsional energy. Thus, eclipsing introduces torsional strain into a molecule.

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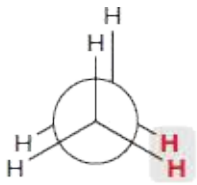


Each H,H eclipsing increases energy by 4.0 kJ/mol.

- ***Torsional strain* is an increase in energy caused by eclipsing interactions.**

The graph in Figure 4.8 shows how the potential energy of ethane changes with dihedral angle as one CH_3 group rotates relative to the other. The staggered conformation is the most stable arrangement, so it is at an *energy minimum*. As the C—H bonds on one carbon are rotated relative to the C—H bonds on the other carbon, the energy increases as the C—H bonds get closer until a maximum is reached after 60° rotation to the eclipsed conformation. As rotation continues, the energy decreases until after 60° rotation, when the staggered conformation is reached once again.

Strain results in an increase in energy. Torsional strain is the first of three types of strain discussed in this text. The other two are steric strain (Section 4.10) and angle strain (Section

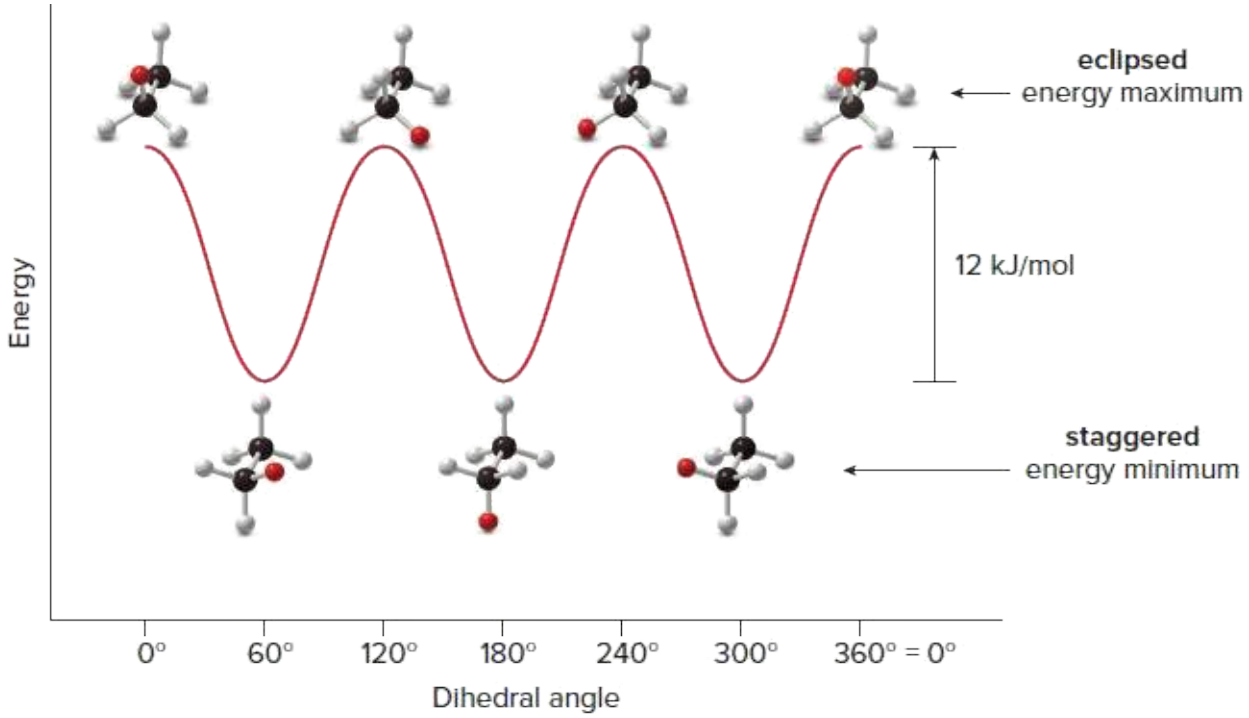
4.11).

- **An energy minimum and maximum occur every 60° as the conformation changes from staggered to eclipsed. Conformations that are neither staggered nor eclipsed are intermediate in energy.**

Problem 4.16

The torsional energy in propane is 14 kJ/mol (3.4 kcal/mol). Because each H,H eclipsing interaction is worth 4.0 kJ/mol (1.0 kcal/mol) of destabilization, how much is one H,CH_3 eclipsing interaction worth in destabilization? (See Section 4.10 for an alternate way to arrive at this value.)

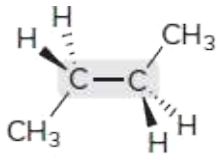
Figure 4.8 **Graph: Energy versus dihedral angle for ethane**



- Note the position of the labeled H atom after each 60° rotation. All three staggered conformations are identical (except for the position of the label), and the same is true for all three eclipsed conformations.

4.10 Conformations of Butane

Butane and higher-molecular-weight alkanes have several carbon–carbon bonds, all capable of rotation.



butane
Consider rotation at C2–C3.
Each C is bonded to 2 H's and 1 CH_3 group.

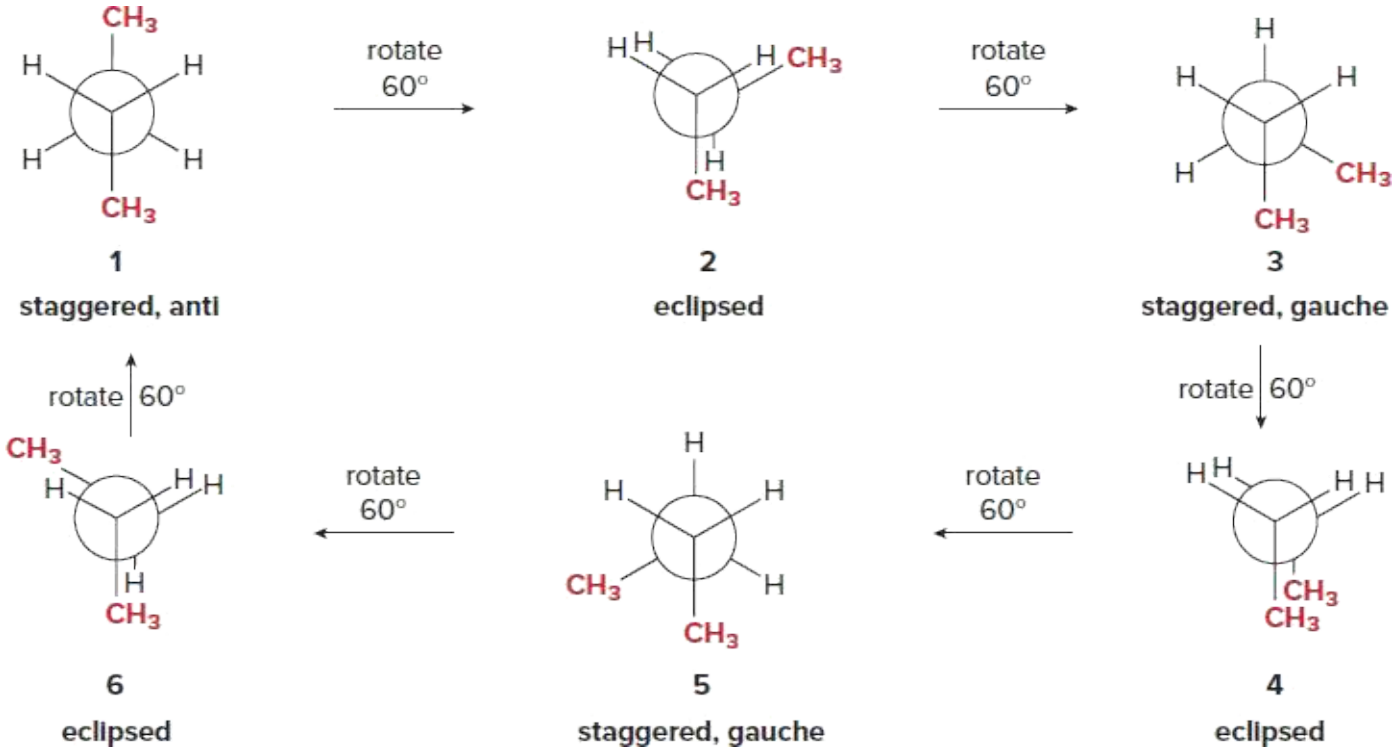
To analyze the different conformations that result from rotation around the C2–C3 bond, begin arbitrarily with one—for example, the staggered conformation that places two CH_3 groups 180° from each other—then,

It takes six 60° rotations to return to the original conformation.

- **Rotate one carbon atom in 60° increments either clockwise or counterclockwise, while keeping the other carbon fixed. Continue until you return to the original conformation.**

Figure 4.9 illustrates the six possible conformations that result from this process.

Figure 4.9 **Six different conformations of butane**



Although each 60° bond rotation converts a staggered conformation into an eclipsed conformation (or vice versa), neither all the staggered conformations nor all the eclipsed conformations are the same. For example, the dihedral angle between the

methyl groups in staggered conformations 3 and 5 are both 60°, whereas it is 180° in staggered conformation 1.

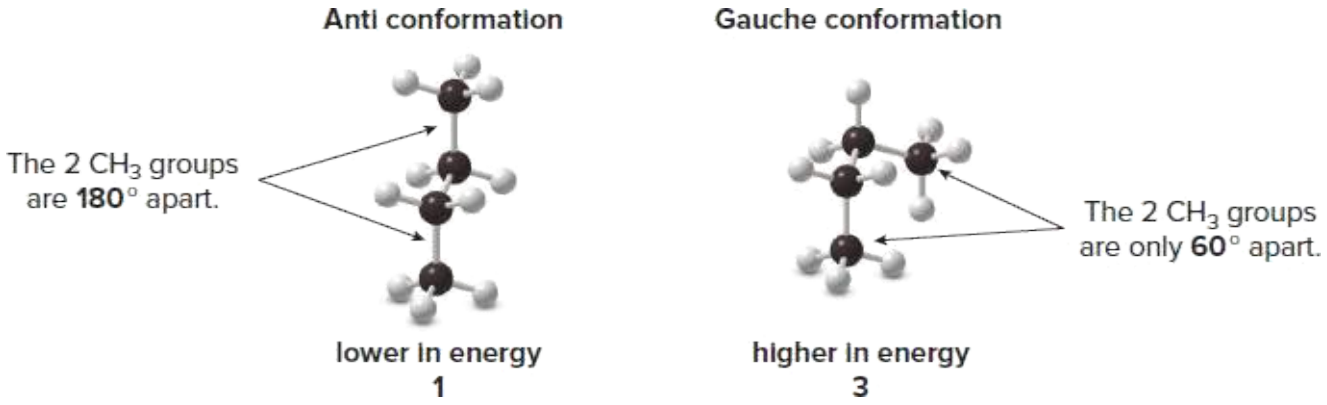
- **A staggered conformation with two larger groups 180° from each other is called *anti.***
- **A staggered conformation with two larger groups 60° from each other is called *gauche.***

Similarly, the methyl groups in conformations 2 and 6 both eclipse hydrogen atoms, whereas they eclipse each other in conformation 4.

The staggered conformations (1, 3, and 5) are lower in energy than the eclipsed conformations (2, 4, and 6), but how do the energies of the individual staggered and eclipsed conformations compare to each other? The relative energies of the individual staggered conformations (or the individual eclipsed conformations) depend on their steric strain.

- ***Steric* strain is an increase in energy resulting when atoms are forced too close to one another.**

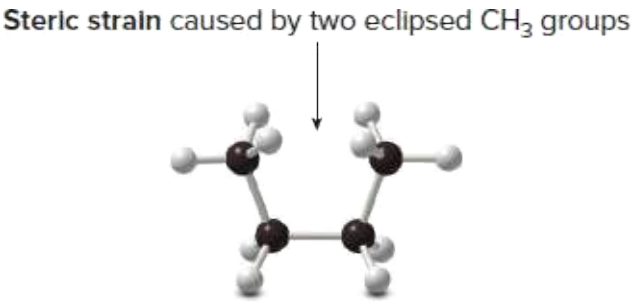
The methyl groups are farther apart in the anti conformation (1) than in the gauche conformations (3 and 5), so among the staggered conformations, 1 is lower in energy (more stable) than 3 and 5. In fact, the anti conformation is 3.8 kJ/mol (0.9 kcal/mol) lower in energy than either gauche conformation because of the steric strain that results from the proximity of the methyl groups in 3 and 5.



- **Gauche conformations are generally *higher* in energy than anti conformations because of steric strain.**

Steric strain also affects the relative energies of eclipsed conformations. Conformation

4 is higher in energy than 2 or 6, because the two larger CH_3 groups are forced close to each other, introducing considerable steric strain.

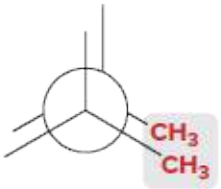


4

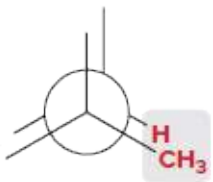
To graph energy versus dihedral angle, keep in mind two considerations:

- **Staggered conformations are at energy minima and eclipsed conformations are at energy maxima.**
- **Unfavorable steric interactions increase energy.**

For butane, this means that anti conformation 1 is lowest in energy, and conformation 4 with two eclipsed CH_3 groups is the highest in energy. The relative energy of other conformations is depicted in the energy versus rotation diagram for butane in Figure 4.10.



CH_3,CH_3 eclipsing
11 kJ/mol destabilization



H,CH_3 eclipsing
6.0 kJ/mol destabilization

We can now use the values in Figure 4.10 to estimate the destabilization caused by other eclipsed groups. For example, conformation 4 is 19 kJ/mol less stable than the anti conformation 1. Conformation 4 possesses two H,H eclipsing interactions, worth 4.0 kJ/mol each in destabilization (Section 4.9), and one CH_3,CH_3 eclipsing interaction. Thus, the CH_3,CH_3 interaction is worth 19 – 2(4.0) = 11 kJ/mol of destabilization.

Similarly, conformation 2 is 16 kJ/mol less stable than the anti conformation 1, and possesses one H,H eclipsing interaction (worth 4.0 kJ/mol of destabilization) and two H,CH_3 interactions. Thus, each H,CH_3 interaction is worth 1/2(16 – 4.0) = 6.0 kJ/mol of destabilization. These values are summarized in Table 4.3.

- **The energy difference between the lowest and highest energy conformations is called the *barrier to rotation*.**

We can use these same principles to determine conformations and relative energies for any acyclic alkane. Because the lowest energy conformation has all bonds staggered and all large groups anti, alkanes are often drawn in zigzag skeletal structures to indicate this.

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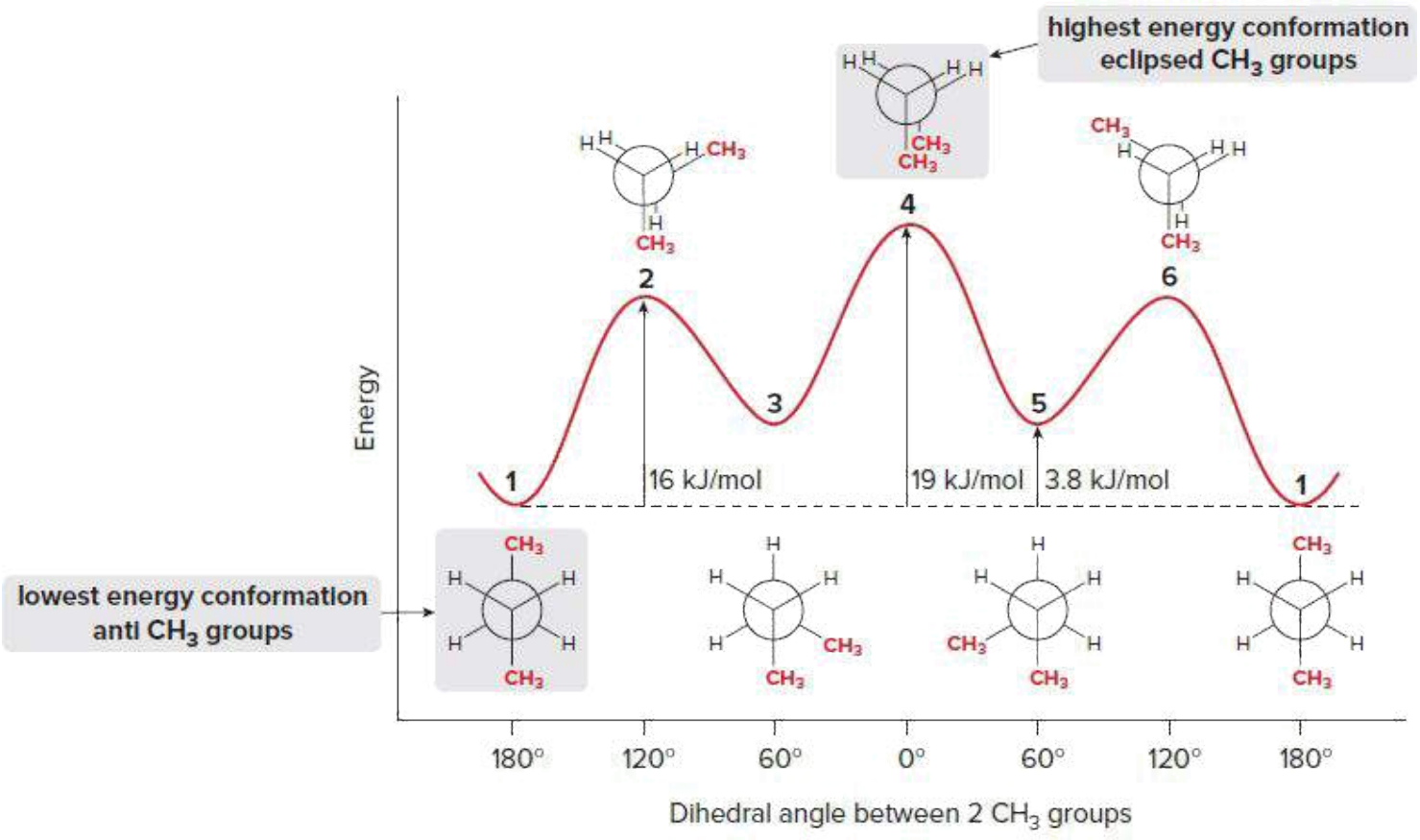
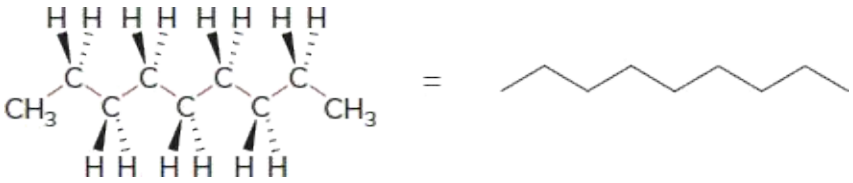
Figure 4.10 **Graph: Energy versus dihedral angle for butane**



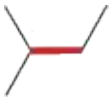
- Staggered conformations **1**, **3**, and **5** are at energy minima.
- Anti conformation **1** is lower in energy than gauche conformations **3** and **5**, which possess steric strain.
- Eclipsed conformations **2**, **4**, and **6** are at energy maxima.
- Eclipsed conformation **4**, which has additional steric strain due to two eclipsed CH_3 groups, is highest in energy.

Table 4.3 **Summary: Torsional and Steric Strain Energies in Acyclic**

Type of interaction	Energy increase	
	kJ/mol	kcal/mol
H,H eclipsing	4.0	1.0
H,CH_3 eclipsing	6.0	1.4
CH_3,CH_3 eclipsing	11	2.6
gauche CH_3 groups	3.8	0.9



Problem 4.17

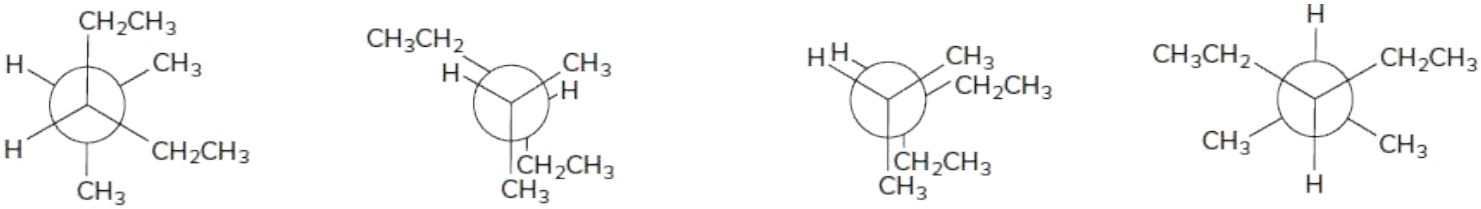


a. Draw the three staggered and three eclipsed conformations that result from rotation around the bond labeled in red using Newman projections.

b. Label the most stable and least stable conformation.

Problem 4.18

Rank the following conformations in order of increasing energy.



Problem 4.19

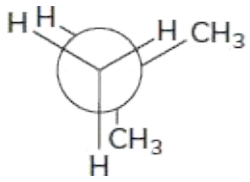
Consider rotation around the carbon–carbon bond in 1,2-dichloroethane ($ClCH_2CH_2Cl$).

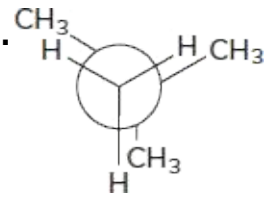
a. Using Newman projections, draw all of the staggered and eclipsed conformations that result from rotation around this bond.

b. Graph energy versus dihedral angle for rotation around this bond.

Problem 4.20

Calculate the destabilization present in each eclipsed conformation.

a. 

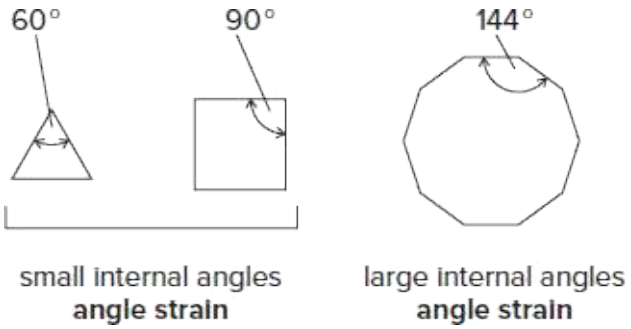
b. 

4.11 An Introduction to Cycloalkanes

Besides torsional strain and steric strain, the conformations of cycloalkanes are affected by angle strain.

- ***Angle* strain is an increase in energy when tetrahedral bond angles deviate from the optimum angle of 109.5°.**

Originally cycloalkanes were thought to be flat rings, with the bond angles between carbon atoms determined by the size of the ring. For example, a flat cyclopropane ring would have 60° internal bond angles, a flat cyclobutane ring would have 90° angles, and large flat rings would have very large angles. It was assumed that rings with bond angles so different from the tetrahedral bond angle would be very strained and highly reactive. This is called the Baeyer strain theory.



It turns out, though, that cycloalkanes with more than three C atoms in the ring are not flat molecules. They are puckered to reduce strain, both angle strain and torsional strain. The three-dimensional structures of some simple cycloalkanes are shown in Figure 4.11. Three- and four-membered rings still possess considerable angle strain, but puckering reduces the internal bond angles in larger rings, thus reducing angle

strain.

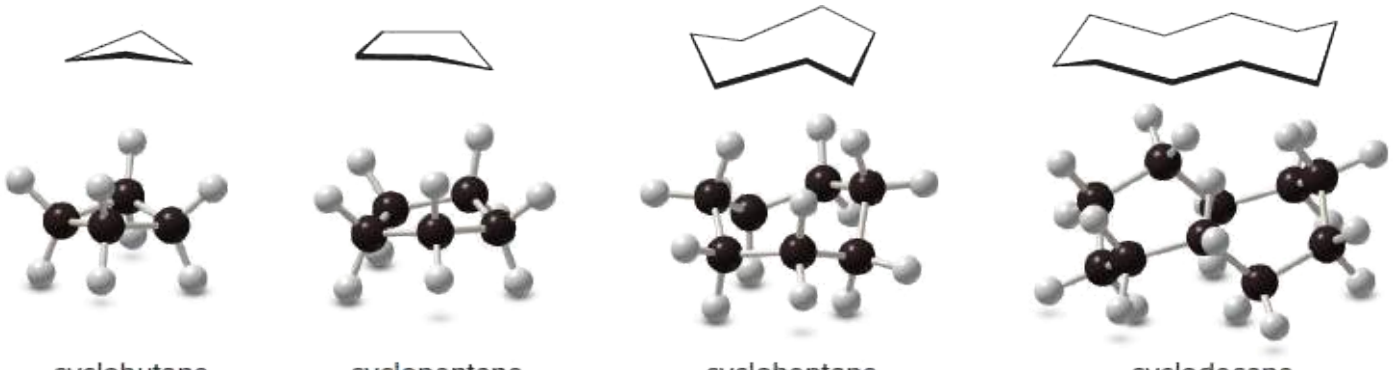
tetrahedrane

cubane

dodecahedrane

Many polycyclic hydrocarbons are of interest to chemists. For example, dodecahedrane, containing 12 five-membered rings bonded together, is one member of a family of three hydrocarbons that contain several rings of one size joined together. The two other members of this family are tetrahedrane, consisting of four three-membered rings, and cubane, consisting of six four-membered rings. These compounds are the simplest regular polyhedra whose structures resemble three of the highly symmetrical Platonic solids: the tetrahedron, the cube, and the dodecahedron.

Figure 4.11 **Three-dimensional structure of some cycloalkanes**



cyclobutane cyclopentane cycloheptane cyclodecane

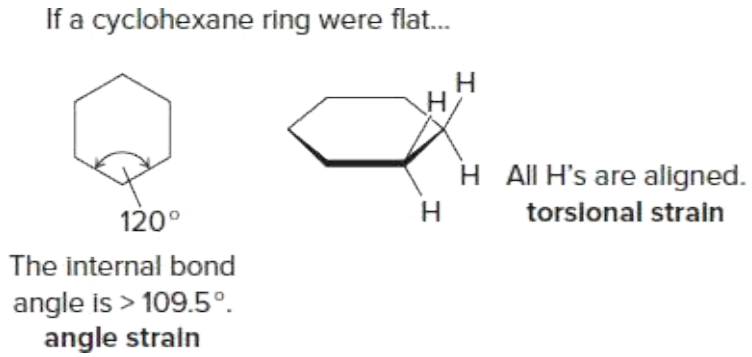
How stable are these compounds? Tetrahedrane (with internal 60° bond angles) is so strained that all attempts to prepare it have been thus far unsuccessful. Although cubane is also highly strained because of its 90° bond angles, it was first synthesized in 1964 and is a stable molecule at room temperature. Finally, dodecahedrane is very stable because it has bond angles very close to the tetrahedral bond angle (108° versus 109.5°). Its synthesis eluded chemists for years not because of its strain or inherent instability, but because of the enormous challenge of joining 12 five-membered rings together to form a sphere.

4.12 Cyclohexane

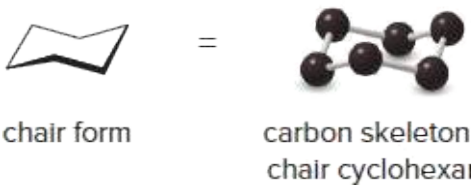
Let's now examine the conformation of cyclohexane, the most common ring size in naturally occurring compounds.

4.12A The Chair Conformation

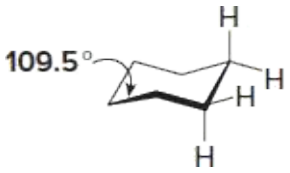
A planar cyclohexane ring would experience angle strain, because the internal bond angle between the carbon atoms would be 120°, and torsional strain, because all of the hydrogens on adjacent carbon atoms would be eclipsed.



In reality, cyclohexane adopts a puckered conformation, called the chair form, which is more stable than any other possible conformation.



The chair conformation is so stable because it eliminates angle strain (all C—C—C bond angles are 109.5°) and torsional strain (all hydrogens on adjacent carbon atoms are staggered, not eclipsed).



All H's are **staggered.**

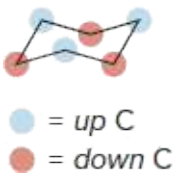
- **In cyclohexane, three C atoms pucker up and three C atoms pucker down, alternating around the ring. These C atoms are called *up* C's and *down* C's.**

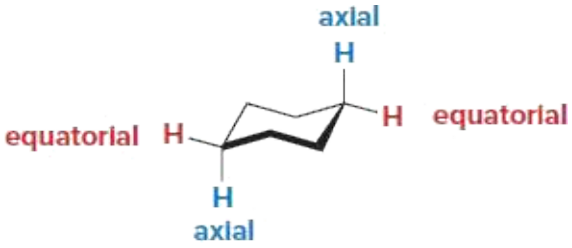
Visualizing the chair. If the cyclohexane chair conformation is tipped downward, we can more easily view it as a chair with a back, seat, and foot support.

Each cyclohexane carbon atom has one axial and one equatorial hydrogen.

Each carbon in cyclohexane has two different kinds of hydrogens.

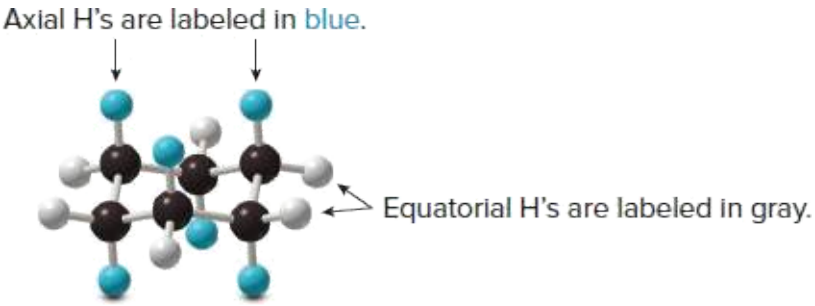
- ***Axial* hydrogens are located above and below the ring (along a perpendicular axis).**
- ***Equatorial* hydrogens are located in the plane of the ring (around the equator).**





A three-dimensional representation of the chair form is shown in Figure 4.12.

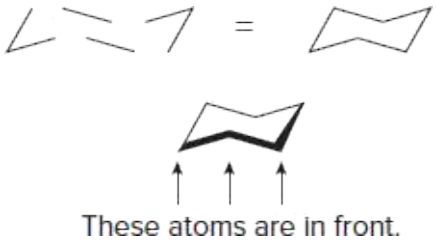
Figure 4.12 **A three-dimensional model of the chair form of cyclohexane with all H atoms drawn**



- Cyclohexane has **six axial H's** and **six equatorial H's.**

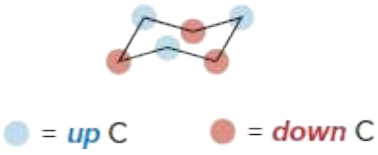
How To Draw the Chair Form of Cyclohexane

Step [1] **Draw the carbon skeleton.**



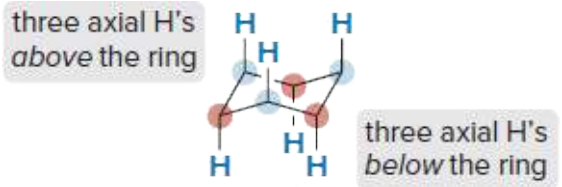
- **Draw three parts of the chair: a wedge, a set of parallel lines, and another wedge.**
- **Then, join them together.**
- **The bottom 3 C's come out of the page, and for this reason, bonds to them are sometimes highlighted in bold.**

Step [2] **Label the *up* C's and *down* C's on the ring.**



- **There are 3 *up* and 3 *down* C's, and they *alternate* around the ring.**

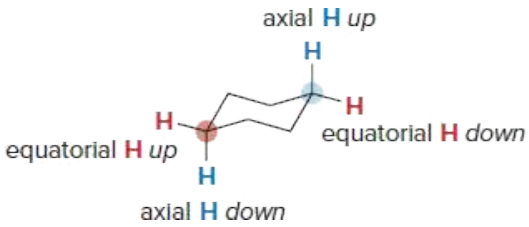
Step [3] **Draw in the axial H atoms.**

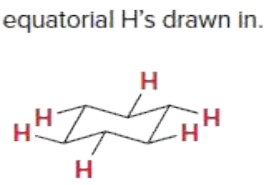


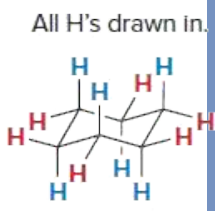
- **On an *up C* the axial H is *up.***
- **On a *down C* the axial H is *down.***

Step [4] Draw in the equatorial H atoms.

- **The axial H is down on a down C, so the equatorial H must be up.**
- **The axial H is up on an up C, so the equatorial H must be down.**

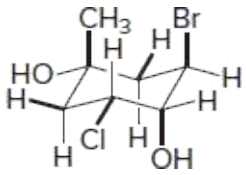






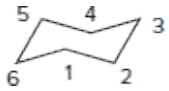
Problem 4.21

Classify the ring carbons as *up* C's or *down* C's. Identify the bonds highlighted in bold as axial or equatorial.



Problem 4.22

Using the cyclohexane with the C's numbered as shown, draw a chair form that fits each description.



a. The ring has an axial CH_3 group at C1 and an equatorial OH on C2.

b. The ring has an equatorial CH_3 group on C6 and an axial OH group on C4.

c. The ring has equatorial OH groups on C1, C2, and C5.

4.12B Ring-Flipping

Like acyclic alkanes, cyclohexane does not remain in a single conformation. The bonds twist and bend, resulting in new arrangements, but the movement is more restricted. One conformational change involves ring-flipping, which can be viewed as a two-step process.

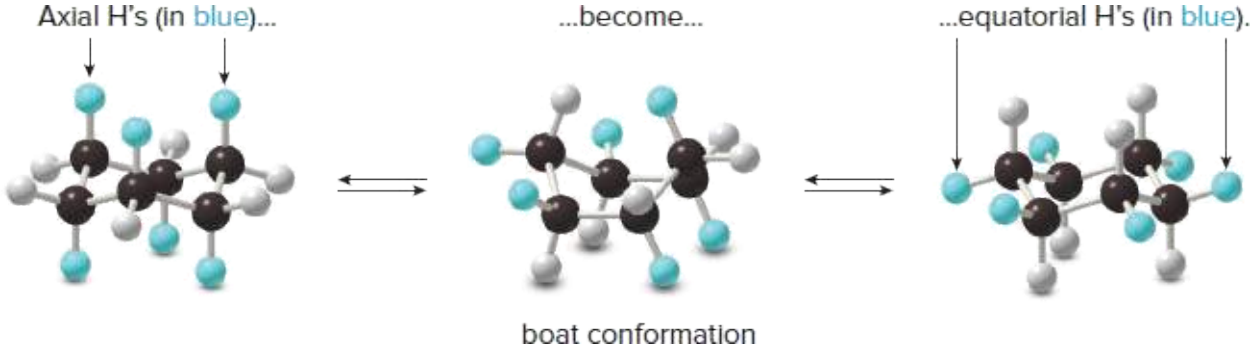
- A *down* carbon flips up. This forms a new conformation of cyclohexane called a boat. The boat form has two carbons oriented above a plane containing the other four carbons.
- The boat form can flip in two possible ways. The carbon labeled with a red circle can flip down, re-forming the initial conformation; or the second *up* carbon, labeled with a blue circle, can flip down. This forms a second chair conformation.

Because of ring-flipping, the *up* carbons become *down* carbons and the *down* carbons become *up* carbons. Thus, cyclohexane exists as two different chair conformations of equal stability, which rapidly interconvert at room temperature.

The process of ring-flipping also affects the orientation of cyclohexane's hydrogen atoms.

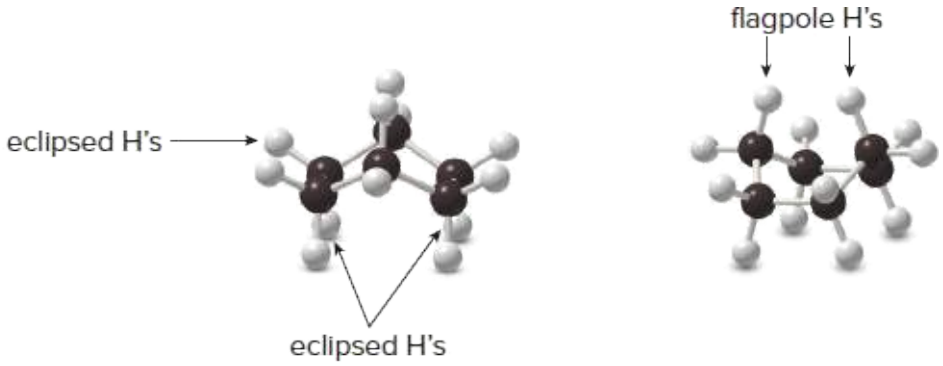
- **Axial and equatorial H atoms are interconverted during a ring flip. Axial H atoms become equatorial H atoms, and equatorial H atoms become axial H atoms (Figure 4.13).**

Figure 4.13 **Ring-flipping interconverts axial and equatorial hydrogens in cyclohexane.**



The chair forms of cyclohexane are 30 kJ/mol more stable than the boat forms. The boat conformation is destabilized by torsional strain because the hydrogens on the four carbon atoms in the plane are eclipsed. Additionally, there is steric strain because two hydrogens at either end of the boat—the flagpole hydrogens—are forced close to each other, as shown in Figure 4.14.

Figure 4.14 **Two views of the boat conformation of cyclohexane**



The boat form of cyclohexane is less stable than the chair forms for two reasons:

- Eclipsing interactions between H's cause **torsional strain.**
- The proximity of the flagpole H's causes **steric strain.**

4.13 Substituted Cycloalkanes

What happens when one hydrogen on cyclohexane is replaced by a larger substituent? Is there a difference in the stability of the two cyclohexane conformations? To answer these questions, remember one rule:

- **The equatorial position has more room than the axial position, so *larger* substituents are more stable in the *equatorial* position.**

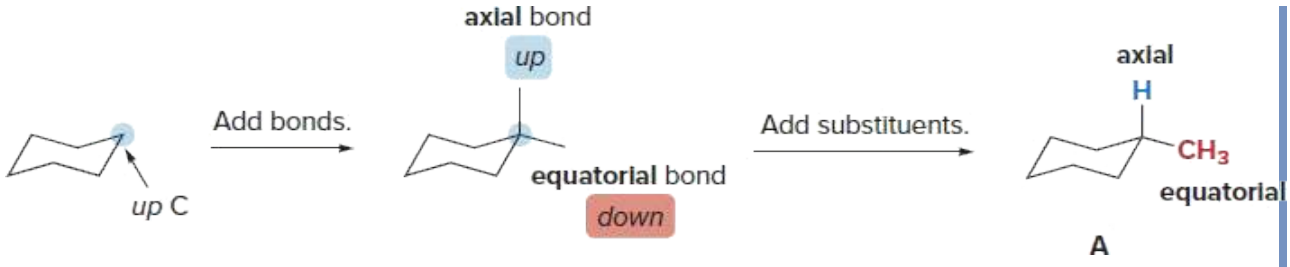
4.13A Cyclohexane with One Substituent

There are two possible chair conformations of a monosubstituted cyclohexane, such as methylcyclohexane, as shown in the following *How To*.

How To **Draw the Two Conformations for a Substituted Cyclohexane**

Step [1] **Draw one chair form and add the substituents.**

- **Arbitrarily pick a ring carbon, classify it as an *up* or *down* carbon, and draw the bonds. Each C has one axial and one equatorial bond.**
- **Add the substituents, in this case H and CH_3, arbitrarily placing one axial and one equatorial. In this example, the CH_3 group is drawn equatorial.**
- **This forms one of the two possible chair conformations, labeled A.**



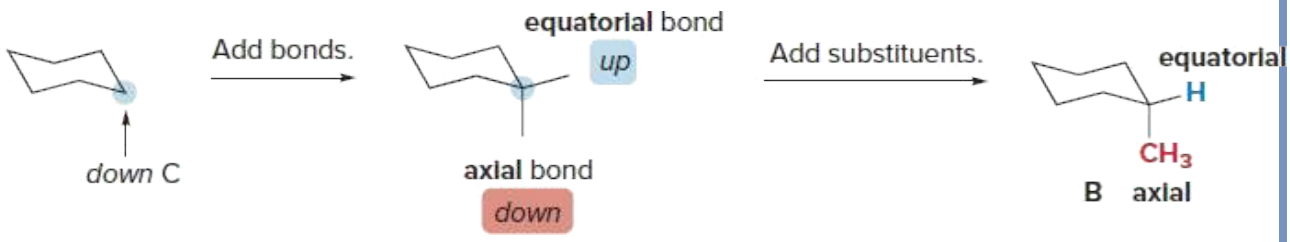
Step [2] Ring-flip the cyclohexane ring.

- **Convert *up* C's to *down* C's and vice versa. The chosen *up* C now puckers down.**

Step [3] Add the substituents to the second conformation.

Page 158

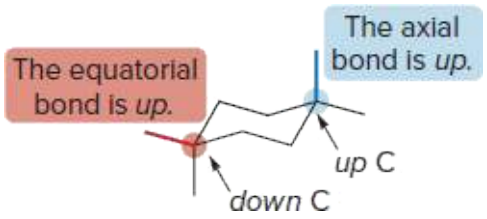
- **Draw axial and equatorial bonds. On a *down* C the axial bond is *down.***
- **Ring-flipping converts axial bonds to equatorial bonds, and vice versa. The equatorial methyl becomes axial.**
- **This forms the other possible chair conformation, labeled B.**



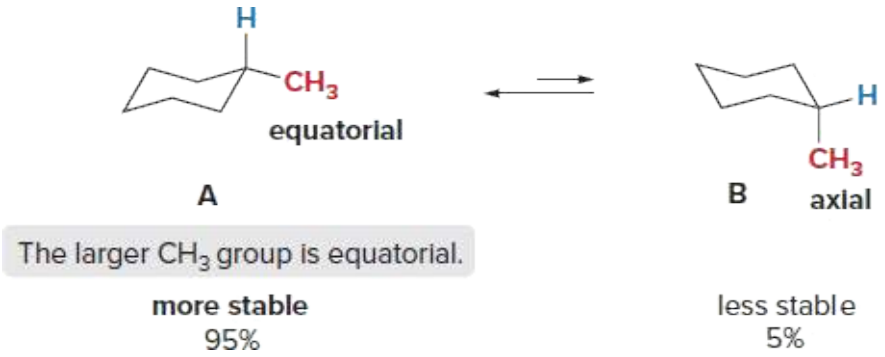
Although the CH_3 group flips from equatorial to axial, it starts on a down bond and stays on a down bond. It *never* flips from below the ring to above the ring.

- **A substituent always stays on the *same side* of the ring—either below or above—during the process of ring-flipping.**

Each carbon atom has one *up* and one *down* bond. An *up* bond can be either axial or equatorial, depending on the carbon to which it is attached. On an *up* C, the axial bond is *up*, but on a *down* C, the equatorial bond is *up*.

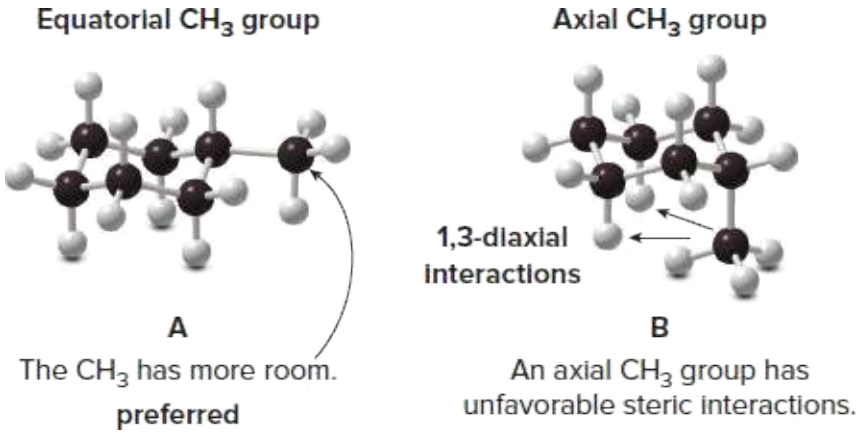


The two conformations of methylcyclohexane are different, so they are not equally stable. In fact, A, which places the larger methyl group in the roomier equatorial position, is considerably more stable than B, which places it axial.



Why is a substituted cyclohexane ring more stable with a larger group in the equatorial position? Figure 4.15 shows that with an equatorial CH_3 group, steric interactions with nearby groups are minimized. An axial CH_3 group, however, is close to two other axial H atoms, creating two destabilizing steric interactions called 1,3-diaxial interactions. Each unfavorable H,CH_3 interaction destabilizes the conformation by 3.8 kJ/mol, so B is 7.6 kJ/mol less stable than A.

Figure 4.15 **Three-dimensional representations for the two conformations of methylcyclohexane**



- **Larger axial substituents create unfavorable 1,3-diaxial interactions, destabilizing a cyclohexane conformation.**

The *larger* the substituent on the six-membered ring, the *higher* the percentage of the conformation containing the equatorial substituent at equilibrium. With a very large substituent like *tert*-butyl [$(CH_3)_3C$–], essentially none of the conformation containing an axial *tert*-butyl group is present at room temperature, so the ring is essentially anchored in a single conformation having an equatorial *tert*-butyl group. This is illustrated in Figure 4.16.

Figure 4.16 **The two conformations of *tert*-butylcyclohexane**

C
highly destabilized

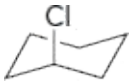
D
100%

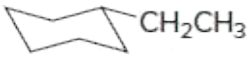
- The large *tert*-butyl group anchors the cyclohexane ring in conformation **D**.

Problem 4.23

Draw a second chair conformation for each cyclohexane. Then decide which conformation is present in higher concentration at equilibrium.

a.

b. 

c. 

Problem 4.24

Draw both conformations for 1-ethyl-1-methylcyclohexane and decide which conformation (if any) is more stable.

4.13B A Disubstituted Cycloalkane

Rotation around the C—C bonds in the ring of a cycloalkane is restricted, so a group on one side of the ring can *never* rotate to the other side of the ring. As a result, there are two different 1,2-dimethylcyclopentanes—one having two CH_3 groups on the same side of the ring and one having them on opposite sides of the ring.

2 CH_3's above the ring

A

cis isomer

1 CH_3 above and 1 CH_3 below

B

trans isomer

Wedges indicate bonds in front of the plane of the ring, and dashed wedges indicate bonds behind. For a review of this convention, see Section 1.7B. If a ring carbon is bonded to a CH_3 group in front of the ring (on a wedge), it is *assumed* that the other atom bonded to this carbon is hydrogen, located behind the ring (on a dashed wedge).

Cis and trans isomers are named by adding the prefixes *cis* and *trans* to the name of the cycloalkane. Thus, A is *cis*-1,2-dimethylcyclopentane, and B is *trans*-1,2-dimethylcyclopentane.

A and B are isomers, because they are different compounds with the same molecular formula, but they represent the second major class of isomers called stereoisomers.

- ***Stereoisomers* are isomers that differ *only* in the way the atoms are oriented in space.**

The prefixes cis and trans are used to distinguish these stereoisomers.

- **The cis isomer has two groups on the *same side* of the ring.**
- **The trans isomer has two groups on *opposite sides* of the ring.**

Problem 4.25

Draw the structure for each compound using wedges and dashed wedges.

a. *cis*-1,2-dimethylcyclopropane

b. *trans*-1-ethyl-2-methylcyclopentane

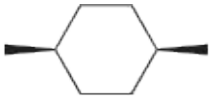
Problem 4.26

For *cis*-1,3-diethylcyclobutane, draw (a) a stereoisomer; (b) a constitutional isomer.

4.13C A Disubstituted Cyclohexane

A disubstituted cyclohexane like 1,4-dimethylcyclohexane also has cis and trans stereoisomers. In addition, each of these stereoisomers has two possible chair conformations.

trans-1,4-dimethylcyclohexane



cis-1,4-dimethylcyclohexane

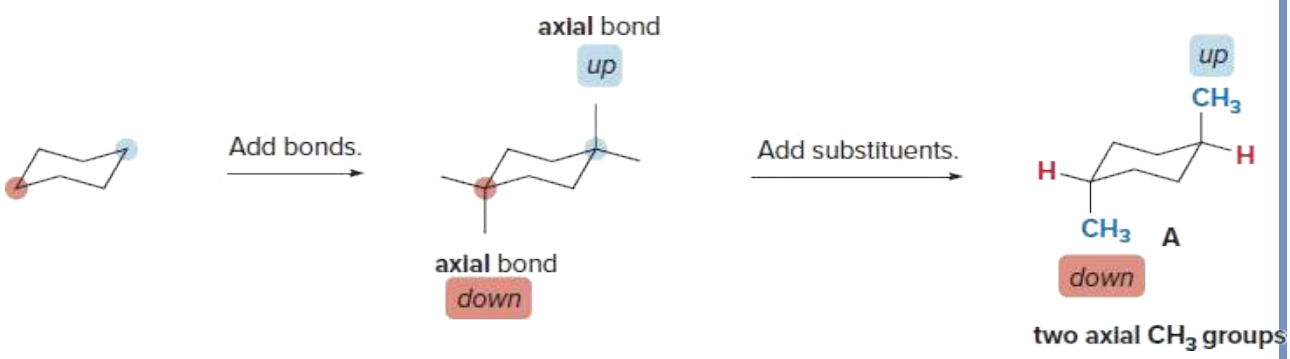
To draw both conformations for each stereoisomer, follow the procedure in Section 4.13A for a monosubstituted cyclohexane, keeping in mind that two substituents must now be added to the ring.

All disubstituted cycloalkanes with two groups bonded to *different* atoms have cis and trans isomers.

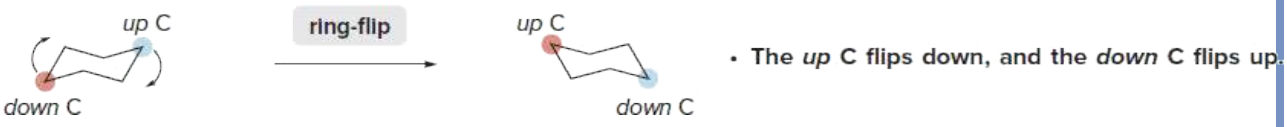
How To Draw Two Conformations for a Disubstituted Cyclohexane

Step [1] Draw one chair form and add the substituents.

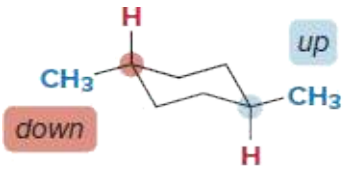
- **For *trans*-1,4-dimethylcyclohexane, arbitrarily pick two C's located 1,4- to each other, classify them as *up* or *down* C's, and draw in the substituents.**
- **The trans isomer must have one group *above* the ring (on an *up* bond) and one group *below* the ring (on a *down* bond). The substituents can be either axial or equatorial, as long as one is up and one is down. The easiest trans isomer to visualize has two axial CH_3 groups. This arrangement is said to be diaxial.**
- **This forms one of the two possible chair conformations, labeled A.**



Step [2] Ring-flip the cyclohexane ring.



Step [3] Add the substituents to the second conformation.

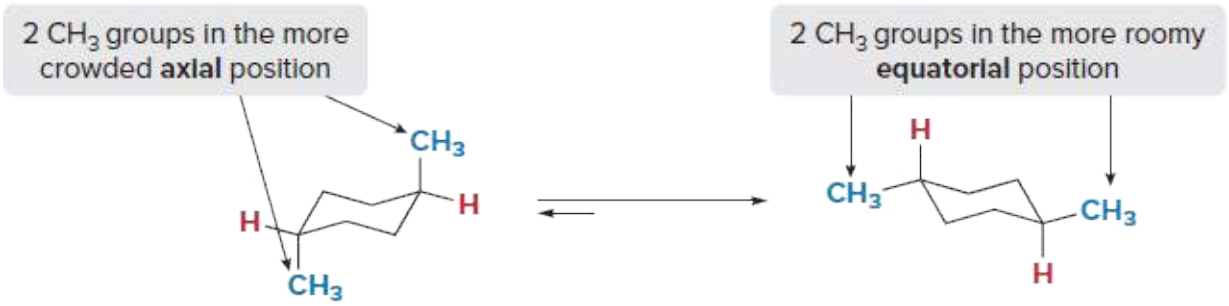


two equatorial CH_3 groups

B

- **Ring-flipping converts axial bonds to equatorial bonds, and vice versa. The diaxial CH_3 groups become diequatorial. This trans conformation is less obvious to visualize. It is still trans, because one CH_3 group is above the ring (on an *up* bond), and one is below (on a *down* bond).**

Conformations A and B are not equally stable. Because B has both larger CH_3 groups in the roomier equatorial position, B is *lower* in energy. Page 161

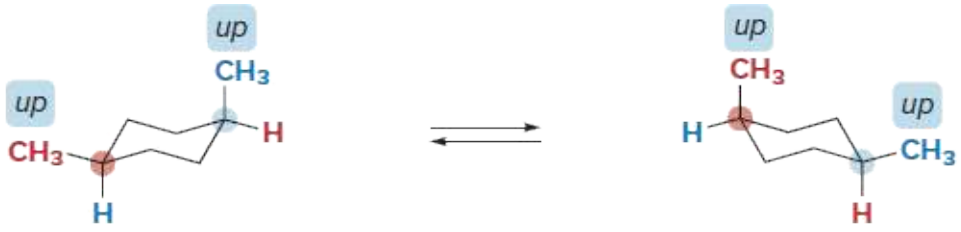


A
diaxial conformation

B
diequatorial conformation
more stable

The cis isomer of 1,4-dimethylcyclohexane also has two conformations, as shown in Figure 4.17. Because each conformation has one CH_3 group axial and one equatorial, they are identical in energy. At room temperature, therefore, the two conformations exist in a 50:50 mixture at equilibrium.

Figure 4.17 **The two conformations of *cis*-1,4-dimethylcyclohexane**



- **A cis isomer has two groups on the same side of the ring,** either both *up* or both *down*. In this example, Conformations **C** and **D** have two CH_3 groups drawn *up*.
- Both conformations have one CH_3 group axial and one equatorial, making them equally stable.

The relative stability of the two conformations of any disubstituted cyclohexane can be analyzed using this procedure.

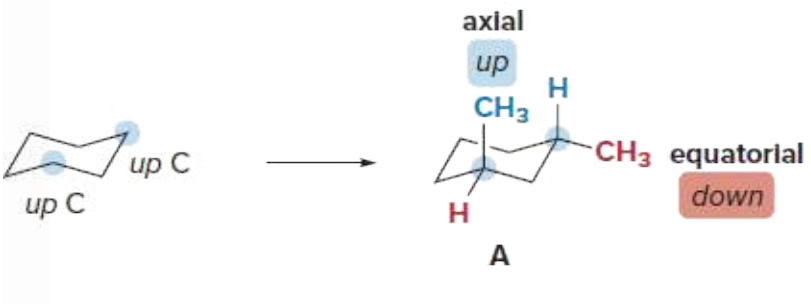
- **A *cis* isomer has two substituents on the *same side*, either both on *up* bonds or both on *down* bonds.**
- **A *trans* isomer has two substituents on *opposite sides*, one *up* and one *down.***
- **Whether substituents are axial or equatorial depends on the relative location of the two substituents (on carbons 1,2-, 1,3-, or 1,4-).**

Sample Problem 4.3 Drawing Two Conformations for a Disubstituted Cycloalkane

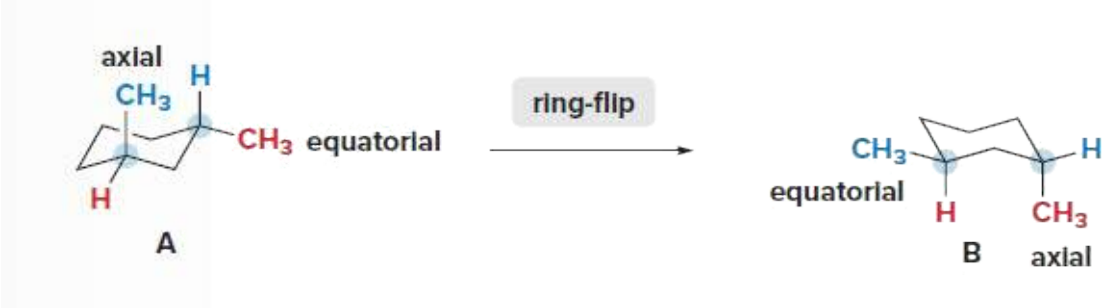
Draw both chair conformations for *trans*-1,3-dimethylcyclohexane.

Solution

Step [1] **Draw one chair form and add substituents.**



- **Pick two C's 1,3- to each other.**
- **The trans isomer has two groups on opposite sides. In Conformation A, one CH_3 is axial (on an *up* bond), and one group is equatorial (on a *down* bond).**



- The two *up* C's flip down.
- The axial CH_3 flips equatorial (still an *up* bond) and the equatorial CH_3 flips axial (still a *down* bond). Conformation B is *trans* because the two CH_3's are still on *opposite* sides.
- Conformations A and B are equally stable because each has one CH_3 equatorial and one axial.

Problem 4.27

Consider 1,2-dimethylcyclohexane.

a. Draw structures for the cis and trans isomers using a hexagon for the six-membered ring.

b. Draw the two possible chair conformations for the cis isomer. Which conformation, if either, is more stable?

c. Draw the two possible chair conformations for the trans isomer. Which conformation, if either, is more stable?

d. Which isomer, cis or trans, is more stable and why?

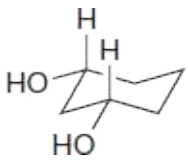
More Practice:

Try Problems 4.53a, b, d; 4.54–4.57; 4.59a.

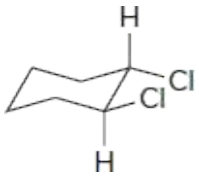
Problem 4.28

Label each compound as cis or trans. Then draw the second chair conformation.

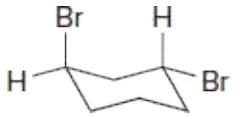
a.



b.



c.



Problem 4.29

Draw a chair conformation of cyclohexane with one CH_3CH_2 group and one CH_3 group that fits each description.

a. a 1,1-disubstituted cyclohexane with an axial CH_3CH_2 group

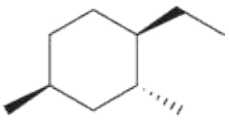
b. a cis-1,2-disubstituted cyclohexane with an axial CH_3 group

c. a trans-1,3-disubstituted cyclohexane with an equatorial CH_3 group

d. a trans-1,4-disubstituted cyclohexane with an equatorial CH_3CH_2 group

Sample Problem 4.4 Converting a Hexagon with Substituents to a Chair Form

Draw the two chair forms for the following trisubstituted cyclohexane, and label the more stable conformation.



Solution

Use the wedges and dashed wedges to determine what groups are above and below the ring, respectively. Start at a substituent and proceed in the *same* direction around the ring—clockwise or counterclockwise—to convert the hexagon to both chair forms.

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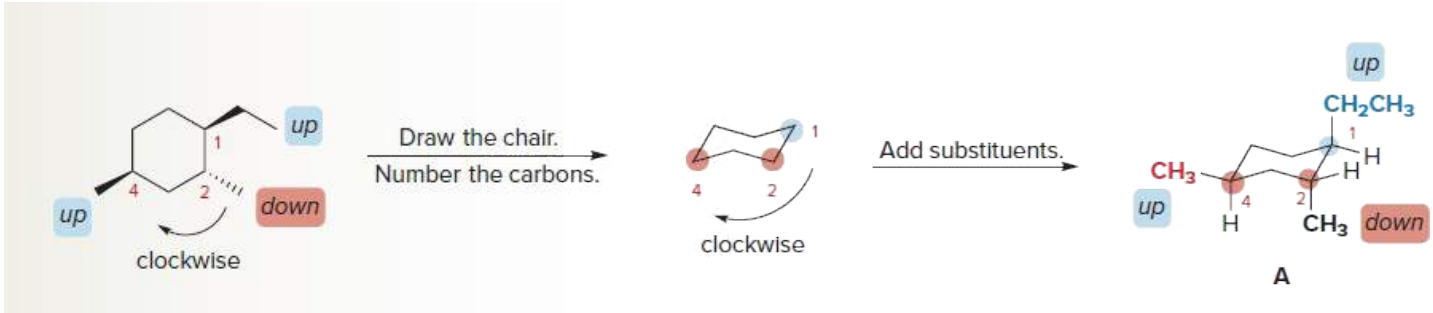
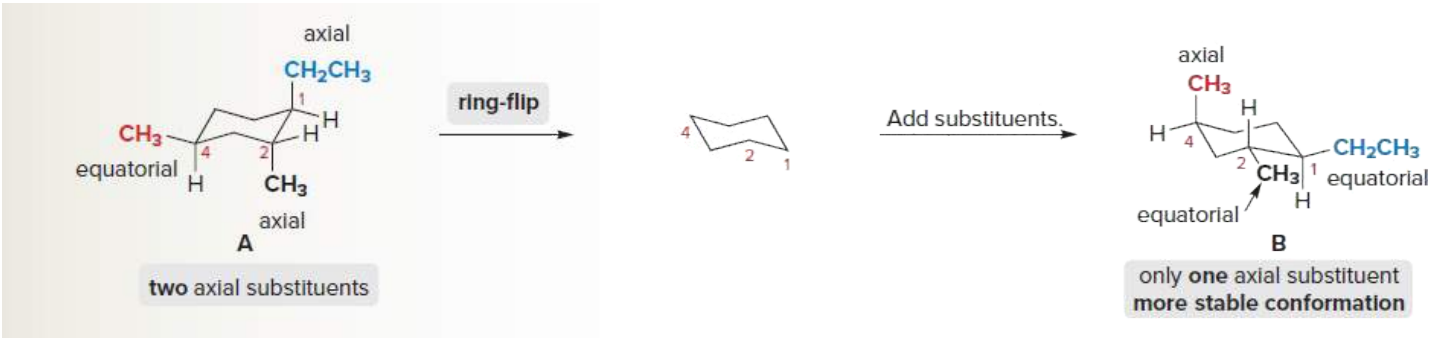
Step [1] Draw one chair form and add substituents.



- **If the ring C's are numbered 1 → 2 → 4 in the *clockwise* direction in the flat hexagon, number the C's in the chair in the *clockwise* direction. Any C in the chair can be assigned C1.**
- **The ethyl group on an *up* bond at C1 is axial, the methyl group on a *down* bond at C2 is axial, and the methyl on an *up* bond at C4 is equatorial.**
- **Conformation A has two axial and one equatorial substituents.**

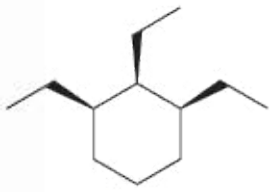
Step [2] Ring-flip and add substituents.



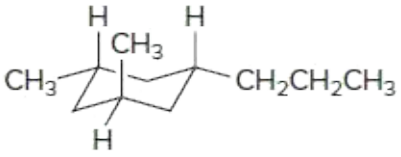
- **Ring-flipping the cyclohexane generates the second chair form B, which now has one axial and two equatorial substituents, making it the more stable conformation.**

Problem 4.30

(a) Draw C in its more stable chair conformation. (b) Convert D to a hexagon with substituents on wedges and dashed wedges.



C



D

More Practice:

Try Problems 4.53c, 4.55a, 4.59b, 4.63c, 4.64.

4.14 Oxidation of Alkanes

In Chapter 3, we learned that a functional group contains a heteroatom or π bond and constitutes the reactive part of a molecule. Alkanes are the only family of organic

molecules that has no functional group, and therefore, alkanes undergo few reactions. In fact, alkanes are inert to reaction unless forcing conditions are used.

In Chapter 4, we consider only one reaction of alkanes—combustion. Combustion is an oxidation–reduction reaction.

4.14A Oxidation and Reduction Reactions

- ***Oxidation*** **is the *loss* of electrons.**
- ***Reduction*** **is the *gain* of electrons.**

Compounds that contain many C—H bonds and few C—Z bonds are said to be in a *reduced state*, whereas those that contain few C—H bonds and more C—Z bonds are in a *more oxidized state.* CH_4 is highly reduced, whereas CO_2 is highly oxidized.

Oxidation and reduction are opposite processes. As in acid–base reactions, there are always two components in these reactions. One component is oxidized and one is reduced.

To determine if an organic compound undergoes oxidation or reduction, we concentrate on the carbon atoms of the starting material and product, and compare the relative number of C—H and C—Z bonds, where Z = an element *more electronegative* than carbon (usually O, N, or X). Oxidation and reduction are then defined in two complementary ways.

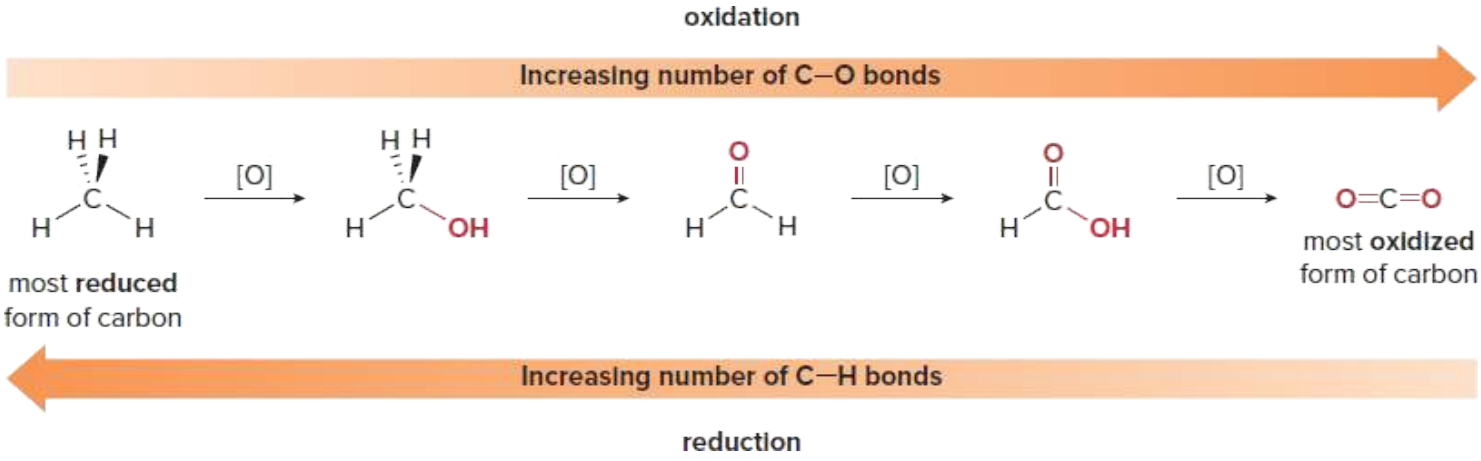
- ***Oxidation*** **results in an *increase* in the number of C—Z bonds; *or***
- ***Oxidation*** **results in a *decrease* in the number of C—H bonds.**

- ***Reduction*** **results in a *decrease* in the number of C—Z bonds; *or***
- ***Reduction*** **results in an *increase* in the number of C—H bonds.**

Because Z is more electronegative than C, replacing C—H bonds with C—Z bonds decreases the electron density around C. Loss of electron density = oxidation.

Figure 4.18 illustrates the oxidation of CH_4 by replacing C—H bonds with C—O bonds (from left to right). The symbol [O] indicates oxidation. Because reduction is the reverse of oxidation, the molecules in Figure 4.18 are progressively reduced moving from right to left, from CO2 to CH4. The symbol [H] indicates reduction.

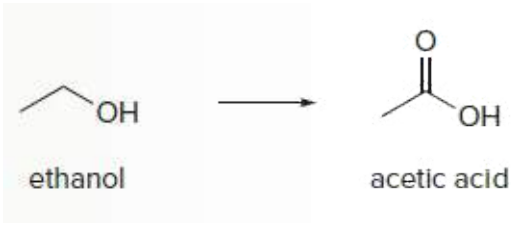
Figure 4.18 The oxidation and reduction of a carbon compound



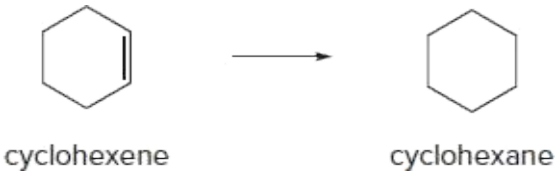
Sample Problem 4.5 Determining Whether a Compound Is Oxidized or Reduced

Determine whether the organic compound is oxidized or reduced in each transformation.

a.



b.



Solution

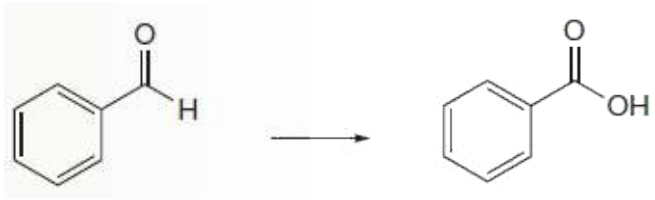
a. The conversion of ethanol to acetic acid is an oxidation because the number of C—O bonds increases: CH_3CH_2OH has one C—O bond and CH_3COOH has three C—O bonds.

b. The conversion of cyclohexene (C_6H_{10}) to cyclohexane (C_6H_{12}) is a reduction because the number of C—H bonds increases: cyclohexane has two more C—H bonds than cyclohexene.

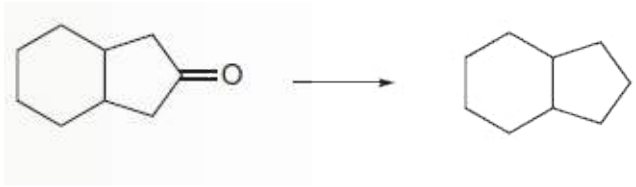
Problem 4.31

Classify each transformation as an oxidation, reduction, or neither.

a.

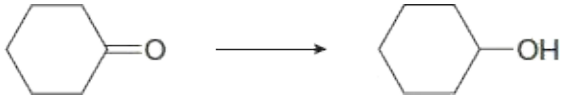


b.



c.

d.



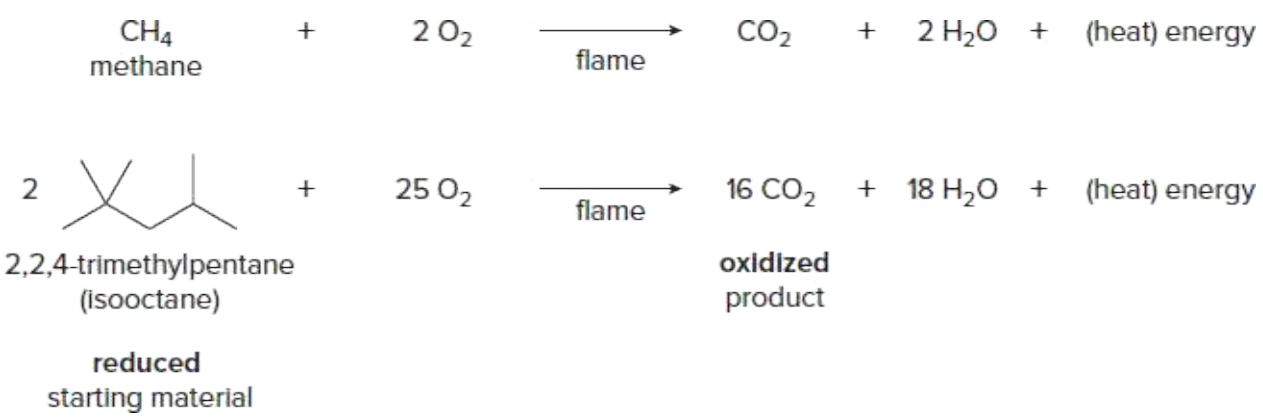
More Practice:

Try Problems 4.66, 4.68a.

4.14B Combustion of Alkanes

When an organic compound is *oxidized* by a reagent, the reagent itself is *reduced.* Similarly, when an organic compound is *reduced* by a reagent, the reagent is *oxidized.* Organic chemists identify a reaction as an oxidation or reduction by what happens to the *organic* component of the reaction.

Alkanes undergo combustion—that is, they burn in the presence of oxygen to form carbon dioxide and water. This is a practical example of oxidation. Every C—H and C—C bond in the starting material is converted to a C—O bond in the product. The products, CO_2 + H_2O, are the same, regardless of the identity of the starting material. Combustion of alkanes in the form of natural gas, gasoline, or heating oil releases energy for heating homes, powering vehicles, and cooking food.



Combustion requires a spark or a flame to initiate the reaction. Gasoline, therefore, which is composed largely of alkanes, can be safely handled and stored in the air, but the presence of a spark or match causes immediate and violent combustion.

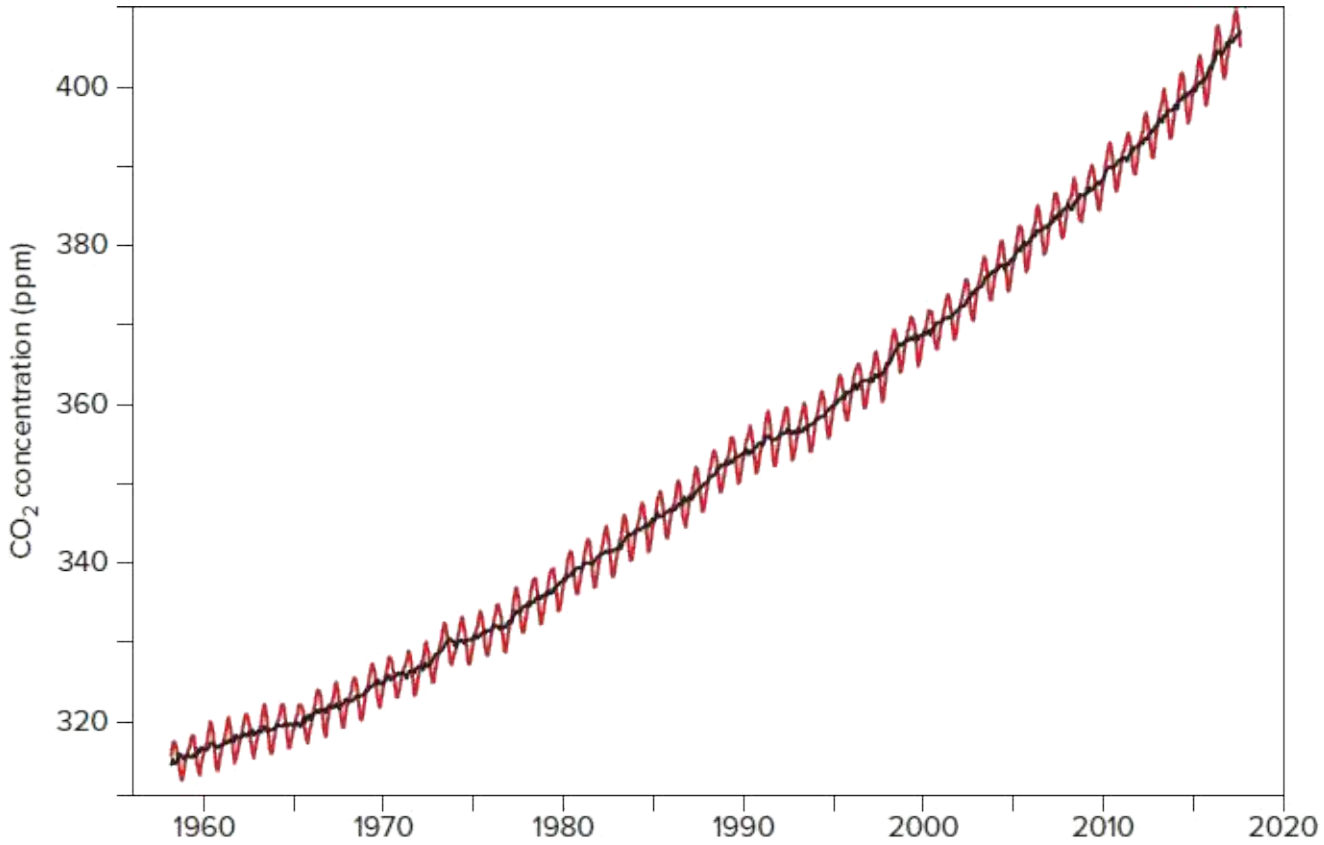
Driving an automobile 10,000 miles at 25 miles per gallon releases ~10,000 lb of CO_2 into the atmosphere.

The combustion of alkanes and other hydrocarbons obtained from fossil fuels adds a tremendous amount of CO_2 to the atmosphere each year. Quantitatively, data show over a 25% increase in the atmospheric concentration of CO_2 in the last 59 years (from 315 parts per million in 1958 to 405 parts per million in 2017; Figure 4.19). Although the composition of the atmosphere has changed over the lifetime of the earth, this may be the first time that the actions of humankind have altered that composition significantly and so quickly.

An increased CO_2 concentration in the atmosphere may have long-range and far-reaching effects. CO_2 absorbs thermal energy that normally radiates from the earth's surface, and redirects it back to the surface. Higher levels of CO_2 may therefore contribute to an increase in the average temperature of the earth's atmosphere. The global climate change resulting from these effects may lead to melting of the polar ice caps, a rise in sea level, and many more unforeseen consequences. How great a role CO_2 plays in this process is hotly debated.

Figure 4.19 **The changing concentration of CO_2 in the atmosphere since 1958**

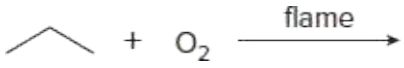
Source: US Department of Commerce, National Oceanic & Atmospheric Administration, "Welcome to Mauna Loa Observatory!" November 2017.

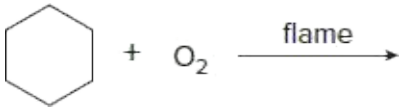


- The increasing level of atmospheric CO_2 is clearly evident on the graph. Two data points are recorded each year. The sawtooth nature of the graph is due to seasonal variation of CO_2 level with the seasonal variation in photosynthesis. (Data recorded at Mauna Loa, Hawai'i)

Problem 4.32

Draw the products of each combustion reaction.

a. 

b. 

4.15 Lipids—Part 1

Lipids that contain carbon–carbon double bonds are discussed in Section 10.6.

Lipids are biomolecules whose properties resemble those of alkanes and other hydrocarbons. They are unlike any other class of biomolecules, because they are defined by a physical property, not by the presence of a particular functional group.

- **Lipids are biomolecules that are soluble in organic solvents and insoluble in water.**

Lipids have varied sizes and shapes, and a diverse number of functional groups. Fat-soluble vitamins like vitamin A and the phospholipids that comprise cell membranes are two examples of lipids that were presented in Sections 3.5A and 3.7A. Other examples are shown in Figure 4.20. One unifying feature accounts for their solubility.

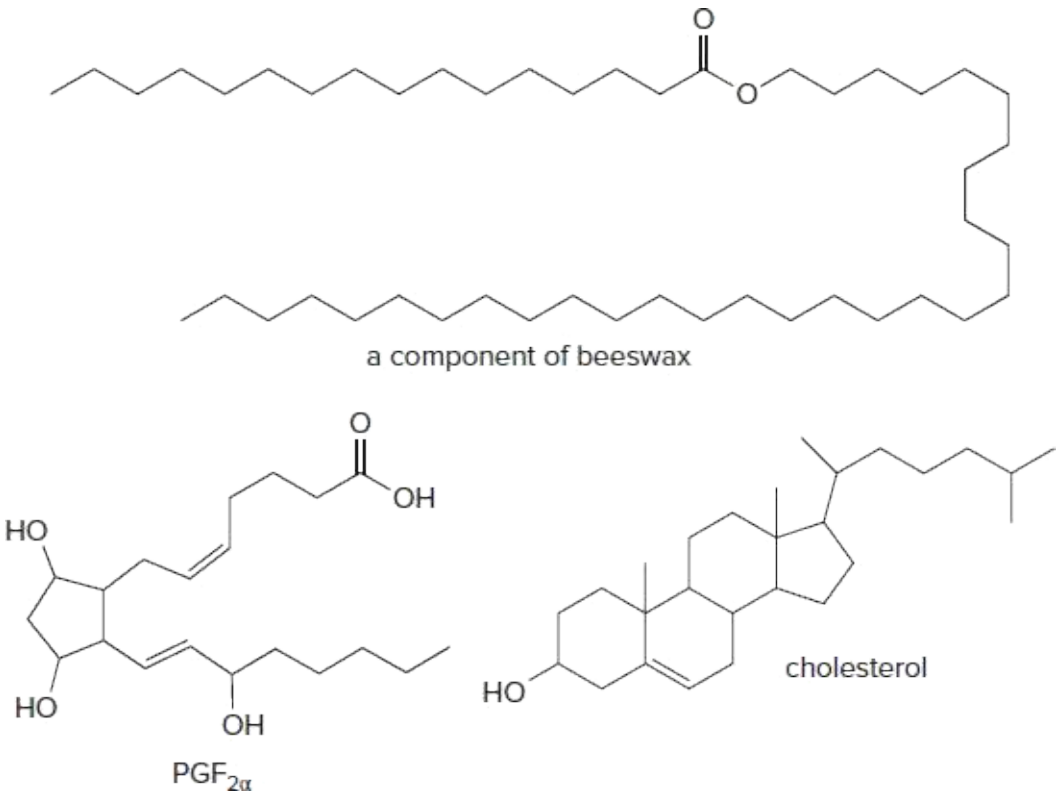
- **Lipids are composed of many nonpolar C—H and C—C bonds, and have few polar functional groups.**

©*Riorita/Getty Images*

Waxes are lipids having two long alkyl chains joined by a single oxygen-containing functional group. Because of their many C—C and C—H bonds, waxes are hydrophobic. They form a protective coating on the feathers of birds to make them water repellent, and on leaves to prevent water evaporation. Bees secrete $CH_3(CH_2)_{14}COO(CH_2)_{29}CH_3$, a wax that forms the honeycomb in which they lay eggs.

$PGF_{2\alpha}$ belongs to a class of lipids called prostaglandins. Prostaglandins contain many C—C and C—H bonds and a single COOH group (a carboxy group). Prostaglandins possess a wide range of biological activities. They control inflammation, affect blood-platelet aggregation, and stimulate uterine contractions. Nonsteroidal anti-inflammatory drugs such as ibuprofen operate by blocking the synthesis of prostaglandins, as discussed in Section 19.5.

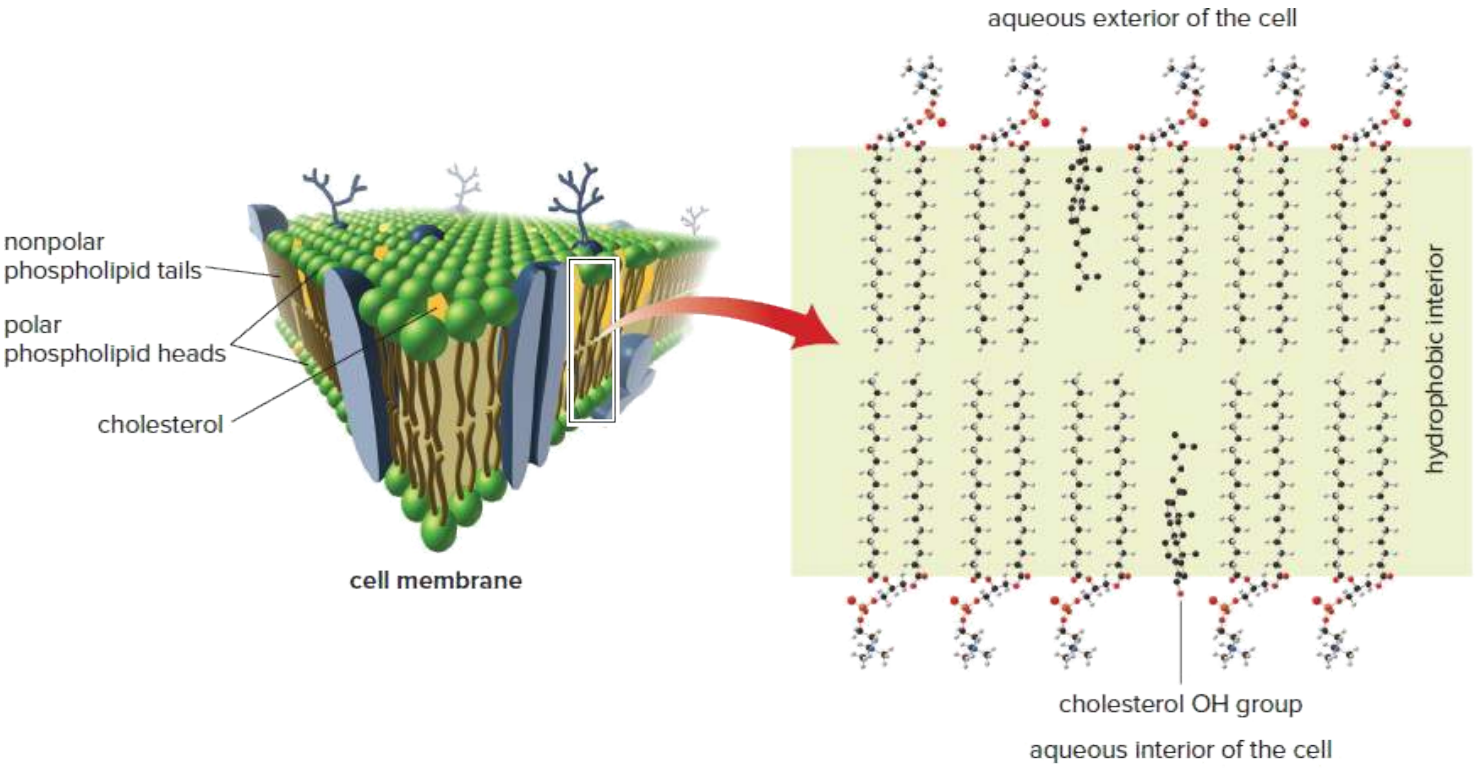
Figure 4.20 **Three representative lipid molecules**



Cholesterol is a member of the steroid family, a group of lipids having four rings joined together. Because it has just one polar OH group, cholesterol is insoluble in the aqueous medium of the blood. It is synthesized in the liver and transported to other cells bound to water-soluble organic molecules. Elevated cholesterol levels can lead to coronary artery disease.

Cholesterol is a vital component of the cell membrane. Its hydrophobic carbon chain is embedded in the interior of the lipid bilayer, and its hydrophilic hydroxy group is oriented toward the aqueous exterior (Figure 4.21). Because its tetracyclic carbon skeleton is quite rigid compared to the long floppy side chains of a phospholipid, cholesterol stiffens the cell membrane somewhat, giving it more strength.

Figure 4.21 **Cholesterol embedded in a lipid bilayer of a cell membrane**



- The nonpolar hydrocarbon skeleton of cholesterol is embedded in the nonpolar interior of the cell membrane. Its rigid carbon skeleton stiffens the fluid lipid bilayer, giving it strength.
- Cholesterol's polar OH group is oriented toward the aqueous media inside and outside the cell.

Lipids have a high energy content, meaning that much energy is released on their metabolism. Because lipids are composed mainly of C—C and C—H bonds, they are oxidized with the release of energy, just like alkanes are. In fact, lipids are the most efficient biomolecules for the storage of energy. The combustion of alkanes provides heat for our homes, and the metabolism of lipids provides energy for our bodies.

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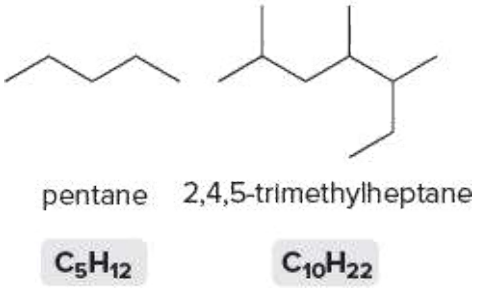
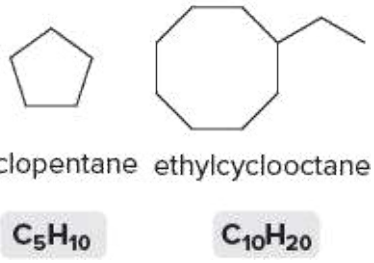
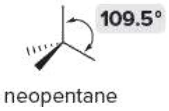
Problem 4.33

Explain why beeswax is insoluble in H_2O, slightly soluble in ethanol (CH_3CH_2OH), and soluble in chloroform ($CHCl_3$).

Chapter 4 REVIEW

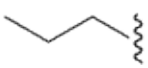
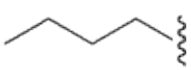
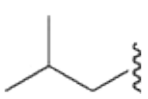
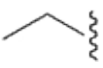
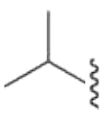
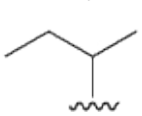
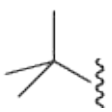
KEY CONCEPTS

[1] General facts about alkanes

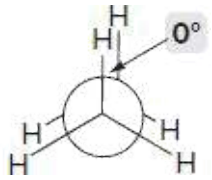
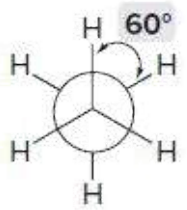
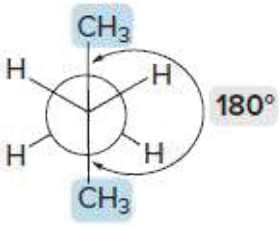
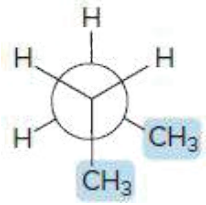
1 Molecular formula (4.1, 4.2)		2 Geometry and hybridizat (4.1)
Acyclic alkanes • C_nH_{2n+2} • saturated hydrocarbons  pentane C_5H_{12} 2,4,5-trimethylheptane $C_{10}H_{22}$	**Cyclic alkanes** • C_nH_{2n} • two fewer H atoms than acyclic alkanes  cyclopentane C_5H_{10} ethylcyclooctane $C_{10}H_{20}$	• tetrahedra • sp^3 hybridize • all 109.5° bond ang  neopentane

See Table 4.2. Try Problems 4.42, 4.43.

[2] Names of alkyl groups (4.4A)

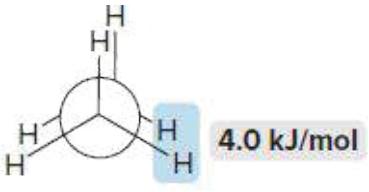
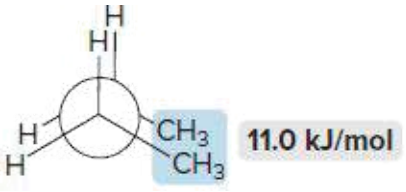
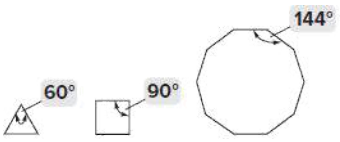
1 Methyl CH_3-	3 Propyl $CH_3CH_2CH_2-$ 	5 Butyl $CH_3CH_2CH_2CH_2-$ 	7 Isobutyl $(CH_3)_2CHCH_2-$ 
2 Ethyl CH_3CH_2- 	4 Isopropyl $(CH_3)_2CH-$ 	6 *sec*-Butyl $CH_3CH_2CHCH_3$ 	8 *tert*-Butyl $(CH_3)_3C-$ 

[3] Conformations of acyclic alkanes (4.9, 4.10)

1 Eclipsed	2 Staggered	3 Anti	4 Gauche
• dihedral angle = 0° 	• dihedral angle = 60°  • lower energy than the eclipsed conformation	• dihedral angle of two CH_3 groups = 180°  • lower energy than the gauche conformation	• dihedra angle o two CH groups 60° 

See Figure 4.9. Try Problems 4.36, 4.44, 4.45, 4.47.

[4] Types of strain

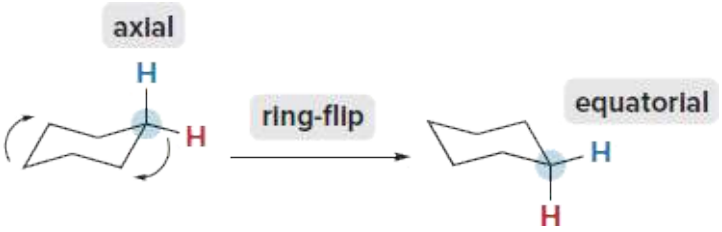
1 Torsional strain (4.9)	2 Steric stain (4.10)	3 Angle strain (4.11)
 • increase in energy caused by eclipsing interactions See Figure 4.8.	 • increase in energy when atoms are forced too close to one another See Figure 4.10.	 • increase in energy when tetrahedral bo angles deviate from the optim angle of 109.5°

Try Problem 4.49.

[5] Chair cyclohexane and monosubstituted cyclohexanes

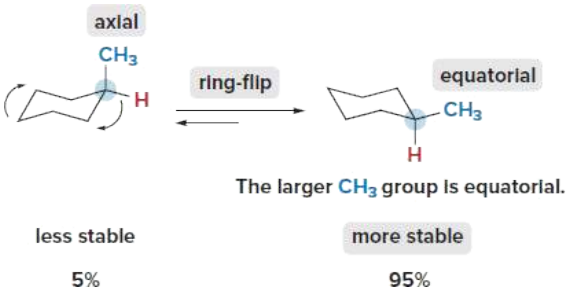
1 Conformations of cyclohexane (4.12)

- Cyclohexane exists as two chair conformations in rapid equilibrium at room temperature.
- Each carbon atom on a cyclohexane ring has one axial and one equatorial hydrogen.



2 Conformations of monosubstituted cyclohexanes (4.13A)

- In substituted cyclohexane groups larger than hydrog are more stable in the roon equatorial position.

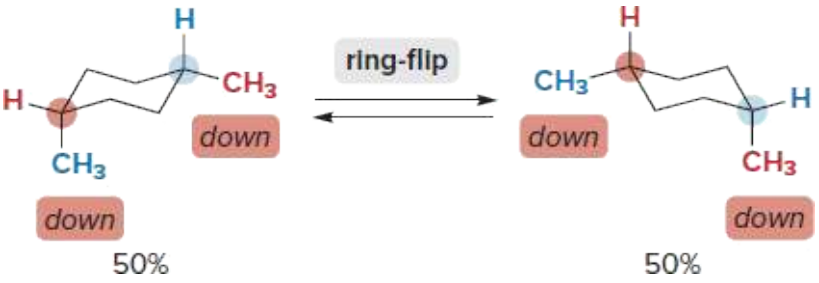


See *How To*'s p. 155, p. 157, Figures 4.13, 4.15, 4.16. Try Problem 4.53a.

[6] Disubstituted cyclohexanes (4.13C)

1 Cis isomers

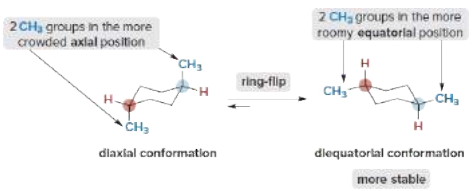
- two groups on the same side of the ring, either both *down* or both *up*



- In this example, both CH_3 groups are down.

2 Trans isomers

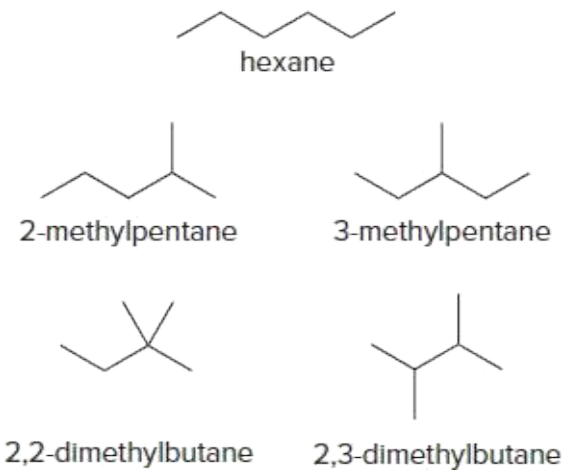
- two groups on the opposite side of the ring, one *up* and one *down*

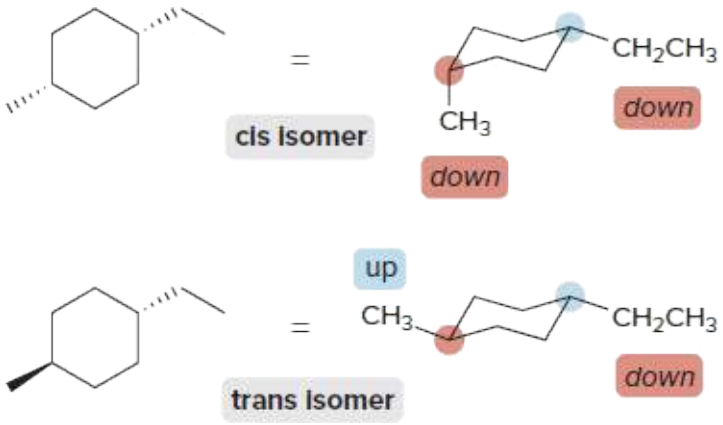


See *How To* p. 160, Figure 4.17, Sample Problem 4.3. Try Problems 4.53–4.55, 4.63b.

[7] Two types of isomers

1 Constitutional isomers (4.1A)	2 Stereoisomers (4.13B)
• compounds with the same molecular formula that differ in the way the atoms are connected to each other	• isomers that differ only in the way t atoms are oriented in space



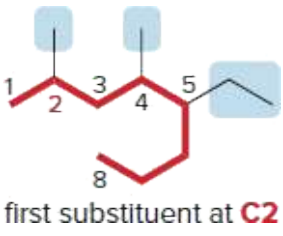


Try Problems 4.37, 4.55, 4.60, 4.62, 4.63, 4.65.

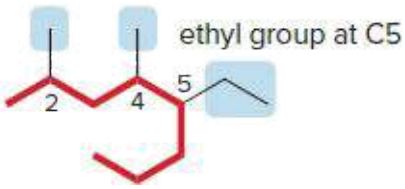
KEY SKILLS

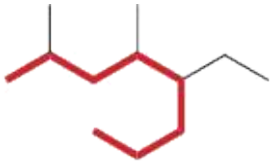
[1] Naming an alkane using the IUPAC system (4.4)

1 Name the parent.	2 Number the chain.	3 Name and number the substituents.
• Count the number of carbons in the longest chain to determine the parent name. • Use the suffix -*ane*.	• Number to give the 1st substituent the lower number.	methyl groups at C2 and C4 ethyl group at C5



first substituent at **C2**





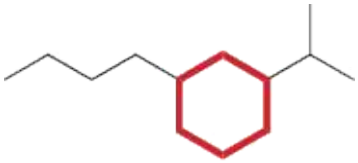
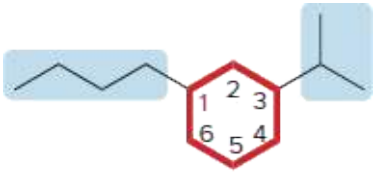
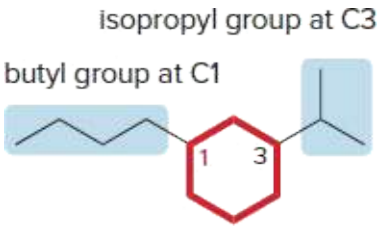
8 C's in the longest chain

octane

- **parent + suffix**

See Table 4.1, *How To* p. 137, Sample Problem 4.1, Figure 4.1. Try Problems 4.34a; 4.38a–d, h, j; 4.41.

[2] Naming a cycloalkane using the IUPAC system (4.5)

1 Name the parent.	2 Number the ring.	3 Name and numbe the substituents.
• Count the number of carbon atoms in the ring to determine the parent name. • Use the suffix - *cycloalkane.*  **6** C's in the ring cyclohexane	• Number to assign the lower number to the substituents alphabetically.  first substituent at C1	

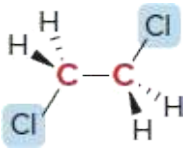
See *How To* p. 141, Figures 4.2, 4.3. Try Problems 4.34b; 4.38e–g, i.

[3] Determining the highest and lowest energy conformations using Newman projections (4.10); example: $ClCH_2CH_2Cl$

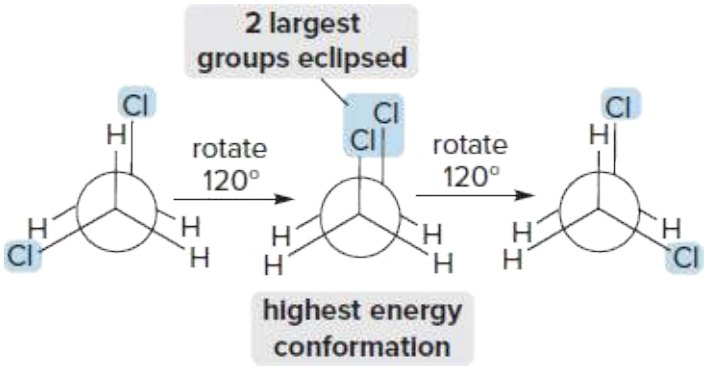
1 Identify the groups	2 Draw the three eclipsed conformations.	3 Draw the staggere conforma

around the C–C bond.

- Each C is bonded to one Cl atom and two H atoms.

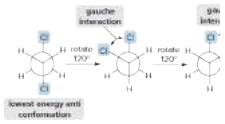


- Begin with an eclipsed conformation, and rotate the groups on the front C atom 120° in the clockwise direction.



- The conformation with the largest groups eclipsed has the highest energy.

- Begin wit staggere conforma and rotat groups o front C at 120° in th clockwis direction



- The conforma with the largest g anti and t fewest ga interactic has the l energy.

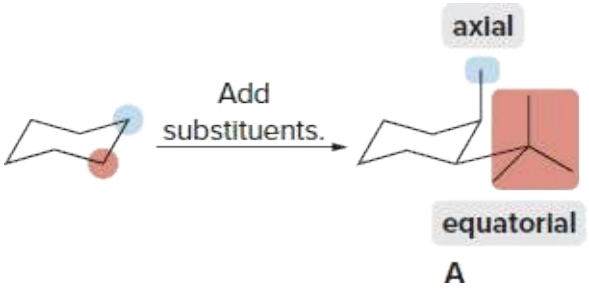
See *How To* p. 147, Figures 4.6, 4.7, 4.9, 4.10. Try Problems 4.44–4.47.

[4] Drawing two conformations for a disubstituted cyclohexane (4.13C); example: *cis*-1-(*tert*-butyl)-2-methylcyclohexane

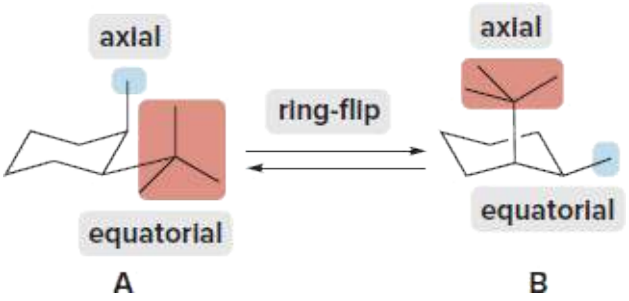
1 Draw one chair form and add the substituents.

1 Ring-flip the cyclohexane ring, and add the substituents.

- Pick two C's located 1,2- to each other, add the substituents, and classify them as axial or equatorial.



- Conformations A and B each have one axial and one equatorial substituent.

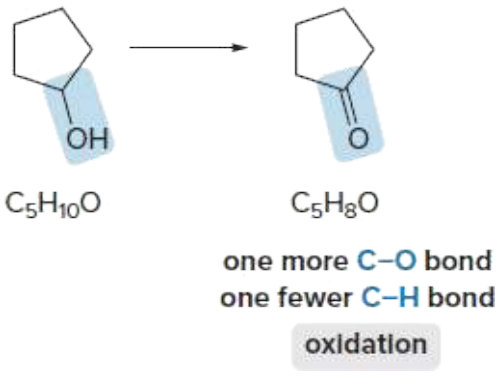


- The axial CH_3 flips equatorial (still an *up* bond) and the equatorial $C(CH_3)_3$ flips axial (still an *up* bond).

See *How To* p. 160, Figure 4.17, Sample Problem 4.3. Try Problems 4.53, 4.55, 4.63.

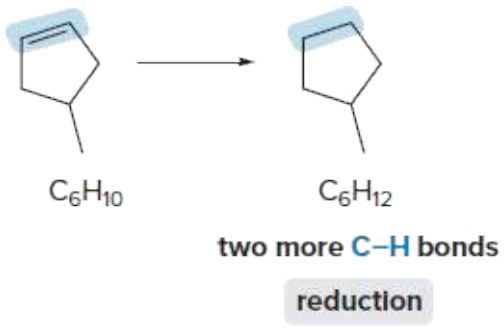
[5] Determining whether a compound is oxidized or reduced (4.14A)

1 Count the number of C—O bonds in the starting material and compare to the product.



- Oxidation results in an *increase* in the number of C—Z bonds or a *decrease* in the number of C—H bonds.

2 Count the number of C—H bonds in the starting material and compare to the product.



- Reduction results in a *decrease* in the number of C—Z bonds or an *increase* in the number of C—H bonds.

See Sample Problem 4.5. Try Problems 4.66, 4.68a.

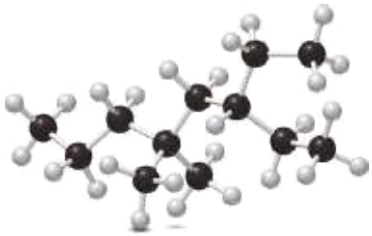
PROBLEMS

Problems Using Three-Dimensional Models

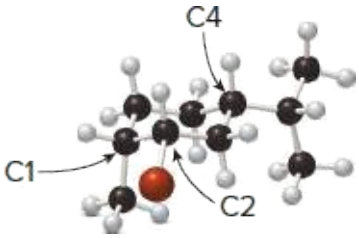
4.34 Name each alkane using the ball-and-stick model, and classify each carbon as 1°, 2°, 3°, or 4°.

a.

b.



4.35 Consider the substituted cyclohexane shown in the ball-and-stick model.



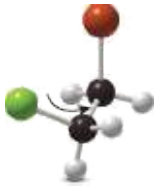
a. Label the substituents on C1, C2, and C4 as axial or equatorial.

b. Are the substituents on C1 and C2 cis or trans to each other?

c. Are the substituents on C2 and C4 cis or trans to each other?

d. Draw the second possible conformation in the chair form, and classify it as more stable or less stable than the conformation shown in the three-dimensional model.

4.36 Convert each three-dimensional model to a Newman projection around the indicated bond.

a. 

b.

c.

Constitutional Isomers

4.37 **Draw the structure of all compounds that fit the following descriptions.**

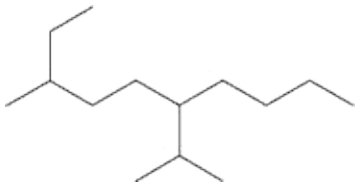
a. five constitutional isomers having the molecular formula C_4H_8

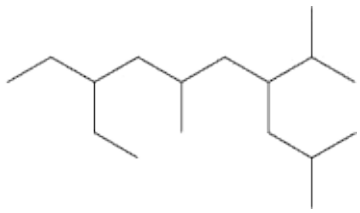
b. nine constitutional isomers having the molecular formula C_7H_{16}

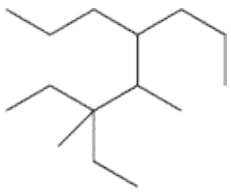
c. twelve constitutional isomers having the molecular formula C_6H_{12} and containing one ring

IUPAC Nomenclature

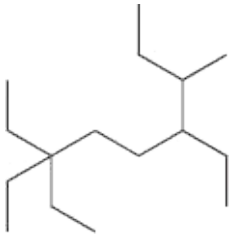
4.38 **Give the IUPAC name for each compound.**

a. 

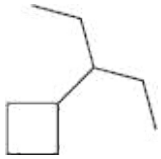
b. 

c. 

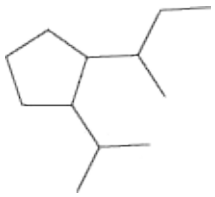
d.



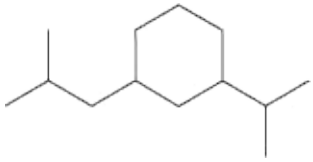
e.



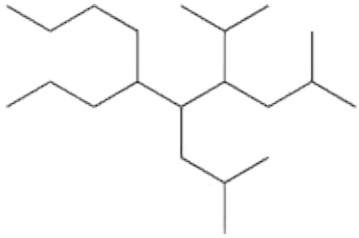
f.



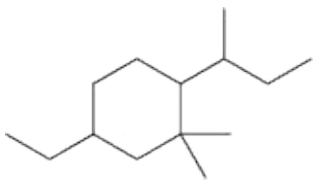
g.



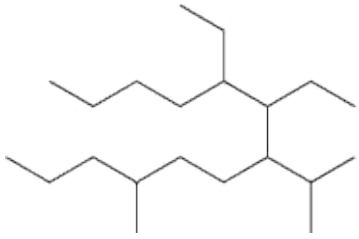
h.



i.



j.



4.39 Draw the structure corresponding to each IUPAC name.

a. 3-ethyl-2-methylhexane

b. *sec*-butylcyclopentane

c. 4-isopropyl-2,4,5-trimethylundecane

d. cyclobutylcycloheptane

e. 3-ethyl-1,1-dimethylcyclohexane

f. 4-butyl-1,1-diethylcyclooctane

g. 6-isopropyl-2,3-dimethyldodecane

h. 2,2,6,6,7-pentamethyloctane

i. *cis*-1-ethyl-3-methylcyclopentane

j. *trans*-1-*tert*-butyl-4-ethylcyclohexane

4.40 Draw the structure of each alkane and cycloalkane from the given incorrect name. Then, give the IUPAC name for each compound.

a. 7-ethyl-3,6-dimethylnonane

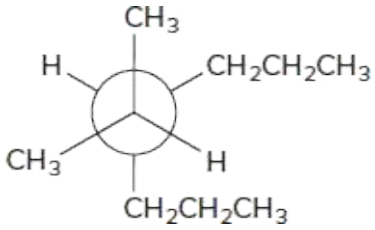
b. 4-ethyl-3-isopropylheptane

c. 3-ethyl-1,4-dimethylcycloheptane

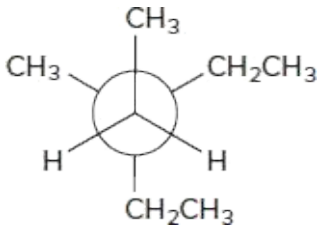
d. 1-ethyl-3-methyl-5-isopropylcyclohexane

4.41 Give the IUPAC name for each compound.

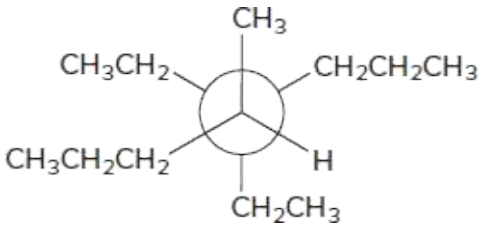
a.



b.



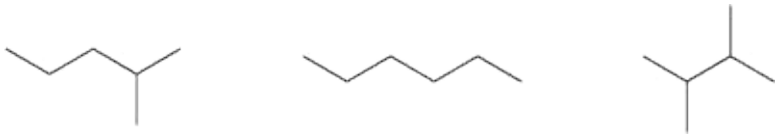
c.



Properties of Alkanes

Students who have already learned about mass spectrometry can try Problems A.1, A.8, A.9, and A.15. Students who have already learned about infrared spectroscopy can try Problem B.12a.

4.42 Rank the following alkanes in order of increasing boiling point.

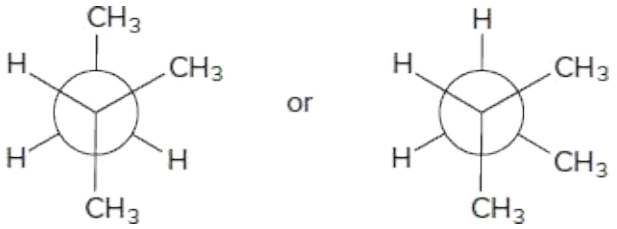


4.43 **The melting points and boiling points of two isomeric alkanes are as follows: $CH_3(CH_2)_6CH_3$, mp = −57 °C and bp = 126 °C; $(CH_3)_3CC(CH_3)_3$, mp = 102 °C and bp = 106 °C. (a) Explain why one isomer has a lower melting point but higher boiling point. (b) Explain why there is a small difference in the boiling points of the two compounds, but a huge difference in their melting points.**

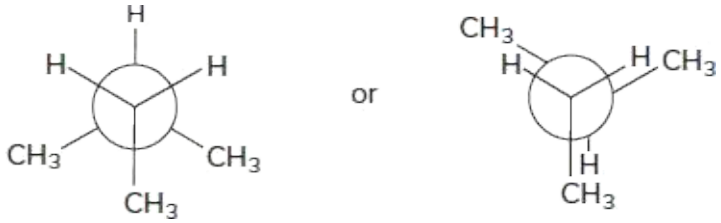
Conformation of Acyclic Alkanes

4.44 **Which conformation in each pair is *higher* in energy? Calculate the energy difference between the two conformations using the values given in Table 4.3.**

a.



b.

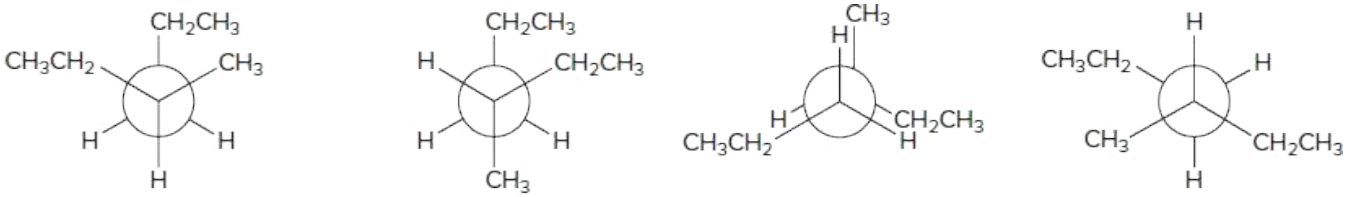


4.45 **Considering rotation around the bond highlighted in red in each compound, draw Newman projections for the most stable and least stable conformations.**

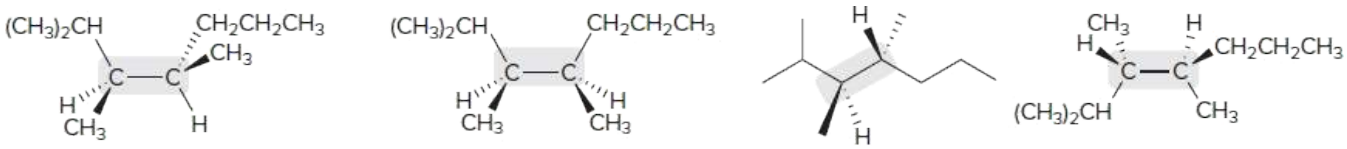
a.

b.

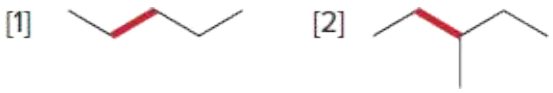
4.46 **Rank the following Newman projections in order of increasing energy.**



4.47 **Classify each conformation as staggered or eclipsed around the indicated bond, and rank the conformations in order of increasing stability.**

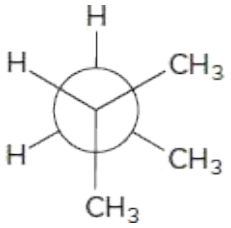


4.48 **(a) Using Newman projections, draw all staggered and eclipsed conformations that result from rotation around the bond highlighted in red in each molecule; (b) draw a graph of energy versus dihedral angle for rotation around this bond.**

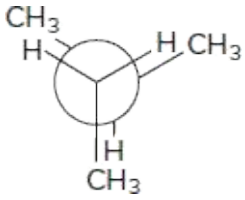


4.49 **Label the sites of torsional and steric strain in each conformation.**

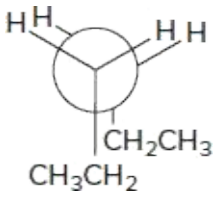
a.



b.

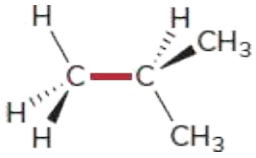


c.

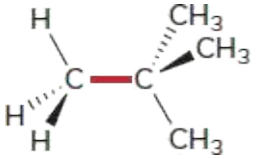


4.50 **Calculate the barrier to rotation for each bond highlighted in red.**

a.



b.



4.51 **The eclipsed conformation of CH_3CH_2Cl is 15 kJ/mol less stable than the staggered conformation. How much is the H,Cl eclipsing interaction worth in destabilization?**

4.52 **(a) Draw the anti and gauche conformations for ethylene glycol ($HOCH_2CH_2OH$). (b) Ethylene glycol is unusual in that the gauche conformation is more stable than the anti conformation. Offer an**

explanation.

Conformations and Stereoisomers in Cycloalkanes

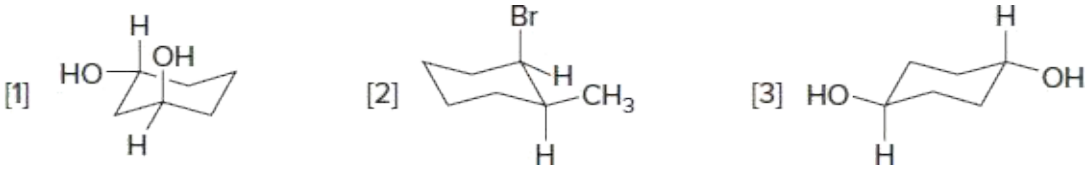
4.53 For each compound drawn below:

a. Label each OH, Br, and CH_3 group as axial or equatorial.

b. Classify each conformation as cis or trans.

c. Translate each structure into a representation with a hexagon for the six-membered ring, and wedges and dashed wedges for groups above and below the ring.

d. Draw the second possible chair conformation for each compound.



4.54 Draw the more stable chair conformation for each compound.

a. *trans*-1-isopropyl-3-methylcyclohexane

b. *cis*-1-*sec*-butyl-4-ethylcyclohexane

c. *cis*-1-ethyl-2-isobutylcyclohexane

d. *trans*-1,2-dibutylcyclohexane

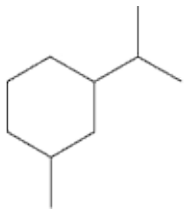
4.55 For each compound drawn below:

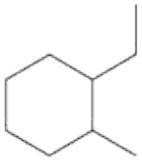
a. Draw representations for the cis and trans isomers using a hexagon for the six-membered ring, and wedges and dashed wedges for substituents.

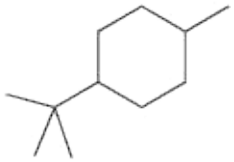
b. Draw the two possible chair conformations for the cis isomer. Which conformation, if either, is more stable?

c. Draw the two possible chair conformations for the trans isomer. Which conformation, if either, is more stable?

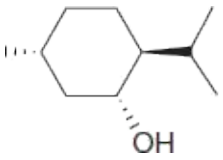
d. Which isomer, cis or trans, is more stable and why?

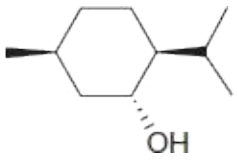
[1] 

[2] 

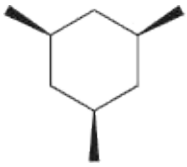
[3] 

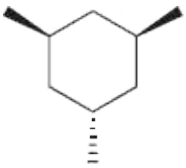
4.56 Convert each of the following structures to its more stable chair form. One structure represents menthol and one represents isomenthol. Menthol, the more stable isomer, is used in lip balms and mouthwash. Which structure corresponds to menthol?

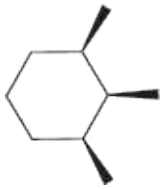


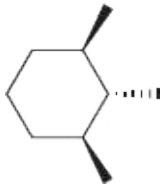


4.57 Draw the more stable chair conformation for each trisubstituted cyclohexane.

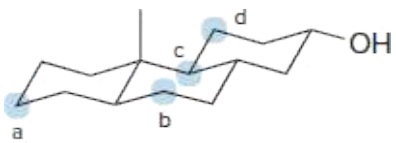
a. 

b. 

c. 

d. 

4.58 Answer the following questions about compound A, which contains a CH_3 group and OH group bonded to the carbon skeleton that consists of three six-membered rings in the conformation shown.



A

a. Are the CH_3 and OH groups oriented cis or trans to each other?

b. Is a substituent on C_a that is cis to the CH_3 group located in the axial

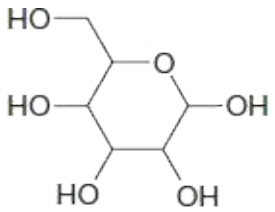
or equatorial position?

c. Is an equatorial Br at C_b oriented cis or trans to the OH group?

d. Is the H atom on C_c located cis or trans to the OH group?

e. Is a substituent on C_d that is trans to the OH group located in the axial or equatorial position?

4.59 Glucose is a simple sugar with five substituents bonded to a six-membered ring.



glucose

a. Using a chair representation, draw the most stable arrangement of these substituents on the six-membered ring.

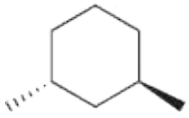
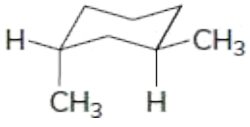
b. Convert this representation to one that uses a hexagon with wedges and dashed wedges.

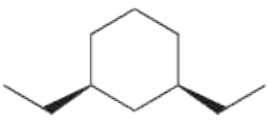
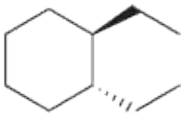
c. Draw a constitutional isomer of glucose.

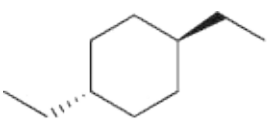
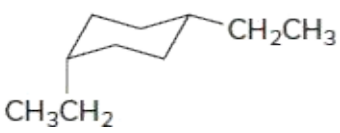
d. Draw a stereoisomer that has an axial OH group on one carbon.

Constitutional Isomers and Stereoisomers

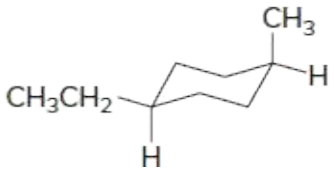
4.60 Classify each pair of compounds as constitutional isomers, stereoisomers, identical molecules, or not isomers of each other.

a.  and 

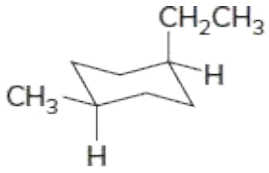
b.  and 

c.  and 

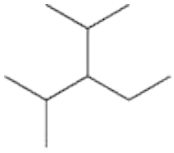
d.



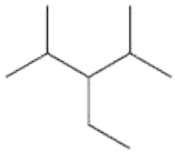
and



4.61 (a) Are compounds B–D identical to or an isomer of A? (b) Give the IUPAC name for A.



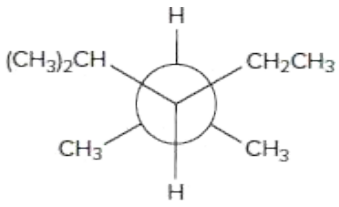
A



B

$(CH_3)_2CHC(CH_3)_2CH(CH_3)_2$

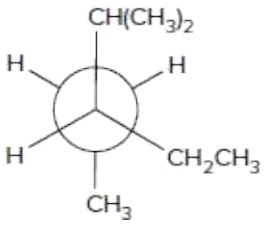
C



D

4.62 Classify each pair of compounds as constitutional isomers or identical molecules.

a.



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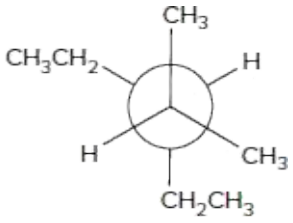
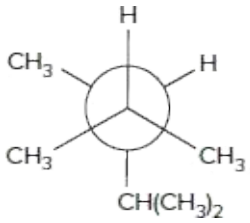
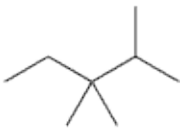


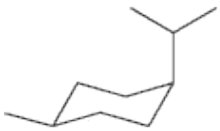
b.



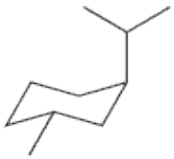
and



4.63 Answer the following questions about compounds A–D.

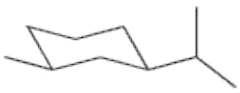


A



B

C



D

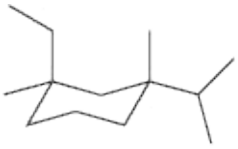
a. How are the compounds in each pair related? Choose from constitutional isomers, stereoisomers, or identical molecules: A and B; A and C; B and D.

b. Label each compound as a cis or trans isomer.

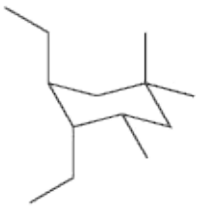
c. Draw B as a hexagon with wedges and dashed wedges to show the stereochemistry of substituents.

d. Draw a stereoisomer of A as a hexagon using wedges and dashed wedges to show the orientation of substituents.

4.64 **(a) Convert each chair cyclohexane to a hexagon with wedges and dashed wedges. (b) Draw a stereoisomer of each compound in its more stable chair conformation.**



A



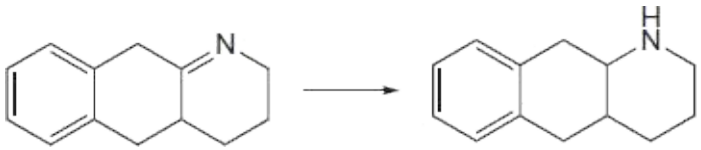
B

4.65 **Draw the three constitutional isomers having molecular formula C_7H_{14} that contain a five-membered ring and two methyl groups as substituents. For each constitutional isomer that can have cis and trans isomers, draw the two stereoisomers.**

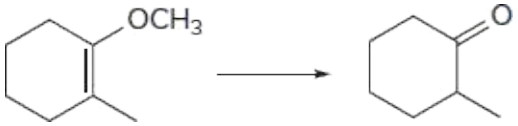
Oxidation and Reduction

4.66 **Classify each reaction as oxidation, reduction, or neither.**

a.

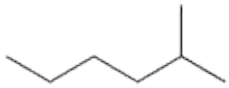


b.

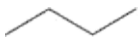


4.67 **Draw the products of combustion of each alkane.**

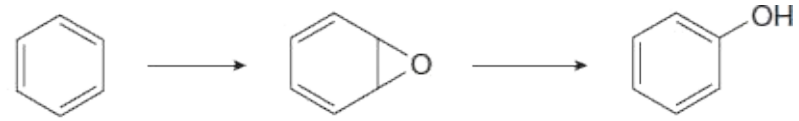
a.



b.



4.68 **Hydrocarbons like benzene are metabolized in the body to arene oxides, which rearrange to form phenols. This is an example of a general process in the body, in which an unwanted compound (benzene) is converted to a more water-soluble derivative called a *metabolite*, so that it can be excreted more readily from the body.**



benzene arene oxide phenol

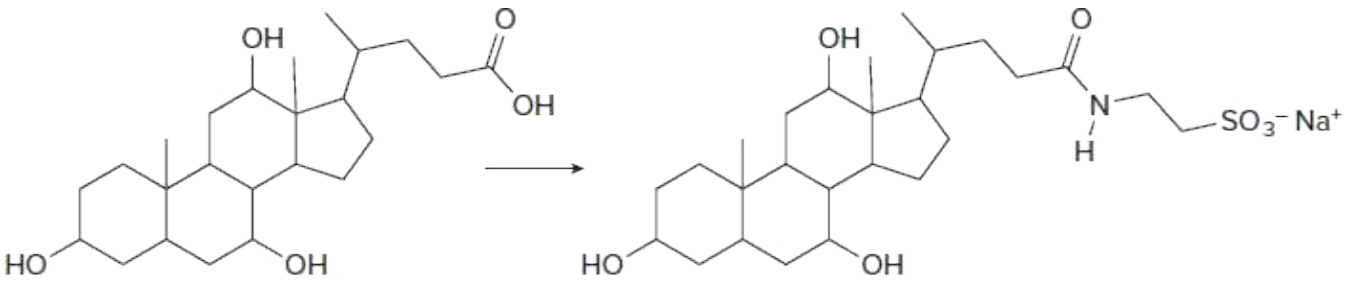
a. Classify each of these reactions as oxidation, reduction, or neither.

b. Explain why phenol is more water soluble than benzene. This means that phenol dissolves in urine, which is largely water, to a greater

extent than benzene.

Lipids

4.69 Cholic acid, a compound called a bile acid, is converted to a bile salt in the body. Bile salts have properties similar to soaps, and they help transport lipids through aqueous solutions. Explain why this is so.

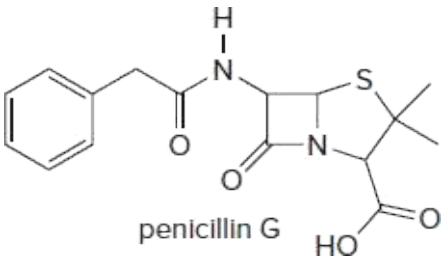


4.70 Mineral oil, a mixture of high-molecular-weight alkanes, is sometimes used as a laxative. Why are individuals who use mineral oil for this purpose advised to avoid taking it at the same time they consume foods rich in fat-soluble vitamins such as vitamin A?

Challenge Problems

4.71 Cyclopropane and cyclobutane have similar strain energy despite the fact that the C—C—C bond angles of cyclopropane are much smaller than those of cyclobutane. Suggest an explanation for this observation, considering all sources of strain discussed in Chapter 4.

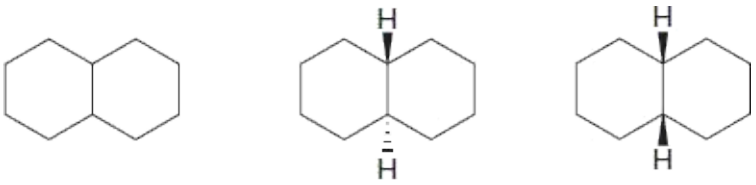
4.72 Although penicillin G has two amide functional groups, one is much more reactive than the other. Which amide is more reactive and why?



4.73 Haloethanes (CH_3CH_2X, X = Cl, Br, I) have similar barriers to rotation (13.4–15.5 kJ/mol) despite the fact that the size of the halogen increases, Cl → Br → I. Offer an explanation.

4.74 When two six-membered rings share a C—C bond, this bicyclic system is called a decalin. There are two possible arrangements: *trans*-decalin having two hydrogen atoms at the ring fusion on opposite sides of the rings, and *cis*-decalin having the two hydrogens at the ring fusion on the

same side.



decalin *trans*-decalin *cis*-decalin

a. Draw *trans*- and *cis*-decalin using the chair form for the cyclohexane rings.

b. The trans isomer is more stable. Explain why.

4.75 Consider the tricyclic structure A. (a) Label each substituent on the rings as axial or equatorial. (b) Draw a skeletal structure for A, using wedges and dashed wedges to show whether the substituents are located above or below the rings.

A

4.76 Consider the tricyclic structure B. (a) Label each substituent on the rings as axial or equatorial. (b) Draw B using chair conformations for each six-membered ring. (c) Label the atoms on the ring fusions (the carbons that join each set of two rings together) as cis or trans to each other.

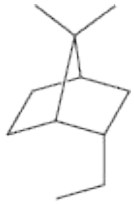
B

4.77 Read Appendix D on naming branched alkyl substituents, and draw all possible alkyl groups having the formula C_5H_{11}–. Give the IUPAC names for the eight compounds of molecular formula $C_{10}H_{20}$ that contain a cyclopentane ring with each of these alkyl groups as a substituent.

4.78 Read Appendix D on naming bicyclic compounds. Then give the IUPAC name for each of the following compounds.

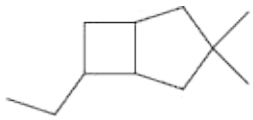
a.

b.



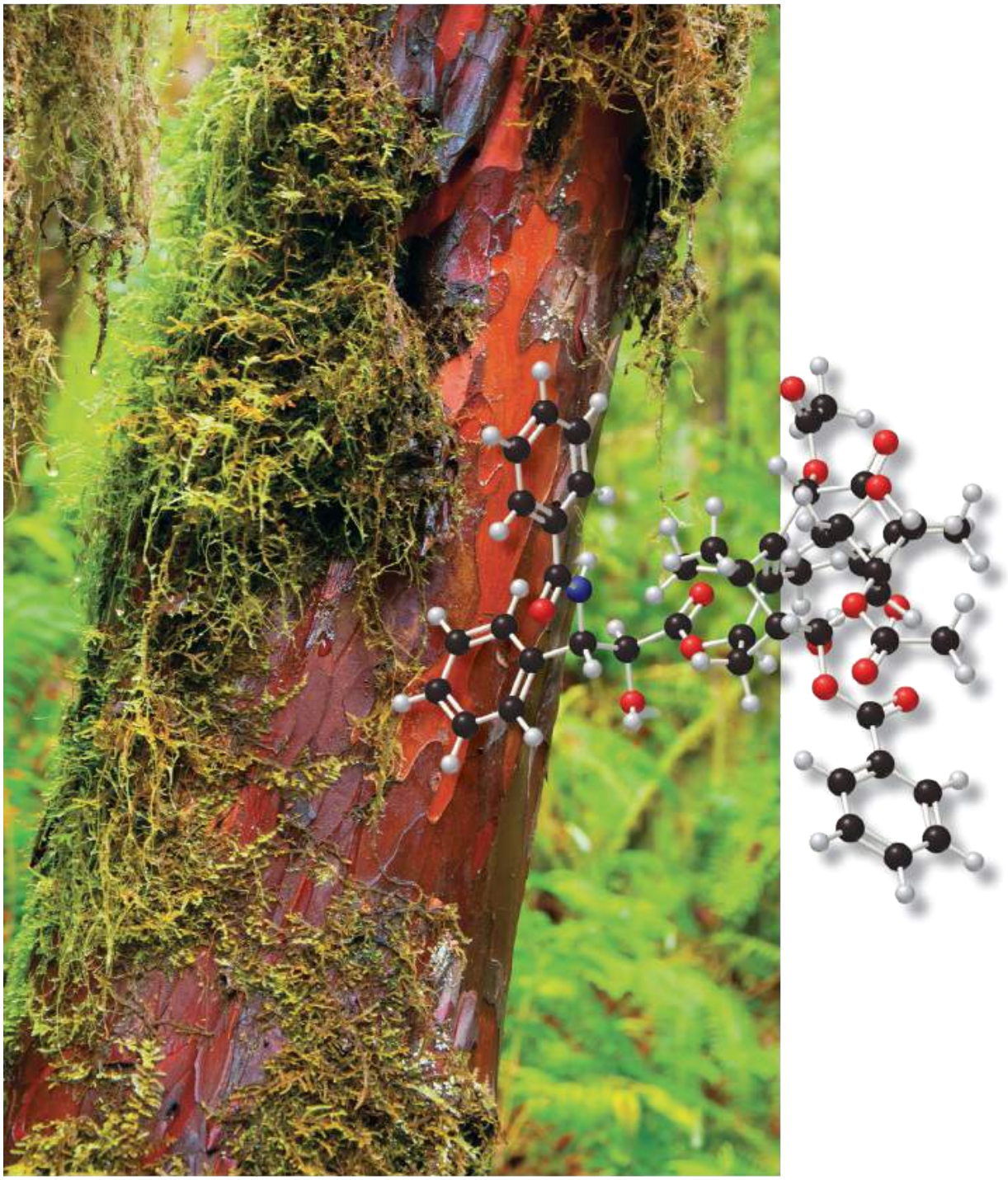
c.

d.



Stereochemistry

5



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5.1 Starch and cellulose

5.2 The two major classes of isomers
5.3 Looking glass chemistry—Chiral and achiral molecules
5.4 Stereogenic centers
5.5 Stereogenic centers in cyclic compounds
5.6 Labeling stereogenic centers with *R* or *S*
5.7 Diastereomers
5.8 Meso compounds
5.9 *R* and *S* assignments in compounds with two or more stereogenic centers
5.10 Disubstituted cycloalkanes
5.11 Isomers—A summary
5.12 Physical properties of stereoisomers
5.13 Chemical properties of enantiomers

Paclitaxel (trade name Taxol), a potent anticancer agent active against ovarian, breast, and several other cancers, was discovered in 1962 and approved for use by the Food and Drug Administration in 1992. Initial studies with paclitaxel were carried out with material isolated from the bark of the Pacific yew tree, but stripping the bark killed these magnificent trees. Paclitaxel was synthesized in the laboratory in 1994, and is now produced by a plant cell fermentation process. Like other widely used drugs, paclitaxel is biologically active because of its complex structure and the particular three-dimensional arrangement of its functional groups. In Chapter 5, we learn about the stereochemistry of molecules like paclitaxel.

Why Study…

Stereochemistry?

Are you left-handed or right-handed? If you're right-handed, you've probably spent little time thinking about your hand preference. If you're left-handed, though, you probably learned at an early age that many objects—like scissors and baseball gloves

—"fit" for righties, but are "backwards" for lefties. Hands, like many objects in the world around us, are mirror images that are *not* identical.

In Chapter 5, we examine the "handedness" of molecules, and learn about the importance of the three-dimensional shape of a molecule.

5.1 Starch and Cellulose

Recall from Chapter 4 that *stereochemistry* is the three-dimensional structure of a molecule. How important is stereochemistry? Two biomolecules—starch and cellulose—illustrate how apparently minute differences in structure can result in vastly different properties.

Starch and cellulose are two polymers that belong to the family of biomolecules called carbohydrates (Figure 5.1). A *polymer* is a large molecule composed of repeating smaller units—called monomers—that are covalently bonded together.

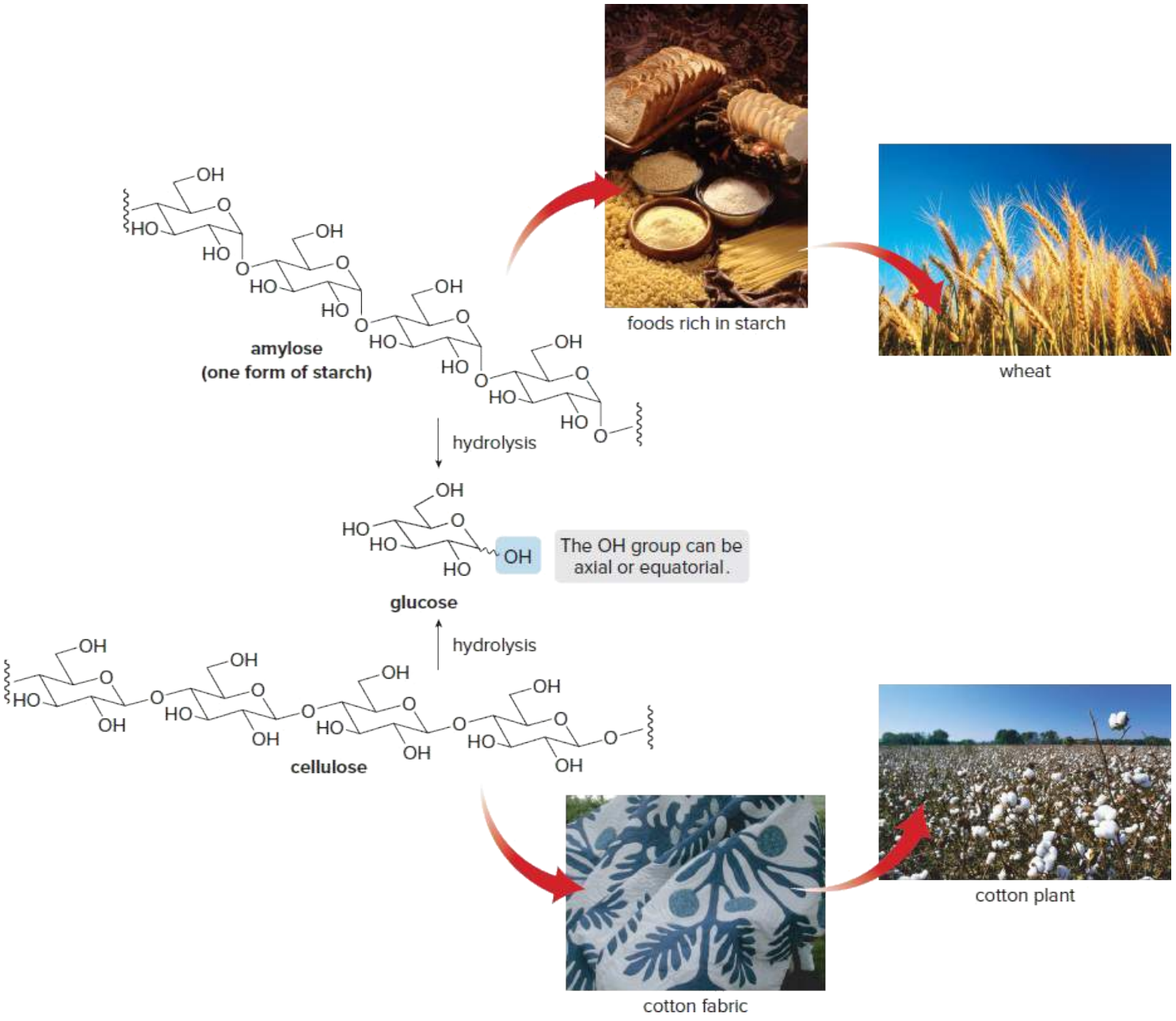


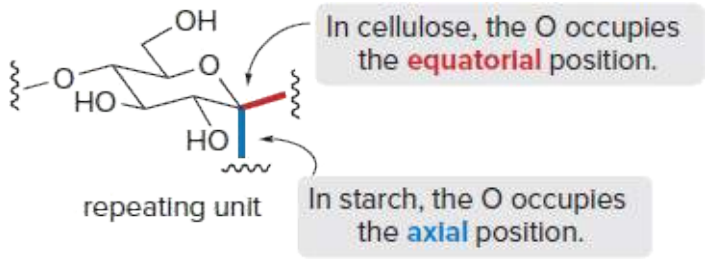
Figure 5.1 **Starch and cellulose—Two common carbohydrates**

Source: (Top left): Scott Bauer/USDA; (top right): ©Pixtal/Age Fotostock; (bottom left): ©Daniel C. Smith; (bottom right): ©Corbis

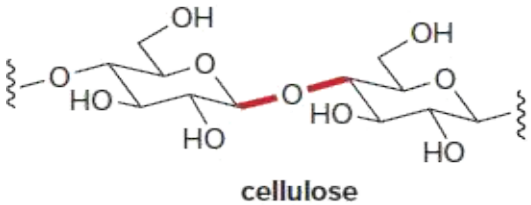
Starch is the main carbohydrate in the seeds and roots of plants. When we humans ingest wheat, rice, or potatoes, we consume starch, which is then hydrolyzed to the simple sugar glucose, one of the compounds our bodies use for energy. Cellulose, nature's most abundant organic material, gives rigidity to tree trunks and plant stems. Wood, cotton, and flax are composed largely of cellulose. Complete hydrolysis of cellulose also forms glucose, but unlike starch, humans cannot metabolize cellulose to glucose. In other words, we can digest starch but not cellulose.

Page 181

Cellulose and starch are both composed of the same repeating unit—a six-membered ring containing an oxygen atom and three OH groups—joined by an oxygen atom. They differ in the position of the O atom joining the rings together.

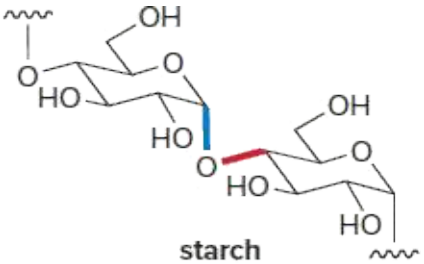


- **In cellulose, the O atom joins two rings using two equatorial bonds.**
- **In starch, the O atom joins two rings using one equatorial and one axial bond.**



cellulose

two equatorial bonds (in red)



starch

one axial bond (in blue) and one equatorial bond (in red)

Starch and cellulose are isomers because they are different compounds with the same molecular formula $(C_6H_{10}O_5)_n$. They are stereoisomers because only the three-dimensional arrangement of atoms is different.

How the six-membered rings are joined together has an enormous effect on the shape and properties of these carbohydrate molecules. Cellulose is composed of long chains held together by intermolecular hydrogen bonds, forming sheets that stack in an

extensive three-dimensional network. The axial`-equatorial ring junction in starch creates chains that fold into a helix (Figure 5.2). Moreover, the human digestive system contains the enzyme necessary to hydrolyze starch by cleaving its axial C–O bond, but not an enzyme to hydrolyze the equatorial C–O bond in cellulose.

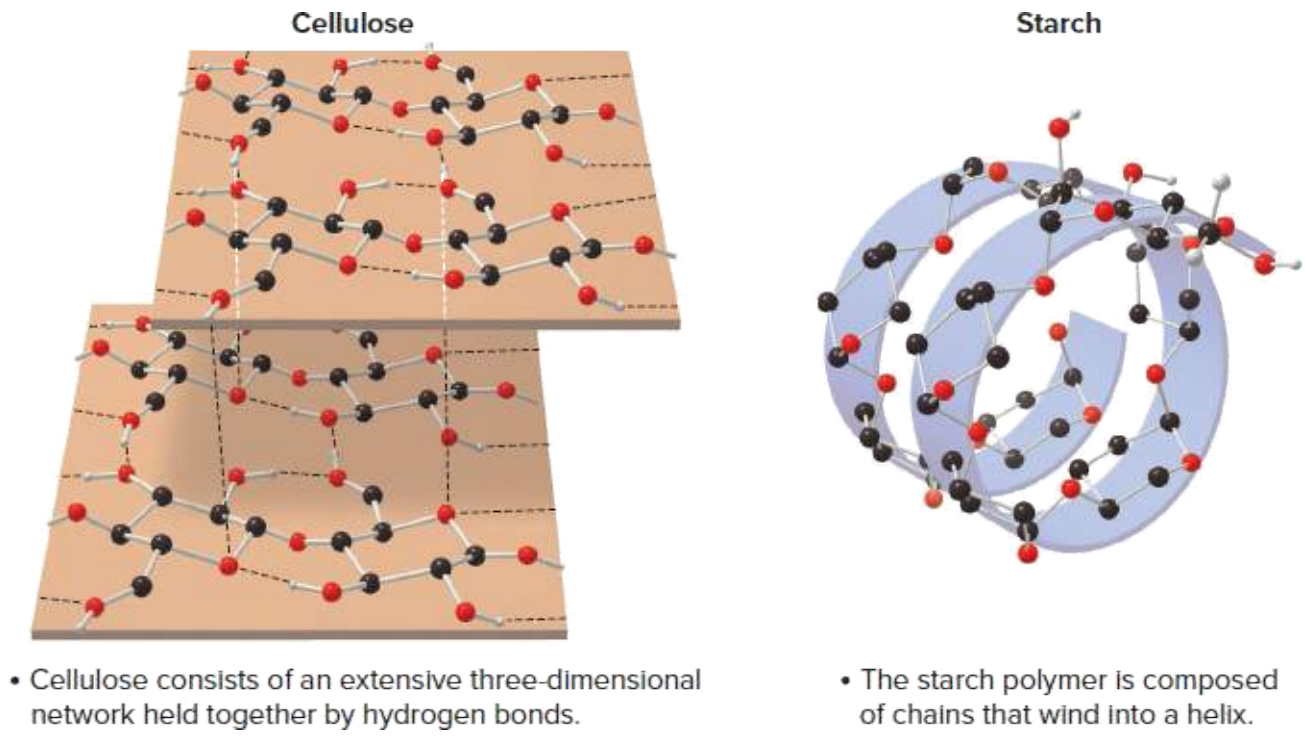


Figure 5.2 **Three-dimensional structure of cellulose and starch**

Thus, an apparently minor difference in the three-dimensional arrangement Page 182 of atoms confers very different properties on starch and cellulose.

Problem 5.1

Cellulose is water insoluble, despite its many OH groups. Considering its three-dimensional structure, why do you think this is so?

5.2 The Two Major Classes of Isomers

Because an understanding of isomers is integral to the discussion of stereochemistry, let's begin with an overview of isomers.

- **Isomers are different compounds with the same molecular formula.**

There are two major classes of isomers: constitutional isomers and stereoisomers. *Constitutional (or structural) isomers* differ in the way the atoms are connected to each other. Constitutional isomers have

- different IUPAC names;
- the same or different functional groups;
- different physical properties, so they are separable by physical techniques such as distillation; and
- different chemical properties. They behave differently or give different products in chemical reactions.

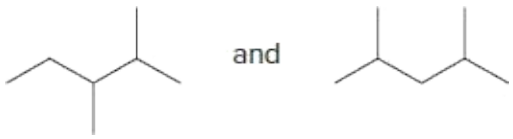
Stereoisomers differ *only* in the way atoms are oriented in space. Stereoisomers have identical IUPAC names (except for a prefix like cis or trans). Because they differ only in the three-dimensional arrangement of atoms, stereoisomers always have the same functional group(s).

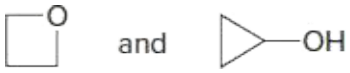
A particular three-dimensional arrangement is called a *configuration*. Thus, stereoisomers differ in configuration. The cis and trans isomers in Section 4.13B and the biomolecules starch and cellulose in Section 5.1 are two examples of stereoisomers.

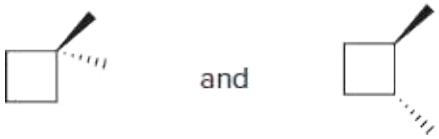
Figure 5.3 illustrates examples of both types of isomers. Chapter 5 concentrates on the types and properties of stereoisomers.

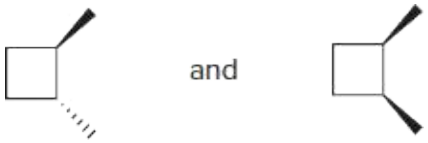
Problem 5.2

Classify each pair of compounds as constitutional isomers or stereoisomers.

a. 

b. 

c. 

d. 

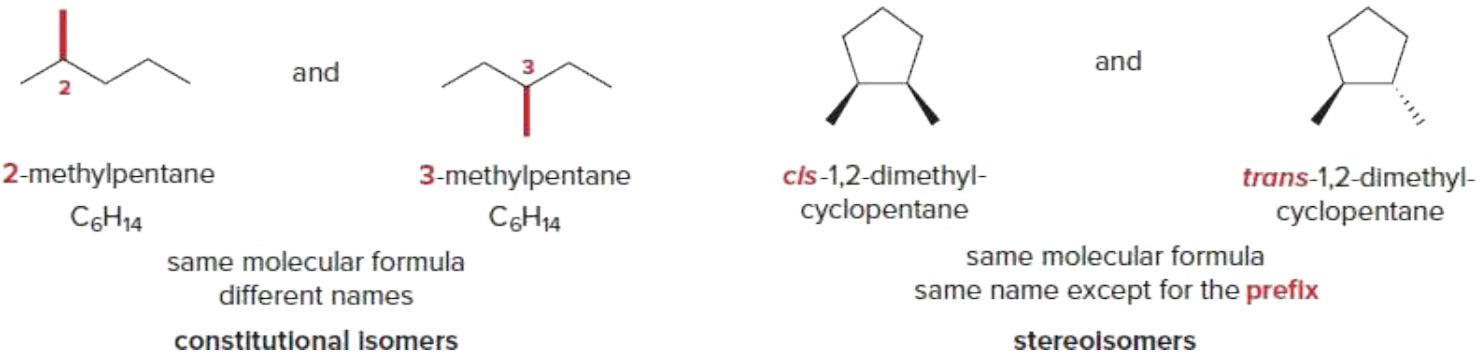


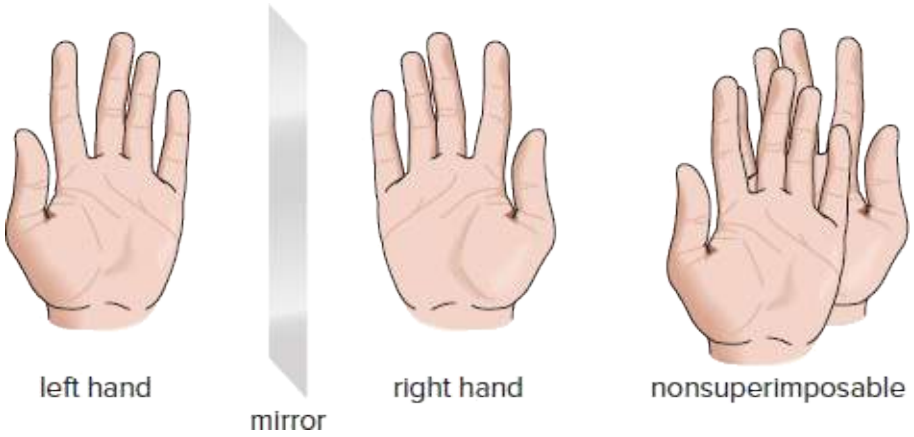
Figure 5.3 **A comparison of constitutional isomers and stereoisomers**

Despite the dominance of right-handedness over left-handedness, even identical twins can exhibit differences in hand preference. Pictured as infants are Zachary (left-handed) and Matthew (right-handed), identical twin sons of the author.
©Daniel C. Smith

5.3 Looking Glass Chemistry—Chiral and Achiral Molecules

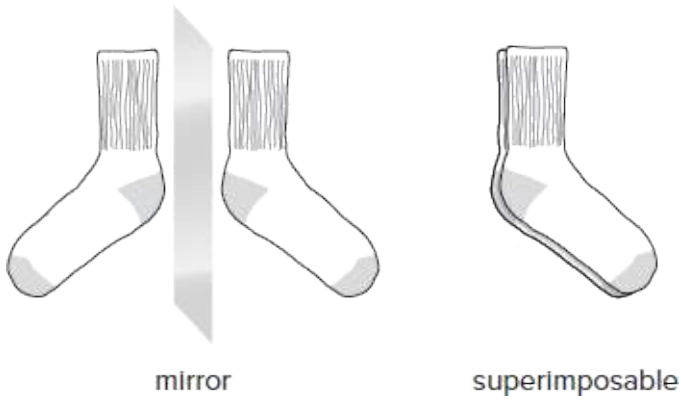
Everything has a mirror image. What's significant is whether a molecule is *identical* to or *different* from its mirror image.

Some molecules are like hands. Left and right hands are mirror images of each other, but they are *not* identical. If you try to mentally place one hand inside the other hand, you can never superimpose either all the fingers, or the tops and palms. To *superimpose* an object on its mirror image means to align *all* parts of the object with its mirror image. With molecules, this means aligning all atoms and all bonds.



- **A molecule (or object) that is *not* superimposable on its mirror image is said to be *chiral.***

Other molecules are like socks. Two socks from a pair are mirror images that *are* superimposable. One sock can fit inside another, aligning toes and heels, and tops and bottoms. A sock and its mirror image are *identical*.



- **A molecule (or object) that *is* superimposable on its mirror image is said to be *achiral.***

The adjective *chiral* comes from the Greek word *cheir*, meaning "hand." Left and right hands are chiral: they are mirror images that do *not* superimpose on each other.

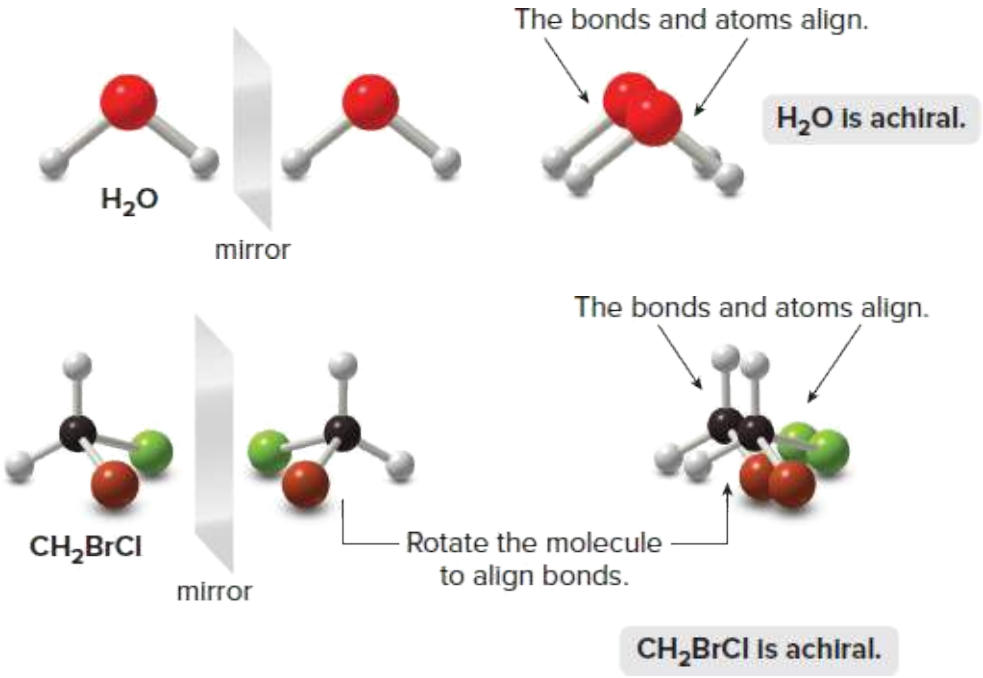
Few beginning students of organic chemistry can readily visualize whether a compound and its mirror image are superimposable by looking at drawings on a two-dimensional page. Molecular models can help a great deal in this process.

Let's determine whether three molecules—H_2O, CH_2BrCl, and CHBrClF—are superimposable on their mirror images; that is, are H_2O, CH_2BrCl, and CHBrClF chiral or achiral?

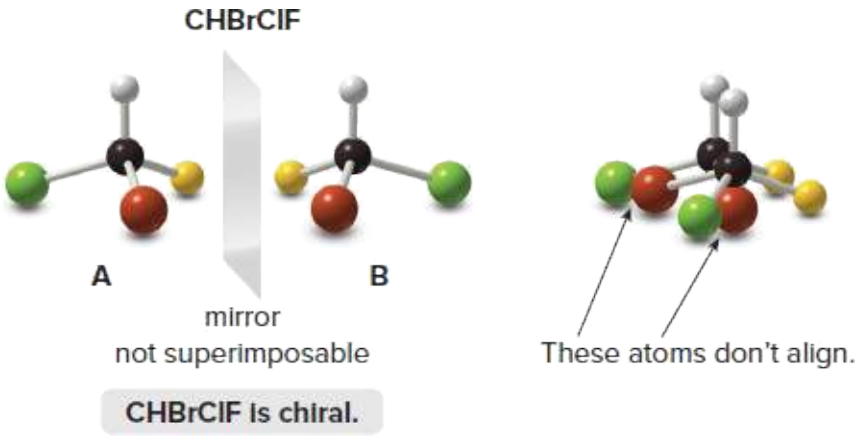
To test chirality:

- Draw the molecule in three dimensions.
- Draw its mirror image.
- Try to align all bonds and atoms. To superimpose a molecule and its mirror image, you can perform any rotation but you cannot break bonds.

Following this procedure, H2O and CH2BrCl are both achiral molecules because each molecule is superimposable on its mirror image.



With CHBrClF, the result is different. The molecule (labeled A) and its mirror image (labeled B) are *not* superimposable. No matter how you rotate A and B, all the atoms never align. CHBrClF is thus a chiral molecule, and A and B are different compounds.



Naming a carbon atom with four different groups is a topic that currently has no firm agreement among organic chemists. The IUPAC recommends the term *chirality center*, but the term has not gained wide acceptance among organic chemists since it was first suggested in 1996. Other terms in common use are chiral center, chiral carbon, asymmetric carbon, stereocenter, and stereogenic center, the term used in this text.

A and B are stereoisomers because they are isomers differing only in the three-dimensional arrangement of substituents. These stereoisomers are called enantiomers.

- ***Enantiomers* are mirror images that are not superimposable.**

CHBrClF contains a carbon atom bonded to four different groups. A carbon atom bonded to four different groups is called a tetrahedral *stereogenic center*. Most chiral molecules contain one or more stereogenic centers.

The general term *stereogenic center* refers to any site in a molecule at which the interchange of two groups forms a stereoisomer. A carbon atom with four different groups is a *tetrahedral* stereogenic center, because the interchange of two groups converts one enantiomer into another. We will learn about another type of stereogenic center in Section 8.2B.

We have now learned two related but different concepts, and it is necessary to distinguish between them.

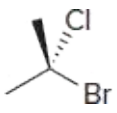
- **A molecule that is not superimposable on its mirror image is a *chiral molecule*.**
- **A carbon atom bonded to four different groups is a *stereogenic center.***

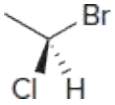
Molecules can contain zero, one, or more stereogenic centers.

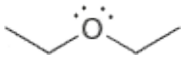
- **With no stereogenic centers, a molecule generally is not chiral. H_2O and CH_2BrCl have *no* stereogenic centers and are *achiral* molecules. (There are a few exceptions to this generalization, as we will learn in Section 15.5.)**
- **With one tetrahedral stereogenic center, a molecule is *always* chiral. CHBrClF is a *chiral* molecule containing *one* stereogenic center.**
- **With two or more stereogenic centers, a molecule *may* or *may not* be chiral, as we will learn in Section 5.8.**

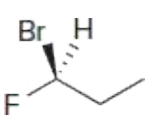
Problem 5.3

Draw the mirror image of each compound. Label each molecule as chiral or achiral.

a. 

b. 

c. 

d. 

When trying to distinguish between chiral and achiral compounds, keep in mind:

- **A *plane of symmetry* is a mirror plane that cuts a molecule in half, so that one half of the molecule is a reflection of the other half.**
- **Achiral molecules usually contain a plane of symmetry, but chiral molecules do not.**

The achiral molecule CH_2BrCl has a plane of symmetry, but the chiral molecule CHBrClF does not.

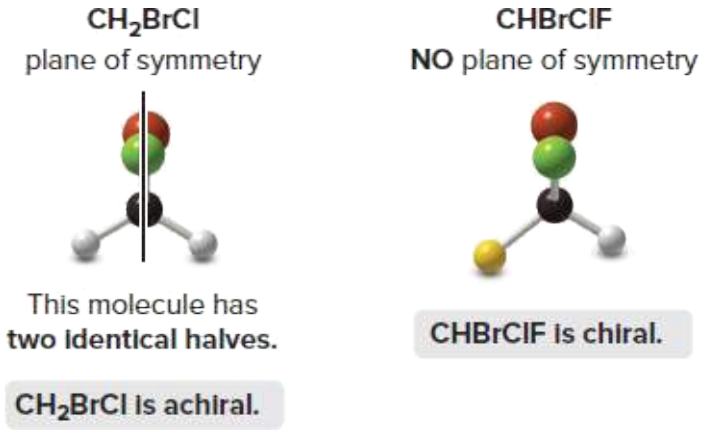


Figure 5.4 summarizes the main facts about chirality we have learned thus far.

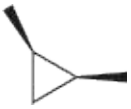
- **Everything has a mirror image. The fundamental question is whether a molecule and its mirror image are superimposable.**
- **If a molecule and its mirror image are *not* superimposable, the molecule and its mirror image are *chiral.***
- **The terms *stereogenic center* and *chiral molecule* are related but distinct. In general, a chiral molecule must have one or more stereogenic centers.**
- **The presence of a *plane of symmetry* makes a molecule achiral.**

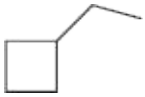
Figure 5.4 **The basic principles of chirality**

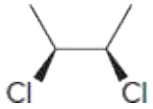
Problem 5.4

Draw in a plane of symmetry for each molecule.

a.

b. 

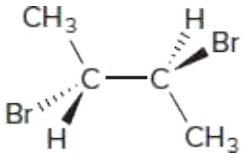
c. 

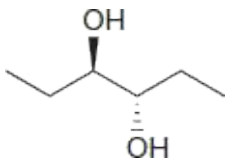
d. 

When a right-handed shell is held in the right hand with the thumb pointing toward the wider end, the opening is on the right side. ©*McGraw-Hill Education/Jill Braaten, photographer*

Problem 5.5

A molecule is achiral if it has a plane of symmetry in *any* conformation. Each of the following conformations does not have a plane of symmetry, but rotation around a carbon–carbon bond forms a conformation that does have a plane of symmetry. Draw this conformation for each molecule.

a. 

b. 

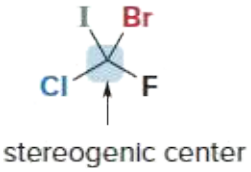
Stereochemistry may seem esoteric, but chirality pervades our very existence. On a molecular level, many biomolecules fundamental to life are chiral. On a macroscopic level, many naturally occurring objects possess handedness. Examples include chiral helical seashells shaped like right-handed screws, and plants such as honeysuckle that wind in a chiral left-handed helix. The human body is chiral, and hands, feet, and ears are not superimposable.

5.4 Stereogenic Centers

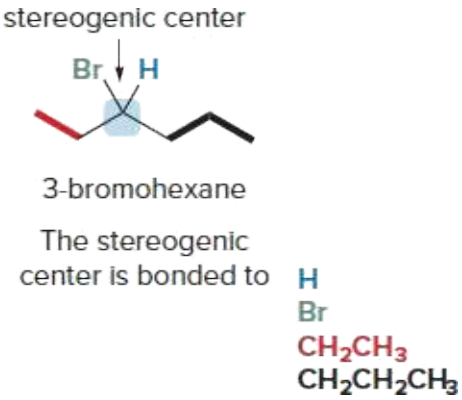
A necessary skill in the study of stereochemistry is the ability to locate and draw tetrahedral stereogenic centers.

5.4A Stereogenic Centers on Carbon Atoms That Are Not Part of a Ring

Recall from Section 5.3 that any carbon atom bonded to four different groups is a tetrahedral stereogenic center. To locate a stereogenic center, examine each *tetrahedral* carbon atom in a molecule, and look at the four *groups*—not the four *atoms*—bonded to it. CBrClFI has one stereogenic center because its central carbon atom is bonded to four different elements. 3-Bromohexane also has one stereogenic center because one carbon is bonded to H, Br, CH_2CH_3, and $CH_2CH_2CH_3$. We consider all atoms in a group as a *whole unit*, not just the atom bonded directly to the carbon in question. Although C3 of 3-bromohexane is bonded to two carbon atoms, one is part of an ethyl group and one is part of a propyl group.



stereogenic center

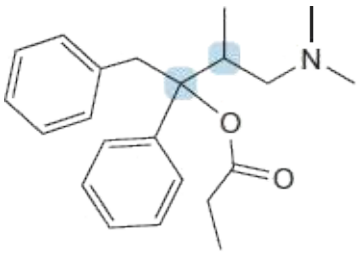


Ephedrine is isolated from ma huang, an herb used to treat respiratory ailments in traditional Chinese medicine. Once a popular drug to promote weight loss and enhance athletic performance, ephedrine has now been linked to episodes of sudden death, heart attack, and stroke. ©*Mark W. Skinner*

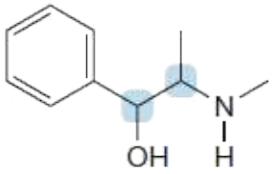
Always omit from consideration all C atoms that can't be tetrahedral stereogenic centers. These include

- CH_2 and CH_3 groups (more than one H bonded to C); and
- any *sp* or sp^2 hybridized C (less than four groups around C).

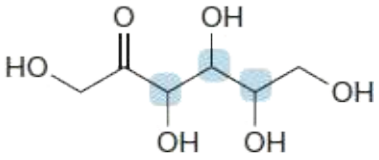
Larger organic molecules can have two, three, or even hundreds of stereogenic centers. Propoxyphene and ephedrine each contain two stereogenic centers, and fructose, a simple carbohydrate, has three.



propoxyphene
Trade name Darvon
(analgesic)



ephedrine
(bronchodilator, decongestant)



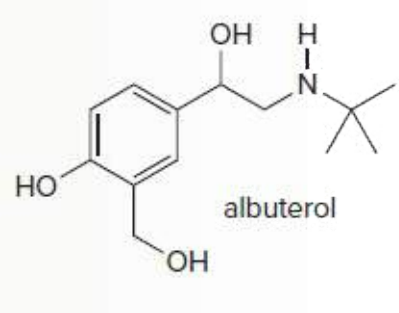
fructose
(a simple sugar)

= stereogenic center

Sample Problem 5.1 Locating Stereogenic Centers

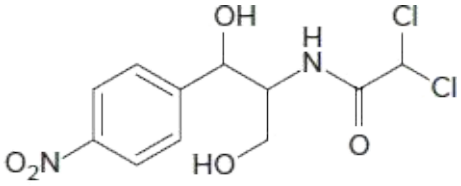
Locate the stereogenic centers in each drug. Albuterol is a bronchodilator—that is, it widens airways—so it is used to treat asthma. Chloramphenicol is an antibiotic used extensively in developing countries because of its low cost.

a.



albuterol

b.



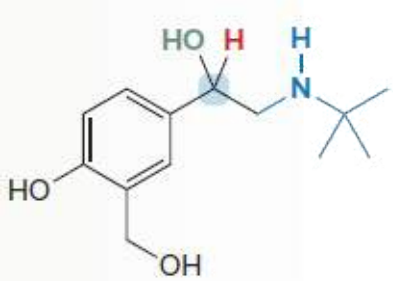
chloramphenicol

Heteroatoms surrounded by four different groups are also stereogenic centers. Stereogenic N atoms are discussed in Chapter 23.

Solution

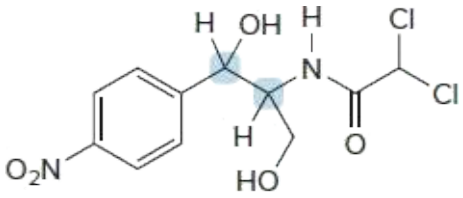
Omit all CH_2 and CH_3 groups and all doubly bonded (sp^2 hybridized) C's. In albuterol, one C has three CH3 groups bonded to it, so it can be eliminated as well. Draw in H atoms on tetrahedral C's in skeletal structures to more clearly see the groups. This leaves one C in albuterol and two C's in chloramphenicol surrounded by four different groups, making them stereogenic centers.

a.



one stereogenic center

b.

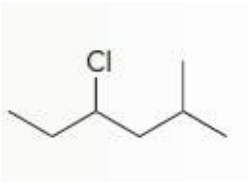


two stereogenic centers

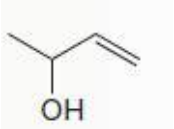
Problem 5.6

Locate the stereogenic centers in each molecule. Compounds may have one or more stereogenic centers.

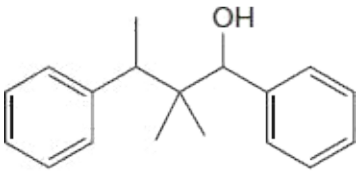
a.



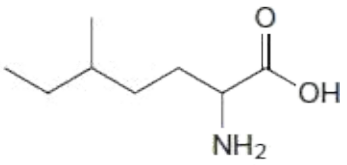
c.



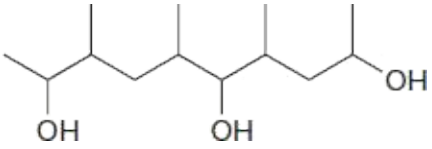
e.



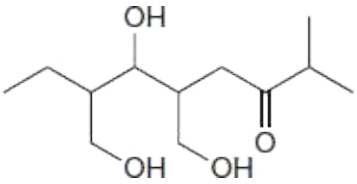
b.



d.



f.

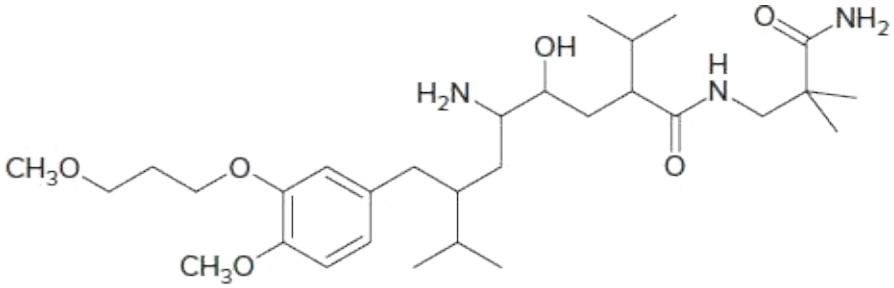


More Practice:

Try Problem 5.45b, c, d.

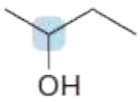
Problem 5.7

The principles in Section 5.4A can be used to locate stereogenic centers in any molecule, no matter how complicated. Always look for carbons surrounded by four different groups. With this in mind, locate the four stereogenic centers in aliskiren, a drug introduced in 2007 for the treatment of hypertension.



aliskiren

5.4B Drawing a Pair of Enantiomers

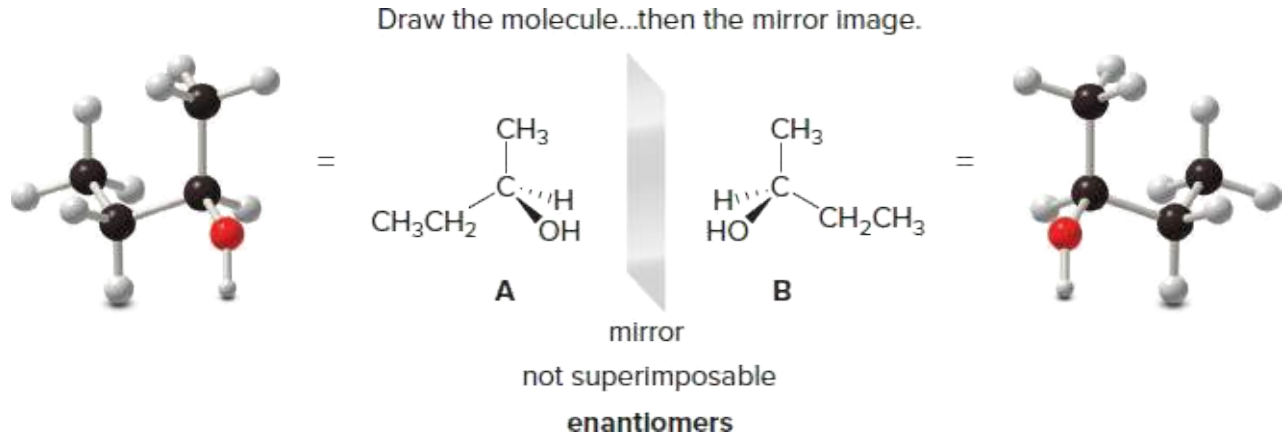


butan-2-ol
one stereogenic center

- **Any molecule with one tetrahedral stereogenic center is a chiral compound and exists as a pair of enantiomers.**

Butan-2-ol, for example, has one stereogenic center. To draw both enantiomers, use the typical convention for depicting a tetrahedron: place two bonds in the plane, one in front of the plane on a wedge, and one behind the plane on a dashed wedge. Then, to form the first enantiomer A, arbitrarily place the four groups—H, OH, CH_3, and CH_2CH_3—on any bond to the stereogenic center.

In Section 26.2, we will learn about Fischer projection formulas, an older convention used for drawing stereogenic centers utilized mainly in carbohydrate chemistry.



Then, draw a mirror plane and arrange the substituents in the mirror image so that they are a reflection of the groups in the first molecule, forming B. No matter how A and B are rotated, it is impossible to align all of their atoms. Because A and B are mirror images and not superimposable, A and B are a pair of enantiomers.

This is just one way to draw an enantiomer, as shown in Figure 5.5a for 3-bromohexane. Another way to draw an enantiomer (Figure 5.5b), especially for compounds with more than one stereogenic center, is to keep the carbon skeleton in the *same* position, but *invert* the configuration at all stereogenic centers by converting bonds in front (on wedges) to bonds in back (on dashed wedges), and vice versa.

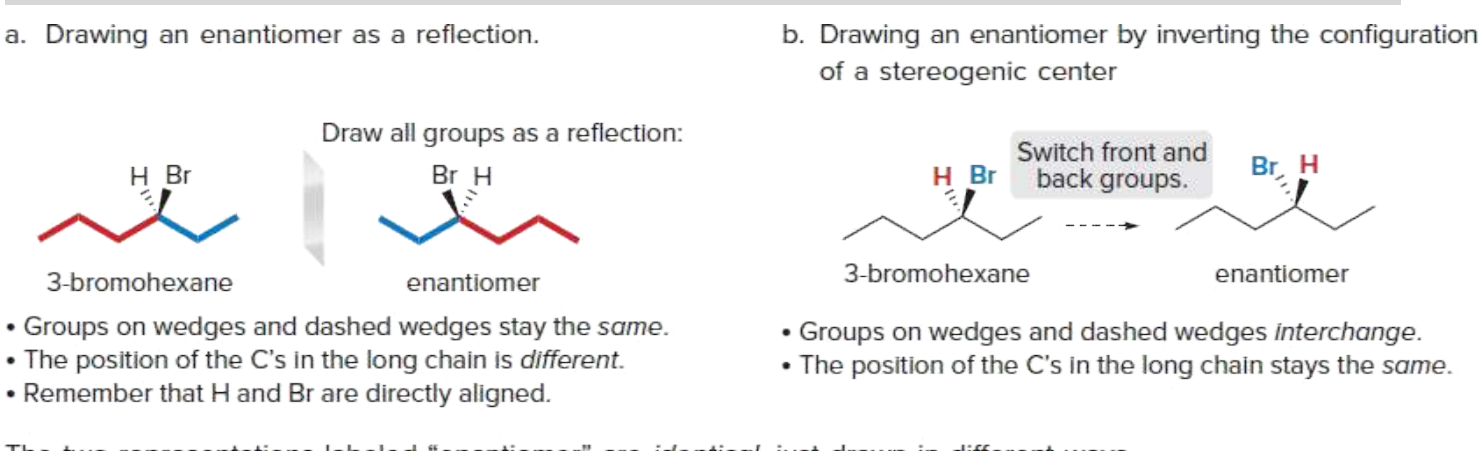
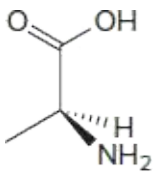


Figure 5.5 Different ways of drawing an enantiomer

The two representations labeled “enantiomer” are *identical*, just drawn in different ways.

Sample Problem 5.2 Different Ways of Drawing an Enantiomer

Locate the stereogenic center in the amino acid alanine, and draw the enantiomer using the two methods shown in Figure 5.5.



alanine

Solution

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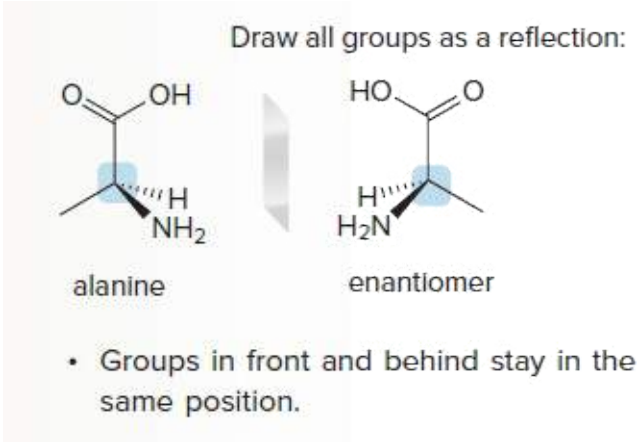
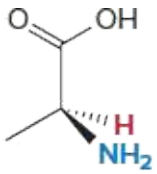
The stereogenic center is the carbon with four different groups, labeled in blue.

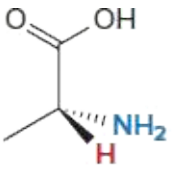
[1] Project a mirror plane and draw all groups on the stereogenic center as a reflection of the groups in alanine.



[2] Keep the carbon skeleton the same, and switch the position of groups that lie in front of and behind the plane.



alanine



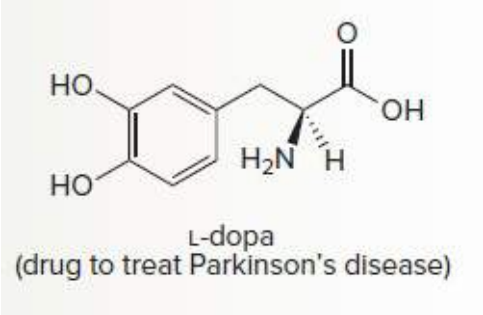
enantiomer

- The H *behind* the plane becomes an H in *front* on a wedge.
- The NH_2 in *front* of the plane becomes an NH_2 in *back* on a dashed wedge.

Problem 5.8

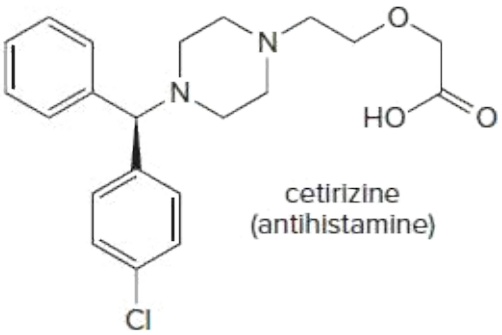
Draw the enantiomer of each compound.

a.



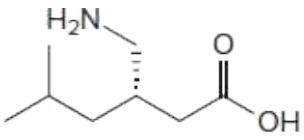
L-dopa
(drug to treat Parkinson's disease)

b.



cetirizine
(antihistamine)

c.



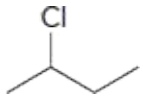
pregabalin
(drug used to treat chronic pain)

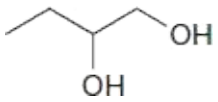
More Practice:

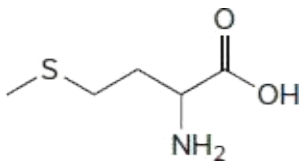
Try Problems 5.47, 5.69b, 5.70d, 5.71b.

Problem 5.9

Locate the stereogenic center in each compound and draw both enantiomers.

a. 

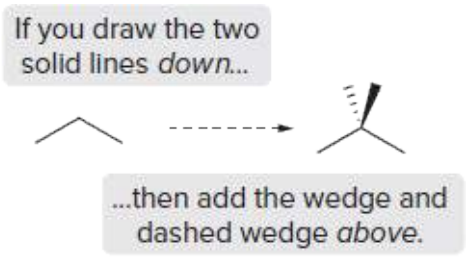
b. 

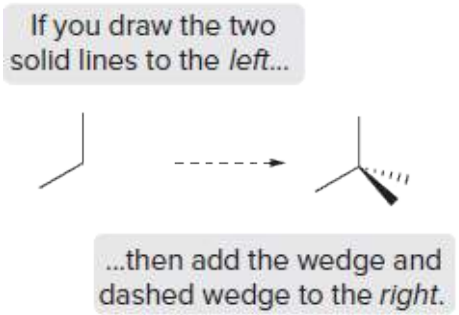
c. 

5.5 Stereogenic Centers in Cyclic Compounds

Stereogenic centers may also occur at carbon atoms that are part of a ring. To find stereogenic centers on ring carbons, always draw the rings as flat polygons, and look for tetrahedral carbons that are bonded to four different groups, as usual. Each ring carbon is bonded to two other atoms in the ring, as well as two substituents attached to the ring. When the two substituents on the ring are *different*, we must compare the ring atoms equidistant from the atom in question.

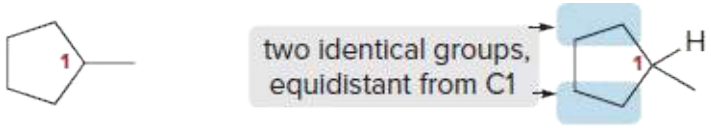
In drawing a tetrahedron using solid lines, wedges, and dashed wedges, always draw the two solid lines *first;* then draw the wedge and the dashed wedge on the *opposite side* of the solid lines.





Two enantiomers are *different* compounds. To convert one enantiomer to another, you must switch the position of two atoms. This amounts to breaking bonds.

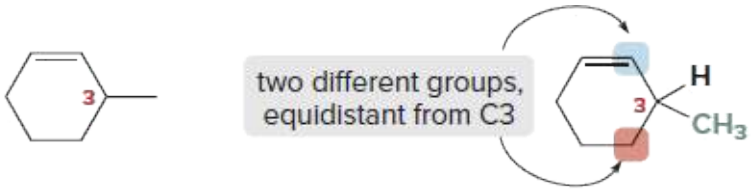
Does methylcyclopentane have a stereogenic center? All of the carbon atoms are bonded to two or three hydrogen atoms except for C1, the ring carbon bonded to the methyl group. Next, compare the ring atoms and bonds on both sides equidistant from C1, and continue until a point of difference is reached, or until both sides meet, either at an atom or in the middle of a bond. In this case, there is no point of difference on either side, so C1 is bonded to identical alkyl groups that happen to be part of a ring. C1, therefore, is *not* a stereogenic center.



methylcyclopentane

C1 is *not* a stereogenic center.

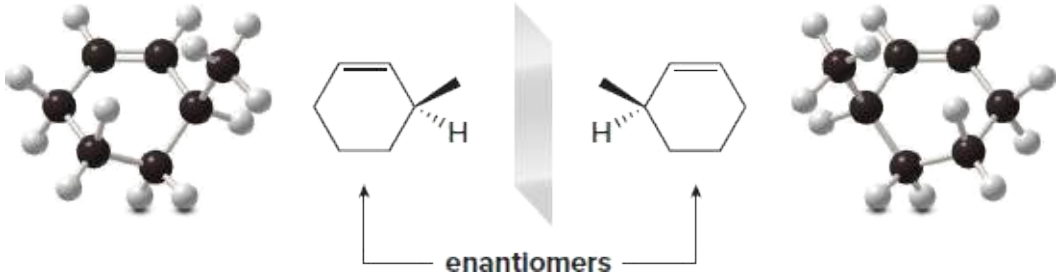
With 3-methylcyclohexene, the result is different. All carbon atoms are bonded to two or three hydrogen atoms or are sp^2 hybridized except for C3, the ring carbon bonded to the methyl group. In this case, the atoms equidistant from C3 are different, so C3 is bonded to *different* alkyl groups in the ring. C3 is therefore bonded to four different groups, making it a stereogenic center.



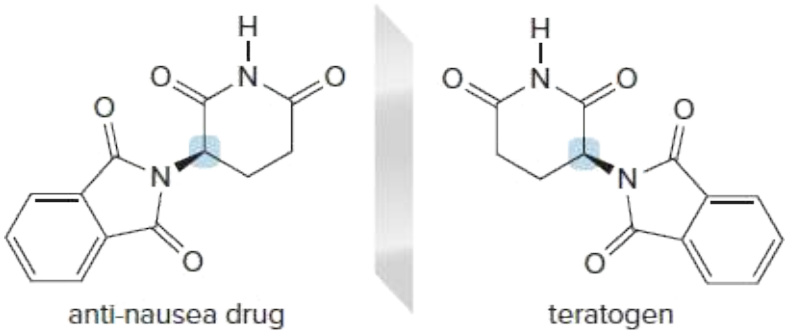
3-methylcyclohexene

C3 is a stereogenic center.

Because 3-methylcyclohexene has one tetrahedral stereogenic center, it is a chiral compound and exists as a pair of enantiomers.



Many biologically active compounds contain one or more stereogenic centers on ring carbons. For example, thalidomide, a drug once prescribed as a sedative and anti-nausea agent for pregnant women in Great Britain and Europe, contains one stereogenic center, so it exists as a pair of enantiomers.



thalidomide
enantiomers

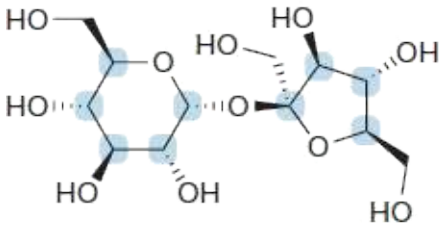
Today, thalidomide is prescribed under strict controls for the treatment of Hansen's disease (leprosy). Because it was once thought to be highly contagious, individuals in Hawai'i with Hansen's disease were sent to Kalaupapa, a remote and inaccessible peninsula on the north shore of the Hawaiian island of Moloka'i. Hansen's disease is now known to be a curable bacterial infection, which is treated by the sulfa drugs discussed in Section 23.15.

©Lokuttara/Shutterstock

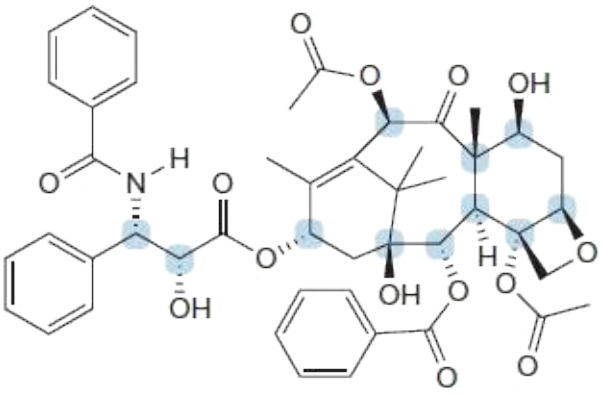
Unfortunately thalidomide was sold as a mixture of its two enantiomers, and each of these stereoisomers has a different biological activity. This is a property not uncommon in chiral drugs, as we will see in Section 5.13A. Although one enantiomer was an effective sedative and anti-nausea drug, the other enantiomer was responsible for thousands of catastrophic birth defects in children born to women who took the drug during pregnancy. Thalidomide was never approved for use in the United States due to the diligence of Frances Oldham Kelsey, a medical reviewing officer for the Food and Drug Administration, who insisted that the safety data on thalidomide were inadequate.

Sucrose and paclitaxel (the chapter-opening molecule) are two useful compounds with several stereogenic centers at ring carbons. Identify the stereogenic centers in these more complicated compounds in exactly the same way, looking at one carbon at a time. Sucrose, with nine stereogenic centers on two rings, is the

carbohydrate used as table sugar. Paclitaxel, with 11 stereogenic centers, is an anticancer agent active against ovarian, breast, and some lung tumors.

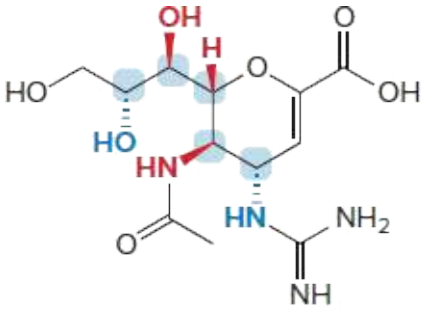


sucrose
(table sugar)

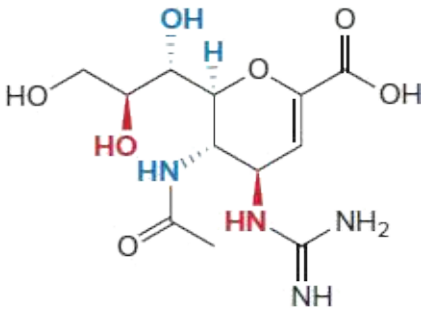


paclitaxel
Trade name Taxol
(anticancer agent)

To draw the enantiomer of a complex compound with many stereogenic centers, change all groups above the plane on wedges to dashed wedges, and all groups behind the plane on dashed wedges to wedges. For example, zanamivir, a medicine used to treat and prevent influenza, has five stereogenic centers, whose configurations are inverted in its enantiomer.



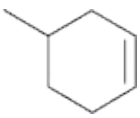
zanamivir

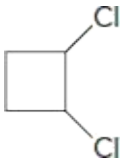


enantiomer

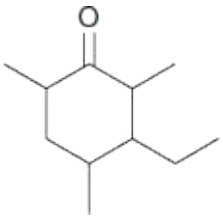
Problem 5.10

Locate the stereogenic centers in each compound. A molecule may have one or more stereogenic centers. Gabapentin enacarbil [part (d)] is used to treat seizures and certain types of chronic pain.

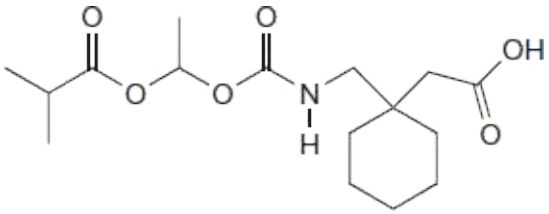
a. 

b. 

c.

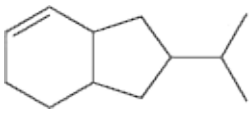


d.

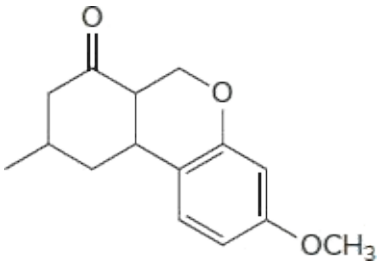


gabapentin enacarbil

e.



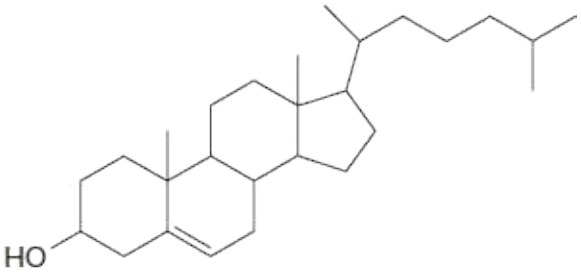
f.



Problem 5.11

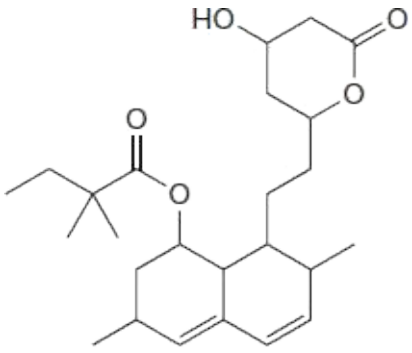
Locate the stereogenic centers in each compound.

a.



cholesterol

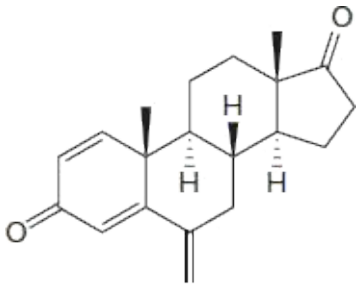
b.



simvastatin
Trade name Zocor
(cholesterol-lowering drug)

Problem 5.12

Exemestane (trade name Aromasin) is a drug used to treat breast cancer. Locate the stereogenic centers in exemestane and draw the enantiomer.



exemestane

Naming enantiomers with the prefix *R* or S is called the Cahn–Ingold–Prelog system after the three chemists who devised it.

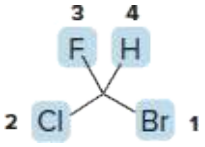
5.6 Labeling Stereogenic Centers with *R* or *S*

Because enantiomers are two different compounds, we need a method to distinguish them by name. This is done by adding the prefix *R* or *S* to the IUPAC name of the enantiomer. To designate an enantiomer as *R* or *S*, first assign a priority (1, 2, 3, or 4) to each group bonded to the stereogenic center, and then use these priorities to label one enantiomer *R* and one S.

Rules Needed to Assign Priority

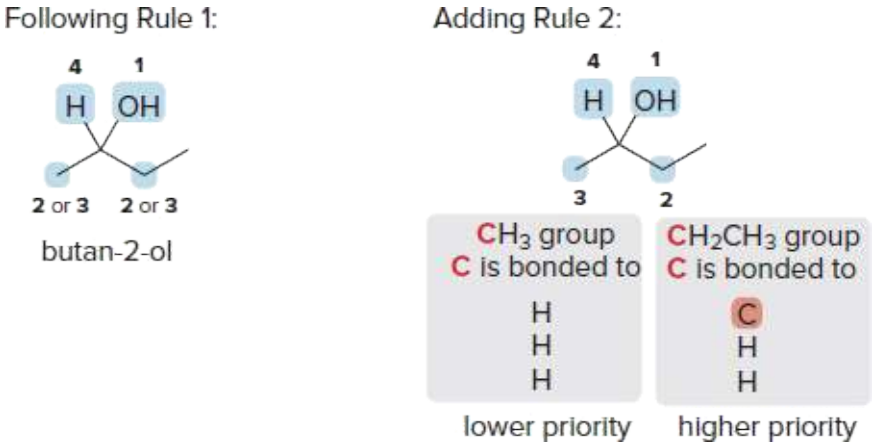
Rule 1 **Assign priorities (1, 2, 3, or 4) to the atoms directly bonded to the stereogenic center in order of *decreasing* atomic number. The atom of *highest* atomic number gets the *highest* priority (1).**

- In CHBrClF, priorities are assigned as follows: Br (1, highest) → Cl (2) → F (3) → H (4, lowest). In many molecules the lowest priority group will be H.



Rule 2 **If two atoms on a stereogenic center are the *same*, assign priority based on the atomic number of the atoms bonded to these atoms. *One* atom of higher atomic number determines a higher priority.**

- With butan-2-ol, the O atom gets highest priority (1) and H gets lowest priority (4) using Rule 1. Butan-2-ol also has two carbon atoms bonded to the stereogenic center, one that is part of a CH3 group and one that is part of a CH2CH3 group. To assign priority (either 2 or 3) to the two C atoms, look at what atoms (other than the stereogenic center) are bonded to each C.



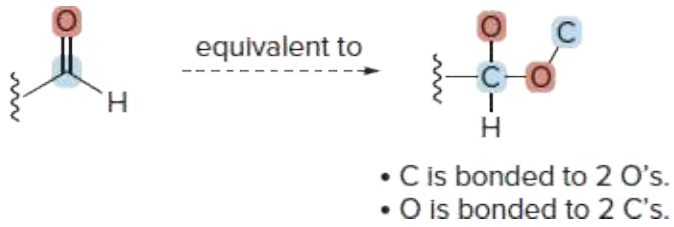
- The CH2CH3 gets higher priority (2) than the CH3 group (priority 3) because the carbon of the ethyl group is bonded to another carbon.
- The order of priority of groups in butan-2-ol is –OH (1), $-CH_2CH_3$ (2), $-CH_3$ (3), and –H (4).
- If priority still cannot be assigned, continue along a chain until a point of difference is reached.

Rule 3 **If two isotopes are bonded to the stereogenic center, assign priorities in order of *decreasing mass* number.**

- In comparing two isotopes of the element hydrogen, deuterium, which has a mass number of two (one proton and one neutron), has a higher priority than hydrogen, which has a mass number of one (one proton only).

Rule 4 **To assign a priority to an atom that is part of a multiple bond, treat a multiply bonded atom as an equivalent number of singly bonded atoms.**

- The C of a C=O is considered to be bonded to two O atoms.



- Other common multiple bonds are drawn below.

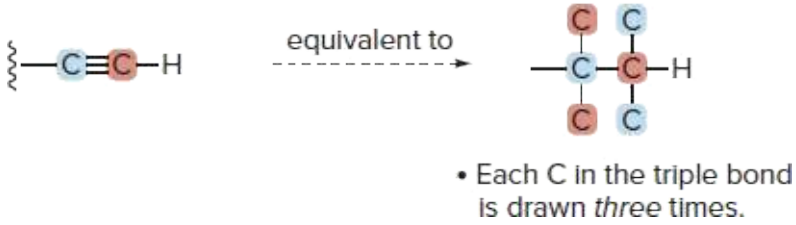


Figure 5.6 gives examples of priorities assigned to stereogenic centers.

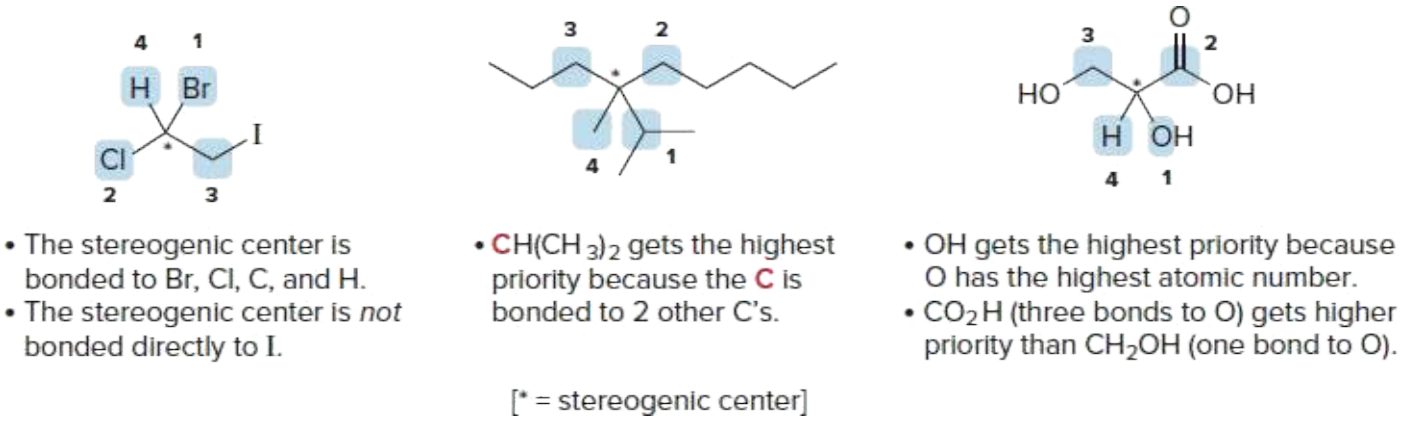


Figure 5.6 **Examples of assigning priorities to stereogenic centers**

Problem 5.13

Which group in each pair is assigned the *higher* priority?

a. $-CH_3$, $-CH_2CH_3$

b. −I, −Br

c. −H, −D

d. $-CH_2Br$, $-CH_2CH_2Br$

e. $-CH_2CH_2Cl$, $-CH_2CH(CH_3)_2$

f. $-CH_2OH$, $-CHO$

***R* is derived from the Latin word *rectus* meaning "right," and *S* is from the Latin word *sinister* meaning "left."**

Problem 5.14

Rank the following groups in order of *decreasing* priority.

a. $-COOH$, $-H$, $-NH_2$, $-OH$

b. $-H$, $-CH_3$, $-Cl$, $-CH_2Cl$

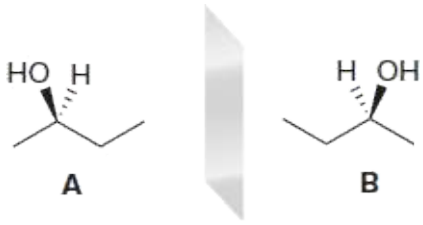
c. $-CH_2CH_3$, $-CH_3$, $-H$, $-CH(CH_3)_2$

d. $-CH{=}CH_2$, $-CH_3$, $-C{\equiv}CH$, $-H$

Once priorities are assigned to the four groups around a stereogenic center, we can use three steps to designate the center as either *R* or *S*.

How To Assign *R* or *S* to a Stereogenic Center

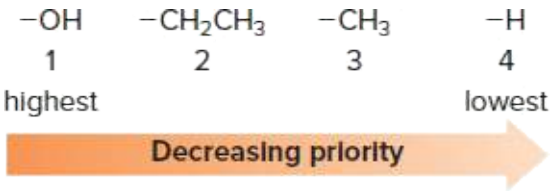
Example Label each enantiomer as *R* or *S*.



two enantiomers of butan-2-ol

Step [1] Assign priorities from 1 to 4 to each group bonded to the stereogenic center.

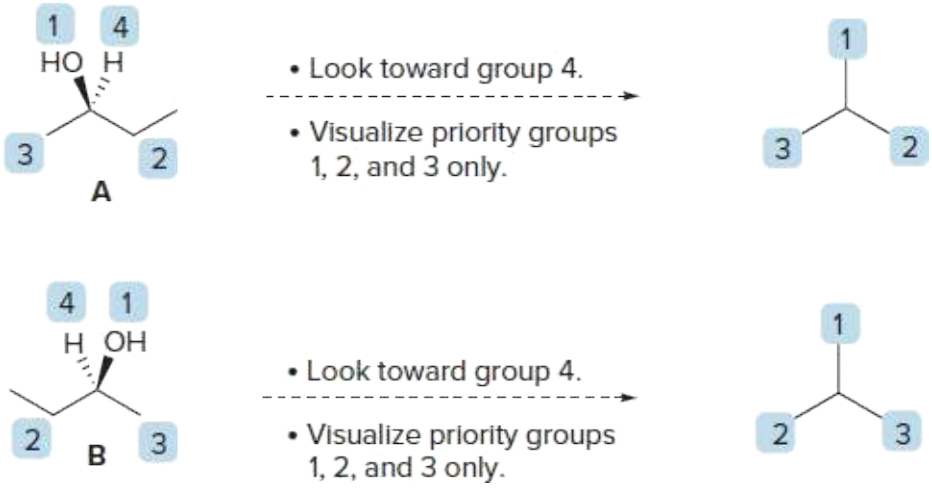
- **The priorities for the four groups around the stereogenic center in butan-2-ol were given in Rule 2, on page 192.**



Step [2] Orient the molecule with the lowest-priority group (4) *back* (on a *dashed wedge*), and visualize the relative positions of the remaining three groups (priorities 1, 2, and 3).

- **For each enantiomer of butan-2-ol, look toward the lowest-**

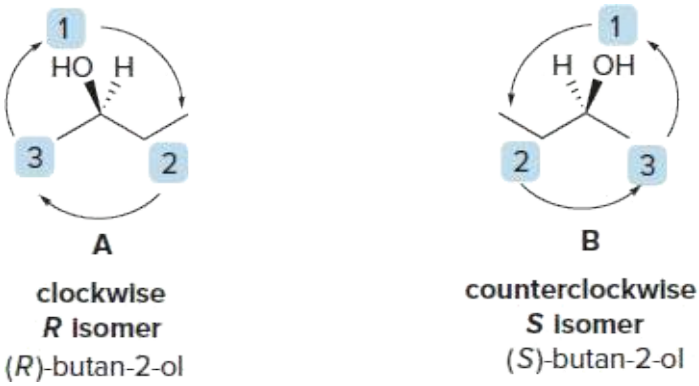
priority group, drawn behind the plane, down the C–H bond.



Step [3] Trace a circle from priority group 1 → 2 → 3.

- **If tracing the circle goes in the clockwise direction—to the right from the noon position—the isomer is named *R*.**
- **If tracing the circle goes in the counterclockwise direction—to the left from the noon position—the isomer is named *S*.**
- **The letter *R* or S precedes the IUPAC name of the molecule.**

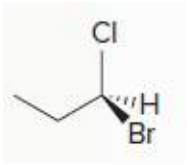
For the enantiomers of butan-2-ol:



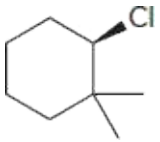
Sample Problem 5.3 Labeling a Stereogenic Center as *R* or *S*

Label the stereogenic center in each compound as *R* or *S*.

a.



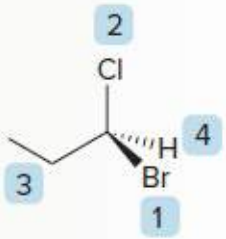
b.



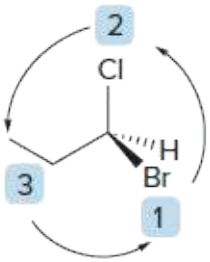
Solution

a.

Assign priorities...



...then look toward the lowest-priority group (H), and trace a circle, 1 → 2 → 3.

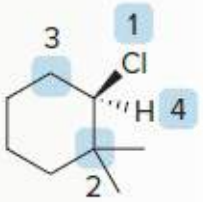


counterclockwise

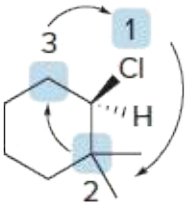
Answer: ***S*** isomer

b.

Assign priorities...



...then look toward the lowest-priority group (H), and trace a circle, 1 → 2 → 3.



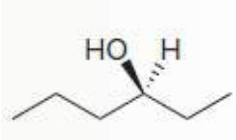
clockwise

Answer: ***R*** isomer

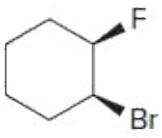
Problem 5.15

Label each stereogenic center in the following compounds as *R* or *S*.

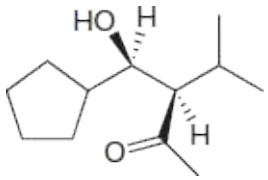
a.



b.



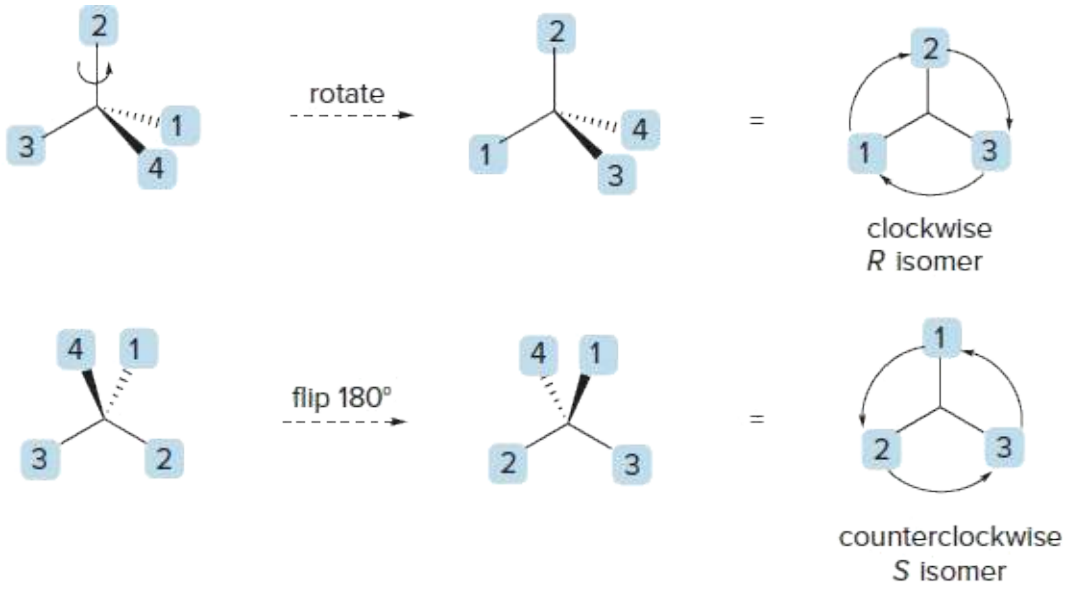
c.



More Practice:

Try Problem 5.50a, e.

How do you assign *R* or *S* to a molecule when the lowest-priority group is not oriented toward the back, on a dashed wedge? You could rotate and flip the molecule until the lowest-priority group is in the back, as shown in Figure 5.7; then follow the stepwise procedure for assigning the configuration. Or, if manipulating and visualizing molecules in three dimensions is difficult for you, try the procedure suggested in Sample Problem 5.4.



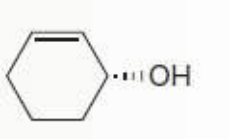
- In rotating a molecule about a single bond, the position of three groups changes.
- In flipping a molecule 180°, the position of all four groups changes.

Figure 5.7 **Orienting the lowest-priority group in back**

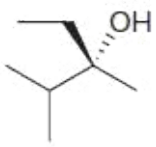
Sample Problem 5.4 Designating a Stereogenic Center as *R* or *S* When he Lowest-Priority Group Is Not Drawn Back

Label each stereogenic center as *R* or *S*.

a.



b.

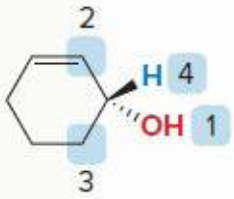


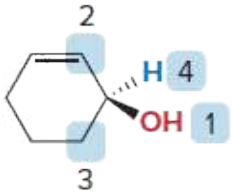
Solution

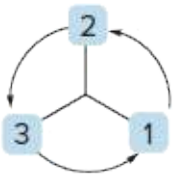
In both parts, the lowest-priority group is not oriented behind the page. To assign *R* or *S* in this case:

- **Switch the position of the lowest-priority group with the group located *behind* the page.**
- **Determine *R* or *S* in the usual manner.**
- **Reverse the answer. Because we switched the position of two groups on the stereogenic center to begin with, and there are only two possibilities, the answer is opposite to the correct answer.**

a. [1] Assign priorities. [2] Switch groups 4 and 1. [3] Trace a circle, 1 → 2 → 3, and reverse the answer.



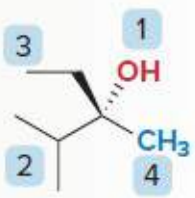


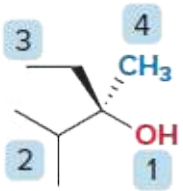


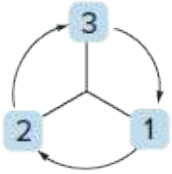
counterclockwise
It looks like an *S* isomer, but we must reverse the answer, because we switched groups 1 and 4, *S* → *R*.

Answer: ***R*** isomer

b. [1] Assign priorities. [2] Switch groups 4 and 1. [3] Trace a circle, 1 → 2 → 3, and reverse the answer.







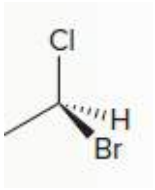
clockwise
It looks like an *R* isomer, but we must reverse the answer, because we switched groups 1 and 4, *R* → *S*.

Answer: ***S*** isomer

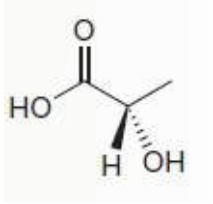
Problem 5.16

Label each stereogenic center as *R* or *S*.

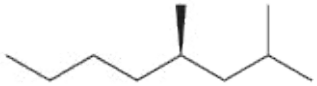
a.



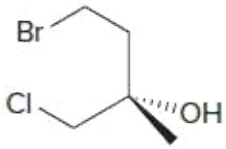
b.



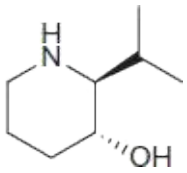
c.



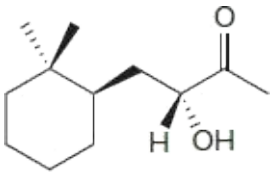
d.



e.



f.

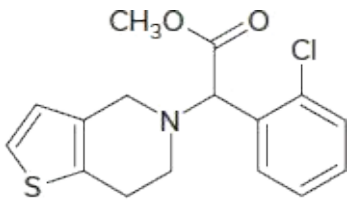


More Practice:

Try Problems 5.39b, 5.50, 5.51, 5.69a, 5.71a.

Problem 5.17

Draw both enantiomers of clopidogrel (trade name Plavix), a drug given to prevent the formation of blood clots in persons who have a history of stroke or coronary artery disease. Plavix is sold as a single enantiomer with the S configuration. Which enantiomer is Plavix?



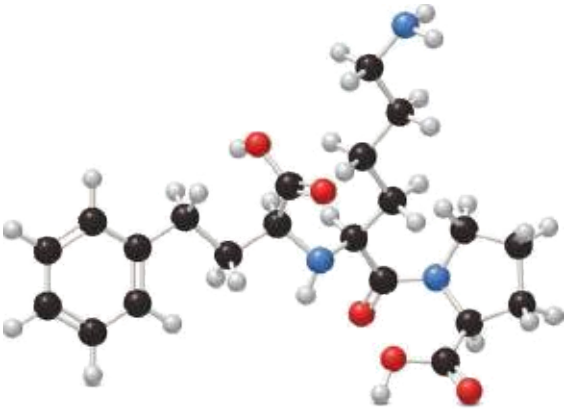
clopidogrel

Lisinopril (trade name Zestril) is an ACE inhibitor, a drug that lowers blood pressure by decreasing the amount of angiotensin in the blood. Angiotensin is a polyamide that narrows blood vessels, thus increasing blood pressure.

©alon harel/Alamy Stock Photo

Problem 5.18

(a) Locate the stereogenic centers in the ball-and-stick model of lisinopril, a drug used to treat high blood pressure. (b) Label each stereogenic center as *R* or *S*.



lisinopril

5.7 Diastereomers

We have now seen many examples of compounds containing one tetrahedral stereogenic center. The situation is more complex for compounds with two stereogenic centers, because more stereoisomers are possible. Moreover, a molecule with two or more stereogenic centers *may* or *may not* be chiral.

- **For *n* stereogenic centers, the maximum number of stereoisomers is 2^n.**

- When $n = 1$, $2^1 = 2$. With one stereogenic center, there are always two stereoisomers and they are enantiomers.
- When $n = 2$, $2^1 = 4$. With two stereogenic centers, the maximum number of

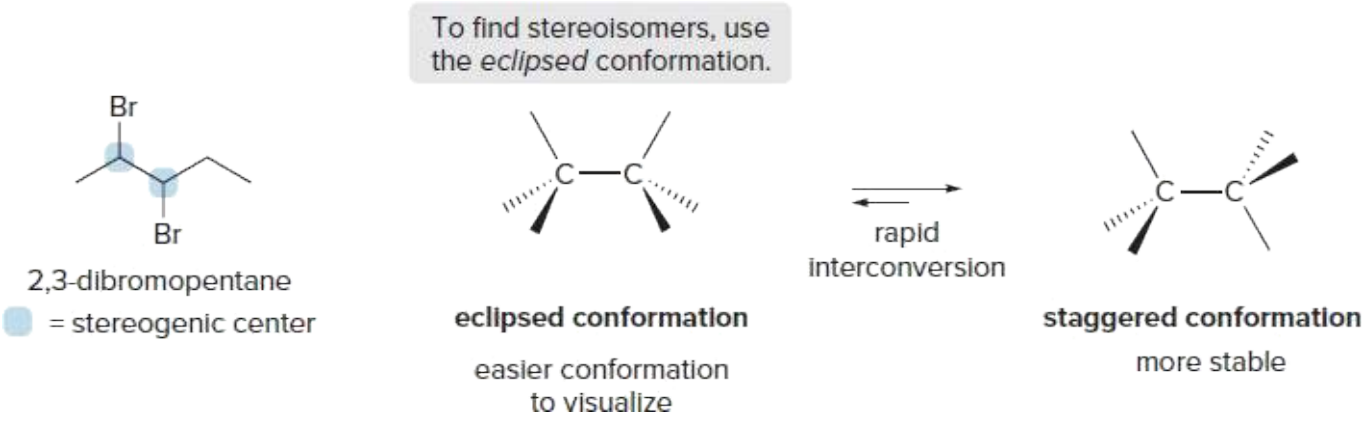
stereoisomers is four, although sometimes there are *fewer* than four.

In testing to see if one compound is superimposable on another, rotate atoms and flip the entire molecule, but do not break any bonds.

Problem 5.19

What is the maximum number of stereoisomers possible for a compound with: (a) three stereogenic centers; (b) eight stereogenic centers?

Let's illustrate a stepwise procedure for finding all possible stereoisomers using 2,3-dibromopentane. Because 2,3-dibromopentane has two stereogenic centers, the maximum number of stereoisomers is four.



How To Find and Draw All Possible Stereoisomers for a Compound with Two Stereogenic Centers

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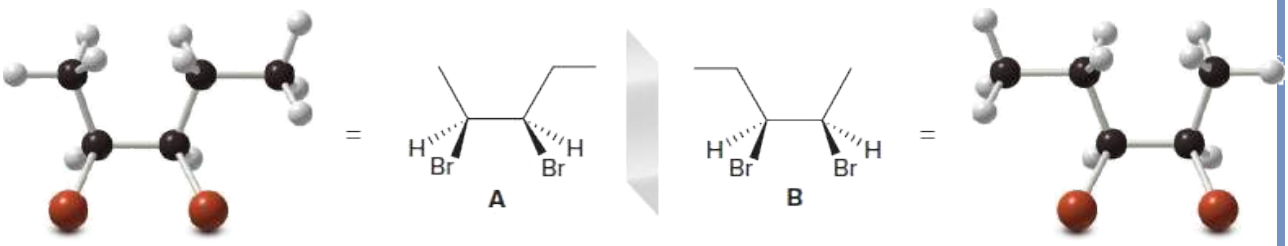
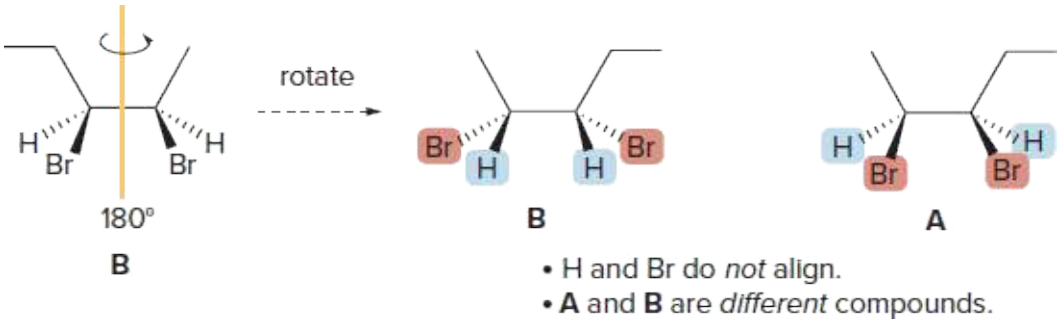
Step [1] Draw one stereoisomer by arbitrarily arranging substituents around the stereogenic centers. Then draw its mirror image.



- **Arbitrarily add the H, Br, CH_3, and CH_2CH_3 groups to the stereogenic centers, forming A. Then draw the mirror image B so that substituents in B are a reflection of the substituents in A.**
- **Determine whether A and B are superimposable by flipping or rotating one molecule to see if all the atoms align.**

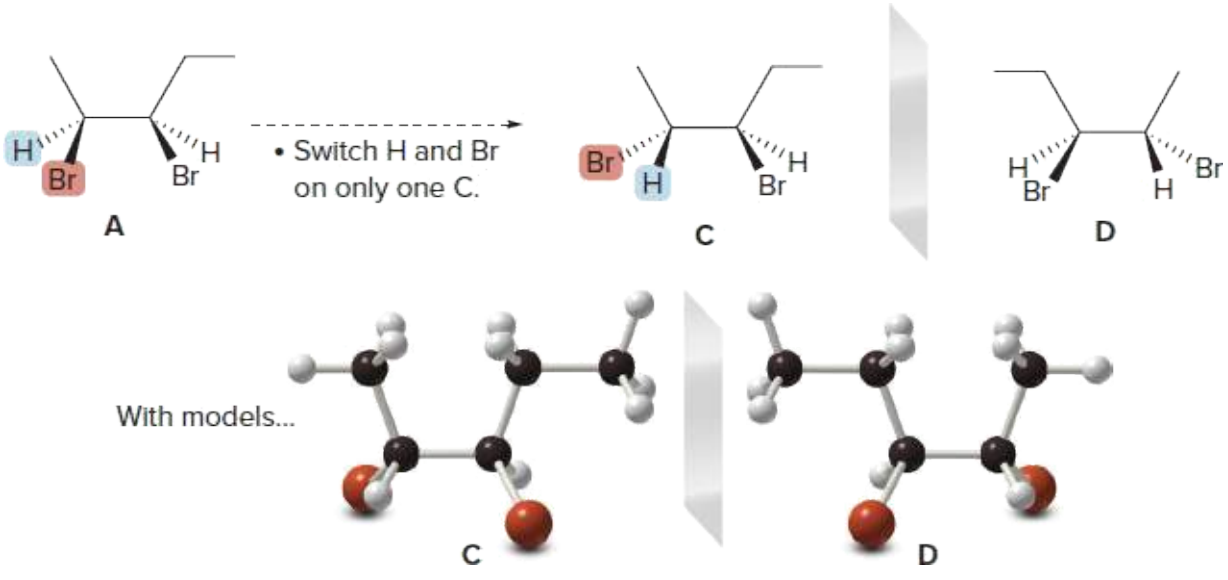
- **If you have drawn the compound and the mirror image in the described manner, you only have to do two operations to see if the atoms align. Place B directly on top of A (either in your mind or use models); and rotate B 180° and place it on top of A to see if the atoms align.**



- **In this case, the atoms of A and B do not align, making A and B nonsuperimposable mirror images—enantiomers. A and B are two of the four possible stereoisomers for 2,3-dibromopentane.**

Step [2] **Draw a third possible stereoisomer by switching the positions of any two groups on only *one* stereogenic center. Then draw its mirror image.**

- **Switching the positions of H and Br (or any two groups) on one stereogenic center of either A or B forms a new stereoisomer (labeled C in this example), which is different from both A and B. Then draw the mirror image of C, labeled D. C and D are nonsuperimposable mirror images—enantiomers. We have now drawn four stereoisomers for 2,3-dibromopentane, the maximum number possible.**



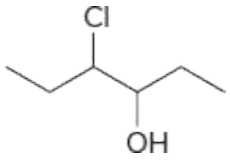
There are only two types of stereoisomers: *Enantiomers* are stereoisomers that *are* mirror images. *Diastereomers* are stereoisomers that are *not* mirror images.

There are four stereoisomers for 2,3-dibromopentane: enantiomers A and B, and enantiomers C and D. What is the relationship between two stereoisomers like A and C? A and C represent the second class of stereoisomers, called diastereomers. *Diastereomers* are stereoisomers that are *not* mirror images of each other. A and B are diastereomers of C and D, and vice versa. Figure 5.8 summarizes the relationships between the stereoisomers of 2,3-dibromopentane.

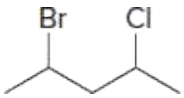
Problem 5.20

Label the two stereogenic centers in each compound and draw all possible stereoisomers.

a.

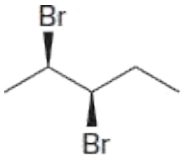


b.

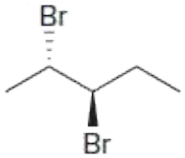


Problem 5.21

Compounds E and F are two isomers of 2,3-dibromopentane drawn in staggered conformations. Which compounds (A–D) in Figure 5.8 are identical to E and F?



E



F

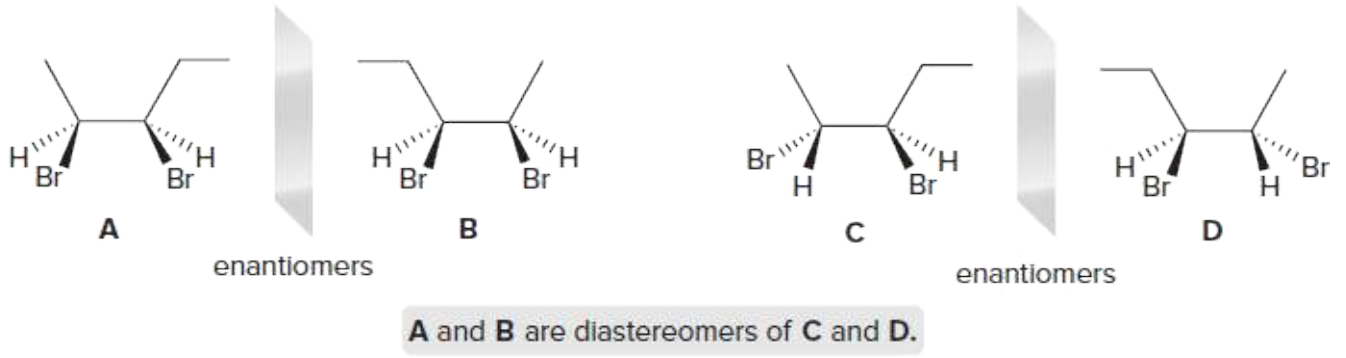
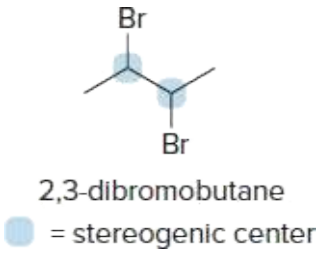


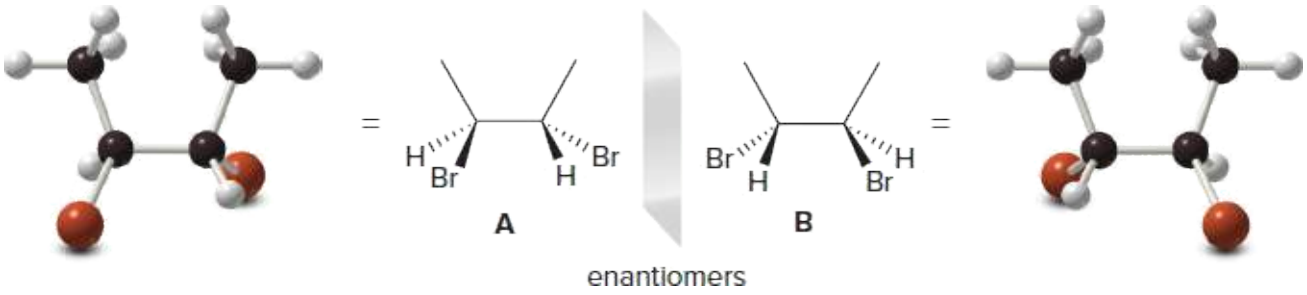
Figure 5.8 **The four stereoisomers of 2,3-dibromopentane**

5.8 Meso Compounds

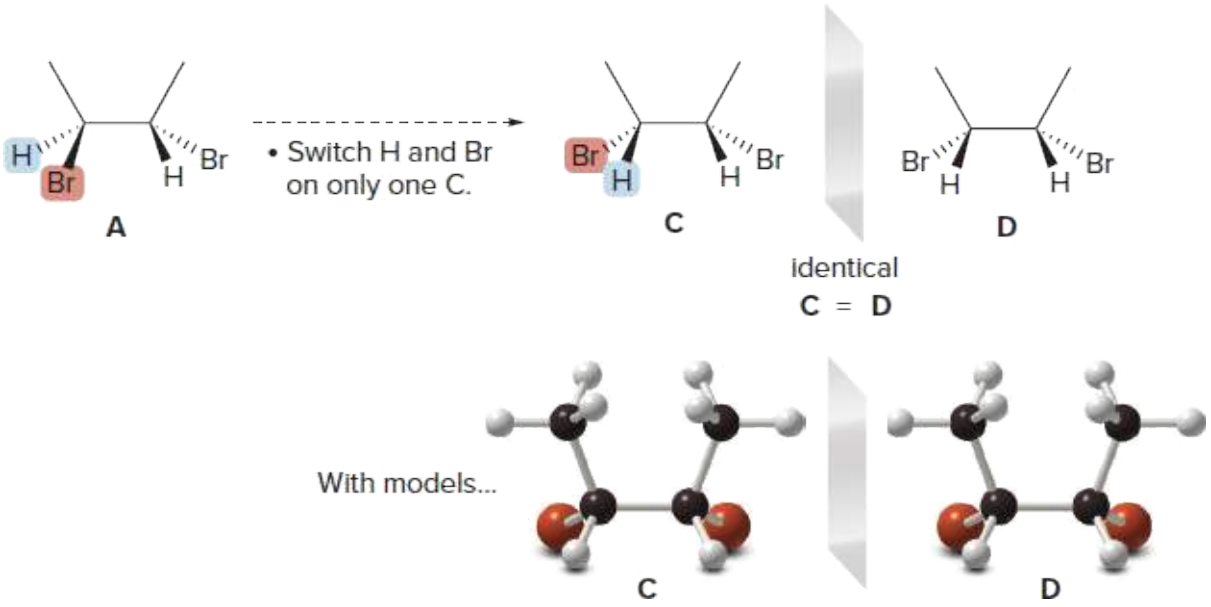
Whereas 2,3-dibromopentane has two stereogenic centers and the maximum of four stereoisomers, 2,3-dibromobutane has two stereogenic centers but fewer than the maximum number of stereoisomers.



To find and draw all the stereoisomers of 2,3-dibromobutane, follow the same stepwise procedure outlined in Section 5.7. Arbitrarily add the H, Br, and CH_3 groups to the stereogenic centers, forming one stereoisomer A, and then draw its mirror image B. A and B are nonsuper-imposable mirror images—enantiomers.



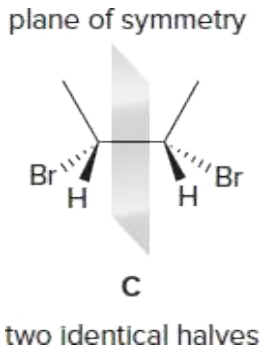
To find the other two stereoisomers (if they exist), switch the position of two groups on *one* stereogenic center of only *one* enantiomer. In this case, switching the positions of H and Br on one stereogenic center of A forms C, which is different from both A and B and is thus a new stereoisomer.



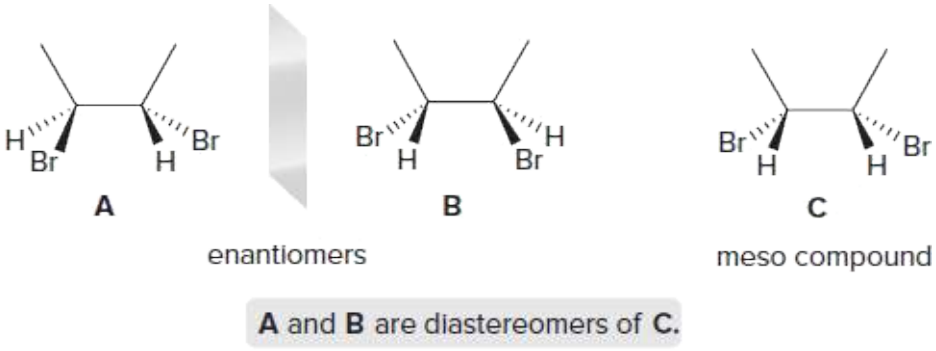
However, the mirror image of C, labeled D, is superimposable on C, so C and D are *identical*. Thus, C is achiral, even though it has two stereogenic centers. C is a meso compound.

- **A *meso compound* is an achiral compound that contains tetrahedral stereogenic centers.**

C contains a plane of symmetry. Meso compounds generally have a plane of symmetry, so they possess two identical halves.



Because one stereoisomer of 2,3-dibromobutane is superimposable on its mirror image, there are only three stereoisomers and not four, as summarized in Figure 5.9.



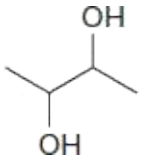
- Pair of enantiomers: **A** and **B**.
- Pairs of diastereomers: **A** and **C**; **B** and **C**.

Figure 5.9 **The three stereoisomers of 2,3-dibromobutane**

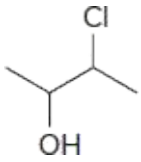
Problem 5.22

Draw all the possible stereoisomers for each compound, and label pairs of enantiomers and diastereomers.

a.



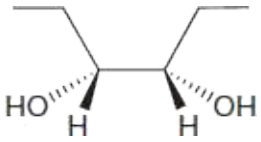
b.



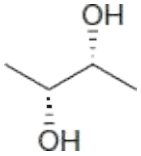
Problem 5.23

Which compounds are meso compounds?

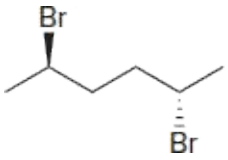
a.



b.



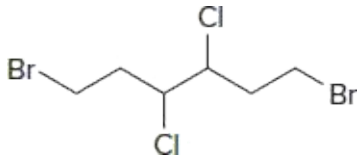
c.



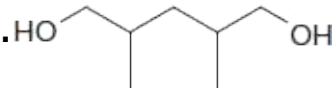
Problem 5.24

Draw a meso compound for each of the following molecules.

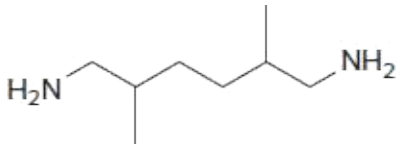
a.



b.

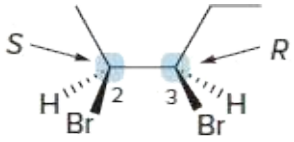


c.



5.9 *R* and *S* Assignments in Compounds with Two or More Stereogenic Centers

When a compound has more than one stereogenic center, the *R* or *S* configuration must be assigned to each of them. In the stereoisomer of 2,3-dibromopentane drawn here, C2 has the *S* configuration and C3 has the *R*, so the complete name of the compound is (2*S*,3*R*)-2,3-dibromopentane.



(2*S*,3*R*)-2,3-dibromopentane

R,*S* configurations can be used to determine whether two compounds are identical, enantiomers, or diastereomers.

Sorbitol (Problem 5.27) occurs naturally in some berries and fruits. It is used as a substitute sweetener in sugar-free—that is, sucrose-free—candy and gum.

©McGraw-Hill Education/Jill Braaten, photographer

- **Identical compounds have the *same* *R*,*S* designations at every tetrahedral stereogenic center.**

- **Enantiomers have exactly *opposite R,S* designations.**
- **Diastereomers have the *same R,S* designation for at least one stereogenic center and the *opposite* for at least one of the other stereogenic centers.**

For example, if a compound has two stereogenic centers, both with the *R* configuration, then its enantiomer is *S,S* and the diastereomers are either *R,S* or *S,R*.

Problem 5.25

If the two stereogenic centers of a compound are *R,S* in configuration, what are the *R,S* assignments for its enantiomer and two diastereomers?

Problem 5.26

Without drawing out the structures, label each pair of compounds as enantiomers or diastereomers.

a. (2*R*,3*S*)-hexane-2,3-diol and (2*R*,3*R*)-hexane-2,3-diol

b. (2*R*,3*R*)-hexane-2,3-diol and (2*S*,3*S*)-hexane-2,3-diol

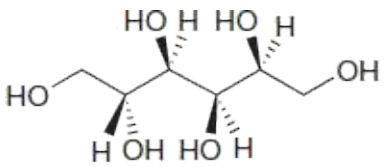
c. (2*R*,3*S*,4*R*)-hexane-2,3,4-triol and (2*S*,3*R*,4*R*)-hexane-2,3,4-triol

Problem 5.27

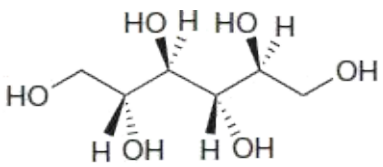
(a) Label the four stereogenic centers in sorbitol as *R* or S.

(b) How are sorbitol and A related?

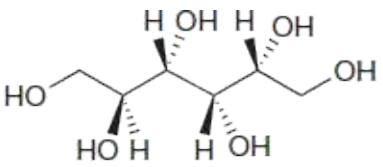
(c) How are sorbitol and B related?



sorbitol



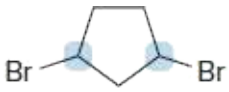
A



B

5.10 Disubstituted Cycloalkanes

Let us now turn our attention to disubstituted cycloalkanes, and draw all possible stereoisomers for 1,3-dibromocyclopentane. Because 1,3-dibromocyclopentane has two stereogenic centers (labeled in blue), it has a maximum of four stereoisomers.



1,3-dibromocyclopentane

To draw all possible stereoisomers, remember that a disubstituted cycloalkane can have two substituents on the *same* side of the ring (cis isomer, labeled A) or on *opposite* sides of the ring (trans isomer, labeled B). These compounds are stereoisomers but not mirror images of each other, making them diastereomers. A and B are two of the four possible stereoisomers.

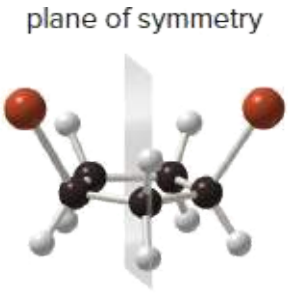
A
cis isomer

B
trans isomer

A and **B** are diastereomers.

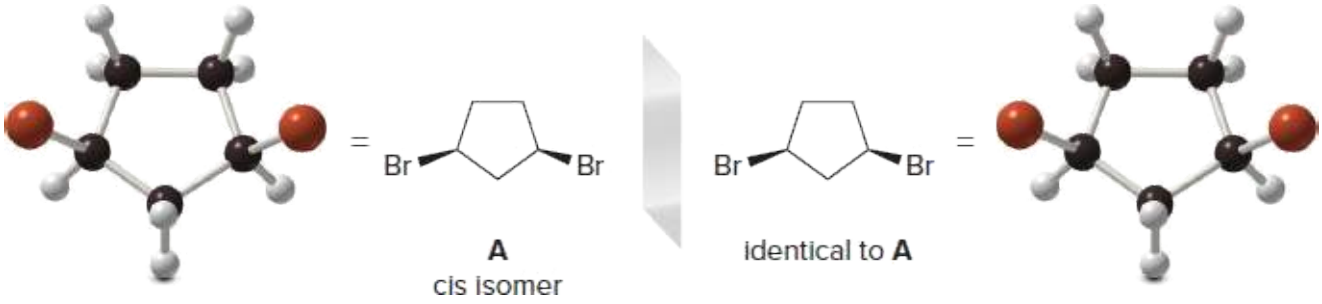
In determining chirality in substituted cycloalkanes, always draw the rings as flat polygons. This is especially true for cyclohexane derivatives, where having two chair forms that interconvert can make analysis especially difficult.

***cis*-1,3-Dibromocyclopentane contains a plane of symmetry.**

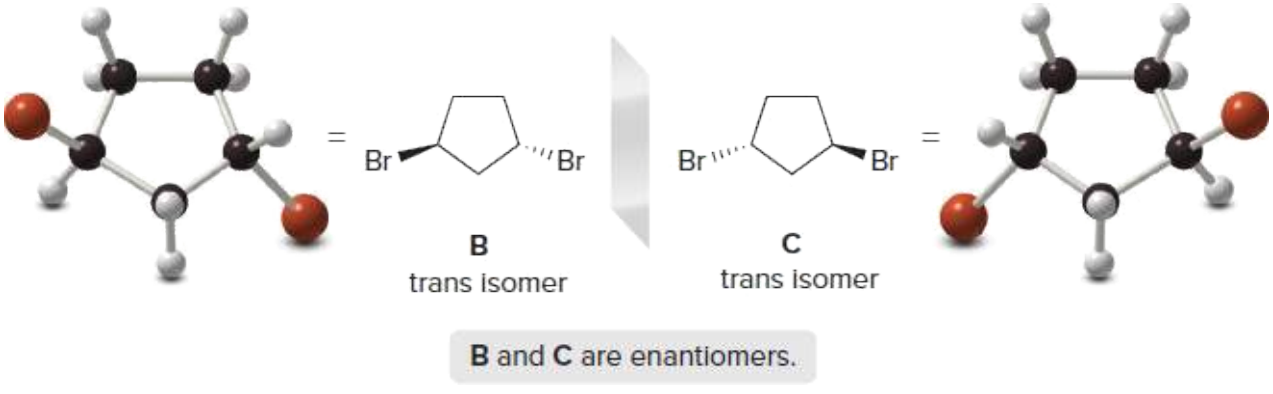


two identical halves

To find the other two stereoisomers (if they exist), draw the mirror image of each compound and determine whether the compound and its mirror image are superimposable.



- The cis isomer is superimposable on its mirror image, making them *identical*. Thus, A is an achiral meso compound.



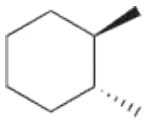
- The trans isomer B is *not* superimposable on its mirror image, labeled C, making B and C different compounds. Thus, B and C are enantiomers.

Because one stereoisomer of 1,3-dibromocyclopentane is superimposable on its mirror image, there are only three stereoisomers, not four. A is an achiral meso compound, and B and C are a pair of chiral enantiomers. A and B are diastereomers, as are A and C.

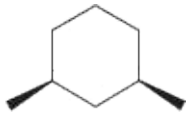
Problem 5.28

Which of the following cyclic molecules are meso compounds?

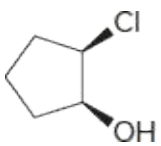
a.



b.



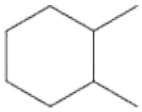
c.

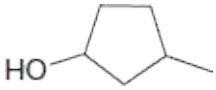


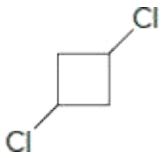
Problem 5.29

Draw all possible stereoisomers for each compound. Label pairs of enantiomers and

diastereomers.

a. 

b. 

c. 

5.11 Isomers—A Summary

Before moving on to other aspects of stereochemistry, take the time to review Figures 5.10 and 5.11. Keep in mind the following facts, and use Figure 5.10 to summarize the types of isomers.

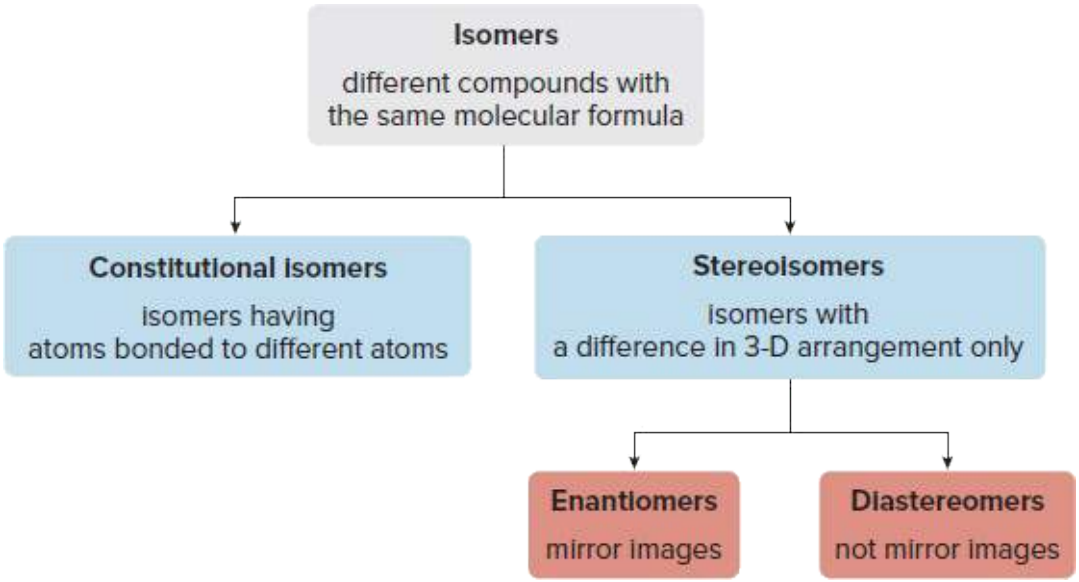


Figure 5.10 **Summary—Types of isomers**

- **There are two major classes of isomers: constitutional isomers and stereoisomers.**
- **There are only two kinds of stereoisomers: enantiomers and diastereomers.**

Then, to determine the relationship between two nonidentical molecules, refer to the flowchart in Figure 5.11.

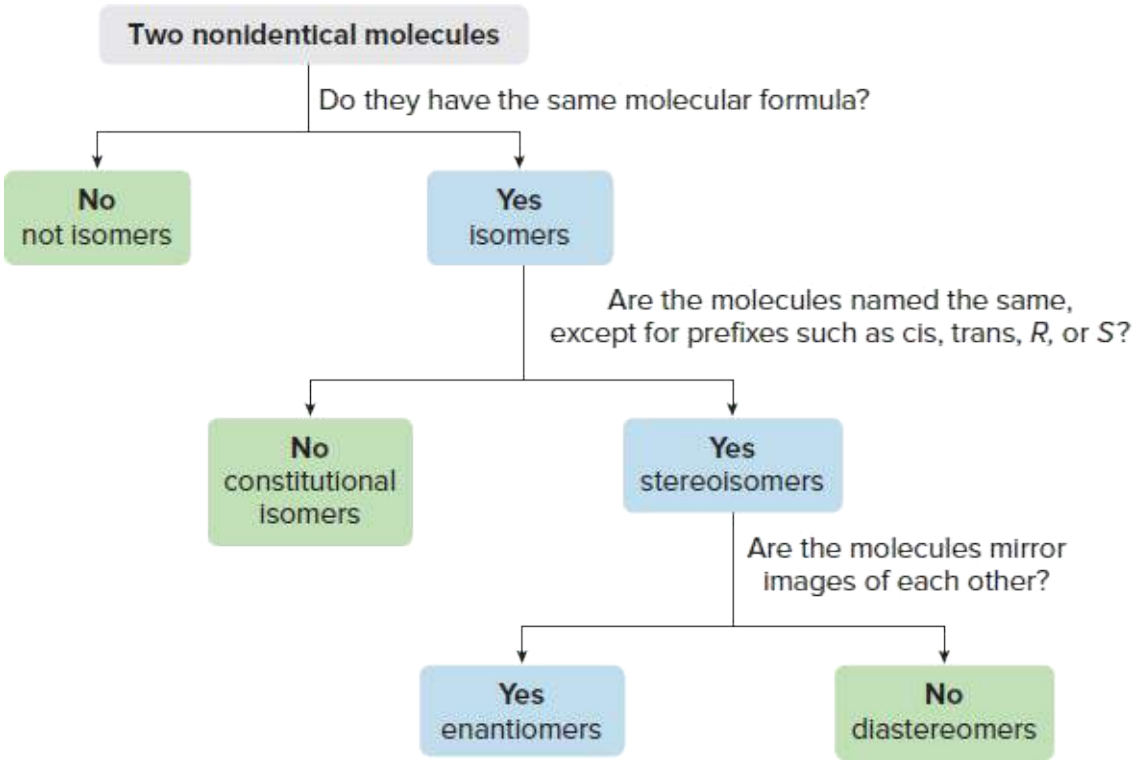
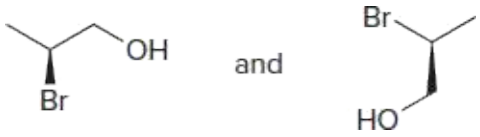
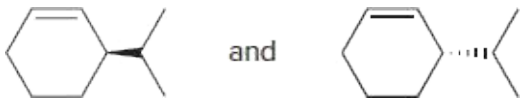


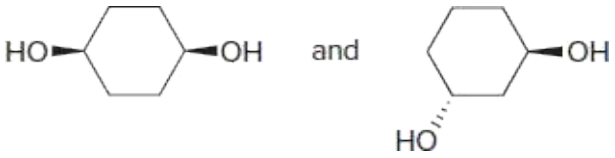
Figure 5.11 **Determining the relationship between two nonidentical molecules**

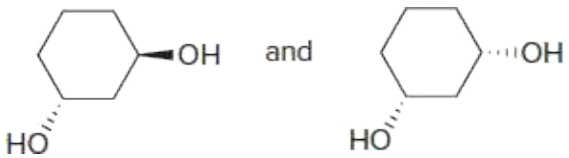
Problem 5.30

State how each pair of compounds is related. Are they enantiomers, diastereomers, constitutional isomers, or identical?

a. 

b. 

c. 

d. 

5.12 Physical Properties of Stereoisomers

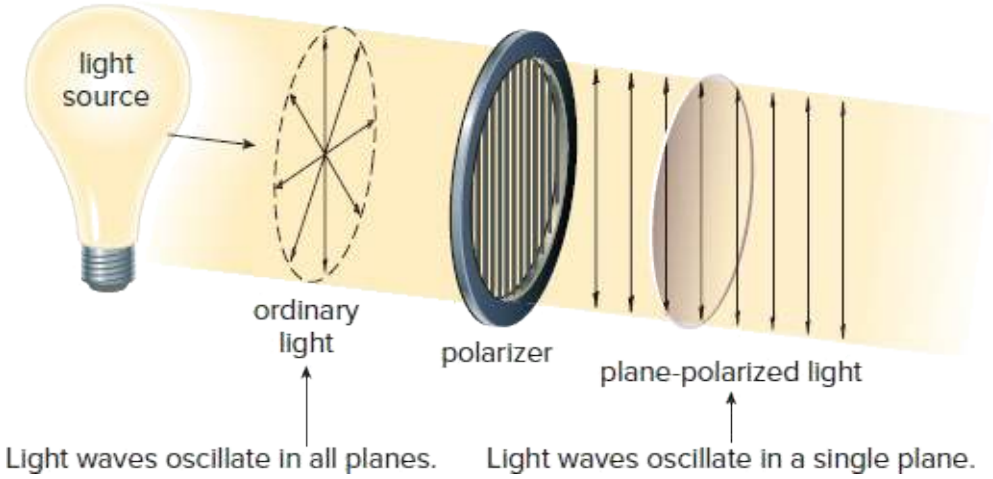
Recall from Section 5.2 that constitutional isomers have different physical and chemical properties. How, then, do the physical and chemical properties of enantiomers compare?

- **The chemical and physical properties of two enantiomers are *identical* except in their interaction with *chiral* substances.**

5.12A Optical Activity

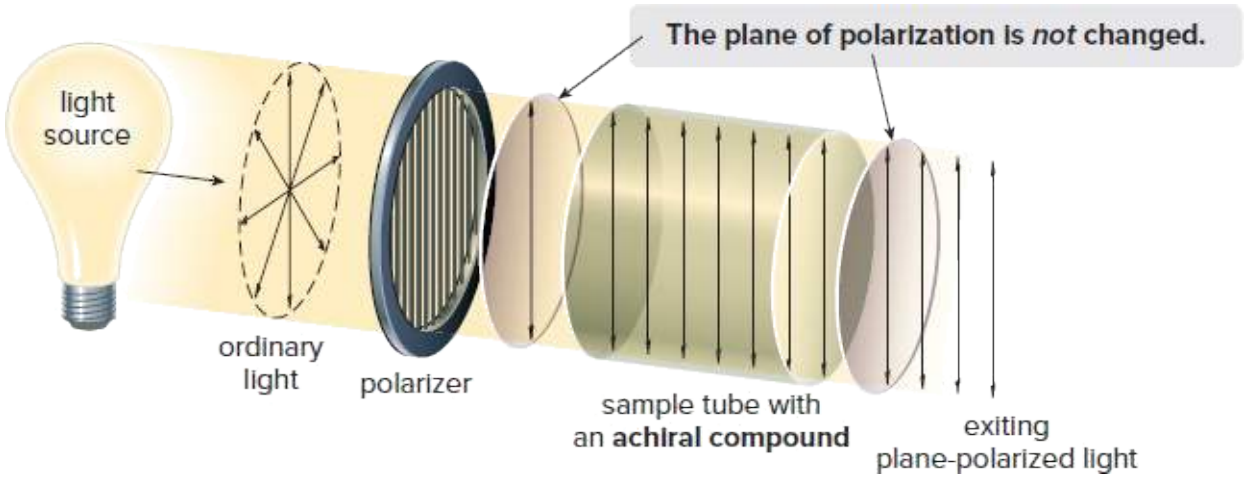
Two enantiomers have identical physical properties—melting point, boiling point, solubility—except for how they interact with plane-polarized light.

What is plane-polarized light? Ordinary light consists of electromagnetic waves that oscillate in all planes perpendicular to the direction in which the light travels. Passing light through a polarizer allows light in only one plane to come through, resulting in plane-polarized light (or simply polarized light). Plane-polarized light has an electric vector that oscillates in a single plane.



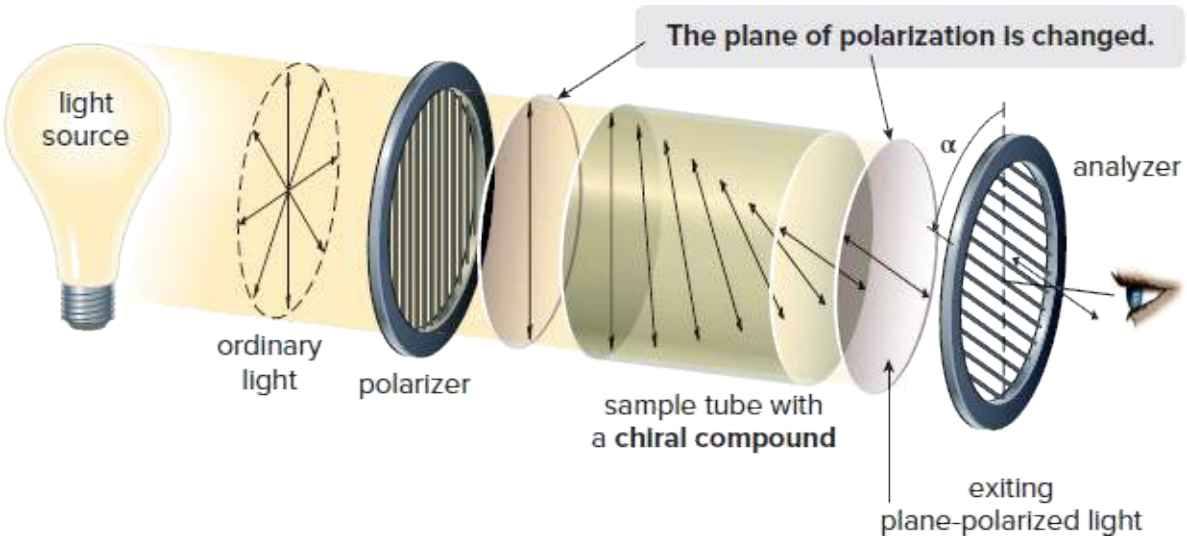
A polarimeter is an instrument that allows plane-polarized light to travel through a sample tube containing an organic compound. After the light exits the sample tube, an analyzer slit is rotated to determine the direction of the plane of the exiting polarized light. With achiral compounds, the light exits the sample tube *unchanged*, and the plane of the polarized light is in the same position it was before entering the sample tube.

- **A compound that does not change the plane of polarized light is said to be *optically inactive*.**



With chiral compounds, the plane of the polarized light is rotated through an angle α. The angle α, measured in degrees (°), is called the observed rotation.

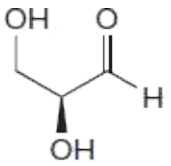
- **A compound that rotates the plane of polarized light is said to be *optically active*.**



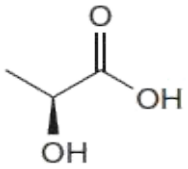
The achiral compound CH_2BrCl is optically *inactive*, whereas a single enantiomer of CHBrClF, a chiral compound, is optically *active*.

The rotation of polarized light can be in the clockwise or counterclockwise direction.

- **If the rotation is *clockwise* (to the right from the noon position), the compound is called *dextrorotatory*. The rotation is labeled *d* or (+).**
- **If the rotation is *counterclockwise* (to the left from noon), the compound is called *levorotatory*. The rotation is labeled *l* or (−).**



(*S*)-(–)-glyceraldehyde



(*S*)-(+)-lactic acid

No relationship exists between the *R* and *S* prefixes that designate configuration and the (+) and (–) designations indicating optical rotation. For example, the *S* enantiomer of lactic acid is dextrorotatory (+), whereas the *S* enantiomer of glyceraldehyde is levorotatory (–).

How does the rotation of two enantiomers compare?

- **Two enantiomers rotate plane-polarized light *to an equal extent* but in the *opposite* direction.**

Thus, if enantiomer A rotates polarized light +5°, then the same concentration of enantiomer B rotates it –5°.

5.12B Racemic Mixtures

What is the observed rotation of an equal amount of two enantiomers? Because two enantiomers rotate plane-polarized light to an equal extent but in opposite directions, the rotations cancel, and no rotation is observed.

- **An equal amount of two enantiomers is called a *racemic mixture* or a *racemate.* A racemic mixture is optically *inactive.***

Besides optical rotation, other physical properties of a racemate are not readily predicted. The melting point and boiling point of a racemic mixture are not necessarily the same as either pure enantiomer, and this fact is not easily explained. The physical properties of two enantiomers and their racemic mixture are summarized in Table 5.1.

Table 5.1 The Physical Properties of Enantiomers A and B Compared

Property	A alone	B alone	Racemic A + B

Melting point	**identical to B**	**identical to A**	**may be different from A and B**
Boiling point	**identical to B**	**identical to A**	**may be different from A and B**
Optical rotation	**equal in magnitude but opposite in sign to B**	**equal in magnitude but opposite in sign to A**	**0°**

5.12C Specific Rotation

The observed rotation depends on the number of chiral molecules that interact with polarized light. This in turn depends on the concentration of the sample and the length of the sample tube. To standardize optical rotation data, the quantity specific rotation ([α]) is defined using a specific sample tube length (usually 1 dm), concentration, temperature (25 °C), and wavelength (589 nm, the D line emitted by a sodium lamp).

$$\text{specific rotation} = [\alpha] = \frac{\alpha}{l \times c}$$

α = observed rotation (°)
l = length of sample tube (dm)
c = concentration (g/mL)

[dm = decimeter
1 dm = 10 cm]

Specific rotations are physical constants just like melting points or boiling points, and are reported in chemical reference books for a wide variety of compounds.

Problem 5.31

The amino acid (*S*)-alanine has the physical characteristics listed under the structure.

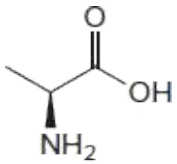
a. What is the melting point of (*R*)-alanine?

b. How does the melting point of a racemic mixture of (*R*)- and (*S*)-alanine compare to the melting point of (*S*)-alanine?

c. What is the specific rotation of (*R*)-alanine, recorded under the same conditions as the reported rotation of (*S*)-alanine?

d. What is the optical rotation of a racemic mixture of (*R*)- and (*S*)-alanine?

e. Label each of the following as optically active or inactive: a solution of pure (S)-alanine; an equal mixture of (*R*)- and (*S*)-alanine; a solution that contains 75% (*S*)- and 25% (*R*)-alanine.



(*S*)-alanine
[α] = +8.5
mp = 297 °C

Problem 5.32

A natural product was isolated in the laboratory, and its observed rotation was +10° when measured in a 1 dm sample tube containing 1.0 g of compound in 10 mL of water. What is the specific rotation of this compound?

5.12D Enantiomeric Excess

Sometimes in the laboratory we have neither a pure enantiomer nor a racemic mixture, but rather a mixture of two enantiomers in which one enantiomer is present in excess of the other. The enantiomeric excess (ee), also called the optical purity, tells how much more there is of one enantiomer.

- **Enantiomeric excess = *ee* = % of one enantiomer – % of the other enantiomer.**

Enantiomeric excess tells how much one enantiomer is present in excess of the racemic mixture. For example, if a mixture contains 75% of one enantiomer and 15% of the other, the enantiomeric excess is 75% – 25% = 50%. There is a 50% excess of one enantiomer over the racemic mixture.

Problem 5.33

What is the *ee* for each of the following mixtures of enantiomers A and B?

a. 95% A and 5% B

b. 85% A and 15% B

Knowing the *ee* of a mixture makes it possible to calculate the amount of each enantiomer present, as shown in Sample Problem 5.5.

Sample Problem 5.5 Using Enantiomeric Excess to Calculate the Amount of Each Enantiomer If the enantiomeric excess is 95%, how much of each

enantiomer is present?

Solution

Label the two enantiomers A and B and assume that A is in excess. A 95% *ee* means that the solution contains an excess of 95% of A, and 5% of the racemic mixture of A and B. Because a racemic mixture is an equal amount of both enantiomers, it has 2.5% of A and 2.5% of B.

- **Total amount of A = 95% + 2.5% = 97.5%**
- **Total amount of B = 2.5% (or 100% − 97.5%)**

Problem 5.34

For the given *ee* values, calculate the percentage of each enantiomer present.

a. 90% *ee*

b. 99% *ee*

c. 60% *ee*

More Practice:

Try Problem 5.68b.

The enantiomeric excess can also be calculated if two quantities are known—the specific rotation [α] of a mixture and the specific rotation [α] of a pure enantiomer.

$$ee = \frac{[\alpha] \text{ mixture}}{[\alpha] \text{ pure enantiomer}} \times 100\%$$

Sample Problem 5.6 Calculating Enantiomeric Excess

Pure cholesterol has a specific rotation of −32. A sample of cholesterol prepared in the lab had a specific rotation of −16. What is the enantiomeric excess of this sample of cholesterol?

Solution

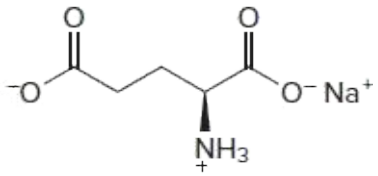
Calculate the *ee* of the mixture using the given formula.

$$ee = \frac{[\alpha] \text{ mixture}}{[\alpha] \text{ pure enantiomer}} \times 100\% = \frac{-16}{-32} \times 100\% = 50\% \; ee$$

Answer

Problem 5.35

Pure MSG, a common flavor enhancer, exhibits a specific rotation of +24. (a) Calculate the *ee* of a solution whose [α] is +10. (b) If the *ee* of a solution of MSG is 80%, what is [α] for this solution?



MSG
monosodium glutamate

More Practice:

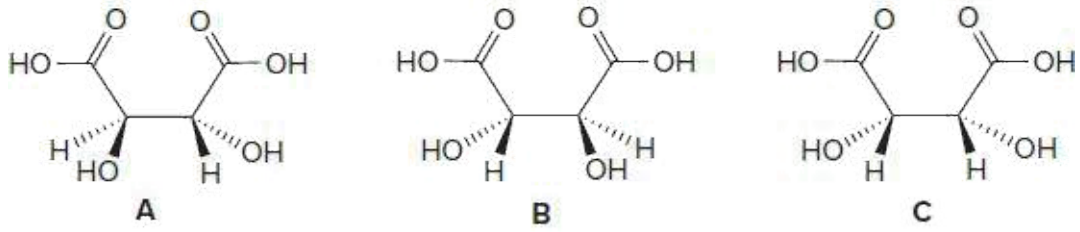
Try Problems 5.68a, d; 5.70f.

Problem 5.36

(*S*)-Lactic acid has a specific rotation of +3.8. (a) If the *ee* of a solution of lactic acid is 60%, what is [α] for this solution? (b) How much of the dextrorotatory and levorotatory isomers does the solution contain?

5.12E The Physical Properties of Diastereomers

Diastereomers are not mirror images of each other, and as such, their physical properties are different, including optical rotation. Figure 5.12 compares the physical properties of the three stereoisomers of tartaric acid, consisting of a meso compound that is a diastereomer of a pair of enantiomers.



- **A** and **B** are enantiomers.
- **A** and **B** are diastereomers of **C**.

Property	A	B	C	A + B (1:1)
melting point (°C)	171	171	146	206
solubility (g/100 mL H_2O)	139	139	125	139
[α]	+13	−13	0	0
R,S designation	*R,R*	*S,S*	*R,S*	—
d,l designation	*d*	*l*	none	*d,l*

- The physical properties of **A** and **B** differ from their diastereomer **C**.
- The physical properties of a racemic mixture of **A** and **B** (last column) can also differ from either enantiomer and diastereomer **C**.
- **C** is an achiral meso compound, so it is optically inactive; [α] = 0.

Figure 5.12 **The physical properties of the three stereoisomers of tartaric acid**

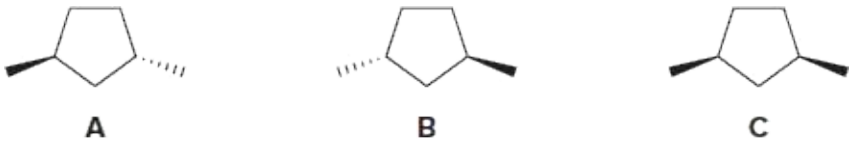
Whether the physical properties of a set of compounds are the same or different has practical applications in the lab. Physical properties characterize a compound's physical state, and two compounds can usually be separated only if their physical properties are different.

Two enantiomers can be separated by the process of resolution, as described in Section 27.3.

- **Because two enantiomers have identical physical properties, they cannot be separated by common physical techniques like distillation.**
- **Diastereomers and constitutional isomers have different physical properties, and therefore they can be separated by common physical techniques.**

Problem 5.37

Compare the physical properties of the three stereoisomers of 1,3-dimethylcyclopentane.



three stereoisomers of 1,3-dimethylcyclopentane

a. How do the boiling points of A and B compare? What about those of A and C?

b. Characterize a solution of each of the following as optically active or optically inactive: pure A; pure B; pure C; an equal mixture of A and B; an equal mixture of A and C.

c. A reaction forms a 1:1:1 mixture of A, B, and C. If this mixture is distilled, how many fractions would be obtained? Which fractions would be optically active and which would be optically inactive?

5.13 Chemical Properties of Enantiomers

When two enantiomers react with an achiral reagent, they react at the same rate, but when they react with a chiral, non-racemic reagent, they react at different rates.

- **Two enantiomers have exactly the same chemical properties except for their reaction with chiral, non-racemic reagents.**

For an everyday analogy, consider what happens when you are handed an achiral object like a pen and a chiral object like a right-handed glove. Your left and right hands are enantiomers, but they can both hold the achiral pen in the same way. With the glove, however, only your right hand can fit inside it, not your left.

We will examine specific reactions of chiral molecules with both chiral and achiral reagents later in this text. Here, we examine two more general applications.

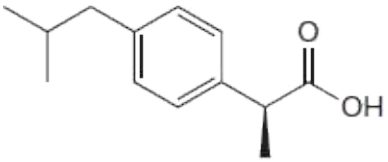
Although (*R*)-ibuprofen shows no anti-inflammatory activity itself, it is slowly converted to the *S* enantiomer in vivo.

5.13A Chiral Drugs

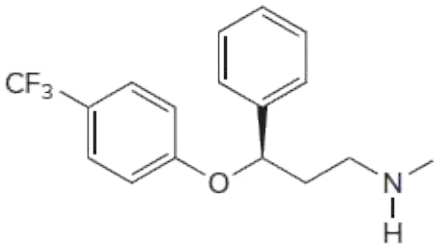
A living organism is a sea of chiral molecules. Many drugs are chiral, and often they must interact with a chiral receptor or a chiral enzyme to be effective. One enantiomer of a drug may treat a disease whereas its mirror image may be ineffective. Alternatively, one enantiomer may trigger one biochemical response and its mirror image may elicit a totally different response.

The drugs ibuprofen and fluoxetine each contain one stereogenic center, and thus exist

as a pair of enantiomers, only one of which exhibits biological activity. (*S*)-Ibuprofen is the active component of the anti-inflammatory agents Motrin and Advil, and (*R*)-fluoxetine is the active component in the antidepressant Prozac.



(*S*)-Ibuprofen
anti-inflammatory agent

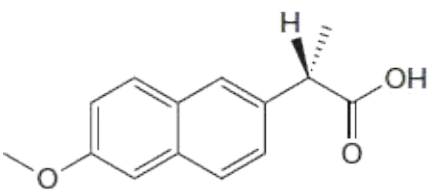


(*R*)-fluoxetine
antidepressant

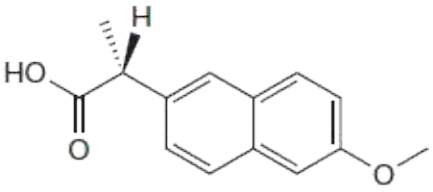
(*S*)-Naproxen is the active drug in the widely used pain relievers Naprosyn and Aleve.
©McGraw-Hill Education/Elite Images

For more examples of two enantiomers that exhibit very different biochemical properties, see *Journal of Chemical Education*, 1996, *73*, 481–484.

Changing the orientation of two substituents to form a mirror image can also alter biological activity to produce an undesirable side effect in the other enantiomer. The *S* enantiomer of naproxen is an active anti-inflammatory agent, but the *R* enantiomer is a harmful liver toxin.



(*S*)-naproxen
anti-inflammatory agent

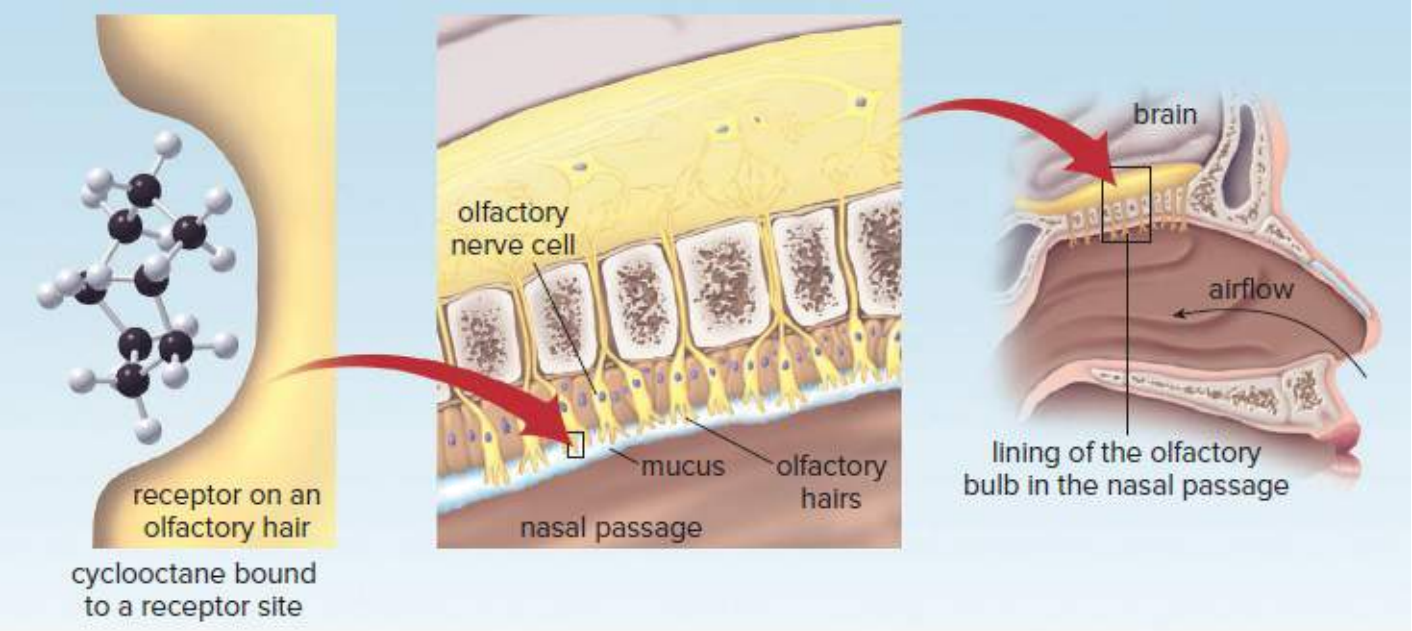


(*R*)-naproxen
liver toxin

If a chiral drug could be sold as a single active enantiomer, it should be possible to use smaller doses with fewer side effects. Many chiral drugs continue to be sold as racemic mixtures, however, because it is more difficult and therefore more costly to obtain a single enantiomer. An enantiomer is not easily separated from a racemic mixture because the two enantiomers have the same physical properties. In Chapter 12, we will study a reaction that can form a single active enantiomer, an important development in making chiral drugs more readily available.

5.13B Enantiomers and the Sense of Smell

Research suggests that the odor of a particular molecule is determined more by its shape than by the presence of a particular functional group. For example, hexachloroethane (Cl_3CCCl_3) and cyclooctane have no obvious structural similarities, but they both have a camphor-like odor, a fact attributed to their similar spherical shape. Each molecule binds to spherically shaped olfactory receptors present on the nerve endings in the nasal passage, resulting in similar odors (Figure 5.13).

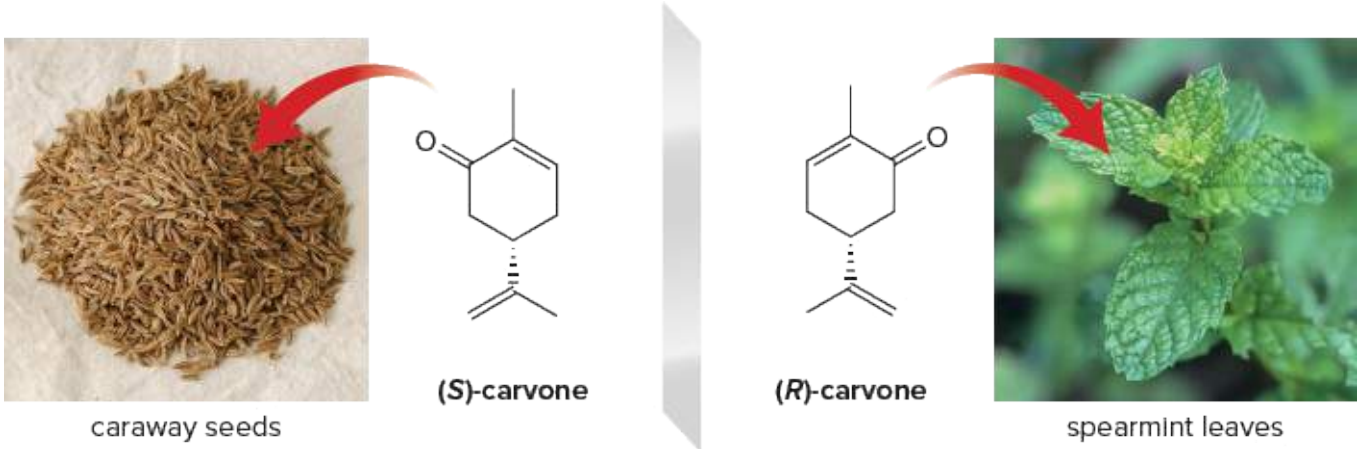


- Cyclooctane and other molecules similar in shape bind to a particular olfactory receptor on the nerve cells that lie at the top of the nasal passage. Binding results in a nerve impulse that travels to the brain, which interprets impulses from particular receptors as specific odors.

Figure 5.13 **The shape of molecules and the sense of smell**

Because enantiomers interact with chiral smell receptors, some enantiomers have different odors. There are a few well-characterized examples of this phenomenon in nature. For example, (*S*)-carvone is responsible for the odor of caraway, whereas (*R*)-carvone is responsible for the odor of spearmint.

(R)-Celery ketone (Problem 5.38) has an odor reminiscent of celery leaves. ***©Aaron Roeth Photography***

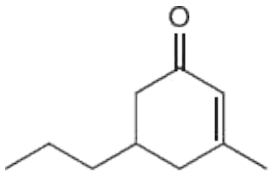


©McGraw-Hill Education/Elite Images
©DAJ/Getty Images

These examples demonstrate that understanding the three-dimensional structure of a molecule is very important in organic chemistry.

Problem 5.38

Like carvone, the two enantiomers of celery ketone smell different. The *R* enantiomer smells like celery leaves, whereas the S enantiomer smells like licorice. Draw each enantiomer and assign its odor.



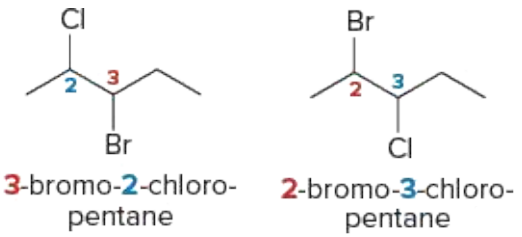
celery ketone

Chapter 5 REVIEW

KEY CONCEPTS

[1] Two types of isomers (5.2, 5.11); example: $C_5H_{10}BrCl$

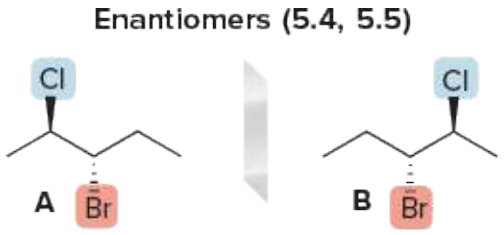
1 Constitutional isomers—same molecular formula, but different connectivity of atoms



- Constitutional isomers have different IUPAC names.

See Figure 5.3.

2 Stereoisomers—same molecular formula and connectivity of atoms but different spatial orientation of atoms



See Figure 5.5.

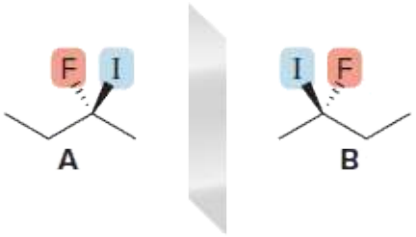
See Figures 5.8, 5.10, 5.11. Try Problems 5.40, 5.41, 5.43, 5.61–5.65, 5.67a.

[2] Stereochemical terms

1 Chiral compounds (5.3–5.5)

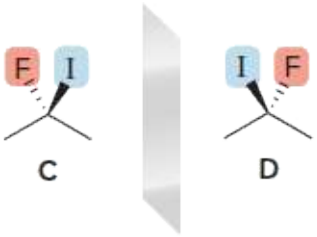
2 Achiral compound (5.3)

3 Me co (5.



nonsuperimposable mirror images
no plane of symmetry
tetrahedral stereogenic center

A and B are chiral.



superimposable mirror images
plane of symmetry
no tetrahedral stereogenic center

C and D are identical and achiral.

- An **achiral compound** is **superimposable on its mirror image.**

4 Ra mi (5.

Try Problems 5.42, 5.44, 5.67b.

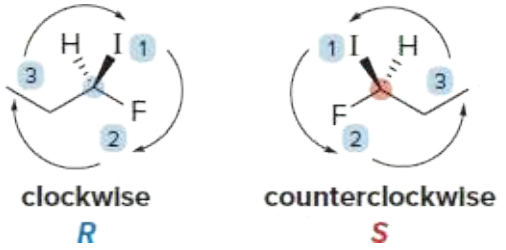
[3] Optical activity (5.12)

1 An optically active solution contains:	**2** An optically inactive solution contains one of the following:		
• a chiral compound	• an achiral compound with no stereogenic centers	• a meso compound	• a racemic mixture of two enantiomers

Try Problems 5.66, 5.67c, g.

[4] The prefixes *R* and S compared with *d* (+) and *l* (−) (5.6, 5.12)

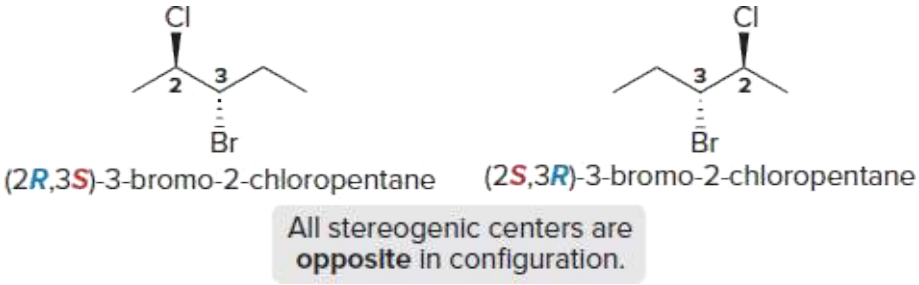
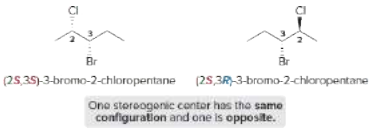
1 *R* and *S* prefixes	**2** *d* (+) and *l* (−) prefixes
• Groups on stereogenic centers are assigned priorities to determine the *R* or *S* prefix used in nomenclature.	• The prefixes *d* and *l* tell the direction a compound rotates plane-polarized light, which is determined experimentally. • *d* (+) = dextrorotatory; that is,



rotating polarized light right or clockwise

- *l* (−) = levorotatory; that is, rotating polarized light left or counterclockwise

[5] *R* and *S* assignments in compounds with two or more stereogenic centers (5.9); example: 3-bromo-2-chloropentane

1 Enantiomers	2 Diastereomers
	

Try Problem 5.57.

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[6] Physical and chemical properties of isomers (5.12, 5.13)

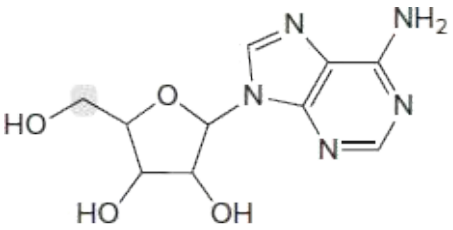
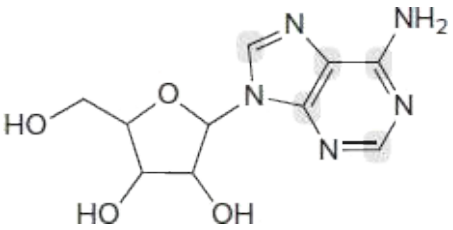
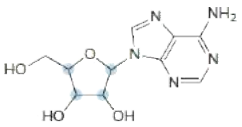
1 Constitutional isomers (5.2)	2 Enantiomers	3 Diastereomers
• *different* physical and chemical properties	• *identical* physical properties except for the direction polarized light is rotated • *identical* chemical properties except for their reaction with chiral, non-	• *different* physical and chemical properties

	racemic reagents	

See Figure 5.12. Try Problems 5.66b, 5.67e.

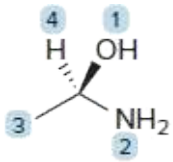
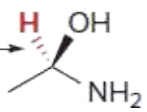
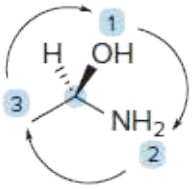
KEY SKILLS

[1] Locating stereogenic centers (5.4, 5.5); example: adenosine

1 Omit CH_2 and CH_3 groups.	2 Omit *sp* and sp^2 hybridized carbons.	3 Identify a carbons with four different groups.
 adenosine		 four stereogenic centers

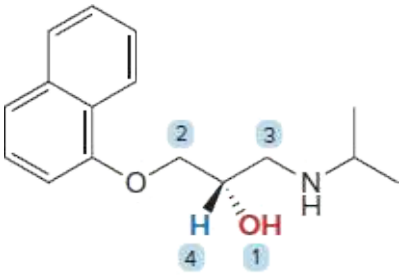
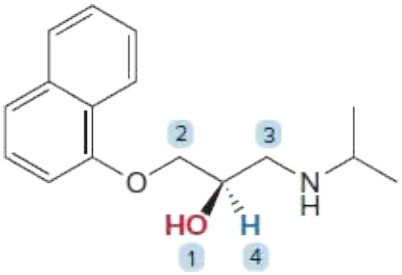
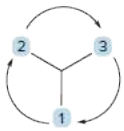
See Sample Problem 5.1. Try Problems 5.39a, 5.45, 5.46, 5.70a.

[2] Labeling stereogenic centers with *R* or *S* (5.6); example: 1-aminoethan-1-ol

1 Assign priorities.	2 Orient the molecule with the lowest-priority group back.	3 Trace a circle.
 1-aminoethan-1-ol	H atom is pointing backwards. 	 clockwise *R* isomer *R* = to the right *S* = to the left

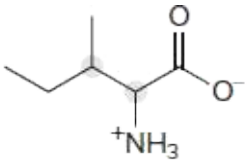
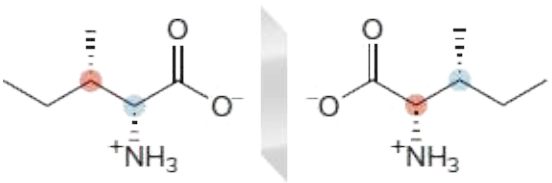
See *How To* p. 194, Sample Problem 5.3, Figure 5.6. Try Problem 5.50a, e.

[3] Assigning *R* or *S* when the lowest-priority group is not oriented toward the back (5.6); example: propranolol

1 Assign priorities.	2 Switch groups 1 and 4.	3 Trace a circle, and reverse th answer.
 propranolol		 clockwise It looks like an *R* isomer, but we must reverse the answer because we switched groups 1 and 4, *R* → *S*. *S* isomer

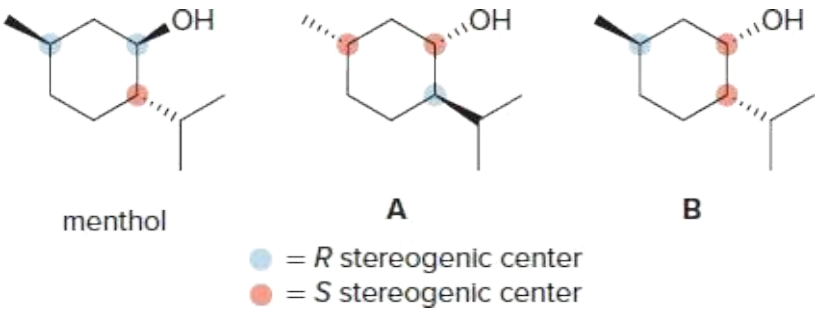
See Figure 5.7, Sample Problem 5.4. Try Problems 5.39b, 5.50, 5.51, 5.55, 5.69a, 5.71a.

[4] Finding and drawing all stereoisomers for a compound with two stereogenic centers (5.7, 5.8)

1 Determine how many stereoisomers are possible.	2 Draw one stereoisomer and its mirror image.	3
 isoleucine For *n* stereogenic centers, the maximum number of stereoisomers is 2^n. In this example, $2^2 = 4$ stereoisomers.	 A enantiomers B = *R* stereogenic center = *S* stereogenic center	

See *How To* p. 198, Figures 5.8, 5.9. Try Problems 5.58, 5.60.

[5] Determining if two nonidentical compounds are constitutional isomers, enantiomers, or diastereomers (5.11); example: menthol and isomers

1 Assess the connectivity of atoms, and assign the *R* or *S* configuration to each stereogenic center.	2 Use configurations to determine whether compounds are enantiomers or diastereomers.
• Menthol and isomers A and B are stereoisomers because they have the same connectivity of atoms, but differ only in the spatial orientation of groups.  	• Menthol and isomer A are enantiomers because they have exactly *opposite R,S* designations at all stereogenic centers. • Menthol and isomer B are diastereomers because they have the *same R,S* designations for two stereogenic centers and the *opposite R,S* designation for one stereogenic center.

See Figure 5.10. Try Problems 5.65, 5.67a.

[6] Calculations involving enantiomeric excess (*ee*) (5.12D)

1 Determine the % of each	2 Determine *ee* given the observed rotation of a mixture.

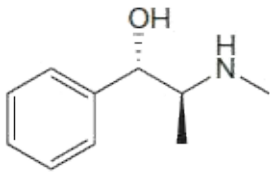
enantiomer given the *ee*.

97% *ee* of enantiomer A (97% excess A over the racemic mixture)

3% racemic mixture of A + B (1.5% A + 1.5% B)

ee = % of one enantiomer −% of the other enantiomer

- Total amount of A = 97% + 1.5% = 98.5%
- Total amount of B = 100% − 98.5% = 1.5%



(1*S*,2*S*)-pseudoephedrine
[α] pure = +51

[α] of **mixture** of enantiomers = **+20**

$$ee = \frac{[\alpha]\ \text{mixture}}{[\alpha]\ \text{pure enantiomer}} \times 100\%$$

$$= \frac{+20}{+51} \times 100\%$$

$$=$$ **39% *ee* of (1*S*,2*S*)-pseudoephedrine**

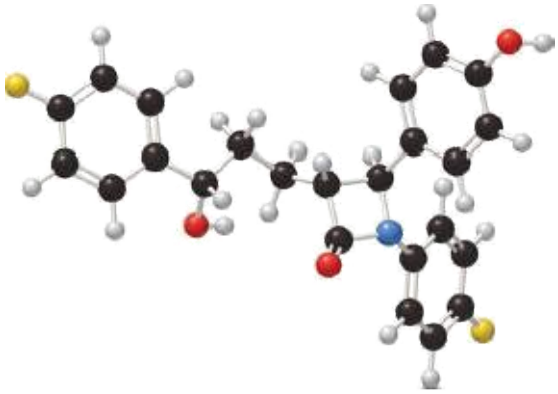
See Sample Problems 5.5, 5.6. Try Problems 5.68, 5.70e, f.

PROBLEMS

Problems Using Three-Dimensional Models

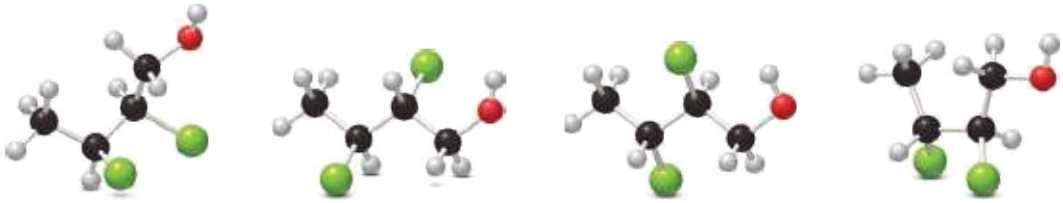
5.39 (a) Locate the stereogenic centers in the ball-and-stick model of ezetimibe (trade name Zetia), a cholesterol-lowering drug.

(b) Label each stereogenic center as R or S.



ezetimibe

5.40 **Consider the ball-and-stick models A–D. How is each pair of compounds related: (a) A and B; (b) A and C; (c) A and D; (d) C and D? Choose from identical molecules, enantiomers, or diastereomers.**

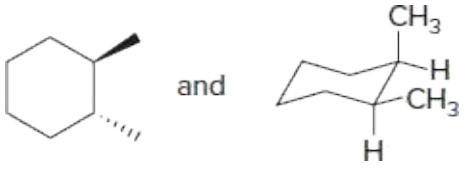


A B C D

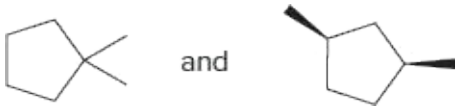
Constitutional Isomers Versus Stereoisomers

5.41 **Label each pair of compounds as constitutional isomers, stereoisomers, or not isomers of each other.**

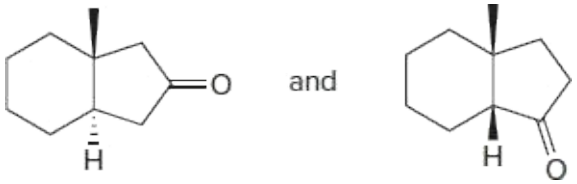
a.



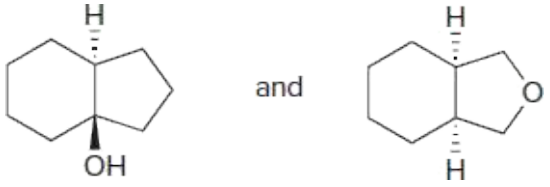
b.



c.



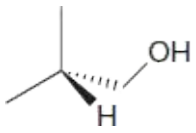
d.



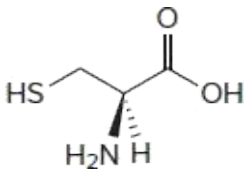
Mirror Images and Chirality

5.42 **Label each compound as chiral or achiral.**

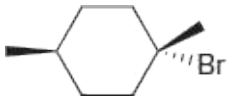
a.



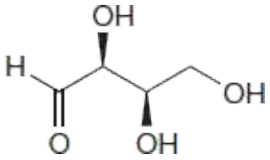
b.



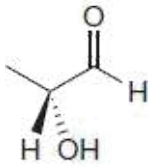
c.



d.

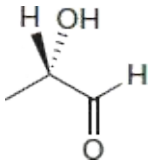


5.43 Determine if each compound is identical to or an enantiomer of A.

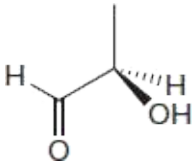


A

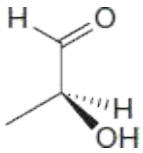
a.



b.

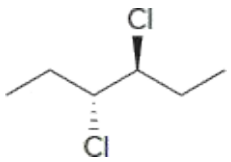


c.

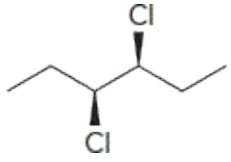


5.44 Indicate a plane of symmetry for each molecule that contains one. A molecule may require rotation around a carbon–carbon bond to see the plane of symmetry.

a.

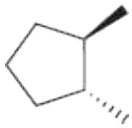


b.



c.

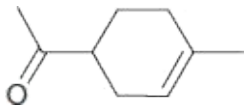
d.



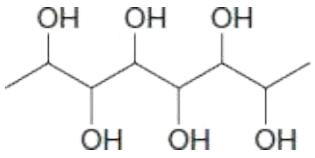
Finding and Drawing Stereogenic Centers

5.45 Locate the tetrahedral stereogenic center(s) in each compound. A molecule may have one or more stereogenic centers.

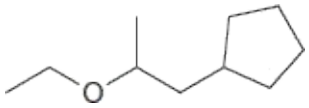
a.



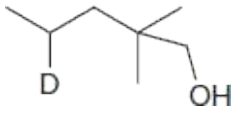
b.



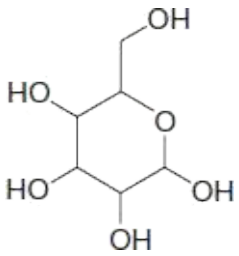
c.



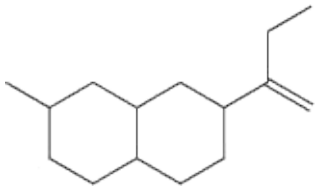
d.



e.

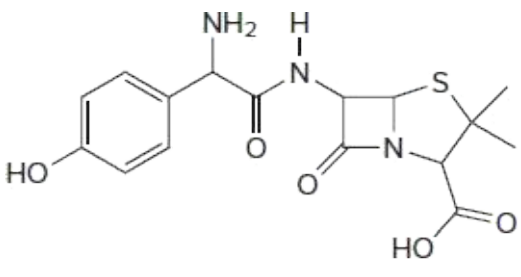


f.



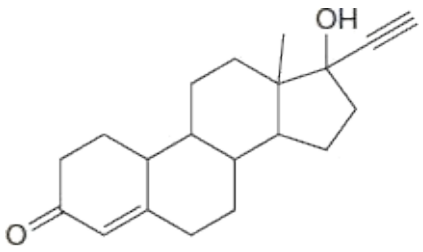
5.46 Locate the stereogenic centers in each drug.

a.



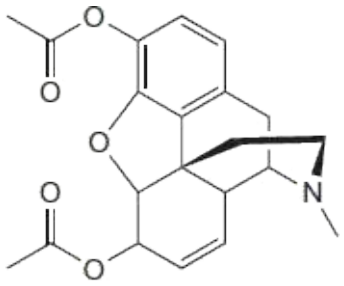
amoxicillin
(an antibiotic)

b.



norethindrone
(oral contraceptive component)

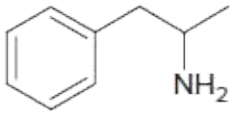
c.



heroin
(an opiate)

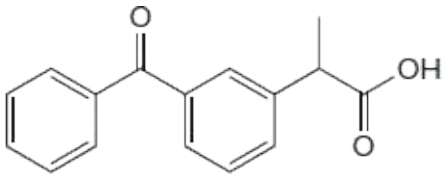
5.47 Draw both enantiomers for each biologically active compound.

a.



amphetamine
(a powerful central nervous stimulant)

b.



ketoprofen
(analgesic and anti-inflammatory agent)

Nomenclature

5.48 Which group in each pair is assigned the higher priority in *R*,*S* nomenclature?

a. $-CD_3$, $-CH_3$

b. $-CH(CH_3)_2$, $-CH_2OH$

c. $-CH_2Cl$, $-CH_2CH_2CH_2Br$

d. $-CH_2NH_2$, $-NHCH_3$

5.49 Rank the following groups in order of decreasing priority.

a. −F, −NH2, −CH3, −OH

b. $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-(CH_2)_3CH_3$

c. $-NH_2$, $-CH_2NH_2$, $-CH_3$, $-CH_2NHCH_3$

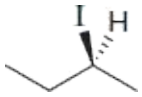
d. −COOH, −CH2OH, −H, −CHO

e. −Cl, −CH3, −SH, −OH

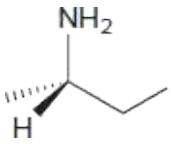
f. $-C{\equiv}CH$, $-CH(CH_3)_2$, $-CH_2CH_3$, $-CH{=}CH_2$

5.50 **Label each stereogenic center as *R* or *S*.**

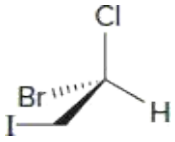
a.



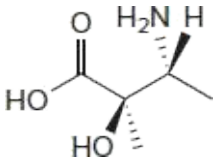
b.



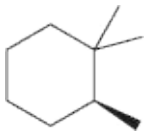
c.



d.



e.



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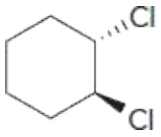
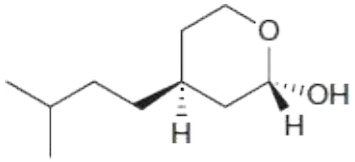


g.



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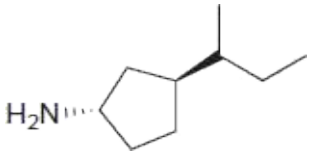
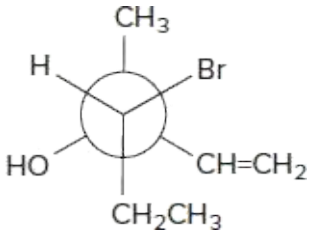
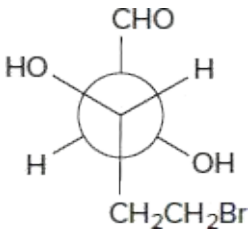


5.51 **Locate the stereogenic centers in each Newman projection and label each center as *R* or *S*.**

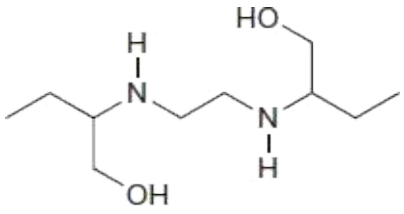
a.



b.



5.52 Draw the structure of (*S,S*)-ethambutol, a drug used to treat tuberculosis that is 10 times more potent than any of its other stereoisomers.



ethambutol

5.53 Draw the structure for each compound.

a. (*R*)-3-methylhexane

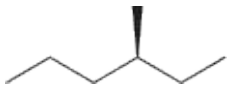
b. (4*R*,5*S*)-4,5-diethyloctane

c. (3*R*,5*S*,6*R*)-5-ethyl-3,6-dimethylnonane

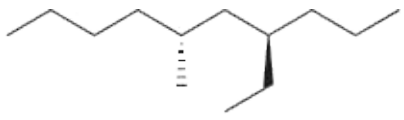
d. (3*S*,6*S*)-6-isopropyl-3-methyldecane

5.54 Give the IUPAC name for each compound, including the *R,S* designation for each stereogenic center.

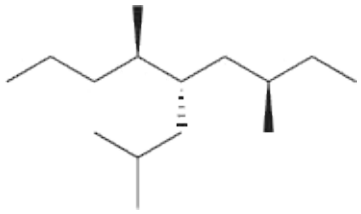
a.



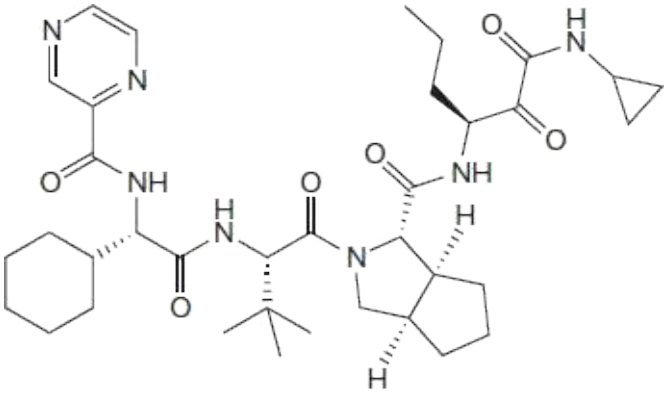
b.



c.



5.55 Locate the stereogenic centers in telaprevir, a drug used to treat hepatitis C, and label each stereogenic center as *R* or *S.*

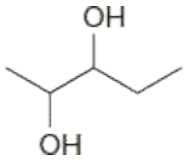


telaprevir

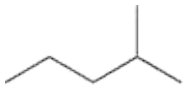
Compounds with More Than One Stereogenic Center

5.56 **What is the maximum number of stereoisomers possible for each compound?**

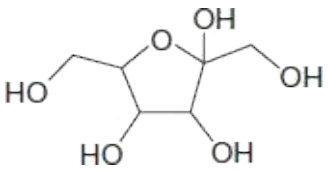
a.



b.



c.



5.57 **The shrub ma huang (Section 5.4A) contains two biologically active stereoisomers—ephedrine and pseudoephedrine—with two stereogenic centers as shown in the given structure. Ephedrine is one component of a once-popular combination drug used by body builders to increase energy and alertness, whereas pseudoephedrine is a nasal decongestant.**

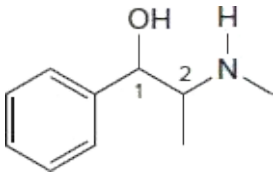
a. Draw the structure of naturally occurring (−)-ephedrine, which has the 1*R*,2*S* configuration.

b. Draw the structure of naturally occurring (+)-pseudoephedrine, which has the 1S,2S configuration.

c. How are ephedrine and pseudoephedrine related?

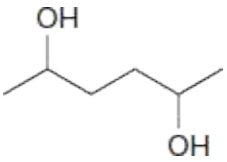
d. Draw all other stereoisomers of (−)-ephedrine and (+)-pseudoephedrine, and give the *R,S* designation for all stereogenic centers.

e. How is each compound drawn in part (d) related to (−)-ephedrine?

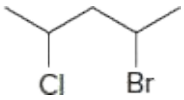


5.58 **Draw all possible stereoisomers for each compound. Label pairs of enantiomers and diastereomers. Label any meso compound.**

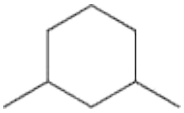
a.



b.



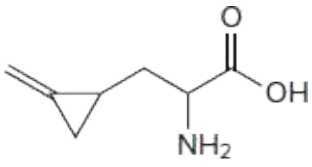
c.



d.

5.59 **Draw all possible constitutional isomers and stereoisomers for a compound of molecular formula C_6H_{12} having a cyclobutane ring and two methyl groups as substituents. Label each compound as chiral or achiral.**

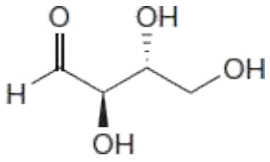
5.60 **Hypoglycin A, an amino acid derivative found in unripened lychee, is a compound that is acutely toxic and can lead to death when ingested in large amounts by undernourished children. Draw all possible stereoisomers for hypoglycin A, and give the *R,S* designation for each stereogenic center.**



hypoglycin A

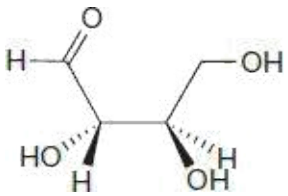
Comparing Compounds: Enantiomers, Diastereomers, and Constitutional Isomers

5.61 **How is each compound related to the simple sugar D-erythrose? Is it an enantiomer, a diastereomer, or an identical molecule?**

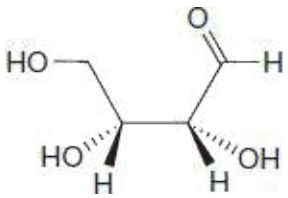


D-erythrose

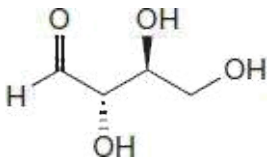
a.



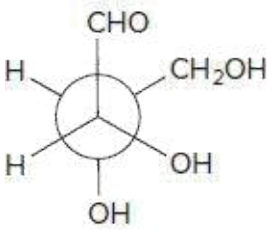
b.



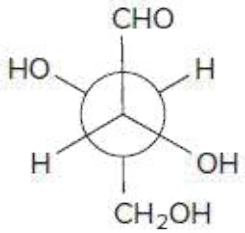
c.



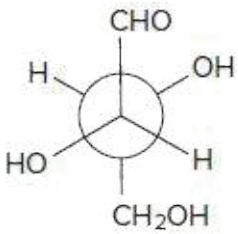
5.62 Consider Newman projections (A–D) for four-carbon carbohydrates. How is each pair of compounds related: (a) A and B; (b) A and C; (c) A and D; (d) C and D? Choose from identical molecules, enantiomers, or diastereomers.



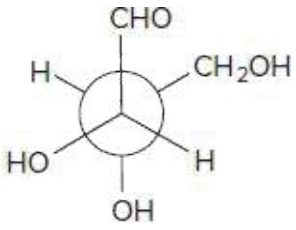
A



B

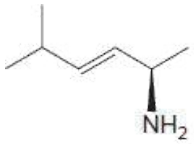


C

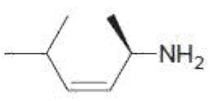


D

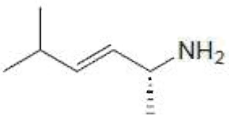
5.63 How is compound A related to compounds B–E? Choose from enantiomers, diastereomers, constitutional isomers, or identical molecules.



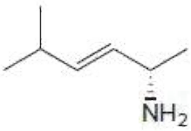
A



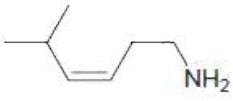
B



C

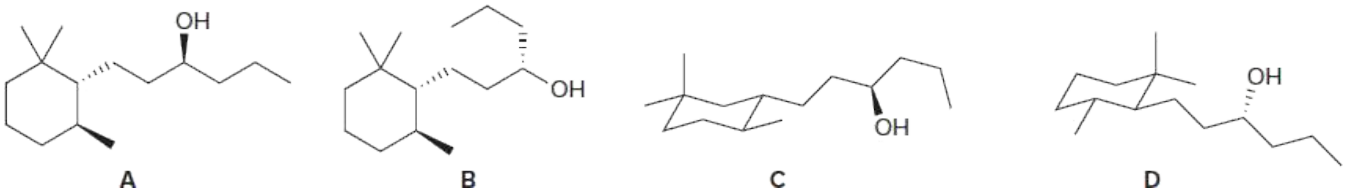


D



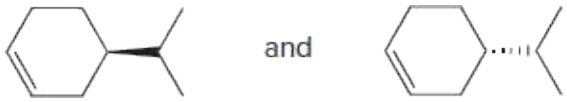
E

5.64 How is each compound (B–D) related to A? Choose from enantiomers, diastereomers, identical molecules, constitutional isomers, or not isomers of each other.

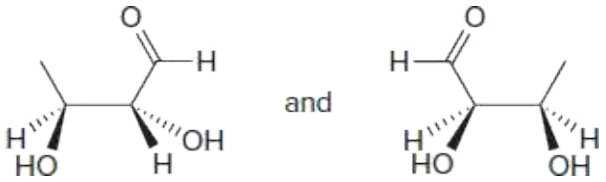


5.65 **How are the compounds in each pair related to each other? Are they identical, enantiomers, diastereomers, constitutional isomers, or not isomers of each other?**

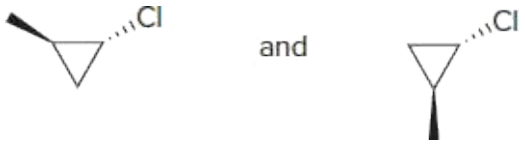
a.



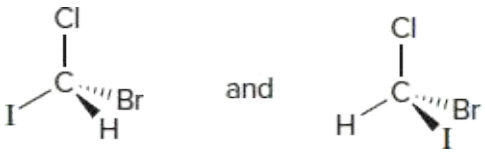
b.



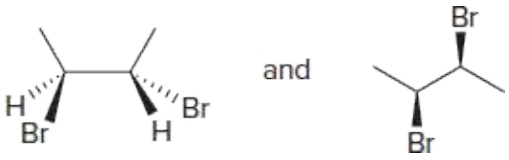
c.



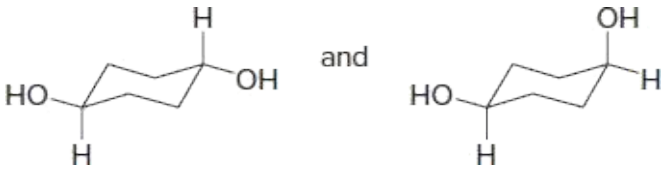
d.



e.

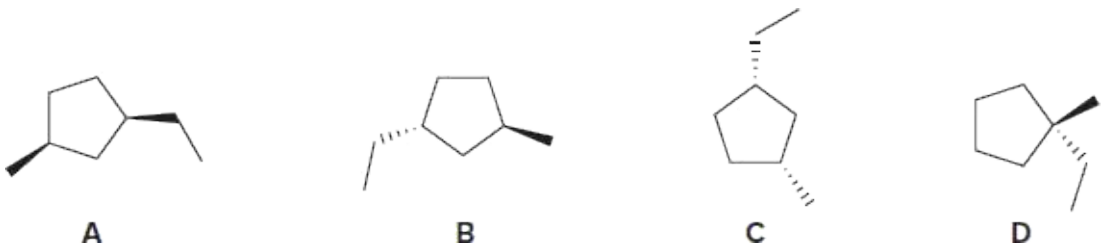


f.



Physical Properties of Isomers

5.66 **A mixture contains equal amounts of compounds A–D.**

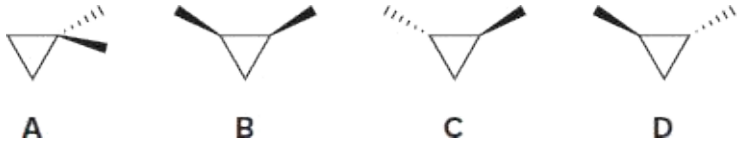


a. Which compounds alone are optically active?

b. If the mixture was subjected to fractional distillation, how many fractions would be obtained?

c. How many of these fractions would be optically active?

5.67 Drawn are four isomeric dimethylcyclopropanes.



a. How are the compounds in each pair related (enantiomers, diastereomers, constitutional isomers): A and B; A and C; B and C; C and D?

b. Label each compound as chiral or achiral.

c. Which compounds alone would be optically active?

d. Which compounds have a plane of symmetry?

e. How do the boiling points of the compounds in each pair compare: A and B; B and C; C and D?

f. Which of the compounds are meso compounds?

g. Would an equal mixture of compounds C and D be optically active? What about an equal mixture of B and C?

5.68 The [α] of pure quinine, an antimalarial drug, is −165.

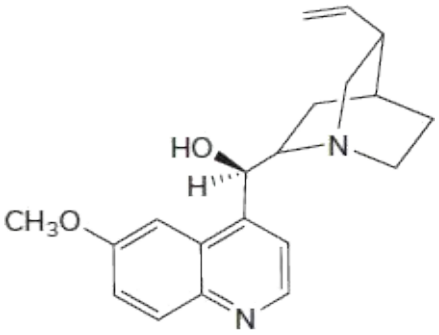
a. Calculate the *ee* of a solution with the following [α] values: −50, −83, and −120.

b. For each *ee*, calculate the percent of each enantiomer present.

c. What is [α] for the enantiomer of quinine?

d. If a solution contains 80% quinine and 20% of its enantiomer, what is the *ee* of the solution?

e. What is [α] for the solution described in part (d)?



quinine
(antimalarial drug)

General Problems

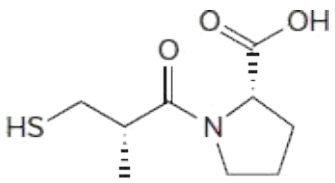
5.69 Captopril is a drug used to treat high blood pressure and congestive heart failure.

a. Designate each stereogenic center as *R* or S.

b. Draw the enantiomer of captopril.

c. What product is formed when captopril is treated with one equivalent of NaH?

d. What product is formed when captopril is treated with two equivalents of NaH?



captopril

5.70 Trabectedin, shown in a ball-and-stick model on the cover of this text, is an anticancer drug sold under the trade name Yondelis.

a. Locate the stereogenic centers in trabectedin.

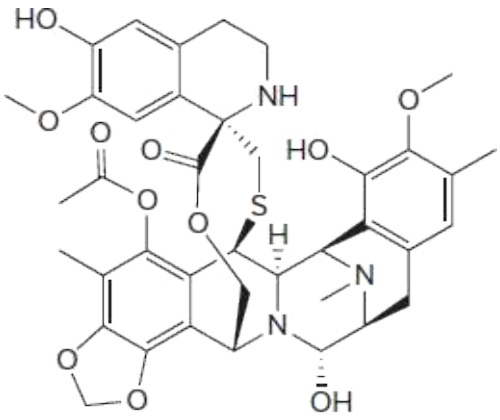
b. What is the maximum number of stereoisomers possible for trabectedin?

c. Draw the enantiomer.

d. Draw a diastereomer.

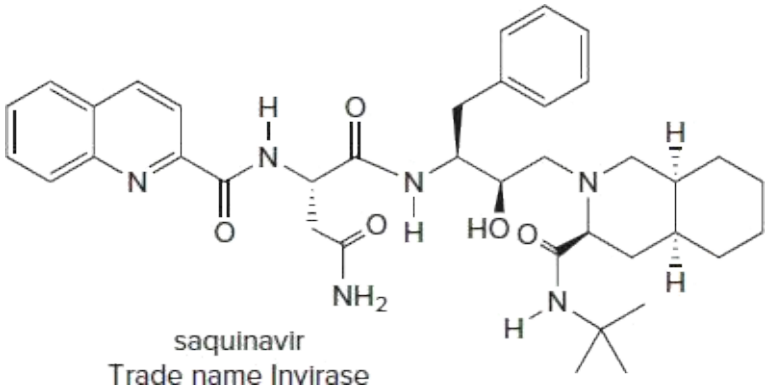
e. If the specific rotation of trabectedin is +41.5, what is the [α] of a solution that contains 75% trabectedin and 25% of its enantiomer?

f. What is the *ee* of a solution with [α] = +10.5?



trabectedin

5.71 Saquinavir (trade name Invirase) is a protease inhibitor, used to treat HIV (human immunodeficiency virus).



saquinavir
Trade name Invirase

a. Locate all stereogenic centers in saquinavir, and label each stereogenic center as *R* or *S*.

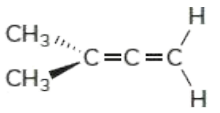
b. Draw the enantiomer of saquinavir.

c. Draw a diastereomer of saquinavir.

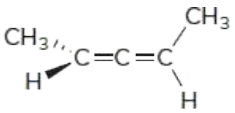
d. Draw a constitutional isomer that contains at least one different functional group.

Challenge Problems

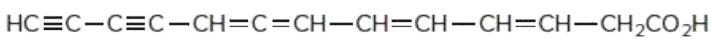
5.72 A limited number of chiral compounds having no stereogenic centers exist. For example, although A is achiral, constitutional isomer B is chiral. Make models and explain this observation. Compounds containing two double bonds that share a single carbon atom are called *allenes.* Locate the allene in the antibiotic mycomycin and decide whether mycomycin is chiral or achiral.



achiral
A



chiral
B

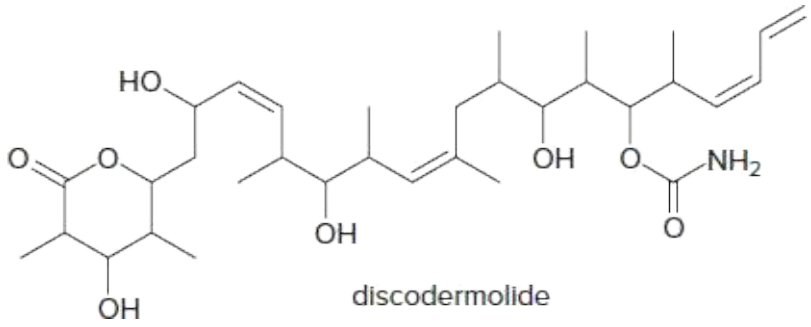


mycomycin

5.73 **a. Locate all the tetrahedral stereogenic centers in discodermolide, a tumor inhibitor isolated from the Caribbean marine sponge *Discodermia dissoluta.***

b. Certain carbon–carbon double bonds can also be stereogenic centers. With reference to the definition in Section 5.3, explain how this can occur, and then locate the three additional stereogenic centers in discodermolide.

c. Considering all stereogenic centers, what is the maximum number of stereoisomers possible for discodermolide?

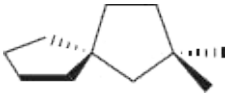


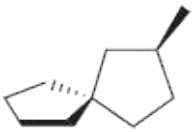
discodermolide

5.74 **Label each compound as chiral or achiral. Compounds that contain a single carbon common to two rings are called spiro compounds. Because carbon is tetrahedral, the two rings are perpendicular to each other.**

a.

b.

c. 

d. 

5.75 **An acid–base reaction of (*R*)-*sec*-butylamine with a racemic mixture of 2-phenylpropanoic acid forms two products having different melting points and somewhat different solubilities. Draw the structure of these two products. Assign *R* and *S* to any stereogenic centers in the products. How are the two products related? Choose from enantiomers, diastereomers, constitutional isomers, or not isomers of each other.**

2-phenylpropanoic acid
(racemic mixture)

(*R*)-*sec*-butylamine

6

Understanding Organic Reactions

©ninikas/Getty Images

6.1 Writing equations for organic reactions

6.2 Kinds of organic reactions

6.3 Bond breaking and bond making

6.4 Bond dissociation energy

6.5 Thermodynamics

6.6 Enthalpy and entropy

6.7 Energy diagrams

6.8 Energy diagram for a two-step reaction mechanism

6.9 Kinetics

6.10 Catalysts

6.11 Enzymes

Glucose, the most abundant simple carbohydrate, is the building block for starch and cellulose and a major sweet-tasting component of honey. Glucose is used as an energy source by most organisms. In humans, when glucose levels are high after a meal is digested, the body stores glucose as glycogen, which is then hydrolyzed when glucose levels fall and energy demands increase. Glucose is transported in the bloodstream and metabolized aerobically to carbon dioxide and water and a great deal of energy. In Chapter 6, we learn about energy changes that accompany chemical reactions.

Why Study…

Organic Reactions?

Reactions are at the heart of organic chemistry. An understanding of chemical processes has made possible the conversion of natural substances into new compounds with different, and sometimes superior, properties. Aspirin, ibuprofen, nylon, and polyethylene are all products of chemical reactions between substances derived from petroleum.

Reactions are difficult to learn when each reaction is considered a unique and isolated event. *Avoid this tendency*. Virtually all chemical reactions are woven together by a few basic themes. After we learn the general principles, specific reactions then fit neatly into a general pattern.

In our study of organic reactions we will begin with the functional groups, looking for electron-rich and electron-deficient sites, and bonds that might be broken easily. These reactive sites give us a clue as to the general type of reaction a particular class of compound undergoes. Finally, we will learn about how a reaction occurs. Does it occur in one step or in a series of steps? Understanding the details of an organic reaction allows us to determine when it might be used in preparing interesting and useful organic compounds.

6.1 Writing Equations for Organic Reactions

Often the solvent and temperature of a reaction are omitted from chemical equations, to further focus attention on the main substances involved in the reaction.

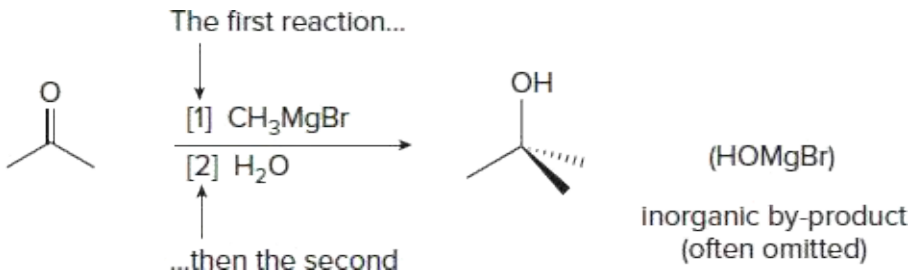
Most organic reactions take place in a liquid solvent. Solvents solubilize key reaction components and serve as heat reservoirs to maintain a given temperature. Chapter 7 presents the two major types of reaction solvents and how they affect substitution reactions.

Like other reactions, equations for organic reactions are usually drawn with a single reaction arrow (→) between the starting material and product, but other conventions make these equations look different from those encountered in general chemistry.

The reagent, the chemical substance with which an organic compound reacts, is sometimes drawn on the left side of the equation with the other reactants. At other times, the reagent is drawn above or below the reaction arrow itself, to focus attention on the organic starting material by itself on the left side. The solvent and temperature of a reaction may be added above or below the arrow. The symbols "*hν*" and "Δ" are used for reactions that require *light* or *heat*, respectively. Figure 6.1 presents an organic reaction in different ways.

When two sequential reactions are carried out without drawing any intermediate compound, the steps are usually numbered above or below the reaction arrow. This

convention signifies that the first step occurs *before* the second, and the reagents are added *in sequence*, not at the same time.



In this equation only the organic product is drawn on the right side of the arrow. Although the reagent CH_3MgBr contains both Mg and Br, these elements do not appear in the organic product, and they are often omitted on the product side of the equation. These elements have not disappeared. They are part of an inorganic by-product (HOMgBr in this case), and are often of little interest to an organic chemist.

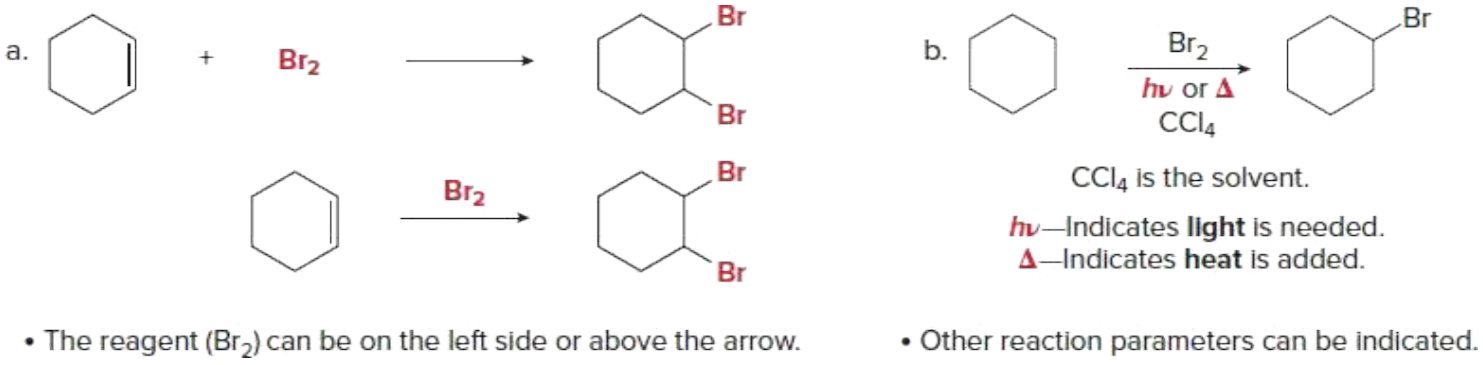


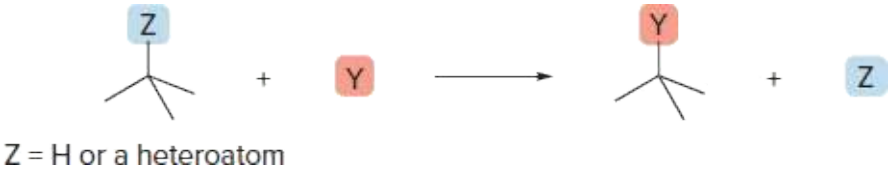
Figure 6.1 **Different ways of writing organic reactions**

6.2 Kinds of Organic Reactions

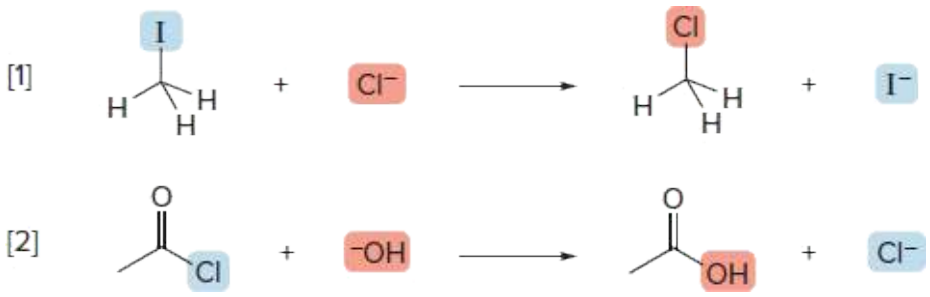
Like other compounds, organic molecules undergo acid–base and oxidation–reduction reactions, as discussed in Chapters 2 and 4. Organic molecules also undergo substitution, elimination, and addition reactions.

6.2A Substitution Reactions

- ***Substitution*** **is a reaction in which an atom or a group of atoms is *replaced* by another atom or group of atoms.**

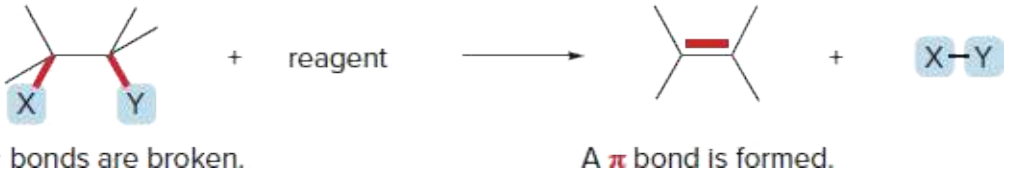


In a general substitution reaction, Y *replaces* Z on a carbon atom. Substitution reactions involve σ bonds: one σ bond breaks and another forms at the same carbon atom. The most common examples of substitution occur when Z is hydrogen or a heteroatom that is more electronegative than carbon.

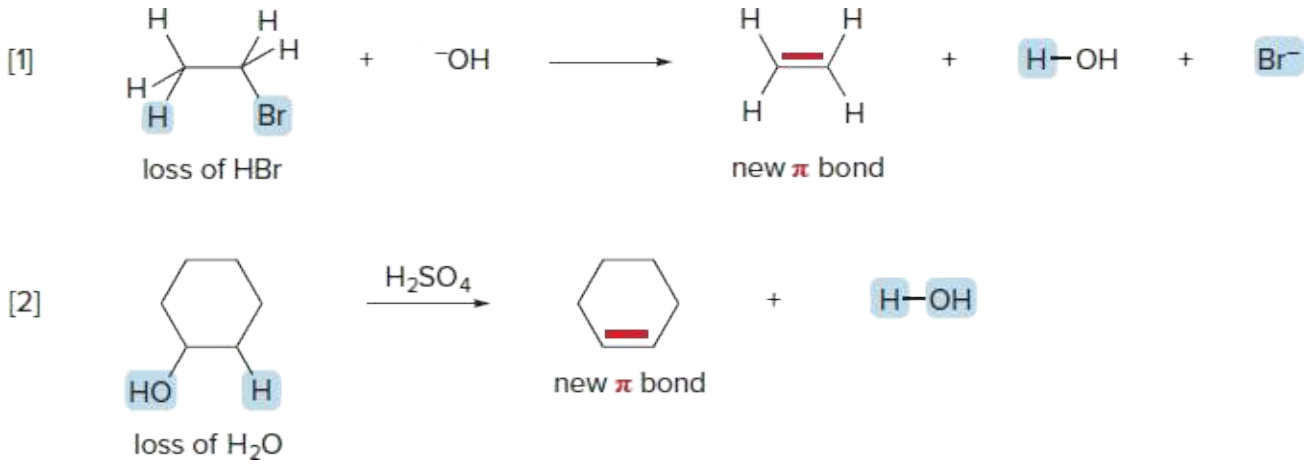


6.2B Elimination Reactions

- ***Elimination*** **is a reaction in which elements of the starting material are "lost" and a π bond is formed.**

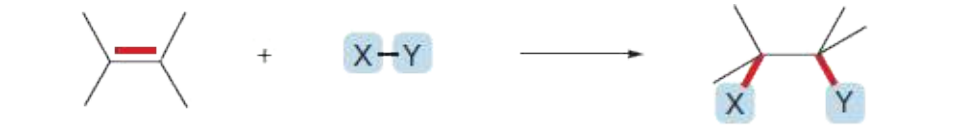


In an elimination reaction, two groups X and Y are removed from a starting material. Two σ bonds are broken, and a π bond is formed between adjacent atoms. The most common examples of elimination occur when X = H and Y is a heteroatom more electronegative than carbon.



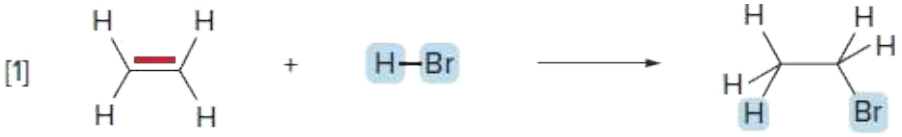
6.2C Addition Reactions

- ***Addition*** **is a reaction in which elements are added to a starting material.**

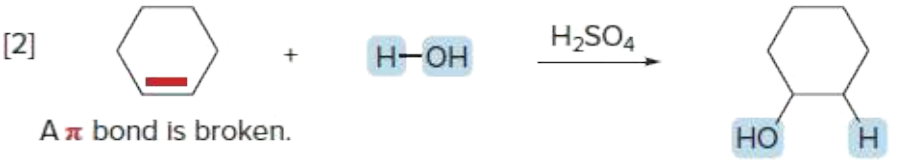


A π bond is broken. Two σ bonds are formed.

In an addition reaction, new groups X and Y are added to a starting material. A π bond is broken and two σ bonds are formed.



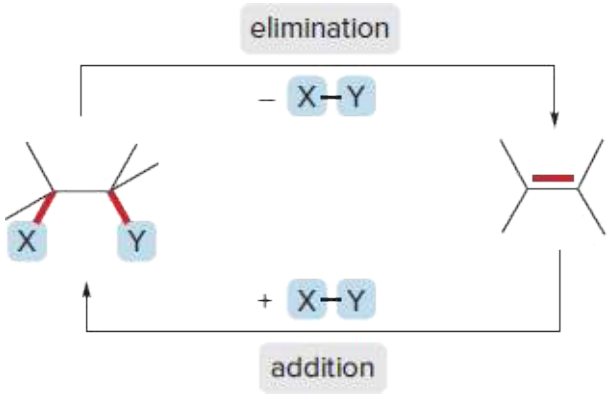
A π bond is broken. HBr is added.



A π bond is broken. H_2O is added.

A summary of the general types of organic reactions is given in Appendix I.

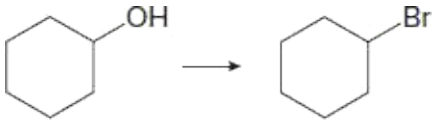
Addition and elimination reactions are exactly opposite. A π bond is *formed* in elimination reactions, whereas a π bond is *broken* in addition reactions.



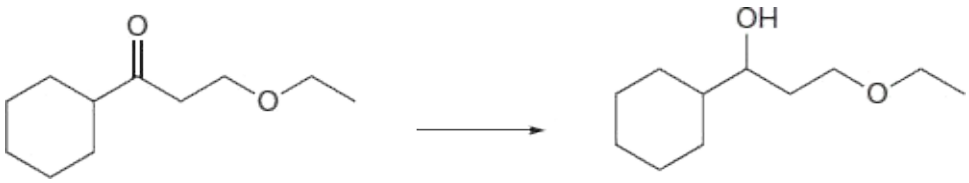
Problem 6.1

Classify each transformation as substitution, elimination, or addition.

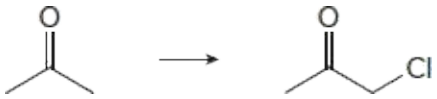
a.



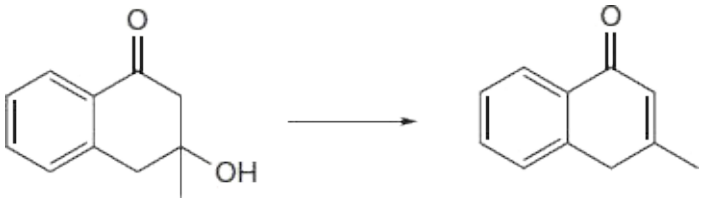
b.



c.



d.



To determine whether a reaction is a substitution, elimination, or addition with a complex starting material, concentrate on the functional groups that *change*. The conversion of amine X and acid chloride Y to the naturally occurring compound capsaicin is a substitution reaction, because the N atom of the amine *replaces* the Cl of the acid chloride.

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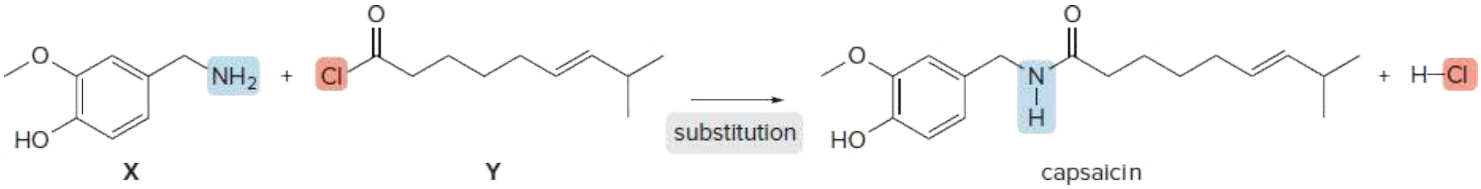
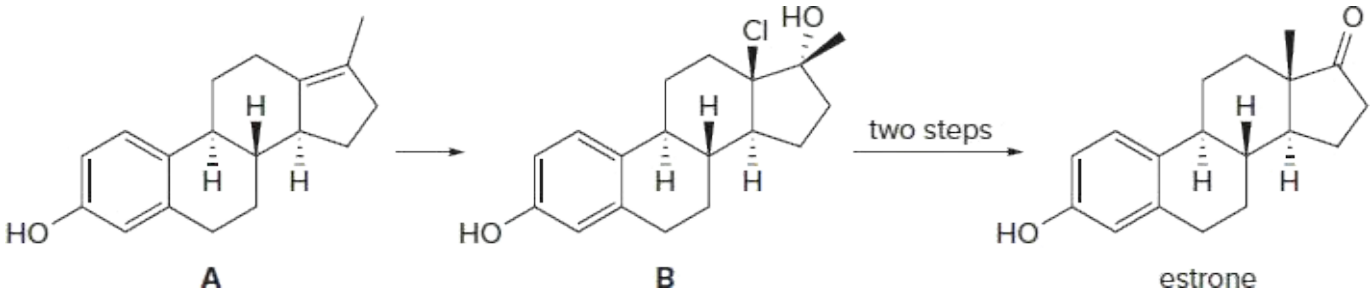


Capsaicin is responsible for the characteristic spicy flavor of jalapeño and habañero peppers. ***©DNY59/Getty Images***

Problem 6.2

Classify the conversion of A to B as a substitution, elimination, or addition. B can be converted to the female sex hormone estrone in two steps.



6.3 Bond Breaking and Bond Making

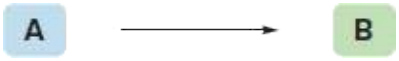
Having now learned how to write and identify some common kinds of organic reactions, we can turn to a discussion of reaction mechanism.

- **A *reaction mechanism* is a detailed description of how bonds are broken and formed as a starting material is converted to a product.**

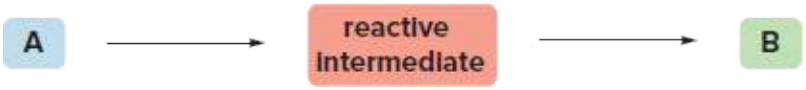
A reaction mechanism describes the relative order and rate of bond cleavage and formation. It explains all the known facts about a reaction and accounts for all products formed, and it is subject to modification or refinement as new details are discovered.

A reaction can occur either in one step or in a series of steps.

- A one-step reaction is called a *concerted reaction*. No matter how many bonds are broken or formed, a starting material is converted *directly* to a product.



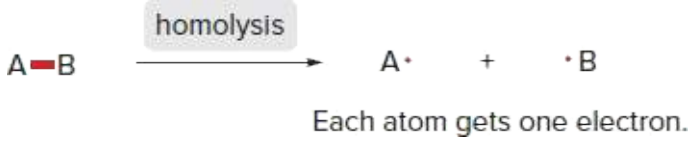
- A stepwise reaction involves more than one step. A starting material is first converted to an unstable intermediate, called a reactive intermediate, which then goes on to form the product.



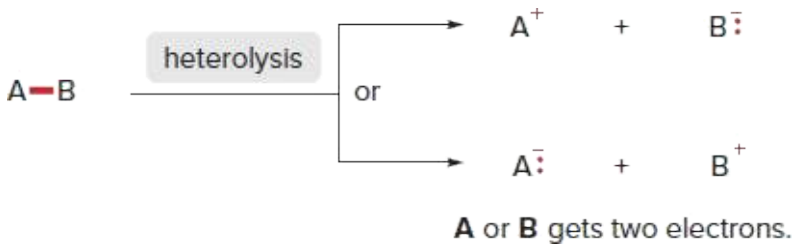
6.3A Bond Cleavage

Bonds are broken and formed in all chemical reactions. When a bond is broken, the electrons in the bond can be divided equally or unequally between the two atoms of the bond.

- **Breaking a bond by *equally dividing* the electrons between the two atoms in the bond is called homolysis or homolytic cleavage.**



- **Breaking a bond by *unequally dividing* the electrons between the two atoms in the bond is called heterolysis or heterolytic cleavage.**



Heterolysis of a bond between A and B can give either A or B the two electrons in the bond. When A and B have different electronegativities, the *electrons normally end up on the more electronegative atom.*

Homolysis and heterolysis require energy. Both processes generate reactive intermediates, but the products are different in each case.

- **Homolysis generates uncharged reactive intermediates with *unpaired* electrons.**
- **Heterolysis generates *charged* intermediates.**

Each of these reactive intermediates has a very short lifetime and reacts quickly to form a stable organic product.

6.3B Radicals, Carbocations, and Carbanions

The curved arrow notation first discussed in Section 1.6B works fine for heterolytic bond cleavage because it illustrates the movement of an electron pair. For homolytic cleavage, however, one electron moves to one atom in the bond and one electron moves to the other, so a different kind of curved arrow is needed.

- **To illustrate the movement of a single electron, use a half-headed curved arrow, sometimes called a *fishhook.***

A full-headed curved arrow ( ) shows the movement of an electron *pair.* A half-headed curved arrow ( ) shows the movement of a *single* electron.

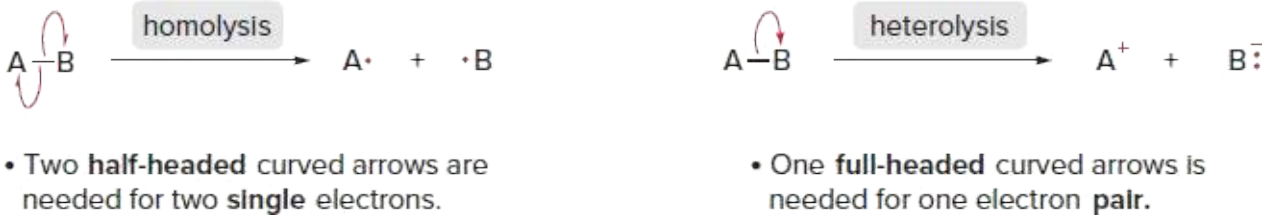


Figure 6.2 illustrates homolysis and two different heterolysis reactions for a carbon

compound using curved arrows. Three different reactive intermediates are formed.

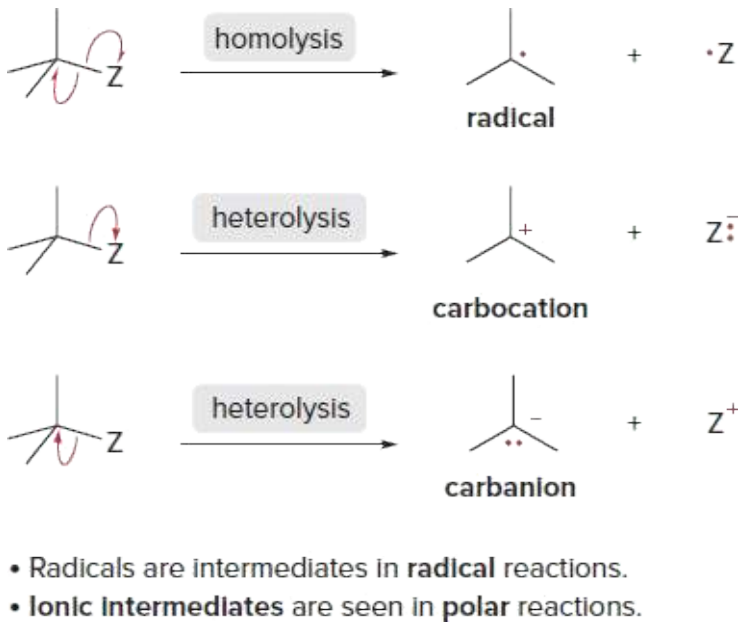


Figure 6.2 **Three reactive intermediates resulting from homolysis and heterolysis of a C–Z bond**

Homolysis of the C–Z bond generates two uncharged products with unpaired Page 228 electrons.

- **A reactive intermediate with a single unpaired electron is called a *radical.***

Most radicals are highly unstable because they contain an atom that does not have an octet of electrons. Radicals typically have no charge. They are intermediates in a group of reactions called *radical reactions*, which are discussed in detail in Chapter 13.

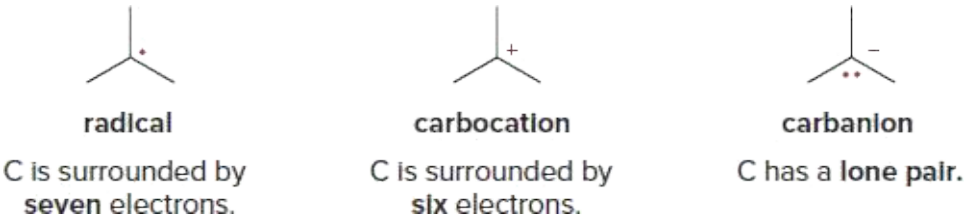
Heterolysis of the C–Z bond can generate a carbocation or a carbanion.

- **Giving two electrons to Z and none to carbon generates a positively charged carbon intermediate called a *carbocation.***
- **Giving two electrons to C and none to Z generates a negatively charged carbon species called a *carbanion.***

Both carbocations and carbanions are unstable reactive intermediates: A carbocation contains a carbon atom surrounded by only six electrons. A carbanion has a negative charge on carbon, which is not a very electronegative atom. Carbocations (electrophiles) and carbanions (nucleophiles) can be intermediates in *polar reactions*—reactions in which a nucleophile reacts with an electrophile.

The chemistry of carbenes, another type of organic reactive intermediate, is discussed in Section 24.4.

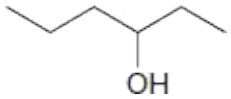
Thus, homolysis and heterolysis generate radicals, carbocations, and carbanions, the three most common reactive intermediates in organic chemistry.



- **Radicals and carbocations are *electrophiles* because they contain a carbon with no octet.**
- **Carbanions are *nucleophiles* because they contain a carbon with a lone pair.**

Problem 6.3

By taking into account electronegativity differences, draw the products formed by heterolysis of the carbon–heteroatom bond in each molecule. Classify the organic reactive intermediate as a carbocation or a carbanion.

a. 

b.

c.

6.3C Bond Formation

Like bond cleavage, bond formation occurs in two different ways. Two radicals can each donate one electron to form a two-electron bond. Alternatively, two ions with unlike charges can come together, with the negatively charged ion donating both electrons to form the resulting two-electron bond. Bond formation always releases energy.

6.3D All Kinds of Arrows

Table 6.1 summarizes the many kinds of arrows used in describing organic reactions. Curved arrows are especially important because they explicitly show what electrons are involved in a reaction, how these electrons move in forming and breaking bonds, and if a reaction proceeds via a radical or polar pathway.

A more complete summary of the arrows used in organic chemistry is given in Appendix B, Common Abbreviations, Arrows, and Symbols.

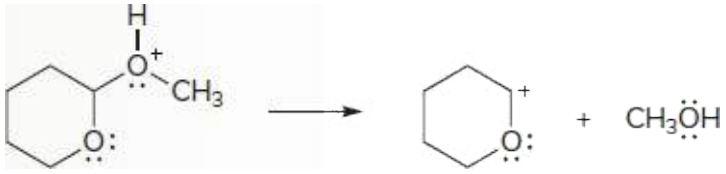
Table 6.1 A Summary of Arrow Types in Chemical Reactions

Arrow	Name	Use
→	Reaction arrow	Drawn between the starting materials and products in an equation (6.1)
⇌	Double reaction arrows (equilibrium arrows)	Drawn between the starting materials and products in an equilibrium equation (2.2)
↔	Double-headed arrow	Drawn between resonance structures (1.6B)
↷	Full-headed curved arrow	Shows movement of an electron pair (1.6B, 2.2)
↶	Half-headed curved arrow (fishhook)	Shows movement of a single electron (6.3B)

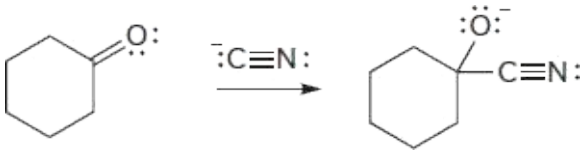
Sample Problem 6.1 Using Curved Arrows in an Equation

Use curved arrows to show the movement of electron pairs in each reaction.

a.



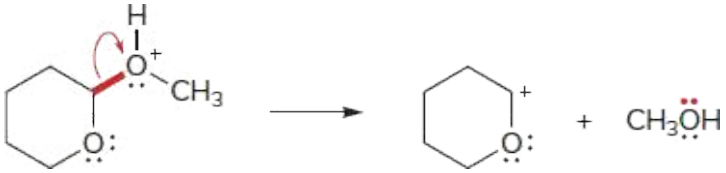
b.



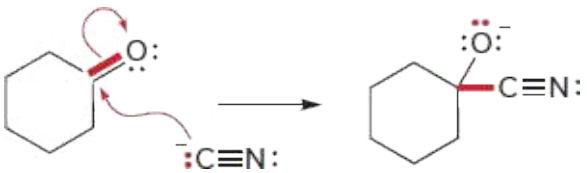
Solution

Concentrate on bonds that are broken or formed, and pay attention to atoms that have different charges in the reactants and products.

a. Only *one* C–O bond is broken, so only *one* curved arrow is needed. The electron pair in the C–O bond (in red) ends up on O.



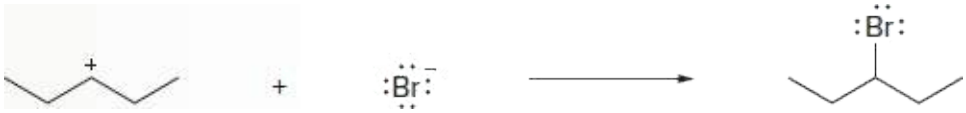
b. *Two* curved arrows are needed because *two* electron pairs are involved. The lone pair on C in ⁻CN forms a new bond to the carbonyl carbon, and an electron pair in the C=O moves onto O.



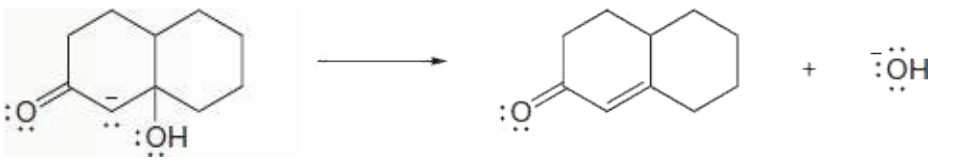
Problem 6.4

Use curved arrows to show the movement of electrons in each equation.

a.



b.

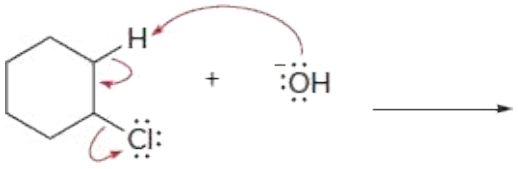


More Practice:

Try Problems 6.29, 6.31a, 6.32a, 6.33, 6.34a, 6.44a, 6.49a, 6.52a, 6.53a.

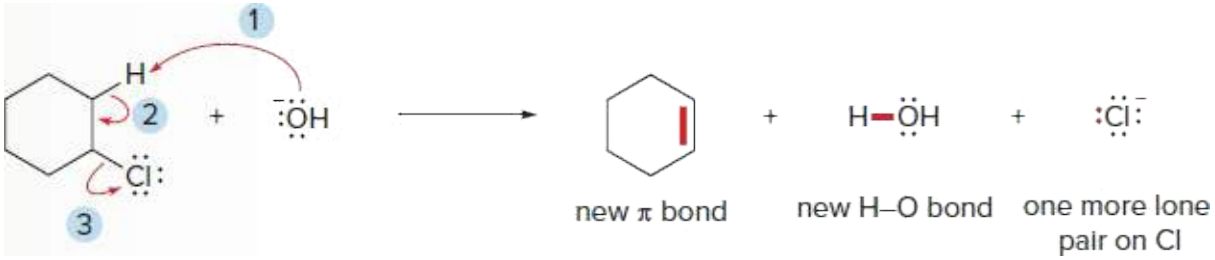
Product

Follow the curved arrows and draw the products of the following reaction.



Solution

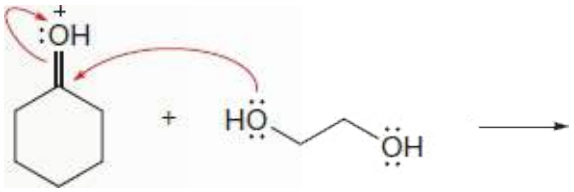
Three full-headed curved arrows are drawn, so three electron *pairs* take part in the reaction. Arrow 1 shows that a lone pair on $^{-}$OH forms a new bond to H, forming H_2O. Arrow 2 indicates that the electron pair in the C–H bond forms a carbon–carbon double bond. Arrow 3 shows that the electron pair in the C–Cl bond ends up on Cl, forming Cl^{-}. After breaking and making bonds, formal charges on the atoms involved in the reaction are adjusted when necessary.



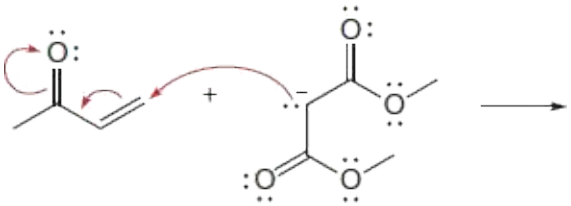
Problem 6.5

Follow the curved arrows and draw the products of each reaction.

a.



b.



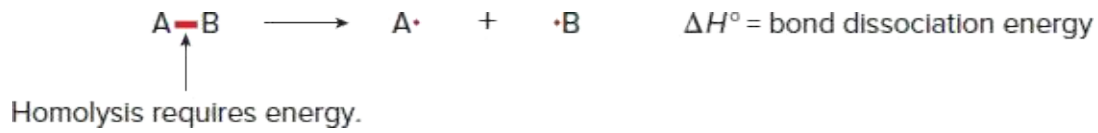
More Practice:

Try Problems 6.30, 6.32b, 6.34b.

6.4 Bond Dissociation Energy

Bond breaking can be quantified using the bond dissociation energy.

- **The *bond dissociation energy* is the energy needed to homolytically cleave a covalent bond.**



The superscript (°) means that values are determined under standard conditions (pure compounds in their most stable state at 25 °C and 1 atm pressure).

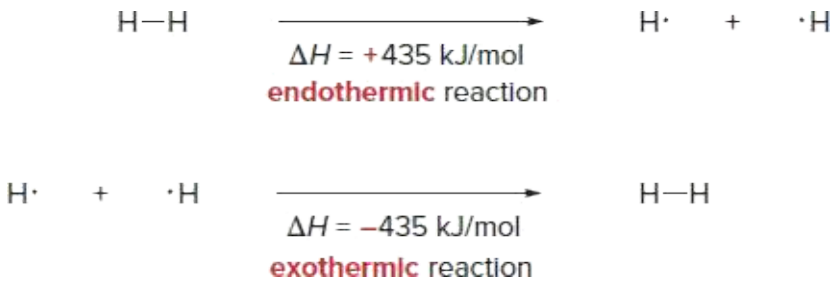
The energy absorbed or released in any reaction, symbolized by ΔH^0, is called the enthalpy change or heat of reaction.

- **When ΔH^0 is positive (+), energy is absorbed and the reaction is *endothermic.***
- **When ΔH^0 is negative (−), energy is released and the reaction is *exothermic.***

A bond dissociation energy is the ΔH^0 for a specific kind of reaction—the homolysis of a covalent bond to form two radicals. Because bond breaking requires energy, bond dissociation energies are always *positive* numbers, and homolysis is always endothermic. Conversely, bond formation always *releases* energy, so this reaction is always exothermic. The H–H bond requires +435 kJ/mol to cleave and releases −435 kJ/mol when formed. Table 6.2 contains a representative list of bond dissociation energies for many common bonds.

Additional bond dissociation energies for C–C multiple bonds are given in Table 1.6.

A table of bond dissociation energies also appears in Appendix E.



Comparing bond dissociation energies is equivalent to comparing bond strength.

- **The *stronger* the bond, the *higher* its bond dissociation energy.**

For example, the H–H bond is stronger than the Cl–Cl bond because its bond dissociation energy is higher [Table 6.2: 435 kJ/mol (H_2) versus 242 kJ/mol (Cl_2)]. The data in Table 6.2 demonstrate that bond dissociation energies *decrease* down a column of the periodic table as the valence electrons used in bonding are farther from the nucleus. Bond dissociation energies for a group of methyl–halogen bonds exemplify this trend.

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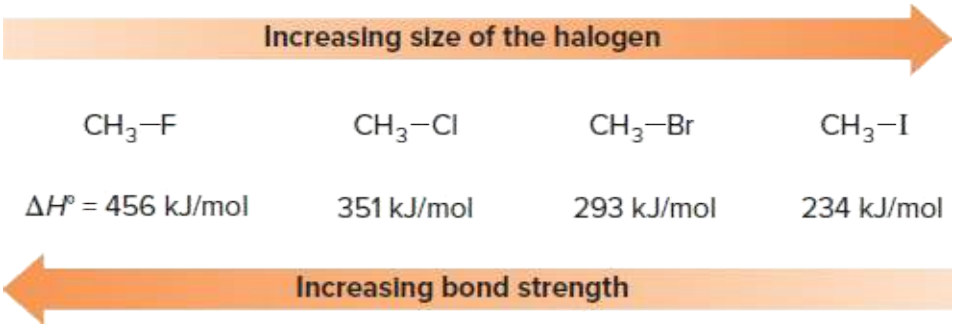
Table 6.2 Bond Dissociation Energies for Some Common Bonds [A–B → A• + •B]

Bond	ΔH^o kJ/mol	(kcal/mol)
H–Z bonds		
H–F	569	(136)
H–Cl	431	(103)
H–Br	368	(88)
H–I	297	(71)
H–OH	498	(119)
Z–Z bonds		
H–H	435	(104)
F–F	159	(38)
Cl–Cl	242	(58)
Br–Br	192	(46)
I–I	151	(36)
HO–OH	213	(51)

R–H bonds		
$CH_3–H$	435	(104)
$CH_3CH_2–H$	410	(98)
$CH_3CH_2CH_2–H$	410	(98)
$(CH_3)_2CH–H$	397	(95)
$(CH_3)_3C–H$	381	(91)
$CH_2=CH–H$	435	(104)
$HC\equiv C–H$	523	(125)
$CH_2=CHCH_2–H$	364	(87)
$C_6H_5–H$	460	(110)
$C_6H_5CH_2–H$	356	(85)
R–R bonds		
$CH_3–CH_3$	368	(88)
$CH_3–CH_2CH_3$	356	(85)
$CH_3–CH=CH_2$	385	(92)
$CH_3–C=CH$	489	(117)
R–X bonds		
$CH_3–F$	456	(109)
$CH_3–Cl$	351	(84)
$CH_3–Br$	293	(70)
$CH_3–I$	234	(56)
$CH_3CH_2–F$	448	(107)
$CH_3CH_2–Cl$	339	(81)
$CH_3CH_2–Br$	285	(68)
$CH_3CH_2–I$	222	(53)
	444	(106)

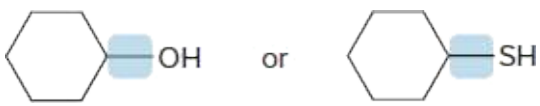
$(CH_3)_2CH–F$		
$(CH_3)_2CH–Cl$	335	(80)
$(CH_3)_2CH–Br$	285	(68)
$(CH_3)_2CH–I$	222	(53)
$(CH_3)_2C–F$	444	(106)
$(CH_3)_3C–Cl$	331	(79)
$(CH_3)_3C–C–Br$	272	(65)
$(CH_3)_3C–C–I$	209	(50)
R–OH bonds		
$CH_3–OH$	389	(93)
$CH_3CH_2–OH$	393	(94)
$CH_3CH_2CH_2–OH$	385	(92)
$(CH_3)_2CH–OH$	401	(96)
$(CH_3)_2C–OH$	401	(96)

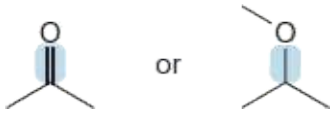


Because bond length increases down a column of the periodic table, bond dissociation energies are a quantitative measure of the general phenomenon noted in Chapter 1—*shorter* bonds are *stronger* bonds.

Problem 6.6

Which bond in each pair has the higher bond dissociation energy?

a. 

b.  or

Bond dissociation energies are also used to calculate the enthalpy change (ΔH^0) in a reaction in which several bonds are broken and formed. ΔH^0 indicates the relative strength of bonds broken and formed in a reaction.

- **When ΔH^0 is *positive*, more energy is needed to break bonds than is released in forming bonds. The bonds broken in the starting material are *stronger* than the bonds formed in the product.**

- **When ΔH^0 is *negative*, more energy is released in forming bonds than is needed to break bonds. The bonds formed in the product are *stronger* than the bonds broken in the starting material.**

To determine the overall ΔH^0 for a reaction:

[1] Beginning with a *balanced* equation, add the bond dissociation energies for all bonds broken in the starting materials. This (+) value represents the energy needed to break bonds.

[2] Add the bond dissociation energies for all bonds formed in the products. This (–) value represents the energy released in forming bonds.

[3] The overall ΔH^0 is the sum in Step [1] *plus* the sum in Step [2].

$$\Delta H^\circ \text{ overall enthalpy change} = \text{sum of } \Delta H^\circ \text{ of bonds broken} + \text{(–) sum of } \Delta H^\circ \text{ of bonds formed}$$

Sample Problem 6.3 Using Bond Dissociation Energies to Calculate ΔH^0

Use the values in Table 6.2 to determine ΔH^0 for the following reaction.

Solution

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[1] Bonds broken

	$\Delta H°$ (kJ/mol)
$(CH_3)_3C-Cl$	+331
H–OH	+498
Total	+829 kJ/mol

Energy needed to break bonds.

[2] Bonds formed

	$\Delta H°$ (kJ/mol)
$(CH_3)_3C-OH$	–401
H–Cl	–431
Total	–832 kJ/mol

Energy released in forming bonds.

[3] Overall $\Delta H°$=

sum in Step [1]
+
sum in Step [2]

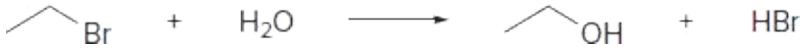
+829 kJ/mol
–832 kJ/mol

Answer: –3 kJ/mol

Because ΔH^o is a negative value, this reaction is exothermic and energy is released. The bonds broken in the starting material are *weaker* than the bonds formed in the product.

Problem 6.7

Use the values in Table 6.2 to calculate ΔH^o for each reaction. Classify each reaction as endothermic or exothermic.

a. 

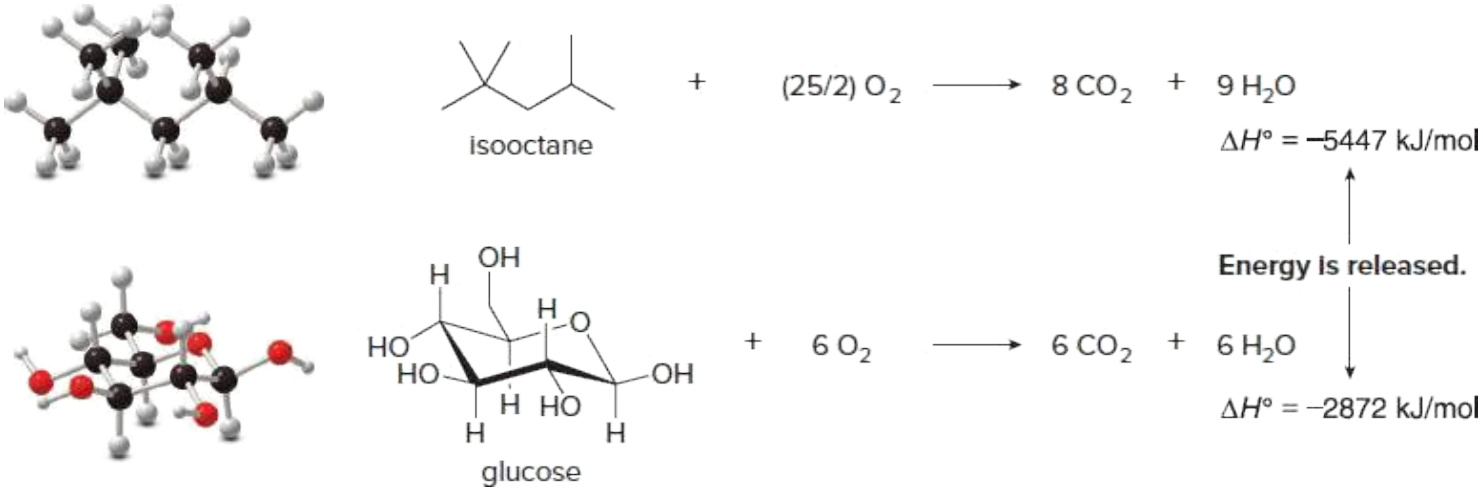
b.

More Practice:

Try Problems 6.36, 6.44b.

The oxidation of both isooctane and glucose, the molecule that introduced Chapter 6, forms CO_2 and H_2O.

The combustion of gasoline containing isooctane and the metabolism of glucose during exercise are exothermic reactions that release energy. ***©S-F/Shutterstock***



ΔH^o is *negative* for both oxidations, so both reactions are *exothermic*. Both isooctane and glucose release energy on oxidation because the bonds in the products are *stronger* than the bonds in the reactants.

Bond dissociation energies have two important limitations. They present only *overall* energy changes. They reveal nothing about the reaction mechanism or how fast a reaction proceeds. Moreover, bond dissociation energies are determined for reactions in the gas phase, whereas most organic reactions are carried out in a liquid solvent where solvation energy contributes to the overall enthalpy of a reaction. As such, bond dissociation energies are imperfect indicators of energy changes in a reaction. Despite these limitations, using bond dissociation energies to calculate ΔH^o gives a useful approximation of the energy changes that occur when bonds are broken and formed in a reaction.

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Problem 6.8

Calculate ΔH^o for each oxidation reaction. Each equation is balanced as written; remember to take into account the coefficients in determining the number of bonds broken or formed. [ΔH^o for O_2 = 497 kJ/mol; ΔH^o for one C=O in CO_2 = 535 kJ/mol]

a. $CH_4 + 2\ O_2 \longrightarrow CO_2 + 2\ H_2O$

b. $2\ CH_3CH_3 + 7\ O_2 \longrightarrow 4\ CO_2 + 6\ H_2O$

6.5 Thermodynamics

For a reaction to be practical, the equilibrium must favor the products, *and* the reaction rate must be fast enough to form them in a reasonable time. These two conditions depend on the thermodynamics and the kinetics of a reaction, respectively.

Reaction kinetics are discussed in Section 6.9.

- ***Thermodynamics*** **describes energy and equilibrium. How do the *energies* of the reactants and the products compare? What are the relative *amounts* of reactants and products at equilibrium?**

- ***Kinetics*** **describes reaction rates. How *fast* are reactants converted to products?**

6.5A Equilibrium Constant and Free Energy Changes

K_{eq} was first defined in Section 2.3 for acid–base reactions.

The equilibrium constant, K_{eq}, is a mathematical expression that relates the amount of starting material and product at equilibrium. For example, when starting materials A and B react to form products C and D, the equilibrium constant is given by the following expression:

$$A + B \rightleftharpoons C + D$$

$$K_{eq} = \frac{[\text{products}]}{[\text{starting materials}]} = \frac{[C][D]}{[A][B]}$$

The size of K_{eq} tells about the position of equilibrium; that is, it expresses whether the starting materials or products predominate once equilibrium has been reached.

- When $K_{eq} > 1$, equilibrium favors the *products* (C and D) and the equilibrium lies to the *right* as the equation is written.
- When $K_{eq} < 1$, equilibrium favors the *starting materials* (A and B) and the equilibrium lies to the *left* as the equation is written.

- **For a reaction to be useful, the equilibrium must favor the products, and $K_{eq} > 1$.**

What determines whether equilibrium favors the products in a given reaction? The position of equilibrium is determined by the relative energies of the reactants and products. The free energy of a molecule, also called its Gibbs free energy, is symbolized by G^o. The change in free energy between reactants and products, symbolized by ΔG^o, determines whether the starting materials or products are favored at equilibrium.

- **ΔG^o is the overall energy difference between reactants and products.**

$$\Delta G^\circ = G^\circ_{\text{products}} - G^\circ_{\text{reactants}}$$

$G^\circ_{\text{products}}$: free energy of the products; $G^\circ_{\text{reactants}}$: free energy of the reactants

ΔG° is related to the equilibrium constant K_{eq} by the following equation:

$$\Delta G^\circ = -2.303RT \log K_{eq}$$

R = 8.314 J/(K·mol), the gas constant
T = Kelvin temperature (K)

At 25 °C, 2.303RT = 5.7 kJ/mol; thus, $\Delta G^\circ = -5.7 \log K_{eq}$.

$K_{eq} > 1$ when $\Delta G^\circ < 0$, and equilibrium favors the *products*.
$K_{eq} < 1$ when $\Delta G^\circ > 0$, and equilibrium favors the *starting materials*.

Using this expression, we can determine the relationship between the equilibrium constant and the free energy change between reactants and products.

- **When $K_{eq} > 1$, $\log K_{eq}$ is positive, making ΔG° negative, and energy is *released*. Thus, equilibrium favors the products when the energy of the products is *lower* than the energy of the reactants.**
- **When $K_{eq} < 1$, $\log K_{eq}$ is negative, making ΔG° positive, and energy is *absorbed*. Thus, equilibrium favors the reactants when the energy of the products is *higher* than the energy of the reactants.**

Compounds that are lower in energy have increased stability. Thus, equilibrium favors the products when they are *more stable* (lower in energy) than the starting materials of a reaction. This is summarized in Figure 6.3.

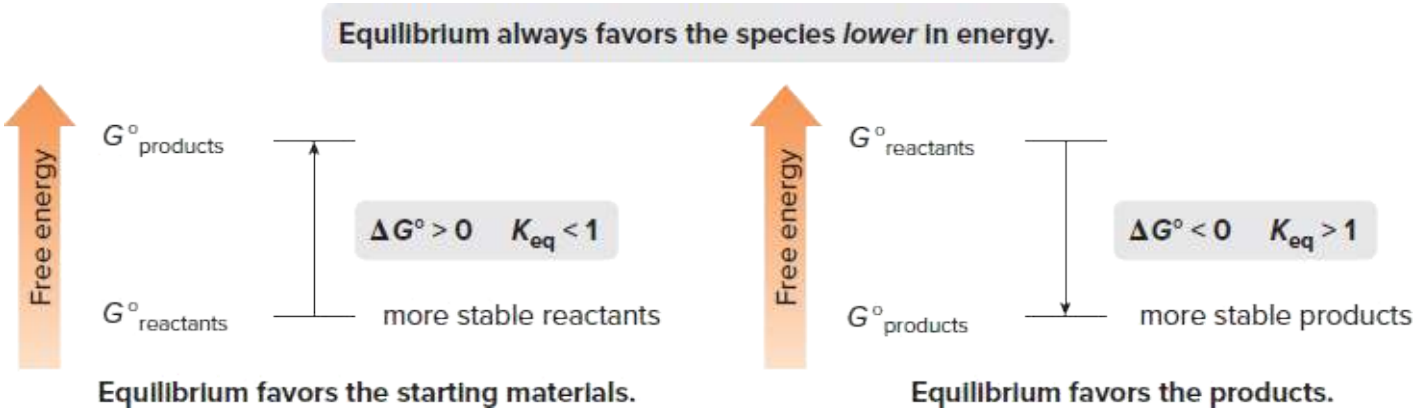


Figure 6.3 Summary of the relationship between ΔG^o and K_{eq}

Table 6.3 Representative Values for ΔG^o and K_{eq} at 25 °C, for a Reaction A → B

ΔG° (kJ/mol)	K_{eq}	Relative amount of A and B at equilibrium
+18	10^{-3}	Essentially all A (99.9%)
+12	10^{-2}	100 times as much A as B
+6	10^{-1}	10 times as much A as B
0	1	Equal amounts of A and B
−6	10^{1}	10 times as much B as A
−12	10^{2}	100 times as much B as A
−18	10^{3}	Essentially all B (99.9%)

Increasing [product]

Because ΔG^o depends on the logarithm of K_{eq}, a small change in energy corresponds to a large difference in the relative amount of starting material and product at equilibrium. Several values of ΔG^o and K_{eq} are given in Table 6.3. For example, a difference in energy of only ~6 kJ/mol means that there is 10 times as much of the more stable species at equilibrium. A difference in energy of ~18 kJ/mol means that there is essentially only one compound, either starting material or product, at equilibrium.

Problem 6.9

(a) Which K_{eq} corresponds to a negative value of ΔG^o, K_{eq} = 1000 or K_{eq} = .001? (b) Which K_{eq} corresponds to a lower value of ΔG^o, $K_{eq} = 10^{-2}$ or $K_{eq} = 10^{-5}$?

The symbol ~ means "approximately."

Problem 6.10

Given each of the following values, is the starting material or product favored at equilibrium?

a. K_{eq} = 5.5

b. ΔG^o = 40 kJ/mol

Problem 6.11

Given each of the following values, is the starting material or product lower in energy?

a. $\Delta G^{o} = 8.0$ kJ/mol

b. $K_{eq} = 10$

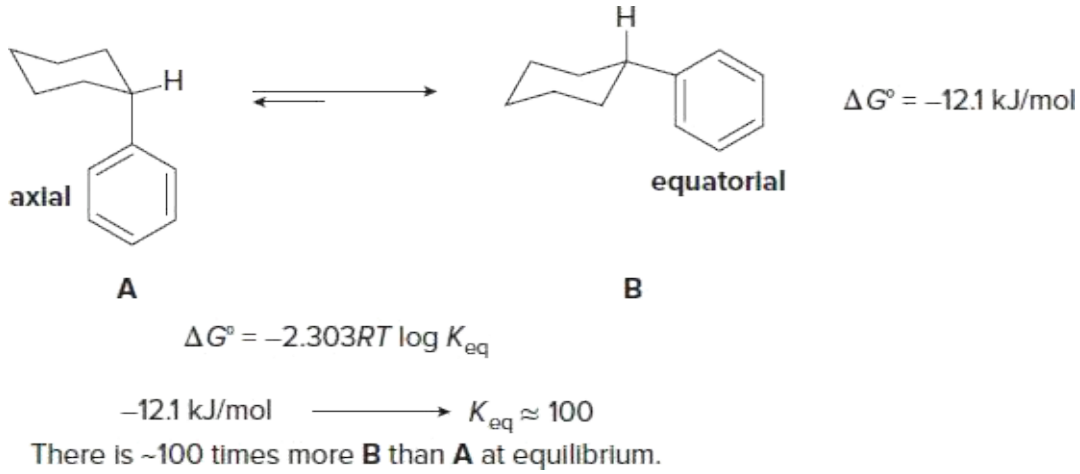
c. $\Delta G^{o} = -12$ kJ/mol

d. $K_{eq} = 10^{-3}$

6.5B Energy Changes and Conformational Analysis

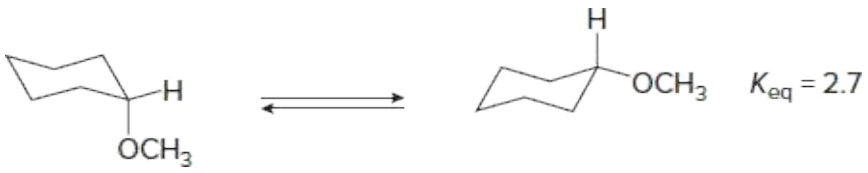
These equations can be used for any process with two states in equilibrium. As an example, monosubstituted cyclohexanes exist as two different chair conformations that rapidly interconvert at room temperature, with the conformation having the substituent in the roomier equatorial position favored (Section 4.13). Knowing the energy difference between the two conformations allows us to calculate the amount of each at equilibrium.

For example, the energy difference between the two chair conformations of phenylcyclohexane is −12.1 kJ/mol, as shown in the accompanying equation. Using the values in Table 6.3, this corresponds to an equilibrium constant of ~100, meaning that there is approximately 100 times more B (equatorial phenyl group) than A (axial phenyl group) at equilibrium.



Problem 6.12

The equilibrium constant for the conversion of the axial to the equatorial conformation of methoxycyclohexane is 2.7.



a. Given these data, which conformation is present in the larger amount at equilibrium?

b. Is ΔG^o for this process positive or negative?

c. From the values in Table 6.3, approximate the size of ΔG^o.

6.6 Enthalpy and Entropy

The free energy change (ΔG^o) depends on the enthalpy change (ΔH^o) and the entropy change (ΔS^o). ΔH^o indicates relative bond strength, but what does ΔS^o measure?

Entropy is a rather intangible concept that comes up again and again in chemistry courses. One way to remember the relation between entropy and disorder is to consider a handful of chopsticks. Dropped on the floor, they are arranged randomly (a state of high entropy). Placed end-to-end in a straight line, they are arranged intentionally (a state of low entropy). The more disordered, random arrangement is favored and easier to achieve.

Entropy (S^o) is a measure of the randomness in a system. The more freedom of motion or the more disorder present, the higher the entropy. Gas molecules move more freely than liquid molecules and are higher in entropy. Cyclic molecules have more restricted bond rotation than similar acyclic molecules and are lower in entropy.

The *entropy change* (ΔS^o) is the change in the amount of disorder between reactants and products. ΔS^o is positive (+) when the products are more disordered than the reactants. ΔS^o is negative (–) when the products are less disordered (more ordered) than the reactants.

- **Reactions resulting in an *increase in entropy* are favored.**

ΔG^o is related to ΔH^o and ΔS^o by the following equation:

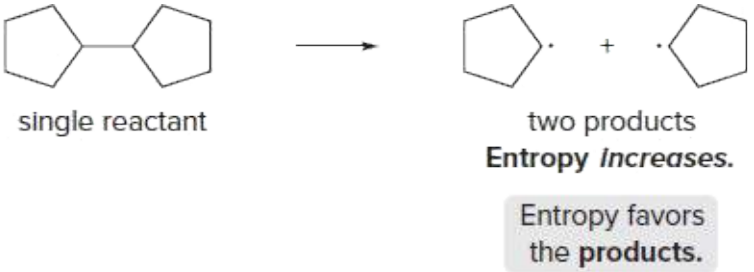
$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$$

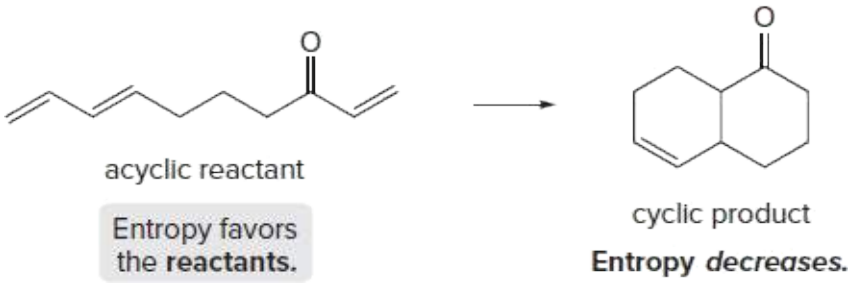
ΔG°	=	ΔH°	−	$T\Delta S^\circ$
total energy change		change in **bonding energy**		change in **disorder**

[T = Kelvin temperature]

This equation tells us that the total energy change in a reaction is due to two factors: the change in the bonding energy and the change in disorder. The change in bonding energy can be calculated from bond dissociation energies (Section 6.4). Entropy changes, on the other hand, are more difficult to assess, but they are important when the number of molecules of starting material *differs* from the number of molecules of product in the balanced chemical equation. The entropy of a system also changes when an acyclic molecule is *cyclized* to a cyclic one, or a cyclic molecule is converted to an acyclic one.

For example, when a single starting material forms two products, as in the homolytic cleavage of a bond to form two radicals, entropy increases and favors formation of the products. In contrast, entropy decreases when an acyclic compound forms a ring, because a ring has fewer degrees of freedom. In this case, therefore, entropy does *not* favor formation of the product.





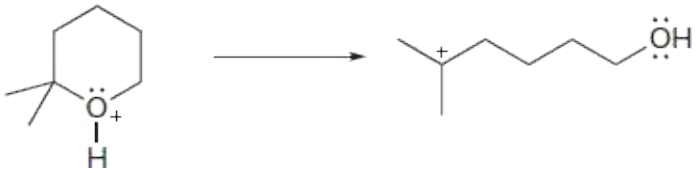
The metabolism of glucose (Section 6.4) is favored by entropy because the number of molecules of products formed (6 CO_2 and 6 H_2O) is greater than the number of molecules of reactants ($C_6H_{12}O_6$ and 6 O_2). Moreover, a cyclic reactant is cleaved to form 12 acyclic product molecules.

Problem 6.13

For which reactions does entropy favor the products?

a.

b.



Recall from Section 6.4 that a reaction is endothermic when ΔH^o is positive and exothermic when ΔH^o is negative. A reaction is endergonic when ΔG^o is positive and exergonic when ΔG^o is negative. ΔG^o is usually approximated by ΔH^o in this text, so the terms endergonic and exergonic are rarely used.

In most reactions that are not carried out at high temperature, the entropy term ($T\Delta S^0$) is small compared to the enthalpy term (ΔH^0) and it can be neglected. Thus, we will often approximate the overall free energy change of a reaction by the change in the bonding energy only. Keep in mind that this is an approximation, but it gives us a starting point from which to decide if the reaction is energetically favorable.

$$\Delta G^\circ \approx \Delta H^\circ$$

According to this approximation:

- **The product is favored when ΔH^o is a *negative* value; that is, the bonds in the product are *stronger* than the bonds in the starting material.**

- **The starting material is favored when ΔH^o is a *positive* value; that is, the bonds in the starting material are *stronger* than the bonds in the product.**

Problem 6.14

Considering each of the following values and neglecting entropy, tell whether the starting material or product is favored at equilibrium: (a) ΔH^o = 80 kJ/mol; (b) ΔH^o = −40 kJ/mol.

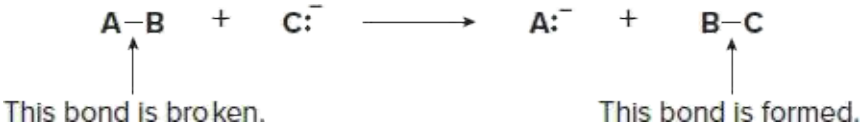
Problem 6.15

For a reaction with ΔH^{o} = 40 kJ/mol, decide which of the following statements is (are) true. Correct any false statement to make it true. (a) The reaction is exothermic; (b) ΔG^{o} for the reaction is positive; (c) K_{eq} is greater than 1; (d) the bonds in the starting materials are stronger than the bonds in the product; and (e) the product is favored at equilibrium.

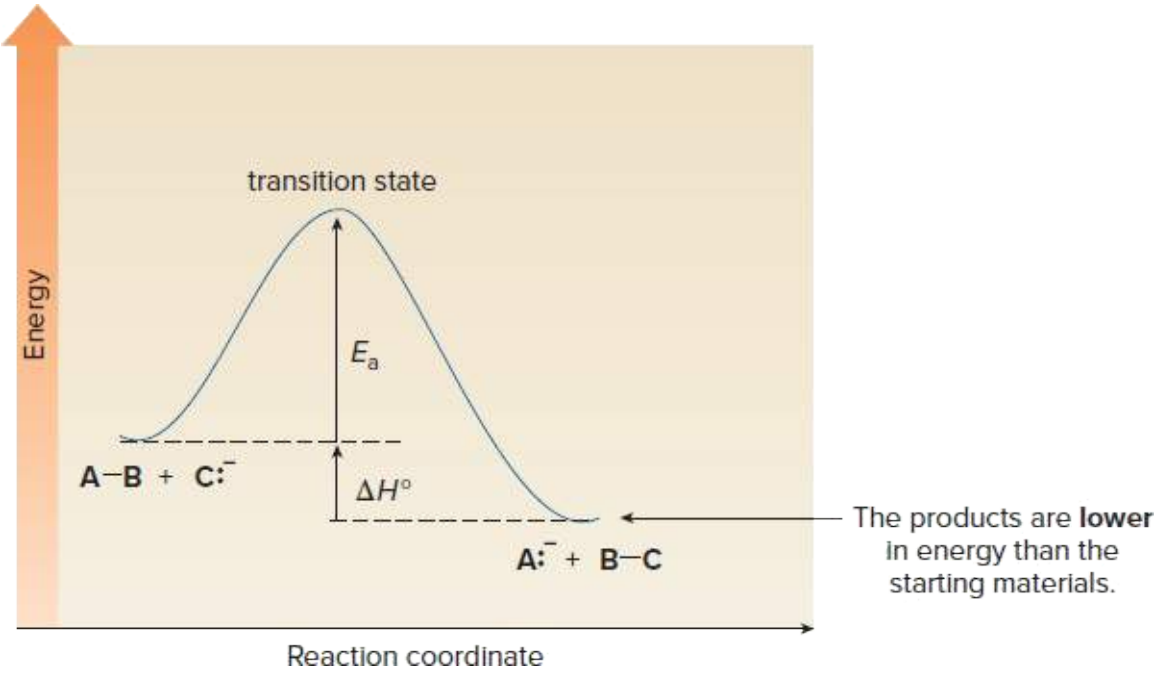
6.7 Energy Diagrams

An energy diagram is a schematic representation of the energy changes that take place as reactants are converted to products. An energy diagram indicates how readily a reaction proceeds, how many steps are involved, and how the energies of the reactants, products, and intermediates compare.

Consider a concerted reaction between molecule A–B with anion C:$^-$ to form products A:$^-$ and B–C. If the reaction occurs in a single step, the bond between A and B is broken *as* the bond between B and C is formed. Let's assume that the products are lower in energy than the reactants in this hypothetical reaction.



An energy diagram plots energy on the *y* axis versus the progress of reaction, often labeled the reaction coordinate, on the *x* axis. As the starting materials A–B and C:$^-$ approach one another, their electron clouds feel some repulsion, causing an increase in energy, until a maximum value is reached. This unstable energy maximum is called the transition state. In the transition state the bond between A and B is partially broken, and the bond between B and C is partially formed. Because it is at the top of an energy "hill," a transition state can never be isolated.



At the transition state, the bond between A and B can re-form to regenerate starting material, *or* the bond between B and C can form to generate product. As the bond forms between B and C, the energy decreases until some stable energy minimum of the products is reached.

- **The energy difference between the reactants and products is ΔH^{o}. Because the products are at lower energy than the reactants, this reaction is *exothermic* and energy is *released.***

- **The energy difference between the transition state and the starting material is called the *energy of activation*, symbolized by E_a.**

The *energy of activation* is the minimum amount of energy needed to break bonds in the reactants. It represents an energy barrier that must be overcome for a reaction to occur. The size of *E*a tells us about the reaction rate.

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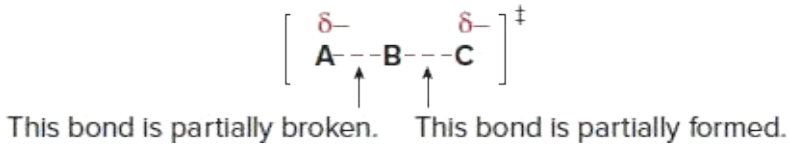
A slow reaction has a large E_a. A fast reaction has a low E_a.

- **The *larger* the E_a, the *greater* the amount of energy that is needed to break bonds, and the *slower* the reaction rate.**

How can we draw the structure of the unstable transition state? The structure of the transition state is somewhere in between the structures of the starting material and product. Any bond that is partially broken or formed is drawn with a *dashed* line. Any

atom that gains or loses a charge contains a *partial charge* in the transition state. Transition states are drawn in brackets, with a superscript double dagger (‡).

In the hypothetical reaction between A–B and C:$^{-}$ to form A:$^{-}$ and B–C, the bond between A and B is partially broken, and the bond between B and C is partially formed. Because A gains a negative charge and C loses a charge in the course of the reaction, each atom bears a partial negative charge in the transition state.



Several energy diagrams are drawn in Figure 6.4. For any energy diagram:

- **E_a determines the height of the energy barrier.**
- **ΔH^o determines the relative position of the reactants and products.**

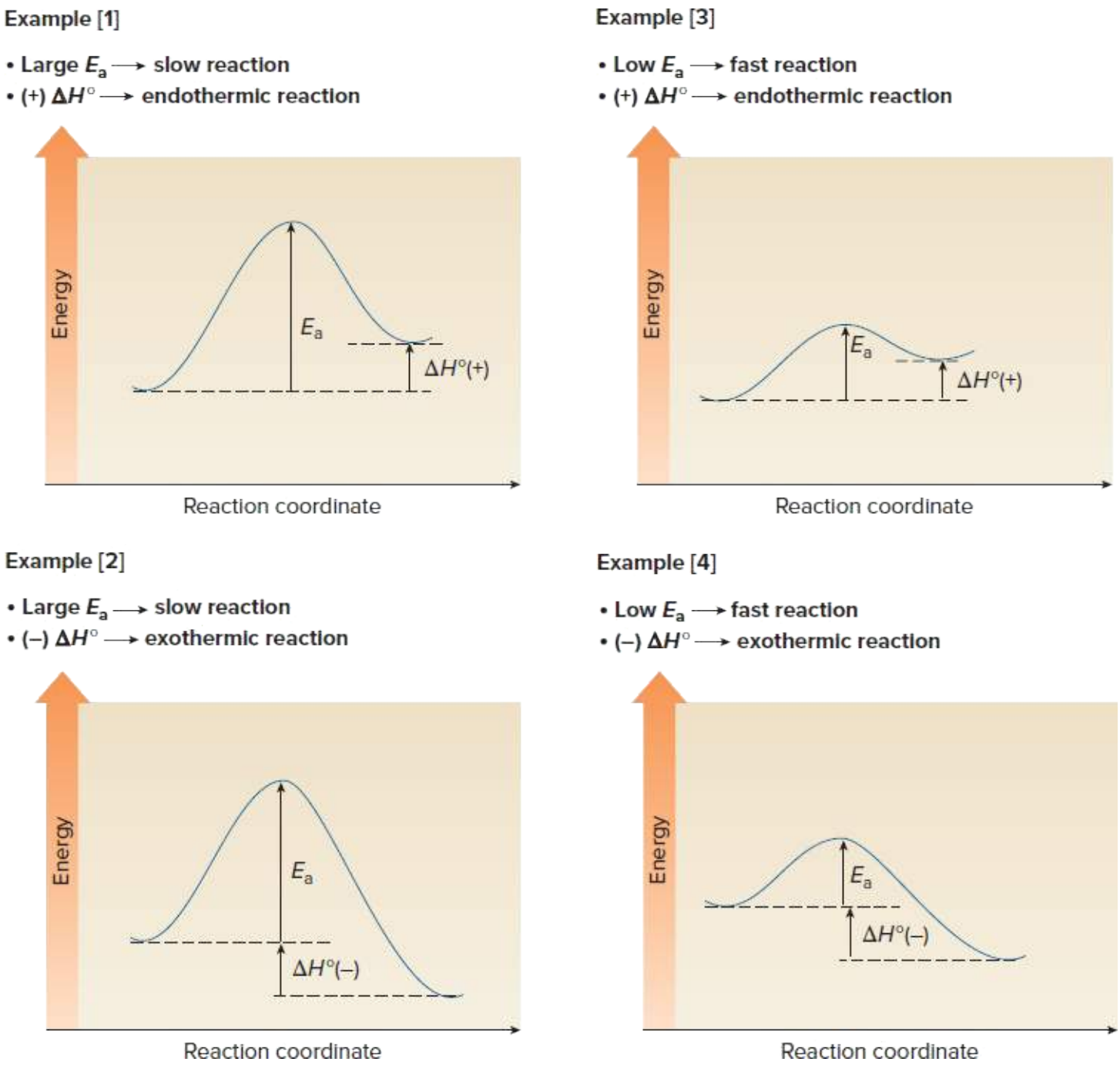


Figure 6.4 **Some representative energy diagrams**

The two variables, E_a and ΔH^o, are independent of each other. Two reactions Page 240 can have identical values for ΔH^o but very different Ea values. For two exothermic reactions with the same negative value of ΔH^o but different E_a values, the reaction with the lower E_a is faster.

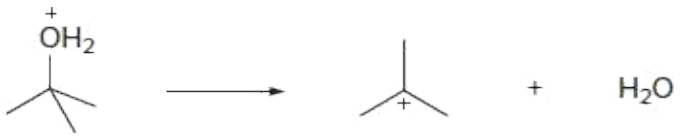
Problem 6.16

Draw an energy diagram for a reaction in which the products are higher in energy than the starting materials and E_a is large. Clearly label all of the following on the diagram: the axes, the starting materials, the products, the transition state, ΔH^o, and E_a.

Problem 6.17

Draw the structure for the transition state in each reaction.

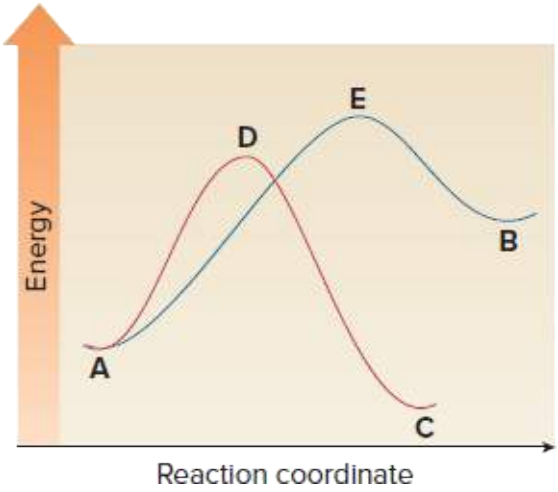
a.



b.

Problem 6.18

Compound A can be converted to either B or C. The energy diagrams for both processes are drawn on the graph below.



a. Label each reaction as endothermic or exothermic.

b. Which reaction is faster?

c. Which reaction generates the product lower in energy?

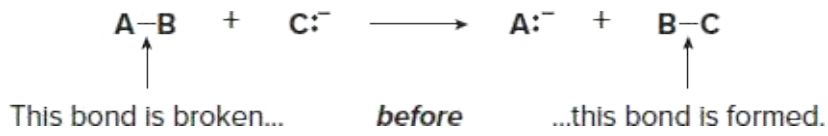
d. Which points on the graphs correspond to transition states?

e. Label the energy of activation for each reaction.

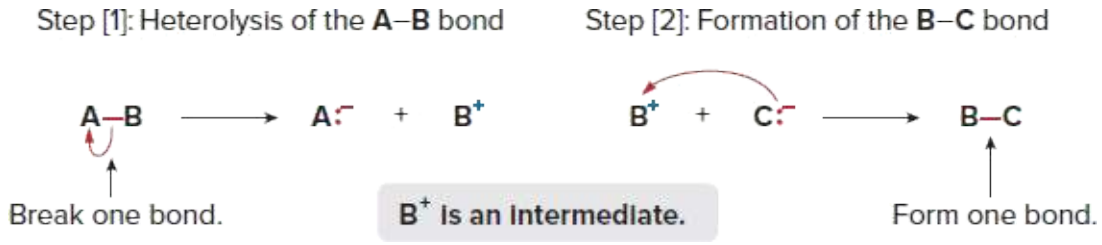
f. Label the ΔH^{o} for each reaction.

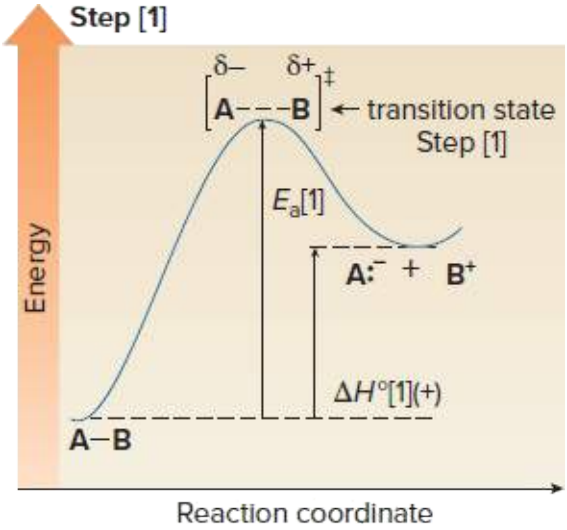
6.8 Energy Diagram for a Two-Step Reaction Mechanism

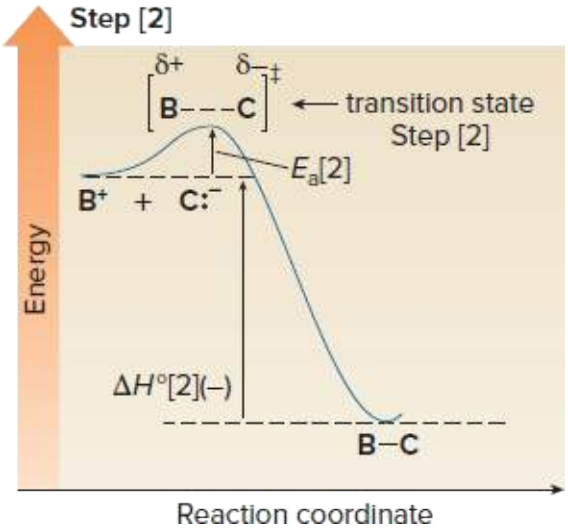
Although the hypothetical reaction in Section 6.7 is concerted, many reactions involve more than one step with formation of a reactive intermediate. Consider the same overall reaction, A–B + C:$^{-}$ to form products A:$^{-}$ + B–C, but in this case begin with the assumption that the reaction occurs by a *stepwise* pathway—that is, bond breaking occurs *before* bond making. Once again, assume that the overall process is exothermic.



One possible stepwise mechanism involves heterolysis of the A–B bond to form two ions A:$^-$ and B$^+$, followed by reaction of B$^+$ with anion C:$^-$ to form product B–C, as outlined in the accompanying equations. Species B$^+$ is a reactive intermediate. B$^+$ is a product in Step [1] that reacts with C:$^-$ in Step [2].







To draw an energy diagram for a two-step mechanism, we must draw an energy diagram for each step, and then combine them together. Each step has its own energy barrier, with a transition state at the energy maximum.

Step [1] is endothermic because energy is needed to cleave the A–B bond, making ΔH^o

a positive value and placing the products of Step [1] at higher energy than the starting materials. In the transition state, the A–B bond is partially broken.

Step [2] is exothermic because energy is released in forming the B–C bond, making ΔH^0 a negative value and placing the products of Step [2] at lower energy than the starting materials of Step [2]. In the transition state, the B–C bond is partially formed.

The overall process is shown in Figure 6.5 as a single energy diagram that combines both steps. Because the reaction has two steps, there are two transition states, each corresponding to an energy barrier. The transition states are separated by an energy minimum, at which the reactive intermediate B^+ is located. Because we made the assumption that the overall two-step process is exothermic, the overall energy difference between the reactants and products, labeled $\Delta H^0_{\text{overall}}$, has a negative value, and the final products are at a lower energy than the starting materials.

The energy barrier for Step [1], labeled $E_a[1]$, is higher than the energy barrier for Step [2], labeled $E_a[2]$, because bond cleavage (Step [1]) is more difficult (requires more energy) than bond formation (Step [2]). A higher-energy transition state for Step [1] makes it the slower step of the mechanism.

- **In a multistep mechanism, the step with the highest-energy transition state is called the rate-determining step.**

In this reaction, the rate-determining step is Step [1].

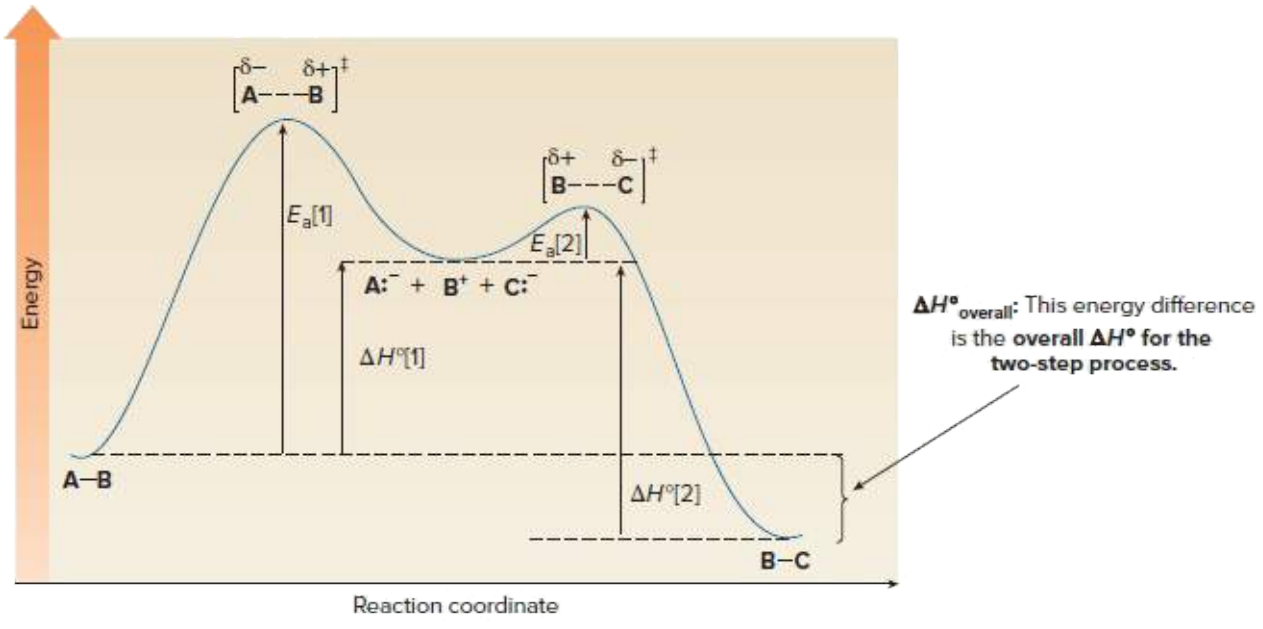
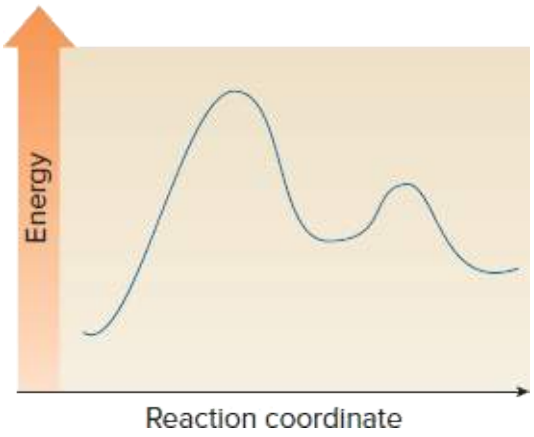


Figure 6.5 **Complete energy diagram for the two-step conversion of A–B + C:⁻ → A:⁻ + B–C**

- The transition states are located at energy maxima, while the reactive intermediate B^+ is located at an energy minimum.
- Each step has its own value of ΔH^o and E_a.
- The overall energy difference between starting material and products is called $\Delta H^o_{overall}$. In this example, the products of the two-step sequence are at lower energy than the starting materials.
- Because Step [1] has the higher-energy transition state, it is the rate-determining step.

Problem 6.19

Consider the following energy diagram.



a. How many steps are involved in this reaction?

b. Label ΔH^o and E_a for each step, and label $\Delta H^o_{overall}$.

c. Label each transition state.

d. Which point on the graph corresponds to a reactive intermediate?

e. Which step is rate-determining?

f. Is the overall reaction endothermic or exothermic?

Problem 6.20

Draw an energy diagram for a two-step reaction, A → B → C, where the relative energy of these compounds is C < A < B, and the conversion of B → C is rate-determining.

6.9 Kinetics

Some reactions have a very favorable equilibrium constant (K_{eq} >> 1), but the rate is very slow. Gasoline can be safely handled in the air because its reaction with O2 is slow unless there is a spark to provide energy to initiate the reaction.

©moodboard/Getty Images

Practically, the effect of temperature on reaction rate is used to an advantage in the kitchen. Food is stored in a cold refrigerator to slow the reactions that cause spoilage.

©McGraw-Hill Education/Jill Braaten, photographer

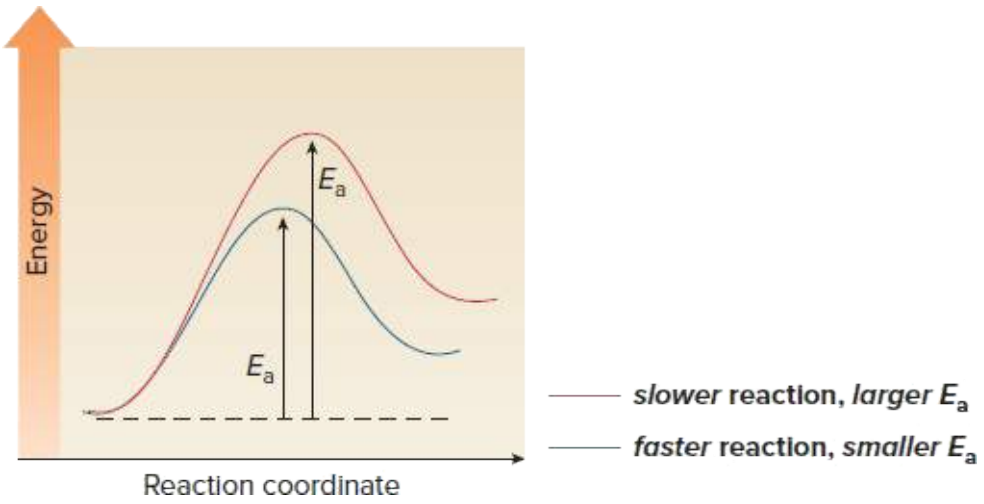
We now turn to a more detailed discussion of reaction rate—that is, how fast a particular reaction proceeds. The study of reaction rates is called *kinetics*.

The rate of chemical processes affects many facets of our lives. Aspirin is an effective anti-inflammatory agent because it rapidly inhibits the synthesis of prostaglandins (Section 19.6). DDT (Section 7.4) is a persistent environmental pollutant because it does not react appreciably with water, oxygen, or any other chemical with which it

comes into contact. These processes occur at different rates, resulting in beneficial or harmful effects.

6.9A Energy of Activation

As we learned in Section 6.7, the energy of activation, E_a, is the energy difference between the reactants and the transition state. It is the energy barrier that must be exceeded for reactants to be converted to products.



- **The *larger* the E_a, the *slower* the reaction.**

Concentration and temperature also affect reaction rate.

- **The *higher* the concentration, the *faster* the rate. Increasing concentration increases the number of collisions between reacting molecules, which in turn increases the rate.**

- **The *higher* the temperature, the *faster* the rate. Increasing temperature increases the average kinetic energy of the reacting molecules. Because the kinetic energy of colliding molecules is used for bond cleavage, increasing the average kinetic energy increases the rate.**

As a rule of thumb, increasing the temperature by 10 °C doubles the reaction rate. Thus, reactions in the lab are often heated to increase their rates so that they occur in a reasonable amount of time. Keep in mind that certain reaction quantities have *no effect* on reaction rate.

- **ΔG^o, ΔH^o, and K_{eq} do *not* determine the rate of a reaction. These quantities indicate the direction of equilibrium and the relative energy**

of reactants and products.

Problem 6.21

Which value (if any) corresponds to a faster reaction: (a) E_a = 40 kJ/mol or E_a = 4 kJ/mol; (b) a reaction temperature of 0 °C or a reaction temperature of 25 °C; (c) K_{eq} = 10 or K_{eq} = 100; (d) ΔH^o = −10 kJ/mol or ΔH^o = 10 kJ/mol?

Problem 6.22

For a reaction with K_{eq} = 0.8 and E_a = 80 kJ/mol, decide which of the following statements is (are) true. Correct any false statement to make it true. Ignore entropy considerations. (a) The reaction is faster than a reaction with K_{eq} = 8 and E_a = 80 kJ/mol. (b) The reaction is faster than a reaction with K_{eq} = 0.8 and E_a = 40 kJ/mol. (c) ΔG^o for the reaction is a positive value. (d) The starting materials are lower in energy than the products of the reaction. (e) The reaction is exothermic.

6.9B Rate Equations

The rate of a chemical reaction is determined by measuring the decrease in the concentration of the reactants over time, or the increase in the concentration of the products over time. A rate law (or rate equation) is an equation that shows the relationship between the rate of a reaction and the concentration of the reactants. A rate law is determined *experimentally*, and it depends on the mechanism of the reaction.

A rate law has two important terms: the rate constant symbolized by k and the concentration of the reactants. Not all reactant concentrations may appear in the rate equation, as we shall soon see.

$$\text{rate} = k[\text{reactants}]$$

k = the rate constant

A rate constant k and the energy of activation E_a are inversely related. A *high* E_a corresponds to a *small* k.

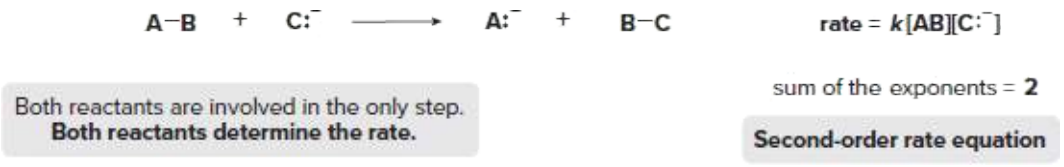
A rate constant k is a fundamental characteristic of a reaction. It is a complex mathematical term that takes into account the dependence of a reaction rate on temperature and the energy of activation.

- ***Fast* reactions have *large* rate constants.**
- ***Slow* reactions have *small* rate constants.**

What concentration terms appear in the rate equation? That depends on the mechanism. For the organic reactions we will encounter:

- **A rate equation contains concentration terms for *all* reactants involved in a *one-step* mechanism.**
- **A rate equation contains concentration terms for *only* the reactants involved in the *rate-determining step* in a multistep reaction.**

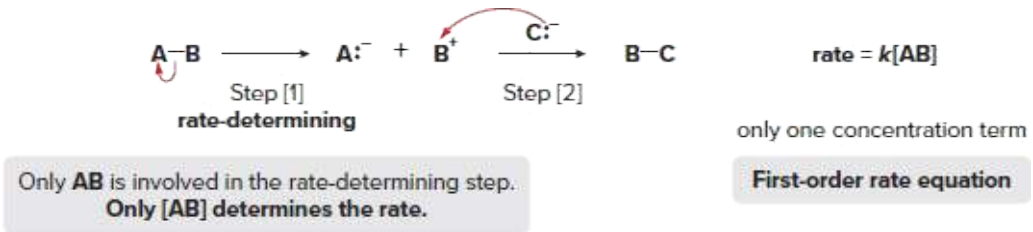
In the one-step reaction of A–B + C:$^-$ to form A:$^-$ + B–C, *both* reactants appear in the transition state of the only step of the mechanism. The concentration of *both* reactants affects the reaction rate, and *both* terms appear in the rate equation. This type of reaction involving two reactants is said to be bimolecular.



The *order* of a rate equation equals the sum of the exponents of the concentration terms in the rate equation. In the rate equation for the concerted reaction of A–B + C:$^-$, there are two concentration terms, each with an exponent of one. Thus, the sum of the exponents is two and the rate equation is *second order* (the reaction follows second-order kinetics).

Because the rate of the reaction depends on the concentration of both reactants, doubling the concentration of *either* A–B or C:$^-$ doubles the rate of the reaction. Doubling the concentration of *both* A–B and C:$^-$ increases the reaction rate by a factor of *four*.

The situation is different in the stepwise conversion of A–B + C:$^-$ to form A:$^-$ + B–C. The mechanism shown in Section 6.8 has two steps: a slow step (the rate-determining step) in which the A–B bond is broken, and a fast step in which the B–C bond is formed.



In a multistep mechanism, a reaction can occur no faster than its rate-determining step. Only the concentrations of the reactants in the rate-determining step appear in the rate equation. In this example, the rate depends on the concentration of A–B *only*, because only A–B appears in the rate-determining step. A reaction involving only one reactant is said to be unimolecular. Because there is only one concentration term (raised to the first power), the rate equation is *first order* (the reaction follows first-order kinetics).

Because the rate of the reaction depends on the concentration of only *one* reactant, doubling the concentration of A–B doubles the rate of the reaction, but doubling the concentration of $C:^-$ has *no effect* on the reaction rate.

This might seem like a puzzling result. If $C:^-$ is involved in the reaction, why doesn't it affect the overall rate of the reaction?

The following analogy is useful. Let's say three students must make 20 peanut butter and jelly sandwiches for a class field trip. Student (1) spreads the peanut butter on the bread. Student (2) spreads on the jelly, and student (3) cuts the sandwiches in half. Suppose student (2) is very slow in spreading the jelly. It doesn't matter how fast students (1) and (3) are; they can't finish making sandwiches any faster than student (2) can add the jelly. Five more students can spread on the peanut butter, or an entirely different individual can replace student (3), and this doesn't speed up the process. How fast the sandwiches are made is determined entirely by the rate-determining step—that is, spreading the jelly.

Rate equations provide very important information about the mechanism of a reaction. Rate laws for new reactions with unknown mechanisms are determined by a set of experiments that measure how a reaction's rate changes with concentration. Then, a mechanism is suggested based on which reactants affect the rate.

Problem 6.23

The rate equation for the reaction of CH_3CH_2Br with ^-OH is: rate = $k[CH_3CH_2Br][^-OH]$. What effect does the indicated concentration change have on the overall rate of the reaction?

a. tripling the concentration of CH_3CH_2Br only

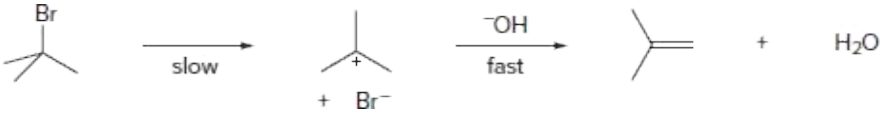
b. tripling the concentration of ^-OH only

c. tripling the concentration of both CH_3CH_2Br and ^-OH

Problem 6.24

Write a rate equation for each reaction, given the indicated mechanism.

a.

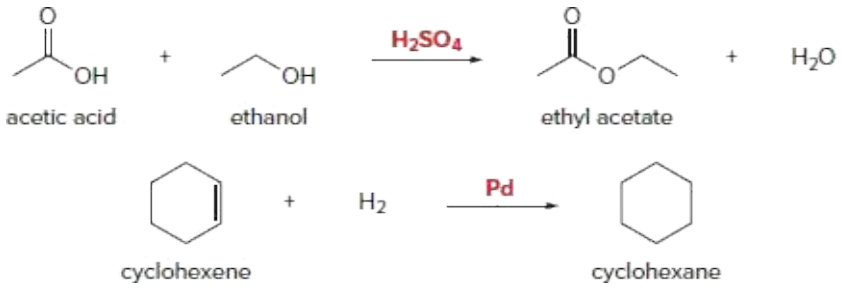
b. 

6.10 Catalysts

Some reactions do not occur in a reasonable time unless a catalyst is added.

- **A *catalyst* is a substance that speeds up the rate of a reaction. A catalyst is recovered unchanged in a reaction, and it does not appear in the product.**

Common catalysts in organic reactions are acids and metals. Two examples are shown with the catalyst drawn in red.

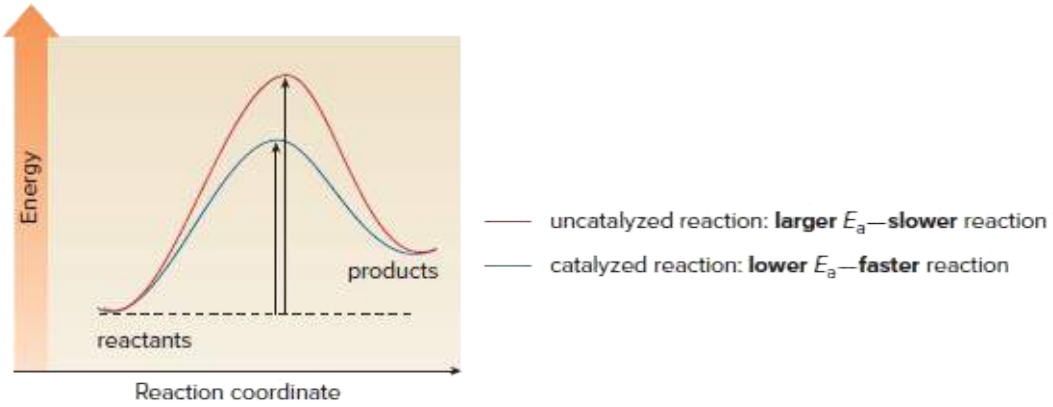


The reaction of acetic acid with ethanol to yield ethyl acetate and water occurs in the presence of an acid catalyst. The acid catalyst is written over or under the arrow to emphasize that it is not part of the starting materials or the products. The details of this reaction are discussed in Chapter 20.

The reaction of cyclohexene with hydrogen to form cyclohexane occurs only in the presence of a metal catalyst such as palladium, platinum, or nickel. The metal provides a surface that binds both the cyclohexene and the hydrogen, and in doing so, facilitates the reaction. We return to this mechanism in Chapter 12.

Catalysts accelerate a reaction by lowering the energy of activation (Figure 6.6). They have no effect on the equilibrium constant, so they do not change the amount of reactant and product at equilibrium. Thus, catalysts affect how *quickly* equilibrium is achieved, but not the relative amounts of reactants and products at equilibrium. If a catalyst is somehow used up in one step of a reaction sequence, it must be regenerated

in another step.



- The catalyst *lowers* the energy of activation, thus ***increasing the rate* of the catalyzed reaction.**
- The energy of the reactants and products is the same in both the uncatalyzed and catalyzed reactions, so the **position of equilibrium is unaffected.**

Figure 6.6 **The effect of a catalyst on a reaction**

Problem 6.25

Identify the catalyst in each equation.

a. $CH_2{=}CH_2 \xrightarrow[H_2SO_4]{H_2O} CH_3CH_2OH$

b. $CH_3Cl \xrightarrow[^-OH]{I^-} CH_3OH + Cl^-$

6.11 Enzymes

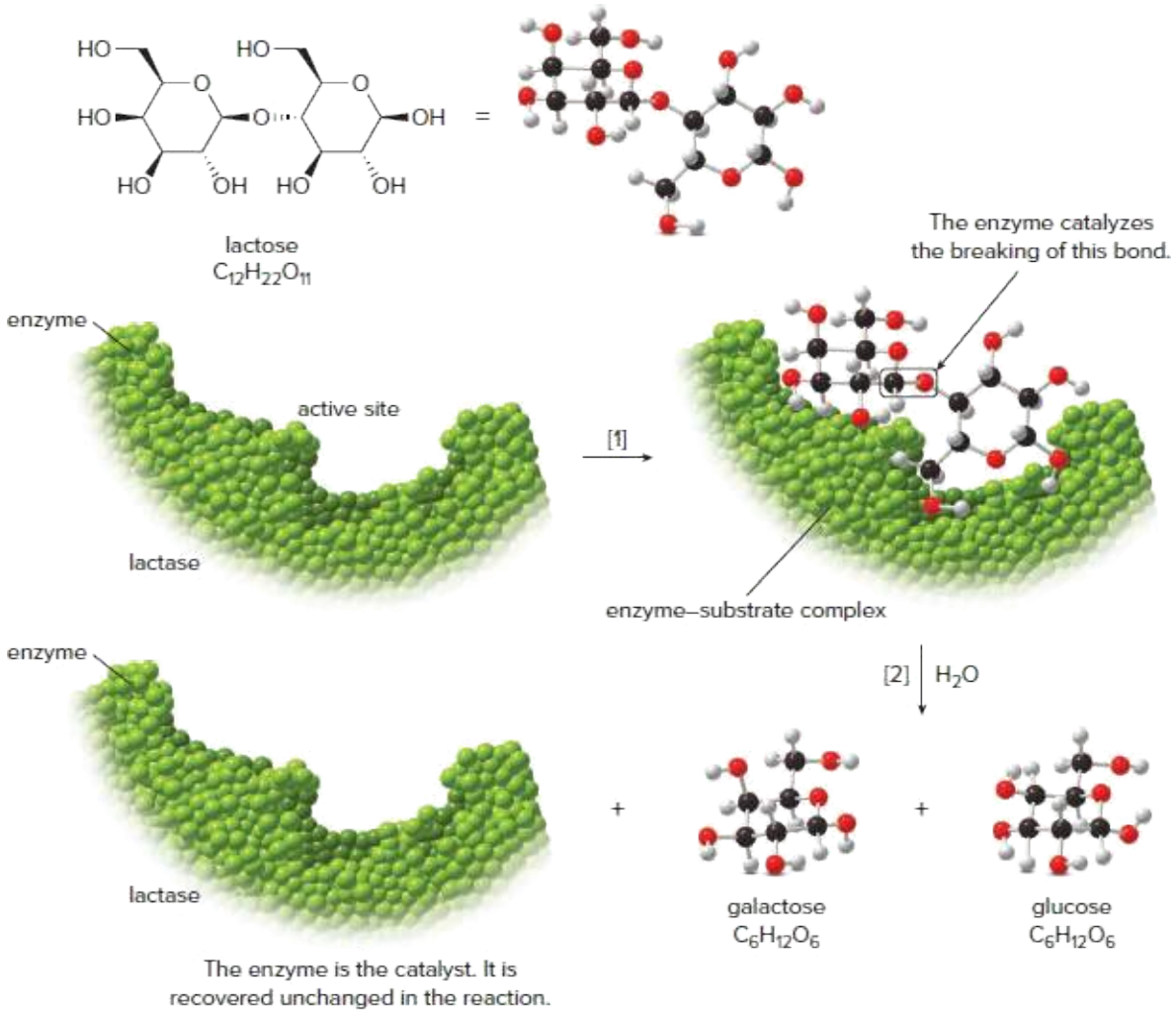
The catalysts that synthesize and break down biomolecules in living organisms are governed by the same principles as the acids and metals in organic reactions. The catalysts in living organisms, however, are usually protein molecules called enzymes.

- ***Enzymes* are biochemical catalysts composed of amino acids held together in a very specific three-dimensional shape.**

An enzyme contains a region called its active site, which binds an organic reactant, called a substrate. When bound, this unit is called the enzyme–substrate complex, as shown schematically in Figure 6.7 for the enzyme lactase, the enzyme that binds lactose, the principal carbohydrate in milk. Once bound, the organic substrate undergoes a very specific reaction at an enhanced rate. In this example, lactose is converted into two simpler sugars, glucose and galactose. When individuals lack adequate amounts of lactase, they are unable to digest lactose, causing abdominal

cramping and diarrhea.

An enzyme speeds up a biological reaction in a variety of ways. It may hold reactants in the proper conformation to facilitate reaction, or it may provide an acidic site needed for a particular transformation. Once the reaction is completed, the enzyme releases the substrate and it is then able to catalyze another reaction.



- The enzyme lactase binds the carbohydrate lactose ($C_{12}H_{22}O_{11}$) in its active site in Step [1]. Lactose then reacts with water to break a bond and form two simpler sugars, galactose and glucose, in Step [2]. This process is the first step in digesting lactose, the principal carbohydrate in milk.

Figure 6.7 **Lactase, an example of a biological catalyst**

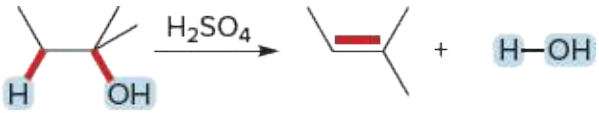
Chapter 6 REVIEW

KEY CONCEPTS

[1] Types of reactions (6.2)

1 Substitution

2 Elimination



two σ bonds broken
loss of H_2O

new π bond

- **Elimination is the opposite of addition.**

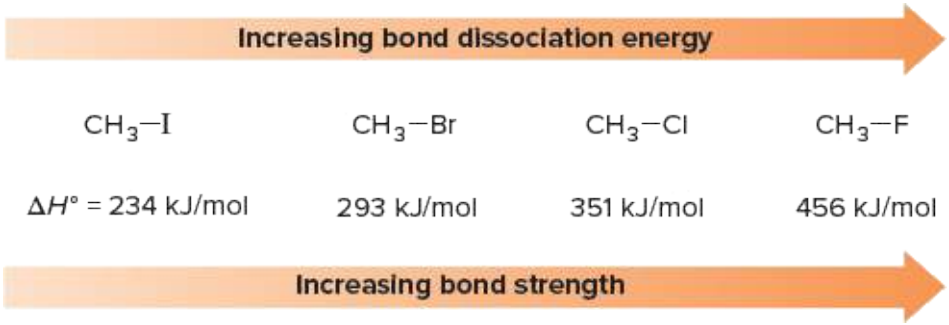
3

-

Try Problems 6.28, 6.31b, 6.49e, 6.51a, 6.53e.

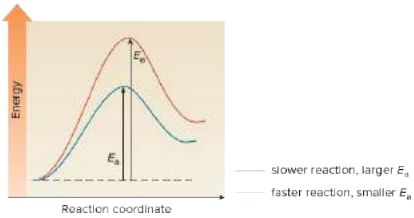
[2] Energy trends

1 Bond dissociation energy (ΔH^o) and bond strength (6.4)



- **The *higher* the ΔH^o, the *stronger* the bond.**

3 Energy of activation (E_a) and reaction rate (6.9A)



- **The *larger* the E_a, the *slower* the reaction.**

2 Energy and stability (6.5A)

- **The *higher the* energy, the *less stable* the species.**

See Figure 6.3.

4 Energy of activation and rate constant (6.9B)

- **The *larger* the E_a, the *smaller* the rate constant (k).**

Try Problems 6.35; 6.50b, d.

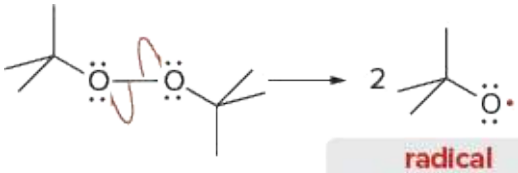
[3] Reactive intermediates (6.3)

1 Homolysis generates radicals with unpaired

2 Heterolysis generates ions.

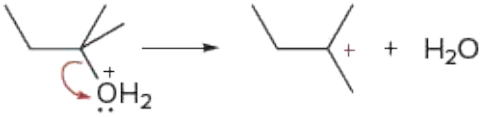
electrons.

Radical formation



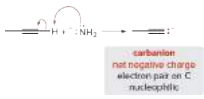
radical
unpaired electron
electrophilic

Carbocation formation



carbocation
positive charge
only six electrons around C
electrophilic

Carbanion formation



Try Problem 6.26.

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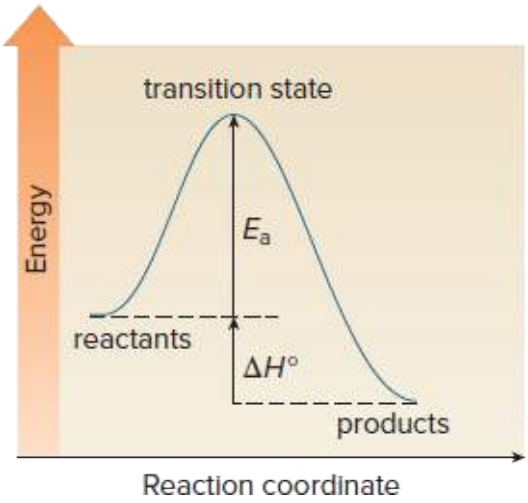
[4] Energy diagrams

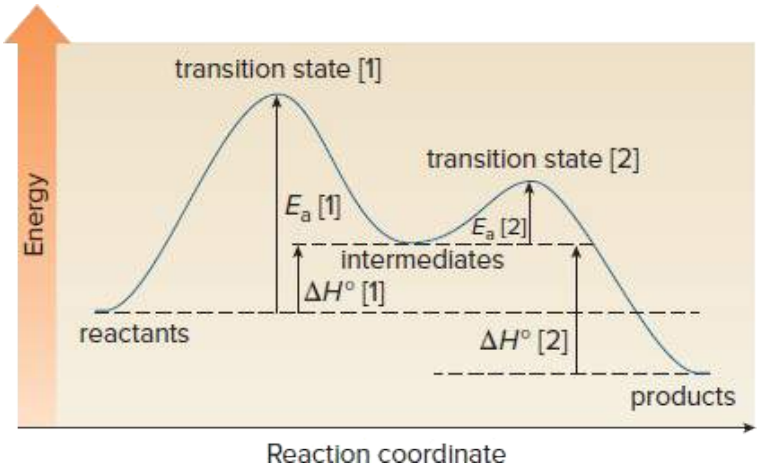
1 **One-step reaction mechanism (6.7)**



See Figure 6.4.

- E_a determines the rate; larger E_a ⇢ slower reaction (6.9).

2 **Two-step reaction mechanism (6.8)**



See Figure

- ΔH^o is the difference in bonding ener between the reactants and products.

Try Problems 6.43; 6.44c; 6.45; 6.46e; 6.54e, f.

[5] Conditions favoring product formation (6.5, 6.6)

1 $K_{eq} > 1$	• More products than reactants are present at equilibrium.
2 $\Delta G^o < 0$	• The free energy of the products is *lower* than the

	free energy of the reactants.
3 $\Delta H^{o} < 0$	• Bonds in the products are *stronger* than bonds in the reactants.
4 $\Delta S^{o} > 0$	• The products are *more disordered* than the reactants. • When a single starting material forms two products, entropy increases.

Try Problems 6.38, 6.39, 6.41.

KEY EQUATIONS

1 $\Delta G^{\circ} = -2.303RT \log K_{eq}$

K_{eq} depends on the energy difference between reactants and products.

[R = 8.314 J/(K•mol), the gas constant
T = Kelvin temperature (K)]

2 $\Delta G^{\circ} = \Delta H^{\circ} - T\Delta S^{\circ}$

free energy change = change in bonding energy − change in disorder

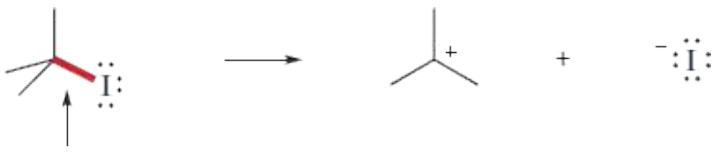
[T = Kelvin temperature (K)]

Try Problems 6.39, 6.40.

KEY SKILLS

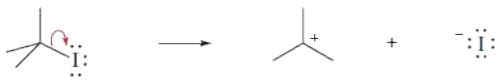
[1] Using full-headed curved arrows to show the movement of electron pairs (6.3D)

1 Look for all bonds that are broken or formed.



This bond is broken.

2 Use full-headed curved arrows for electron pairs.

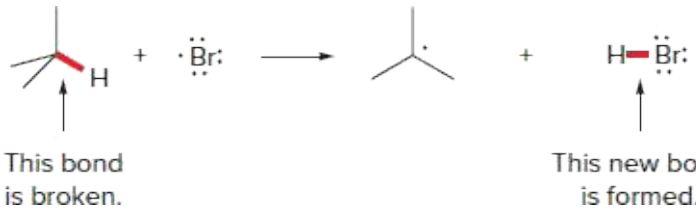


The **full-headed curved arrow** shows movement of an **electron pair.**

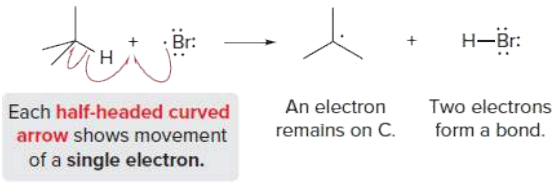
See Figure 6.2, Sample Problems 6.1, 6.2. Try Problems 6.29a, c, d; 6.30–6.33; 6.49a; 6.52a; 6.53a.

[2] Using half-headed curved arrows to show the movement of single electrons (6.3B)

1 **Look for all bonds that are broken or formed.**

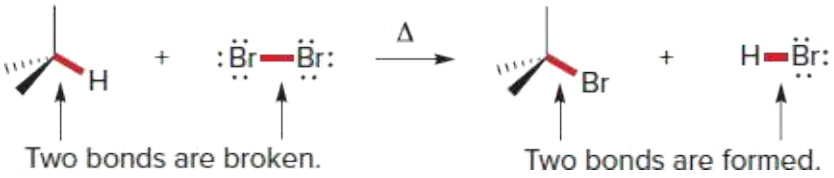


2 **Use half-headed curved arrows for single electrons**



See Figure 6.2. Try Problems 6.29b, 6.34, 6.44a.

[3] Calculating ΔH^{o} of a reaction (6.4)



1 **Bonds broken**

	$\Delta H°$ (kJ/mol)
$(CH_3)_3C–H$	+381
Br–Br	+192
Total	+573 kJ/mol

Energy needed to break bonds.

2 **Bonds formed**

	$\Delta H°$ (kJ/mol)
$(CH_3)_3C–Br$	–272
H–Br	–368
Total	–640 kJ/mol

Energy released in forming bonds.

3 **O**
Δ

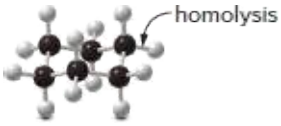
See Table 6.2, Sample Problem 6.3. Try Problems 6.36, 6.44b.

PROBLEMS

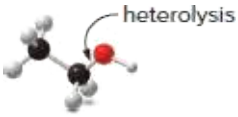
Problems Using Three-Dimensional Models

6.26 **Draw the products of homolysis or heterolysis of each indicated bond. Use electronegativity differences to decide on the location of charges in the heterolysis reaction. Classify each carbon reactive intermediate as a radical, carbocation, or carbanion.**

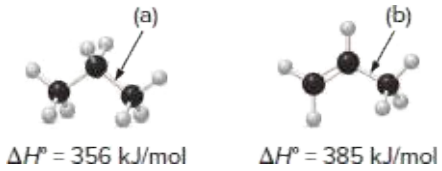
a.



b.



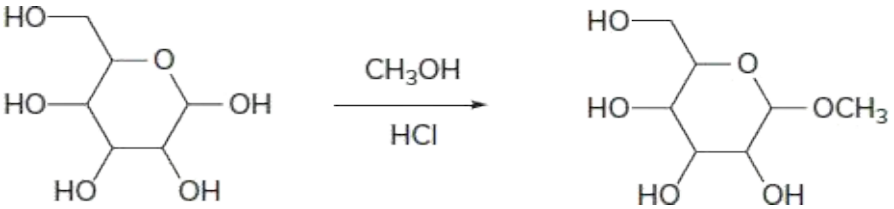
6.27 **Explain why the bond dissociation energy for bond (a) is lower than the bond dissociation energy for bond (b).**



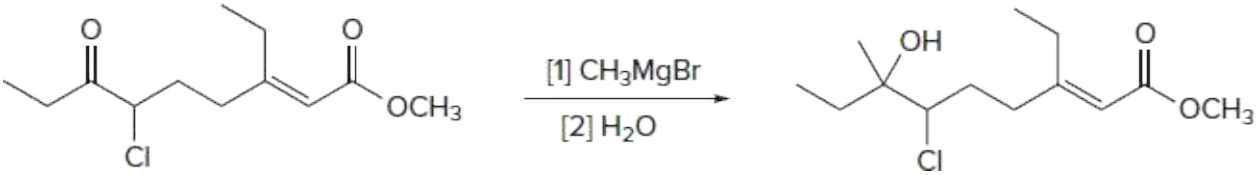
Types of Reactions

6.28 **Classify each transformation as substitution, elimination, or addition.**

a.



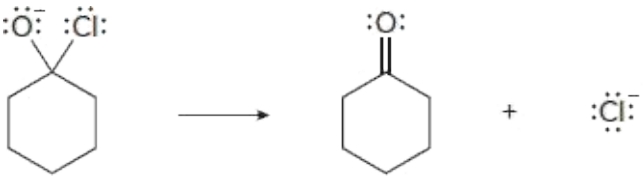
b.



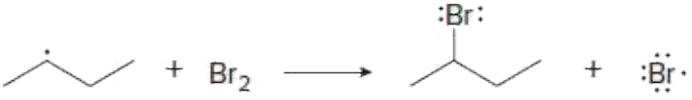
Curved Arrows

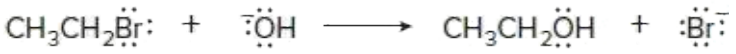
6.29 **Use full-headed or half-headed curved arrows to show the movement of electrons in each reaction.**

a.



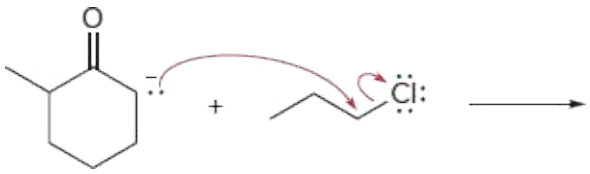
b.

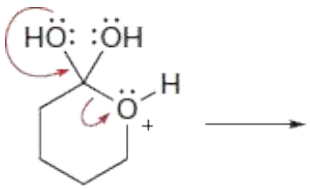


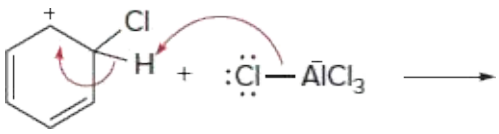
c. 

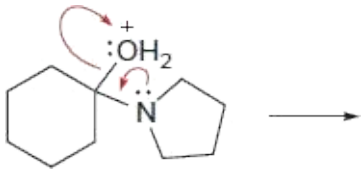
d.

6.30 Draw the products of each reaction by following the curved arrows.

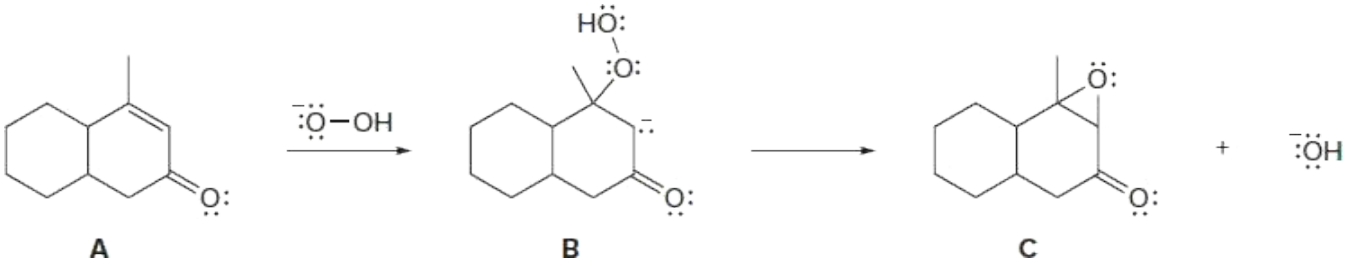
a. 

b. 

c. 

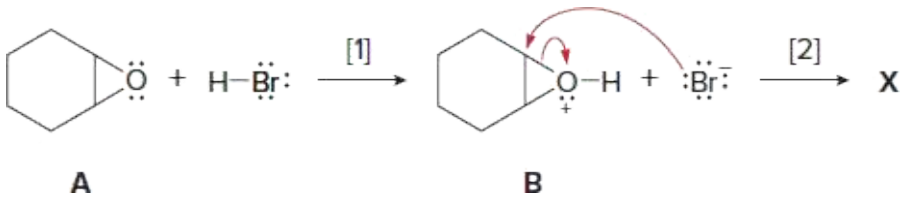
d. 

6.31 (a) Add curved arrows for each step to show how A is converted to the epoxy ketone C. (b) Classify the conversion of A to C as a substitution, elimination, or addition. (c) Draw one additional resonance structure for B.



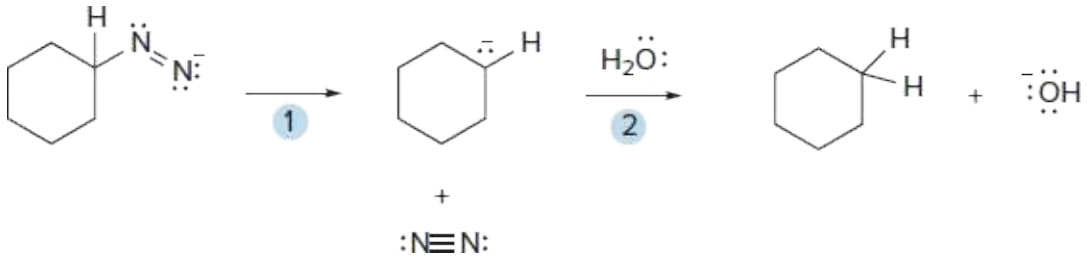
A **B** **C**

6.32 (a) Draw in the curved arrows to show how A is converted to B in Step [1]. (b) Identify X, using the curved arrows drawn for Step [2].

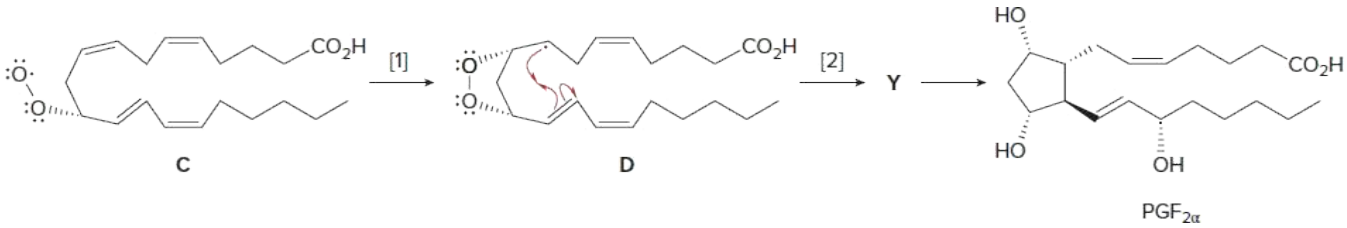


A **B**

6.33 Add curved arrows to each step in the following reaction sequence.

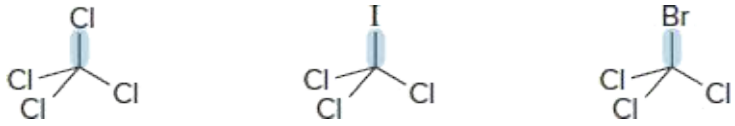


6.34 **$PGF_{2\alpha}$ (Section 4.15) is synthesized in cells using a cyclooxygenase enzyme that catalyzes a multistep radical pathway. Two steps in the pathway are depicted in the accompanying equations. (a) Draw in curved arrows to illustrate how C is converted to D in Step [1]. (b) Identify Y, the product of Step [2], using the curved arrows that are drawn on compound D.**



Bond Dissociation Energy and Calculating ΔH^o

6.35 **Rank the indicated bonds in order of increasing bond dissociation energy.**

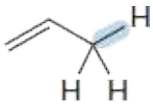


6.36 **Calculate ΔH^o for each reaction.**

a. $HO\bullet + CH_4 \longrightarrow \bullet CH_3 + H_2O$

b. $CH_3OH + HBr \longrightarrow CH_3Br + H_2O$

6.37 **Homolysis of the indicated C–H bond in propene forms a resonance-stabilized radical.**



propene

a. Draw the two possible resonance structures for this radical.

b. Use half-headed curved arrows to illustrate how one resonance structure can be converted to the other.

c. Draw a structure for the resonance hybrid.

Thermodynamics, ΔG^o, ΔH^o, ΔS^o, and K_{eq}

6.38 Given each value, determine whether the starting material or product is favored at equilibrium.

a. $K_{eq} = 0.5$

b. $\Delta G^o = -100$ kJ/mol

c. $\Delta H^o = 8.0$ kJ/mol

d. $K_{eq} = 16$

e. $\Delta G^o = 2.0$ kJ/mol

f. $\Delta H^o = 200$ kJ/mol

g. $\Delta S^o = 8$ J/(K•mol)

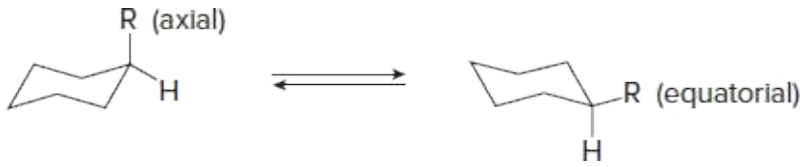
h. $\Delta S^o = -8$ J/(K•mol)

6.39 a. Which value corresponds to a negative value of ΔG^o: $K_{eq} = 10^{-2}$ or $K_{eq} = 10^2$?

b. In a unimolecular reaction with five times as much starting material as product at equilibrium, what is the value of K_{eq}? Is ΔG^o positive or negative?

c. Which value corresponds to a larger K_{eq}: $\Delta G^o = -8$ kJ/mol or $\Delta G^o = 20$ kJ/mol?

6.40 As we learned in Chapter 4, monosubstituted cyclohexanes exist as an equilibrium mixture of two conformations having either an axial or equatorial substituent. When R = CH_2CH_3, K_{eq} for this process is 23. When R = $C(CH_3)_3$, K_{eq} for this process is 4000.



a. When R = CH_2CH_3, which conformation is present in higher concentration?

b. Which R shows the higher percentage of equatorial conformation at equilibrium?

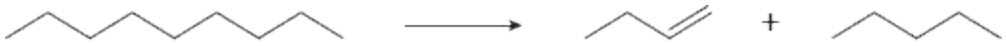
c. Which R shows the higher percentage of axial conformation at

equilibrium?

d. For which R is ΔG^o more negative?

e. How is the size of R related to the amount of axial and equatorial conformations at equilibrium?

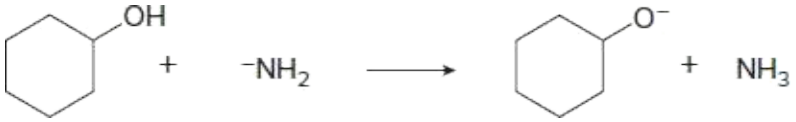
6.41 For which of the following reactions is ΔS^o a positive value?

a. 

b.

Energy Diagrams and Transition States

6.42 Draw the transition state for each reaction.

a. 

b.

6.43 Draw an energy diagram for each reaction. Label the axes, the starting material, product, transition state, ΔH^o, and E_a.

a. a concerted reaction with ΔH^o = −80 kJ/mol and E_a = 16 kJ/mol

b. a two-step reaction, A → B → C, in which the relative energy of the compounds is A < C < B, and the step A → B is rate-determining

6.44 Consider the following reaction: $CH_4 + Cl\bullet \rightarrow \bullet CH_3 + HCl$.

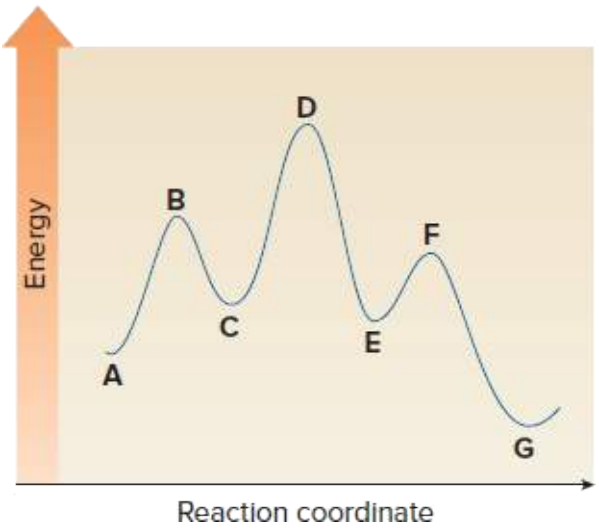
a. Use curved arrows to show the movement of electrons in this radical reaction.

b. Calculate ΔH^o using the bond dissociation energies in Table 6.2.

c. Draw an energy diagram assuming that E_a = 16 kJ/mol.

d. What is E_a for the reverse reaction ($\bullet CH_3 + HCl \rightarrow CH_4 + Cl\bullet$)?

6.45 Consider the following energy diagram for the conversion of A → G.



a. **Which points on the graph correspond to transition states?**

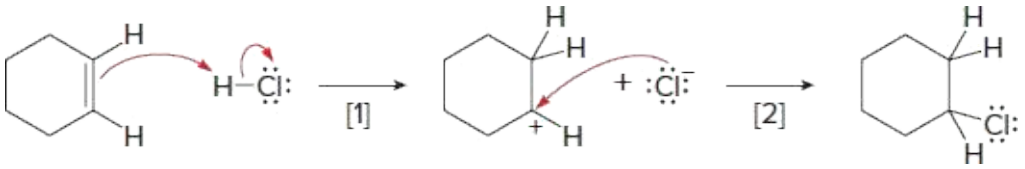
b. **Which points on the graph correspond to reactive intermediates?**

c. **How many steps are present in the reaction mechanism?**

d. **Label each step of the mechanism as endothermic or exothermic.**

e. **Label the overall reaction as endothermic or exothermic.**

6.46 Consider the following two-step reaction:



a. **How many bonds are broken and formed in Step [1]? Would you predict the ΔH^{o} of Step [1] to be positive or negative?**

b. **How many bonds are broken and formed in Step [2]? Would you predict the ΔH^{o} of Step [2] to be positive or negative?**

c. **Which step is rate-determining?**

d. **Draw the structure for the transition state in both steps of the mechanism.**

e. **If $\Delta H^{o}_{overall}$ is negative for this two-step reaction, draw an energy diagram illustrating all of the information in parts (a)–(d).**

Kinetics and Rate Laws

6.47 Indicate which factors affect the rate of a reaction.

a. **ΔG^{o}**

b. ΔH^o

c. E_a

d. temperature

e. concentration

f. k_{eq}

g. k

h. catalysts

6.48 The following is a concerted, bimolecular reaction: $CH_3Br + NaCN \rightarrow CH_3CN + NaBr$.

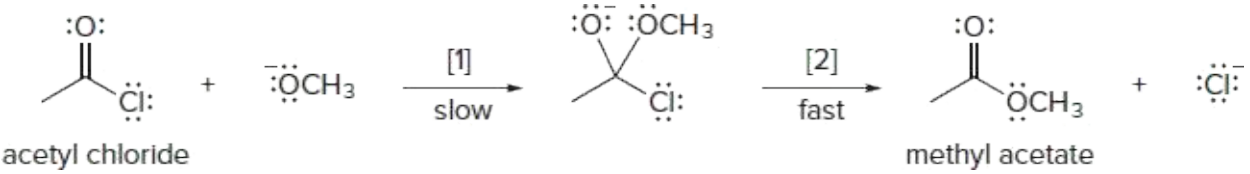
a. What is the rate equation for this reaction?

b. What happens to the rate of the reaction if $[CH_3Br]$ is doubled?

c. What happens to the rate of the reaction if [NaCN] is halved?

d. What happens to the rate of the reaction if $[CH_3Br]$ and [NaCN] are both increased by a factor of five?

6.49 The conversion of acetyl chloride to methyl acetate occurs via the following two-step mechanism:



acetyl chloride methyl acetate

a. Add curved arrows to show the movement of the electrons in each step.

b. Write the rate equation for this reaction, assuming the first step is rate-determining.

c. If the concentration of $^-OCH_3$ were increased 10 times, what would happen to the rate of the reaction?

d. If the concentrations of both CH_3COCl and $^-OCH_3$ were increased 10 times, what would happen to the rate of the reaction?

e. Classify the conversion of acetyl chloride to methyl acetate as an addition, elimination, or substitution.

6.50 **Label each statement as true or false. Correct any false statement to make it true.**

a. Increasing temperature increases reaction rate.

b. If a reaction is fast, it has a large rate constant.

c. A fast reaction has a large negative ΔG^{o} value.

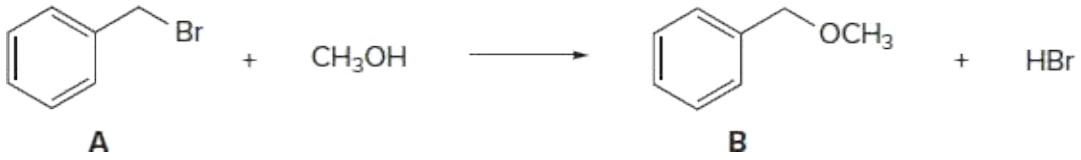
d. When E_a is large, the rate constant k is also large.

e. Fast reactions have equilibrium constants > 1.

f. Increasing the concentration of a reactant always increases the rate of a reaction.

General Problems

6.51 **Consider the conversion of alkyl halide A to ether B.**

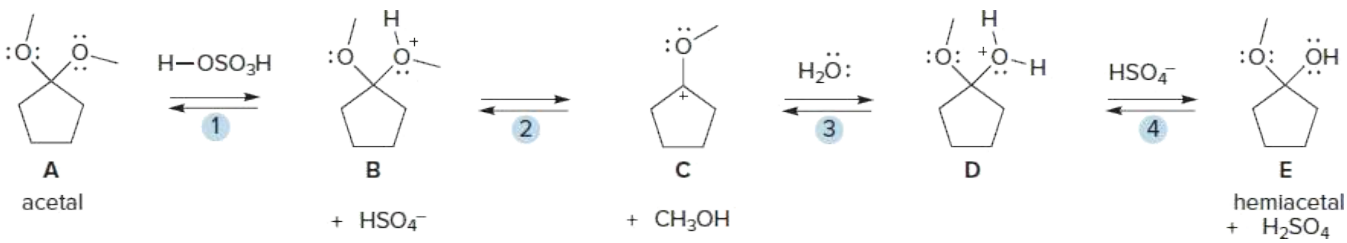


a. Classify the conversion of A to B as substitution, elimination, or addition.

b. The reaction rate depends on the concentration of A only. Write the rate equation for the reaction, and explain why the reaction mechanism must involve more than one step.

c. Heterolysis of the polar bond in A forms a resonance-stabilized intermediate. Draw all reasonable resonance structures for this intermediate.

6.52 **In Chapter 18, we will learn about the hydrolysis of acetals to aldehydes and ketones. Four of the seven steps in the mechanism for this process are shown in the conversion of acetal A to hemiacetal E.**



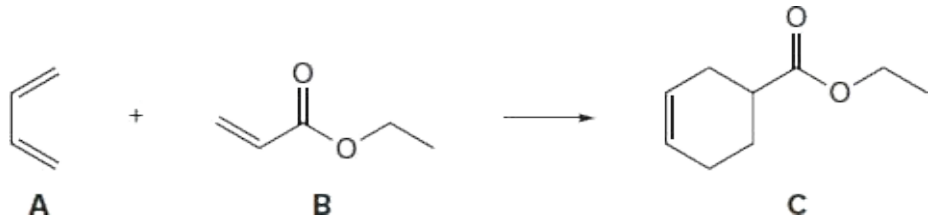
a. Add curved arrows for each step.

b. Draw another resonance structure for C.

c. Identify the nucleophile and electrophile in Step [3].

d. Which steps are Brønsted–Lowry acid–base reactions?

6.53 The Diels–Alder reaction, a powerful reaction discussed in Chapter 14, occurs when a 1,3-diene such as A reacts with an alkene such as B to form the six-membered ring in C.



a. Draw curved arrows to show how A and B react to form C.

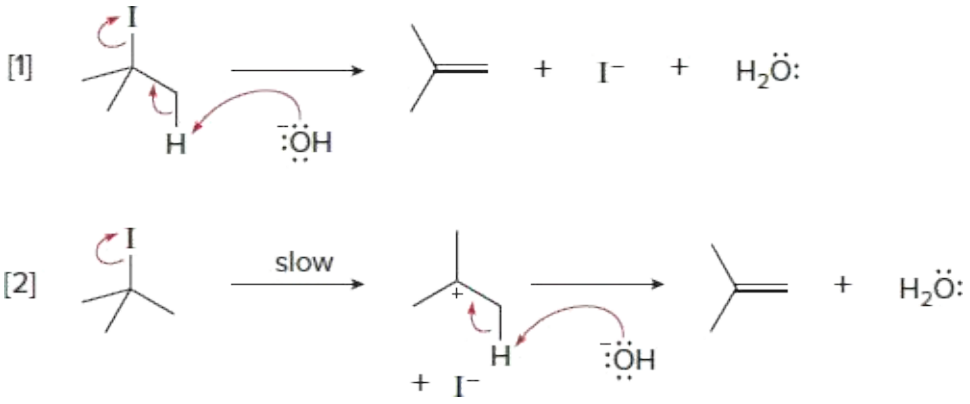
b. What bonds are broken and formed in this reaction?

c. Would you expect this reaction to be endothermic or exothermic?

d. Does entropy favor the reactants or products?

e. Is the Diels–Alder reaction a substitution, elimination, or addition?

6.54 The conversion of $(CH_3)_3CI$ to $(CH_3)_2C{=}CH_2$ can occur by either a one-step or a two-step mechanism, as shown in Equations [1] and [2].



a. What rate equation would be observed for the mechanism in Equation [1]?

b. What rate equation would be observed for the mechanism in Equation [2]?

c. What is the order of each rate equation (i.e., first, second, and so forth)?

d. How can these rate equations be used to show which mechanism is the right one for this reaction?

e. Assume Equation [1] represents an endothermic reaction and draw an energy diagram for the reaction. Label the axes, reactants, products, E_a, and ΔH^o. Draw the structure for the transition state.

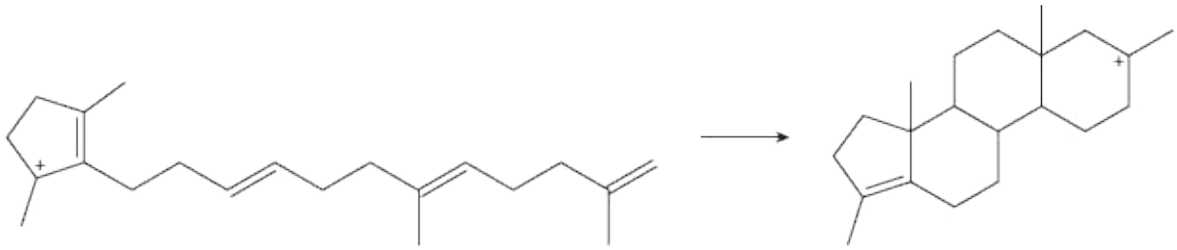
f. Assume Equation [2] represents an endothermic reaction and that the product of the rate-determining step is higher in energy than the reactants or products. Draw an energy diagram for this two-step reaction. Label the axes, reactants and products for each step, and the E_a and ΔH^o for each step. Label $\Delta H^o_{overall}$. Draw the structure for both transition states.

Challenge Problems

6.55 Explain why HC≡CH is more acidic than CH_3CH_3, even though the C–H bond in HC≡CH has a higher bond dissociation energy than the C–H bond in CH_3CH_3.

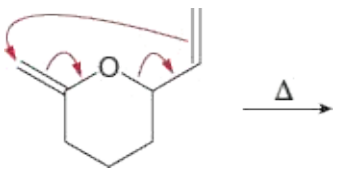
6.56 The use of curved arrows is a powerful tool that illustrates even complex reactions.

a. Add curved arrows to show how carbocation A is converted to carbocation B. Label each new σ bond formed. Similar reactions have been used in elegant syntheses of steroids.

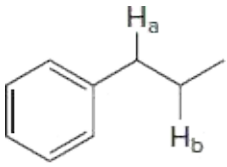


A B

b. Draw the product by following the curved arrows. This reaction is an example of a [3,3] sigmatropic rearrangement, as we will learn in Chapter 25.



6.57



propylbenzene

a. What carbon radical is formed by homolysis of the C–H_a bond in propylbenzene? Draw all reasonable resonance structures for this radical.

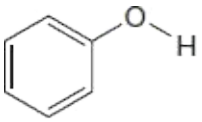
b. What carbon radical is formed by homolysis of the C–H_b bond in propylbenzene? Draw all reasonable resonance structures for this radical.

c. The bond dissociation energy of one of the C–H bonds is considerably less than the bond dissociation energy of the other. Which C–H bond is weaker? Offer an explanation.

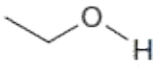
6.58 As we will learn in Section 13.12, many antioxidants–compounds that prevent unwanted radical oxidation reactions from occurring–are phenols, compounds that contain an OH group bonded directly to a benzene ring.

a. Explain why homolysis of the O–H bond in phenol requires considerably less energy than homolysis of the O–H bond in ethanol (362 kJ/mol vs. 438 kJ/mol).

b. Why is the C–O bond in phenol shorter than the C–O bond in ethanol?



phenol



ethanol

7

Alkyl Halides and Nucleophilic Substitution

Source: Claire Fackler, CINMS/NOAA

7.1 Introduction to alkyl halides

7.2 Nomenclature

7.3 Properties of alkyl halides

7.4 Interesting alkyl halides

7.5 The polar carbon–halogen bond

7.6 General features of nucleophilic substitution

7.7 The leaving group

7.8 The nucleophile

7.9 Possible mechanisms for nucleophilic substitution

7.10 Two mechanisms for nucleophilic substitution

7.11 The S_N2 mechanism

7.12 The S_N1 mechanism

7.13 Carbocation stability

7.14 The Hammond postulate

7.15 When is the mechanism S_N1 or S_N2?

7.16 Biological nucleophilic substitution

7.17 Vinyl halides and aryl halides

7.18 Organic synthesis

Giant kelp, a type of marine algae that grows in dense forests in cold ocean waters, is a major source of atmospheric chloromethane, the simplest alkyl chloride. Chloromethane is also produced by evergreen trees and is released during volcanic eruptions. Although some chloromethane in the atmosphere is man-made, most is natural in origin. In Chapter 7, we learn about alkyl halides like chloromethane and one of their characteristic reactions, nucleophilic substitution.

Why Study…

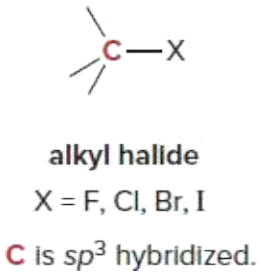
Alkyl Halides?

This is the first of three chapters dealing with an in-depth study of the organic reactions of compounds containing C–Z σ bonds, where Z is an element more electronegative than carbon. In Chapter 7, we learn about alkyl halides and one of their characteristic reactions, nucleophilic substitution, a key step in the synthesis of several useful drugs and natural products. In Chapter 8, we look at elimination, a second general reaction of alkyl halides. We conclude this discussion in Chapter 9 by examining other molecules that also undergo nucleophilic substitution and elimination reactions. In these chapters, we will learn about many specific details that explain how and why key reactions take place.

7.1 Introduction to Alkyl Halides

Alkyl halides are organic molecules containing a halogen atom X bonded to an sp^3 hybridized carbon atom. As we learned in Section 3.2, alkyl halides are classified as primary (1°), secondary (2°), or tertiary (3°) depending on the number of carbons bonded to the carbon with the halogen. Whether an alkyl halide is 1°, 2°, or 3° is the *most important factor* in determining the course of its chemical reactions.

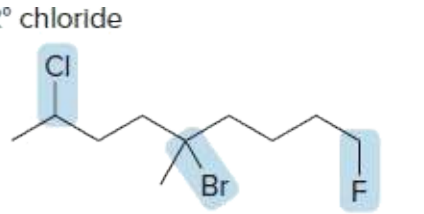
Alkyl halides have the general molecular formula $C_nH_{2n+1}X$, and are formally derived from an alkane by replacing a hydrogen atom with a halogen.



alkyl halide

X = F, Cl, Br, I

C is sp^3 hybridized.



3° bromide 1° fluoride

Four types of organic halides having the halogen atom in close proximity to a π bond are illustrated in Figure 7.1. Vinyl halides have a halogen atom bonded to a carbon–carbon double bond, and aryl halides have a halogen atom bonded to a benzene ring. These two types of organic halides with X bonded directly to an sp^2 hybridized carbon atom do *not* undergo the reactions presented in Chapter 7, as discussed in Section 7.17.

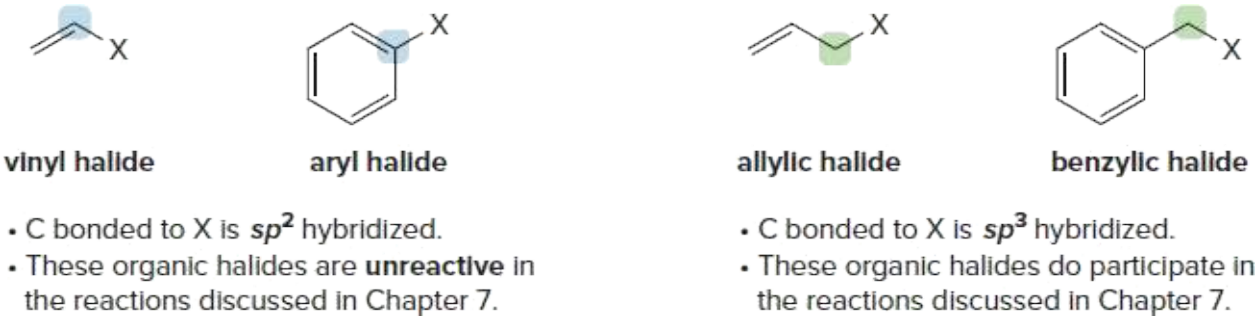
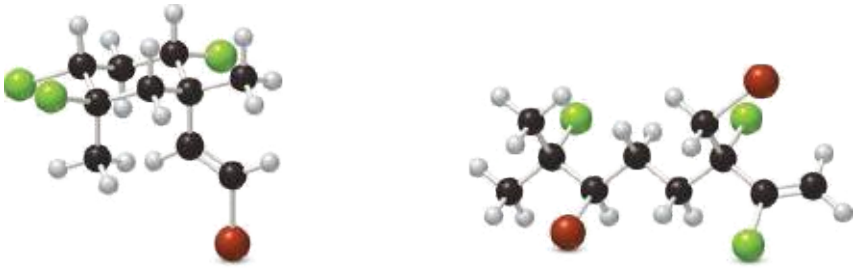


Figure 7.1 **Four types of organic halides (RX) having X near a π bond**

Allylic halides and benzylic halides have halogen atoms bonded to sp^3 hybridized carbon atoms and *do* undergo the reactions described in Chapter 7. Allylic halides have X bonded to the carbon atom *adjacent* to a carbon–carbon double bond, and benzylic halides have X bonded to the carbon atom *adjacent* to a benzene ring. The synthesis of allylic and benzylic halides is discussed in Sections 13.10 and 16.14, respectively.

Problem 7.1

Telfairine, a naturally occurring insecticide, and halomon, an antitumor agent, are two polyhalogenated compounds isolated from red algae. (a) Classify each halide bonded to an sp^3 hybridized carbon as 1°, 2°, or 3°. (b) Label each halide as vinyl, allylic, or neither.



telfairine halomon

7.2 Nomenclature

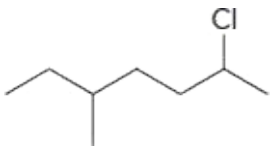
The systematic (IUPAC) method for naming alkyl halides follows from the basic rules described in Chapter 4.

7.2A IUPAC System

An alkyl halide is named as an alkane with a halogen substituent—that is, as a *halo alkane*. To name a halogen substituent, change the *-ine* ending of the name of the halogen to the suffix *-o* (*chlorine* → chloro).

How To **Name an Alkyl Halide Using the IUPAC System**

Example Give the IUPAC name of the following alkyl halide:



Step [1] Find the parent carbon chain and name it as an alkane.

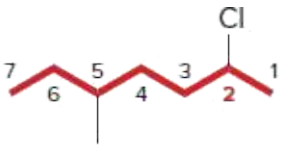
- Name the parent chain as an ***alkane***, with the halogen as a substituent bonded to the longest chain.

7 C's in the longest chain

7 C's ⟶ heptane

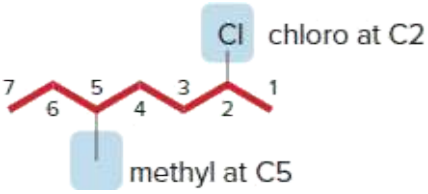
Step [2] Apply all other rules of nomenclature.

a. Number the chain.



- Begin at the end nearest the first substituent, either alkyl or halogen.

b. Name and number the substituents.



c. Alphabetize: c for chloro, then m for methyl.

Answer: 2-chloro-5-methylheptane

7.2B Common Names

Common names for alkyl halides are used only for simple alkyl halides. To assign a common name:

- **Name all the carbon atoms of the molecule as a single alkyl group.**
- **Name the halogen bonded to the alkyl group. To name the halogen, change the *-ine* ending of the halogen name to the suffix *-ide;* for example, bromine → bromide.**

- **Combine the names of the alkyl group and halide, separating the words with a space.**

Other examples of alkyl halide nomenclature are given in Figure 7.2.

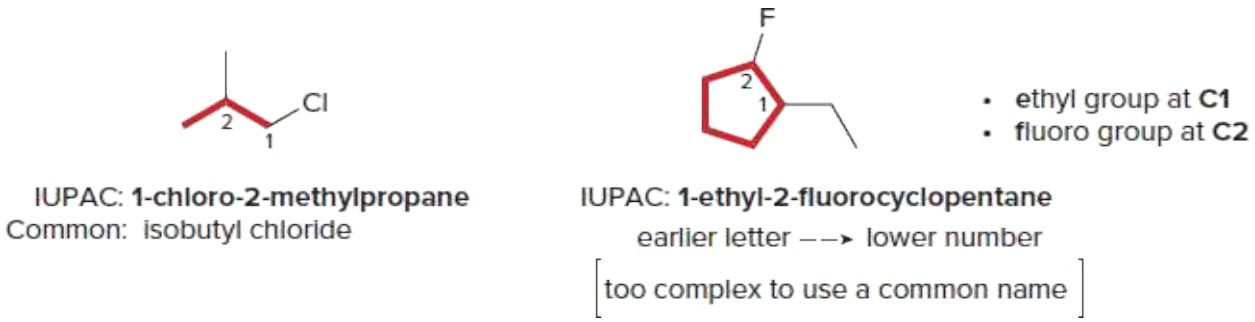
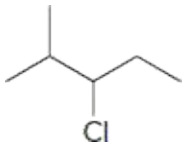


Figure 7.2 **Examples: Nomenclature of alkyl halides**

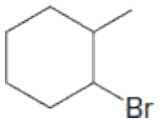
Problem 7.2

Give the IUPAC name for each compound.

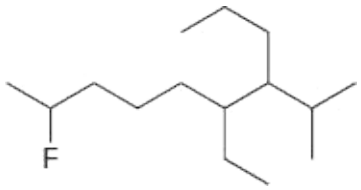
a.



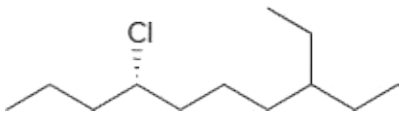
b.



c.



d.



Problem 7.3

Give the structure corresponding to each name.

a. 3-chloro-2-methylhexane

b. 4-ethyl-5-iodo-2,2-dimethyloctane

c. ***cis*-1,3-dichlorocyclopentane**

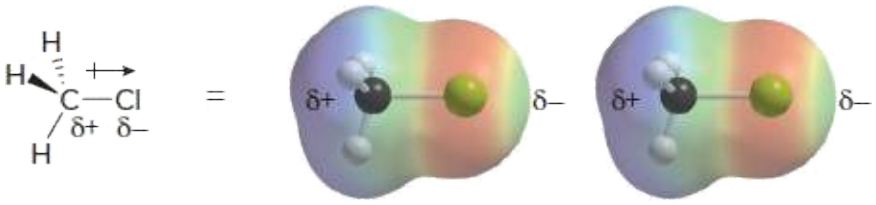
d. 1,1,3-tribromocyclohexane

e. 6-ethyl-3-iodo-3,5-dimethylnonane

f. (*R*)-1-fluoro-2,6,6-trimethylnonane

7.3 Properties of Alkyl Halides

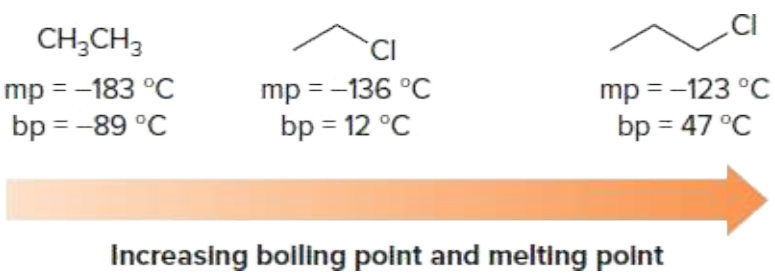
Alkyl halides are weakly polar molecules. They exhibit dipole–dipole interactions because of their polar C–X bond, but because the rest of the molecule contains only C–C and C–H bonds they are incapable of intermolecular hydrogen bonding. How this affects their physical properties is summarized in Table 7.1.

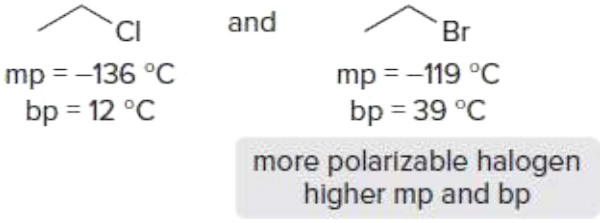


Opposite ends of the dipoles interact.

The spectroscopic properties of alkyl halides are discussed in Chapters A–C. Of particular note are the characteristic features of the mass spectra of alkyl chlorides and alkyl bromides, which are discussed in Section A.2.

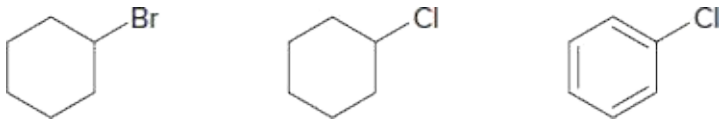
Table 7.1 Physical Properties of Alkyl Halides

Property	Observation
Boiling point and melting point	• **Alkyl halides have higher bp's and mp's than alkanes having the same number of carbons.** • **Bp's and mp's increase as the size of R increases.** 
	• **Bp's and mp's increase as the size of X**

	increases. 
Solubility	• RX is soluble in organic solvents. • RX is insoluble in water.

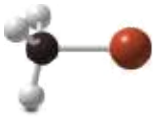
Problem 7.4

An sp^3 hybridized C–Cl bond is more polar than an sp^2 hybridized C–Cl bond. (a) Explain why this phenomenon arises. (b) Rank the following compounds in order of increasing boiling point.



7.4 Interesting Alkyl Halides

Many simple alkyl halides make excellent solvents because they are not flammable and dissolve a wide variety of organic compounds. Compounds in this category include $CHCl_3$ (chloroform or trichloromethane) and CCl_4 (carbon tetrachloride or tetrachloromethane). Large quantities of these solvents are produced industrially each year, but like many chlorinated organic compounds, both chloroform and carbon tetrachloride are toxic if inhaled or ingested. Other simple alkyl halides are shown in Figure 7.3.

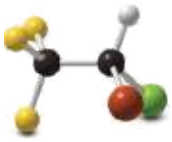


CH_3Br

- **Bromomethane (CH_3Br),** a naturally occurring alkyl halide in the atmosphere, is a soil fumigant phased out in most developed countries because of its ozone-depleting properties. Strawberry growers were allowed a special exemption for the continued use of bromomethane until some time in 2017. New production methods and novel strawberry varieties are being examined to provide cost-effective, more environmentally friendly fruit.

CH_2Cl_2

- **Dichloromethane (or methylene chloride, CH_2Cl_2)** is an important solvent, once used to decaffeinate coffee. Coffee is now decaffeinated by using supercritical CO_2 due to concerns over the possible ill effects of trace amounts of residual CH_2Cl_2 in the coffee. Subsequent studies on rats have shown, however, that no cancers occurred when animals ingested the equivalent of over 100,000 cups of decaffeinated coffee per day.

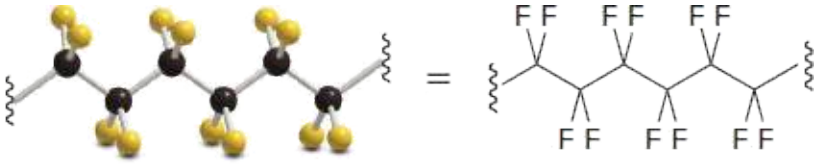


$CF_3CHClBr$

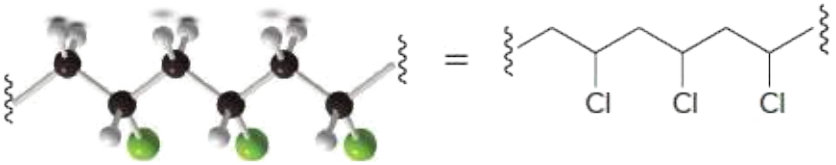
- **Halothane ($CF_3CHClBr$)** is a safe general anesthetic compared to other organic anesthetics such as $CHCl_3$, which causes liver and kidney damage, and $CH_3CH_2OCH_2CH_3$ (diethyl ether), which is very flammable.

Figure 7.3 **Some simple alkyl halides**

Synthetic organic halides are also used in insulating materials, plastic wrap, and coatings. Two such compounds are Teflon and poly(vinyl chloride) (PVC).



Teflon
(nonstick coating)



poly(vinyl chloride) (PVC)
(plastic used in films, pipes, and insulation)

Several useful drugs contain one or more fluorine atoms. Examples include fluticasone, an aerosol inhalant used for the treatment of seasonal nasal allergies and asthma, and roflumilast, which was approved by the FDA in 2015 for the treatment of severe cases of chronic obstructive pulmonary disease (COPD).

Fluticasone (trade name Flonase) is a synthetic steroid used to treat the chronic inflammation of asthma.

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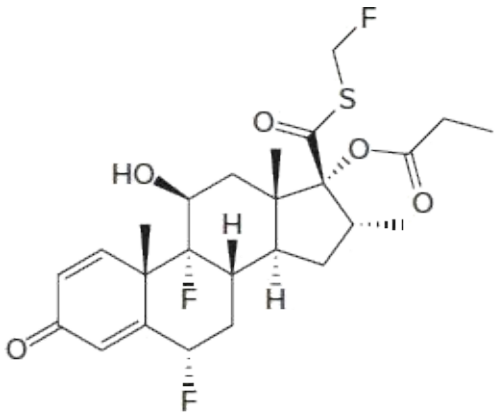
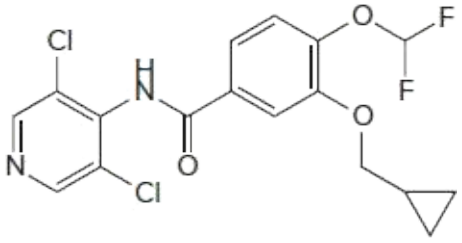
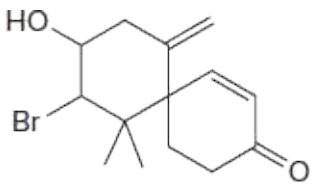


fluticasone

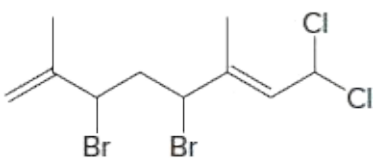


roflumilast

Thousands of organic halides have now been isolated from a variety of marine organisms. The characteristic smell of the ocean is due in part to simple alkyl halides found in seaweed. While many sponges and corals use these compounds as a chemical defense against predators and parasites, recent research has shown that some may have novel medicinal properties that offer treatment for cancer and other diseases. Two halogenated compounds are ma‘ilione, isolated from the Hawaiian red alga *Laurencia cartilaginea*, and plocoralide B, which kills esophageal cancer cells.



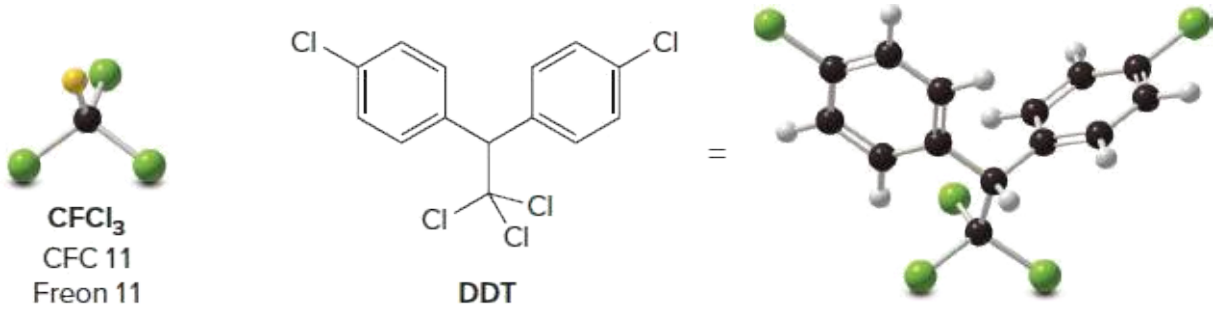
ma‘ilione



plocoralide B

Hundreds of organic halides with diverse structures and biological activities have been isolated from red algae of the genus *Laurencia*, seaweed that grows in shallow water at the edges of reefs. ***©Michael Guiry***

Although the beneficial effects of many organic halides are undisputed, certain synthetic chlorinated organics such as the chlorofluorocarbons and the pesticide DDT have caused lasting harm to the environment.



DDT, a nonbiodegradable pesticide, has been labeled both a "miraculous" discovery by Winston Churchill in 1945 and the "elixir of death" by Rachel Carson in her 1962 book *Silent Spring.* DDT use was banned in the United States in 1973, but because of its effectiveness and low cost, it is still widely used to control inspect populations in developing countries.

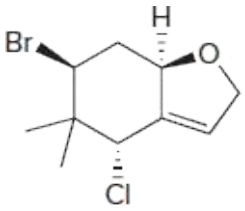
Chlorofluorocarbons (CFCs) have the general molecular structure CF_xCl_{4-x}. Trichloro-fluoromethane [$CFCl_3$, CFC 11, or Freon 11 (trade name)] is an example of these easily vaporized compounds, having been extensively used as a refrigerant and an aerosol propellant. CFCs slowly rise to the stratosphere, where sunlight catalyzes their decomposition, a process that contributes to the destruction of the ozone layer, the thin layer of atmosphere that shields the earth's surface from harmful ultraviolet radiation (Section 13.9). Although it is now easy to second-guess the extensive use of CFCs, it is also easy to see why they were used so widely. CFCs made refrigeration available to the general public. Would you call your refrigerator a comfort or a

necessity?

The story of the insecticide DDT (dichlorodiphenyltrichloroethane) follows the same theme: DDT is an organic molecule with valuable short-term effects that has caused long-term problems. DDT kills insects that spread diseases such as malaria and typhus, and in controlling insect populations, DDT has saved millions of lives worldwide. DDT is a weakly polar organic compound that persists in the environment for years. Because DDT is soluble in organic media, it accumulates in fatty tissues. Most adults in the United States have low concentrations of DDT (or a degradation product of DDT) in their bodies. DDT is acutely toxic to many types of marine life (crayfish, sea shrimp, and some fish), but the long-term effect on humans is not known.

Problem 7.5

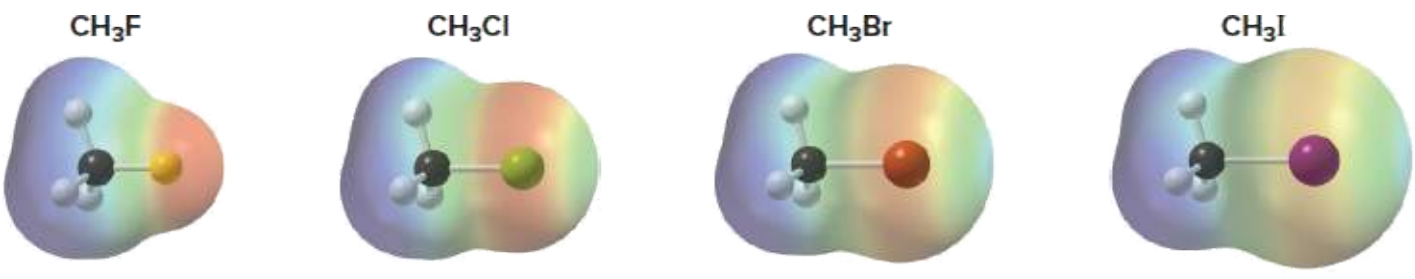
Chondrocole A is a marine natural product isolated from red seaweed that grows in regions of heavy surf in the Pacific Ocean. (a) Predict the solubility of chondrocole A in water and CH_2Cl_2. (b) Locate the stereogenic centers and label each as *R* or *S*. (c) Draw a stereoisomer and a constitutional isomer of chondrocole A.



chondrocole A

7.5 The Polar Carbon–Halogen Bond

The properties of alkyl halides dictate their reactivity. The electrostatic potential maps of four simple alkyl halides in Figure 7.4 illustrate that the electronegative halogen X creates a polar C–X bond, making the carbon atom electron deficient. The chemistry of alkyl halides is determined by this polar C–X bond.

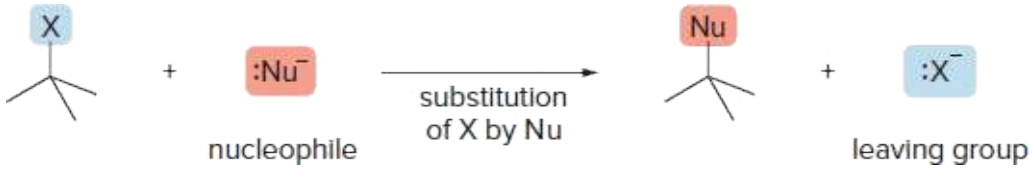


- The polar C–X bond makes the carbon atom *electron deficient* in each CH_3X molecule.

Figure 7.4 **Electrostatic potential maps of four halomethanes (CH_3X)**

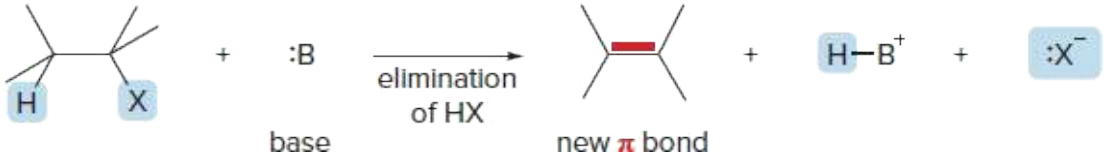
What kind of reactions do alkyl halides undergo? The characteristic reactions of alkyl halides are substitution and elimination. Because alkyl halides contain an electrophilic carbon, they react with electron-rich reagents—Lewis bases (nucleophiles) and Brønsted–Lowry bases.

- **Alkyl halides undergo substitution reactions with nucleophiles.**



In a substitution reaction of an alkyl halide, the halogen X is replaced by an electron-rich nucleophile $:Nu^-$. The C–X σ bond is broken and the C–Nu σ bond is formed.

- **Alkyl halides undergo elimination reactions with Brønsted–Lowry bases.**



In an elimination reaction of an alkyl halide, the elements of HX are removed by a Brønsted–Lowry base :B.

The remainder of Chapter 7 is devoted to a discussion of the substitution reactions of alkyl halides. Elimination reactions are discussed in Chapter 8.

7.6 General Features of Nucleophilic Substitution

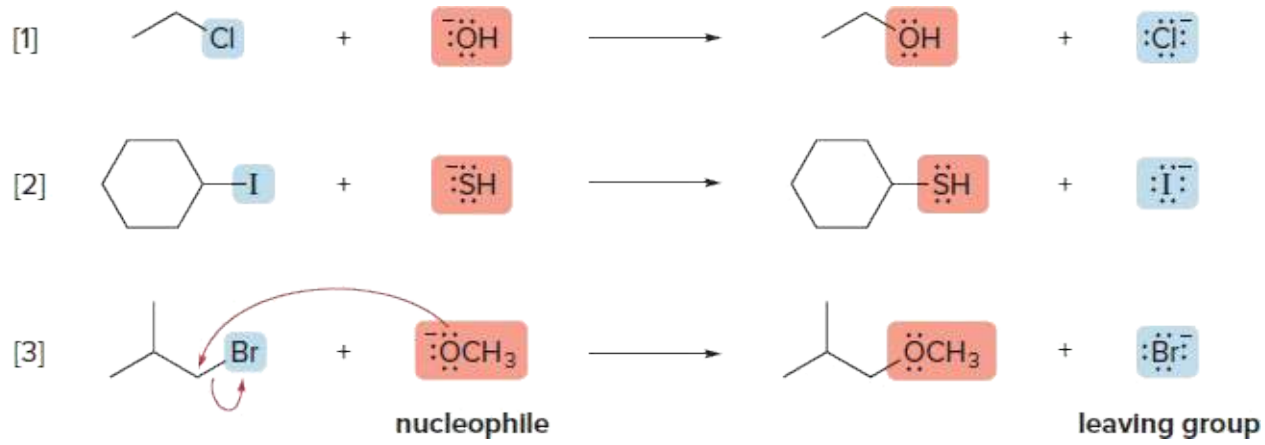
Three components are necessary in any substitution reaction.

[1] An alkyl group containing an sp^3 hybridized carbon bonded to X.

[2] X—An atom X (or a group of atoms) called a leaving group, which is able to accept the electron density in the C–X bond. The most common leaving groups are halide anions (X^-), but H_2O (from ROH_2^+) and N_2 (from RN_2^+) are also encountered.

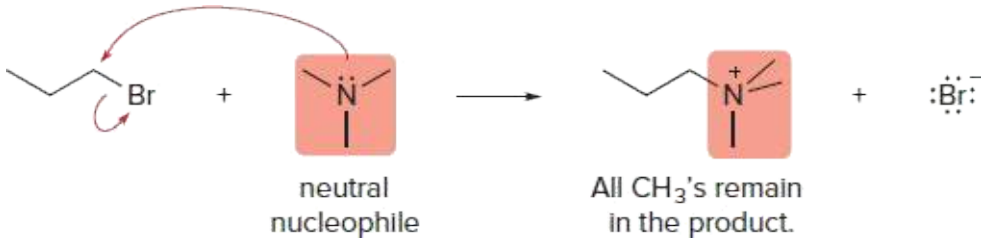
[3] :Nu⁻—A nucleophile. Nucleophiles contain a lone pair or a π bond but not necessarily a negative charge.

Because these substitution reactions involve electron-rich nucleophiles, they are called *nucleophilic* substitution reactions. Examples are shown in Equations [1]–[3]. Nucleophilic substitutions are Lewis acid–base reactions. The nucleophile donates its electron pair, the alkyl halide (Lewis acid) accepts it, and the C–X bond is heterolytically cleaved. Curved arrow notation can be used to show the movement of electron pairs, as shown in Equation [3].



Negatively charged nucleophiles like $^{-}$OH and $^{-}$SH are used as salts with Li^{+}, Na^{+}, or K^{+} counterions to balance charge. The identity of the cation is usually inconsequential, and therefore it is often omitted from the chemical equation.

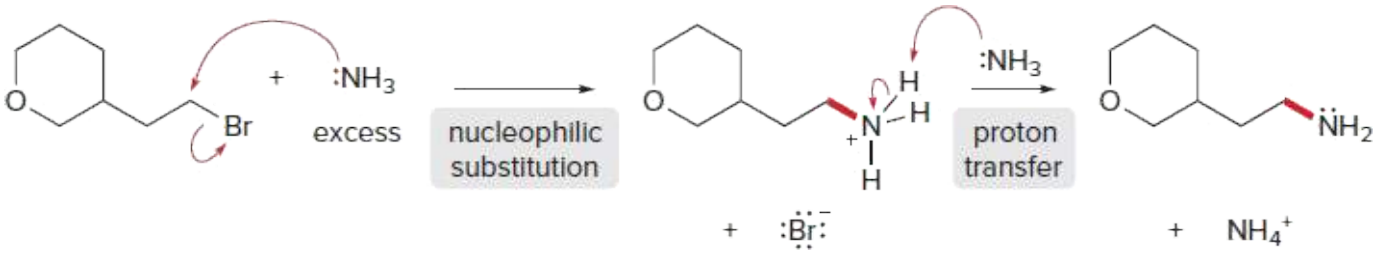
When a neutral nucleophile is used, the substitution product bears a positive charge. All atoms originally bonded to the nucleophile stay bonded to it after substitution occurs. All three CH_3 groups stay bonded to the N atom in the given example.



The reaction of alkyl halides with NH_3 to form amines (RNH_2) is discussed in Chapter 23.

Furthermore, when the substitution product bears a positive charge and also contains

a *proton* bonded to O or N, the initial substitution product readily loses a proton in a Brønsted–Lowry acid–base reaction, forming a neutral product.



All of these reactions are nucleophilic substitutions and have the same overall result—replacement of the leaving group by the nucleophile, regardless of the identity or charge of the nucleophile. To draw any nucleophilic substitution product:

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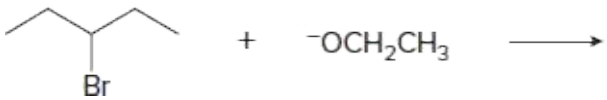
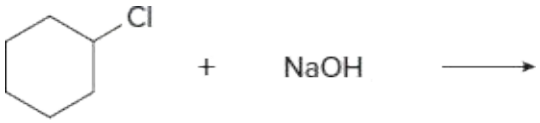
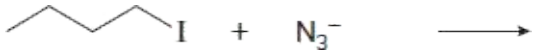
- **Find the sp^3 hybridized carbon with the leaving group.**
- **Identify the nucleophile, the species with a lone pair or π bond.**
- **Substitute the nucleophile for the leaving group and assign charges (if necessary) to any atom that is involved in bond breaking or bond formation.**

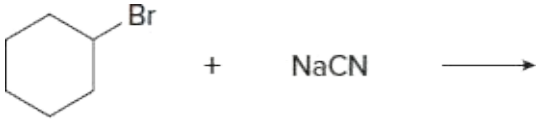
Problem 7.6

Identify the nucleophile and leaving group and draw the products of each substitution reaction.

a. 

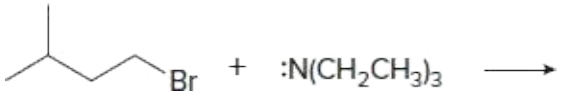
b. 

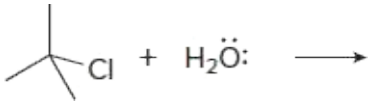
c. 

d. 

Problem 7.7

Draw the product of nucleophilic substitution with each neutral nucleophile. When the initial substitution product can lose a proton to form a neutral product, draw the product after proton transfer.

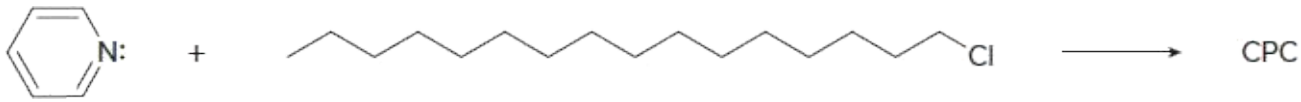
a. 

b. 

Cepacol throat lozenges and Crest Pro-Health mouthwash contain the antiseptic CPC, which is prepared by nucleophilic substitution (Problem 7.8). ***©Jill Braaten***

Problem 7.8

CPC (cetylpyridinium chloride), an antiseptic found in throat lozenges and mouthwash, is synthesized by the following reaction. Draw the structure of CPC.



Problem 7.9

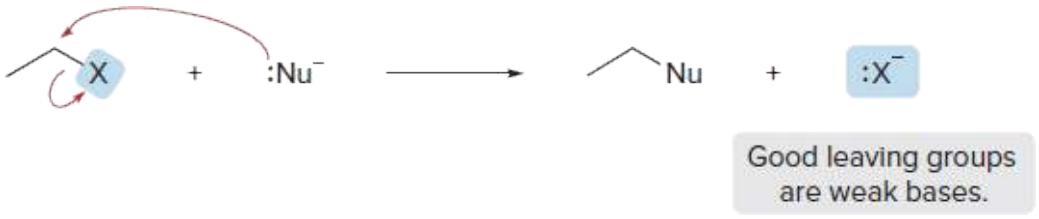
What neutral nucleophile is needed to convert dihalide A to ticlopidine, an antiplatelet drug used to reduce the risk of strokes?

7.7 The Leaving Group

Nucleophilic substitution is a general reaction of organic compounds. Why, then, are alkyl halides the most common substrates, and halide anions the most common leaving groups? To answer this question, we must understand leaving group ability. What makes a good leaving group?

In a nucleophilic substitution reaction of R–X, the C–X bond is heterolytically cleaved, and the leaving group departs with the electron pair in that bond, forming $X:^-$. The more stable the leaving group $X:^-$, the better able it is to accept an electron pair, giving rise to the following generalization:

- **In comparing two leaving groups, the *better* leaving group is the *weaker* base.**



For example, H_2O is a better leaving group than ^-OH because H_2O is a weaker base. Moreover, the periodic trends in basicity can now be used to identify periodic trends in leaving group ability:

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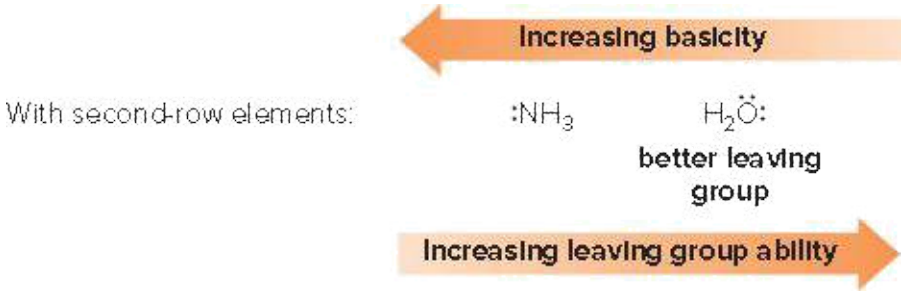
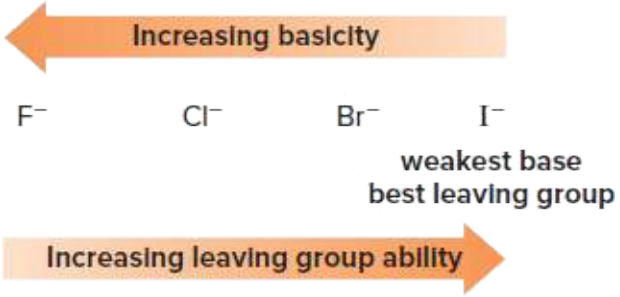
- **Left-to-right across a row of the periodic table, basicity *decreases* so leaving group ability *increases.***



- **Down a column of the periodic table, basicity *decreases* so leaving group ability *increases.***



All good leaving groups are weak bases with strong conjugate acids having low pK_a values. Thus, all halide anions except F^- are good leaving groups because their conjugate acids (HCl, HBr, and HI) have low pK_a values. Tables 7.2 and 7.3 list good

and poor leaving groups for nucleophilic substitution reactions, respectively. Nucleophilic substitution does not occur with any of the leaving groups in Table 7.3 because these leaving groups are strong bases.

Table 7.2 Good Leaving Groups for Nucleophilic Substitution

Starting material	Leaving group	Conjugate acid	pK_a
R—Cl	$:\ddot{Cl}:^-$	HCl	−7
R—Br	$:\ddot{Br}:^-$	HBr	−9
R—I	$:\ddot{I}:^-$	HI	−10
$R-\overset{+}{O}H_2$	$H_2\ddot{O}:$	H_3O^+	−1.7

Table 7.3 Poor Leaving Groups for Nucleophilic Substitution

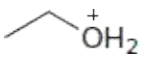
Starting material	Leaving group	Conjugate acid	pK_a
R—F	$:\ddot{F}:^-$	HF	3.2
R—OH	$:\ddot{O}H^-$	H_2O	15.7
$R-NH_2$	$:\ddot{N}H_2^-$	NH_3	38
R—H	$H:^-$	H_2	35
R—R	$R:^-$	RH	50

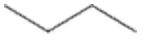
Problem 7.10

Which molecules contain good leaving groups?

a.

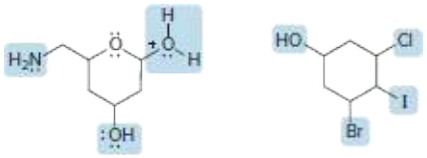
b.

c. 

d. 

Problem 7.11

(a) Which of the labeled atoms in each molecule is the best leaving group? (b) Which of the labeled atoms in each molecule is the worst leaving group?



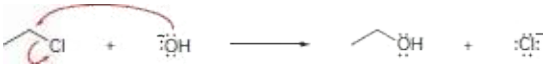
Given a particular nucleophile and leaving group, how can we determine whether the equilibrium will favor products in a nucleophilic substitution? We can often correctly predict the direction of equilibrium by comparing the basicity of the nucleophile and the leaving group.

- **Equilibrium favors the products of nucleophilic substitution when the leaving group is a *weaker base* than the nucleophile.**

Sample Problem 7.1 illustrates how to apply this general rule.

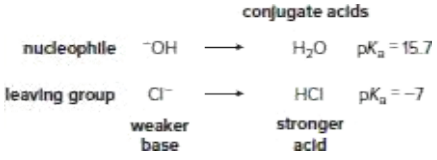
Sample Problem 7.1 Using Basicity to Determine If a Substitution Is Likely to Occur

Will the following substitution reaction favor formation of the products?



Solution

Determine the basicity of the nucleophile ($^-$OH) and the leaving group (Cl^-) by comparing the pK_a values of their conjugate acids. The stronger the conjugate acid, the weaker the base, and the better the leaving group.



Because Cl^-, the leaving group, is a weaker base than $^-$OH, the nucleophile, the reaction favors the products.

Problem 7.12

Does the equilibrium favor the reactants or the products in each substitution reaction?

a.

b.

More Practice:

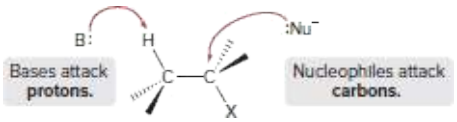
Try Problem 7.48.

7.8 The Nucleophile

Nucleophiles and bases are structurally similar: both have a lone pair or a π bond. They differ in what they attack.

We use the word *base* to mean *Brønsted–Lowry* base and the word *nucleophile* to mean a *Lewis base* that reacts with electrophiles *other than protons.*

- **Bases attack protons. Nucleophiles attack other electron-deficient atoms (usually carbons).**



7.8A Nucleophilicity Versus Basicity

How is nucleophilicity (nucleophile strength) related to basicity? Although it is generally true that a strong base is a strong nucleophile, nucleophile size and steric factors can sometimes change this relationship.

Nucleophilicity parallels basicity in three instances.

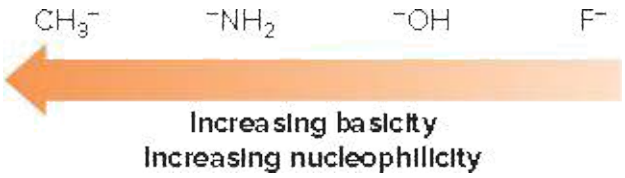
[1] For two nucleophiles with the same nucleophilic atom, the *stronger* base is the *stronger* nucleophile.

- The relative nucleophilicity of ^{-}OH and $CH_3CO_2^{-}$, two oxygen nucleophiles, is determined by comparing the pK_a values of their conjugate acids (H_2O and CH_3CO_2H). CH_3CO_2H (pK_a = 4.8) is a stronger acid than H_2O (pK_a = 15.7), so ^{-}OH is a stronger base and stronger nucleophile than $CH_3CO_2^{-}$.

[2] A negatively charged nucleophile is always *stronger* than its conjugate acid.

- ^{-}OH is a stronger base and stronger nucleophile than H_2O, its conjugate acid.

[3] Right-to-left across a row of the periodic table, nucleophilicity *increases* as basicity *increases.*



Problem 7.13

Identify the stronger nucleophile in each pair.

a. NH_3, $^-NH_2$

b. CH_3NH_2, CH_3OH

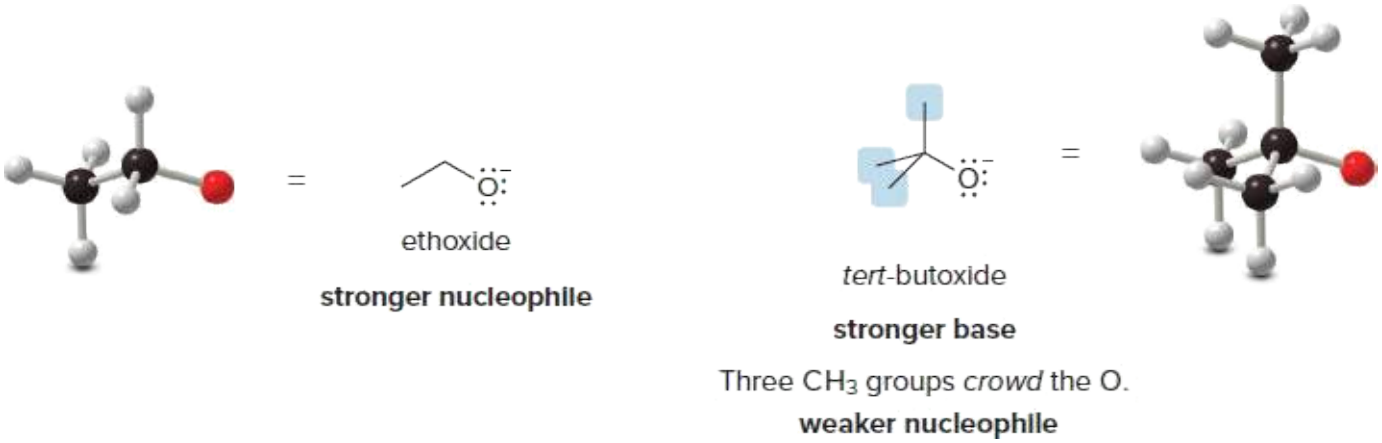
c. $CH_3CO_2^-$, $CH_3CH_2O^-$

7.8B Steric Effects and Nucleophilicity

All steric effects arise because two atoms cannot occupy the same space. In Chapter 4, for example, we learned that steric strain is an increase in energy when big groups (occupying a large volume) are forced close to each other.

Nucleophilicity does not parallel basicity when steric hindrance becomes important. *Steric hindrance* is a decrease in reactivity resulting from the presence of bulky groups at the site of a reaction.

For example, although pK_a tables indicate that *tert*-butoxide [$(CH_3)_3CO^-$] is a stronger base than ethoxide ($CH_3CH_2O^-$), ethoxide is the *stronger* nucleophile. The three CH_3 groups around the O atom of *tert*-butoxide create steric hindrance, making it more difficult for this big, bulky base to attack a tetravalent carbon atom.



Steric hindrance decreases nucleophilicity but *not* basicity. Because bases pull off small, easily accessible protons, they are unaffected by steric hindrance. Nucleophiles, on the other hand, must attack a crowded tetrahedral carbon, so bulky groups decrease reactivity.

Sterically hindered bases that are poor nucleophiles are called *nonnucleophilic bases*. Potassium *tert*-butoxide [K+ $^{-}OC(CH_3)_3$] is a strong, nonnucleophilic base.

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7.8C Comparing Nucleophiles of Different Size—Solvent Effects

Atoms vary greatly in size down a column of the periodic table, and in this case, nucleophilicity depends on the solvent used in a substitution reaction. Although solvent has thus far been ignored, most organic reactions take place in a liquid solvent that dissolves all reactants to some extent. Because substitution reactions involve polar starting materials, polar solvents are used to dissolve them. There are two main kinds of polar solvents: polar *protic* solvents and polar *aprotic* solvents.

Polar Protic Solvents

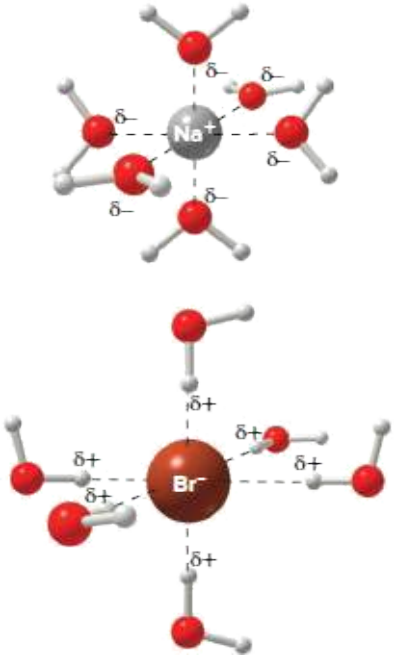
In addition to dipole–dipole interactions, polar *protic* solvents are capable of intermolecular hydrogen bonding, because they contain an O–H or N–H bond. The most common polar protic solvents are water and alcohols (ROH) (Figure 7.5). Polar protic solvents solvate *both* cations and anions well.

- **Cations are solvated by ion–dipole interactions.**
- **Anions are solvated by hydrogen bonding.**

H_2O	CH_3OH methanol	CH_3CH_2OH ethanol	$(CH_3)_3COH$ *tert*-butanol	CH_3CO_2H acetic acid

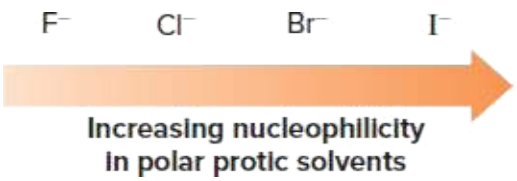
Figure 7.5 **Polar protic solvents**

For example, if the salt NaBr is used as a source of the nucleophile Br^- in H_2O, the Na^+ cations are solvated by ion–dipole interactions with H_2O molecules, and the Br^- anions are solvated by strong hydrogen bonding interactions.



I^- is a *weak base* but a *strong nucleophile* in polar protic solvents.

How do polar protic solvents affect nucleophilicity? In polar protic solvents, nucleophilicity *increases* down a column of the periodic table as the size of the anion increases. This is *opposite* to basicity. A small electronegative anion like F^- is very well solvated by hydrogen bonding, effectively *shielding* it from reaction. On the other hand, a large, less electronegative anion like I^- does not hold onto solvent molecules as tightly. The *solvent does not "hide" a large nucleophile* as well, and the nucleophile is much more able to donate its electron pairs in a reaction. Thus, nucleophilicity increases down a column even though basicity decreases, giving rise to the following trend in polar protic solvents:



Polar Aprotic Solvents

Polar *aprotic* solvents also exhibit dipole–dipole interactions, but they have no O–H or N–H bond so they are incapable of hydrogen bonding. Examples of polar aprotic solvents are shown in Figure 7.6. Polar aprotic solvents solvate only cations well.

- **Cations are solvated by ion–dipole interactions.**
- **Anions are not well solvated because the solvent cannot hydrogen bond to them.**

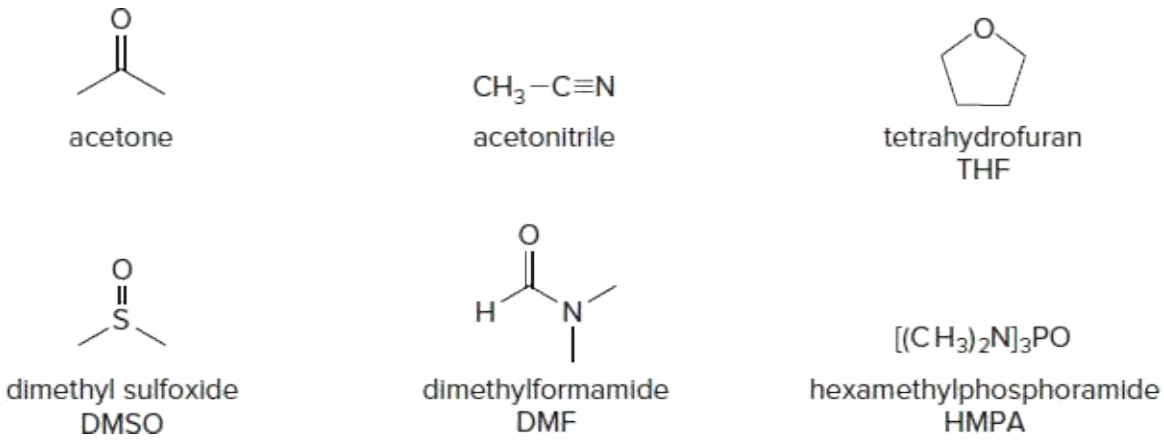
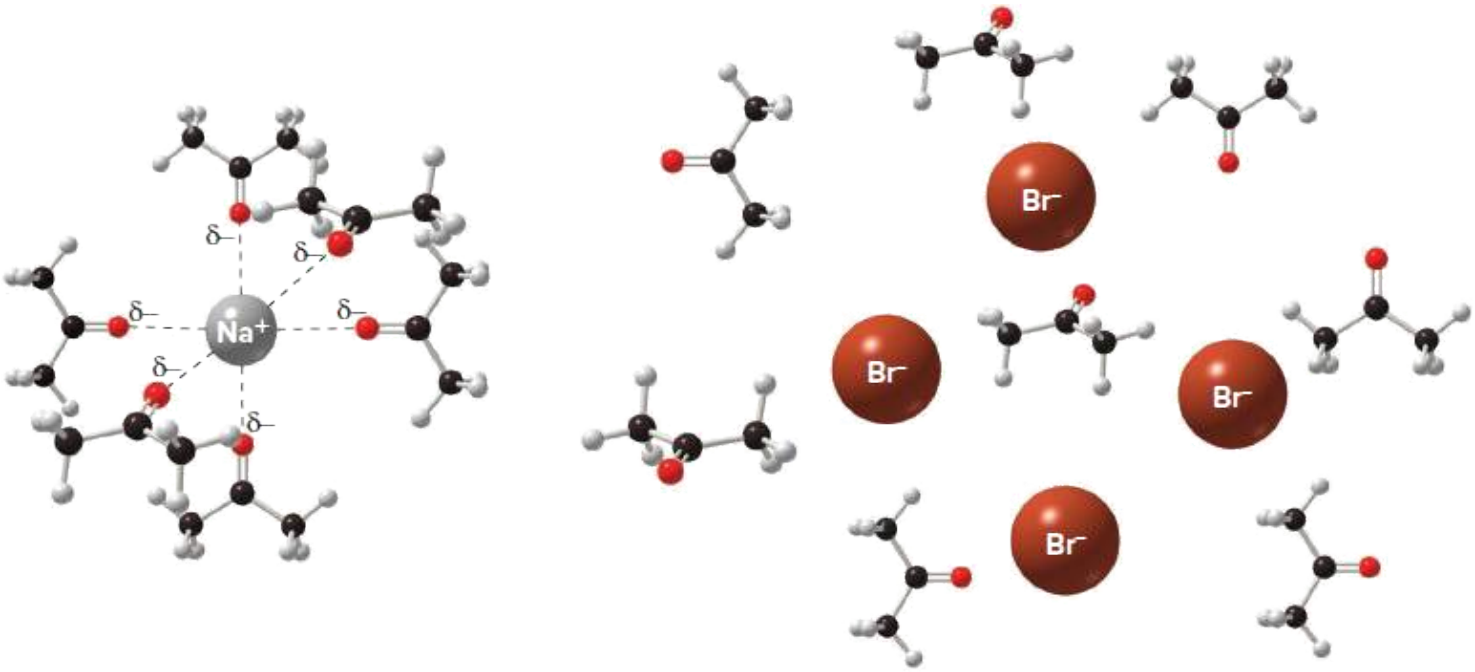


Figure 7.6 **Polar aprotic solvents**

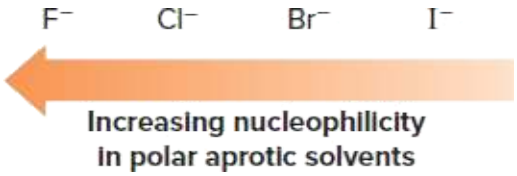
Abbreviations are often used in organic chemistry, instead of a compound's complete name. A list of common abbreviations is given in Appendix B.

When the salt NaBr is dissolved in acetone, $(CH_3)_2C{=}O$, the Na^+ cations are solvated by ion–dipole interactions with the acetone molecules, but, with no possibility for hydrogen bonding, the Br^- anions are not well solvated. Often these anions are called naked anions because they are not bound by tight interactions with solvent.



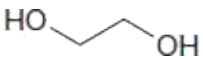
Br^- anions are surrounded by solvent but not well solvated by the $(CH_3)_2C{=}O$ molecules.

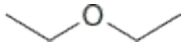
How do polar aprotic solvents affect nucleophilicity? Because anions are not well solvated in polar aprotic solvents, there is no need to consider whether solvent molecules more effectively hide one anion than another. Nucleophilicity parallels basicity and the stronger base is the stronger nucleophile. Because basicity decreases with size down a column, nucleophilicity decreases as well:

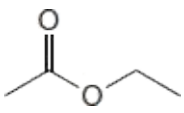


Problem 7.14

Classify each solvent as protic or aprotic.

a. 

b. 

c. 

Problem 7.15

Identify the stronger nucleophile in each pair of anions.

a. **Br^- or Cl^- in a polar protic solvent**

b. **HO^- or Cl^- in a polar aprotic solvent**

c. HS^- or F^- in a polar protic solvent

7.8D Summary

This discussion of nucleophilicity has brought together many new concepts, such as steric hindrance and solvent effects, both of which we will meet again in our study of organic chemistry. Keep in mind the central relationship between nucleophilicity and basicity in comparing two nucleophiles.

- **It is generally true that the *stronger* base is the *stronger* nucleophile.**
- **In polar *protic* solvents, however, nucleophilicity *increases* with increasing size of an anion (opposite to basicity).**
- **Steric hindrance *decreases* nucleophilicity without decreasing basicity, making $(CH_3)_3CO^-$ a stronger base but a weaker nucleophile than $CH_3CH_2O^-$.**

Table 7.4 lists some common nucleophiles used in nucleophilic substitution reactions.

Problem 7.16

Rank the nucleophiles in each group in order of increasing nucleophilicity.

a. ^-OH, $^-NH_2$, H_2O

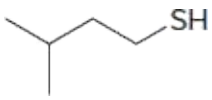
b. ^-OH, Br^-, F^- (polar aprotic solvent)

c. H_2O, ^-OH, $CH_3CO_2^-$

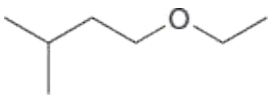
Problem 7.17

What nucleophile is needed to convert $(CH_3)_2CHCH_2CH_2Br$ to each product?

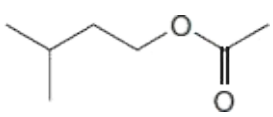
a.



b.



c.



d.

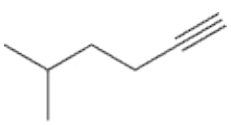


Table 7.4 Common Nucleophiles in Organic Chemistry

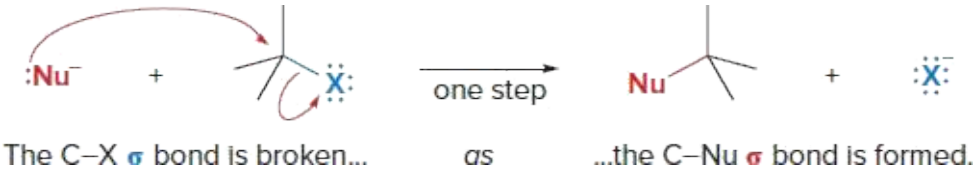
	Negatively charged nucleophiles			Neutral nucleophiles	
Oxygen	^-OH	^-OR	$CH_3CO_2^-$	H_2O	ROH
Nitrogen	N_3^-			NH_3	RNH_2
Carbon	^-CN	$HC{\equiv}C^-$			
Halogen	Cl^-	Br^-	I^-		
Sulfur	HS^-	RS^-		H_2S	RSH

7.9 Possible Mechanisms for Nucleophilic Substitution

Now that you know something about the general features of nucleophilic substitution, you can begin to understand the mechanism.

Nucleophilic substitution at an sp^3 hybridized carbon involves two σ bonds: the bond to the leaving group is broken and the bond to the nucleophile is formed. To understand the mechanism of this reaction, though, we must know the timing of these two events; that is, what is the order of bond breaking and bond making? Do they happen at the same time, or does one event precede the other? Consider two possibilities:

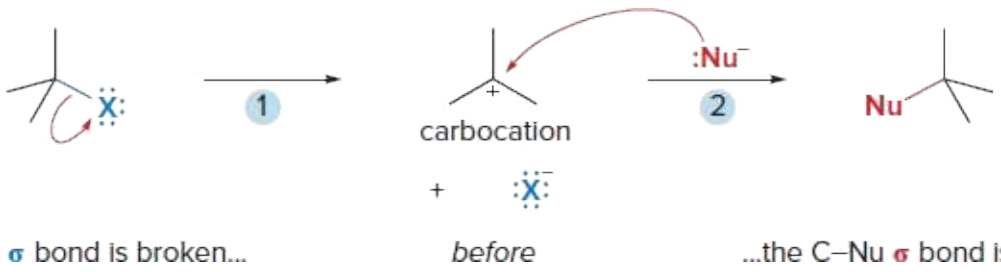
[1] The mechanism has one step, and bond breaking and bond making occur at the *same* time.



- If the C–X bond is broken *as* the C–Nu bond is formed, the mechanism has one step. As we learned in Section 6.9, the rate of such a bimolecular reaction depends on the concentration of *both* reactants; that is, the rate equation is

second order, and rate = k[RX][:Nu$^-$].

[2] The mechanism has two steps, and bond breaking occurs *before* bond making.



- If the C–X bond is broken *first* and then the C–Nu bond is formed, the mechanism has two steps and a carbocation is formed as an intermediate. Because the first step is rate-determining, the rate depends on the concentration of RX *only*; that is, the rate equation is first order, and rate = k[RX].

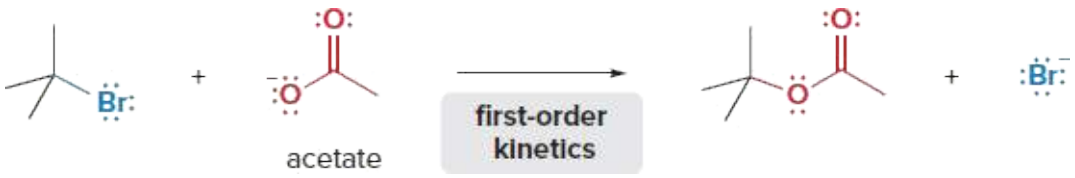
In Section 7.10, we look at data for two specific nucleophilic substitution reactions and see if those data fit either of these proposed mechanisms.

7.10 Two Mechanisms for Nucleophilic Substitution

Rate equations for two different reactions give us insight into the possible mechanism for nucleophilic substitution.

Reaction of bromomethane (CH3Br) with acetate ($CH_3CO_2^-$) affords the substitution product methyl acetate with loss of Br^- as the leaving group (Equation [1]). Kinetic data show that the reaction rate depends on the concentration of *both* reactants; that is, the rate equation is second order. This suggests a bimolecular reaction with a one-step mechanism in which the C–X bond is broken *as* the C–Nu bond is formed.

Equation [2] illustrates a similar nucleophilic substitution reaction with a different alkyl halide, $(CH_3)_3CBr$, which also leads to substitution of Br^- by $CH_3CO_2^-$. Kinetic data show that this reaction rate depends on the concentration of only *one* reactant, the alkyl halide; that is, the rate equation is first order. This suggests a two-step mechanism in which the rate-determining step involves the alkyl halide only.



The numbers 1 and 2 in the names S_N1 and S_N2 refer to the kinetic order of the reactions. For example, S_N2 means that the kinetics are second order. The number 2 does *not* refer to the number of steps in the mechanism.

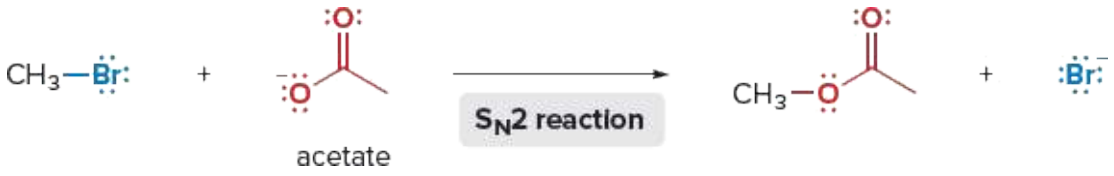
How can these two different results be explained? Although these two reactions have the same nucleophile and leaving group, there must be two different mechanisms because there are two different rate equations. These equations are specific examples of two well-known mechanisms for nucleophilic substitution at an sp^3 hybridized carbon:

- **S_N2 mechanism (substitution nucleophilic bimolecular).**
- **S_N1 mechanism (substitution nucleophilic unimolecular).**

The reaction in Equation [1] illustrates an S_N2 mechanism, whereas the Page 272 reaction in Equation [2] illustrates an SN1 mechanism.

7.11 The S_N2 Mechanism

The reaction of CH_3Br with $CH_3CO_2^-$ is an example of an S_N2 reaction. What are the general features of this mechanism?



7.11A Kinetics

An S_N2 reaction exhibits second-order kinetics; that is, the reaction is bimolecular and both the alkyl halide and the nucleophile appear in the rate equation.

- **rate = $k[CH_3Br][CH_3CO_2^-]$**

Changing the concentration of *either* reactant affects the rate. For example, doubling the concentration of *either* the nucleophile or the alkyl halide doubles the rate.

Doubling the concentration of *both* reactants increases the rate by a factor of *four*.

Problem 7.18

What happens to the rate of an S_N2 reaction under each of the following conditions?

a. [RX] is tripled, and [:Nu$^-$] stays the same.

b. Both [RX] and [:Nu$^-$] are tripled.

c. [RX] is halved, and [:Nu$^-$] stays the same.

d. [RX] is halved, and [:Nu$^-$] is doubled.

7.11B A One-Step Mechanism

The most straightforward explanation for the observed second-order kinetics is a concerted reaction—bond breaking and bond making occur at the *same* time, as shown in Mechanism 7.1.

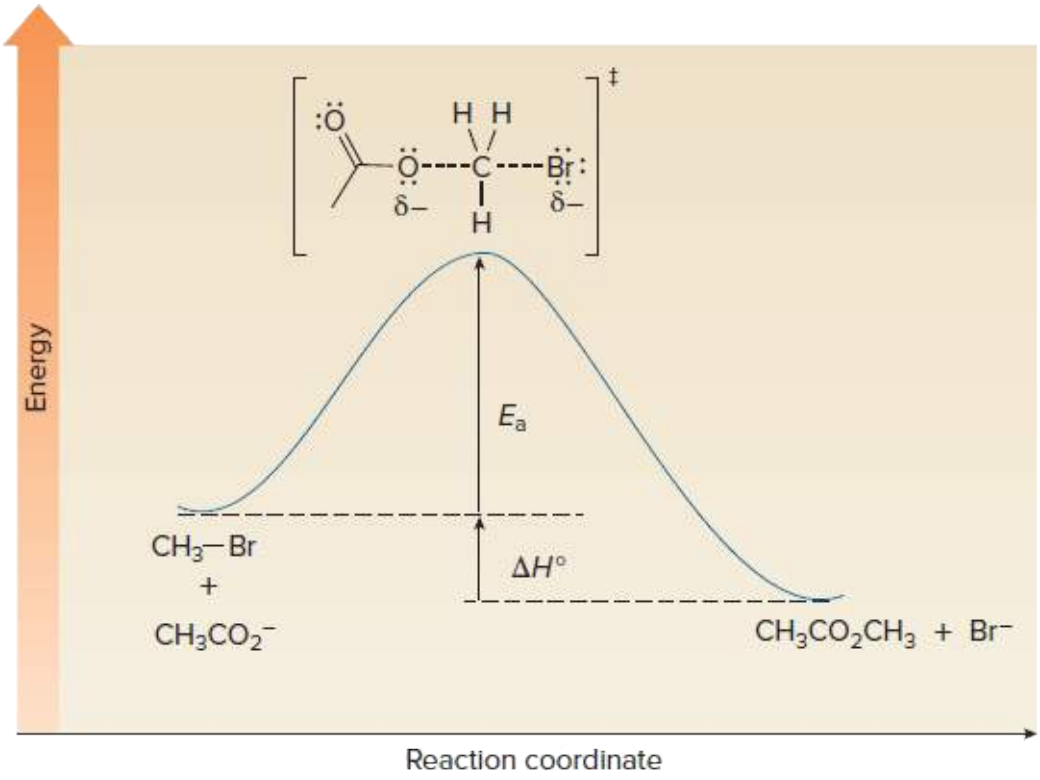
Mechanism 7.1 The S_N2 Mechanism

One step The C–Br bond breaks as the C–O bond forms.

An energy diagram for the reaction of CH_3Br + $CH_3CO_2^-$ is shown in Figure 7.7. The reaction has one step, so there is one energy barrier between reactants and products. Because the equilibrium for this S_N2 reaction favors the products, the products are drawn at lower energy than the starting materials.

Problem 7.19

Draw an energy diagram for the following S_N2 reaction. Label the axes, the starting materials, and the product. Draw the structure of the transition state.



- In the transition state, the C—Br bond is partially broken, the C—O bond is partially formed, and both the attacking nucleophile and the departing leaving group bear a partial negative charge.

Figure 7.7 **An energy diagram for the S_N2 reaction: $CH_3Br + CH_3CO_2^- \rightarrow CH_3CO_2CH_3 + Br^-$**

7.11C Stereochemistry of the S_N2 Reaction

From what direction does the nucleophile approach the substrate in an S_N2 reaction? There are two possibilities.

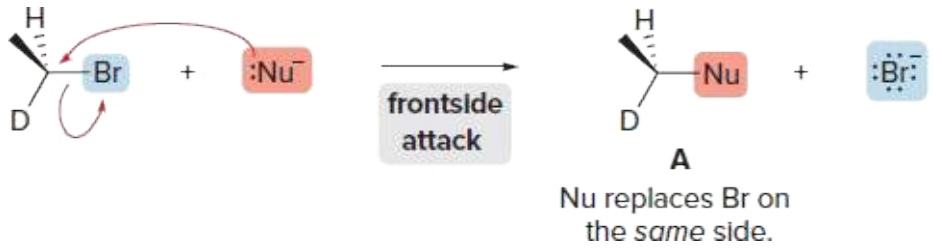
- Frontside attack: The nucleophile approaches from the *same* side as the leaving group.
- Backside attack: The nucleophile approaches from the side *opposite* the leaving group.

The results of frontside and backside attack of a nucleophile are illustrated with $CH_3CH(D)Br$ as substrate and the general nucleophile $:Nu^-$. This substrate has the leaving group bonded to a stereogenic center, thus allowing us to see the structural difference that results when the nucleophile attacks from two different directions.

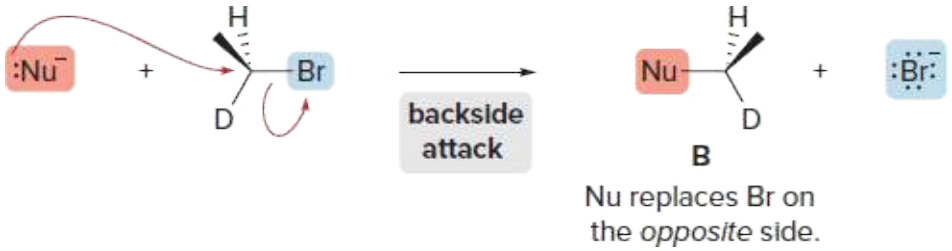
In frontside attack, the nucleophile approaches from the same side as the leaving group, forming A. In this example, the leaving group was drawn on the *right*, so the nucleophile attacks from the *right*, and all other groups remain in their original positions. Because the nucleophile and leaving group are in the same position relative

to the other three groups on carbon, frontside attack results in retention of configuration around the stereogenic center.

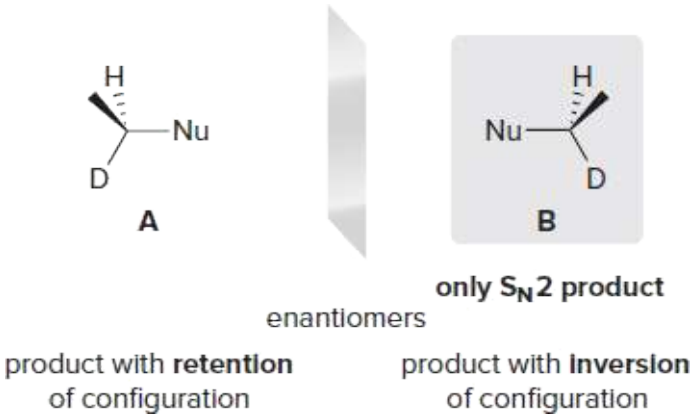
Recall from Section 1.1 that D stands for the isotope deuterium (^{2}H).



In backside attack, the nucleophile approaches from the opposite side to the leaving group, forming B. In this example, the leaving group was drawn on the *right*, so the nucleophile attacks from the *left*. Because the nucleophile and leaving group are in the opposite position relative to the other three groups on carbon, backside attack results in inversion of configuration around the stereogenic center.



The products of frontside and backside attack are *different* compounds. A Page 274 and B are stereoisomers that are nonsuperimposable—they are enantiomers.



Inversion of configuration in an S_N2 reaction is often called Walden inversion, after Latvian chemist Dr. Paul Walden, who first observed this process in 1896.

Backside attack occurs in all S_N2 reactions, but we can

observe this change only when the leaving group is bonded to a stereogenic center.

Which product is formed in an S_N2 reaction? When the stereochemistry of the product is determined, only B, the product of backside attack, is formed.

- **All S_N2 reactions proceed with *backside attack* of the nucleophile, resulting in *inversion* of configuration at a stereogenic center.**

One explanation for backside attack is based on an electronic argument. Both the nucleophile and leaving group are electron rich, and these like charges *repel* each other. Backside attack keeps these two groups as far away from each other as possible. In the transition state, the nucleophile and leaving group are 180° away from each other, and the other three groups around carbon occupy a plane, as illustrated in Figure 7.8.

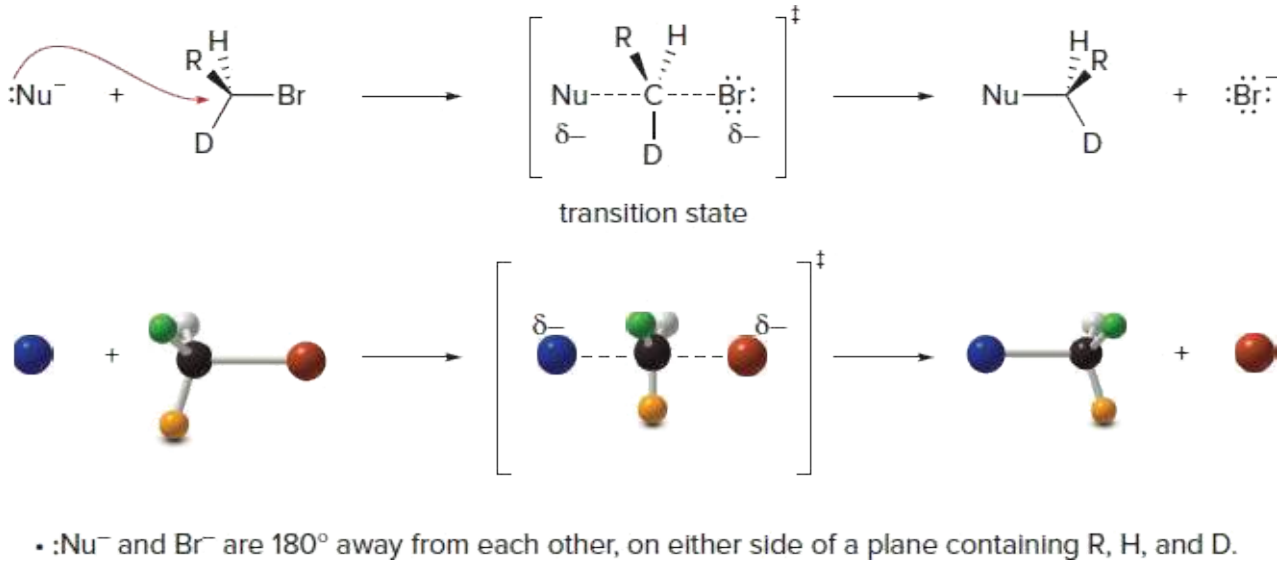


Figure 7.8 **Stereochemistry of the S_N2 reaction**

Two additional examples of inversion of configuration in S_N2 reactions are given in Figure 7.9.

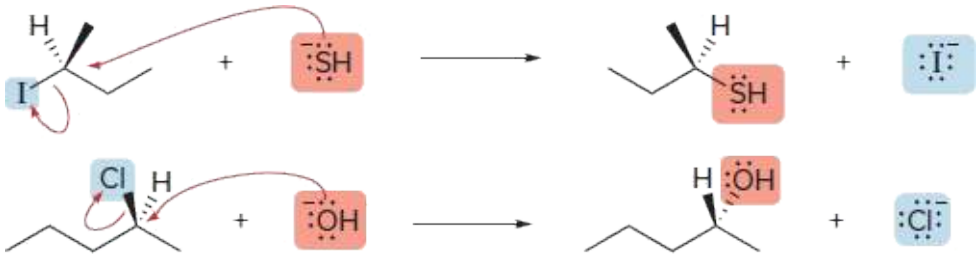
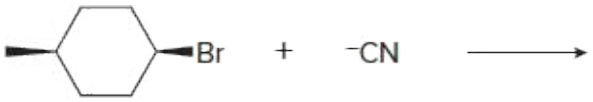


Figure 7.9 Two examples of inversion of configuration in the S_N2 reaction

Sample Problem 7.2 Drawing the Product of Inversion in an S_N2 Reaction

Label the nucleophile and leaving group, and draw the product (including stereochemistry) of the following S_N2 reaction.



Solution

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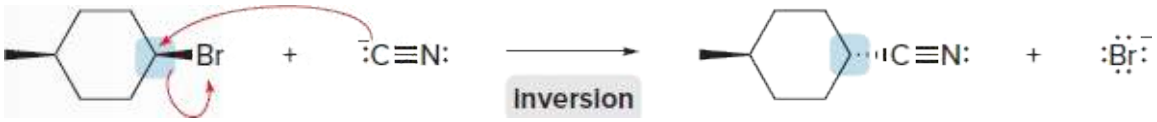
Br^- is the leaving group and ^-CN is the nucleophile. Because S_N2 reactions proceed with inversion of configuration and the leaving group is drawn *above* the ring (on a wedge), the nucleophile must come in from *below* (ending up on a dashed wedge).

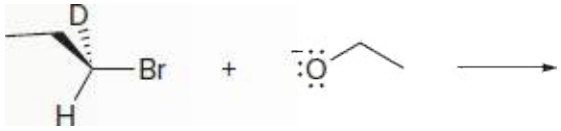


- **Inversion of configuration occurs at the C–Br bond.**
- **Backside attack converts the cis starting material to a trans product because the nucleophile (^-CN) attacks from *below* the plane of the ring.**

Problem 7.20

Draw the product of each S_N2 reaction and indicate stereochemistry.

a.



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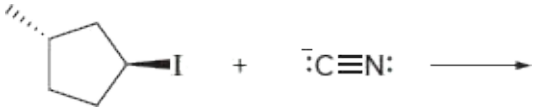


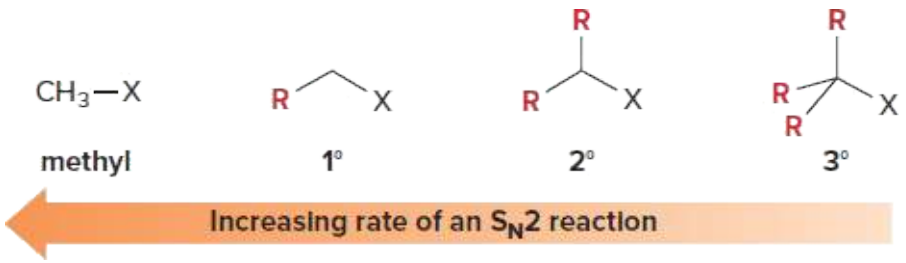
More Practice:

Try Problem 7.53.

7.11D The Identity of the R Group

How does the rate of an S_N2 reaction change as the alkyl group in the substrate alkyl halide changes from CH_3 1° 2° 3°?

- **As the number of R groups on the carbon with the leaving group *increases*, the rate of an S_N2 reaction *decreases.***



- **Methyl and 1° alkyl halides undergo S_N2 reactions with ease.**
- **2° Alkyl halides react more slowly.**
- **3° Alkyl halides *do not* undergo S_N2 reactions.**

This order of reactivity can be explained by steric effects. As small H atoms are replaced by larger alkyl groups, steric hindrance caused by bulky R groups makes nucleophilic attack from the back side more difficult, slowing the reaction rate. Figure 7.10 illustrates the effect of increasing steric hindrance in a series of alkyl halides.

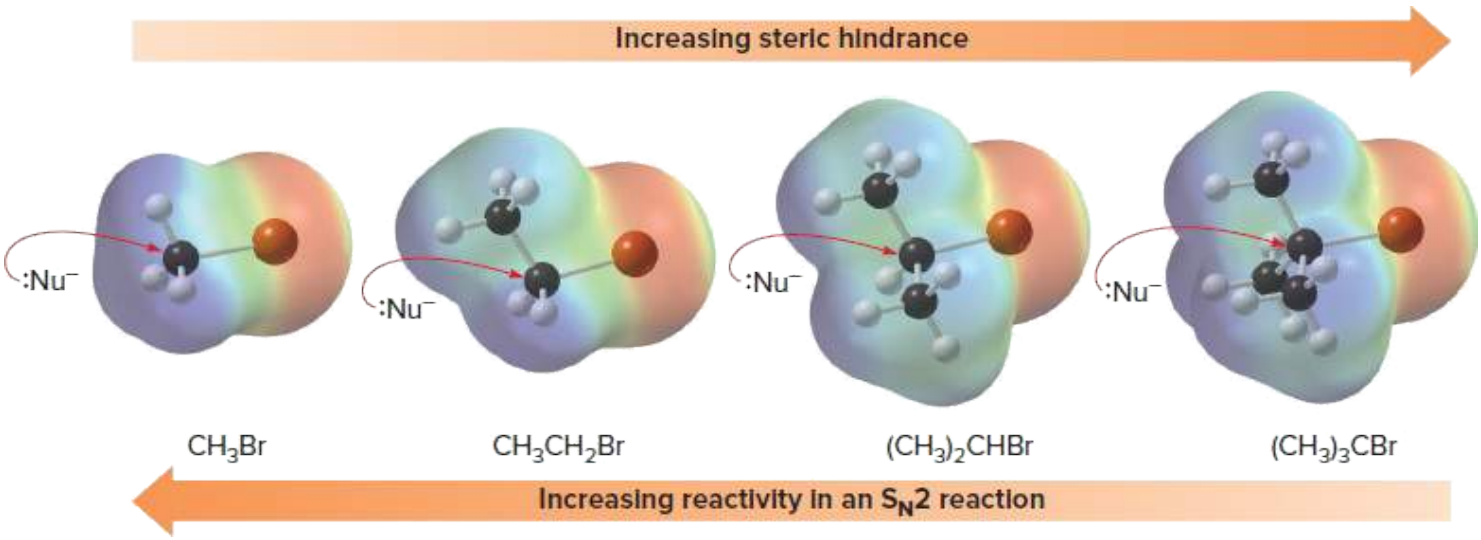


Figure 7.10 **Steric effects in the S_N2 reaction**

- **The S_N2 reaction is fastest with unhindered halides.**

Table 7.5 summarizes what we have learned thus far about the S_N2 mechanism. Page 276

Table 7.5 **Characteristics of the S_N2 Mechanism**

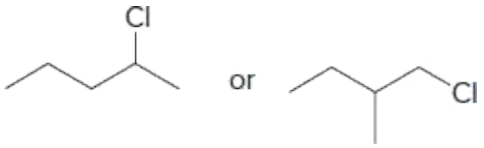
Characteristic	Result

Kinetics	• Second-order kinetics; rate = k[RX][:Nu$^-$]
Mechanism	• One step
Stereochemistry	• Backside attack of the nucleophile • Inversion of configuration at a stereogenic center
Identity of R	• Unhindered halides react fastest. • Rate: $CH_3X > RCH_2X > R_2CHX > R_3CX$

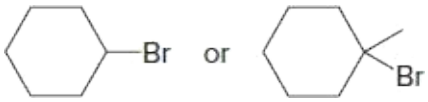
Problem 7.21

Which compound in each pair undergoes a faster S_N2 reaction?

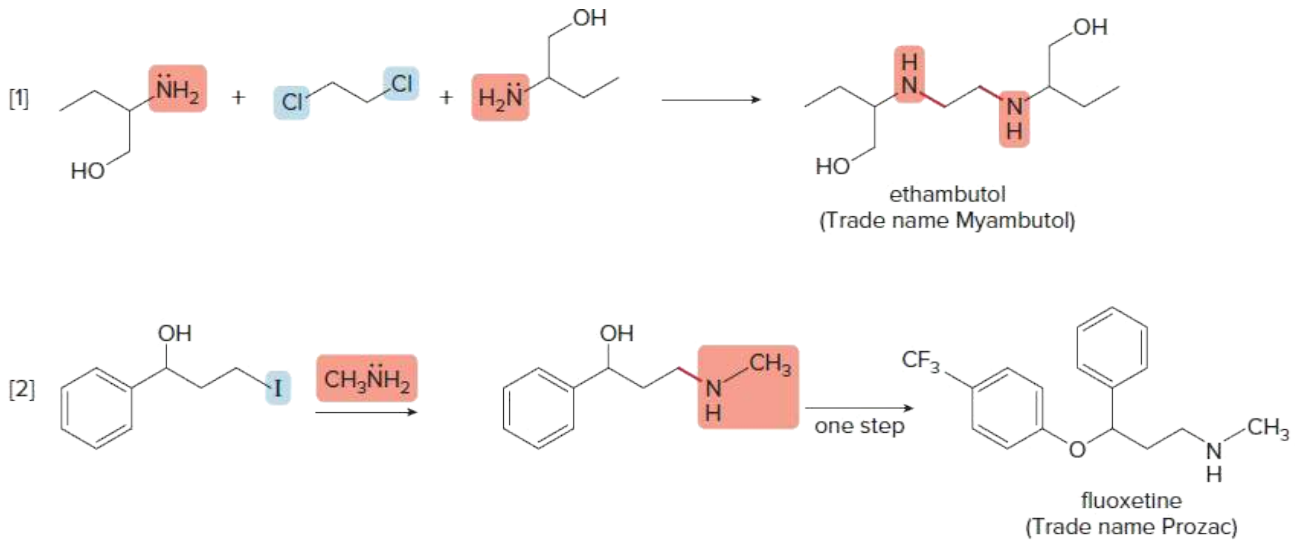
a.



b.



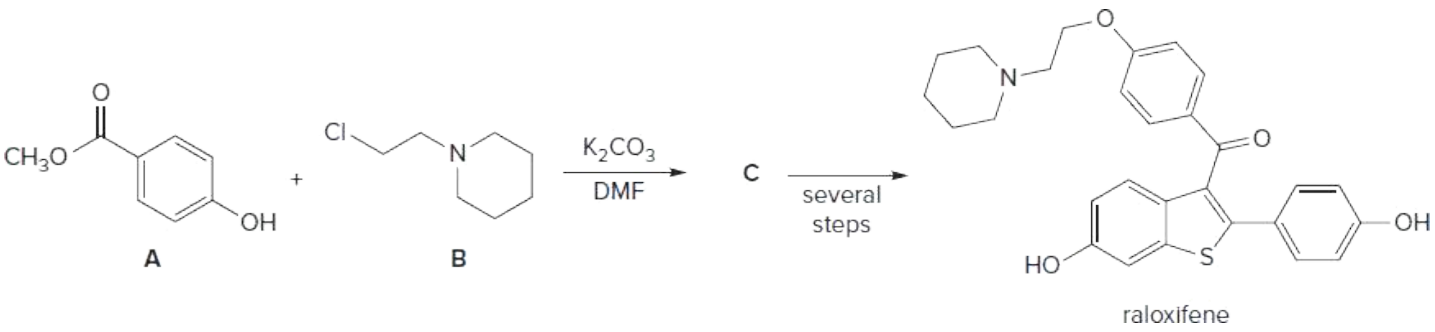
The S_N2 reaction is a key step in the laboratory synthesis of many drugs including ethambutol (trade name Myambutol), used in the treatment of tuberculosis, and fluoxetine (trade name Prozac), an antidepressant, as illustrated in Figure 7.11. Often an S_N2 reaction is preceded by an acid–base reaction that generates a stronger nucleophile, as shown in Sample Problem 7.3.



- In both examples, the initial substitution product bears a positive charge and goes on to lose a proton to form the product drawn.
- The NH_2 group serves as a neutral nucleophile to displace halogen in each synthesis. The new bonds formed by nucleophilic substitution are drawn in red in the products.

Figure 7.11 **Nucleophilic substitution in the synthesis of two useful drugs**

Identify C, the product of an S_N2 reaction in the synthesis of raloxifene, a drug used to reduce the risk of invasive breast cancer in postmenopausal women.

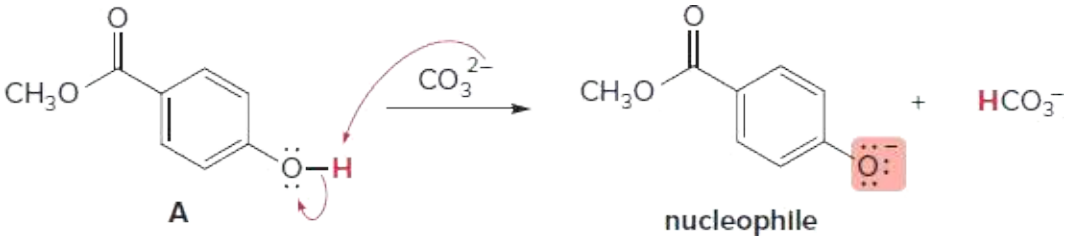


Solution

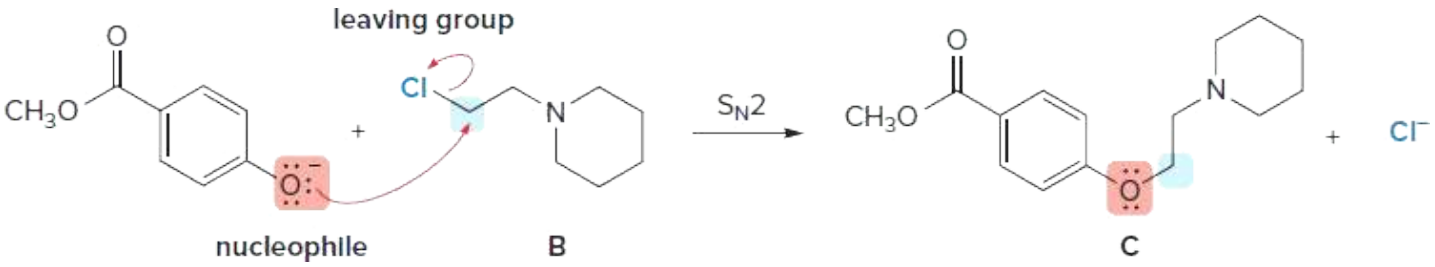
Even though both starting materials have two functional groups, follow the same strategy used in simpler reactions.

[1] Identify the nucleophile and the leaving group. There are only a limited number of leaving groups (Table 7.2). Because B contains a Cl bonded to an sp^3 hybridized C, B contains the leaving group, so A contains the nucleophile.

Because this reaction is carried out in the presence of base (K_2CO_3) the most acidic proton in either reactant is removed, and that is the OH proton in A. Removal of the OH proton in A forms the negatively charged conjugate base, the nucleophile.



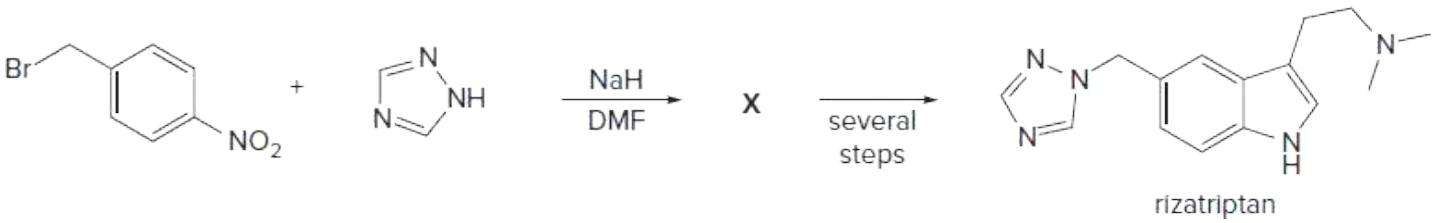
[2] Substitute the nucleophile for the leaving group.



Nucleophilic substitution forms C with a new C–O bond.

Problem 7.22

Draw the product X of the following S_N2 reaction. X was a key intermediate in the synthesis of rizatriptan, a drug introduced in 1998 for the treatment of migraines.

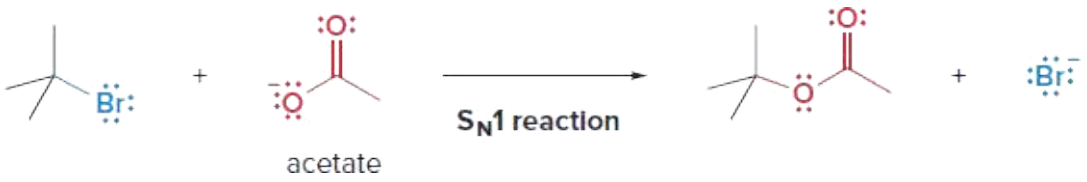


More Practice:

Try Problems 7.54–7.56.

7.12 The S_N1 Mechanism

The reaction of $(CH_3)_3CBr$ with $CH_3CO_2^-$ is an example of the second mechanism for nucleophilic substitution, the S_N1 mechanism. What are the general features of this mechanism?



7.12A Kinetics

The S_N1 reaction exhibits first-order kinetics.

- **rate = $k[(CH_3)_3CBr]$**

As we learned in Section 7.10, the kinetics suggest that the S_N1 mechanism involves more than one step, and that the slow step is unimolecular, involving *only* the alkyl halide. The identity and concentration of the nucleophile have *no effect* on the reaction rate. Doubling the concentration of $(CH_3)_3CBr$ doubles the rate, but doubling the concentration of the nucleophile has *no effect*.

Problem 7.23

What happens to the rate of an S_N1 reaction under each of the following conditions?

a. **[RX] is tripled, and [:Nu$^-$] stays the same.**

b. **Both [RX] and [:Nu$^-$] are tripled.**

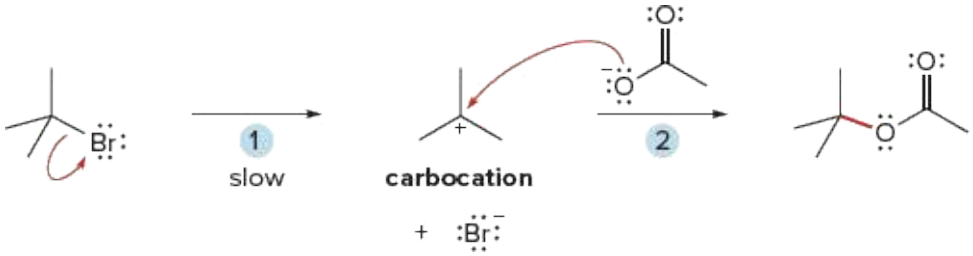
c. **[RX] is halved, and [:Nu$^-$] stays the same.**

d. **[RX] is halved, and [:Nu$^-$] is doubled.**

7.12B A Two-Step Mechanism

The most straightforward explanation for the observed first-order kinetics is a two-step mechanism in which bond breaking occurs *before* bond making, as shown in Mechanism 7.2.

Mechanism 7.2 The S_N1 Mechanism

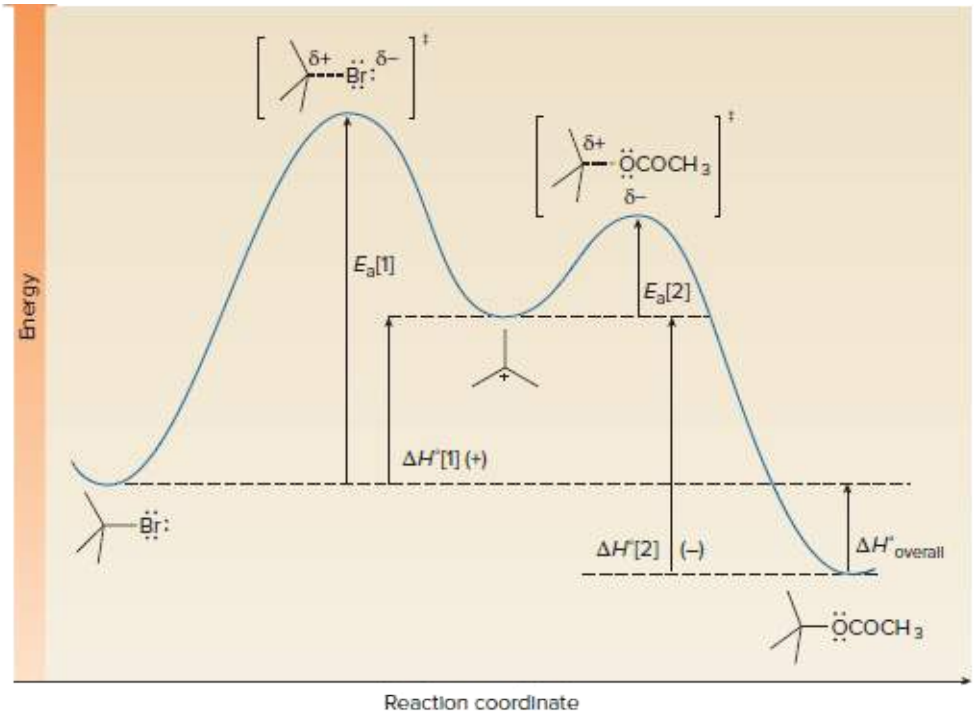


1. **Heterolysis of the C–Br bond forms a carbocation in the rate-determining step.**
2. **Nucleophilic attack of acetate (a Lewis base) on the carbocation (a Lewis acid) forms the new C–O bond.**

The key features of the S_N1 mechanism are:

- **The mechanism has two steps.**
- **Carbocations are formed as reactive intermediates.**

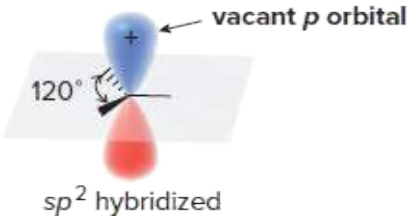
An energy diagram for the reaction of $(CH_3)_3CBr + CH_3CO_2^-$ is shown in Figure 7.12. Each step has its own energy barrier, with a transition state at each energy maximum. Because the transition state for Step [1] is at higher energy, Step [1] is rate-determining. $\Delta H°$ for Step [1] has a positive value because only bond breaking occurs, whereas $\Delta H°$ of Step [2] has a negative value because only bond making occurs. The overall reaction is assumed to be exothermic, so the final product is drawn at lower energy than the initial starting material.



- The S_N1 mechanism has **two steps**, so there are **two energy barriers.**
- E_a[1] > E_a[2] because Step [1] involves bond breaking and Step [2] involves bond formation.
- In each step only one bond is broken or formed, so the transition state for each step has one partial bond.

Figure 7.12 **An energy diagram for the S_N1 reaction: $(CH_3)_3CBr + CH_3CO_2^- \rightarrow (CH_3)_3COCOCH_3 + Br^-$**

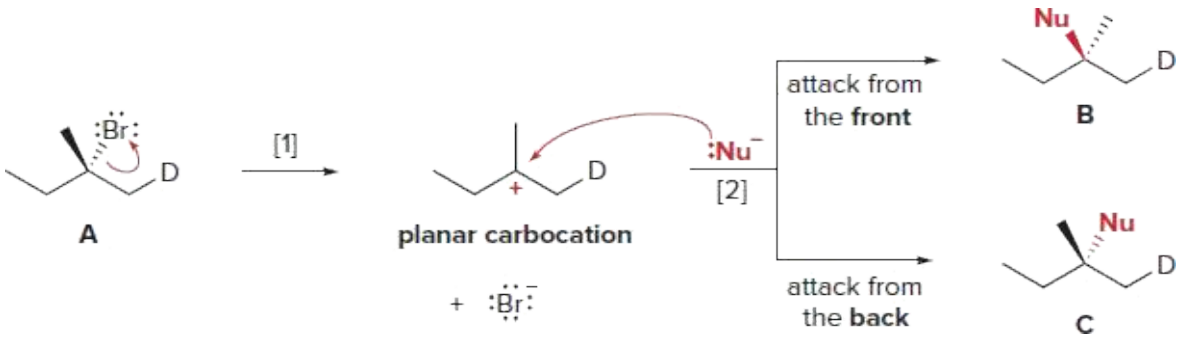
7.12C Stereochemistry of the S_N1 Reaction



To understand the stereochemistry of the S_N1 reaction, we must examine the geometry of the carbocation intermediate.

- **A carbocation (with three groups around C) is sp^2 hybridized and trigonal planar, and contains a vacant *p* orbital extending above and below the plane.**

To illustrate the consequences of having a trigonal planar carbocation formed as a reactive intermediate, we examine the S_N1 reaction of a 3° alkyl halide A having the leaving group bonded to a stereogenic center.

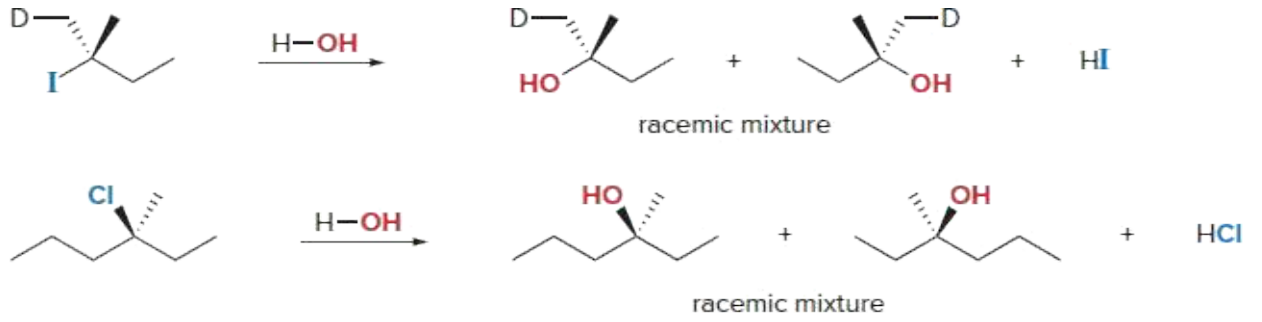


Nucleophilic attack from both sides of a planar carbocation occurs in S_N1 reactions, but we see the result of this phenomenon only when the leaving group is bonded to a stereogenic center.

Loss of the leaving group in Step [1] generates a planar carbocation that is now *achiral*. Attack of the nucleophile in Step [2] can occur from either the front or the back to afford two products, B and C. These two products are *different* compounds containing one stereogenic center. B and C are stereoisomers that are not superimposable—they are enantiomers. Because there is no preference for nucleophilic attack from either direction, an equal amount of the two enantiomers is formed—a racemic mixture. We say that *racemization* has occurred.

- ***Racemization*** **is the formation of equal amounts of two enantiomeric products from a single starting material.**
- **S_N1 reactions proceed with *racemization* at a single stereogenic center.**

Two additional examples of racemization in S_N1 reactions are given in Figure 7.13.

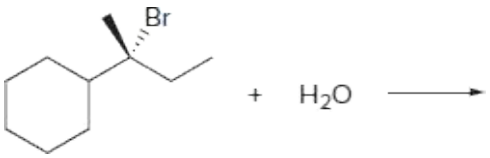


- Nucleophilic substitution of each starting material by an S_N1 mechanism forms a **racemic mixture** of two products.
- With H_2O, a neutral nucleophile, the initial product of nucleophilic substitution (ROH_2^+) loses a proton to form the final neutral product, ROH (Section 7.6).

Figure 7.13 Two examples of racemization in the S_N1 reaction

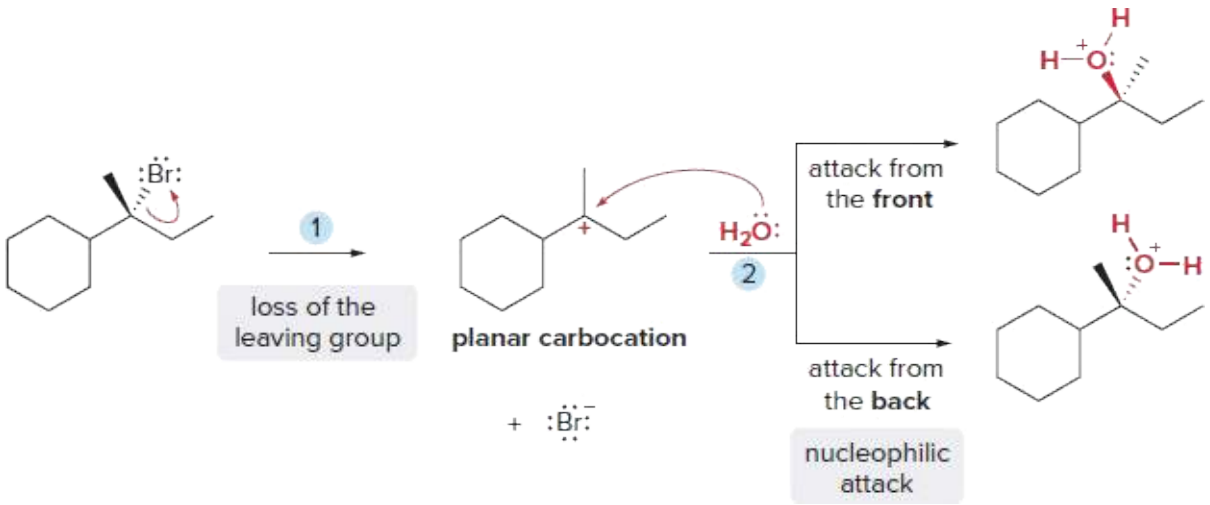
Sample Problem 7.4 Drawing the Products of an S_N1 Reaction

Label the nucleophile and leaving group, and draw the products (including stereochemistry) of the following S_N1 reaction.

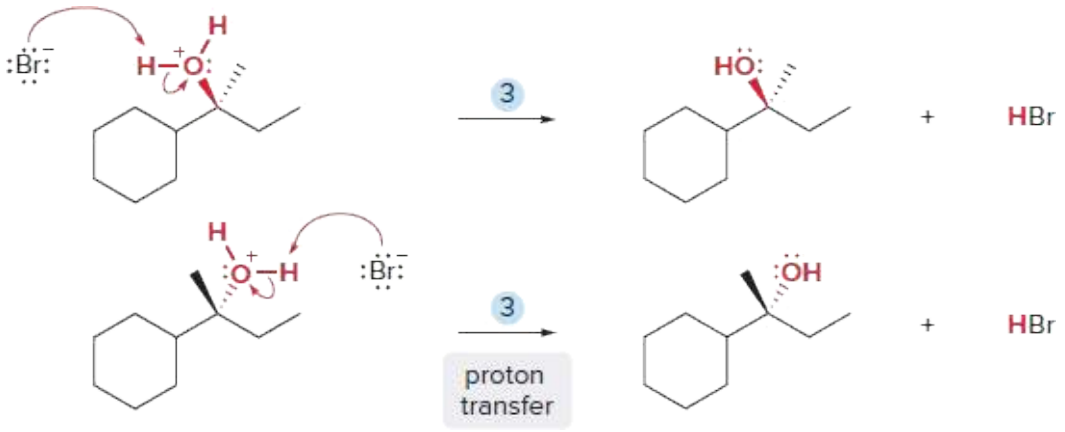


Solution

Br^- is the leaving group and H_2O is the nucleophile. Loss of the leaving group generates a trigonal planar carbocation, which can react with the nucleophile from either direction to form two products.



In this example, the initial products of nucleophilic substitution bear a positive charge. They readily lose a proton to form neutral products. The overall process with a neutral nucleophile thus has three steps: the first two constitute the two-step S_N1 mechanism (loss of the leaving group and attack of the nucleophile), and the third is a Brønsted–Lowry acid–base reaction leading to a neutral organic product.



The two products in this reaction are nonsuperimposable mirror images—enantiomers. Because nucleophilic attack on the trigonal planar carbocation occurs with equal frequency from both directions, a racemic mixture is formed.

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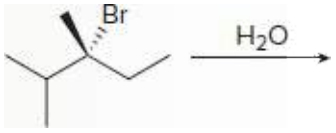
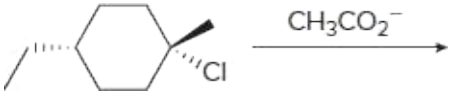
Problem 7.24

Draw the products of each S_N1 reaction and indicate the stereochemistry of any stereogenic centers.

a.



b.



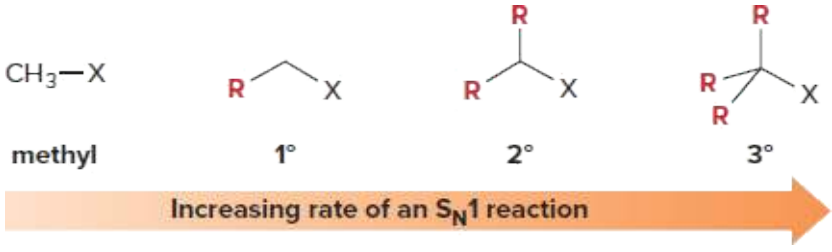
More Practice:

Try Problem 7.60.

7.12D The Identity of the R Group

How does the rate of an S_N1 reaction change as the alkyl group in the substrate alkyl halide changes from CH_3 1° 2° 3°?

- **As the number of R groups on the carbon with the leaving group *increases*, the rate of an S_N1 reaction *increases.***



- **3° Alkyl halides undergo S_N1 reactions rapidly.**
- **2° Alkyl halides react more slowly.**
- **Methyl and 1° alkyl halides do *not* undergo S_N1 reactions.**

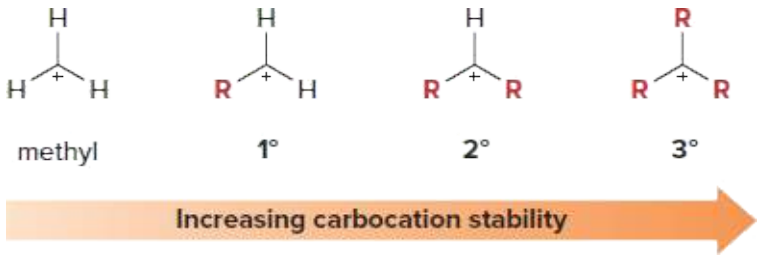
This trend is exactly opposite to that observed for the S_N2 mechanism. To explain this result, we must examine the rate-determining step, the formation of the carbocation, and learn about the effect of alkyl groups on carbocation stability. Table 7.6 summarizes the characteristics of the S_N1 mechanism.

Table 7.6 Characteristics of the S_N1 Mechanism

Characteristic	Result
Kinetics	• First-order kinetics; rate = k[RX]
Mechanism	• Two steps
Stereochemistry	• Trigonal planar carbocation intermediate • Racemization at a single stereogenic center
Identity of R	• More-substituted halides react fastest. • Rate: $R_3CX > R_2CHX > RCH_2X > CH_3X$

7.13 Carbocation Stability

Carbocations are classified as primary (1°), secondary (2°), or tertiary (3°) by the number of R groups bonded to the charged carbon atom. As the number of R groups on the positively charged carbon atom increases, the stability of the carbocation increases.

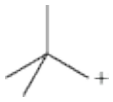


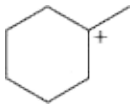
We will examine the reason for this order of stability by invoking two different principles: inductive effects and hyperconjugation.

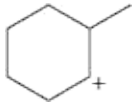
Problem 7.25

Classify each carbocation as 1°, 2°, or 3°.

a.

b. 

c. 

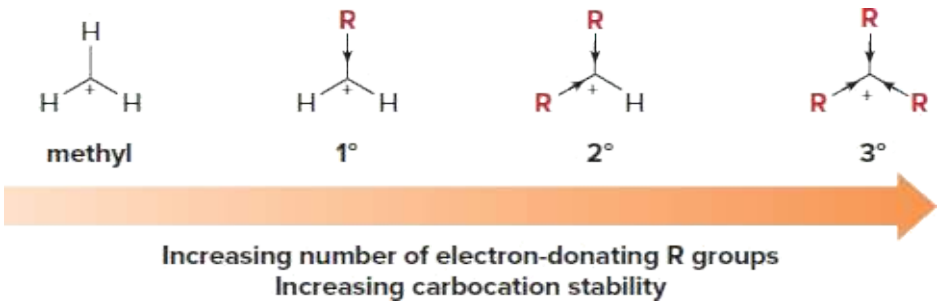
d. 

7.13A Inductive Effects

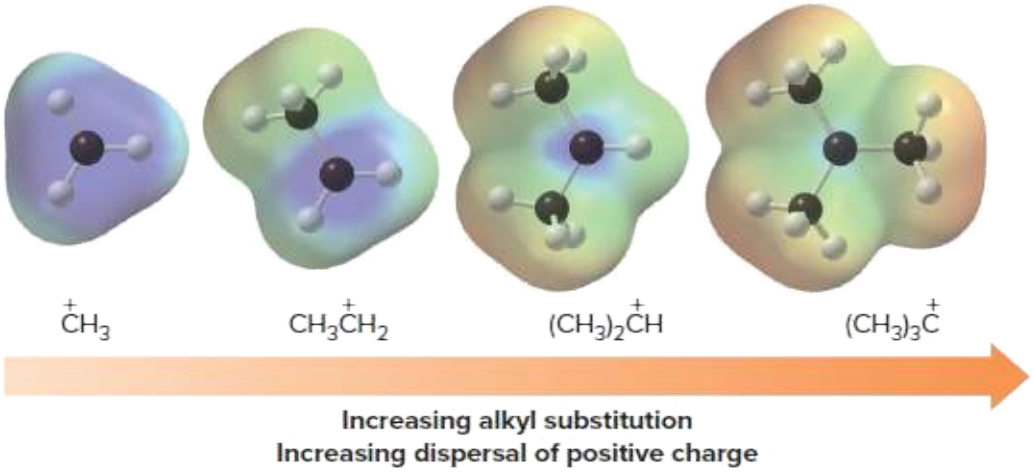
Inductive effects are electronic effects that occur through σ bonds. In Section 2.5B, for example, we learned that more-electronegative atoms stabilize a negative charge by an electron-withdrawing inductive effect.

Electron-donor groups (Z) stabilize a (+) charge; $Z \rightarrow Y^+$.
Electron-withdrawing groups (W) stabilize a (−) charge; $W \leftarrow Y^-$.

To stabilize a positive charge, electron-donating groups are needed. Alkyl groups are electron-donor groups that stabilize a positive charge. An alkyl group with several σ bonds is more polarizable than a hydrogen atom, and more able to donate electron density. Thus, as R groups successively replace the H atoms in CH_3^+, the positive charge is more dispersed on the electron-donor R groups, and the carbocation is more stabilized.



Electrostatic potential maps for four carbocations in Figure 7.14 illustrate the effect of increasing alkyl substitution on the positive charge of the carbocation.

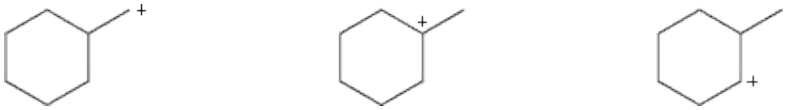


- Dark blue areas in electrostatic potential plots indicate regions low in electron density. As alkyl substitution increases, the region of positive charge is less concentrated on carbon.

Figure 7.14 **Electrostatic potential maps for different carbocations**

Problem 7.26

Rank the following carbocations in order of increasing stability.

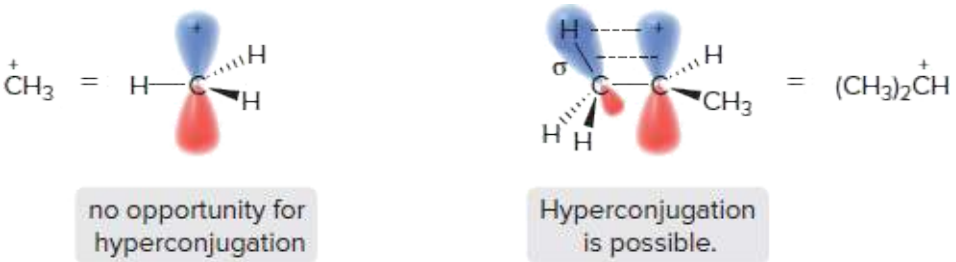


7.13B Hyperconjugation

A second explanation for the observed trend in carbocation stability is based on orbital overlap. A 3° carbocation is more stable than a 2°, 1°, or methyl carbocation because the positive charge is *delocalized* over more than one atom.

- **Spreading out charge by the overlap of an empty *p* orbital with an adjacent σ bond is called *hyperconjugation.***

For example, CH_3^+ cannot be stabilized by hyperconjugation, but $(CH_3)_2CH^+$ can:



Both carbocations contain an sp^2 hybridized carbon, so both are trigonal planar with a vacant *p* orbital extending above and below the plane. There are no adjacent C–H σ bonds with which the *p* orbital can overlap in CH_3^+, but there *are* adjacent C–H σ

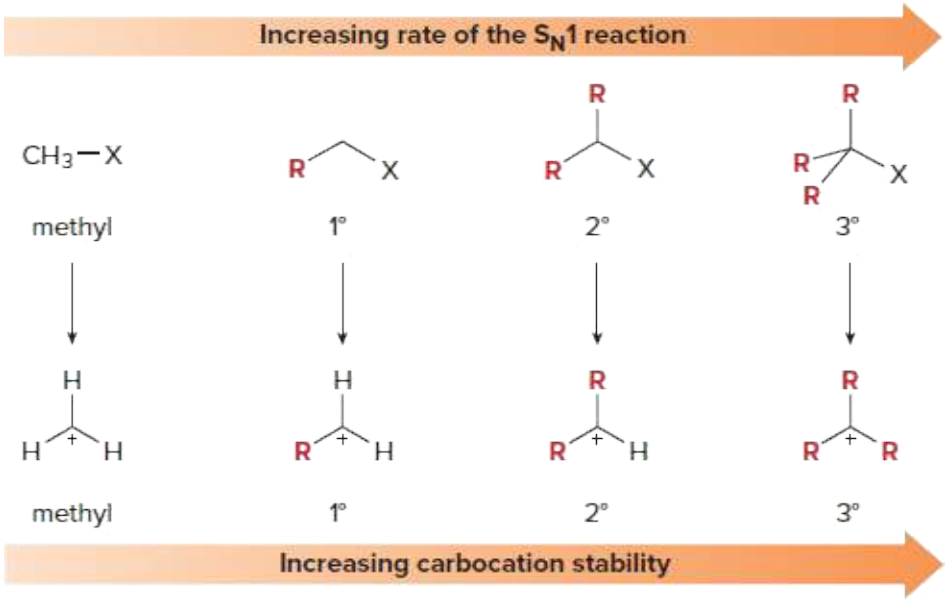
bonds in $(CH_3)_2CH^+$. This overlap (the hyperconjugation) delocalizes the positive charge on the carbocation, spreading it over a larger volume, and this stabilizes the carbocation.

The larger the number of alkyl groups on the adjacent carbons, the greater the possibility for hyperconjugation, and the larger the stabilization. Hyperconjugation thus provides an alternate way of explaining why carbocations with a larger number of R groups are more stabilized.

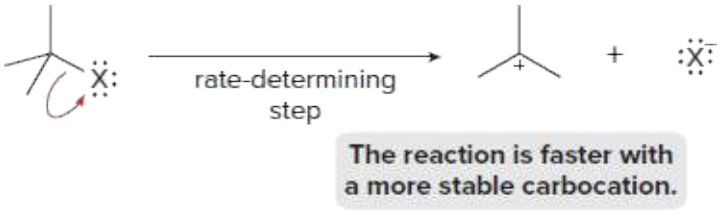
7.14 The Hammond Postulate

The rate of an S_N1 reaction depends on the rate of formation of the carbocation (the product of the rate-determining step) via heterolysis of the C–X bond.

- **The rate of an S_N1 reaction *increases* as the number of R groups on the carbon with the leaving group *increases.***
- **The stability of a carbocation *increases* as the number of R groups on the positively charged carbon *increases.***



- **Thus, the rate of an S_N1 reaction *increases* as the stability of the carbocation *increases.***

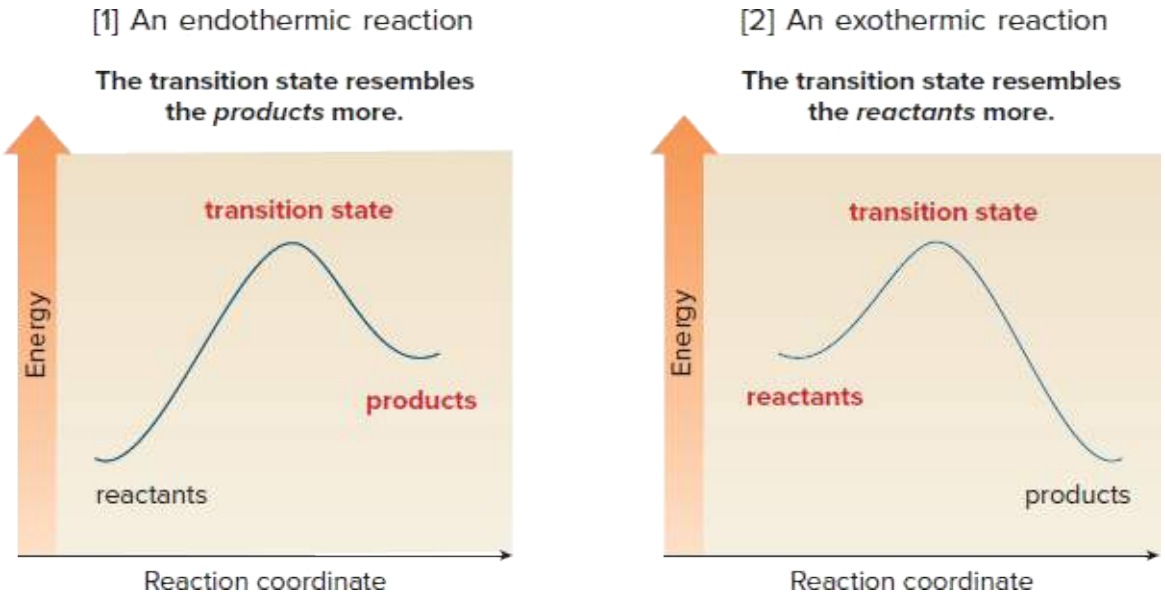


The rate of a reaction depends on the magnitude of E_a, and the stability of a product depends on ΔG^o. The Hammond postulate, first proposed in 1955, relates rate to stability.

7.14A The General Features of the Hammond Postulate

The Hammond postulate provides a qualitative estimate of the energy of a transition state. Because the energy of the transition state determines the energy of activation and therefore the reaction rate, predicting the relative energy of two transition states allows us to determine the relative rates of two reactions.

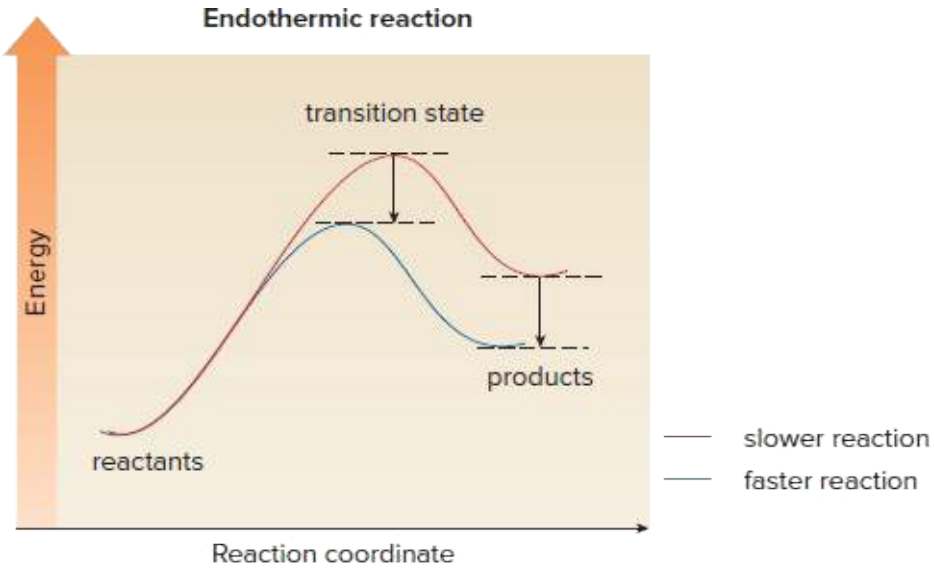
According to the Hammond postulate, the transition state of a reaction resembles the structure of the species (reactant or product) to which it is closer in energy. In endothermic reactions, the transition state is closer in energy to the products. In exothermic reactions, the transition state is closer in energy to the reactants.



- **Transition states in *endothermic* reactions resemble the *products.***
- **Transition states in *exothermic* reactions resemble the *reactants.***

What happens to the reaction rate if the energy of the product is lowered? In an endothermic reaction, the transition state resembles the products, so anything that stabilizes the product stabilizes the transition state, too. Lowering the energy of the transition state *decreases* the energy of activation (E_a), which *increases* the reaction rate.

Suppose there are two possible products of an endothermic reaction, but one is more stable (lower in energy) than the other (Figure 7.15). According to the Hammond postulate, the transition state to form the more stable product is lower in energy, so this reaction should occur faster.

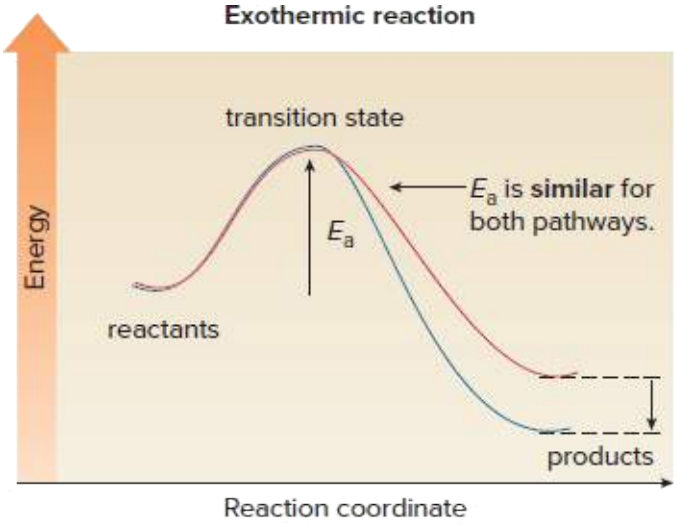


• The *lower* energy transition state leads to the *lower* energy product.

Figure 7.15 **An endothermic reaction—how the energies of the transition state and products are related**

- **In an endothermic reaction, the *more stable* product forms *faster.***

What happens to the reaction rate of an exothermic reaction if the energy of the product is lowered? The transition state resembles the reactants, so lowering the energy of the products has little or no effect on the energy of the transition state. If E_a is unaffected, then the reaction rate is unaffected, too, as shown in Figure 7.16.



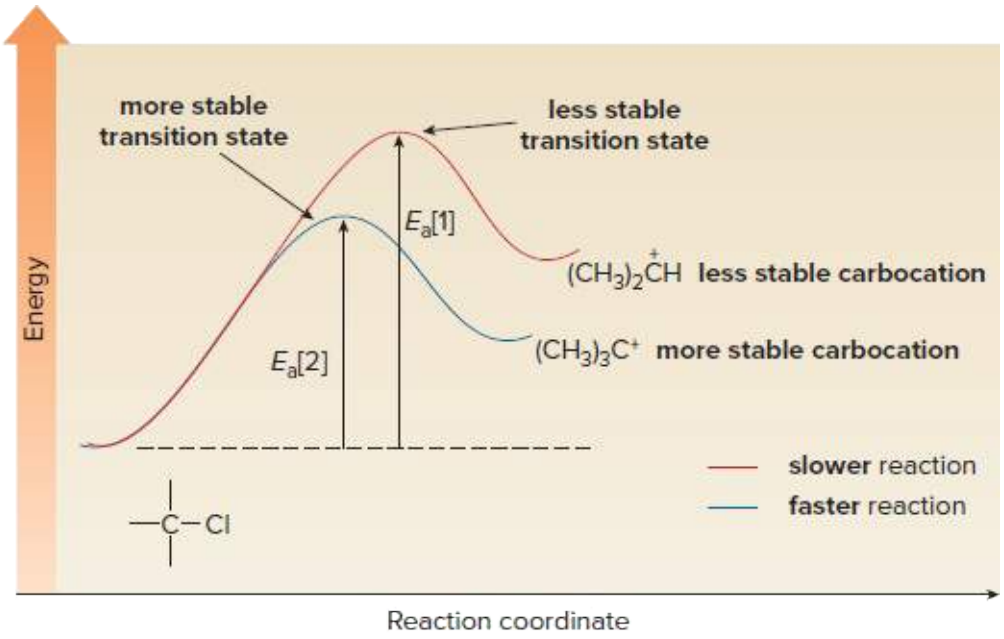
• Decreasing the energy of the product often has *little effect* on the energy of the transition state.

Figure 7.16 **An exothermic reaction—how the energies of the transition state and products are related**

- **In an exothermic reaction, the more stable product may or may not form faster because E_a is *similar* for both products.**

7.14B The Hammond Postulate and the S_N1 Reaction

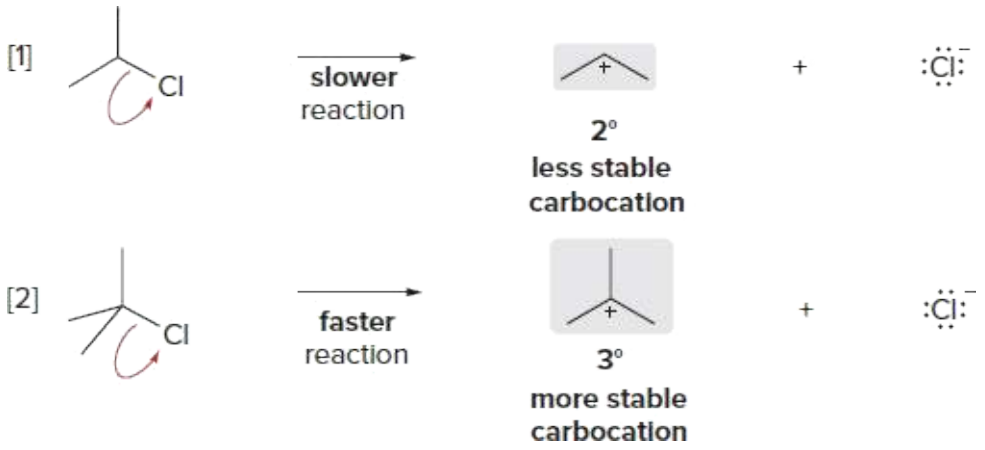
In the S_N1 reaction, the rate-determining step is the formation of the carbocation, an *endothermic* reaction. According to the Hammond postulate, the stability of the carbocation determines the rate of its formation.



- $(CH_3)_2CH^+$ is less stable than $(CH_3)_3C^+$, so $E_a[1] > E_a[2]$, and Reaction [1] is slower.

Figure 7.17 Energy diagram for carbocation formation in two different S_N1 reactions

For example, heterolysis of the C–Cl bond in $(CH_3)_2CHCl$ affords a less stable 2° carbocation, $(CH_3)_2CH^+$ (Equation [1]), whereas heterolysis of the C–Cl bond in $(CH_3)_3CCl$ affords a more stable 3° carbocation, $(CH_3)_3C^+$ (Equation [2]). The Hammond postulate states that Reaction [2] is faster than Reaction [1], because the transition state to form the more stable 3° carbocation is lower in energy. Figure 7.17 depicts an energy diagram comparing these two endothermic reactions.

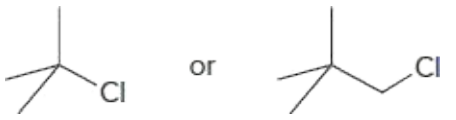


In conclusion, the Hammond postulate can be used to predict the relative rates of two reactions. In the S_N1 reaction the rate-determining step is endothermic, so the more stable carbocation is formed faster.

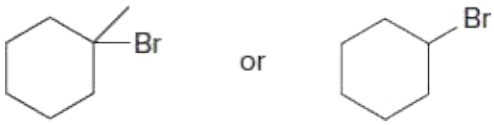
Problem 7.27

Which alkyl halide in each pair reacts faster in an S_N1 reaction?

a.



b.



7.15 When Is the Mechanism S_N1 or S_N2?

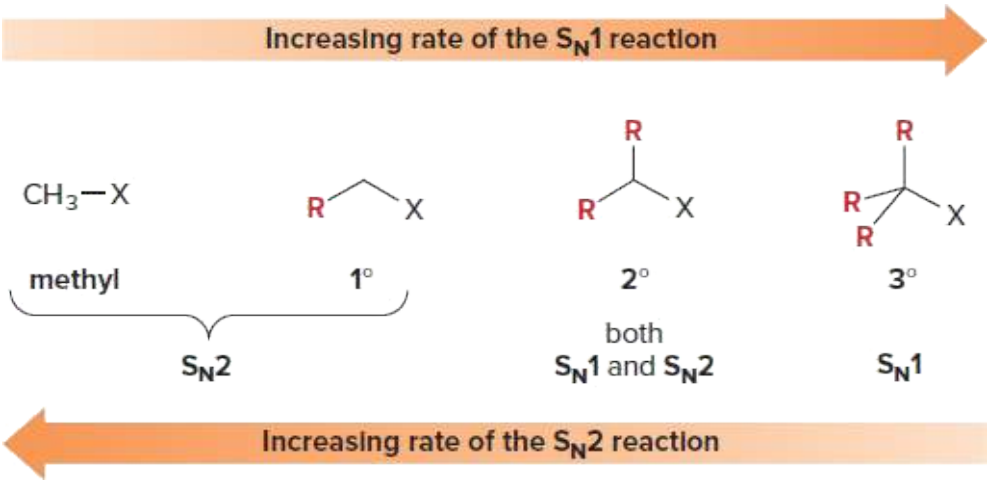
Given a particular starting material and nucleophile, how do we know whether a reaction occurs by the S_N1 or S_N2 mechanism? Four factors are examined:

- The alkyl halide—CH_3X, RCH_2X, R_2CHX, or R_3CX
- The nucleophile—strong or weak
- The leaving group—good or poor
- The solvent—protic or aprotic

7.15A The Alkyl Halide—The Most Important Factor

The most important factor in determining whether a reaction follows the S_N1 or S_N2 mechanism is the *identity of the alkyl halide.*

- ***Increasing*** **alkyl substitution favors S_N1.**
- ***Decreasing*** **alkyl substitution favors S_N2.**



- **Methyl and 1° halides (CH_3X and RCH_2X) undergo only S_N2 reactions.**
- **3° Alkyl halides (R_3CX) undergo only S_N1 reactions.**
- **2° Alkyl halides (R_2CHX) undergo both S_N1 and S_N2 reactions. Other factors determine the mechanism.**

Examples are given in Figure 7.18.

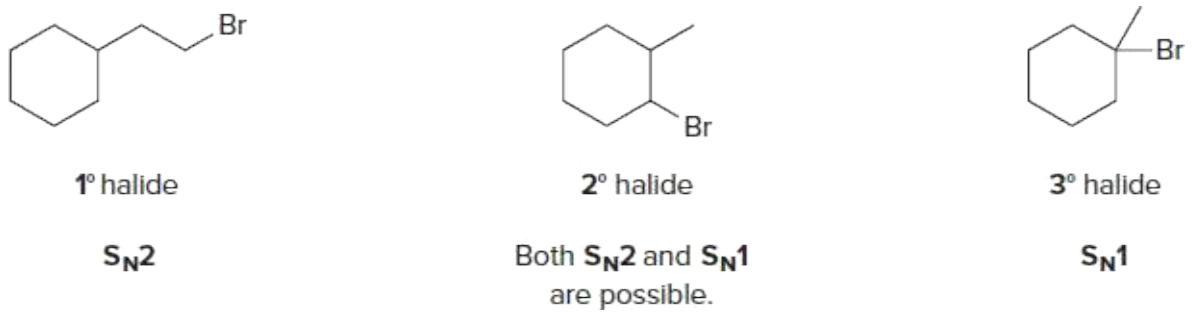
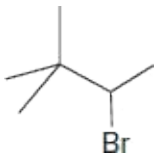
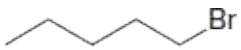


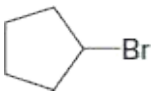
Figure 7.18 **The identity of RX and the mechanism of nucleophilic substitution**

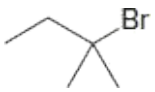
Problem 7.28

What is the likely mechanism of nucleophilic substitution for each alkyl halide?

a.


b.


c.


d.


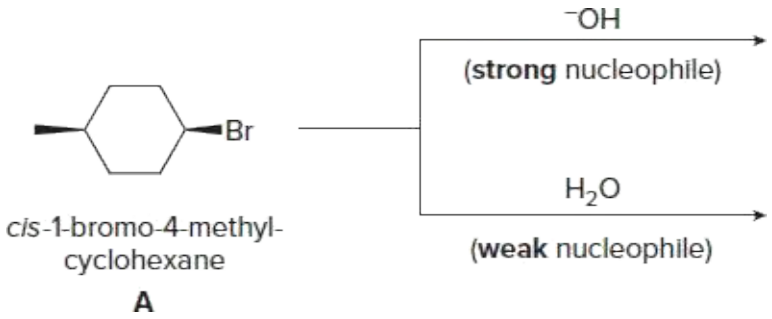
7.15B The Nucleophile

How does the strength of the nucleophile affect an S_N1 or S_N2 mechanism? The rate of the S_N1 reaction is unaffected by the identity of the nucleophile because the nucleophile does not appear in the rate equation (rate = k[RX]). The identity of the nucleophile *is* important for the S_N2 reaction, however, because the nucleophile does appear in the rate equation for this mechanism (rate = k[RX][:Nu^-]).

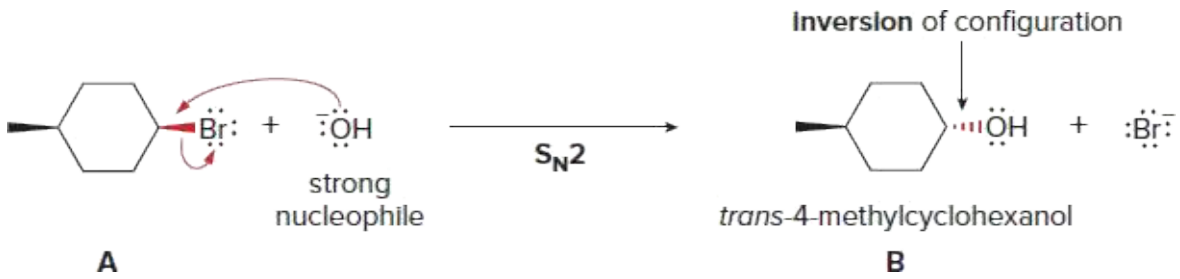
- ***Strong*** **nucleophiles present in high concentration favor S_N2 reactions.**
- ***Weak*** **nucleophiles favor S_N1 reactions by decreasing the rate of any competing S_N2 reaction.**

The most common nucleophiles in S_N2 reactions bear a net negative charge. Page 288 The most common nucleophiles in S_N1 reactions are weak nucleophiles such as H_2O and ROH. The identity of the nucleophile is especially important in determining the mechanism and therefore the stereochemistry of nucleophilic substitution when 2° alkyl halides are starting materials.

Let's compare the substitution products formed when the 2° alkyl halide A (*cis*-1-bromo-4-methylcyclohexane) is treated with either the strong nucleophile $^-$OH or the weak nucleophile H_2O. Because a 2° alkyl halide can react by either mechanism, the strength of the nucleophile determines which mechanism takes place.

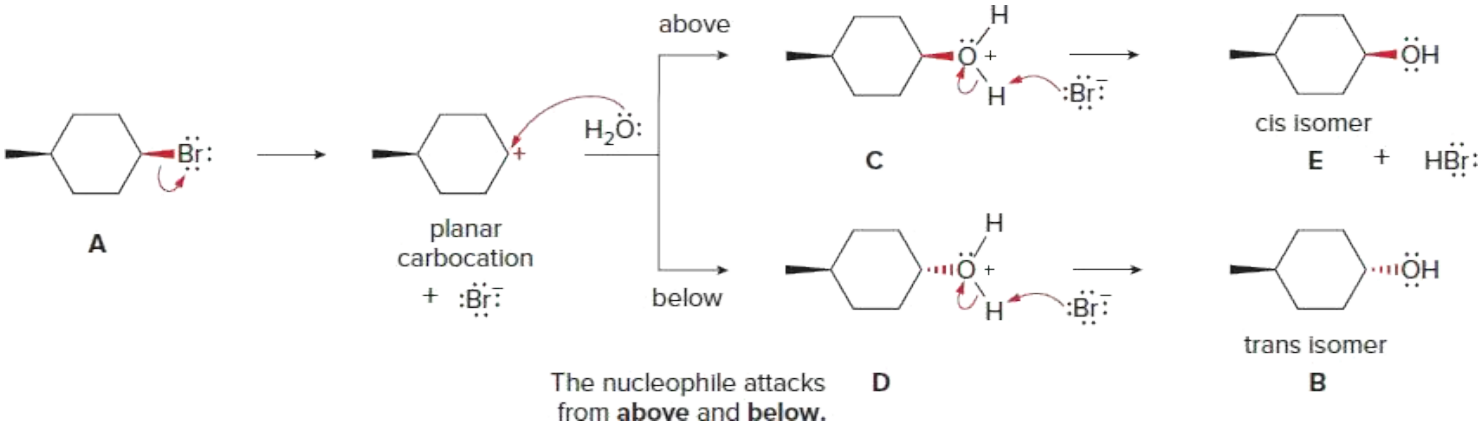


The strong nucleophile $^-$OH favors an S_N2 reaction, which occurs with backside attack of the nucleophile, resulting in inversion of configuration. Because the leaving group Br^- is *above* the plane of the ring, the nucleophile attacks from *below*, and a single product B is formed.



The weak nucleophile H_2O favors an S_N1 reaction, which occurs by way of an

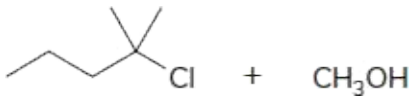
intermediate carbocation. Loss of the leaving group in A forms the carbocation, which undergoes nucleophilic attack from both above and below the plane of the ring to afford two products, C and D. Loss of a proton by proton transfer forms the final products, B and E. B and E are diastereomers of each other (B is a trans isomer and E is a cis isomer).

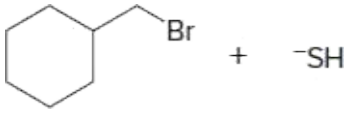


Thus, the mechanism of nucleophilic substitution determines the stereochemistry of the products formed.

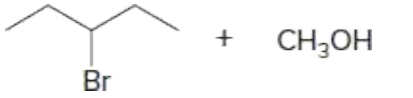
Problem 7.29

For each alkyl halide and nucleophile: [1] Draw the product of nucleophilic substitution; [2] determine the likely mechanism (S_N1 or S_N2) for each reaction.

a. 

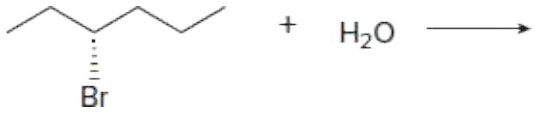
b. 

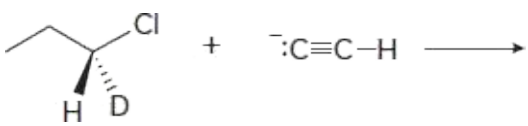
c.

d. 

Problem 7.30

Draw the products (including stereochemistry) for each reaction.

a. 

b. 

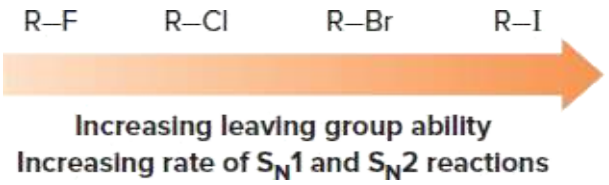
7.15C The Leaving Group

How does the identity of the leaving group affect an S_N1 or S_N2 reaction?

- **A *better* leaving group increases the rate of *both* S_N1 and S_N2 reactions.**

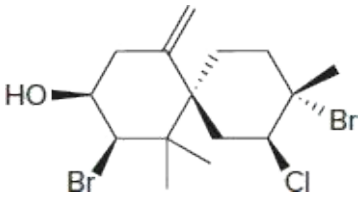
Because the bond to the leaving group is partially broken in the transition state of the only step of the S_N2 mechanism and the slow step of the S_N1 mechanism, a better leaving group increases the rate of both reactions. The better the leaving group, the more willing it is to accept the electron pair in the C–X bond, and the faster the reaction.

For alkyl halides, the following order of reactivity is observed for the S_N1 and the S_N2 mechanisms:



Problem 7.31

Rank the alkyl halides in the following marine natural product in order of increasing reactivity in the S_N1 reaction.



7.15D The Solvent

Polar protic solvents and polar aprotic solvents affect the rates of S_N1 and S_N2 reactions differently.

- **Polar *protic* solvents are especially good for S_N1 reactions.**
- **Polar *aprotic* solvents are especially good for S_N2 reactions.**

Summary of solvent effects:

- **Polar protic solvents favor S_N1 reactions because the**

ionic intermediates are stabilized by solvation.

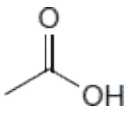
- **Polar aprotic solvents favor S_N2 reactions because nucleophiles are not well solvated, and therefore are more nucleophilic.**

Polar protic solvents like H_2O and ROH solvate both cations and anions well, and this characteristic is important for the S_N1 mechanism, in which two ions (a carbocation and a leaving group) are formed by heterolysis of the C–X bond. The carbocation is solvated by ion–dipole interactions with the polar solvent, and the leaving group is solvated by hydrogen bonding, in much the same way that Na^+ and Br^- are solvated in Section 7.8C. These interactions stabilize the reactive intermediate. In fact, a polar protic solvent is generally needed for an S_N1 reaction.

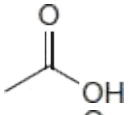
Polar aprotic solvents exhibit dipole–dipole interactions but not hydrogen bonding, and as a result, they do not solvate anions well. This has a pronounced effect on the nucleophilicity of anionic nucleophiles. Because these nucleophiles are not "hidden" by strong interactions with the solvent, they are more nucleophilic. Because stronger nucleophiles favor S_N2 reactions, polar aprotic solvents are especially good for S_N2 reactions.

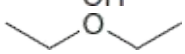
Problem 7.32

Which solvents favor S_N1 reactions and which favor S_N2 reactions?

a. 

b. CH_3CN

c. 

d. 

Problem 7.33

Decide on the mechanism for each substitution, and then pick the solvent that affords the faster reaction.

a. $(CH_3CH_2)_2CClCH_3$ + CH_3OH in CH_3OH or DMSO

b. $CH_3CH_2CH_2Br$ + ^-OH in H_2O or DMF

c. $(CH_3CH_2)_2CHCl$ + CH_3O^- in CH_3OH or HMPA

7.15E Summary of Factors That Determine Whether the S_N1

or S_N2 Mechanism Occurs

Table 7.7 summarizes the factors that determine whether a reaction occurs by the S_N1 or S_N2 mechanism. Sample Problems 7.5 and 7.6 illustrate how these factors are used to determine the mechanism of a given reaction.

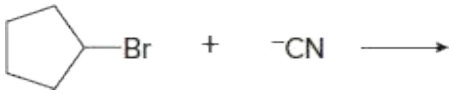
Table 7.7 Summary of Factors That Determine the S_N1 or S_N2 Mechanism

Alkyl halide	Mechanism	Other factors
CH_3X RCH_2X (1°)	S_N2	**Favored by** • strong nucleophiles (usually a net negative charge) • polar aprotic solvents
R_3CX (3°)	S_N1	**Favored by** • weak nucleophiles (usually neutral) • polar protic solvents
R_2CHX (2°)	S_N1 or S_N2	**The mechanism depends on the conditions.** • Strong nucleophiles favor the S_N2 mechanism over the S_N1 mechanism. RO^- is a stronger nucleophile than ROH, so RO^- favors the S_N2 reaction and ROH favors the S_N1 reaction. • Protic solvents favor the S_N1 mechanism and aprotic solvents favor the S_N2 mechanism. H_2O and CH_3OH are polar protic solvents that favor the S_N1 mechanism, whereas acetone $[(CH_3)_2C{=}O]$ and DMSO $[(CH_3)_2S{=}O]$ are polar aprotic solvents that favor the S_N2 mechanism.

Sample Problem 7.5 Determining the Mechanism of Nucleophilic Substitution

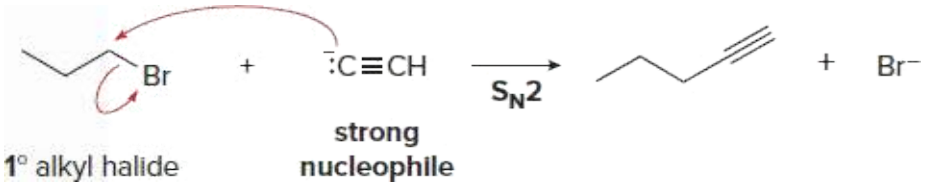
Determine the mechanism of nucleophilic substitution for each reaction and draw the products.

a.

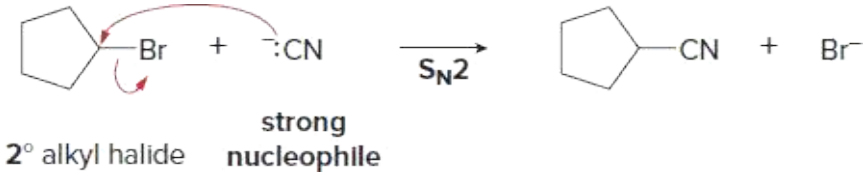
b. 

Solution

a. The alkyl halide is 1°, so it must react by an S_N2 mechanism with the nucleophile $^{-}$:C≡CH.

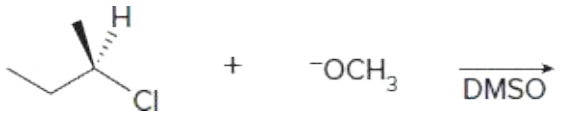


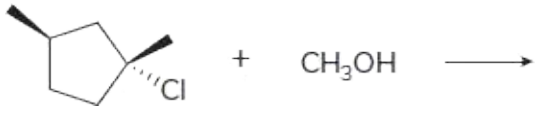
b. The alkyl halide is 2°, so it can react by either the S_N1 or S_N2 mechanism. The strong nucleophile ($^{-}$CN) favors the S_N2 mechanism.



Sample Problem 7.6 Determining the Mechanism and Stereochemistry in Nucleophilic Substitution

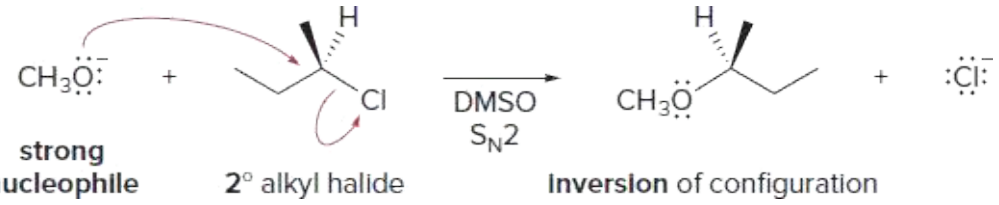
Determine the mechanism of nucleophilic substitution for each reaction and draw the products, including stereochemistry.

a. 

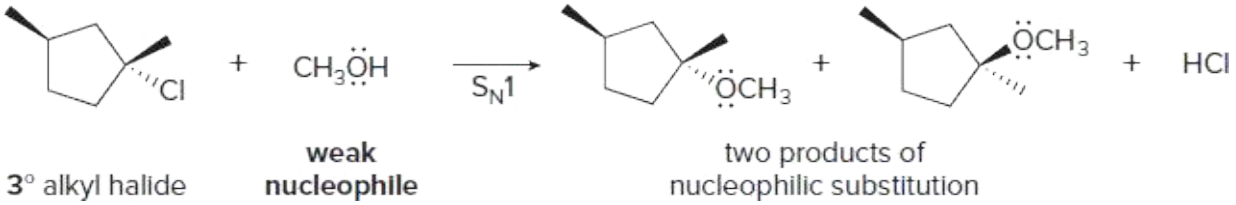
b. 

Solution

a. The 2° alkyl halide can react by either the S_N1 or S_N2 mechanism. The strong nucleophile ($^{-}OCH_3$) favors the S_N2 mechanism, as does the polar aprotic solvent (DMSO). S_N2 reactions proceed with inversion of configuration.



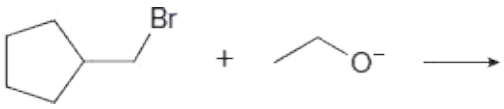
b. The alkyl halide is 3°, so it reacts by an S_N1 mechanism with the weak nucleophile CH_3OH. S_N1 reactions proceed with racemization at a single stereogenic center, so two products are formed.



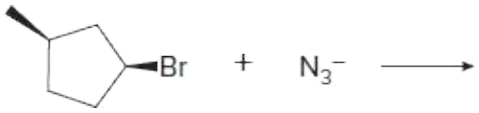
Problem 7.34

Determine the mechanism and draw the products of each reaction. Include the stereochemistry at all stereogenic centers.

a.

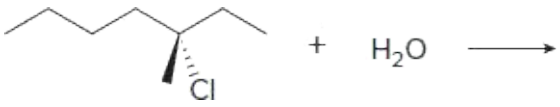


b.



c.

d.



More Practice:

Try Problem 7.64.

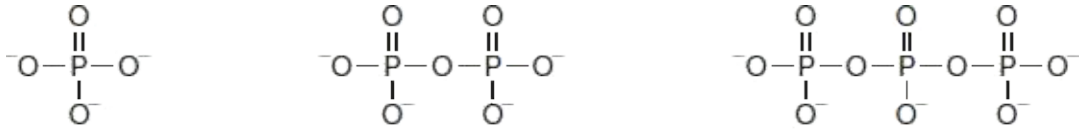
7.16 Biological Nucleophilic Substitution

Nucleophilic substitution occurs in a wide variety of biological reactions.

7.16A Leaving Groups Derived from Phosphorus

In contrast to nucleophilic substitutions run in the laboratory that use alkyl halides as substrates and halide anions as leaving groups, biological substitutions often occur with phosphorus leaving groups, such as phosphate (PO_4^{3-}, abbreviated as P_i for

inorganic phosphate), diphosphate ($P_2O_7^{4-}$, abbreviated as PP_i), and triphosphate ($P_3O_{10}^{5-}$, abbreviated as PPP_i). These anions are excellent leaving groups because they are weak, resonance-stabilized bases.

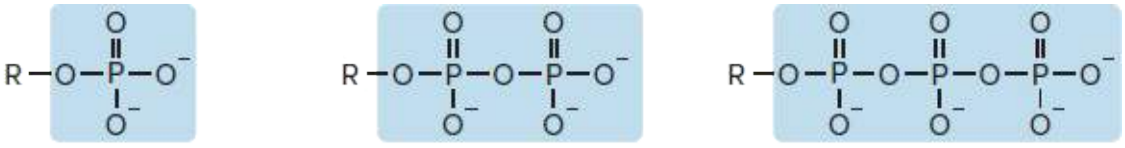


phosphate
P_i

diphosphate
PP_i

triphosphate
PPP_i

When an organic compound contains a carbon bonded to one of these leaving groups, the compound is called an organic monophosphate, diphosphate, or triphosphate.



organic monophosphate

R—OP

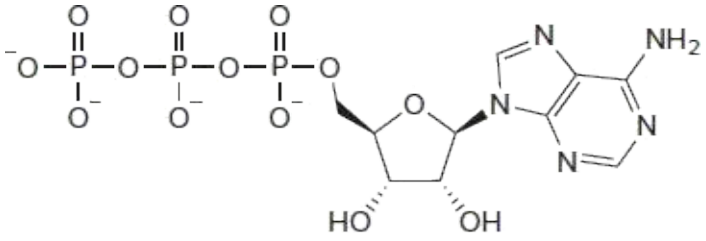
organic diphosphate

R—OPP

organic triphosphate

R—OPPP

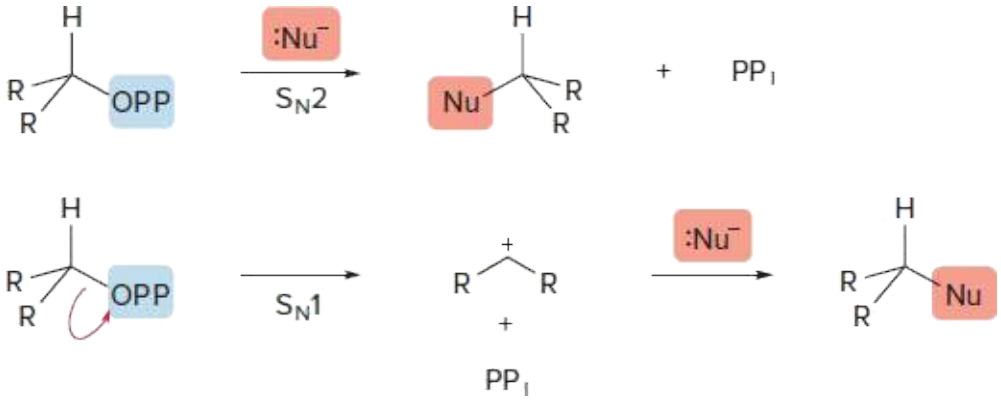
Adenosine triphosphate (ATP) is an organic triphosphate.



adenosine triphosphate

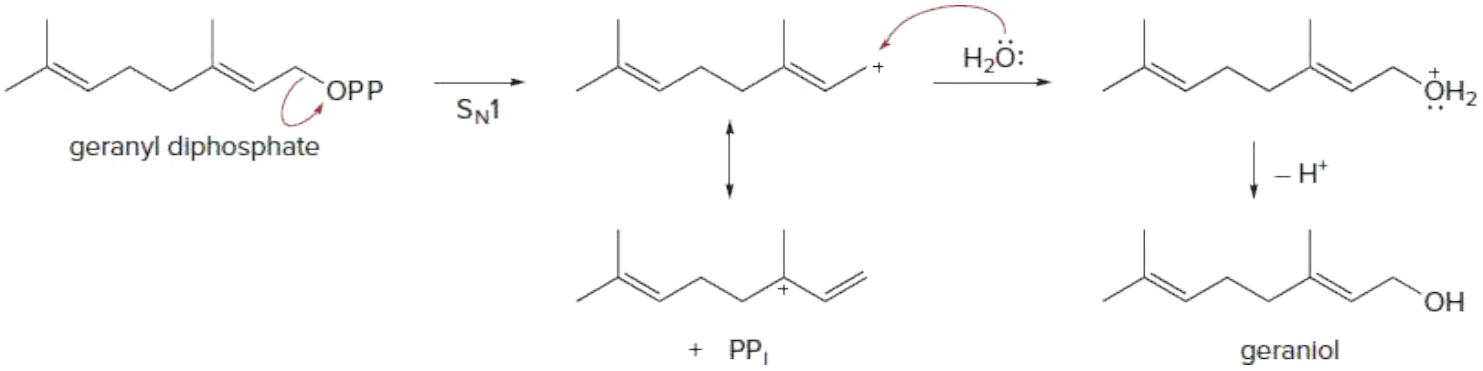
ATP

Nucleophilic substitutions with these substrates may proceed by either an S_N2 or S_N1 pathway, as shown with the general diphosphate R_2CHOPP.



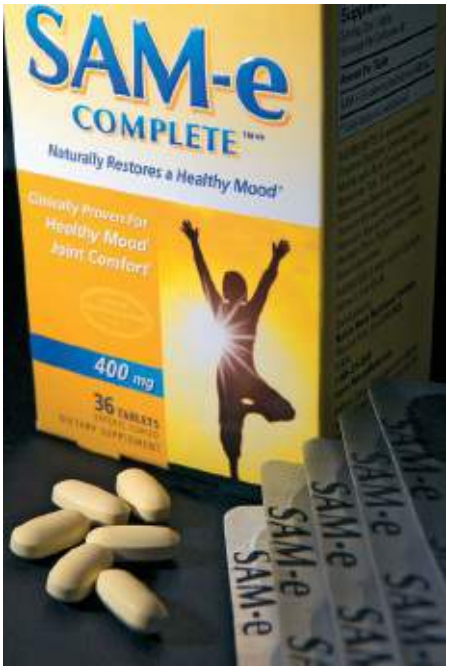
The final step in the biosynthesis of geraniol, a component of rose oil used in perfumery, is an S_N1 reaction of geranyl diphosphate with water. This

reaction occurs by way of a resonance-stabilized carbocation. We will learn more about reactions of diphosphates in Chapter 14.



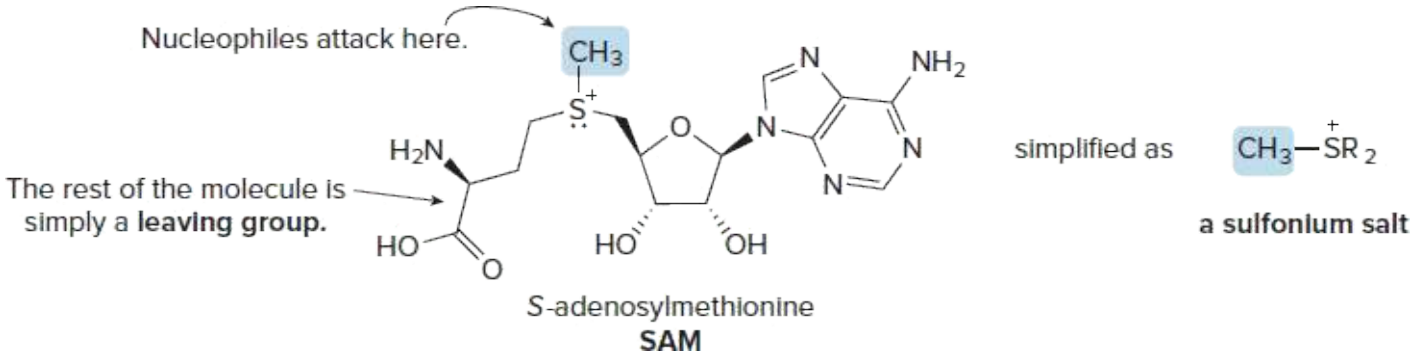
7.16B *S*-Adenosylmethionine

A common nucleophilic substitution occurs with *S*-adenosylmethionine, or SAM. SAM is the cell's equivalent of CH_3I. The many polar functional groups in SAM make it soluble in the aqueous environment in the cell.

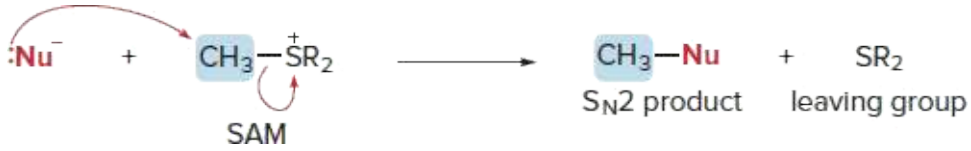


SAM, a nutritional supplement sold under the name SAM-e (pronounced sammy), has been used in Europe to treat depression and arthritis for over 20 years. In cells, SAM is used in nucleophilic substitutions that synthesize key amino acids, hormones, and neurotransmitters.

©Jill Braaten



The CH_3 group in SAM [abbreviated as $(CH_3SR_2)^+$] is part of a sulfonium salt, a positively charged sulfur species that contains a good leaving group. Nucleophilic attack at the CH_3 group of SAM displaces R_2S, a good neutral leaving group. This reaction is called methylation, because a CH_3 group is transferred from one compound (SAM) to another ($:Nu^-$).



For example, adrenaline (epinephrine) is a hormone synthesized in the adrenal glands from noradrenaline (norepinephrine) by nucleophilic substitution using SAM (Figure 7.19). When an individual senses danger or is confronted by stress, the hypothalamus region of the brain signals the adrenal glands to synthesize and release adrenaline, which enters the bloodstream and then stimulates a response in many organs. Stored carbohydrates are metabolized in the liver to form glucose, which is further metabolized to provide an energy boost. Heart rate and blood pressure increase, and lung passages are dilated. These physiological changes result from the "rush of adrenaline," and prepare an individual for "fight or flight."

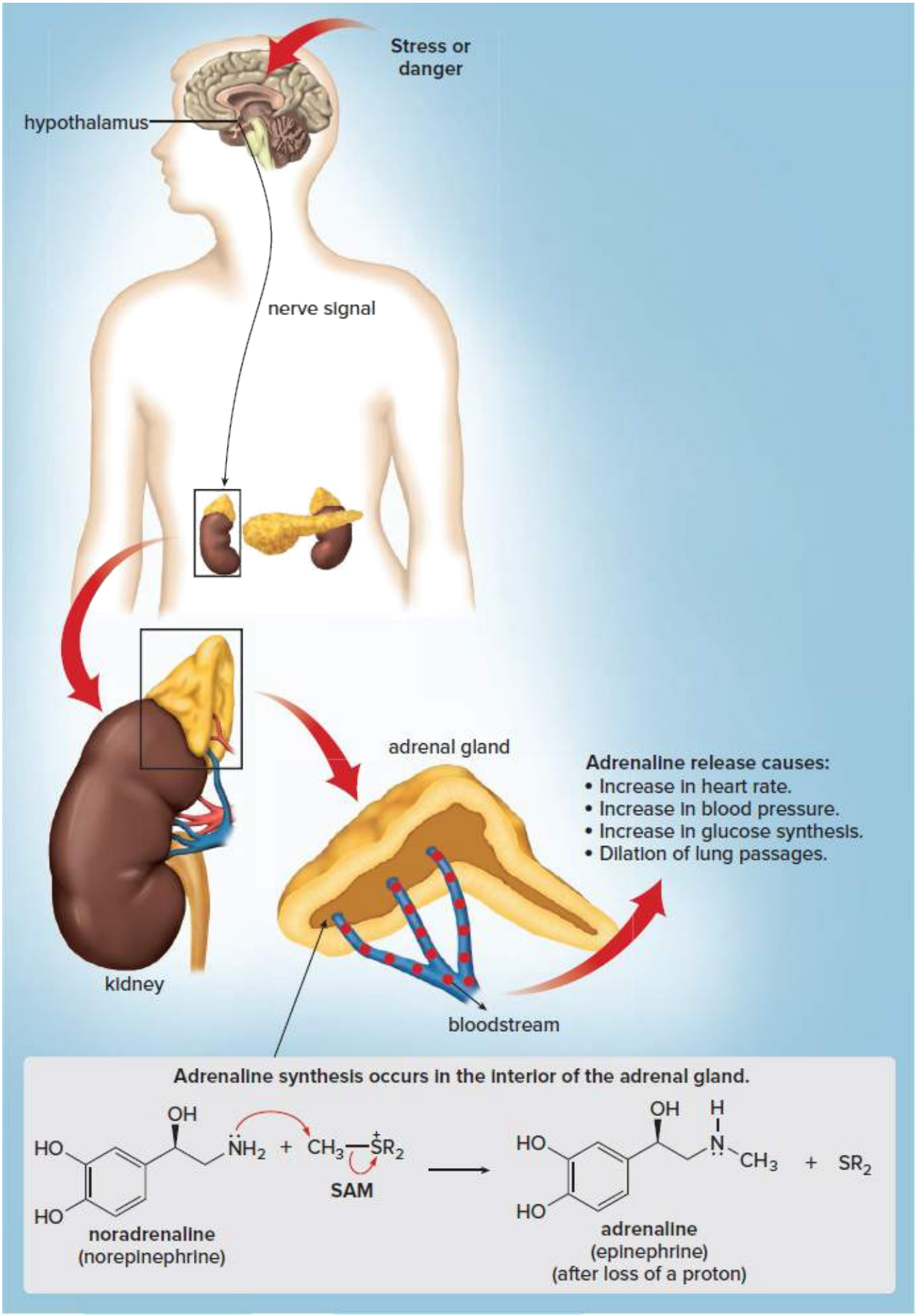
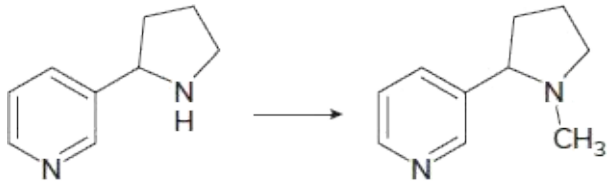


Figure 7.19 **Adrenaline synthesis from noradrenaline in response to stress**

Problem 7.35

Nicotine, a toxic and addictive component of tobacco, is synthesized from A using SAM. Write out the reaction that converts A into nicotine.



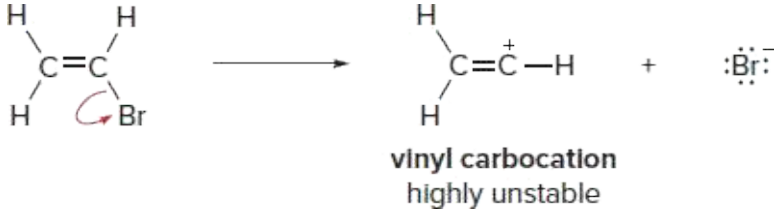
7.17 Vinyl Halides and Aryl Halides

S_N1 and S_N2 reactions occur only at sp^3 hybridized carbon atoms. Now that we have learned about the mechanisms for nucleophilic substitution, we can understand why vinyl halides and aryl halides, which have a halogen atom bonded to an sp^2 hybridized C, do not undergo nucleophilic substitution by either the S_N1 or S_N2 mechanism. The discussion here centers on vinyl halides, but similar arguments hold for aryl halides as well.

C bonded to X is sp^2 hybridized.

Vinyl halides do not undergo S_N2 reactions in part because of the percent *s*-character in the hybrid orbital of the carbon atom in the C–X bond. The higher percent *s*-character in the sp^2 hybrid orbital of the vinyl halide compared to the sp^3 hybrid orbital of the alkyl halide (33% vs. 25%) makes the bond shorter and stronger.

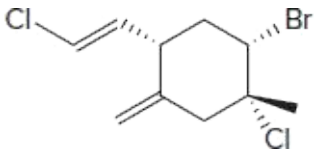
Vinyl halides do not undergo SN1 reactions because heterolysis of the C–X bond would form a highly unstable vinyl carbocation. Because this carbocation has only two groups around the positively charged carbon, it is *sp* hybridized. These carbocations are even less stable than 1° carbocations, so the S_N1 reaction does not take place.



vinyl carbocation
highly unstable

Problem 7.36

Rank the alkyl halides in the following marine natural product in order of increasing reactivity in the S_N2 reaction.



7.18 Organic Synthesis

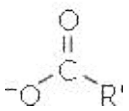
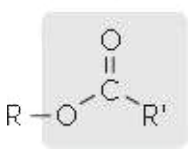
Thus far we have concentrated on the starting material in nucleophilic substitution—the alkyl halide—and have not paid much attention to the product formed. Nucleophilic substitution reactions, and in particular S_N2 reactions, introduce a wide variety of different functional groups in molecules, depending on the nucleophile. For example, when ^-OH, ^-OR, and ^-CN are used as nucleophiles, the products are alcohols (ROH), ethers (ROR), and nitriles (RCN), respectively. Table 7.8 lists some functional groups readily introduced using nucleophilic substitution.

By thinking of nucleophilic substitution as a reaction that *makes* a particular kind of organic compound, we begin to think about *synthesis*.

- **Organic synthesis is the systematic preparation of a compound from a readily available starting material by one or many steps.**

Table 7.8 Molecules Synthesized from R–X by the S_N2 Reaction

Page 296

	Nucleophile ($:Nu^-$)	Product	Name
Oxygen compounds	^-OH $^-OR'$ 	R–OH R–OR' 	alcohol ether ester
Carbon compounds	**^-CN** **$^-:C\equiv C-H$**	R–CN R–C≡C–H	nitrile alkyne
Nitrogen compounds	**N_3^-**		azide

	:NH_3	R—N_3 R—NH_2	amine
Sulfur compounds	**⁻SH** **⁻SR′**	R—SH R—SR'	thiol sulfide

7.18A Background on Organic Synthesis

Chemists synthesize molecules for many reasons. Sometimes a natural product, a compound isolated from natural sources, has useful medicinal properties, but is produced by an organism in only minute quantities. Synthetic chemists then prepare this molecule from simpler starting materials, so that it can be made available to a large number of people.

Aspirin is synthesized by a two-step procedure from simple, cheap starting materials.

©Jill Braaten

Phenol, the starting material for the aspirin synthesis, is a petroleum product, like most of the starting materials used in large quantities in industrial syntheses. A shortage of petroleum reserves thus affects the availability not only of fuels for transportation, but also of raw materials needed for most chemical synthesis.

Sometimes, chemists prepare molecules that do not occur in nature (although they may be similar to those in nature), because these molecules have superior properties to their naturally occurring relatives. Aspirin, or acetylsalicylic acid (Section 2.7), is a

well-known example. Acetylsalicylic acid is prepared from phenol, a product of the petroleum industry, by a two-step procedure (Figure 7.20). Aspirin has become one of the most popular and widely used drugs in the world because it has excellent analgesic and anti-inflammatory properties, *and* it is inexpensive and readily available.

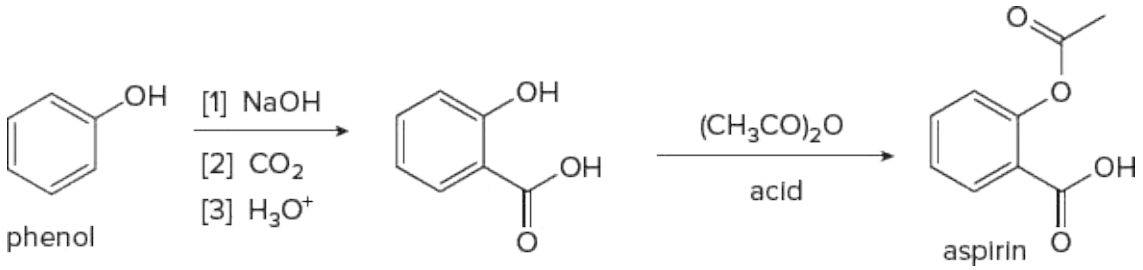
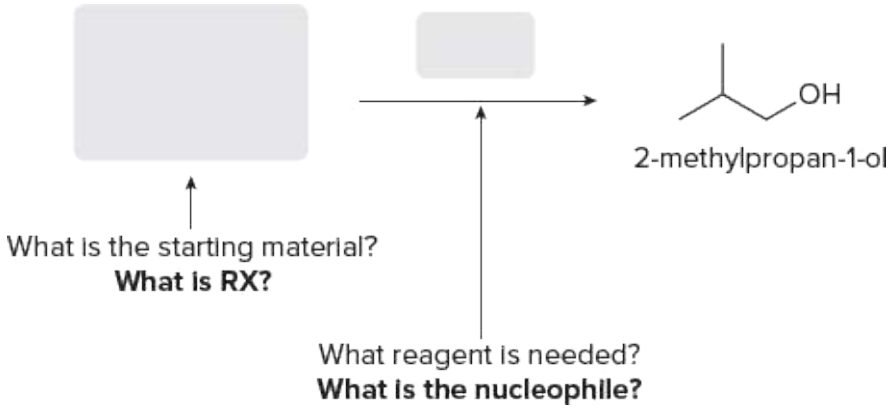


Figure 7.20 **Synthesis of aspirin**

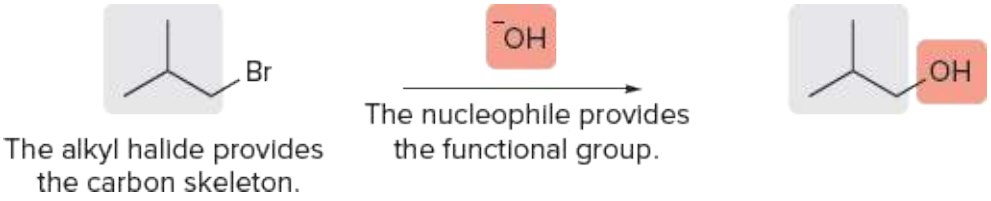
7.18B Nucleophilic Substitution and Organic Synthesis

To carry out synthesis we must think backwards. We examine a compound and ask: What starting material and reagent are needed to make it? If we are using nucleophilic substitution, we must determine what alkyl halide and what nucleophile can be used to form a specific product. This is the simplest type of synthesis because it involves only one step. In Chapter 11, we will learn about multistep syntheses.

Suppose, for example, that we are asked to prepare $(CH_3)_2CHCH_2OH$ (2-methylpropan-1-ol) from an alkyl halide and any required reagents. To accomplish this synthesis, we must "fill in the boxes" for the starting material and reagent in the accompanying equation.



To determine the two components needed for the synthesis, remember that the carbon atoms come from the organic starting material, in this case a 1° alkyl halide $[(CH_3)_2CHCH_2Br]$. The functional group comes from the nucleophile, ^-OH in this case. With these two components, we can "fill in the boxes" to complete the synthesis.

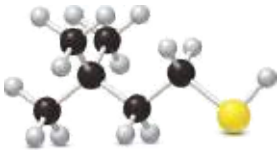


After any synthesis is proposed, check to see if it is reasonable, given what we know about reactions. Will the reaction written give a high yield of product? The synthesis of $(CH_3)_2CHCH_2OH$ is reasonable, because the starting material is a 1° alkyl halide and the nucleophile (^-OH) is strong, and both facts contribute to a successful S_N2 reaction.

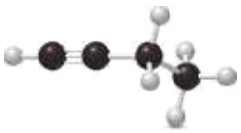
Problem 7.37

What alkyl halide and nucleophile are needed to prepare each compound?

a.

b. 

c.

d. 

Problem 7.38

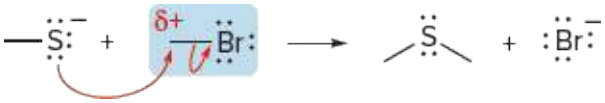
The ether, $CH_3OCH_2CH_3$, can be prepared by two different nucleophilic substitution reactions, one using CH_3O^- as nucleophile and the other using $CH_3CH_2O^-$ as nucleophile. Draw both routes.

Chapter 7 REVIEW

KEY CONCEPTS

[1] General facts about the reactions of alkyl halides (RX)

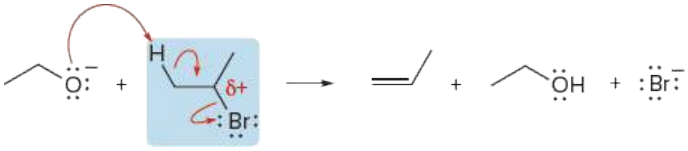
1 Reactivity with nucleophiles (7.5)



- An alkyl halide is electrophilic because of its polar C–X bond.

See Figure 7.4.

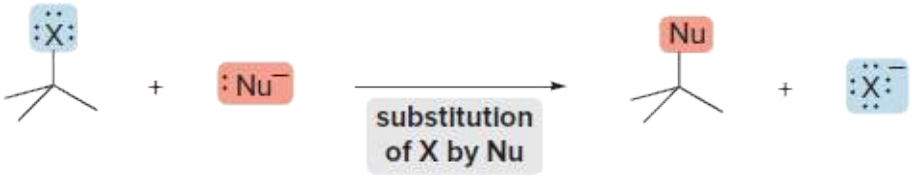
2 Reactivity with bases (7.5)



- The proton adjacent to the polar X bond is removed to form an alkene.

[2] Nucleophilic substitution (7.6)

- A nucleophile replaces a leaving group on an sp^3 hybridized carbon.
- One σ bond is broken and one σ bond is formed. There are two possible mechanisms: S_N1 and S_N2.

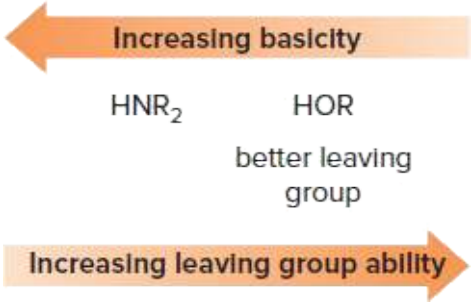


Try Problems 7.45, 7.56.

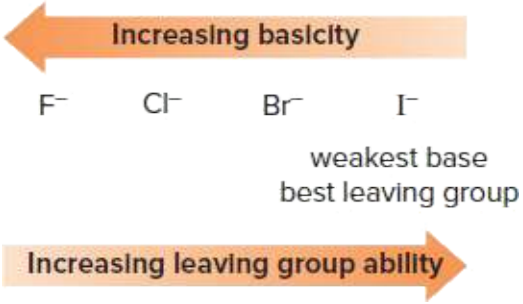
[3] Periodic Trends

1 Leaving groups (7.7)

- across a row of the periodic table



- down a column of the periodic table



- The best leaving group is the weakest base.

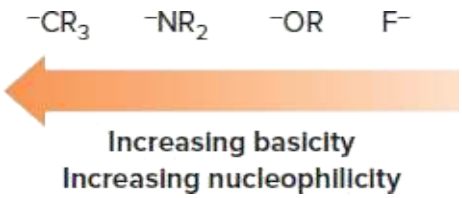
3 Nuc… in p… sol…

- dow… colu… per…

2 **Nucleophilicity versus basicity (7.8A)**

4 **Nuc in p apr sol**

- across a row of the periodic table

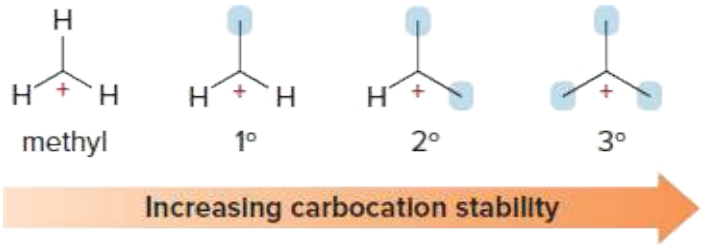


- **dov col per**

Try Problems 7.47, 7.49, 7.50.

[4] Carbocation stability (7.13)

- **The stability of a carbocation increases as the number of electron-donating groups, such as alkyl groups, bonded to the positively charged carbon increases.**



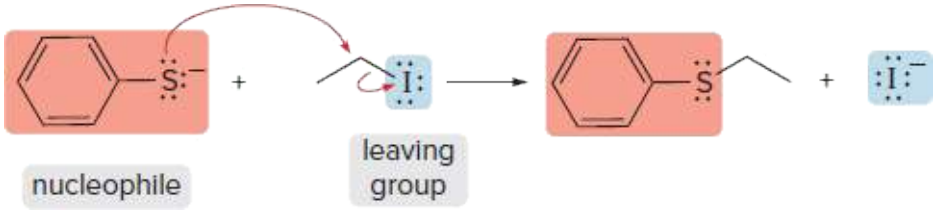
Try Problems 7.57, 7.58.

Page 299

KEY SKILLS

[1] Comparing the nucleophile and leaving group to determine if products are favored (7.7)

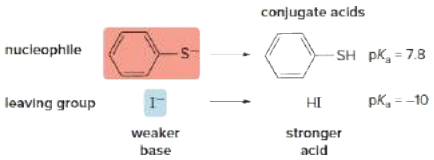
1 **Identify the nucleophile and leaving group, and draw curved arrows**



2 **Draw the conjugate acids and compare the pK_a values**

- **The stronger the conjugate acid, the weaker the base an the better the leavi**

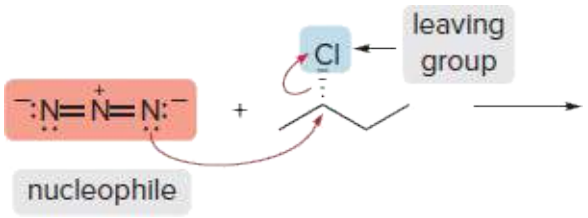
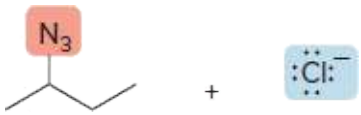
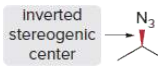
group.



Answer: **Products favored.**

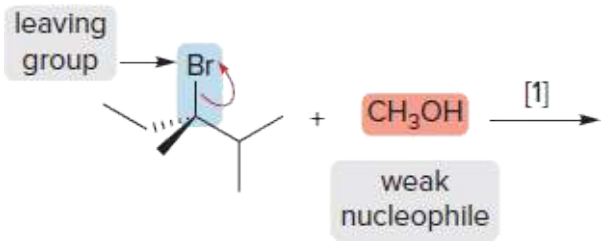
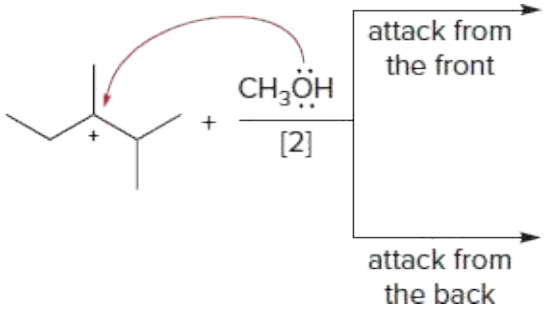
See Sample Problem 7.1. Try Problem 7.48.

[2] Drawing the product(s) of an S_N2 reaction (7.11)

1 Identify the nucleophile and leaving group, and draw curved arrows	**2** Substitute the nucleophile for the leaving group	**3** Invert config at the bond
		
• The leaving group is pointing back, so the nucleophile approaches from the front.		• The N group up or front the mole

See Sample Problem 7.2, Figures 7.8, 7.9. Try Problems 7.53, 7.54.

[3] Drawing the product(s) of an S_N1 reaction (7.12)

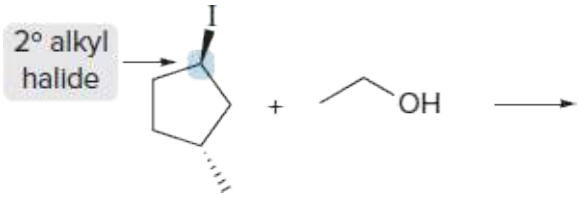
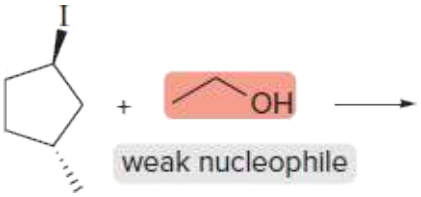
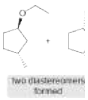
1 Draw the curved arrow for Step [1]—loss of the leaving group	**2** Draw the curved arrow for Step [2]—nucleophilic attack
	

- Heterolysis of the C–Br bond on the 3° alkyl halide occurs in the presence of the weak nucleophile.

- Nucleophilic attack occurs from both sides of the planar carbocation.

See Sample Problem 7.4, Figure 7.13. Try Problem 7.60.

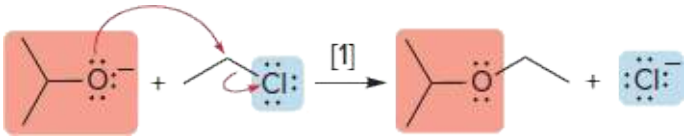
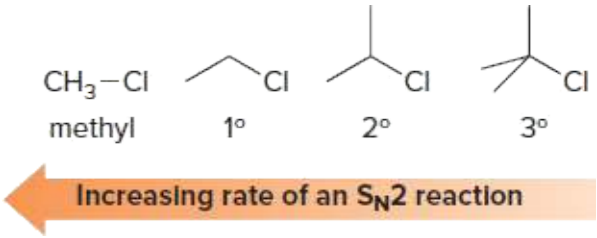
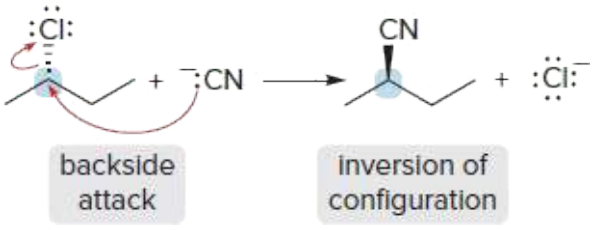
[4] Deciding if a reaction proceeds by S_N1 or S_N2 (7.15E)

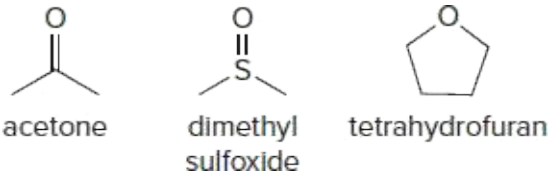
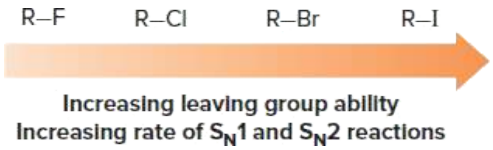
1 Classify the R–X.	2 Determine whether the nucleophile is weak or strong	3 Dra pro
		
• 2° Alkyl halides may react by either the S_N1 or S_N2 mechanism.	• Weak nucleophiles favor the S_N1 mechanism.	• Th nu ad bo of co

See Sample Problems 7.5, 7.6, Table 7.7. Try Problem 7.64.

KEY MECHANISM CONCEPTS

Comparison of S_N1 and S_N2 reactions

	S_N2 mechanism	S_N1 me
1 Mechanism	• one step (7.11B) 	• two (7.1
2 Rate equation	• rate = *k*[RCl][:Nu⁻] • second-order kinetics (7.11A)	• rat • firs kin (7.1
3 Alkyl halide	• order of reactivity (7.11D)  • faster with less steric hindrance around the C–X bond	• orc rea (7.1 • fas mo (mo sul car are (7.1
4 Stereochemistry	• backside attack by the nucleophile (7.11C) 	• trig pla car int (7.1
5 Nucleophile Page 301	• favored by strong nucleophiles that usually bear a negative charge (7.15B) • common examples:	• fav we nuc tha

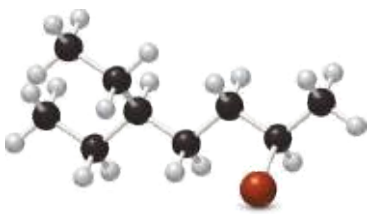
	^-CN N_3^- ^-OR HS^-	bea cha (7. • cor exa ROH
6 Solvent	• favored by polar aprotic solvents (7.15D)  See Figure 7.6.	• fav pol sol (7. See
7 Leaving group	• better leaving group → faster reaction for S_N2 (7.15C)  	*both* S_N

See Tables 7.5, 7.6, 7.7. Try Problems 7.47, 7.49, 7.50, 7.64.

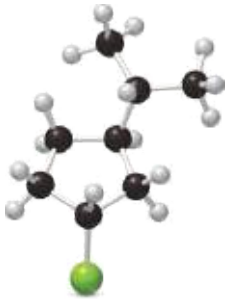
PROBLEMS

Problems Using Three-Dimensional Models

7.39 Give the IUPAC name for each compound, including any *R,S* designation.

a. 

b.



7.40 Draw the products formed when each alkyl halide is treated with NaCN.

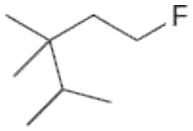
a.

b.

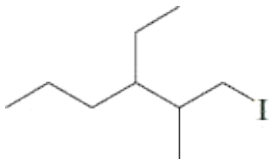
Nomenclature

7.41 Give the IUPAC name for each compound.

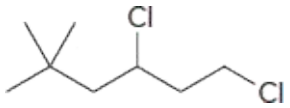
a.



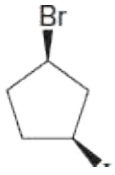
b.



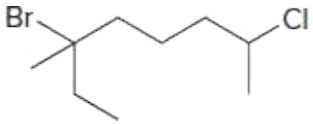
c.



d.



e.



f.

Include the *R,S* designation in the name.

7.42 Give the structure corresponding to each name.

a. 3-bromo-4-ethylheptane

b. 1,1-dichloro-2-methylcyclohexane

c. 1-bromo-4-ethyl-3-fluorooctane

d. (*S*)-3-iodo-2-methylnonane

e. (1*R*,2*R*)-*trans*-1-bromo-2-chlorocyclohexane

f. (*R*)-4,4,5-trichloro-3,3-dimethyldecane

7.43 Draw the eight constitutional isomers having the molecular formula $C_5H_{11}Cl$.

a. Give the IUPAC name for each compound (ignoring *R* and *S* designations).

b. Classify each alkyl halide as 1°, 2°, or 3°.

c. Label any stereogenic centers.

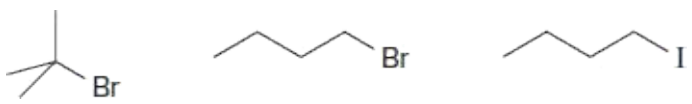
d. For each constitutional isomer that contains a stereogenic center, draw all possible stereoisomers, and label each stereogenic center as *R* or *S*.

Properties

Students who have already learned about mass spectrometry can try Problems A.5; A.6a, b; A.7; A.16d, e; and A.22(A), (B).

Students who have learned about nuclear magnetic resonance spectroscopy can try Problem C.58a, b.

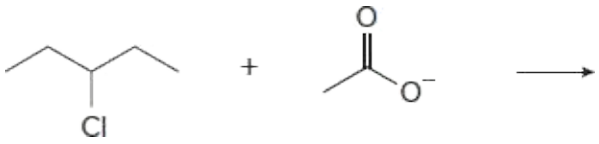
7.44 Rank the following alkyl halides in order of increasing boiling point.



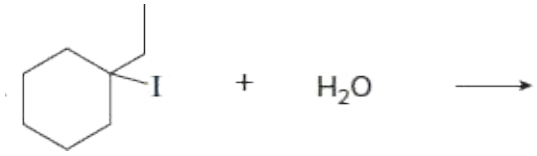
General Nucleophilic Substitution, Leaving Groups, and Nucleophiles

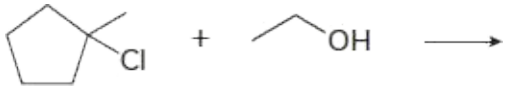
7.45 Draw the products of each nucleophilic substitution reaction.

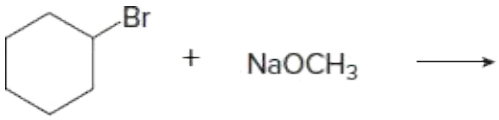
a.



b.

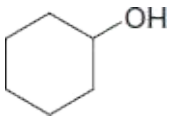
c. 

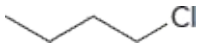
d. 

e. 

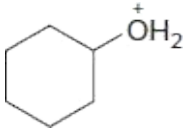
f.

7.46 Which of the following molecules contain a good leaving group?

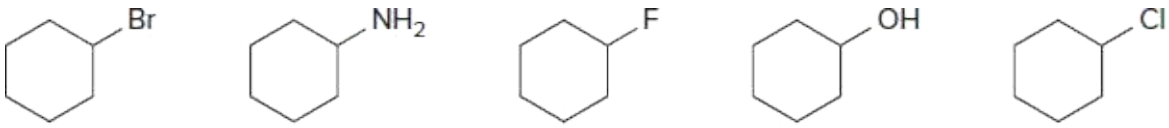
a. 

b. 

c.

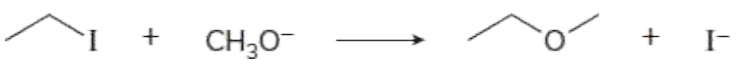
d. 

7.47 Rank the following compounds in order of increasing reactivity in a substitution reaction with ^{-}CN as nucleophile.



7.48 Which of the following nucleophilic substitution reactions will take place?

a.

b. 

7.49 Rank the anions in order of increasing nucleophilicity in acetone: CH_3S^-, CH_3NH^-, I^-, Br^-, and CH_3O^-.

7.50 Classify each solvent as protic or aprotic.

a. $(CH_3)_2CHOH$

b. CH_3NO_2

c. CH_2Cl_2

d. NH_3

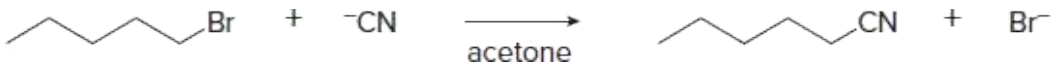
e. $N(CH_3)_3$

f. $HCONH_2$

7.51 Why is the amine N atom more nucleophilic than the amide N atom in $CH_3CONHCH_2CH_2CH_2NHCH_3$?

The S_N2 Reaction

7.52 Consider the following S_N2 reaction.



a. Draw a mechanism using curved arrows.

b. Draw an energy diagram. Label the axes, the reactants, products, E_a, and $\Delta H°$. Assume that the reaction is exothermic.

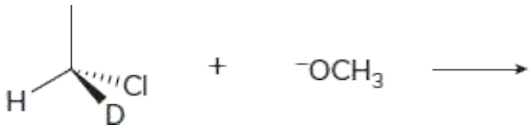
c. Draw the structure of the transition state.

d. What is the rate equation?

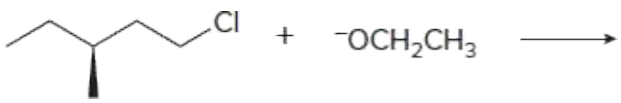
e. What happens to the reaction rate in each of the following instances? [1] The leaving group is changed from Br^- to I^-; [2] The solvent is changed from acetone to CH_3CH_2OH; [3] The alkyl halide is changed from $CH_3(CH_2)_4Br$ to $CH_3CH_2CH_2CH(Br)CH_3$; [4] The concentration of ^-CN is increased by a factor of five; and [5] The concentrations of both the alkyl halide and ^-CN are increased by a factor of five.

7.53 Draw the products of each S_N2 reaction and indicate the stereochemistry where appropriate.

a.



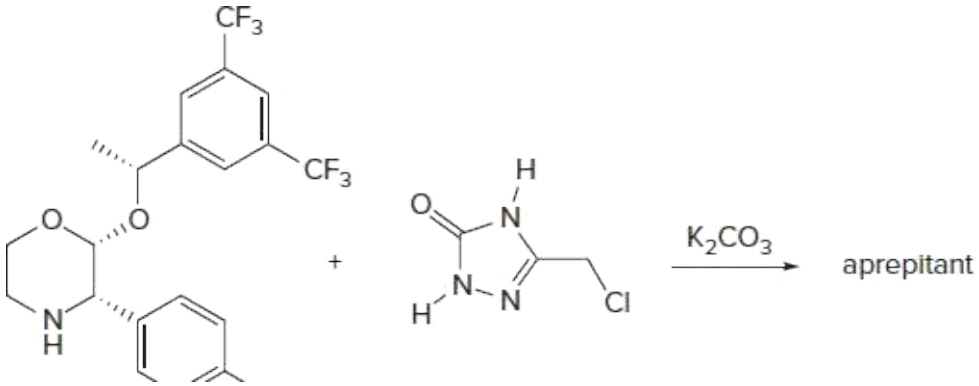
b.



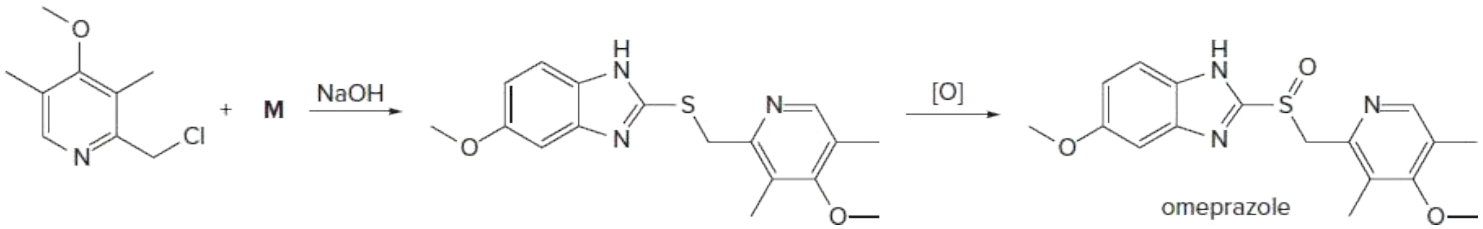
c.

7.54 Draw the product of the following S_N2 reaction, including the

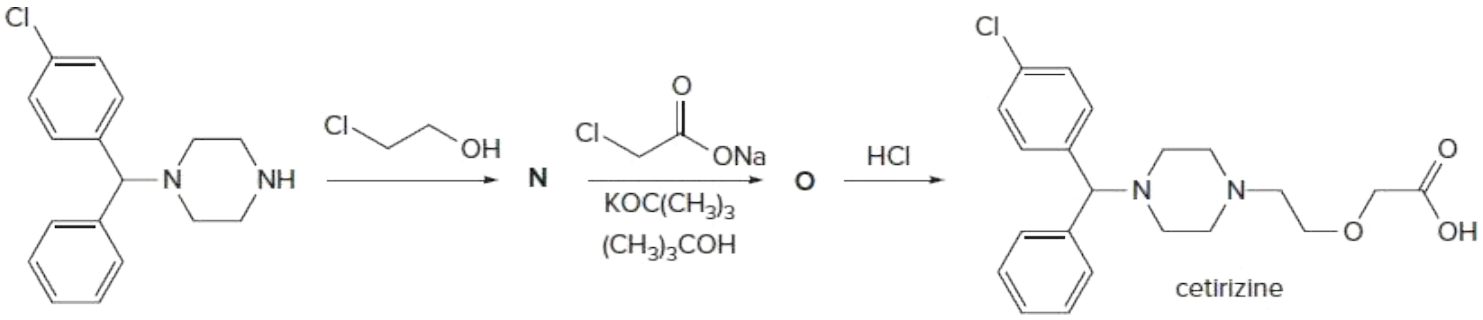
stereochemistry at all stereogenic centers. The product of this reaction is aprepitant, a drug used to treat nausea and emesis (vomiting) in chemotherapy patients.



7.55 Identify M in the following reaction sequence used to prepare the antiulcer drug omeprazole (trade name Prilosec).



7.56 The non-sedating antihistamine cetirizine (trade name Zyrtec) is prepared by a reaction sequence that involves two consecutive substitution reactions. Identify N and O in the following reaction sequence.



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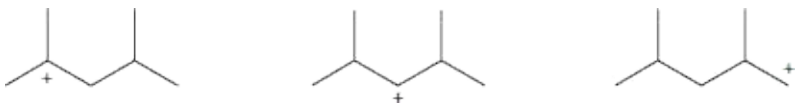
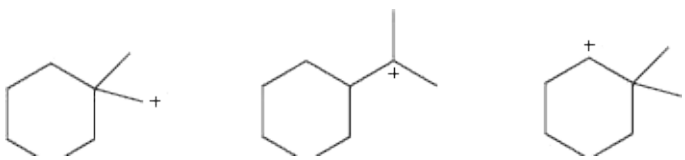
Carbocations

7.57 Classify the carbocations as 1°, 2°, or 3°, and rank the carbocations in each group in order of increasing stability.

a.

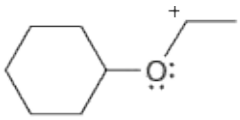


b.

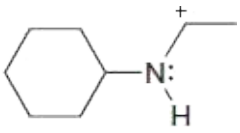


7.58 Which of the following carbocations (A or B) is more stable? Explain

your choice.



A



B

The S_N1 Reaction

7.59 **Consider the following S_N1 reaction.**

a. Draw a mechanism for this reaction using curved arrows.

b. Draw an energy diagram. Label the axes, starting material, product, E_a, and $\Delta H°$. Assume that the starting material and product are equal in energy.

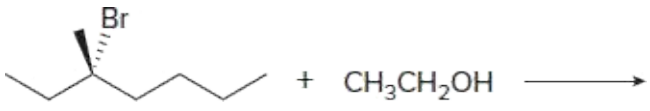
c. Draw the structure of any transition states.

d. What is the rate equation for this reaction?

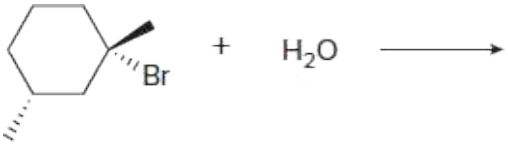
e. What happens to the reaction rate in each of the following instances? [1] The leaving group is changed from I^- to Cl^-; [2] The solvent is changed from H_2O to DMF; [3] The alkyl halide is changed from $(CH_3)_2C(I)CH_2CH_3$ to $(CH_3)_2CHCH(I)CH_3$; and [4] The concentrations of both the alkyl halide and H_2O are increased by a factor of five.

7.60 **Draw the products of each SN1 reaction and indicate the stereochemistry when necessary.**

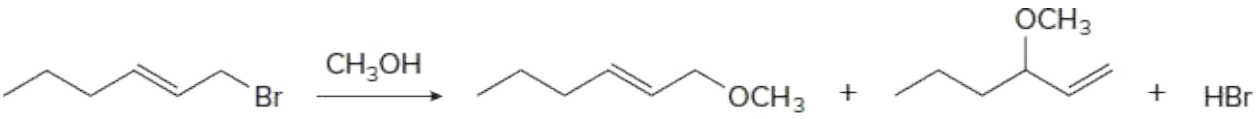
a.



b.



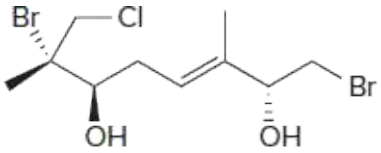
7.61 **Draw a stepwise mechanism for the following reaction that illustrates how two substitution products are formed. Explain why 1-bromohex-2-ene reacts rapidly with a weak nucleophile (CH_3OH) under S_N1 reaction conditions, even though it is a 1 ° alkyl halide.**



1-bromohex-2-ene

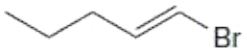
S_N1 and S_N2 Reactions

7.62 **(a) Which halide in the following marine natural product reacts fastest in the S_N2 reaction? (b) Which halide in the following marine natural product reacts fastest in the S_N1 reaction?**

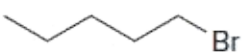


plocamenol A

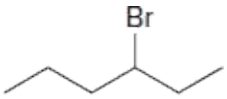
7.63 **(a) Rank A, B, and C in order of increasing S_N2 reactivity. (b) Rank A, B, and C in order of increasing S_N1 reactivity.**



A



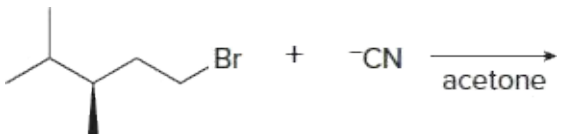
B



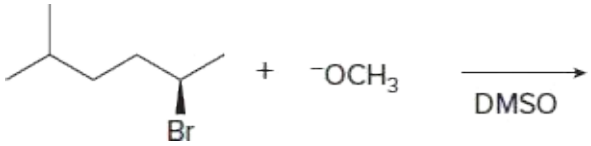
C

7.64 **Determine the mechanism of nucleophilic substitution of each reaction and draw the products, including stereochemistry.**

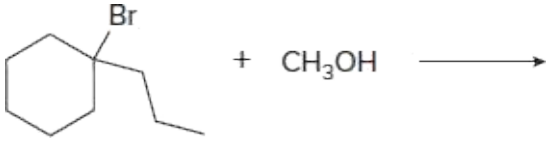
a.



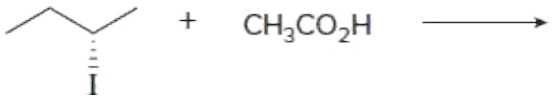
b.



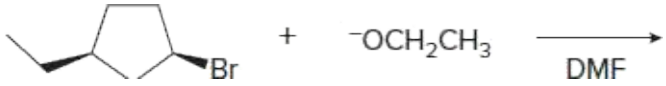
c.



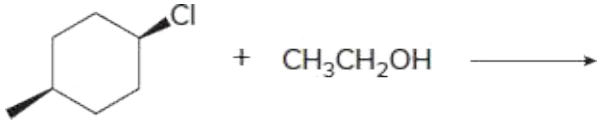
d.



e.

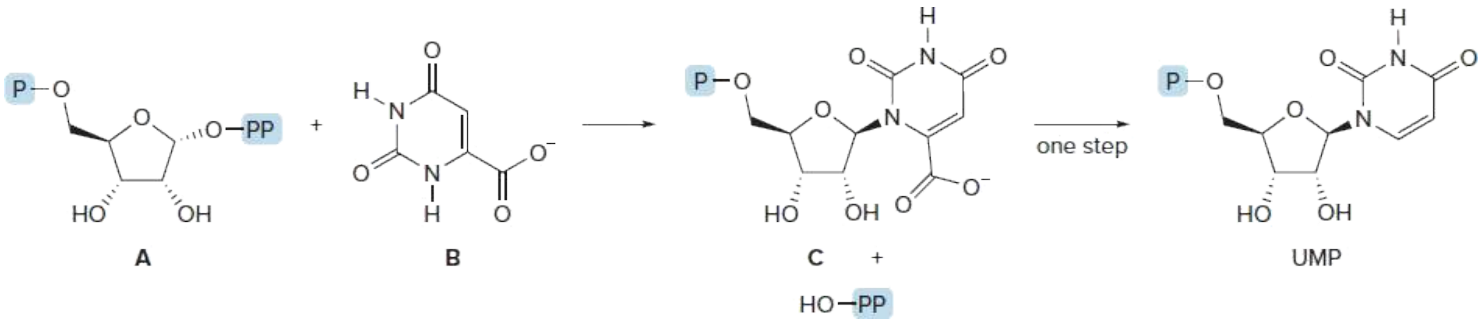


f.

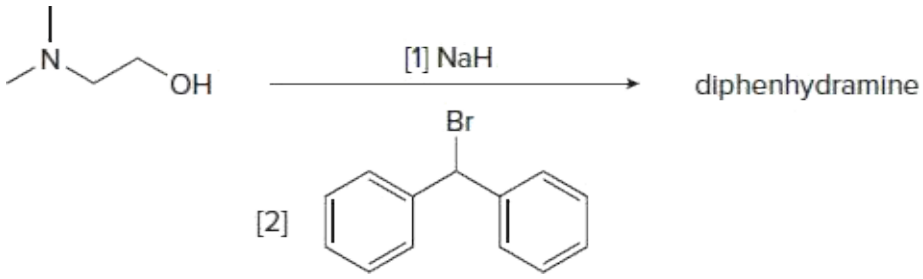


7.65 **Uridine monophosphate (UMP) is one of the four nucleotides that**

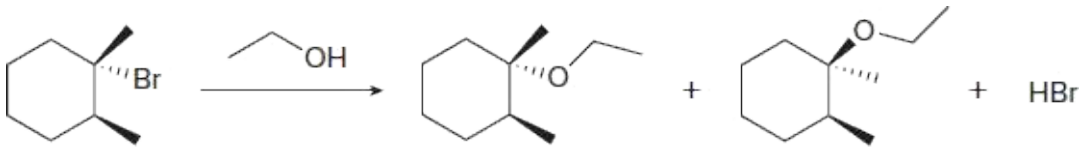
compose RNA, the nucleic acid that translates the genetic information of DNA into proteins needed by cells for proper function and development. A key step in the synthesis of UMP is the S_N1 reaction of A with B to form C, which is then converted to UMP in one step. Draw a stepwise mechanism for this S_N1 reaction.



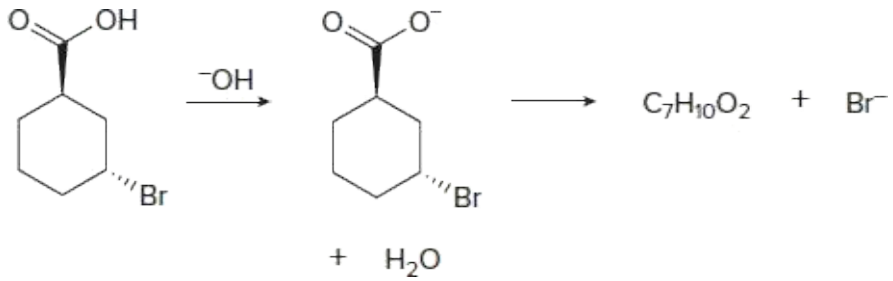
7.66 Diphenhydramine, the antihistamine in Benadryl, can be prepared by the following two-step sequence. What is the structure of diphenhydramine?



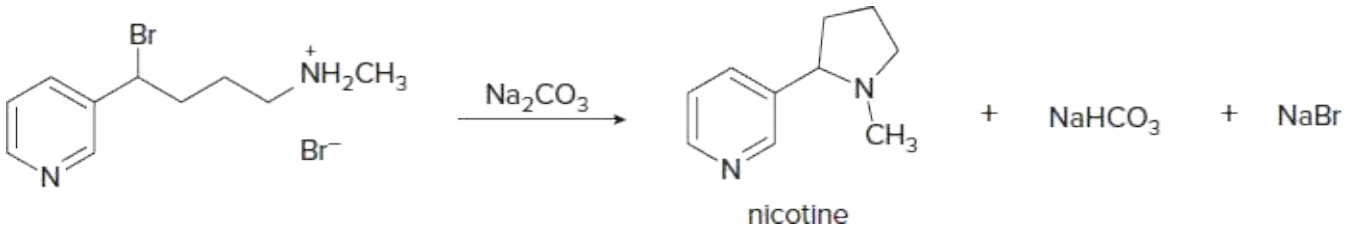
7.67 Draw a stepwise, detailed mechanism for the following reaction. Use curved arrows to show the movement of electrons.



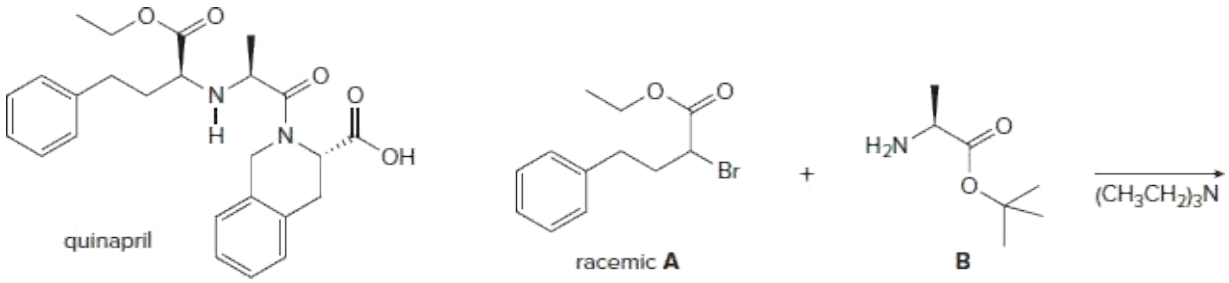
7.68 When a single compound contains both a nucleophile and a leaving group, an intramolecular reaction may occur. With this in mind, draw the product of the following reaction.



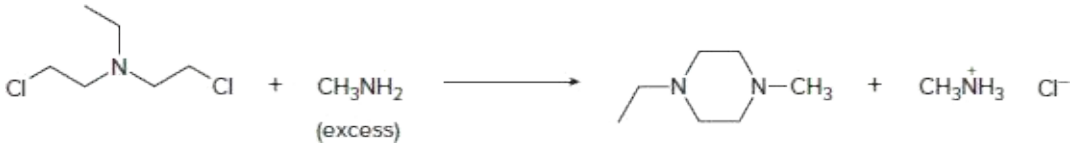
7.69 Nicotine can be made when the following ammonium salt is treated with Na_2CO_3. Draw a stepwise mechanism for this reaction.



7.70 **Quinapril (trade name Accupril) is used to treat high blood pressure and congestive heart failure. One step in the synthesis of quinapril involves reaction of the racemic alkyl bromide A with a single enantiomer of the amino ester B. (a) What two products are formed in this reaction? (b) Given the structure of quinapril, which one of these two products is needed to synthesize the drug?**



7.71 **Draw a stepwise, detailed mechanism for the following reaction.**



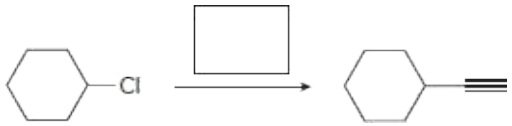
7.72 **When (*R*)-6-bromo-2,6-dimethylnonane is dissolved in CH_3OH, nucleophilic substitution yields an optically inactive solution. When the isomeric halide (*R*)-2-bromo-2,5-dimethylnonane is dissolved in CH_3OH under the same conditions, nucleophilic substitution forms an optically active solution. Draw the products formed in each reaction, and explain why the difference in optical activity is observed.**

Synthesis

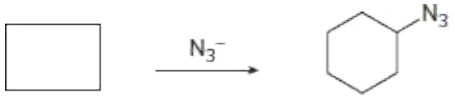
7.73 **Fill in the appropriate reagent or starting material in each of the following reactions.**

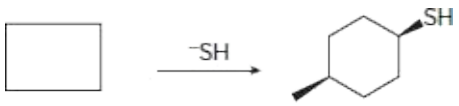
a.

b.

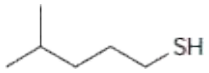


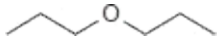
c.

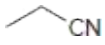


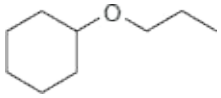
d. 

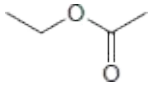
7.74 **Devise a synthesis of each compound from an alkyl halide using any other organic or inorganic reagents.**

a. 

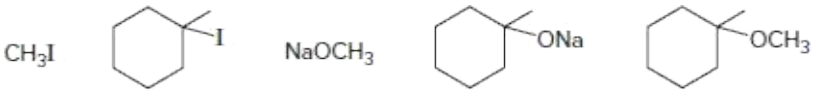
b. 

c. 

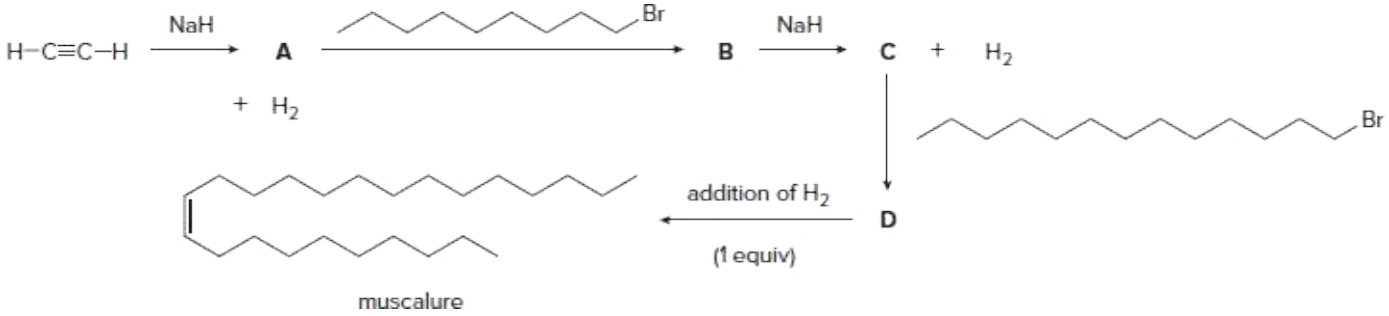
d. 

e. 

7.75 **Suppose you have compounds A–D at your disposal. Using these compounds, devise two different ways to make E. Which one of these methods is preferred, and why?**



7.76 **Muscalure, the sex pheromone of the common housefly, can be prepared by a reaction sequence that uses two nucleophilic substitutions. Identify compounds A–D in the following synthesis of muscalure.**

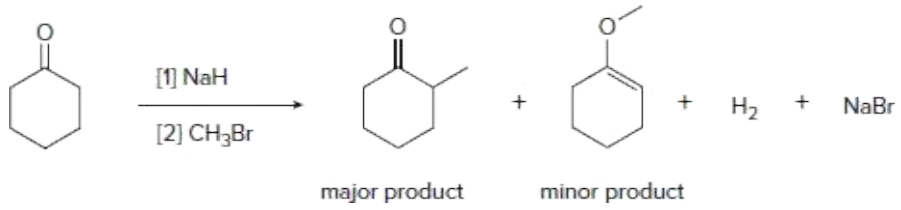


Challenge Problems

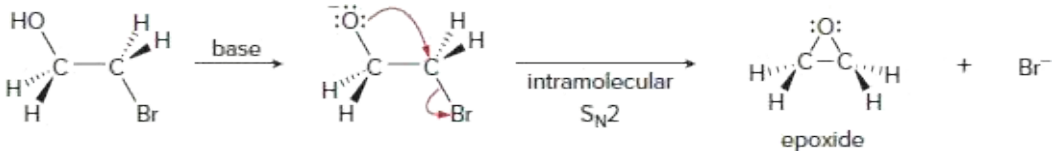
7.77 **Explain why quinuclidine is a much more reactive nucleophile than triethylamine, even though both compounds have N atoms surrounded by three R groups.**

quinuclidine triethylamine

7.78 **Draw a stepwise mechanism for the following reaction sequence.**

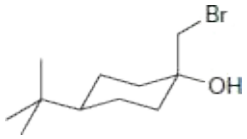


7.79 As we will learn in Chapter 9, an epoxide is an ether with an oxygen atom in a three-membered ring. Epoxides can be made by intramolecular S_N2 reactions of intermediates that contain a nucleophile and a leaving group on adjacent carbons, as shown.

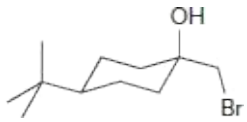


Assume that each of the following starting materials can be converted to an epoxide by this reaction. Draw the product formed (including stereochemistry) from each starting material. Why might some of these reactions be more difficult than others in yielding nucleophilic substitution products?

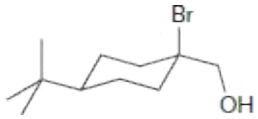
a.



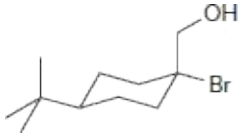
b.



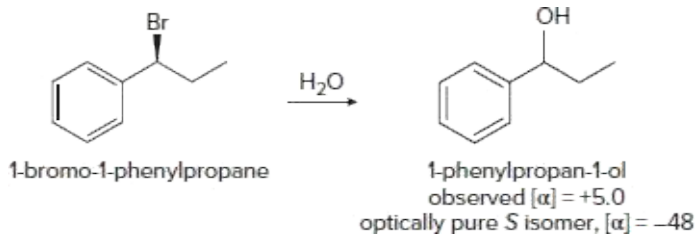
c.



d.

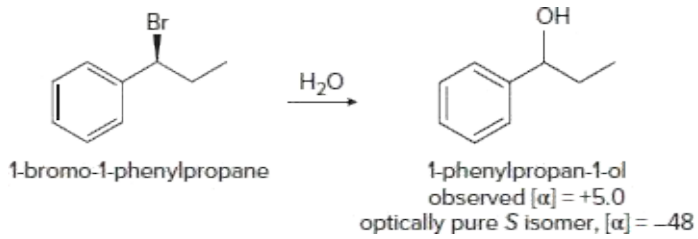


7.80 When trichloride J is treated with CH_3OH, nucleophilic substitution forms the dihalide K. Draw a mechanism for this reaction and explain why one Cl is much more reactive than the other two Cl's so that a single substitution product is formed.



7.81 In some nucleophilic substitutions under S_N1 conditions, complete racemization does not occur and a small excess of one enantiomer is

present. For example, treatment of optically pure 1-bromo-1-phenylpropane with water forms 1-phenylpropan-1-ol. (a) Calculate how much of each enantiomer is present using the given optical rotation data. (b) Which product predominates—the product of inversion or the product of retention of configuration? (c) Suggest an explanation for this phenomenon.

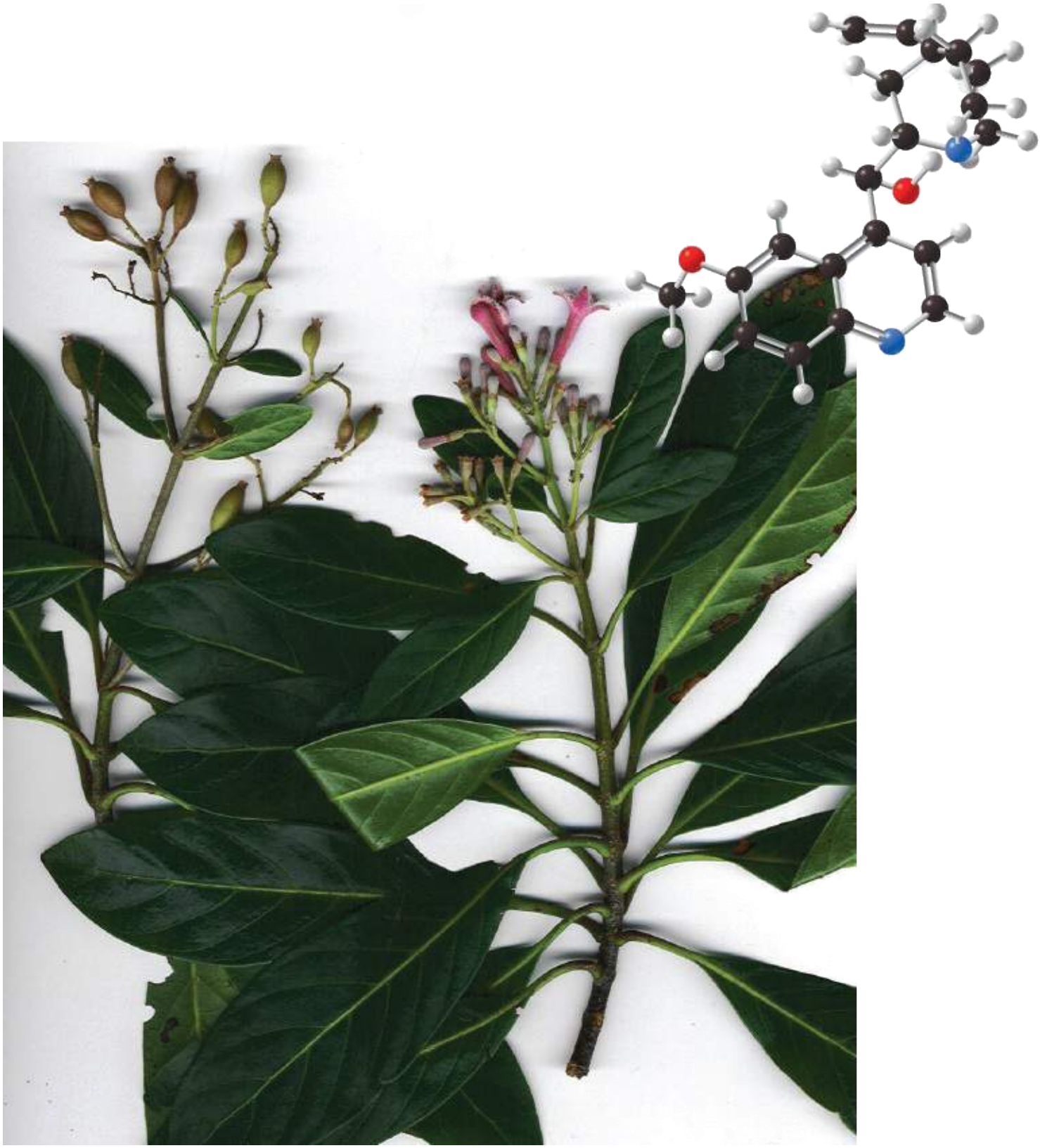


1-bromo-1-phenylpropane

1-phenylpropan-1-ol
observed [α] = +5.0
optically pure *S* isomer, [α] = –48

8

Alkyl Halides and Elimination Reactions



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8.1 General features of elimination

8.2 Alkenes—The products of elimination reactions

8.3 The mechanisms of elimination

8.4 The E2 mechanism

8.5 The Zaitsev rule

8.6 The E1 mechanism

8.7 S_N1 and E1 reactions

8.8 Stereochemistry of the E2 reaction

8.9 When is the mechanism E1 or E2?

8.10 E2 reactions and alkyne synthesis

8.11 When is the reaction S_N1, S_N2, E1, or E2?

The elegant synthesis of quinine in 1944 is considered by many scientists to be the beginning of modern-day organic synthesis. Quinine, a natural product isolated from the bark of the cinchona tree native to the Andes Mountains, is a powerful antipyretic—that is, it reduces fever—and for centuries, it was the only effective treatment for malaria. Its bitter taste gives tonic water its characteristic flavor. One of the steps in a lengthy synthesis of quinine involves elimination, a characteristic reaction of alkyl halides and the subject of Chapter 8.

Why Study…

Elimination Reactions?

Elimination reactions introduce π bonds into organic compounds, so they can be used to synthesize alkenes and alkynes—hydrocarbons that contain one and two π bonds, respectively. Elimination reactions are valuable in organic synthesis because they form functional groups that span two carbons. Like nucleophilic substitution, elimination reactions can occur by two different pathways, depending on the

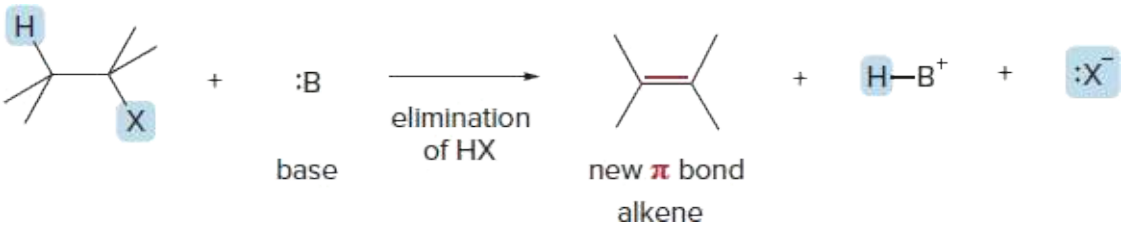
conditions. By the end of Chapter 8, therefore, you will have learned four different reaction mechanisms, two for nucleophilic substitution (S_N1 and S_N2) and two for elimination (E1 and E2).

The biggest challenge with this material is learning how to sort out two different reactions that follow four different mechanisms. Will a particular alkyl halide undergo substitution or elimination with a given reagent, and by which of the four possible mechanisms? To answer this question, we conclude Chapter 8 with a summary that allows you to predict which reaction and mechanism are likely for a given substrate.

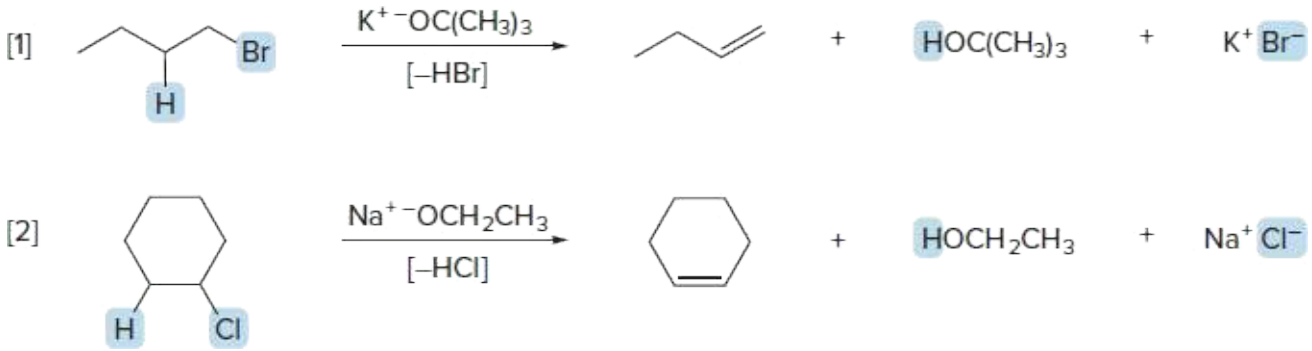
8.1 General Features of Elimination

All elimination reactions involve loss of elements from the starting material to form a new π bond in the product.

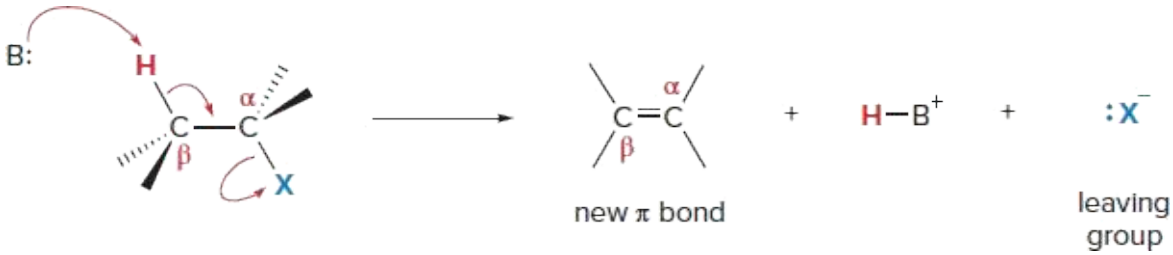
- **Alkyl halides undergo elimination reactions with Brønsted–Lowry bases. The elements of HX are lost and an alkene is formed.**



Equations [1] and [2] illustrate examples of elimination reactions. In both reactions a base removes the elements of an acid, HBr or HCl, from the organic starting material.



Removal of the elements of HX, called dehydrohalogenation, is one of the most common methods to introduce a π bond and prepare an alkene. Dehydrohalogenation is an example of β elimination, because it involves loss of elements from two adjacent atoms: the α carbon bonded to the leaving group X, and the β carbon adjacent to it. Three curved arrows illustrate how four bonds are broken or formed in the process.



- The base (B:) removes a proton on the β carbon, thus forming $H–B^+$.
- The electron pair in the β C–H bond forms the new π bond between the α and β carbons.
- The electron pair in the C–X bond ends up on halogen, forming the leaving group: X^-.

The most common bases used in elimination reactions are negatively charged oxygen compounds such as ^-OH and its alkyl derivatives, ^-OR, called alkoxides, listed in Table 8.1. Potassium *tert*-butoxide, K+ $^-OC(CH_3)_3$, a bulky nonnucleophilic base, is especially useful (Section 7.8B).

Table 8.1
Common Bases Used in Dehydrohalogenation

Structure	Name
$Na^+ \ ^-OH$	**Sodium hydroxide**
$K^+ \ ^-OH$	**Potassium hydroxide**
$Na^+ \ ^-OCH_3$	**Sodium methoxide**
$Na^+ \ ^-OCH_2CH_3$	**Sodium ethoxide**
$K^+ \ ^-OC(CH_3)_3$	**Potassium *tert*-butoxide**

To draw any product of dehydrohalogenation:

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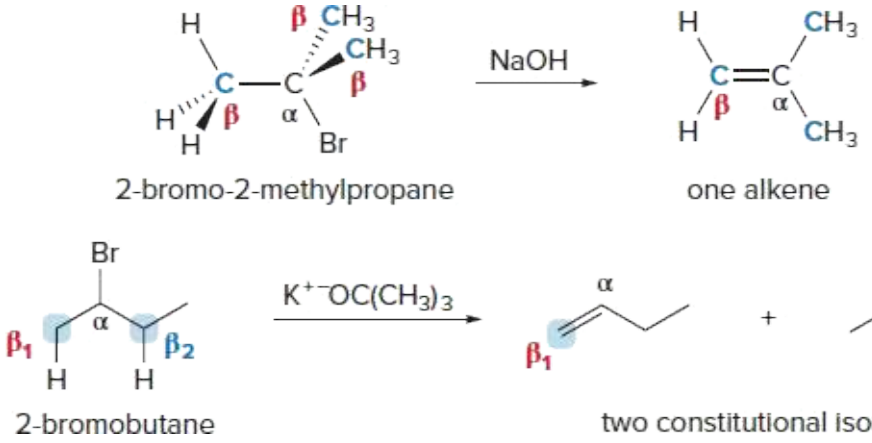
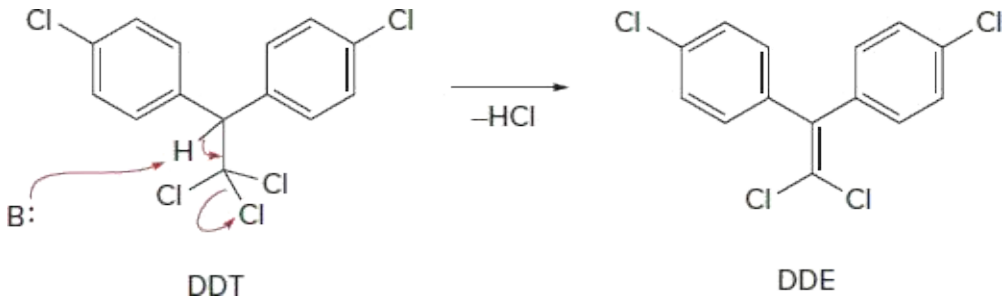
- **Find the α carbon—the sp^3 hybridized carbon bonded to the leaving group.**
- **Identify all β carbons with H atoms.**
- **Remove the elements of H and X from the α and β carbons and form a π bond.**

For example, 2-bromo-2-methylpropane has three β carbons (three CH_3 groups), but because all three are *identical*, only *one* alkene is formed upon elimination of HBr. In

contrast, 2-bromobutane has two *different* β carbons (labeled β_1 and β_2), so elimination affords *two* constitutional isomers by loss of HBr across either the α and β_1 carbons, or the α and β_2 carbons. We learn about which product predominates and why in Section 8.5.



An elimination reaction is the first step in the slow degradation of the pesticide DDT (Section 7.4). Elimination of HCl from DDT forms the degradation product DDE (dichlorodiphenyldichloroethylene). This stable alkene is found in minute concentration in the fatty tissues of most adults in the United States.



DDE and DDT accumulate in the fatty tissues of predator birds such as osprey. When DDE and DDT concentration is high, female osprey produce eggs with thin shells that are easily crushed, so fewer osprey chicks hatch.

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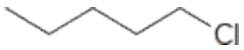
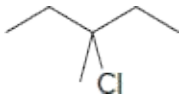
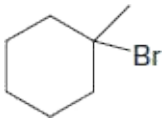
Problem 8.1

Label the α and β carbons in each alkyl halide. Draw all possible elimination products formed when each alkyl halide is treated with $K^{+-}OC(CH_3)_3$.

a. 

b. 

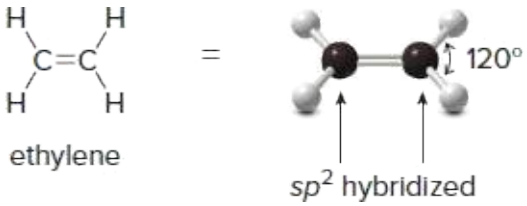
c. 

8.2 Alkenes—The Products of Elimination Reactions

Because elimination reactions of alkyl halides form alkenes, let's review earlier material on alkene structure and learn some additional facts as well.

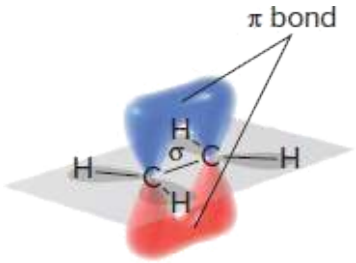
8.2A Bonding in a Carbon-Carbon Double Bond

Recall from Section 1.10B that alkenes are hydrocarbons containing a carbon–carbon double bond. Each carbon of the double bond is sp^2 hybridized and trigonal planar, and all bond angles are 120°.



Ethylene, the simplest alkene, is a hormone that regulates plant growth and fruit ripening. A ripe banana placed next to unripe tomatoes speeds up their ripening because the banana gives off ethylene. ***©McGraw-Hill Education/Jill Braaten, photographer***

The double bond of an alkene consists of a σ bond and a π bond.



- **The σ bond, formed by end-on overlap of the two sp^2 hybrid orbitals, lies in the plane of the molecule.**
- **The π bond, formed by side-by-side overlap of two 2*p* orbitals, lies perpendicular to the plane of the molecule. The π bond is formed during elimination.**

Alkenes are classified according to the number of carbon atoms bonded to the carbons of the double bond. A monosubstituted alkene has *one* carbon atom bonded to the carbons of the double bond. A disubstituted alkene has *two* carbon atoms bonded to the carbons of the double bond, and so forth.

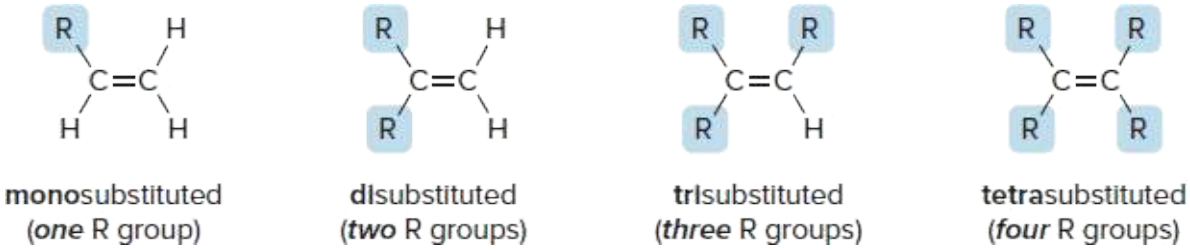
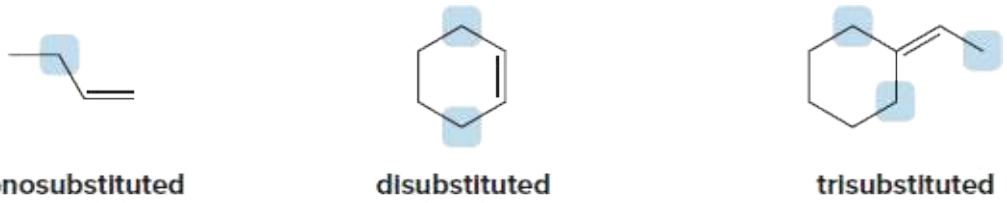


Figure 8.1 shows several alkenes and how they are classified. You must be able to classify alkenes in this way to determine the major and minor products of elimination reactions, when a mixture of alkenes is formed.



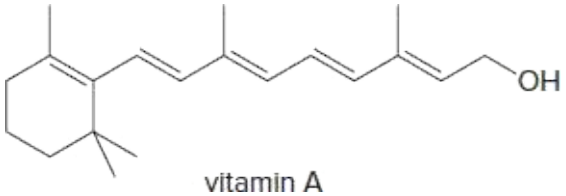
- Carbon atoms bonded to the double bond are screened in blue.

Figure 8.1 **Classifying alkenes by the number of R groups bonded to the double bond**

Problem 8.2

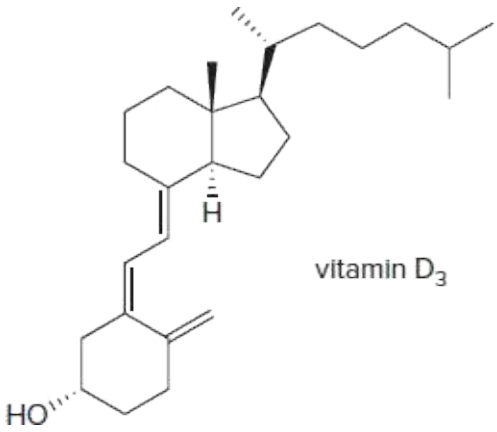
Classify each alkene in the following vitamins by the number of carbon substituents bonded to the double bond.

a.



vitamin A

b.



vitamin D_3

8.2B Restricted Rotation

Figure 8.2 shows that there is free rotation about the carbon–carbon single bonds of butane, but *not* about the carbon–carbon double bond of but-2-ene. Because of restricted rotation, two stereoisomers of but-2-ene are possible.

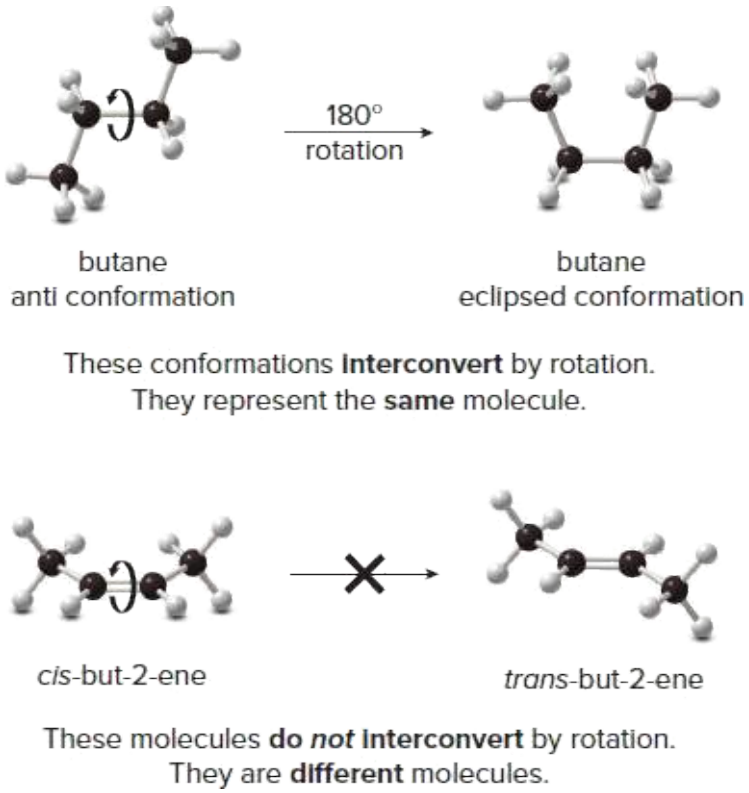
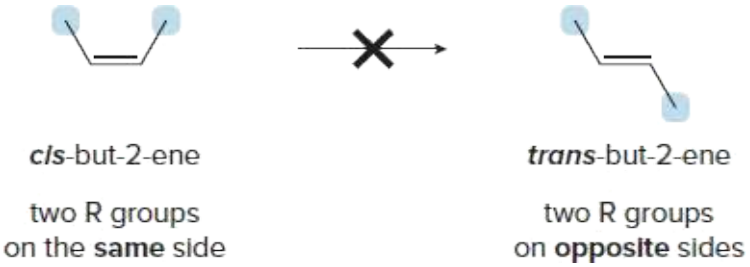


Figure 8.2 **Rotation around C–C and C=C compared**

The concept of cis and trans isomers was first introduced for disubstituted cycloalkanes in Chapter 4. In both cases, a ring

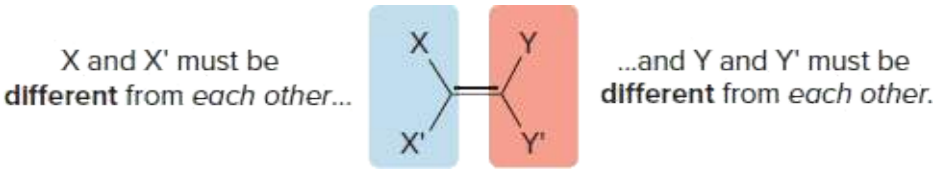
or a double bond restricts motion, preventing the rotation of a group from one side of the ring or double bond to the other.

- **The cis isomer has two groups on the *same side* of the double bond.**
- **The trans isomer has two groups on *opposite sides* of the double bond.**



cis-But-2-ene and *trans*-but-2-ene are stereoisomers, but not mirror images of each other, so they are diastereomers.

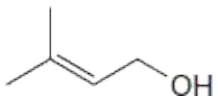
The cis and trans isomers of but-2-ene are a specific example of a general type of stereoisomer occurring at carbon–carbon double bonds. Whenever the two groups on *each* end of a carbon–carbon double bond are *different from each other*, two diastereomers are possible.



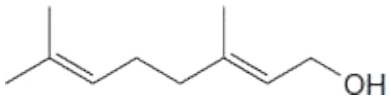
Problem 8.3

For which double bonds are stereoisomers possible?

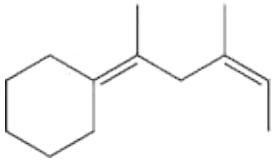
a.



b.

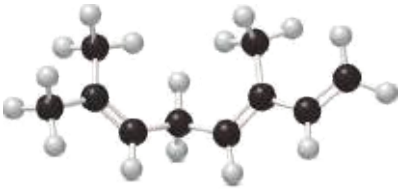


c.



Problem 8.4

(a) Which double bonds in (*E*)-ocimene, a major component of the odor of lilac flowers, can exhibit stereoisomerism? (b) Draw a diastereomer of (*E*)-ocimene.

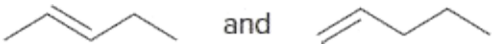


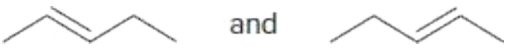
(*E*)-ocimene

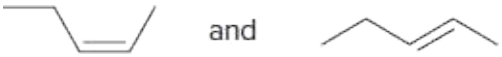
The characteristic fragrance of lilac flowers (Problem 8.4) is a mixture of (*E*)-ocimene and other volatile ethers, aldehydes, and alcohols. ***©Steven P. Lynch***

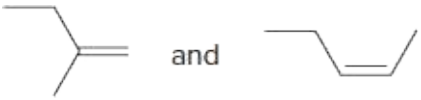
Problem 8.5

Label each pair of alkenes as constitutional isomers, stereoisomers, or identical.

a.  and

b.  and

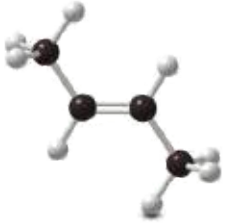
c.  and

d.  and

8.2C Stability of Alkenes

Some alkenes are more stable than others. For example, trans alkenes are generally more stable than cis alkenes because the larger groups bonded to the double bond carbons are farther apart, reducing steric interactions.

The trans isomer has the CH_3 groups *farther* away from each other.

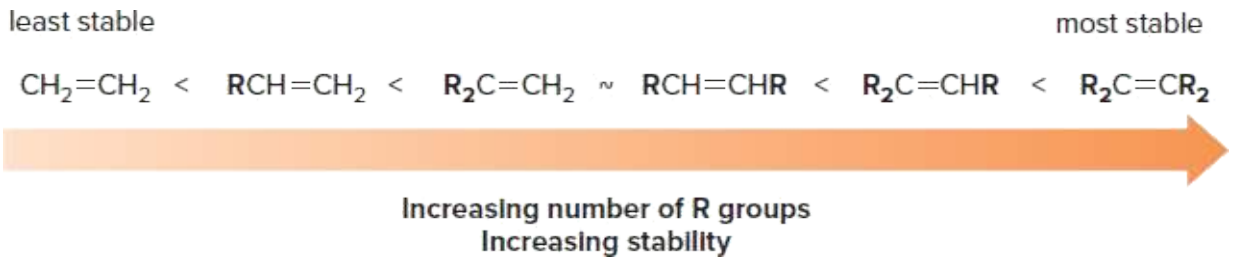


more stable

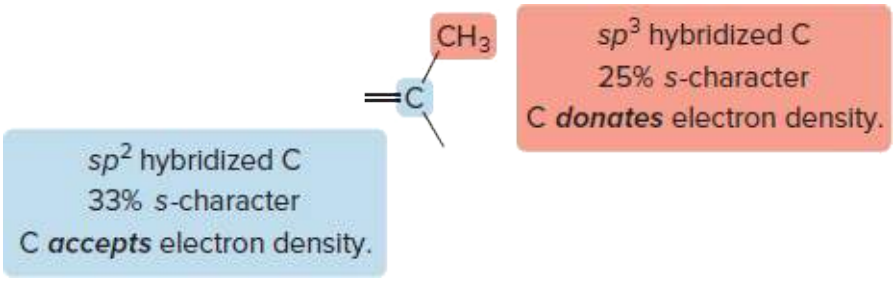
Steric interactions of the CH_3 groups *destabilize* the cis isomer.

less stable

The stability of an alkene *increases*, moreover, as the number of R groups bonded to the double bond carbons *increases*.

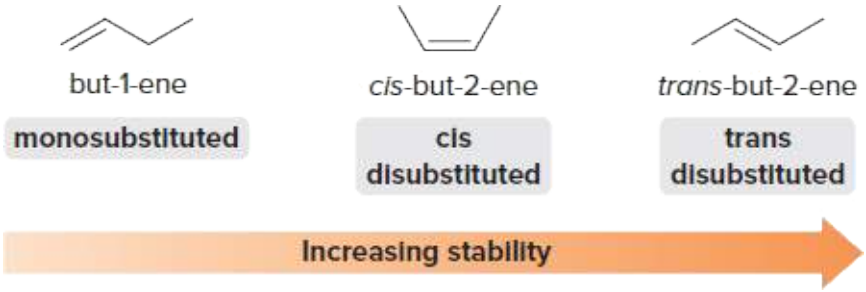


R groups increase the stability of an alkene because R groups are sp^3 hybridized, whereas the carbon atoms of the double bond are sp^2 hybridized. Recall from Sections 1.11B and 2.5D that the percent *s*-character of a hybrid orbital increases from 25% to 33% in going from sp^3 to sp^2. The higher the percent *s*-character, the more readily an atom accepts electron density. Thus, sp^2 hybridized carbon atoms are more able to *accept* electron density, and sp^3 hybridized carbon atoms are more able to *donate* electron density.



- **As a result, *increasing* the number of electron-donating R groups on a carbon atom able to accept electron density makes the alkene *more stable.***

Thus, *trans*-but-2-ene (a disubstituted alkene) is more stable than *cis*-but-2-ene (another disubstituted alkene), but both are more stable than but-1-ene (a monosubstituted alkene).



In summary:

- **Trans alkenes are *more stable* than cis alkenes because they have**

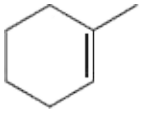
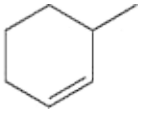
fewer steric interactions.

- *Increasing* alkyl substitution *stabilizes* an alkene by an electron-donating inductive effect.

Problem 8.6

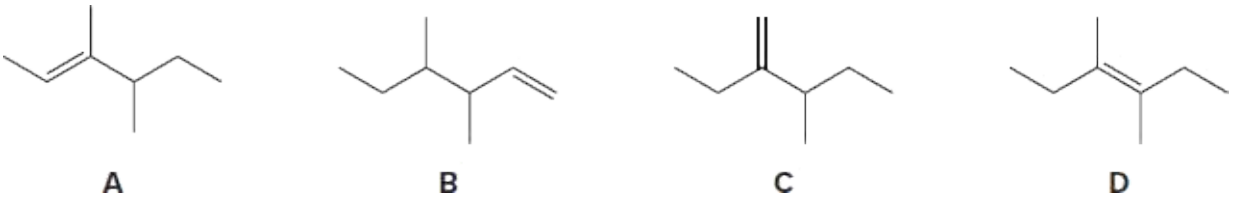
Which alkene in each pair is more stable?

a. or

b.  or 

Problem 8.7

Rank the following alkenes in order of increasing stability.



8.3 The Mechanisms of Elimination

What is the mechanism for elimination? What is the order of bond breaking and bond making? Is the reaction a one-step process or does it occur in many steps?

There are two mechanisms for elimination—E2 and E1—just as there are two mechanisms for nucleophilic substitution—S_N2 and S_N1.

- **The E2 mechanism (bimolecular elimination)**
- **The E1 mechanism (unimolecular elimination)**

The E2 and E1 mechanisms differ in the timing of bond cleavage and bond formation, analogous to the S_N2 and S_N1 mechanisms. In fact, E2 and S_N2 reactions have some features in common, as do E1 and S_N1 reactions.

8.4 The E2 Mechanism

The most common mechanism for dehydrohalogenation is the E2 mechanism. For example, $(CH_3)_3CBr$ reacts with ^-OH to form $(CH_3)_2C{=}CH_2$ via an E2 mechanism.

8.4A Kinetics

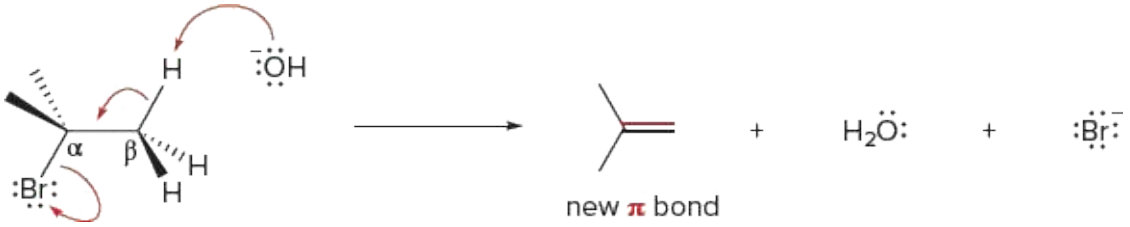
An E2 reaction exhibits second-order kinetics; that is, the reaction is bimolecular, and both the alkyl halide and the base appear in the rate equation.

- **rate = $k[(CH_3)_3CBr][^-OH]$**

8.4B A One-Step Mechanism

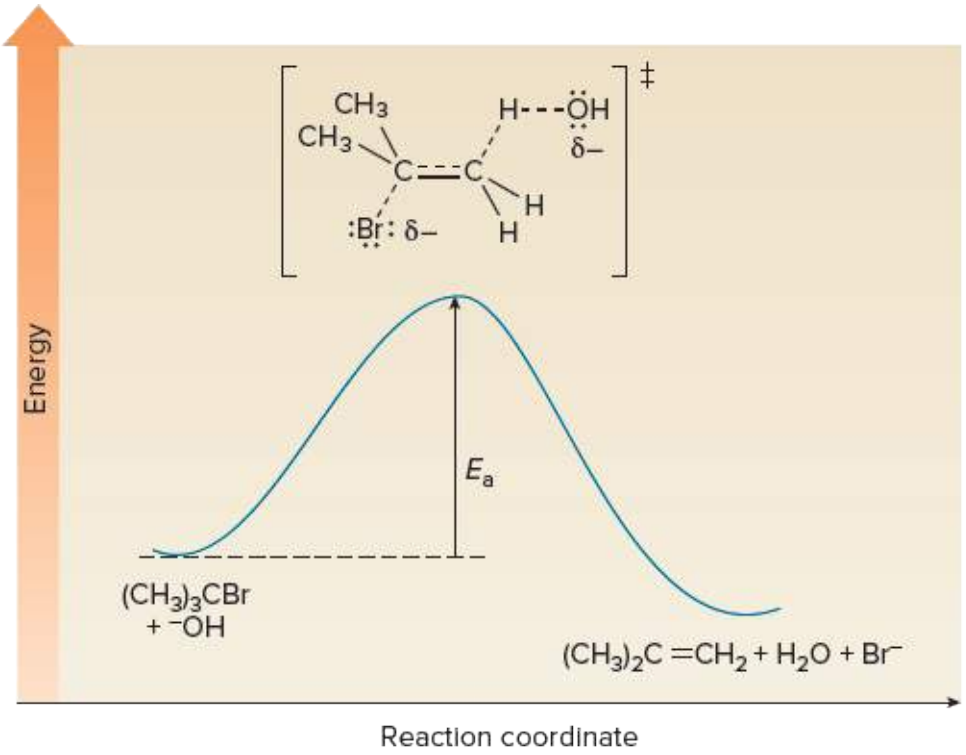
The most straightforward explanation for the second-order kinetics is a concerted reaction: all bonds are broken and formed in a single step, as shown in Mechanism 8.1.

Mechanism 8.1 The E2 Mechanism



- **The base ^-OH removes a proton from the β carbon, forming H_2O (a by-product).**
- **The electron pair in the β C–H bond forms the new π bond.**
- **The leaving group Br^- comes off with the electron pair in the C–Br bond.**

An energy diagram for the reaction of $(CH_3)_3CBr$ with ^-OH is shown in Figure 8.3. The reaction has one step, so there is one energy barrier between reactants and products. Two bonds are broken (C–H and C–Br) and two bonds are formed (H–OH and the π bond) in a single step, so the transition state contains four partial bonds, with the negative charge distributed over the base and the leaving group. Entropy favors the products of an E2 reaction because two molecules of starting material form three molecules of product.

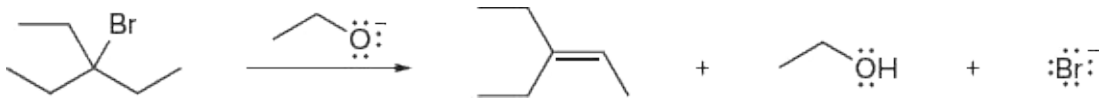


- In the transition state, the C—H and C—Br bonds are partially broken, the O—H and π bonds are partially formed, and both the base and the departing leaving group bear a partial negative charge.

Figure 8.3 **An energy diagram for an E2 reaction: $(CH_3)_3CBr + {}^-OH \rightarrow (CH_3)_2C{=}CH_2 + H_2O + Br^-$**

Problem 8.8

Use curved arrows to show the movement of electrons in the following E2 mechanism. Draw the structure of the transition state.



There are close parallels between the E2 and S_N2 mechanisms in how the identity of the base, the leaving group, and the solvent affect the rate.

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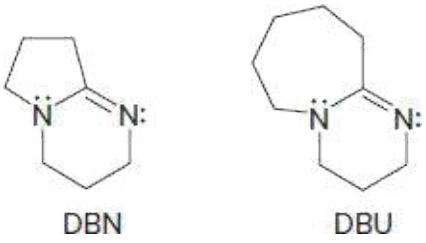
The Base

- **The base appears in the rate equation, so the rate of the E2 reaction *increases* as the strength of the base *increases.***

E2 reactions are generally run with strong, negatively charged bases like ${}^-OH$ and ${}^-OR$. Two strong, sterically hindered nitrogen bases, called DBN and DBU, are also sometimes used. An example of an E2 reaction with DBN is shown in Figure 8.4.



The IUPAC names for DBN and DBU are rarely used because the names are complex. DBN stands for 1,5-diazabicyclo[4.3.0]-non-5-ene, and DBU stands for 1,8-diazabicyclo[5.4.0]-undec-7-ene.

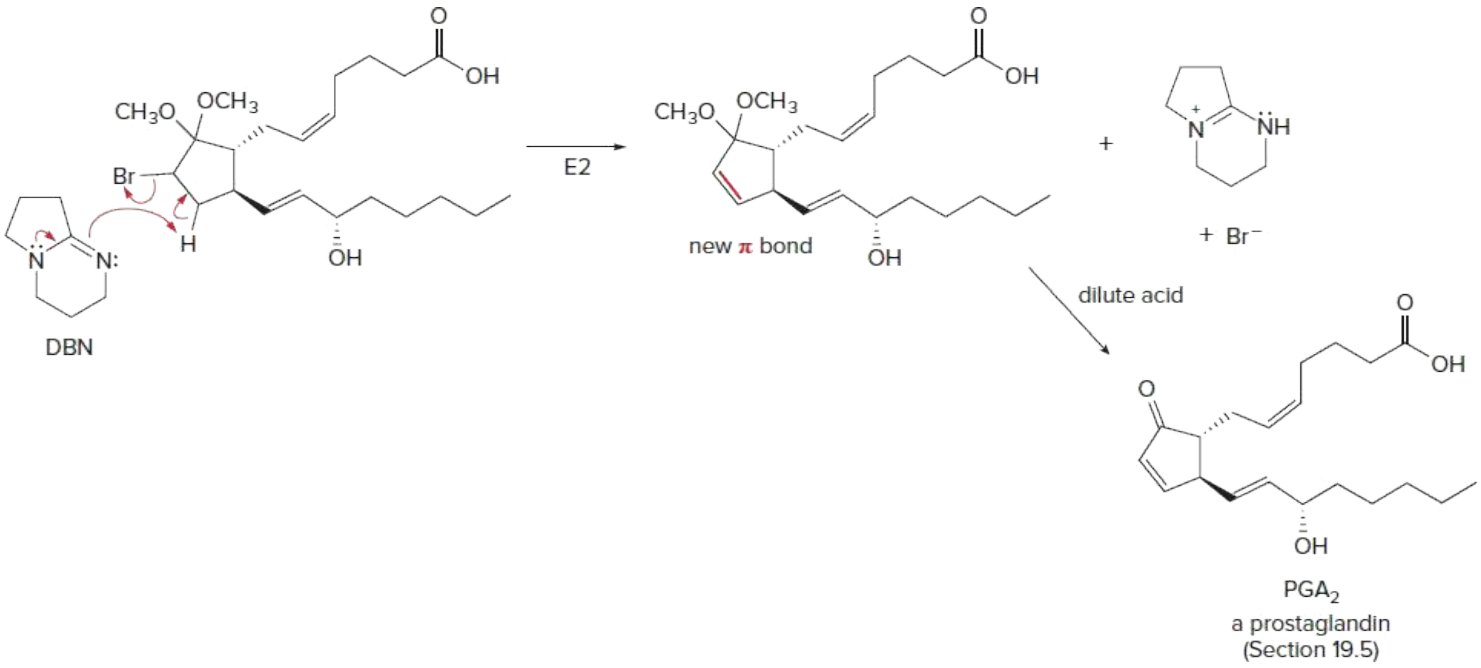
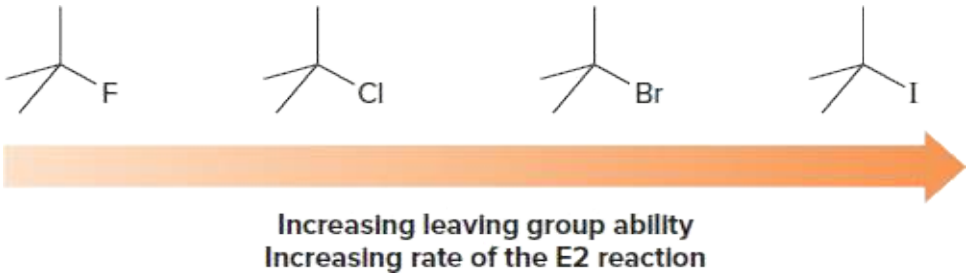


Figure 8.4 **An E2 elimination with DBN used as the base**

The Leaving Group

- **Because the bond to the leaving group is partially broken in the transition state, the *better* the leaving group the *faster* the E2 reaction.**



The Solvent

- **Polar aprotic solvents *increase* the rate of E2 reactions.**

Because polar aprotic solvents like $(CH_3)_2C{=}O$ do not solvate anions well, a negatively charged base is not "hidden" by strong interactions with the solvent (Section 7.15D), and the base is stronger. A stronger base increases the reaction rate.

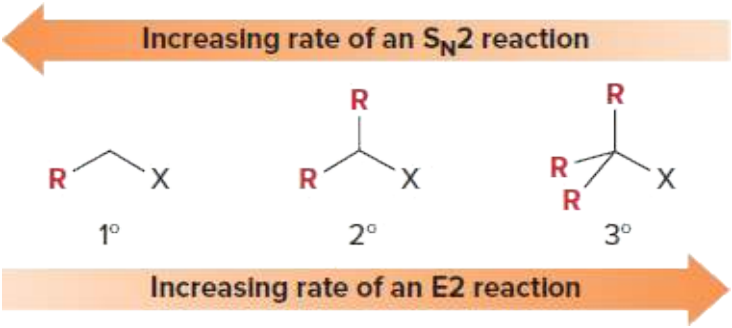
Problem 8.9

Consider an E2 reaction between CH_3CH_2Br and $KOC(CH_3)_3$. What effect does each of the following changes have on the rate of elimination? (a) The base is changed to KOH. (b) The alkyl halide is changed to CH_3CH_2Cl.

8.4C The Identity of the Alkyl Halide

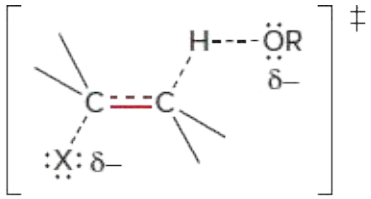
The S_N2 and E2 mechanisms differ in how the R group affects the reaction rate.

- **As the number of R groups on the carbon with the leaving group *increases*, the rate of the E2 reaction *increases.***



This trend is exactly *opposite* to the reactivity of alkyl halides in S_N2 reactions, where increasing alkyl substitution decreases the rate of reaction (Section 7.11D).

Why does increasing alkyl substitution increase the rate of an E2 reaction? In the transition state, the double bond is partially formed, so *increasing the stability* of the double bond with alkyl substituents *stabilizes* the transition state (i.e., it lowers E_a), which *increases* the rate of the reaction.

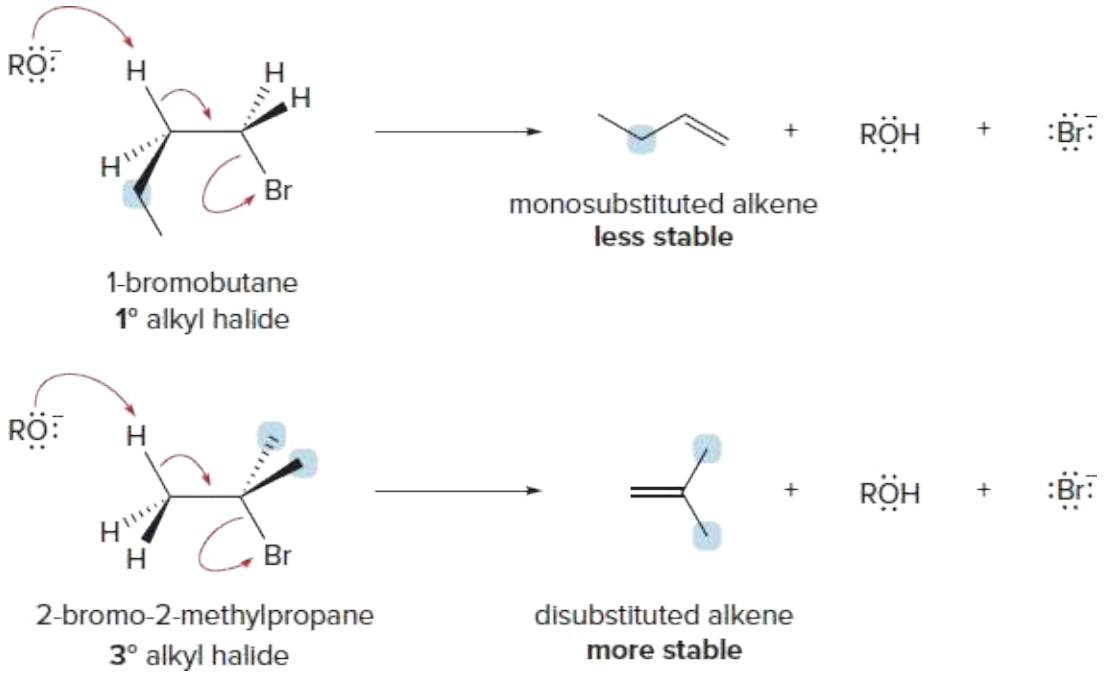


The double bond is partially formed.

- **Increasing the number of R groups on the carbon with the leaving**

group forms more highly substituted, *more stable* alkenes in E2 reactions.

For example, the E2 reaction of a 1° alkyl halide (1-bromobutane) forms a monosubstituted alkene, whereas the E2 reaction of a 3° alkyl halide (2-bromo-2-methylpropane) forms a disubstituted alkene. The disubstituted alkene is more stable, so the 3° alkyl halide reacts faster than the 1° alkyl halide.



Elimination reactions are often steps in the synthesis of complex natural products. For example, elimination of HCl from compound A forms alkene B, which was converted to the anti-malarial drug quinine, the chapter-opening molecule.

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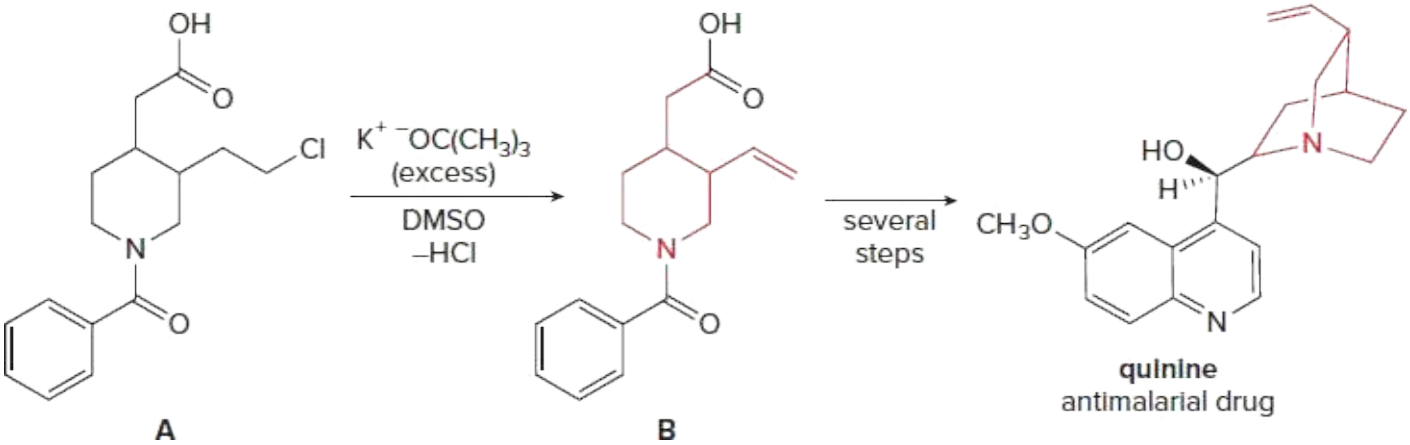


Table 8.2 summarizes the characteristics of the E2 mechanism.

Table 8.2 Characteristics of the E2 Mechanism

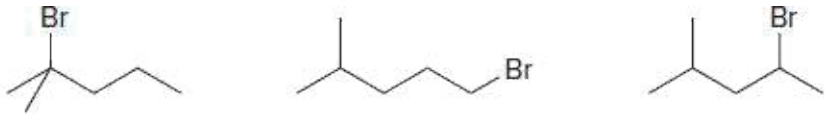
Characteristic	Result
Kinetics	

	• Second order
Mechanism	• One step
Identity of R	• More substituted halides react faster. • Rate: $R_3CX > R_2CHX > RCH_2X$
Base	• Favored by strong bases
Leaving group	• Better leaving group ⇢ faster reaction
Solvent	• Favored by polar aprotic solvents

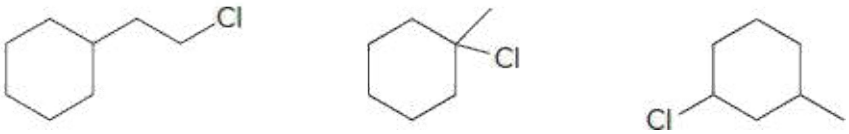
Problem 8.10

Rank the alkyl halides in each group in order of increasing reactivity in an E2 reaction.

a.



b.



Problem 8.11

How does each of the following changes affect the rate of an E2 reaction?

a. tripling [RX]

b. halving [B:]

c. changing the solvent from CH_3OH to DMSO

d. changing the leaving group from I^- to Br^-

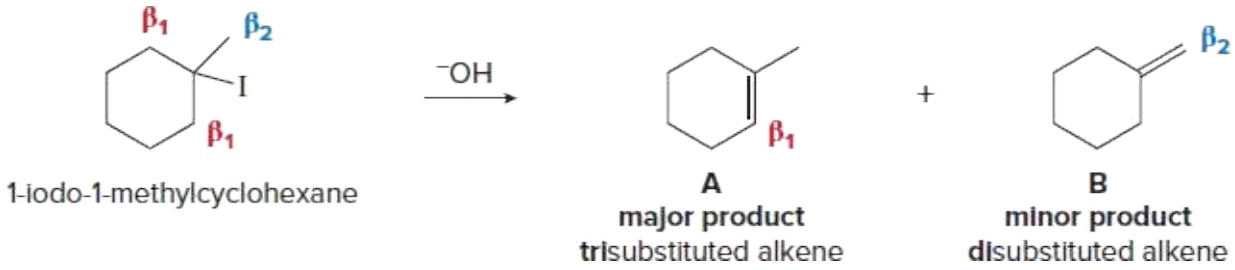
e. changing the base from ^-OH to H_2O

f. changing the alkyl halide from CH_3CH_2Br to $(CH_3)_2CHBr$

8.5 The Zaitsev Rule

Recall from Section 8.1 that a mixture of alkenes can form from the dehydrohalogenation of alkyl halides having two or more different β carbon atoms. When this occurs, one of the products usually predominates. The major product is the

more stable product—the one with the more substituted double bond. For example, elimination of the elements of H and I from 1-iodo-1-methylcyclohexane yields two constitutional isomers: the trisubstituted alkene A (the major product) and the disubstituted alkene B (the minor product).



1-iodo-1-methylcyclohexane

A
major product
trisubstituted alkene

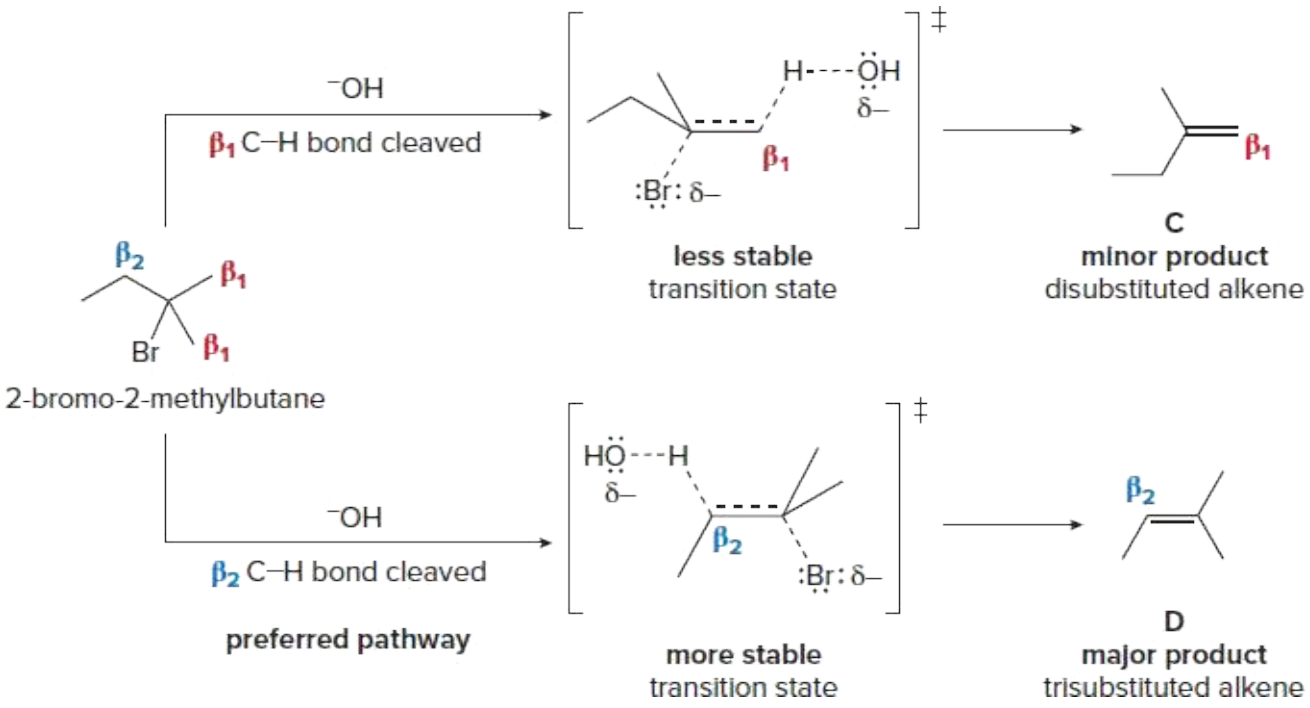
B
minor product
disubstituted alkene

This phenomenon is called the Zaitsev rule (also called the Saytzeff rule, depending on the translation) for the Russian chemist who first noted this trend.

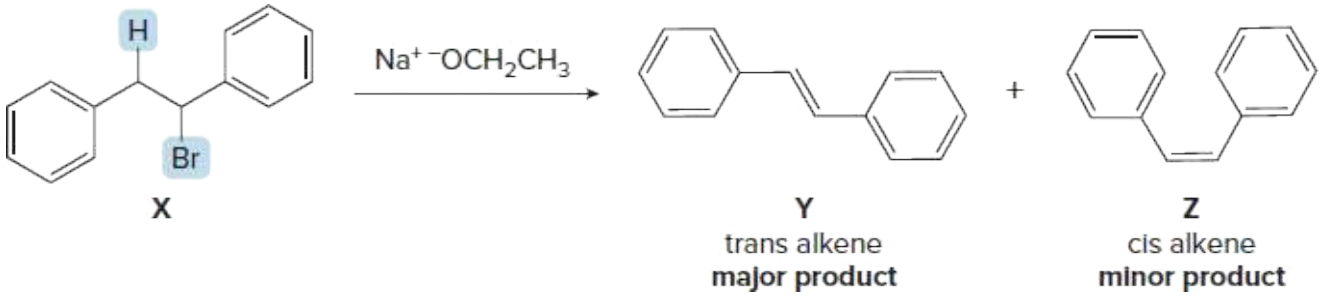
- **The Zaitsev rule: The major product in β elimination has the more substituted double bond.**

A reaction is *regioselective* when it yields predominantly or exclusively one constitutional isomer when more than one is possible. The E2 reaction is regioselective because the more substituted alkene predominates.

The Zaitsev rule results because the double bond is partially formed in the transition state for the E2 reaction. Thus, increasing the stability of the double bond by adding R groups lowers the energy of the transition state, which increases the reaction rate. E2 elimination of HBr from 2-bromo-2-methylbutane yields alkenes C and D. D, having the more substituted double bond, is the major product, because the transition state leading to its formation is lower in energy.



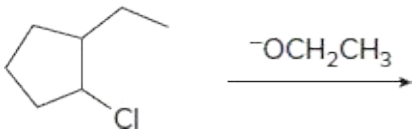
When a mixture of stereoisomers is possible from dehydrohalogenation, the major product is the more stable stereoisomer. Dehydrohalogenation of alkyl halide X forms a mixture of trans and cis alkenes, Y and Z. The trans alkene Y is the major product because it is more stable.



A reaction is *stereoselective* when it forms predominantly or exclusively one stereoisomer when two or more are possible. The E2 reaction is stereoselective because one stereoisomer is formed preferentially.

Sample Problem 8.1 Determining the Major Product of an E2 Reaction

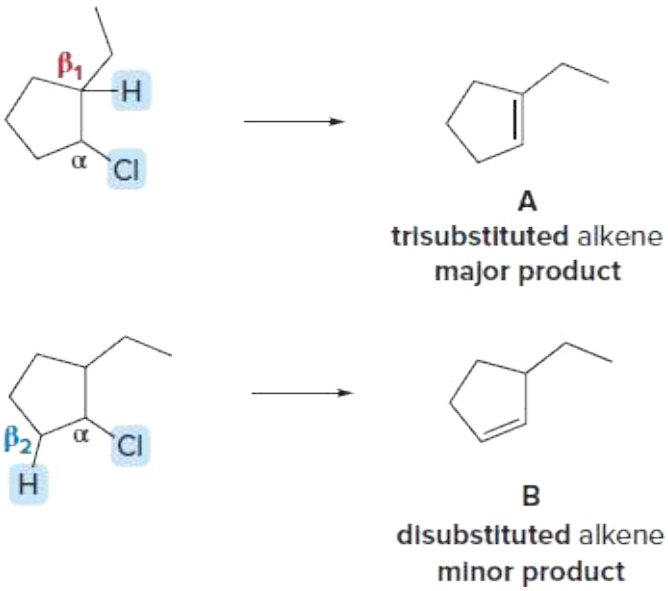
Predict the major product in the following E2 reaction.



Solution

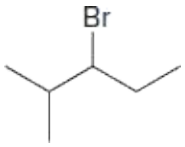
The alkyl halide has two different β C atoms (labeled β_1 and β_2), so two different alkenes are possible: one formed by removal of HCl across the α

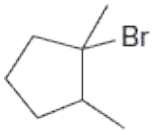
and carbons, and one formed by removal of HCl across the α and β_2 carbons. Using the Zaitsev rule, the major product should be A, because it has the more substituted double bond.

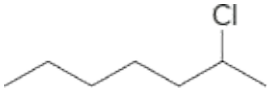


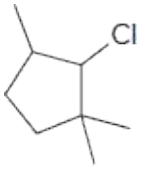
Problem 8.12

What alkenes are formed from each alkyl halide by an E2 reaction? Use the Zaitsev rule to predict the major product.

a. 

b. 

c. 

d. 

More Practice:

Try Problems 8.33, 8.40.

8.6 The E1 Mechanism

The dehydrohalogenation of $(CH_3)_3CI$ with H_2O to form $(CH_3)_2C{=}CH_2$ can be used to

illustrate the second general mechanism of elimination, the E1 mechanism.

8.6A Kinetics

An E1 reaction exhibits first-order kinetics.

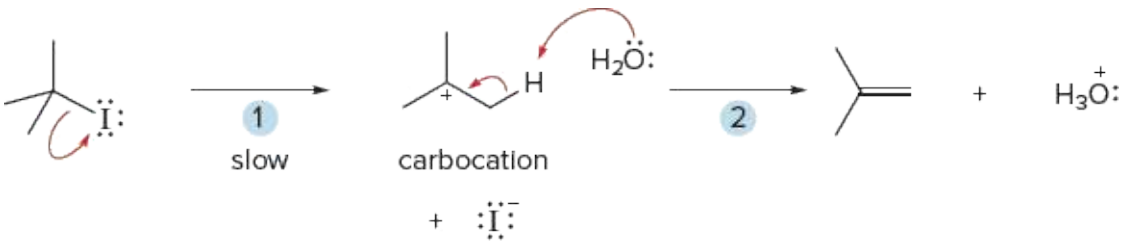
- **rate = $k[(CH_3)_3CI]$**

Like the S_N1 mechanism, the kinetics suggest that the reaction mechanism involves more than one step, and that the slow step is unimolecular, involving *only* the alkyl halide.

8.6B A Two-Step Mechanism

The most straightforward explanation for the observed first-order kinetics is a two-step reaction: the bond to the leaving group breaks first *before* the π bond is formed, as shown in Mechanism 8.2.

Mechanism 8.2 The E1 Mechanism



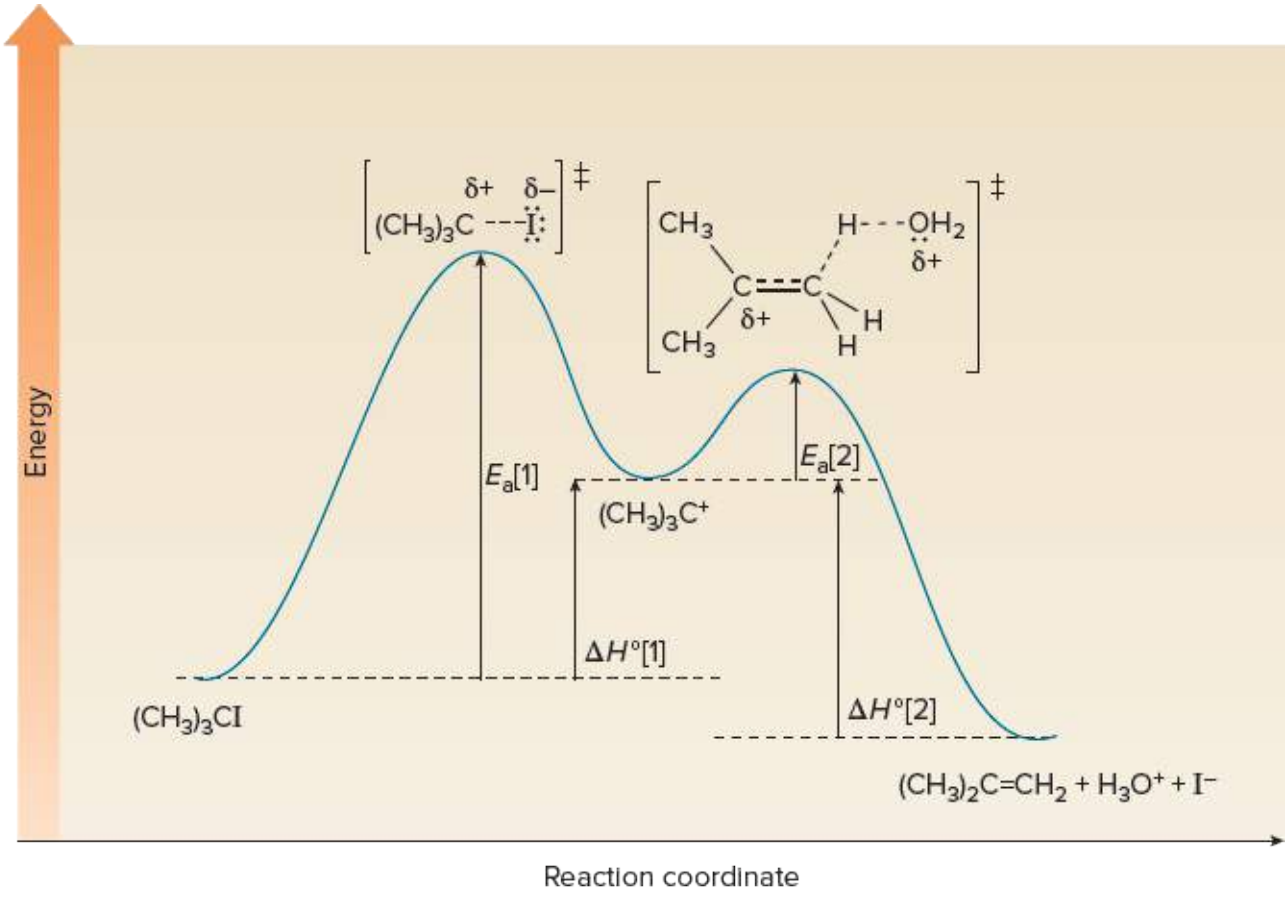
1. **Heterolysis of the C–I bond forms a carbocation in the rate-determining step.**
2. **A base (either H_2O or I^-) removes a proton from a carbon adjacent to the carbocation, and the electron pair in the C–H bond forms the π bond.**

The E1 and E2 mechanisms both involve the same number of bonds broken and formed. The only difference is the timing.

- **In an E1 reaction, the leaving group comes off *before* the β proton is removed, and the reaction occurs in *two* steps.**

- **In an E2 reaction, the leaving group comes off *as* the β proton is removed, and the reaction occurs in *one* step.**

An energy diagram for the reaction of $(CH_3)_3CI + H_2O$ is shown in Figure 8.5. Each step has its own energy barrier, with a transition state at each energy maximum. Because its transition state is higher in energy, Step [1] is rate-determining. $\Delta H°$ for Step [1] is positive because only bond breaking occurs, whereas $\Delta H°$ of Step [2] is negative because two bonds are formed and only one is broken.

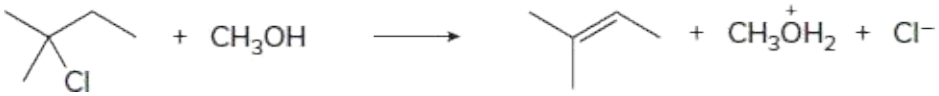


- The E1 mechanism has **two steps**, so there are two energy barriers.
- **Step [1] is rate-determining.**

Figure 8.5 **Energy diagram for an E1 reaction: $(CH_3)_3CI + H_2O \dashrightarrow (CH_3)_2C{=}CH_2 + H_3O^+ + I^-$**

Problem 8.13

Draw an E1 mechanism for the following reaction. Draw the structure of the transition state for each step.

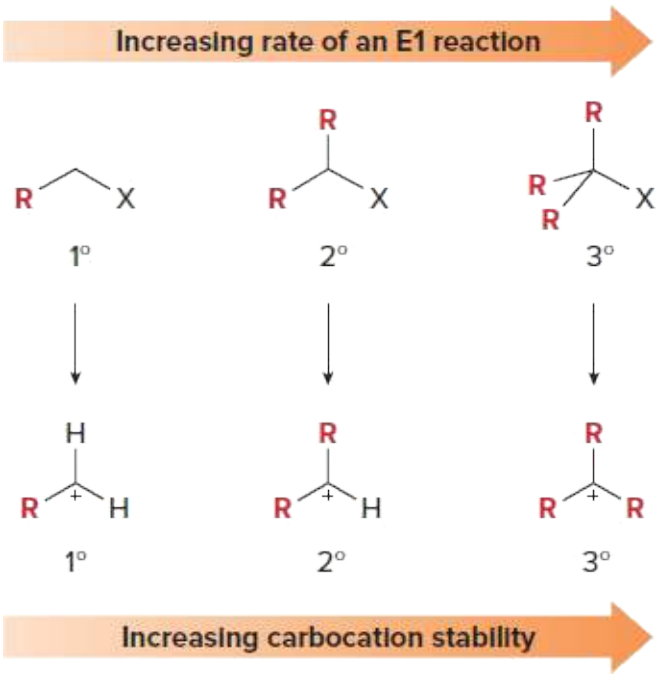


8.6C Other Characteristics of E1 Reactions

Three other features of E1 reactions are worthy of note.

[1] The rate of an E1 reaction *increases* as the number of R groups on the carbon with the leaving group *increases*.

Increasing alkyl substitution has the same effect on the rate of *both* an E1 and E2 reaction; increasing rate of the E1 and E2 reactions: RCH_2X (1°) < R_2CHX (2°) < R_3CX (3°).



Like an S_N1 reaction, more substituted alkyl halides yield more substituted (and more stable) carbocations in the rate-determining step. Increasing the stability of a carbocation, in turn, decreases E_a for the slow step, which increases the rate of the E1 reaction according to the Hammond postulate.

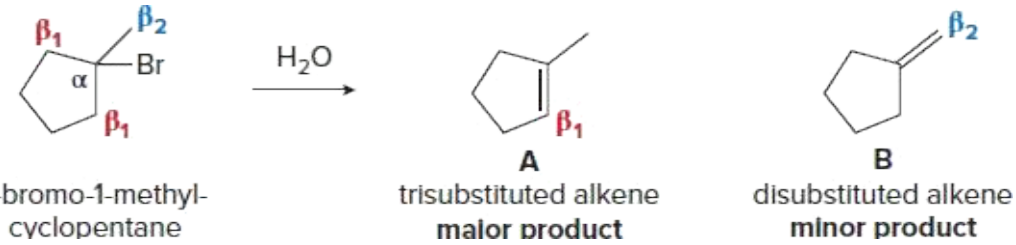
[2] Because the base does not appear in the rate equation, *weak bases* favor E1 reactions.

The strength of the base usually determines whether a reaction follows the E1 or E2 mechanism.

- **bases like ^-OH and ^-OR favor E2 reactions, whereas *weaker* bases like H_2O and ROH favor E1 reactions.**

[3] E1 reactions are regioselective, favoring formation of the more substituted, more stable alkene.

The Zaitsev rule applies to E1 reactions, too. For example, E1 elimination of HBr from 1-bromo-1-methylcyclopentane yields alkenes A and B. A, having the more substituted double bond, is the major product.



1-bromo-1-methyl-cyclopentane

A
trisubstituted alkene
major product

B
disubstituted alkene
minor product

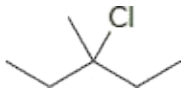
Table 8.3 summarizes the characteristics of E1 reactions.

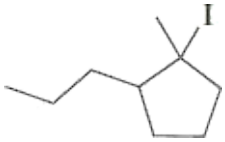
Table 8.3 Characteristics of the E1 Mechanism

Characteristic	Result
Kinetics	• First order
Mechanism	• Two steps
Identity of R	• More substituted halides react faster. • Rate: $R_3CX > R_2CHX > RCH_2X$
Base	• Favored by weaker bases such as H_2O and ROH
Leaving group	• A better leaving group makes the reaction faster because the bond to the leaving group is partially broken in the rate-determining step.
Solvent	• Polar protic solvents that solvate the ionic intermediates are needed.

Problem 8.14

What alkenes are formed from each alkyl halide by an E1 reaction? Use the Zaitsev rule to predict the major product.

a. 

b. 

Problem 8.15

How does each of the following changes affect the rate of an E1 reaction?

a. doubling [RX]

b. doubling [B:]

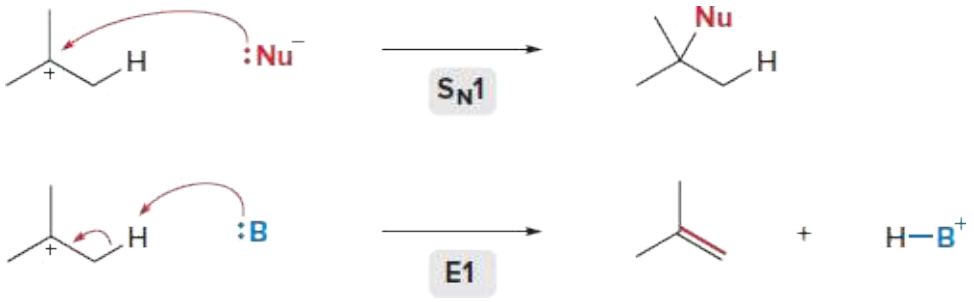
c. changing the halide from $(CH_3)_3CBr$ to $CH_3CH_2CH_2Br$

d. changing the leaving group from Cl^- to Br^-

e. changing the solvent from DMSO to CH_3OH

8.7 S_N1 and E1 Reactions

S_N1 and E1 reactions have exactly the same first step—formation of a carbocation. They differ in what happens to the carbocation.



- **In an S_N1 reaction, a nucleophile attacks the carbocation, forming a substitution product.**
- **In an E1 reaction, a base removes a proton, forming a new π bond.**

The same conditions that favor substitution by an S_N1 mechanism also favor elimination by an E1 mechanism: a 3° alkyl halide as substrate, a weak nucleophile or base as reagent, and a polar protic solvent. As a result, both reactions usually occur in the same reaction mixture to afford a mixture of products, as illustrated in Sample Problem 8.2.

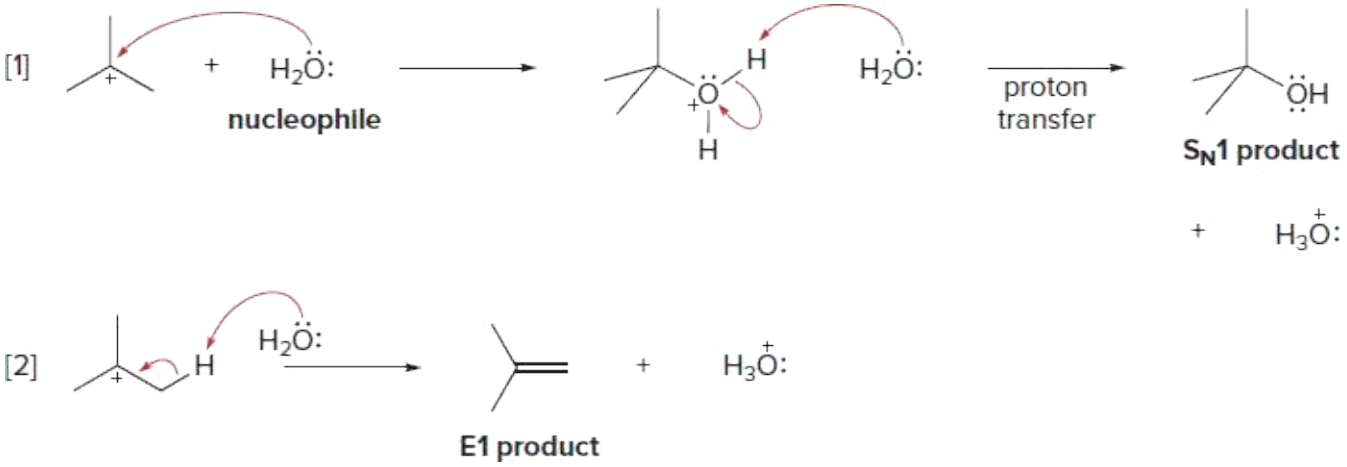
Sample Problem 8.2 **Drawing the S_N1 and E1 Products in a Reaction**

Draw the S_N1 and E1 products formed in the reaction of $(CH_3)_3CBr$ with H_2O.

Solution

The first step in both reactions is heterolysis of the C–Br bond to form a carbocation.

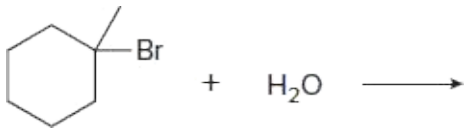
Reaction of the carbocation with H_2O as a nucleophile affords the Page 324 **substitution product (Reaction [1]). Alternatively, H_2O acts as a base to remove a proton, affording the elimination product (Reaction [2]). Two products are formed.**



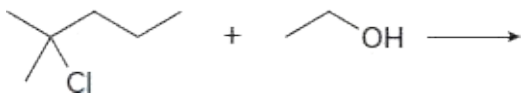
Problem 8.16

Draw both the S_N1 and E1 products of each reaction.

a.



b.



More Practice:

Try Problems 8.54b, c, h; 8.55a; 8.57a; 8.59.

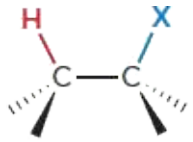
Because E1 reactions often occur with a competing S_N1 reaction, E1 reactions of alkyl halides are *much less useful* than E2 reactions.

8.8 Stereochemistry of the E2 Reaction

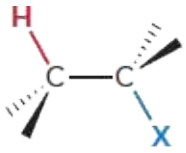
The transition state of the E2 reaction consists of four atoms that react at the same time, and they react only if they possess a particular stereochemical arrangement.

8.8A General Stereochemical Features

The transition state of an E2 reaction consists of four atoms from the alkyl halide—one hydrogen atom, two carbon atoms, and the leaving group (X)—all aligned in a plane. There are two ways for the C–H and C–X bonds to be coplanar:



syn periplanar



anti periplanar

- **The H and X atoms can be oriented on the same side of the molecule. This geometry is called *syn periplanar.***
- **The H and X atoms can be oriented on opposite sides of the molecule. This geometry is called *anti periplanar.***

The dihedral angle for the C–H and C–X bonds equals 0° for the syn periplanar arrangement and 180° for the anti periplanar arrangement.

All evidence suggests that E2 elimination occurs most often in the anti periplanar geometry. This arrangement allows the molecule to react in the lower-energy *staggered* conformation. It also allows two electron-rich species, the incoming base and the departing leaving group, to be farther away from each other, as illustrated in Figure 8.6.

Anti periplanar geometry is the preferred arrangement for any alkyl halide undergoing E2 elimination, regardless of whether it is cyclic or acyclic. This stereochemical requirement has important consequences for compounds containing six-membered rings.

- An **anti periplanar** arrangement has a **staggered** conformation.
- The two electron-rich groups are far apart.

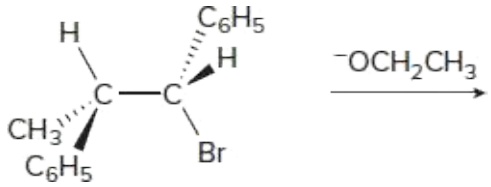
- A **syn periplanar** arrangement has an **eclipsed** conformation.
- The two electron-rich groups are close.

Figure 8.6 **Two possible geometries for the E2 reaction**

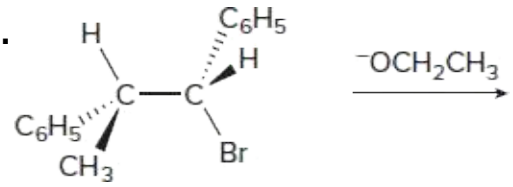
Problem 8.17

Given that an E2 reaction proceeds with anti periplanar stereochemistry, draw the products of each elimination. The alkyl halides in (a) and (b) are diastereomers of each other. How are the products of these two reactions related? Recall from Section 3.2A that C_6H_5– is a phenyl group, a benzene ring bonded to another group.

a.

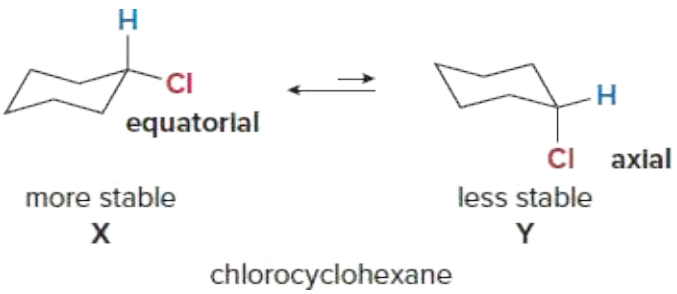


b.

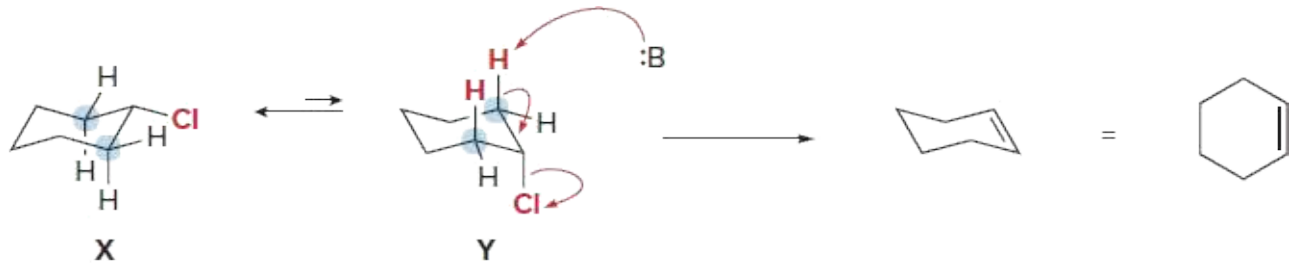


8.8B Anti Periplanar Geometry and Halocyclohexanes

Recall from Section 4.13 that cyclohexane exists as two chair conformations that rapidly inter-convert, and that substituted cyclohexanes are more stable with substituents in the roomier equatorial position. Chlorocyclohexane exists as two chair conformations, but X is preferred because the Cl group is equatorial.



For E2 elimination, the C–Cl bond must be anti periplanar to a C–H bond on a β carbon, and this occurs only when the H and Cl atoms are both in the axial position. This requirement for trans diaxial geometry means that E2 elimination must occur from the less stable conformation Y, as shown in Figure 8.7.



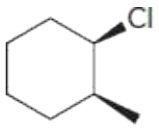
This conformation does *not* react.

This conformation reacts.

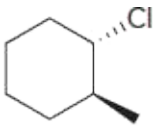
- In conformation **X** (**equatorial** Cl group), a β C—H bond and a C—Cl bond are *never* anti periplanar; therefore, **no E2** elimination can occur. β Carbons are highlighted in blue.
- In conformation **Y** (**axial** Cl group), two β C—H bonds and the C—Cl bond are **trans diaxial;** therefore, **E2 elimination occurs**. Axial H's on β carbons that can react are shown in red.

Figure 8.7 **The trans diaxial geometry for the E2 elimination in chlorocyclohexane**

Sometimes this rigid stereochemical requirement affects the regioselectivity Page 326 of the E2 reaction of substituted cyclohexanes. Dehydrohalogenation of *cis*- and *trans*-1-chloro-2-methylcyclohexane via an E2 mechanism illustrates this phenomenon.

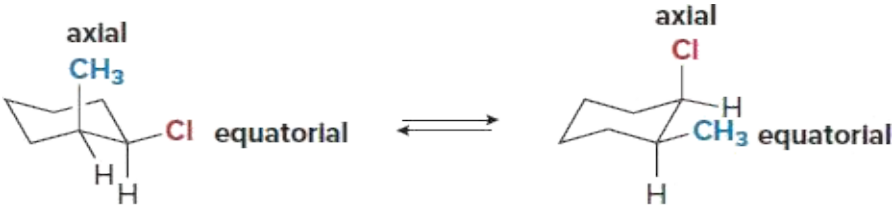


cis-1-chloro-2-methyl-cyclohexane

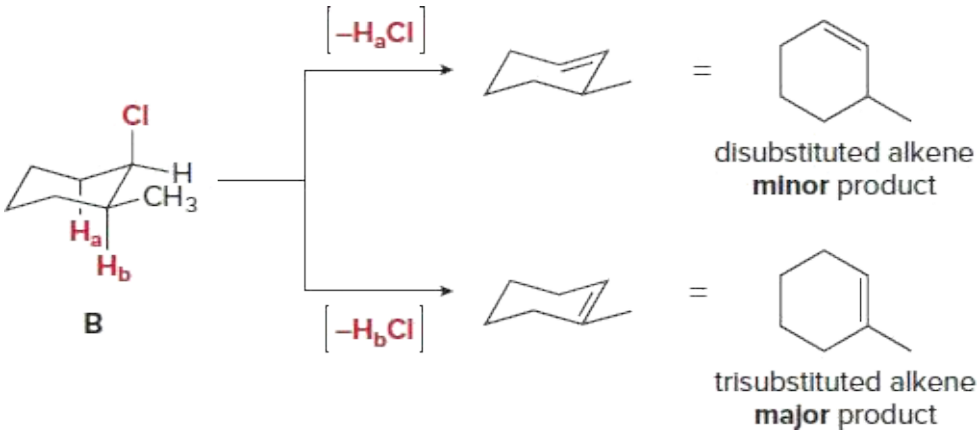


trans-1-chloro-2-methyl-cyclohexane

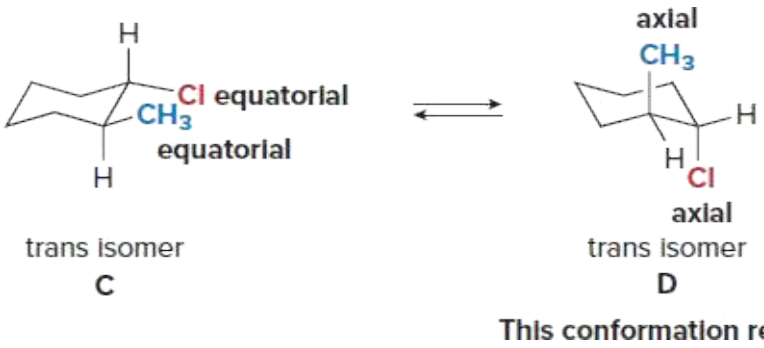
The cis isomer exists as two conformations (A and B), each of which has one group axial and one group equatorial. E2 reaction must occur from conformation B, which contains an axial Cl atom.



Because conformation B has two different axial β H atoms, labeled H_a and H_b, E2 reaction occurs in two different directions to afford two alkenes. The major product contains the more stable trisubstituted double bond, as predicted by the Zaitsev rule.

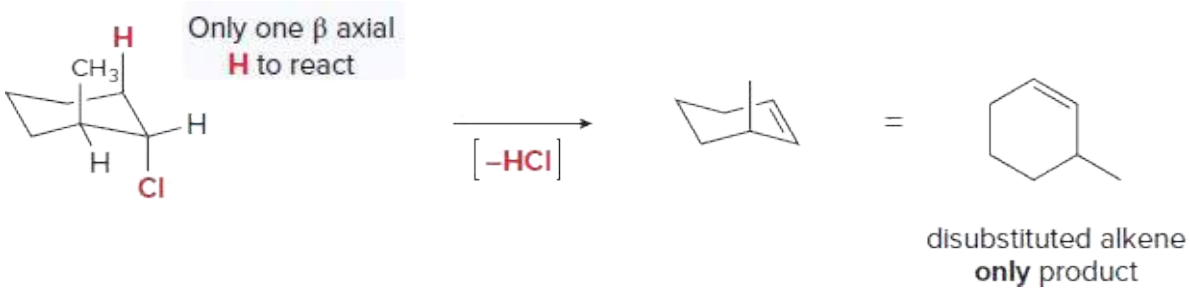


The trans isomer exists as two conformations, C, having two equatorial substituents, and D, having two axial substituents. E2 reaction must occur from conformation D, which contains an axial Cl atom.



Because conformation D has only one axial β H, E2 reaction occurs in only *one* direction to afford a single product, having the disubstituted double bond. This is *not* predicted by the Zaitsev rule. E2 reaction requires H and Cl to be trans and diaxial, and with the trans isomer, this is possible only when the less stable alkene is formed as product.

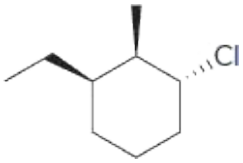
Page 327



- **With substituted cyclohexanes, E2 elimination must occur with a trans diaxial arrangement of H and X, and as a result of this requirement, the more substituted alkene is not necessarily the major product.**

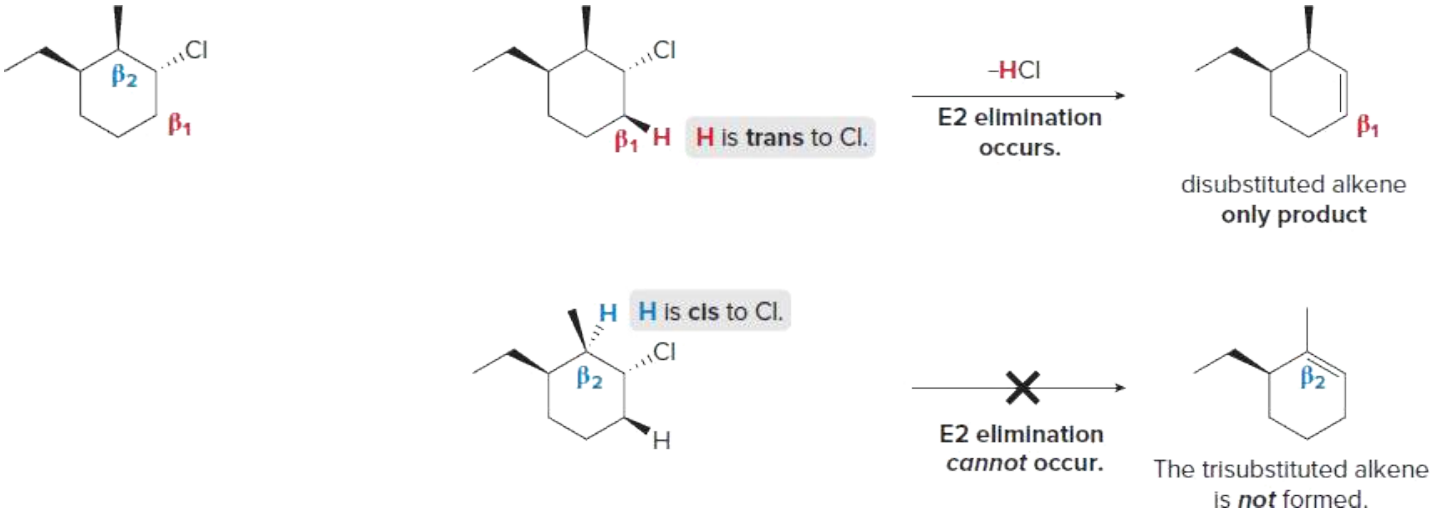
Sample Problem 8.3 Drawing an E2 Product from a Halocyclohexane

Draw the major E2 elimination product formed from the following alkyl halide.



Solution

To draw the elimination products, locate the β carbons and look for H atoms that are trans to the leaving group. The given alkyl chloride has two different β carbons, labeled β_1 and β_2. Elimination can occur only when the leaving group (Cl) and a H atom on the β carbon are *trans*.

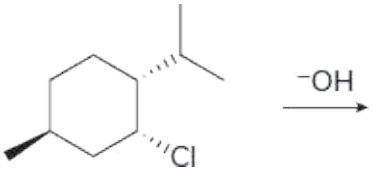


The β_1 C has a H atom *trans* to Cl, so E2 elimination occurs to form a disubstituted alkene. Because there is no trans H on the β_2 C, E2 elimination *cannot* occur in this direction, and the more stable trisubstituted alkene is *not* formed. Although this result is not predicted by the Zaitsev rule, it is consistent with the requirement that the H and X atoms in an E2 elimination must be located trans to each other.

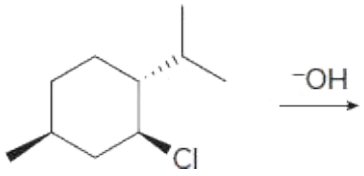
Problem 8.18

Draw the major E2 elimination products from each of the following alkyl halides.

a.



b.



More Practice:

Try Problems 8.26, 8.36, 8.41, 8.42, 8.44, 8.45, 8.47.

Problem 8.19

Explain why *cis*-1-chloro-2-methylcyclohexane undergoes E2 elimination much faster than its trans isomer.

8.9 When Is the Mechanism E1 or E2?

Given a particular starting material and base, how do we know whether a reaction occurs by the E1 or E2 mechanism?

Because the rate of *both* the E1 and E2 reactions increases as the number of R groups on the carbon with the leaving group increases, you cannot use the identity of the alkyl halide to decide which elimination mechanism occurs.

- **The strength of the base is the most important factor in determining the mechanism for elimination. Strong bases favor the E2 mechanism. Weak bases favor the E1 mechanism.**

Table 8.4 compares the E1 and E2 mechanisms.

Table 8.4 A Comparison of the E1 and E2 Mechanisms

Mechanism	Comment
E2 mechanism	• Much more common and useful • Favored by strong, negatively charged bases, especially $^{-}$OH and $^{-}$OR • The reaction occurs with 1°, 2°, and 3° alkyl halides. Order of reactivity: $R_3CX > R_2CHX > RCH_2X$.
E1 mechanism	• Much less useful because a mixture of S_N1 and E1

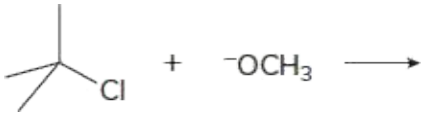
products usually results

- Favored by weaker, neutral bases, such as H_2O and ROH
- This mechanism does not occur with 1° RX because they form highly unstable 1° carbocations.

Problem 8.20

Which mechanism, E1 or E2, will occur in each reaction?

a.



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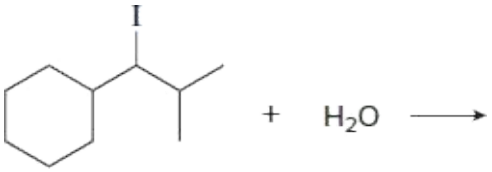

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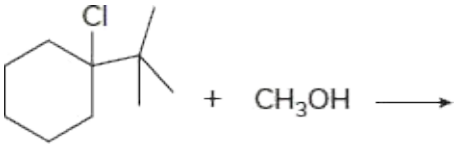

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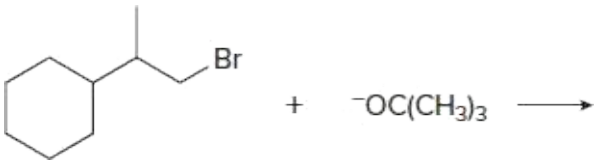
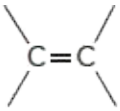


Recall from Section 1.10C that the carbon–carbon triple bond of alkynes consists of one σ and two π bonds.

8.10 E2 Reactions and Alkyne Synthesis

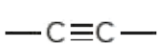
A single elimination reaction produces the π bond of an alkene. Two consecutive elimination reactions produce the two π bonds of an alkyne.



alkene

one π bond

One elimination reaction is needed.



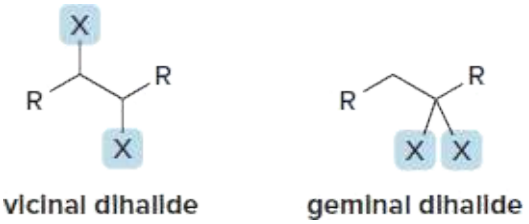
alkyne

two π bonds

Two elimination reactions are needed.

- **Alkynes are prepared by two successive dehydrohalogenation reactions.**

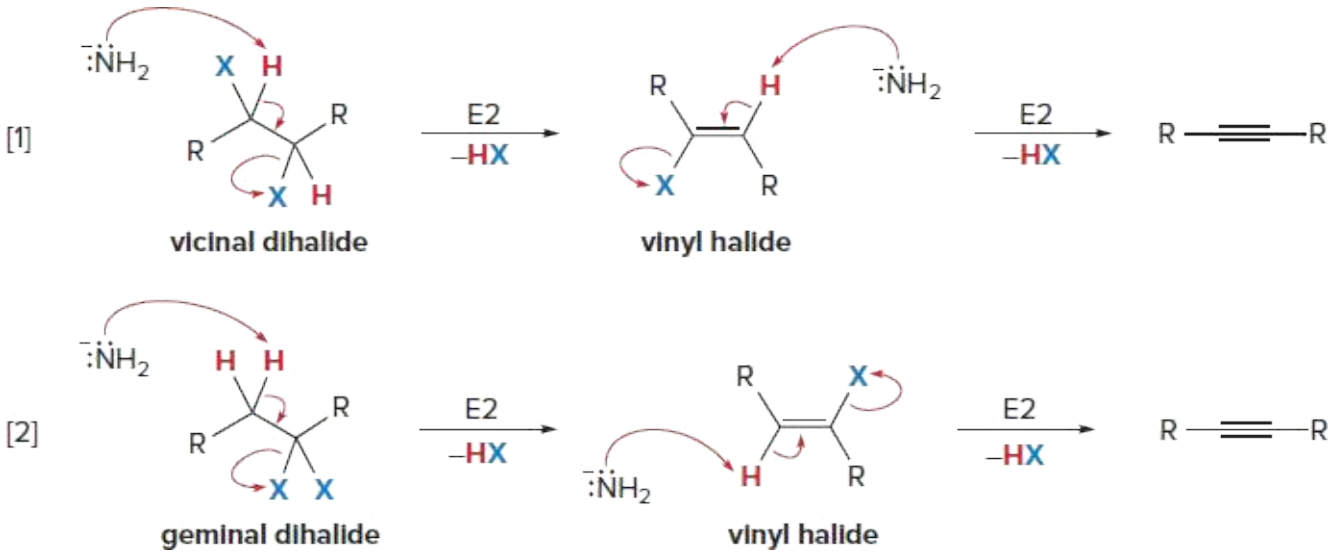
Two elimination reactions are needed to remove two moles of HX from a dihalide as substrate. Two different starting materials can be used.



The word *geminal* comes from the Latin *geminus*, meaning "twin."

- **A vicinal dihalide has two X atoms on *adjacent* carbon atoms.**
- **A geminal dihalide has two X atoms on the *same* carbon atom.**

Equations [1] and [2] illustrate how two moles of HX can be removed from these dihalides with base. Two equivalents of strong base are used and each step follows an E2 mechanism.



The relative strength of C–H bonds depends on the hybridization of the carbon atom: *sp* > sp^2 > sp^3. For more information, review Section 1.11B.

Stronger bases are needed to synthesize alkynes by dehydrohalogenation than are

needed to synthesize alkenes. The typical base is amide ($^{-}NH_2$), used as the sodium salt $NaNH_2$ (sodium amide). $KOC(CH_3)_3$ can also be used with DMSO as solvent. Because DMSO is a polar aprotic solvent, the anionic base is not well solvated, thus increasing its basicity and making it strong enough to remove two equivalents of HX. Examples are given in Figure 8.8.

The strongly basic conditions needed for alkyne synthesis result from the difficulty of removing the second equivalent of HX from the intermediate vinyl halide, RCH=C(R)X. Because H and X are both bonded to sp^2 hybridized carbons, these bonds are shorter and stronger than the sp^3 hybridized C–H and C–X bonds of an alkyl halide, necessitating the use of a stronger base.

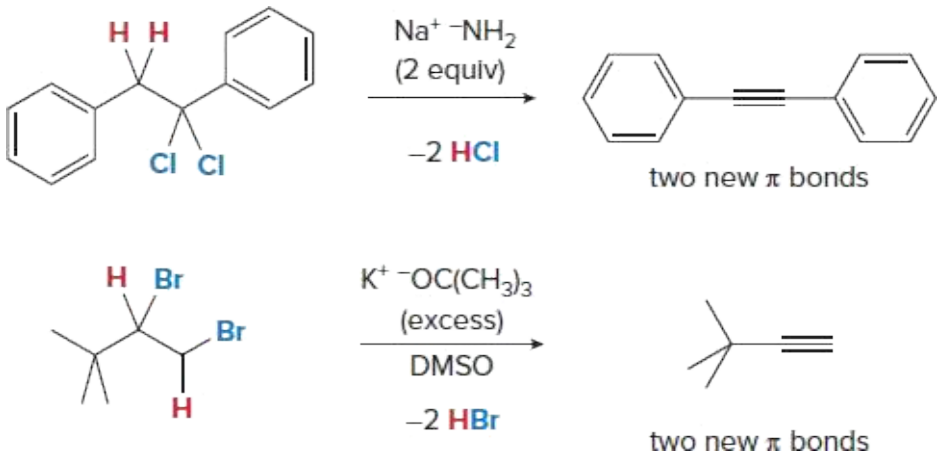
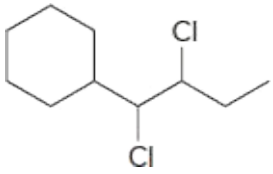


Figure 8.8 **Examples of dehydrohalogenation of dihalides to afford alkynes**

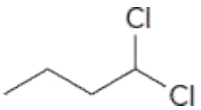
Problem 8.21

Draw the alkynes formed when each dihalide is treated with excess base.

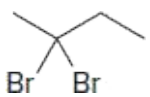
a.



b.



c.



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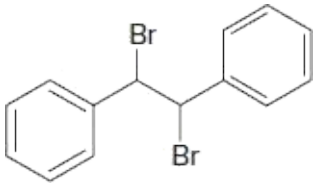


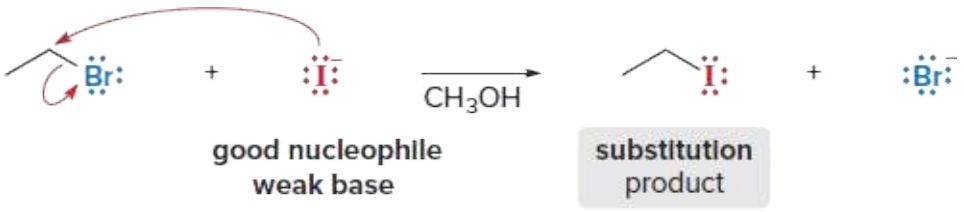
8.11 When Is the Reaction S_N1, S_N2, E1, or E2?

We have now considered two different kinds of reactions (substitution and elimination) and four different mechanisms (S_N1, S_N2, E1, and E2) that begin with one class of compounds (alkyl halides). How do we know if a given alkyl halide will undergo substitution or elimination with a given base or nucleophile, and by what mechanism?

Unfortunately, there is no easy answer, and often mixtures of products result. Two generalizations help to determine whether substitution or elimination occurs.

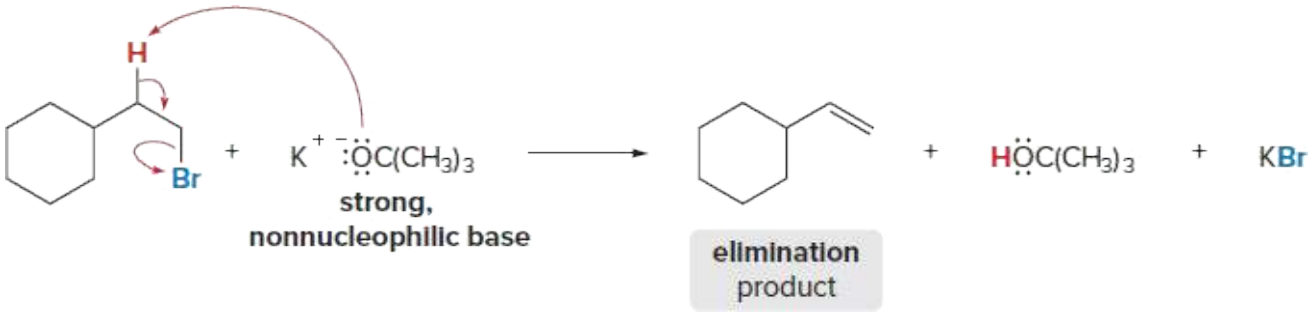
[1] *Good* nucleophiles that are *weak* bases favor *substitution* over elimination.

Certain anions generally give products of substitution because they are good nucleophiles but weak bases. These include I^-, Br^-, HS^-, ^-CN, and $CH_3CO_2^-$.



[2] *Bulky*, nonnucleophilic bases favor *elimination* over substitution.

$KOC(CH_3)_3$, DBU, and DBN are too sterically hindered to attack a tetravalent carbon, but are able to remove a small proton, favoring elimination over substitution.



Most often, however, we will have to rely on other criteria to predict the outcome of these reactions. To determine the product of a reaction with an alkyl halide:

[1] Classify the alkyl halide as 1°, 2°, or 3°.

[2] Classify the base or nucleophile as strong, weak, or bulky.

Predicting the substitution and elimination products of a reaction can then be

organized by the type of alkyl halide, as summarized in Table 8.5. The explanation that follows the table is organized with 2° alkyl halides last, because their reactions can follow any of the four mechanisms and product mixtures often result.

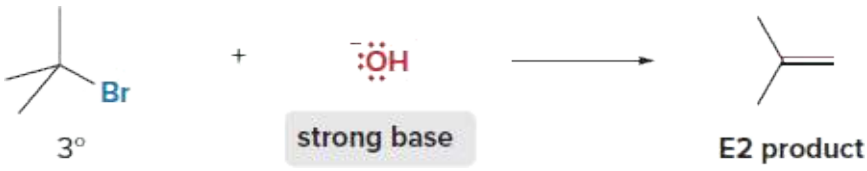
Table 8.5 Summary of Alkyl Halides and S_N1, S_N2, E1, and E2 Mechanisms

Alkyl halide type	Reaction with		Mechanism
1° RCH_2X	• Strong nucleophile • Strong bulky base	⇢ ⇢	S_N2 E2
2° R_2CHX	• Strong base and nucleophile • Strong bulky base • Weak base and nucleophile	⇢ ⇢ ⇢	S_N2 and E2 E2 S_N1 and E1
3° R_3CX	• Weak base and nucleophile • Strong base	⇢ ⇢	S_N1 and E1 E2

8.11A Tertiary Alkyl Halides

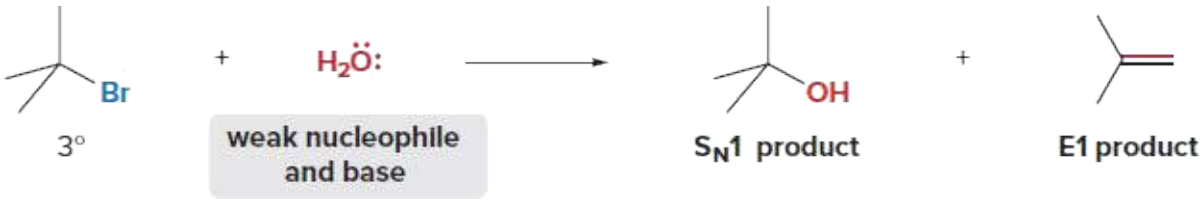
Tertiary alkyl halides react by all mechanisms *except* S_N2.

- **With strong bases, elimination occurs by an E2 mechanism.**



A strong base or nucleophile favors an S_N2 or E2 mechanism, but 3° halides are too sterically hindered to undergo an S_N2 reaction, so only E2 elimination occurs.

- **With weak nucleophiles or bases, a mixture of S_N1 and E1 products results.**



A weak base or nucleophile favors S_N1 and E1 mechanisms and both occur.

8.11B Primary Alkyl Halides

Primary alkyl halides react by S_N2 and E2 mechanisms.

- **With strong nucleophiles, substitution occurs by an S_N2 mechanism.**

A strong base or nucleophile favors S_N2 or E2, but 1° halides are the *least* reactive halide type in elimination, so only S_N2 reaction occurs.

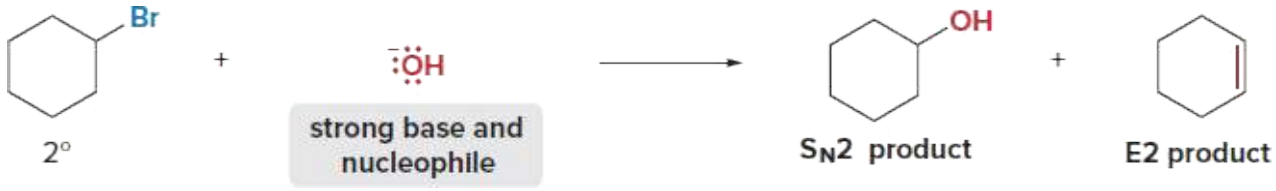
- **With strong, bulky bases, elimination occurs by an E2 mechanism.**

A strong, bulky base cannot act as a nucleophile, so elimination occurs and the mechanism is E2.

8.11C Secondary Alkyl Halides

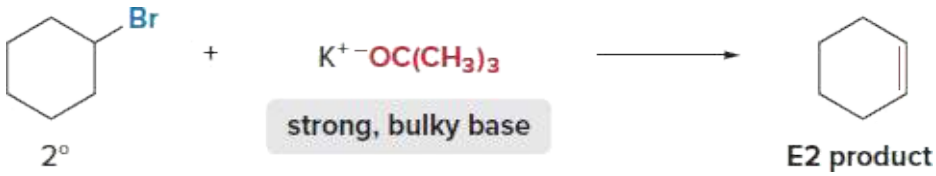
Secondary alkyl halides react by *all* mechanisms.

- **With strong bases and nucleophiles, a mixture of S_N2 and E2 products results.**



A strong base that is also a strong nucleophile gives a mixture of S_N2 and E2 products.

- **With strong, bulky bases, elimination occurs by an E2 mechanism.**



A strong, bulky base cannot act as a nucleophile, so elimination occurs and the mechanism is E2.

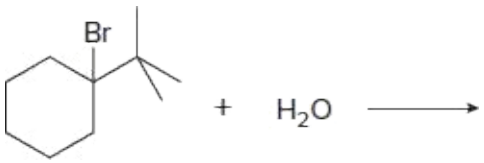
- **With weak nucleophiles or bases, a mixture of S_N1 and E1 products results.**

A weak base or nucleophile favors S_N1 and E1 mechanisms and both occur.

Sample Problems 8.4–8.6 illustrate how to apply the information in Table 8.5 to specific alkyl halides.

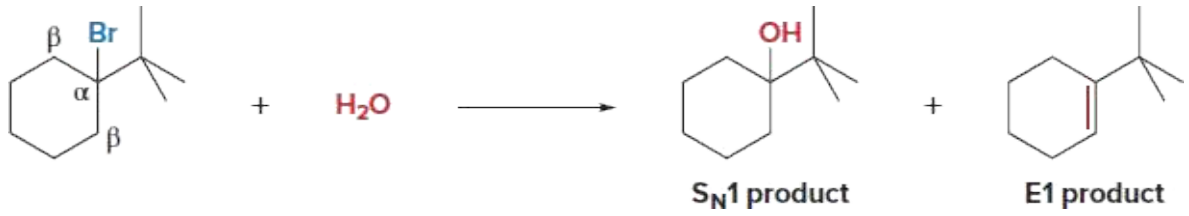
Sample Problem 8.4 Determining the Substitution and Elimination Products rom an Alkyl Halide

Draw the products of the following reaction.



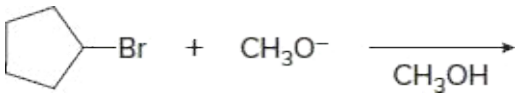
Solution

- **Classify the halide as 1°, 2°, or 3° and the reagent as a strong or weak base (and nucleophile) to determine the mechanism. In this case, the alkyl halide is 3° and the reagent (H_2O) is a weak base and nucleophile, so products of both S_N1 and E1 mechanisms are formed.**
- **To draw the S_N1 product, substitute the nucleophile (H_2O) for the leaving group (Br^-), and draw the neutral product after loss of a proton.**
- **To draw the E1 product, remove the elements of H and Br from the α and β carbons. There are two identical β C atoms with H atoms, so only one elimination product is possible.**



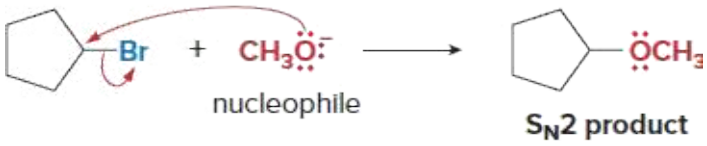
Sample Problem 8.5 Drawing Substitution and Elimination Products from a 2° Alkyl Halide

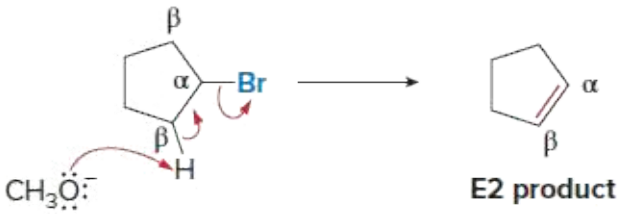
Draw the products of the following reaction.



Solution

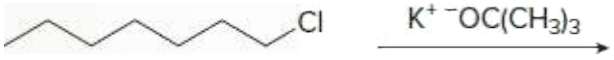
- **Classify the halide as 1°, 2°, or 3° and the reagent as a strong or weak base (and nucleophile) to determine the mechanism. In this case, the alkyl halide is 2° and the reagent (CH_3O^-) is a strong base and nucleophile, so products of both S_N2 and E2 mechanisms are formed.**
- **To draw the S_N2 product, substitute the nucleophile (CH_3O^-) for the leaving group (Br^-).**
- **To draw the E2 product, remove the elements of H and Br from the α and β carbons. There are two identical β C atoms with H atoms, so only one elimination product is possible.**

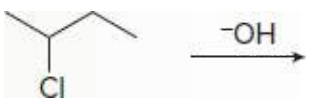


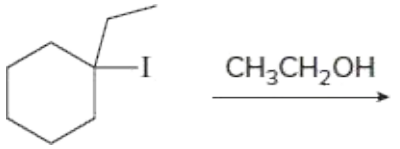


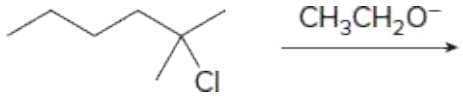
Problem 8.22

Draw the products in each reaction.

a. 

b. 

c. 

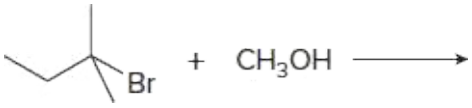
d. 

More Practice:

Try Problems 8.52, 8.54, 8.55, 8.58, 8.60.

Sample Problem 8.6 Drawing the Mechanism When a Reaction Involves Both Substitution and Elimination

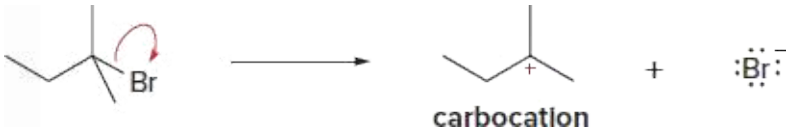
Draw the products of the following reaction, and include the mechanism showing how each product is formed.



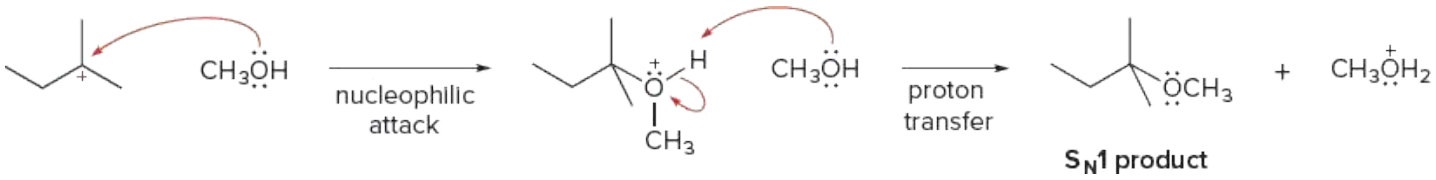
Solution

[1] Classify the halide as 1°, 2°, or 3° and the reagent as a strong or weak base (and nucleophile) to determine the mechanism. In this case, the alkyl halide is 3° and the reagent (CH_3OH) is a weak base and nucleophile, so products of both S_N1 and E1 mechanisms are formed.

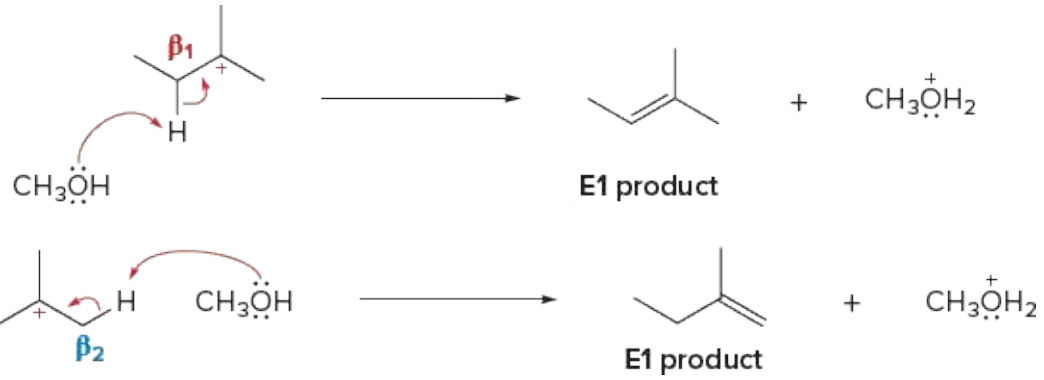
[2] Draw the steps of the mechanisms to give the products. Both mechanisms begin with the same first step: loss of the leaving group to form a carbocation.



- **For S_N1: The carbocation reacts with a nucleophile. Nucleophilic attack of CH_3OH on the carbocation generates a positively charged intermediate that loses a proton to afford the neutral S_N1 product.**



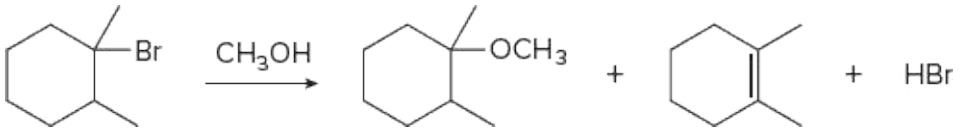
- **For E1: A base (CH_3OH or Br^-) removes a proton from the carbocation. Two different products of elimination can form because the carbocation has two different β carbons.**



In this problem, three products are formed: one from an S_N1 reaction and two from E1 reactions.

Problem 8.23

Draw a stepwise mechanism for the following reaction.



More Practice:

Try Problems 8.57, 8.59.

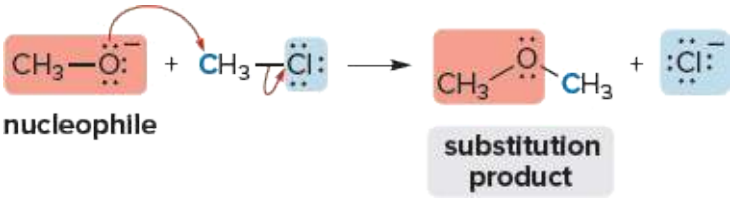
Chapter 8 REVIEW

KEY CONCEPTS

[1] Nucleophilic substitution versus β elimination

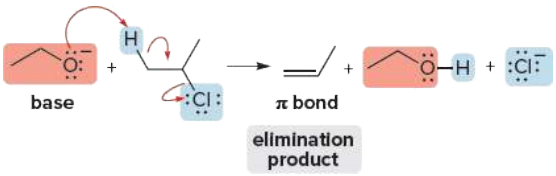
1 Nucleophilic substitution (7.6)

- A nucleophile attacks a carbon atom.



2 β Elimination (8.1)

- A Brønsted–Lowry base removes a proton to form bond.



- R —Cl acts as an electrophile, reacting with an electron-rich reagent.
- A good leaving group Cl^- accepts the electron density in the C–Cl bond.

Try Problem 8.27.

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[2] Nucleophiles and bases in S_N1, S_N2, E1, and E2 reactions (8.11)

1 Nucleophiles that are weak bases

^-SH Br^-

^-CN I^-

$CH_3CO_2^-$

- Substitution is favored over elimination.

2 Strong, bulky bases

$^-OC(CH_3)_3$

DBU

DBN

- E2 elimination is favored over substitution.

3 Strong nucleophiles and strong bases

^-OH

^-OR

- S_N2 and E2 mechanisms are favored.

4 Weak nucleopl and wea bases

H_2O

ROH

- S_N1 and mechani are favo

Try Problems 8.58, 8.60.

KEY SKILLS

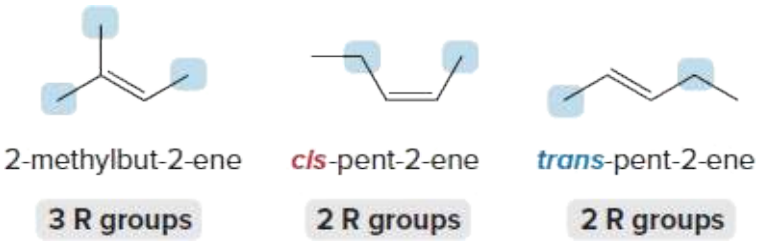
[1] Comparing the stability of alkenes (8.2)

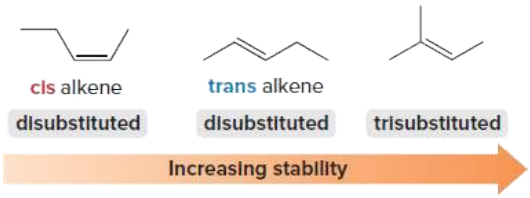
1 Classify alkenes by the number of R

2 Arrange alkenes from lea

groups bonded to the C=C. With 2 R groups on the C=C, classify the alkene as cis or trans.

to most stable.

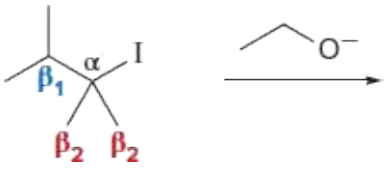
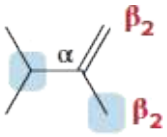
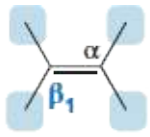




- The stability of an alkene increases as the number of R groups bonded to the double bond carbons increases.
- Trans alkenes are generally more stable than cis alkenes.

Try Problems 8.24, 8.31.

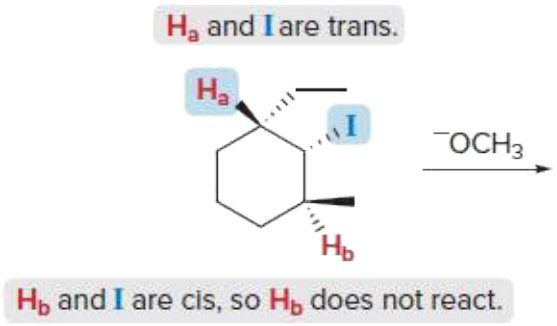
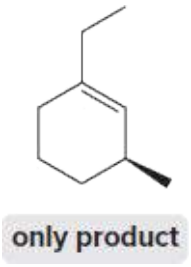
[2] Drawing all products and predicting the major product of an elimination reaction (8.5)

1 Identify the α and β carbon atoms.	2 Remove H–I to give the less substituted product.	3 Remove H–I to give the more substituted product.
	 disubstituted • I is removed from the α carbon. • H is removed from one of the two equivalent β_2 carbons.	 tetrasubstituted major product • I is removed from the α carbon. • H is removed from the β_1 carbon.

		• R groups stabilize the transition states of elimination reactions, so the more substituted product is favored.

See Sample Problem 8.1. Try Problems 8.33, 8.37.

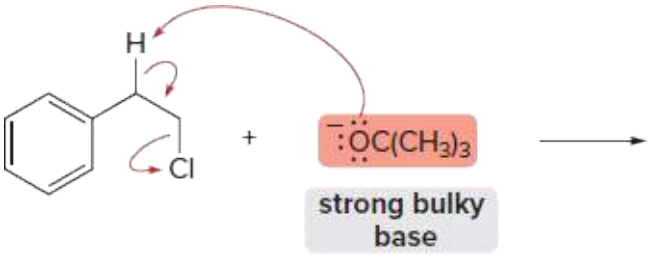
[3] Drawing the product of an E2 reaction of a halocyclohexane when loss of HX must be anti periplanar (8.8B)

1 Identify the C–H bond(s) that are trans to the C–I bond.	2 Remove H–I to give the product.
	
• Elimination can occur only when the leaving group I^- and a H atom on the β carbon are trans and the C–I bond and C–H bond are anti periplanar.	• H_a is removed to give a single E2 reaction product.

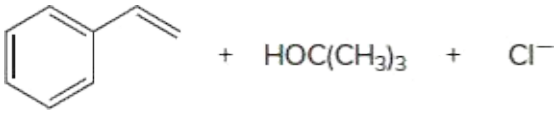
See Figure 8.7, Sample Problem 8.3. Try Problems 8.25, 8.42, 8.43, 8.45.

[4] Deciding if a β elimination reaction proceeds by an E1 or E2 mechanism (8.9)

1 Determine whether the base is strong, weak, or bulky.	2 Draw the product(s).



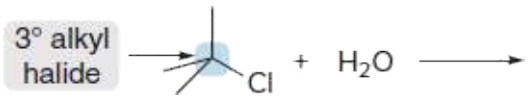
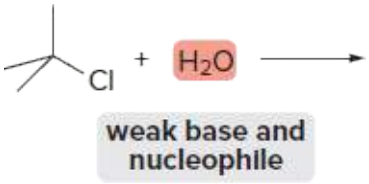
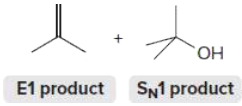
- **Strong *bulky* bases favor E2 reactions.**



- **Answer: β Elimination occurs via an E2 mechanism.**

See Table 8.4. Try Problem 8.39.

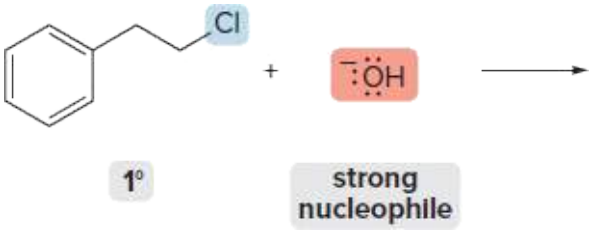
[5] Deciding if a reaction proceeds by S_N1, S_N2, E1, or E2 (8.11)

1 Classify the R–Cl.	**2** Classify the base/nucleophile as strong, weak, or bulky.	**3** Use Table 8.5 to draw the product(s)
		
• **3° Alkyl halides may react by an S_N1, E1, or E2 mechanism.**	• **Weak bases and nucleophiles favor the S_N1 and E1 mechanisms.**	• **A mixture of products forms.**

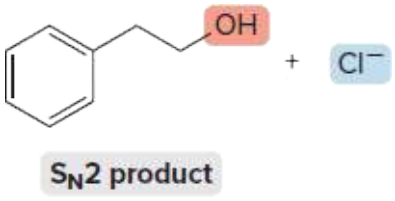
Try Problems 8.52, 8.54, 8.55.

[6] Drawing the product(s) of a reaction with a 1° alkyl halide (8.11B)

1 Classify the base/nucleophile as strong, weak, or bulky.	**2** Draw the product(s).



- With a 1° alkyl halide, $^-$OH acts as a strong nucleophile.



- When strong nucleophiles react with 1° alkyl halides, S_N2 products result.

Try Problem 8.52a, b, d.

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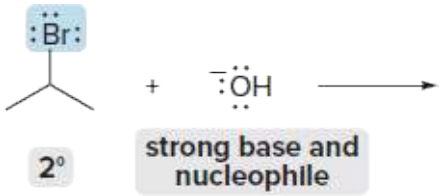
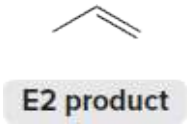
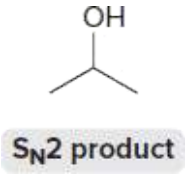
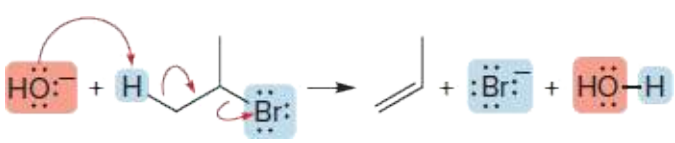
[7] Drawing the product(s) of a reaction with a 2° alkyl halide (8.11C)

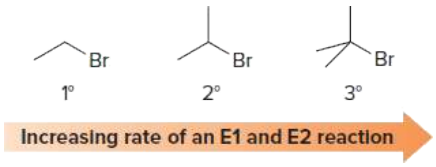
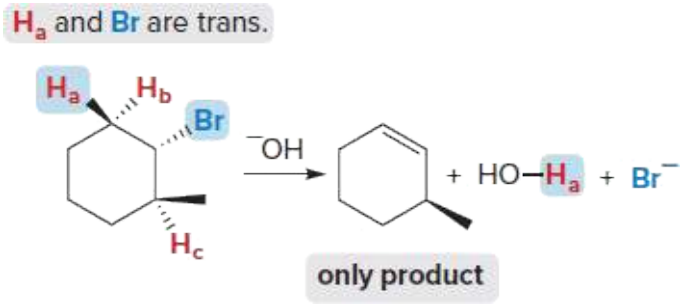
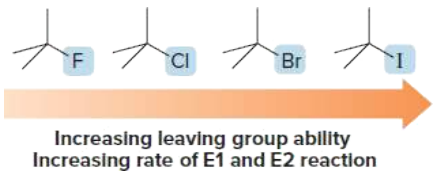
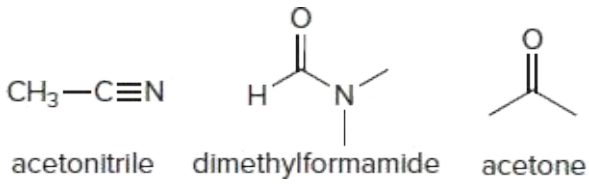
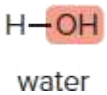
1 Classify the base/nucleophile as strong, weak, or bulky.	2 Draw the elimination product(s).	3 Draw the substitution product(s).
		
• With a 2° alkyl halide, $^-$OH acts as a strong base and nucleophile.	• When strong bases and nucleophiles react with 2° alkyl halides, a mixture of E2 and S_N2 products results.	

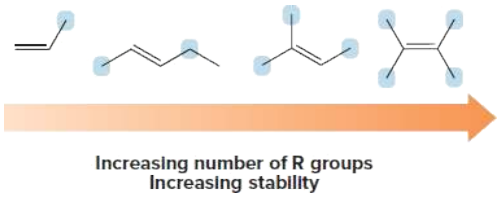
See Sample Problem 8.5. Try Problems 8.52e; 8.54a, b, d, e, g, h.

KEY MECHANISM CONCEPTS

[1] Comparison of E1 and E2 reactions

	E2 mechanism (Table 8.2)	E1 mec
1 Mechanism	• one step (8.4B) 	• two

2 Rate equation	• rate = *k*[RBr][B:] • second-order kinetics (8.4A)	• rat • firs
3 Alkyl halide	• order of reactivity (8.4C, 8.6C)  • E1 reactions are faster when more-stable carboc	
4 Stereochemistry	• anti periplanar arrangement of trans H and Br (8.8)  	• trig inte
5 Base	• favored by stronger bases (8.4B) $^-NH_2$ ^-OR ^-OH	• fav (8.6
6 Leaving group Page 338	• better leaving group ⇢ faster reaction (8.4B)  	
7 Solvent	• favored by polar aprotic solvents (8.4B)  	• fav sol 

8 Product	• More substituted alkene favored in E2 and E1 rea 8.6C) 

Try Problems 8.35, 8.55–8.57, 8.59.

[2] Summary of S_N1, S_N2, E1, and E2 reactions (8.11)

Alkyl halide type	Reaction with	Mechanism
1 1° RCH_2X	• strong nucleophile ⇢ • strong *bulky* base ⇢	S_N2 E2
2 2° R_2CHX	• strong base and nucleophile ⇢ • strong *bulky* base ⇢ • weak base and nucleophile ⇢	S_N2 + E2 E2 S_N1 + E1
3 3° R_3CX	• weak base and nucleophile ⇢ • strong base ⇢	S_N1 + E1 E2

PROBLEMS

Problems Using Three-Dimensional Models

8.24 Rank the alkenes shown in the ball-and-stick models (A–C) in order of increasing stability.

A

B

C

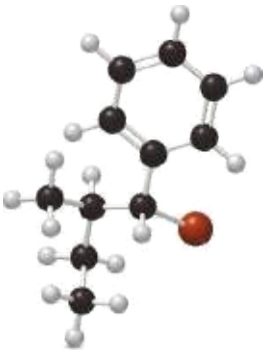
8.25 **Name each compound and decide which stereoisomer will react faster in an E2 elimination reaction. Explain your choice.**

D

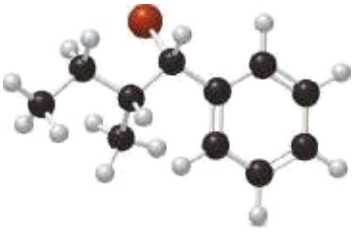
E

8.26 **What is the major E2 elimination product formed from each alkyl halide?**

a.



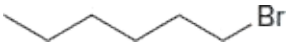
b.



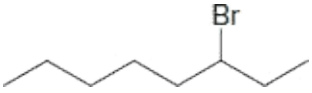
General Elimination

8.27 **Draw all possible constitutional isomers formed by dehydrohalogenation of each alkyl halide.**

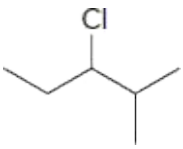
a.

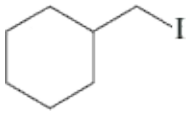


b.

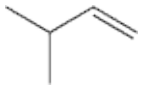


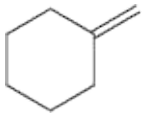
c.

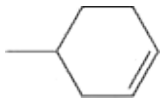


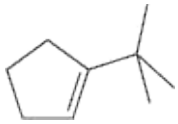
d. 

8.28 **What alkyl halide forms each of the following alkenes as the *only* product in an elimination reaction?**

a. 

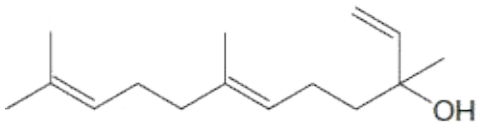
b. 

c. 

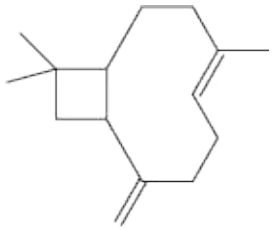
d. 

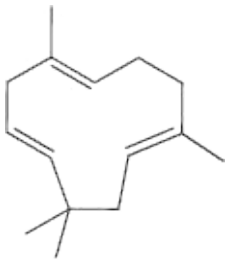
Alkenes

8.29 **Which double bonds in the following natural products can exhibit stereoisomerism? Nerolidol is isolated from the angel's trumpet plant, caryophyllene is present in hemp, and humulene comes from hops.**

a. 

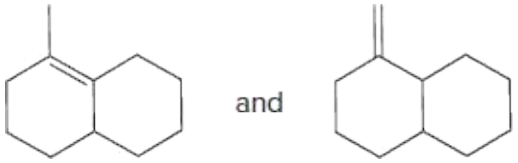
nerolidol

b. 
caryophyllene

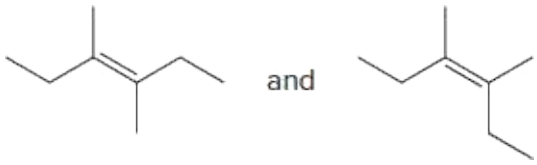
c. 
humulene

8.30 **Label each pair of alkenes as constitutional isomers, stereoisomers, or identical.**

a.

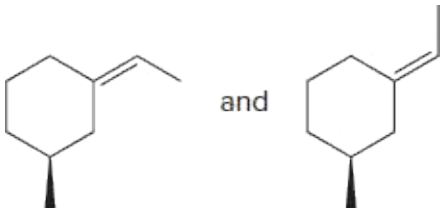


b.

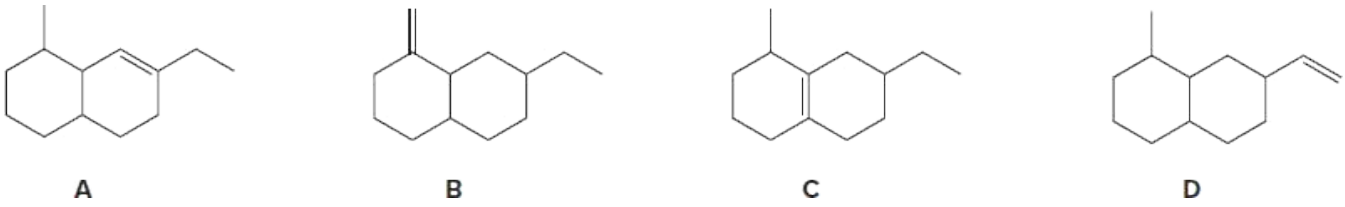


c.

d.



8.31 Rank the following alkenes in order of increasing stability.



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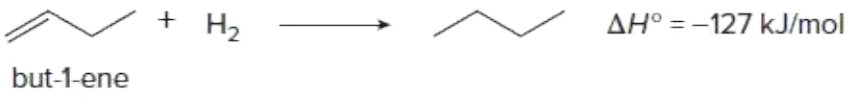
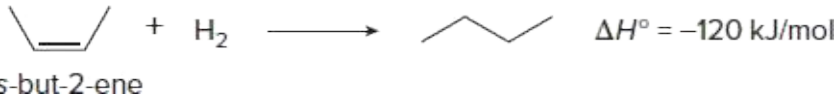
8.32 Δ*H*° values obtained for a series of similar reactions are one set of experimental data used to determine the relative stability of alkenes. Explain how the following data suggest that *cis*-but-2-ene is more stable than but-1-ene (Section 12.3A).



but-1-ene

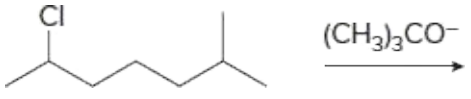


cis-but-2-ene

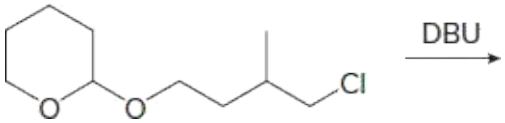
E2 Reaction

8.33 Draw all constitutional isomers formed in each E2 reaction, and predict the major product using the Zaitsev rule.

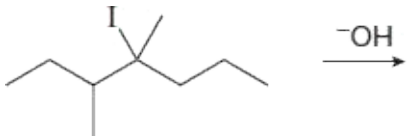
a.



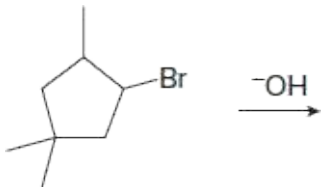
b.



c.

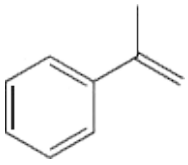


d.

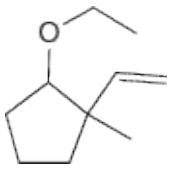


8.34 For each of the following alkenes, draw the structure of two different alkyl halides that yield the given alkene as the only product of dehydrohalogenation.

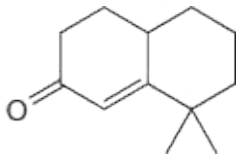
a.



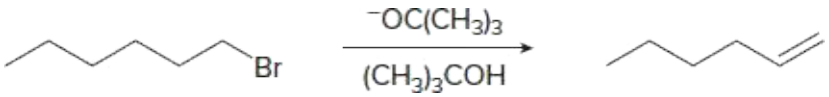
b.



c.



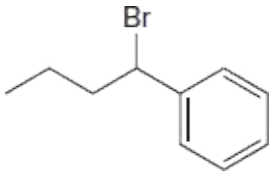
8.35 Consider the following E2 reaction.

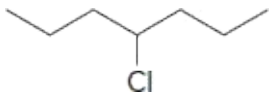


a. Draw the by-products of the reaction and use curved arrows to show the movement of electrons.

b. What happens to the reaction rate with each of the following changes? [1] The solvent is changed to DMF. [2] The concentration of $^{-}OC(CH_3)_3$ is decreased. [3] The base is changed to ^{-}OH. [4] The halide is changed to $CH_3CH_2CH_2CH_2CH(Br)CH_3$. [5] The leaving group is changed to I^{-}.

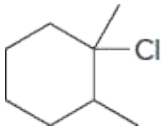
8.36 What is the major stereoisomer formed when each alkyl halide is treated with $KOC(CH_3)_3$?

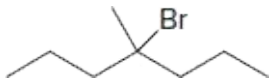
a. 

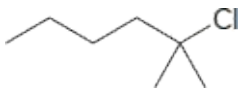
b. 

E1 Reaction

8.37 What alkene is the major product formed from each alkyl halide in an E1 reaction?

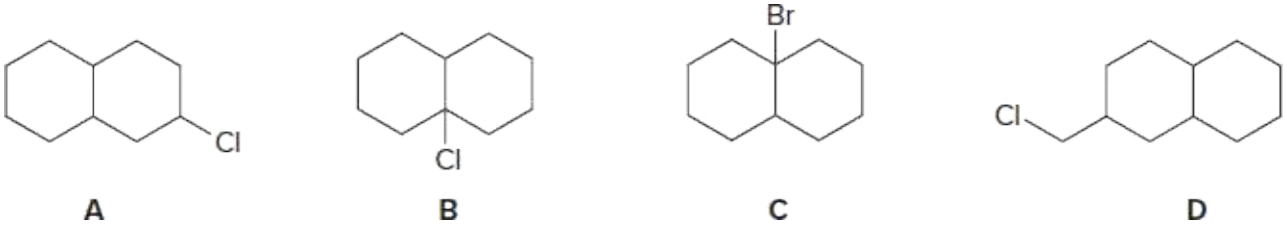
a. 

b. 

c. 

E1 and E2

8.38 Rank the following alkyl halides in order of increasing reactivity in E2 elimination. Then do the same for E1 elimination.

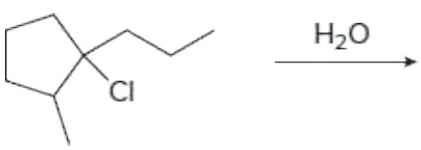


8.39 Draw all constitutional isomers formed in each elimination reaction. Label the mechanism as E2 or E1.

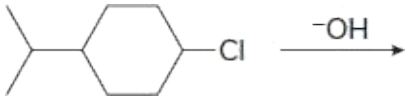
a.

b.

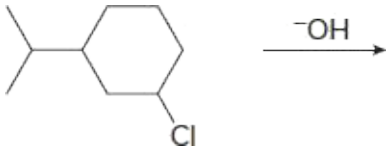
c.

d. 

e.



f.

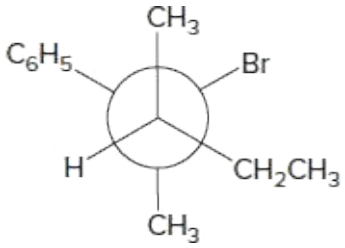


8.40 **In the dehydrohalogenation of bromocyclodecane, the major product is *cis*-cyclodecene rather than *trans*-cyclodecene. Offer an explanation.**

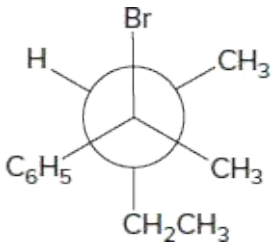
Stereochemistry and the E2 Reaction

8.41 **What is the major E2 elimination product formed from each halide?**

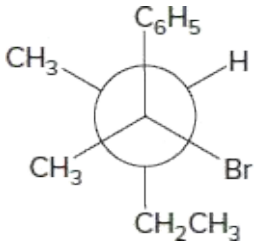
a.



b.

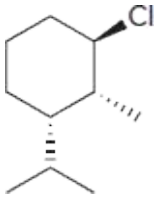


c.

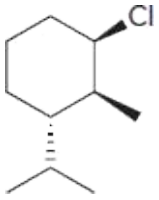


8.42 **Taking into account anti periplanar geometry, predict the major E2 product formed from each starting material.**

a.



b.



8.43 **Does *cis*- or *trans*-1-bromo-4-*tert*-butylcylohexane react faster in an E2 reaction?**

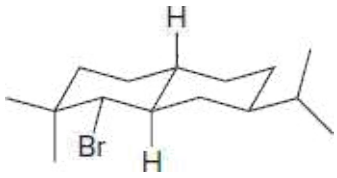
8.44 **a. Draw three-dimensional representations for all stereoisomers of 2-chloro-3-methylpentane, and label pairs of enantiomers.**

b. Considering dehydrohalogenation across only C2 and C3, draw the E2 product that results from each of these alkyl halides. How many different products have you drawn?

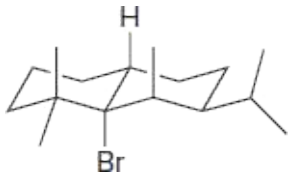
c. How are these products related to each other?

8.45 **Which of the following compounds undergoes E2 elimination with strong base? For compounds that undergo elimination, draw the product. For compounds that do not undergo elimination, explain why they are unreactive.**

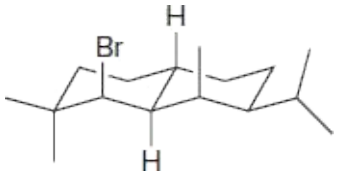
a.



b.

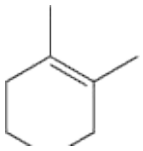


c.

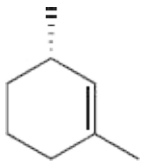


8.46 **Draw the structure (including stereochemistry) of an alkyl chloride that forms each alkene as the exclusive E2 elimination product.**

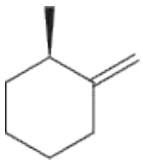
a.



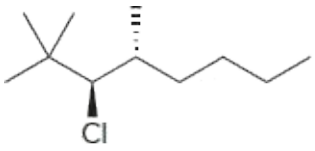
b.



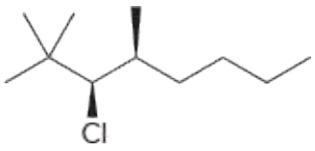
c.



8.47 **Draw the major stereoisomer formed when each compound is treated with NaOH.**



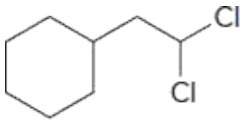
A

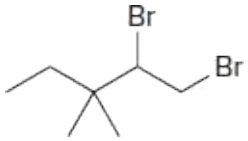


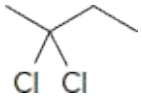
B

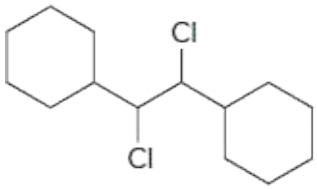
Alkynes

8.48 **Draw the products formed when each dihalide is treated with excess $NaNH_2$.**

a. 

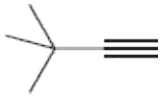
b. 

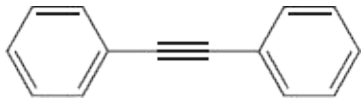
c. 

d. 

8.49 **Draw the structure of a dihalide that could be used to prepare each alkyne. There may be more than one possible dihalide.**

a.

b. 

c. 

8.50 **Under certain reaction conditions, 2,3-dibromobutane reacts with two equivalents of base to give three products, each of which contains two new π bonds. Product A has two *sp* hybridized carbon atoms, product B has one *sp* hybridized carbon atom, and product C has none. What are the structures of A, B, and C?**

S_N1, S_N2, E1, and E2 Mechanisms

8.51 **For which reaction mechanisms—S_N1, S_N2, E1, or E2—are each of the following statements true? A statement may be true for one or more mechanisms.**

a. The mechanism involves carbocation intermediates.

b. The mechanism has two steps.

c. The reaction rate increases with better leaving groups.

d. The reaction rate increases when the solvent is changed from CH_3OH to $(CH_3)_2SO$.

e. The reaction rate depends on the concentration of only the alkyl halide.

f. The mechanism is concerted.

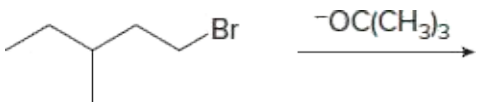
g. The reaction of CH_3CH_2Br with NaOH occurs by this mechanism.

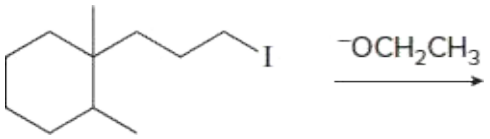
h. Racemization at a stereogenic center occurs.

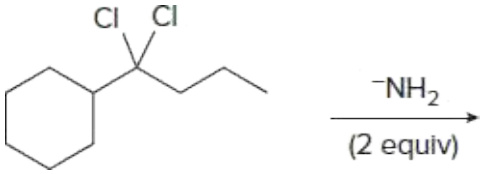
i. Tertiary (3°) alkyl halides react faster than 2° or 1° alkyl halides.

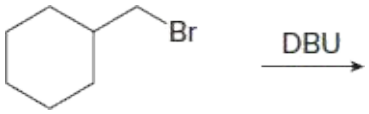
j. The reaction follows a second-order rate equation.

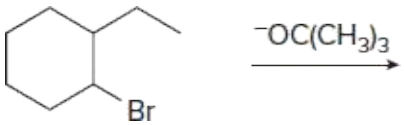
8.52 Draw the organic products formed in each reaction.

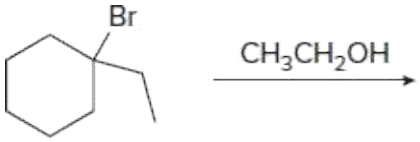
a. 

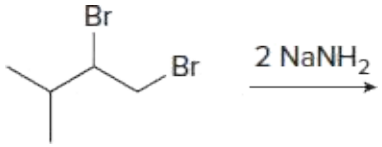
b. 

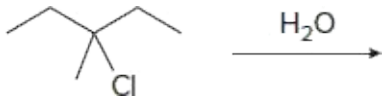
c. 

d. 

e. 

f. 

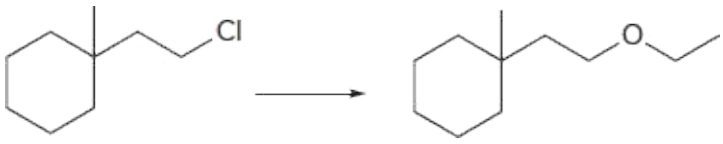
g. 

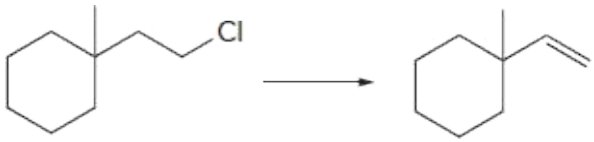
h. 

8.53 What reagents and reaction conditions are needed for each of the following conversions?

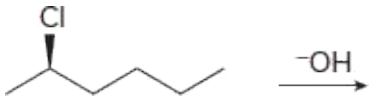
a.

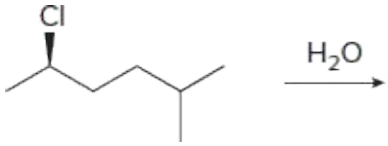
b.

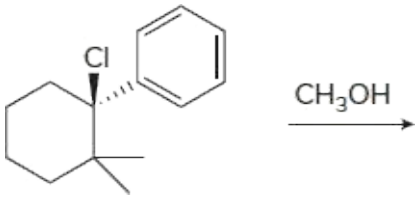
c. 

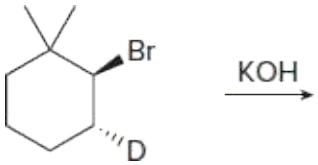
d. 

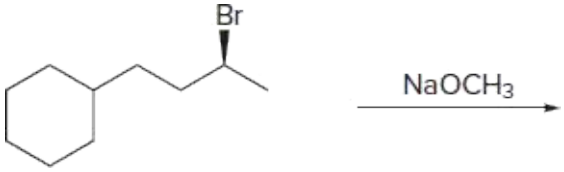
8.54 Draw all products, including stereoisomers, in each reaction.

a. 

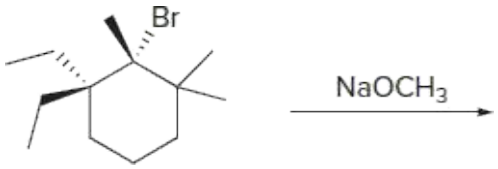
b. 

c. 

d. 

e. 

f.



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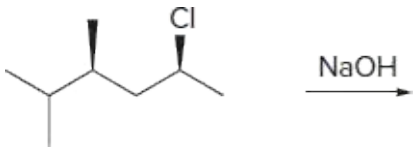

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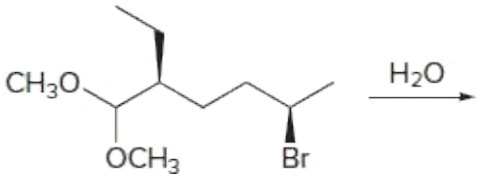
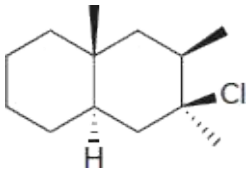
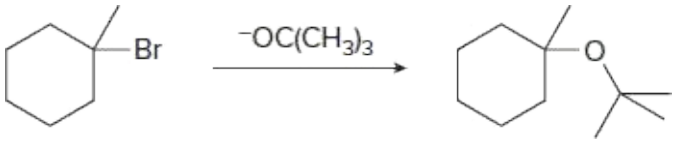


8.55 Draw all of the substitution and elimination products formed from the given alkyl halide with each reagent: (a) CH_3OH; (b) KOH. Indicate the stereochemistry around the stereogenic centers present in the products, as well as the mechanism by which each product is formed.

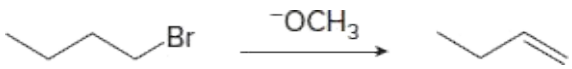


8.56 The following reactions do not afford the major product that is given. Explain why this is so, and draw the structure of the major product actually formed.

a.



b.



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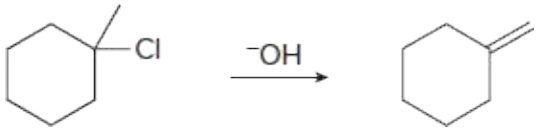
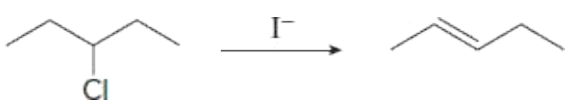
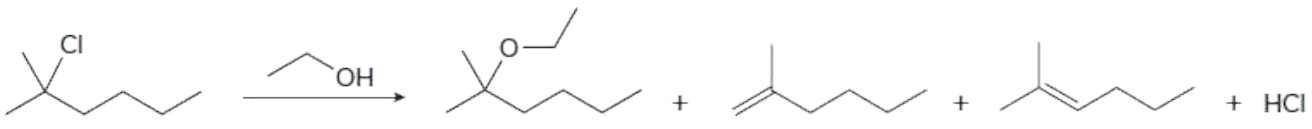


d.

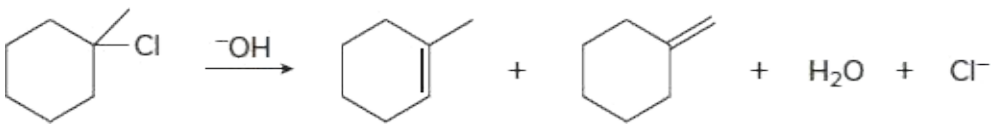


8.57 Draw a stepwise, detailed mechanism for each reaction.

a.

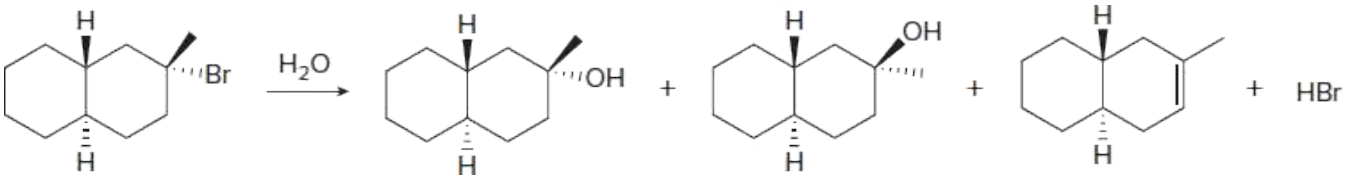


b.



8.58 Draw the major product formed when (*R*)-1-chloro-3-methylpentane is treated with each reagent: (a) $NaOCH_2CH_3$; (b) KCN; (c) DBU.

8.59 Draw a stepwise, detailed mechanism for the following reaction.



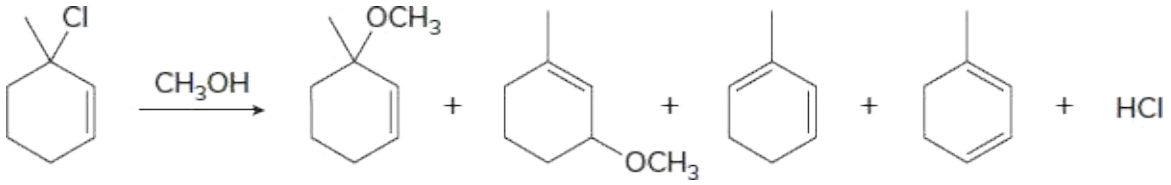
8.60 Explain why the reaction of 2-bromopropane with $NaOCOCH_3$ gives $(CH_3)_2CHOCOCH_3$ exclusively as product, but the reaction of 2-bromopropane with $NaOCH_2CH_3$ gives a mixture of $(CH_3)_2CHOCH_2CH_3$ (20%) and $CH_3CH{=}CH_2$ (80%).

Challenge Problems

8.61 Explain why alkene A is more stable than alkene B, even though B contains more carbon atoms bonded to the double bond. Would you expect C to be more or less stable than A and B?

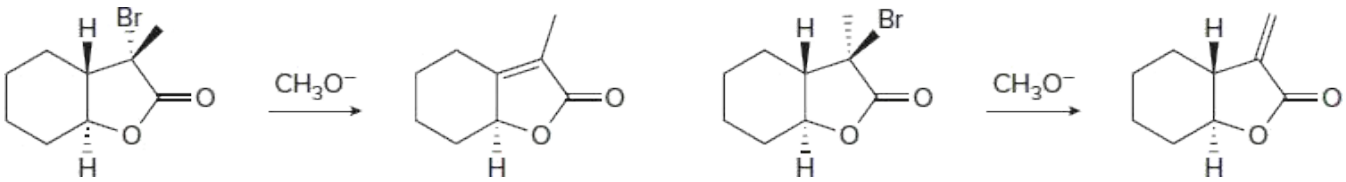
A B C

8.62 Draw a stepwise detailed mechanism that illustrates how four organic products are formed in the following reaction.



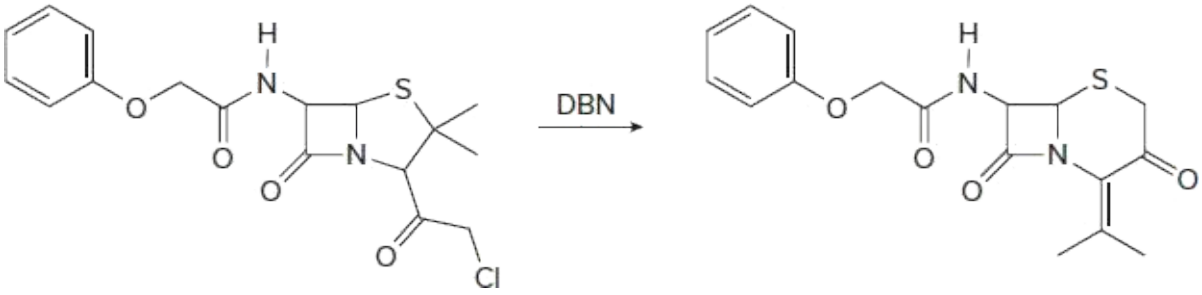
8.63 Although there are nine stereoisomers of 1,2,3,4,5,6-hexachlorocyclohexane, one stereoisomer reacts 7000 times more slowly than any of the others in an E2 elimination. Draw the structure of this isomer and explain why this is so.

8.64 Explain the selectivity observed in the following reactions.



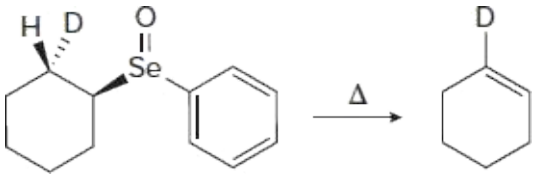
8.65 Draw a stepwise mechanism for the following reaction. The four-membered ring in the starting material and product is called a β-lactam. This functional group confers biological activity on penicillin and many

related antibiotics, as is discussed in Chapter 20. (Hint: The mechanism begins with β elimination and involves only two steps.)

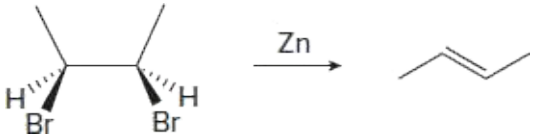


8.66 Although dehydrohalogenation occurs with anti periplanar geometry, some eliminations have syn periplanar geometry. Examine the starting material and product of each elimination, and state whether the elimination occurs with syn or anti periplanar geometry.

a.

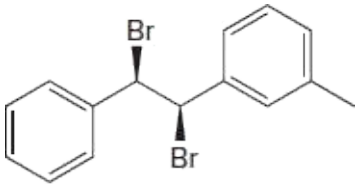


b.



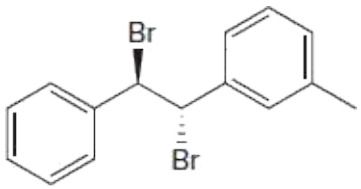
8.67 (a) Draw all products formed by treatment of each dibromide (A and B) with one equivalent of $NaNH_2$. (b) Label pairs of diastereomers and constitutional isomers.

a.



A

b.



B

9

Alcohols, Ethers, and Related Compounds

©Daniel C. Smith

9.1 Introduction

9.2 Structure and bonding

9.3 Nomenclature

9.4 Properties of alcohols, ethers, and epoxides

9.5 Interesting alcohols, ethers, and epoxides

9.6 Preparation of alcohols, ethers, and epoxides

9.7 General features—Reactions of alcohols, ethers, and epoxides

9.8 Dehydration of alcohols to alkenes

9.9 Carbocation rearrangements

9.10 Dehydration using $POCl_3$ and pyridine

9.11 Conversion of alcohols to alkyl halides with HX

9.12 Conversion of alcohols to alkyl halides with $SOCl_2$ and PBr_3

9.13 Tosylate—Another good leaving group

9.14 Reaction of ethers with strong acid

9.15 Thiols and sulfides

9.16 Reactions of epoxides

9.17 Application: Epoxides, leukotrienes, and asthma

9.18 Application: Benzo[*a*]-pyrene, epoxides, and cancer

Linalool is a 10-carbon alcohol found in a wide variety of scented herbs, laurels, and citrus fruits. The *R* enantiomer is one of the two main components of lavender oil, whereas the *S* enantiomer is found in coriander and sweet orange flowers. Because of its pleasant odor, linalool is used commercially in scented soaps and lotions, and as an insecticide for controlling fleas and cockroaches. In Chapter 9, we learn about alcohols like linalool, as well as related oxygen- and sulfur-containing functional groups.

Why Study…

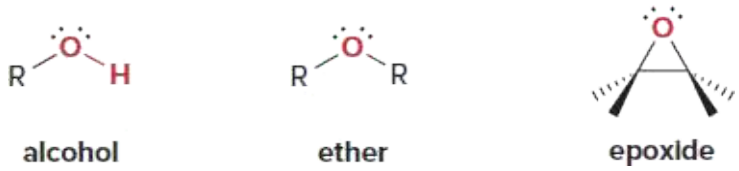
Alcohols, Ethers, Epoxides, Thiols, and Sulfides?

In **Chapter 9**, we take the principles learned in Chapters 7 and 8 about leaving groups, nucleophiles, and bases, and apply them to alcohols, ethers, and epoxides, three new functional groups that contain polar C—O bonds. The hydroxy group (OH) of an alcohol is especially common in many natural products, and the reactions of alcohols are widely used in organic synthesis. In Chapter 9, you will discover that all of the reactions follow one of the four mechanisms introduced in Chapters 7 and 8—S_N1, S_N2, E1, or E2—so there are no new general mechanisms to learn.

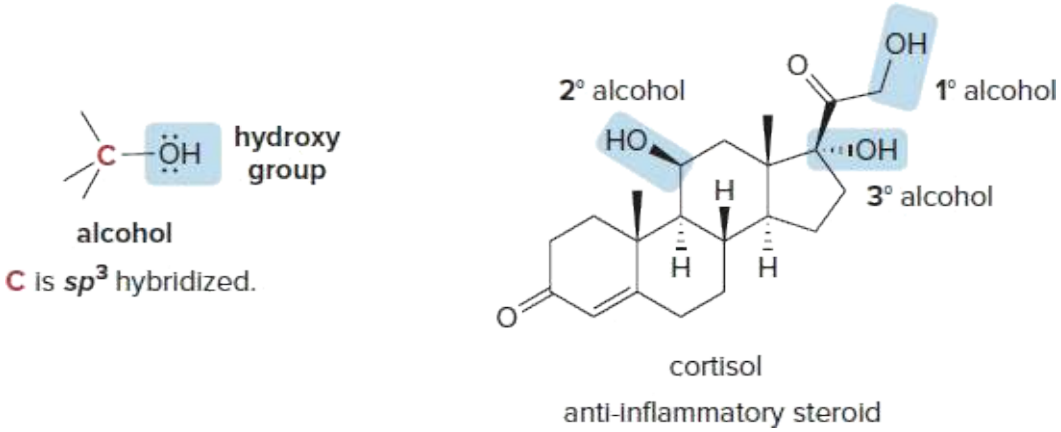
Later in the chapter, we will also examine thiols (RSH) and sulfides (R_2S), sulfur analogues of alcohols and ethers, respectively. These functional groups play a key role in the chemistry of biomolecules, especially the proteins discussed in Chapter 27.

9.1 Introduction

Alcohols, ethers, and epoxides are three functional groups that contain carbon–oxygen σ bonds.



Alcohols contain a hydroxy group (OH group) bonded to an sp^3 hybridized carbon atom. As we learned in Section 3.2, alcohols are classified as primary (1°), secondary (2°), or tertiary (3°) based on the number of carbon atoms bonded to the carbon with the OH group.



Compounds having a hydroxy group on an sp^2 hybridized carbon atom—enols and phenols—undergo different reactions than alcohols and are discussed in Chapters 11 and 19, respectively. Enols have an OH group on a carbon of a C—C double bond.

Phenols have an OH group on a benzene ring.

enol **phenol**

- C bonded to OH is sp^2 hybridized.

Ethers have two alkyl groups bonded to an oxygen atom. An ether is symmetrical if the two alkyl groups are the same, and unsymmetrical if they are different. Both alcohols and ethers are organic derivatives of H2O, formed by replacing one or both of the hydrogens on the oxygen atom by R groups, respectively.

ether

symmetrical ether
identical R groups

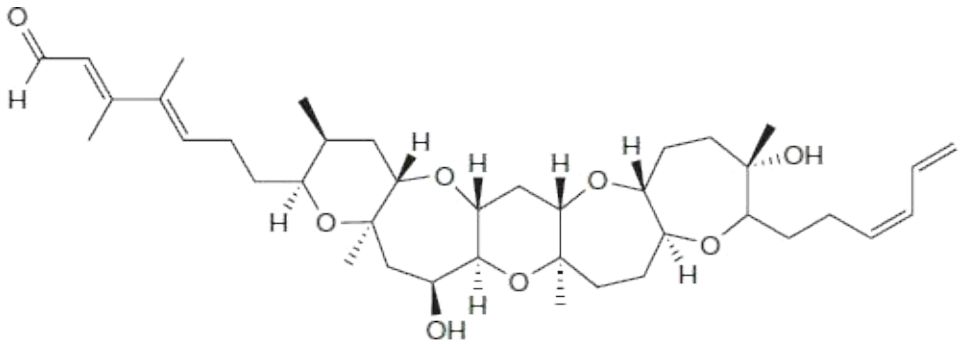
unsymmetrical ether
different R groups

Epoxides are ethers having the oxygen atom in a three-membered ring. Page 347 Epoxides are also called oxiranes.

epoxide or **oxirane**

Problem 9.1

Label each ether and alcohol in brevenal, a marine natural product. Classify each alcohol as 1°, 2°, or 3°.

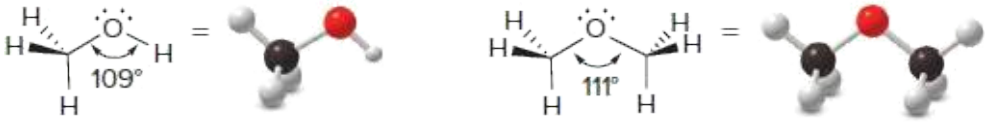


brevenal

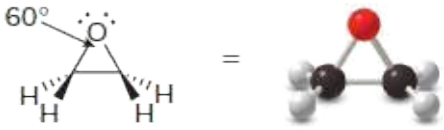
Brevenal (Problem 9.1) is a nontoxic marine polyether produced by *Karenia brevis*, a single-celled organism that proliferates during red tides, vast algal blooms that turn the ocean water red, brown, or green. ***©Purestock/Alamy Stock Photo***

9.2 Structure and Bonding

Alcohols, ethers, and epoxides each contain an oxygen atom surrounded by two atoms and two nonbonded electron pairs, making the O atom tetrahedral and sp^3 hybridized. Because only two of the four groups around O are atoms, alcohols and ethers have a bent shape like H_2O.

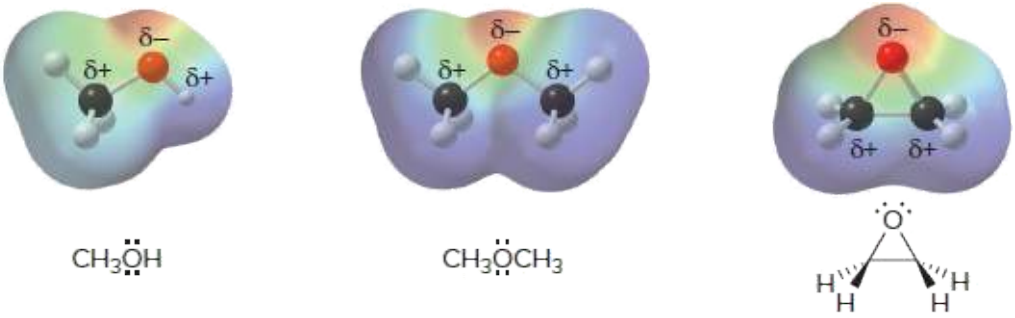


The bond angle around the O atom in an alcohol or ether is similar to the tetrahedral bond angle of 109.5°. In contrast, the C—O—C bond angle of an epoxide must be 60°, a considerable deviation from the tetrahedral bond angle. For this reason, epoxides have angle strain, making them much more reactive than other ethers.



a strained, three-membered ring

Because oxygen is much more electronegative than carbon or hydrogen, the C—O and O—H bonds are all polar, with the O atom electron rich and the C and H atoms electron poor. The electrostatic potential maps in Figure 9.1 show these polar bonds for all three functional groups.



$CH_3\ddot{O}H$ $CH_3\ddot{O}CH_3$

- Electron-rich regions are shown by the red around the O atoms.

Figure 9.1 **Electrostatic potential maps for a simple alcohol, ether, and epoxide**

9.3 Nomenclature

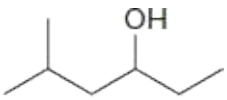
To name an alcohol, ether, or epoxide using the IUPAC system, we must learn how to name the functional group either as a substituent or by using a suffix added to the parent name.

9.3A Naming Alcohols

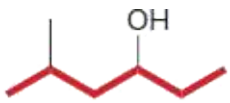
- **In the IUPAC system, alcohols are identified by the suffix *-ol.***

How To Name an Alcohol Using the IUPAC System

Example Give the IUPAC name of the following alcohol:



Step [1] **Find the longest carbon chain containing the carbon bonded to the OH group.**



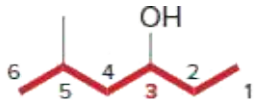
6 C's in the longest chain

6 C's → **hexane** → **hexanol**

- **Change the *-e* ending of the parent alkane to the suffix *-ol.***

Step [2] **Number the carbon chain to give the OH group the lower number, and apply all other rules of nomenclature.**

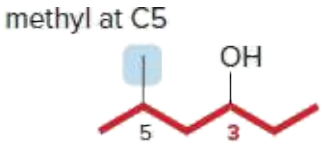
a. Number the chain.



- Number the chain to put the OH group at C3, not C4.

hexan-3-ol

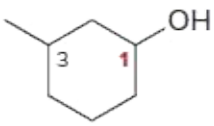
b. Name and number the substituents.



Answer: 5-methylhexan-3-ol

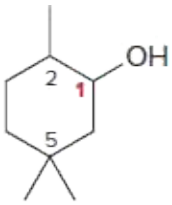
$CH_3CH_2CH_2CH_2OH$ is named as 1-butanol using the 1979 IUPAC recommendations and butan-1-ol using the 1993 IUPAC recommendations.

When an OH group is bonded to a ring, the ring is numbered beginning with the OH group. Because the functional group is always at C1, the "1" is usually omitted from the name. The ring is then numbered in a clockwise or counterclockwise fashion to give the next substituent the lower number. Representative examples are given in Figure 9.2.



3-methylcyclohexanol

The OH group is at C1; the second substituent (CH_3) gets the lower number.



2,5,5-trimethylcyclohexanol

The OH group is at C1; the second substituent (CH_3) gets the lower number.

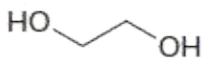
Figure 9.2 **Examples: Naming cyclic alcohols**

Common names are often used for simple alcohols. To assign a common name: Page 349

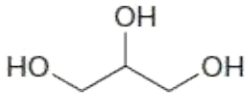
- **Name all the carbon atoms of the molecule as a single alkyl group.**
- **Add the word *alcohol*, separating the words with a space.**

isopropyl alcohol

Compounds with two hydroxy groups are called diols (using the IUPAC system) or glycols. Compounds with three hydroxy groups are called triols, and so forth. To name a diol, for example, the suffix *-diol* is added to the name of the parent alkane, and numbers are used to indicate the location of the two OH groups.

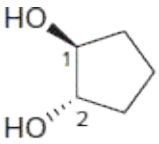


ethylene glycol
(ethane-1,2-diol)



glycerol
(propane-1,2,3-triol)

Common names are usually used for these simple compounds.

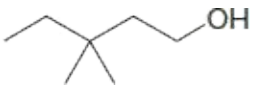


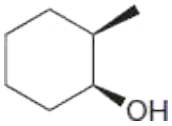
***trans*-cyclopentane-1,2-diol**

Numbers are needed to show the location of **two** OH groups.

Problem 9.2

Give the IUPAC name for each compound.

a.


b.


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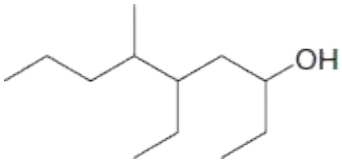

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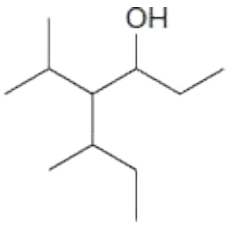

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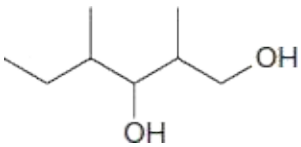

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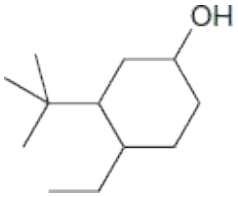


Problem 9.3

Give the structure corresponding to each name.

a. 7,7-dimethyloctan-4-ol

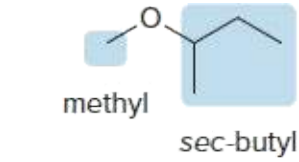
b. 5-methyl-4-propylheptan-3-ol

c. 2-*tert*-butyl-3-methylcyclohexanol

d. *trans*-cyclohexane-1,2-diol

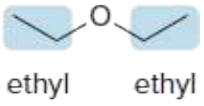
9.3B Naming Ethers

Simple ethers are usually assigned common names. To do so, name both alkyl groups bonded to the oxygen, arrange these names alphabetically, and add the word *ether*. For symmetrical ethers, name the alkyl group and add the prefix *di-*.



***sec*-butyl methyl ether**

Alphabetize the **b** of **butyl** before the **m** of **methyl**.



diethyl ether

More complex ethers are named using the IUPAC system. One alkyl group is named as a hydrocarbon chain, and the other is named as part of a substituent bonded to that chain.

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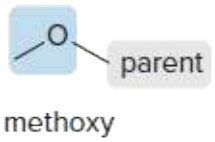
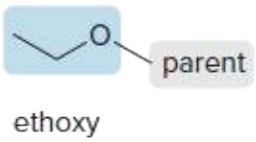
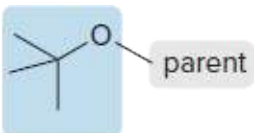
- **Name the simpler alkyl group + O atom as an alkoxy substituent by changing the *-yl* ending of the alkyl group to *-oxy*.**
- **Name the remaining alkyl group as an alkane, with the alkoxy group as a substituent bonded to this chain.**



methoxy



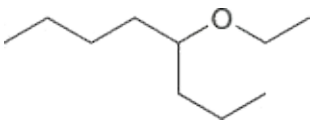
ethoxy



tert-butoxy

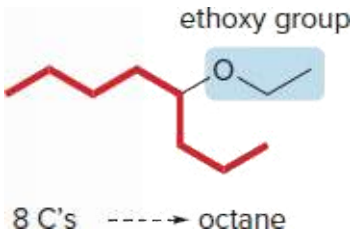
Sample Problem 9.1 Naming an Ether Using IUPAC Nomenclature

Give the IUPAC name for the following ether.

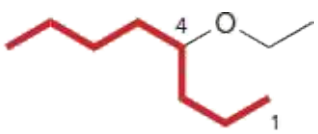


Solution

[1] Name the longer chain as an alkane and the shorter chain as an alkoxy group.



[2] Apply the other nomenclature rules to complete the name.

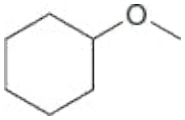


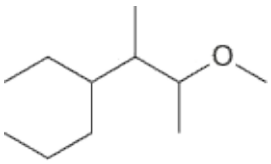
Answer: 4-ethoxyoctane

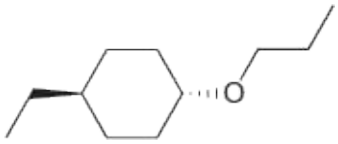
Problem 9.4

Name each of the following ethers.

a.

b. 

c. 

d. 

More Practice:

Try Problems 9.36b; 9.40a, b.

tetrahydrofuran
THF

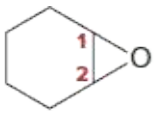
Cyclic ethers have an O atom in a ring. A common cyclic ether is tetrahydrofuran (THF), a polar aprotic solvent used in nucleophilic substitution (Section 7.8C) and many other organic reactions.

9.3C Naming Epoxides

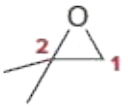
Any cyclic compound containing a heteroatom is called a *heterocycle.*

Epoxides are named in three different ways—epoxyalkanes, oxiranes, or alkene oxides.

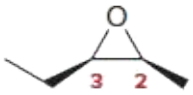
To name an epoxide as an epoxyalkane, first name the alkane chain or ring to which the oxygen is attached, and use the prefix *epoxy* to name the epoxide as a substituent. Use two numbers to designate the location of the atoms to which the O's are bonded.



1,2-epoxycyclohexane



1,2-epoxy-2-methylpropane



cis-2,3-epoxypentane

Epoxides bonded to a chain of carbon atoms can also be named as derivatives of oxirane, the simplest epoxide having two carbons and one oxygen atom in a ring. The oxirane ring is numbered to put the O atom at position "1" and the first substituent at position "2." No number is used for a substituent in a monosubstituted oxirane.

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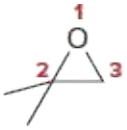
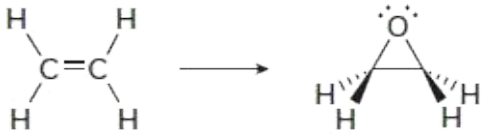
oxirane



2,2-dimethyloxirane

Epoxides are also named as alkene oxides, because they are often prepared by adding an O atom to an alkene (Chapter 12). To name an epoxide this way, mentally replace the epoxide oxygen by a double bond, name the alkene (Section 10.3), and then add the word *oxide*. For example, the common name for oxirane is ethylene oxide, because it is an epoxide derived from the alkene ethylene. We will use this method of naming epoxides after the details of alkene nomenclature are presented in Chapter 10.

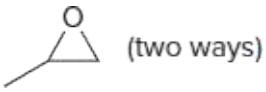


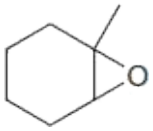
ethylene

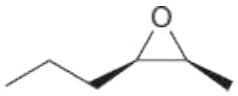
ethylene oxide
oxirane

Problem 9.5

Name each epoxide.

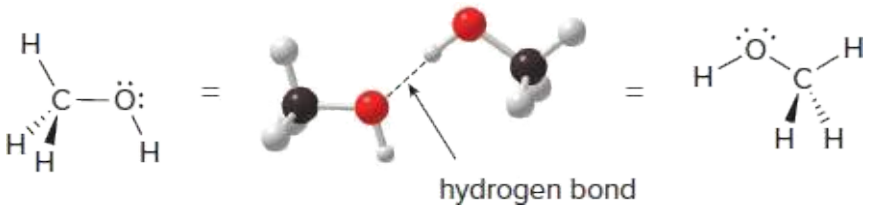
a.  (two ways)

b. 

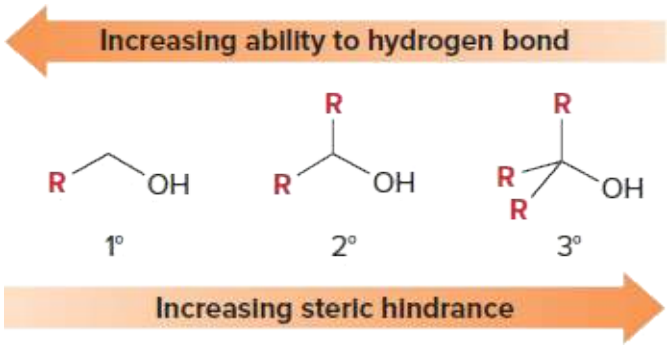
c.  (two ways)

9.4 Properties of Alcohols, Ethers, and Epoxides

Alcohols, ethers, and epoxides exhibit dipole–dipole interactions because they have a bent structure with two polar bonds. Alcohols are also capable of intermolecular hydrogen bonding because they possess a hydrogen atom on an oxygen, making alcohols much more polar than ethers and epoxides.



Steric factors affect the extent of hydrogen bonding. Although all alcohols can hydrogen bond, increasing the number of R groups around the carbon atom bearing the OH group decreases the extent of hydrogen bonding. Thus, 3° alcohols are least able to hydrogen bond, whereas 1° alcohols are most able to.



How these factors affect the physical properties of alcohols, ethers, and epoxides is summarized in Table 9.1.

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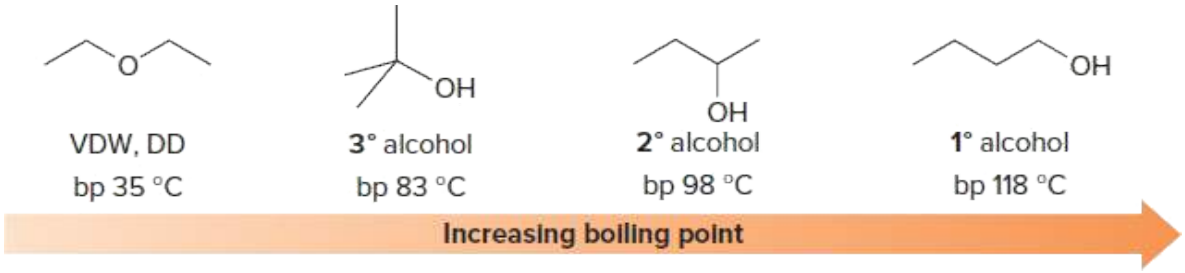
Table 9.1 Physical Properties of Alcohols, Ethers, and Epoxides

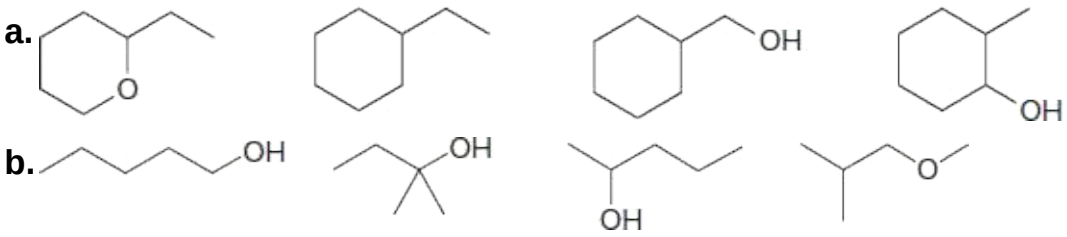
Property	Observation
Boiling point and melting	• For compounds of comparable molecular weight, the stronger intermolecular forces, the higher the bp or mp. • Bp's increase as the extent of hydrogen bonding increases.

point	
Solubility	• Alcohols, ethers, and epoxides having ≤ 5 C's are H_2O solu because they each have an oxygen atom capable of hydro bonding to H_2O (Section 3.4C). • Alcohols, ethers, and epoxides having > 5 C's are H_2O *insolu* because the nonpolar alkyl portion is too large to dissolve in H_2O • Alcohols, ethers, and epoxides of any size are soluble in orga solvents.

Key: VDW = van der Waals forces; DD = dipole–dipole

Problem 9.6

Rank the following compounds in order of increasing boiling point.



Students who have already been exposed to spectroscopy or who would like to learn about the spectroscopic properties of alcohols and ethers are referred to the following sections:

- Mass spectrometry: Section A.4B and Figure A.6
- Infrared spectroscopy: Section B.4B, Sample Problem B.3
- Nuclear magnetic resonance spectroscopy: Section C.9A, Figures C.12 and C.14a, Sample Problems C.3 and C.6

9.5 Interesting Alcohols, Ethers, and Epoxides

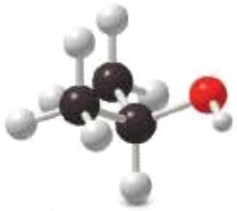
A large number of alcohols, ethers, and epoxides have interesting and useful properties.

9.5A Interesting Alcohols

The structure and properties of three simple alcohols—methanol, propan-2-ol, and ethylene glycol—are given in Figure 9.3. Ethanol (CH_3CH_2OH), formed by the fermentation of the carbohydrates in grains, grapes, and potatoes, is the alcohol present in alcoholic beverages. It is perhaps the first organic compound synthesized by humans, because alcohol production has been known for at least 4000 years. Ethanol depresses the central nervous system, increases the production of stomach acid, and dilates blood vessels, producing a flushed appearance. Ethanol is also a common laboratory solvent, which is sometimes made unfit to ingest by adding small amounts of benzene or methanol (both of which are toxic).

CH_3OH

- **Methanol (CH_3OH)** is also called wood alcohol, because it can be obtained by heating wood at high temperatures in the absence of air. Methanol is extremely toxic because of the oxidation products formed when it is metabolized in the liver (Section 12.14). Ingestion of as little as 15 mL causes blindness, and 100 mL causes death.



$(CH_3)_2CHOH$

- **Propan-2-ol [$(CH_3)_2CHOH$]** is the major component of rubbing alcohol. When rubbed on the skin it evaporates readily, producing a pleasant cooling sensation. Because it has weak antibacterial properties, propan-2-ol is used to clean skin before minor surgery and to sterilize medical instruments.

$HOCH_2CH_2OH$

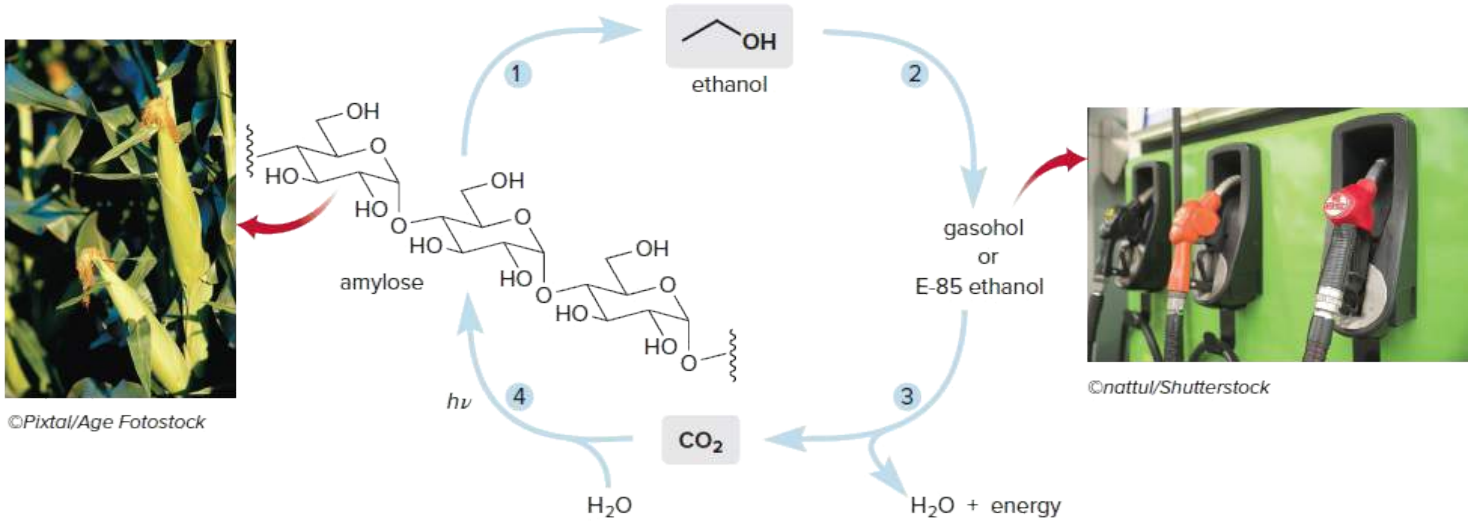
- **Ethylene glycol ($HOCH_2CH_2OH$)** is the major component of antifreeze. It is readily prepared from ethylene oxide by reactions discussed in Section 9.16. It is sweet tasting but toxic.

Figure 9.3 **Some simple alcohols**

Ethanol is a common gasoline additive, widely touted as an environmentally friendly fuel source. Two common gasoline–ethanol fuels are gasohol, which contains 10% ethanol, and E-85, which contains 85% ethanol. Ethanol is now routinely prepared from the carbohydrates in corn (Figure 9.4). Starch, a complex carbohydrate polymer, can be hydrolyzed to the simple sugar glucose, which forms ethanol by the process of fermentation. Combining ethanol with gasoline forms a usable fuel, which combusts to form CO_2, H_2O, and a great deal of energy.

Because green plants use sunlight to convert CO_2 and H_2O to carbohydrates during photosynthesis, next year's corn crop removes CO_2 from the atmosphere to make new molecules of starch as the corn grows. While in this way ethanol is a *renewable* fuel

source, the need for large-scale farm equipment and the heavy reliance on fertilizers and herbicides make ethanol expensive to produce. Moreover, many criticize the use of valuable farmland for an energy-producing crop rather than for food production. As a result, discussion continues on ethanol as an alternative to fossil fuels.

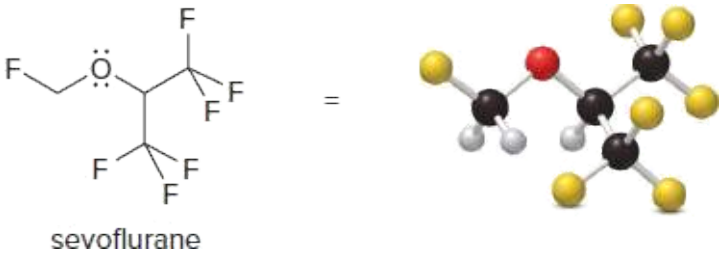


- Hydrolysis of amylose (one form of starch) and **fermentation** of the resulting simple sugars (Step [1]) yield ethanol, which is mixed with hydrocarbons from petroleum refining (Step [2]) to form usable fuels.
- **Combustion** of this ethanol–hydrocarbon fuel forms CO_2 and releases a great deal of energy (Step [3]).
- **Photosynthesis** converts atmospheric CO_2 back to plant carbohydrates in Step [4], and the cycle continues.

Figure 9.4 **Ethanol from corn, a renewable fuel source**

9.5B Interesting Ethers

The discovery that diethyl ether ($CH_3CH_2OCH_2CH_3$) is a general anesthetic revolutionized surgery in the nineteenth century. Diethyl ether is an imperfect anesthetic, but given the alternatives in the nineteenth century, it was considered a miracle drug that allowed patients to tolerate the excruciating pain of surgery. It is safe, easy to administer, and causes little patient mortality, but it is highly flammable and causes nausea in many patients. For these reasons, it has largely been replaced by sevoflurane and other halogenated ethers, which are nonflammable and cause little patient discomfort.

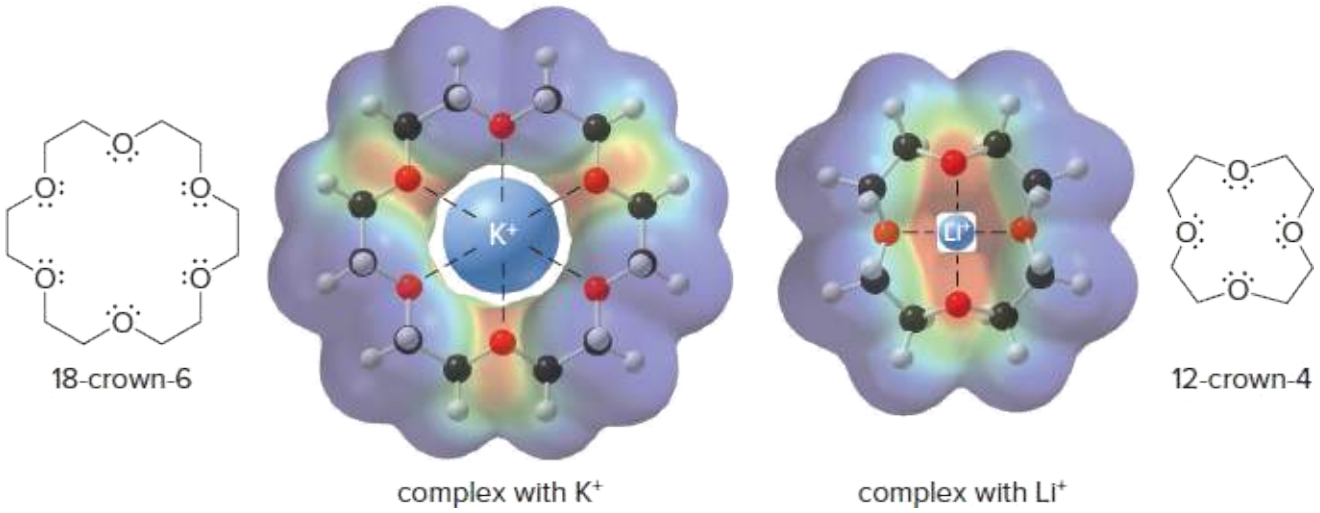


sevoflurane

Recall from Section 3.7B that crown ethers are named as *x*-

crown-*y*, where *x* is the total number of atoms in the ring and *y* is the number of O atoms.

Recall from Section 3.7B that some cyclic polyethers—compounds with two or more ether linkages—contain cavities that can complex specific-sized cations. For example, 18-crown-6 binds K^+, whereas 12-crown-4 binds Li^+.



- **A crown ether–cation complex is called a *host–guest* complex. The crown ether is the *host* and the cation is the *guest.***
- **The ability of a host molecule to bind specific guests is called *molecular recognition.***

The ability of crown ethers to complex cations can be exploited in nucleophilic substitution reactions, as shown in Figure 9.5. Nucleophilic substitution reactions are usually run in polar solvents to dissolve both the polar organic substrate and the ionic nucleophile. With a crown ether, though, the reaction can be run in a *nonpolar* solvent under conditions that enhance nucleophilicity.

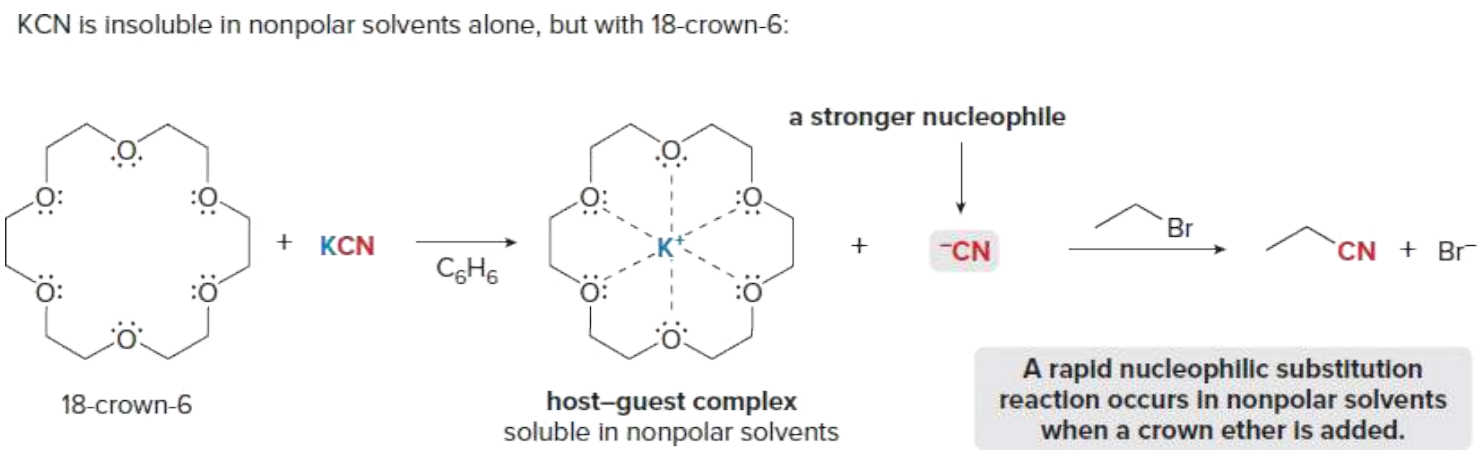


Figure 9.5 **The use of crown ethers in nucleophilic substitution reactions**

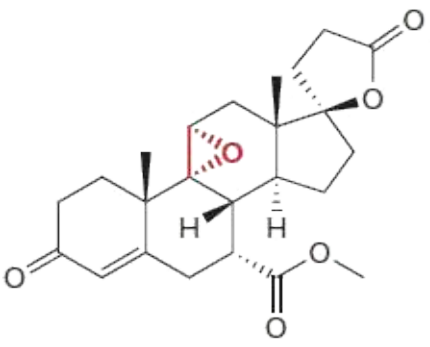
When 18-crown-6 is added to the reaction of CH_3CH_2Br with KCN, for example, the crown ether forms a tight complex with K^+ that has nonpolar C—H bonds on the outside, making the complex soluble in nonpolar solvents like benzene (C_6H_6) or hexane. When the crown ether/K^+ complex dissolves in the nonpolar solvent, it carries the ^-CN along with it to maintain electrical neutrality. The result is a solution of tightly complexed cation and relatively unsolvated anion (nucleophile). The anion, therefore, is extremely nucleophilic because it is not hidden from the substrate by solvent molecules.

Problem 9.7

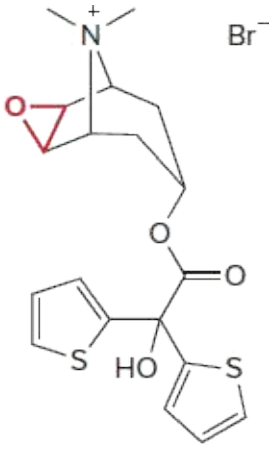
Which mechanism is favored by the use of crown ethers in nonpolar solvents, S_N1 or S_N2?

9.5C Interesting Epoxides

Although epoxides occur less widely in natural products than alcohols or ethers, interesting epoxides are also known. Examples include two useful drugs, eplerenone and tiotropium bromide. Eplerenone (trade name Inspra) is prescribed to reduce cardiovascular risk in patients who have already had a heart attack. Tiotropium bromide (trade name Spiriva) is a long-acting bronchodilator used to treat the chronic obstructive pulmonary disease (COPD) of smokers and those routinely exposed to secondhand smoke.



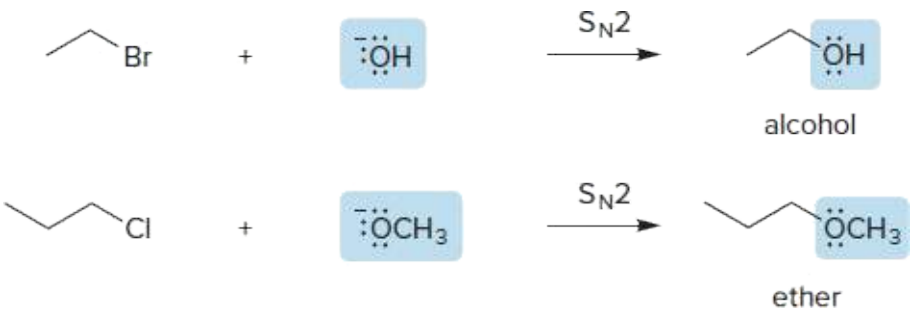
eplerenone



tiotropium bromide

9.6 Preparation of Alcohols, Ethers, and Epoxides

Alcohols and ethers are both common products of nucleophilic substitution. They are synthesized from alkyl halides by S_N2 reactions using strong nucleophiles. As in all S_N2 reactions, highest yields of products are obtained with unhindered methyl and 1° alkyl halides.



The preparation of ethers by this method is called the Williamson ether synthesis, and, although it was first reported in the 1800s, it is still the most general method to prepare an ether. Unsymmetrical ethers can be synthesized in two different ways, but often one path is preferred.

For example, ethyl isopropyl ether can be prepared from $CH_3CH_2O^-$ and 2-bromopropane (Path [a]), or from $(CH_3)_2CHO^-$ and bromoethane (Path [b]). Because the mechanism is S_N2, the preferred path uses the less sterically hindered halide, CH_3CH_2Br—Path [b].

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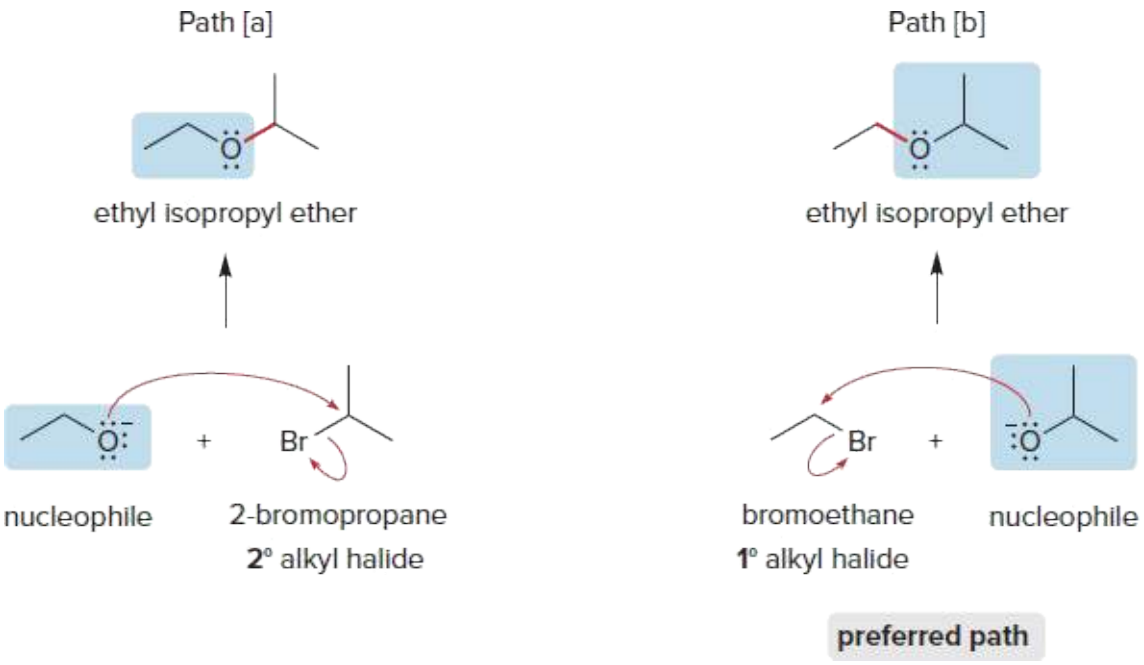
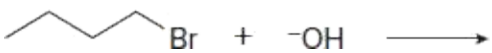
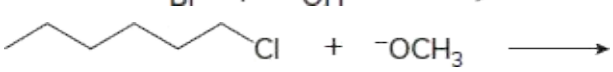
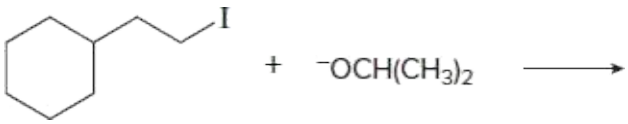


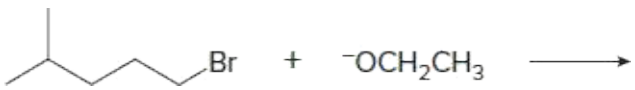
Problem 9.8

Draw the organic product of each reaction.

a. 

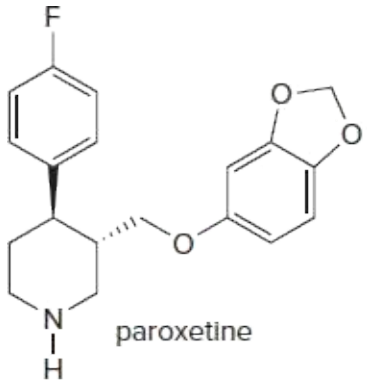
b. 

c. 

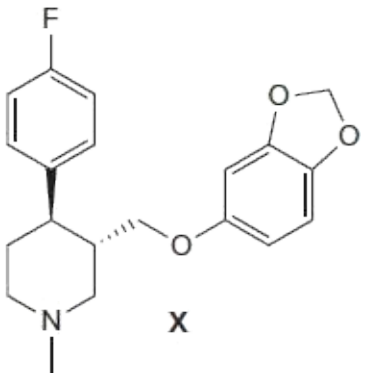
d. 

Problem 9.9

A key step in the synthesis of the antidepressant paroxetine (trade name Paxil) involves a Williamson ether synthesis of the acyclic ether in X. Draw two different routes to this ether and state which is preferred.



paroxetine



X

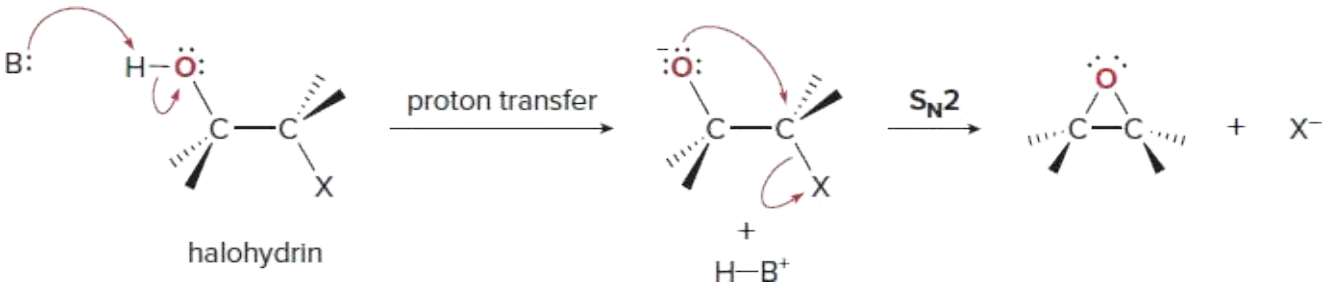
A hydroxide nucleophile is needed to synthesize an alcohol, and salts such as NaOH and KOH are inexpensive and commercially available. An alkoxide salt is needed to make an ether. Simple alkoxides such as sodium methoxide ($NaOCH_3$) can be purchased, but others are prepared from alcohols by a Brønsted–Lowry acid–base reaction. For example, sodium ethoxide ($NaOCH_2CH_3$) is prepared by treating ethanol with NaH.

NaH is an especially good base for forming an alkoxide, because the by-product of the reaction, H_2, is a gas that just bubbles out of the reaction mixture.

alkoxide nucleophile

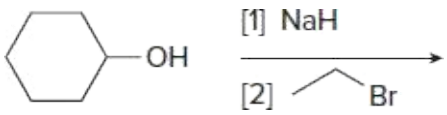
sodium ethoxide

When an organic compound contains both a hydroxy group and a halogen atom on adjacent carbon atoms, an *intramolecular* version of this reaction forms an epoxide. The starting material for this two-step sequence, a halohydrin, is prepared from an alkene, as we will learn in Chapter 10.



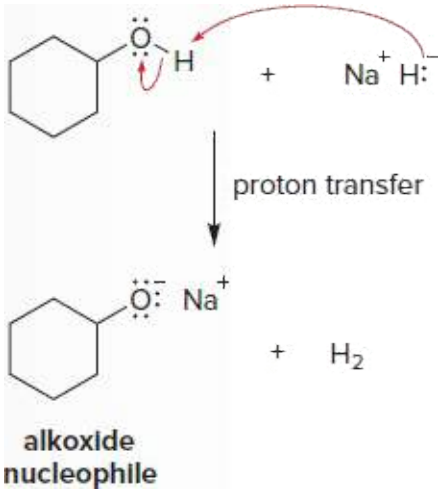
Sample Problem 9.2 Synthesizing an Ether by a Two-Step Reaction Sequence

Draw the product of the following two-step reaction sequence.

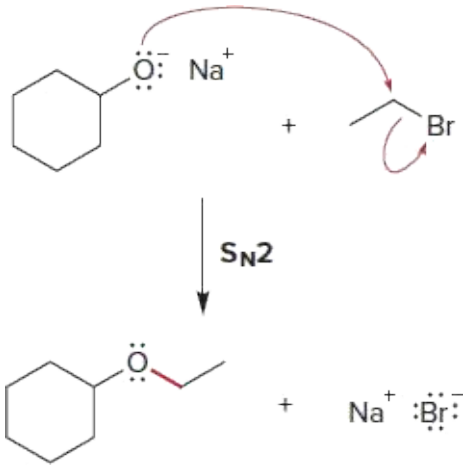


Solution

[1] The base removes a proton from the OH group, forming an alkoxide.



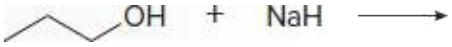
[2] The alkoxide acts as a nucleophile in an S_N2 reaction, forming an ether.



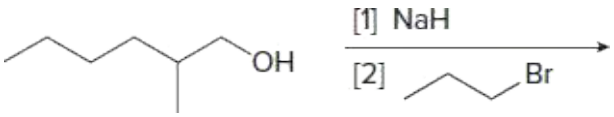
- **This two-step sequence converts an alcohol to an ether. The new C—O bond of the ether is shown in red.**

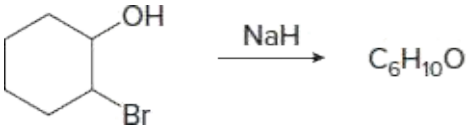
Problem 9.10

Draw the products of each reaction.

a. 

b.

c. 

d. 

More Practice:

Try Problems 9.43h, 9.46a, 9.64i.

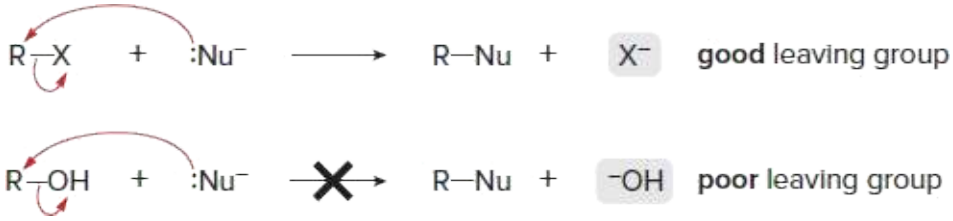
9.7 General Features—Reactions of Alcohols, Ethers, and Epoxides

We begin our discussion of the chemical reactions of alcohols, ethers, and epoxides with a look at the general reactive features of each functional group.

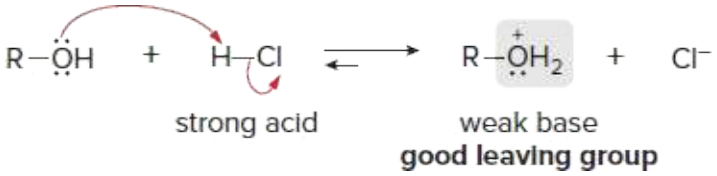
9.7A Alcohols

Unlike many families of molecules, the reactions of alcohols do *not* fit neatly into a single reaction class. In Chapter 9, we discuss only the substitution and β elimination reactions of alcohols. Alcohols are also key starting materials in oxidation reactions (Chapter 12), and their polar O—H bond makes them more acidic than many other organic compounds, a feature we will explore in Chapter 19.

Alcohols are similar to alkyl halides in that both contain an electronegative element bonded to an sp^3 hybridized carbon atom. Alkyl halides contain a good leaving group (X^-), however, whereas alcohols do *not*. Nucleophilic substitution with ROH as starting material would displace ^-OH, a strong base and therefore a poor leaving group.

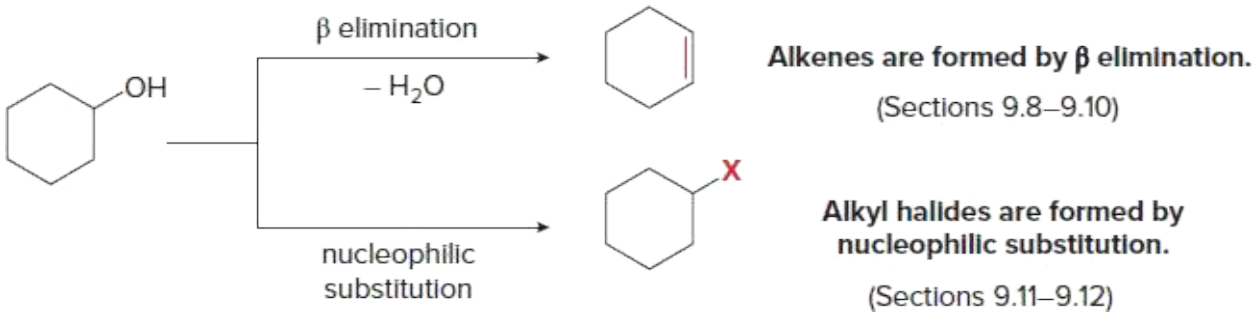


For an alcohol to undergo a nucleophilic substitution or elimination reaction, the OH group must be converted into a *better* leaving group. This can be done by reaction with acid. Treatment of an alcohol with a strong acid like HCl or H_2SO_4 protonates the O atom via an acid–base reaction. This transforms the $^-$OH leaving group into H_2O, a weak base and therefore a *good* leaving group.



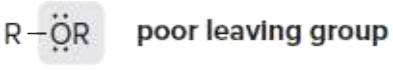
If the OH group of an alcohol is made into a good leaving group, alcohols *can* undergo β elimination and nucleophilic substitution, as described in Sections 9.8–9.12.

Because the pK_a of $(ROH_2)^+$ is ~−2, protonation of an alcohol occurs only with very strong acids–namely, those having a p$K_a \leq -2$.

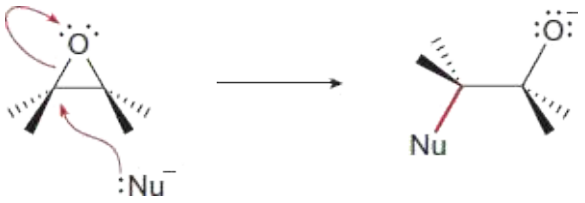


9.7B Ethers and Epoxides

Like alcohols, ethers do *not* contain a good leaving group, which means that nucleophilic substitution and β elimination do not occur directly. Ethers undergo fewer useful reactions than alcohols.



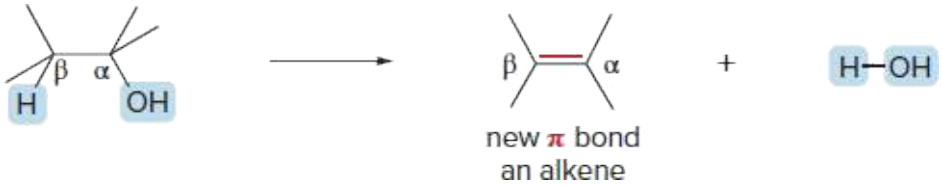
Epoxides don't have a good leaving group either, but they have one characteristic that neither alcohols nor ethers have: the “leaving group” is contained in a strained three-membered ring. Nucleophilic attack opens the three-membered ring and relieves angle strain, making nucleophilic attack a favorable process that occurs even with the poor leaving group. Specific examples are presented in Section 9.16.



9.8 Dehydration of Alcohols to Alkenes

The dehydrohalogenation of alkyl halides, discussed in Chapter 8, is one way to introduce a π bond into a molecule. Another way is to eliminate water from an alcohol in a dehydration reaction.

- **Dehydration is a β elimination reaction in which the elements of OH and H are removed from the a and β carbon atoms, respectively.**

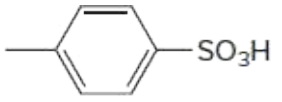


Dehydration is typically carried out using H_2SO_4 and other strong acids, or phosphorus oxychloride ($POCl_3$) in the presence of an amine base. We consider dehydration in acid first, followed by dehydration with $POCl_3$ in Section 9.10.

9.8A General Features of Dehydration in Acid

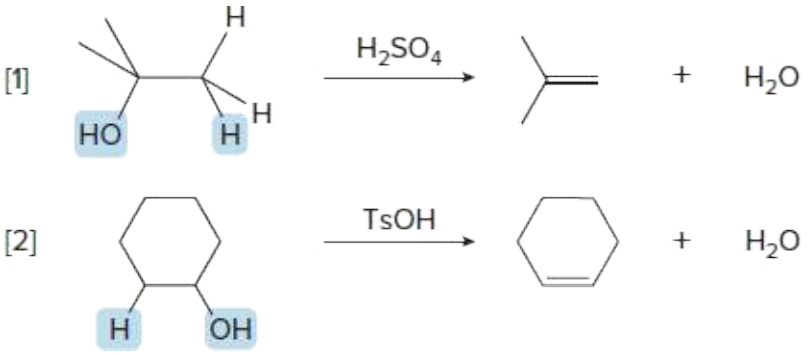
Alcohols undergo dehydration in the presence of strong acid to afford alkenes, as illustrated in Equations [1] and [2]. Typical acids used for this conversion are H_2SO_4 or *p*-toluenesulfonic acid (abbreviated as TsOH).

Recall from Section 2.6 that *p*-toluenesulfonic acid is a strong organic acid ($pK_a = -7$).

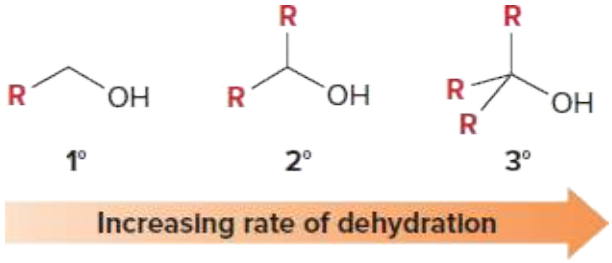


p-toluenesulfonic acid

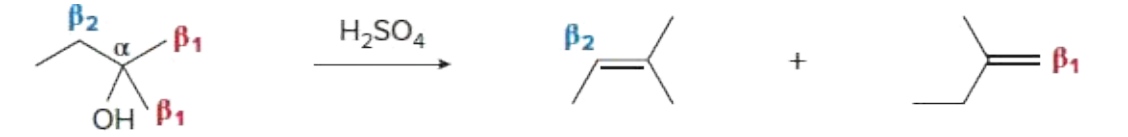
TsOH



More substituted alcohols dehydrate more readily, giving rise to the following order of reactivity:



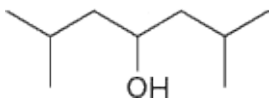
When an alcohol has two or three different β carbons, dehydration is regioselective and follows the Zaitsev rule. The more substituted alkene is the major product when a mixture of constitutional isomers is possible. For example, elimination of H and OH from 2-methylbutan-2-ol yields two constitutional isomers: the trisubstituted alkene A as *major* product and the disubstituted alkene B as *minor* product.



Problem 9.11

Draw the products formed when each alcohol undergoes dehydration with TsOH, and label the major product when a mixture results.

a.



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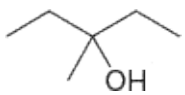
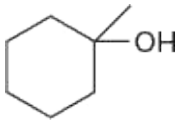
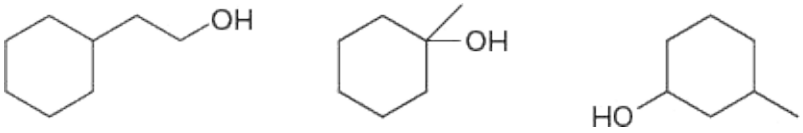


c.



Problem 9.12

Rank the alcohols in order of increasing reactivity when dehydrated with H_2SO_4.

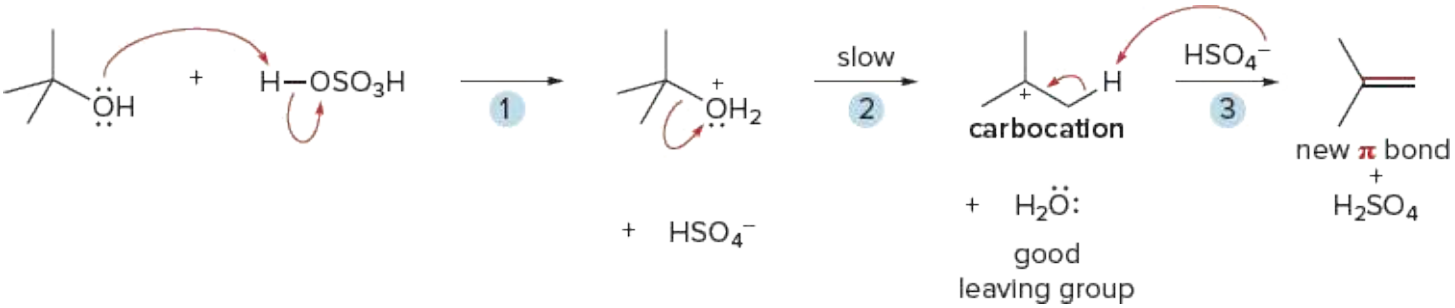


9.8B The E1 Mechanism for the Dehydration of 2° and 3° Alcohols

The mechanism of dehydration depends on the structure of the alcohol: 2° and 3° alcohols react by an E1 mechanism, whereas 1° alcohols react by an E2 mechanism. Regardless of the type of alcohol, however, strong acid is *always* needed to protonate the O atom to form a good leaving group.

The E1 dehydration of 2° and 3° alcohols is illustrated with $(CH_3)_3COH$ (a 3° alcohol) as starting material to form $(CH_3)_2C{=}CH_2$ as product (Mechanism 9.1). The mechanism consists of three steps.

Mechanism 9.1 Dehydration of 2° and 3° ROH—An E1 Mechanism



1. **Protonation of the oxygen atom converts the poor leaving group ($^-$OH) into a good leaving group (H_2O).**
2. **Heterolysis of the C—O bond forms a carbocation in the rate-determining step.**
3. **A base (such as HSO_4^- or H_2O) removes a proton from a carbon adjacent to the carbocation to form the new π bond.**

Thus, dehydration of 2° and 3° alcohols occurs via an E1 mechanism with an added first step. Step [1] protonates the OH group to make a good leaving group. Steps [2] and [3] are the two steps of an E1 mechanism: loss of a leaving group (H_2O in this case) to form a carbocation, followed by removal of a β proton to form a π bond. The acid used to protonate the alcohol in Step [1] is regenerated upon removal of the

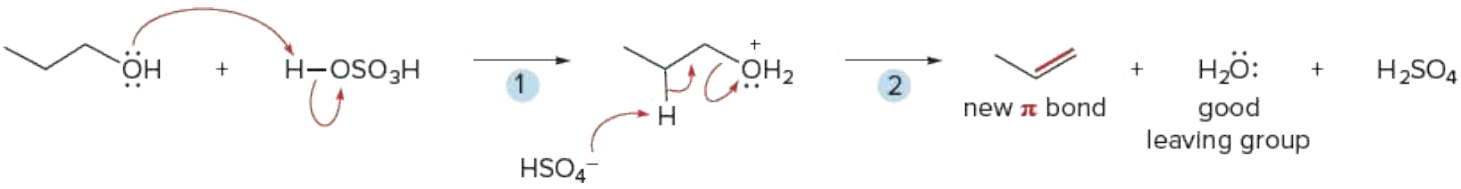
proton in Step [3], so dehydration is acid-catalyzed.

The E1 dehydration of 2° and 3° alcohols with acid gives clean elimination products without by-products formed from an S_N1 reaction. This makes the E1 dehydration of alcohols much more synthetically useful than the E1 dehydrohalogenation of alkyl halides (Section 8.7). Clean elimination takes place because the reaction mixture contains no good nucleophile to react with the intermediate carbocation, so no competing S_N1 reaction occurs.

9.8C The E2 Mechanism for the Dehydration of 1° Alcohols

Because 1° carbocations are highly unstable, the dehydration of 1° alcohols cannot occur by an E1 mechanism involving a carbocation intermediate. With 1° alcohols, therefore, dehydration follows an E2 mechanism. The two-step process for the conversion of $CH_3CH_2CH_2OH$ (a 1° alcohol) to $CH_3CH{=}CH_2$ with H_2SO_4 as acid catalyst is shown in Mechanism 9.2.

Mechanism 9.2 Dehydration of a 1° ROH—An E2 Mechanism



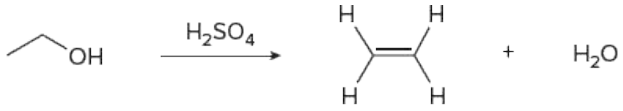
1. **Protonation of the oxygen atom converts the poor leaving group ($^-$OH) into a good leaving group (H_2O).**
2. **Two bonds are broken and two bonds are formed. The base (HSO_4^- or H_2O) removes a proton from the β carbon; the electron pair in the β C—H bond forms the new π bond and the leaving group (H_2O) departs.**

The dehydration of a 1° alcohol begins with the protonation of the OH group to form a good leaving group, just as in the dehydration of a 2° or 3° alcohol. With 1° alcohols, however, loss of the leaving group and removal of a β proton occur at the *same* time, so that no highly unstable 1° carbocation is generated.

9.8D Le Châtelier's Principle

Although entropy favors product formation in dehydration (one molecule of reactant forms two molecules of products), enthalpy does *not*, because the two σ bonds broken in the reactant are stronger than the σ and π bonds formed in the products. For

example, $\Delta H°$ for the dehydration of CH_3CH_2OH to $CH_2{=}CH_2$ is +38 kJ/mol (Figure 9.6).



ΔH° calculation:

[1] Bonds broken

	ΔH° (kJ/mol)
CH_3CH_2–OH	+393
$HOCH_2CH_2$–H	+410
Total	+803 kJ/mol

Energy needed to break bonds.

[2] Bonds formed

	ΔH° (kJ/mol)
$CH_2{=}CH_2$ π bond	−267
H–OH	−498
Total	−765 kJ/mol

Energy released in forming bonds.

[3] Overall ΔH° =

sum in Step [1]
+
sum in Step [2]

+803 kJ/mol
−765 kJ/mol

$\Delta H° = +38$ kJ/mol

The reaction is endothermic.

[Values taken from Appendix E.]

Figure 9.6 The dehydration of CH_3CH_2OH to $CH_2{=}CH_2$—An endothermic reaction

According to Le Châtelier's principle, a system at equilibrium will react to counteract any disturbance to the equilibrium. Thus, removing a product from a reaction mixture as it is formed drives the equilibrium to the *right*, forming more product.

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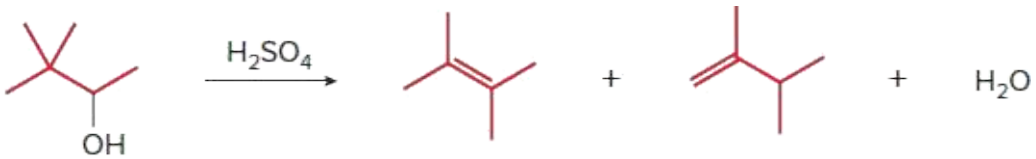
Le Châtelier's principle can be used to favor products in dehydration reactions because the alkene product has a lower boiling point than the alcohol reactant. Thus, the alkene can be distilled from the reaction mixture as it is formed, leaving the alcohol and acid to react further, forming more product.

9.9 Carbocation Rearrangements

Sometimes “unexpected” products are formed in dehydration; that is, the carbon skeletons of the starting material and product might be different, or the double bond might be in an unexpected location. For example, the dehydration of 3,3-dimethylbutan-2-ol yields two alkenes, whose carbon skeletons do not match the carbon framework of the starting material.

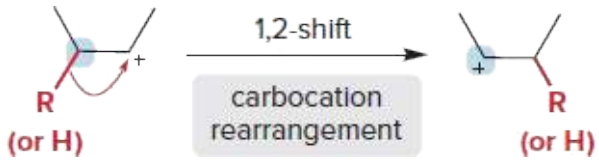


3,3-dimethylbutan-2-ol

This phenomenon sometimes occurs when carbocations are reactive intermediates. A less stable carbocation can rearrange to a more stable carbocation by shift of a

hydrogen atom or an alkyl group. These 1,2-shifts involve migration of an alkyl group or hydrogen atom from one carbon to an adjacent carbon atom. The migrating group moves with the two electrons that bonded it to the carbon skeleton.

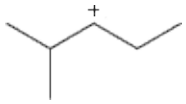
Because the migrating group in a 1,2-shift moves with two bonding electrons, the carbon it leaves behind now has only three bonds (six electrons), giving it a net positive (+) charge.

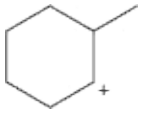


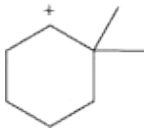
- **Movement of a hydrogen atom is called a 1,2-hydride shift.**
- **Movement of an alkyl group is called a 1,2-alkyl shift.**

Problem 9.13

Show how a 1,2-shift forms a more stable carbocation from each intermediate.

a. 

b. 

c. 

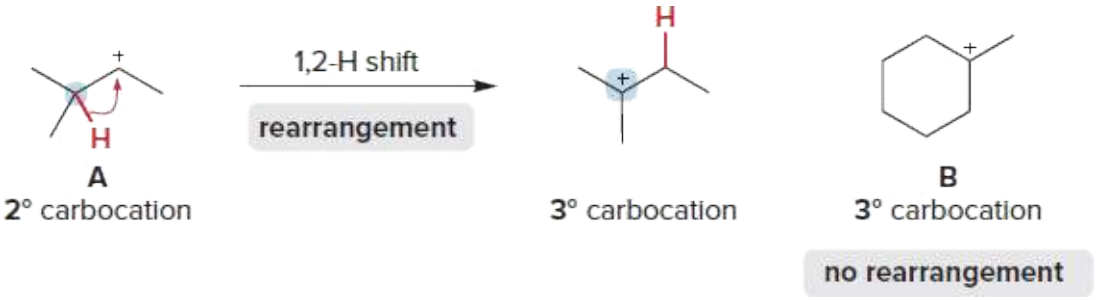
The dehydration of 3,3-dimethylbutan-2-ol illustrates the rearrangement of a 2° to a 3° carbocation by a 1,2-methyl shift, as shown in Mechanism 9.3. The carbocation rearrangement occurs in Step [3] of the four-step mechanism.

Steps [1], [2], and [4] in the mechanism for the dehydration of 3,3-dimethylbutan-2-ol are exactly the same steps previously seen in dehydration: protonation, loss of H_2O, and loss of a proton. Only Step [3], rearrangement of the less stable 2° carbocation to the more stable 3° carbocation, is new.

- **1,2-Shifts convert a less stable carbocation to a more stable carbocation.**

For example, 2° carbocation A rearranges to the more stable 3° carbocation by a 1,2-

hydride shift, whereas carbocation B does not rearrange because it is 3° to begin with.



Mechanism 9.3 A 1,2-Methyl Shift—Carbocation Rearrangement During Dehydration

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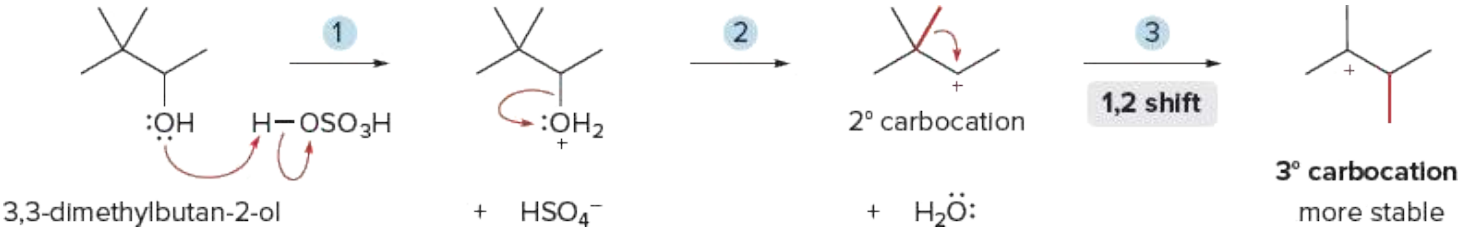
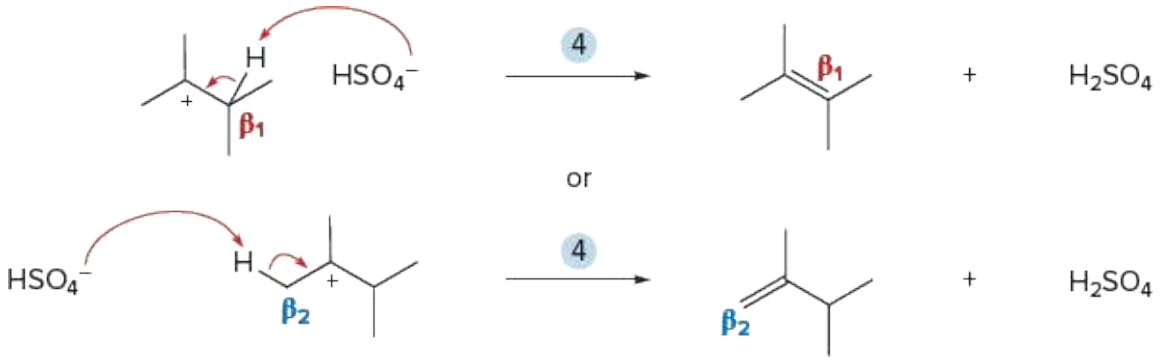
Part [1] Formation of a 2° carbocation and rearrangement



1. Protonation of the oxygen atom converts the poor leaving group ($^-$OH) into a good leaving group (H_2O).
2. Heterolysis of the C—O bond forms a 2° carbocation.
3. 1,2-Shift of a CH_3 group converts a 2° carbocation to a more stable 3° carbocation.

Part [2] Loss of a proton to form the π bond

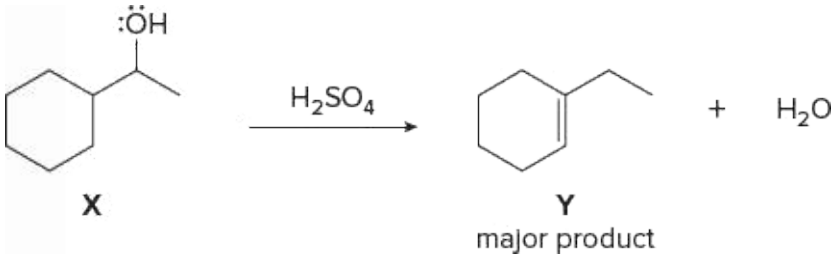


4. Loss of a proton from a β carbon (β_1 or β_2) forms two different alkenes.

Sample Problem 9.3 illustrates a dehydration reaction that occurs with a 1,2-hydride shift.

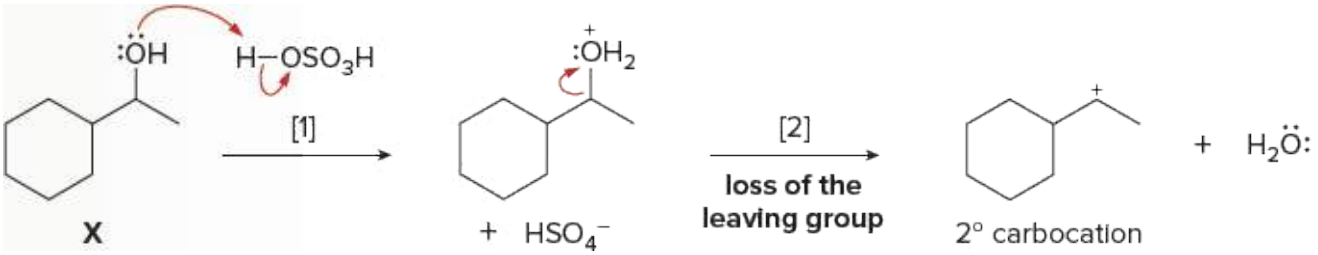
Sample Problem 9.3 Drawing a Dehydration Reaction with a Rearrangement

Show how the dehydration of alcohol X forms alkene Y using a 1,2-hydride shift.



Solution

Steps [1] and [2] Protonation of X and loss of H_2O form a 2° carbocation.



Steps [3] and [4] Rearrangement of the 2° carbocation by a 1,2-hydride shift forms a more stable 3° carbocation. Loss of a proton from a γ carbon forms alkene Y.

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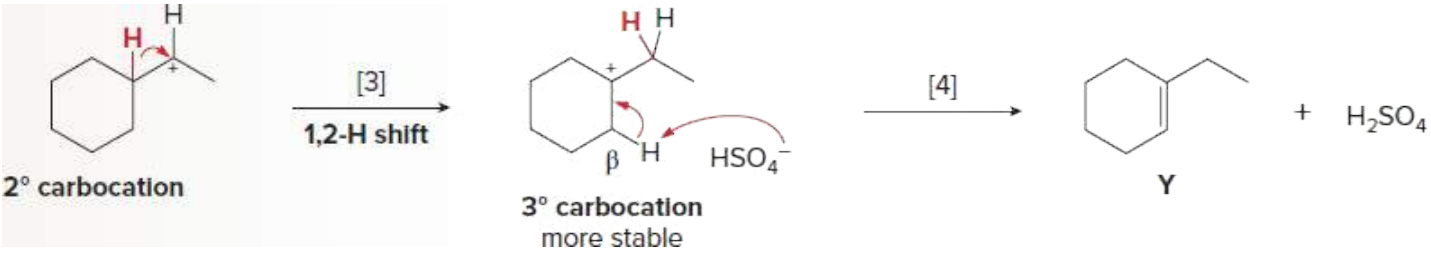


Problem 9.14

What other alkene is also formed along with Y in Sample Problem 9.3? What alkenes would form from X if no carbocation rearrangement occurred?

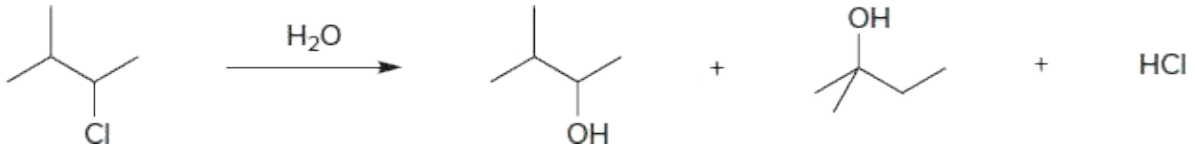
More Practice:

Try Problems 9.47a, 9.49, 9.50.

Rearrangements are not unique to dehydration reactions. Rearrangements can occur whenever a carbocation is formed as reactive intermediate, meaning any S_N1 or E1 reaction. In fact, the formation of rearranged products often indicates the presence of a carbocation intermediate.

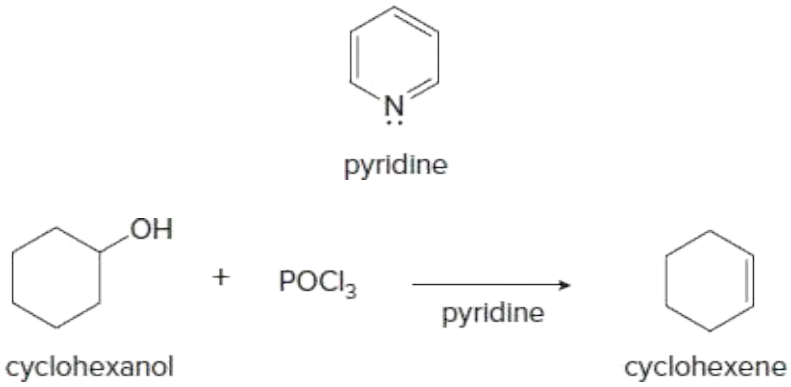
Problem 9.15

Explain why two substitution products are formed in the following reaction.



9.10 Dehydration Using $POCl_3$ and Pyridine

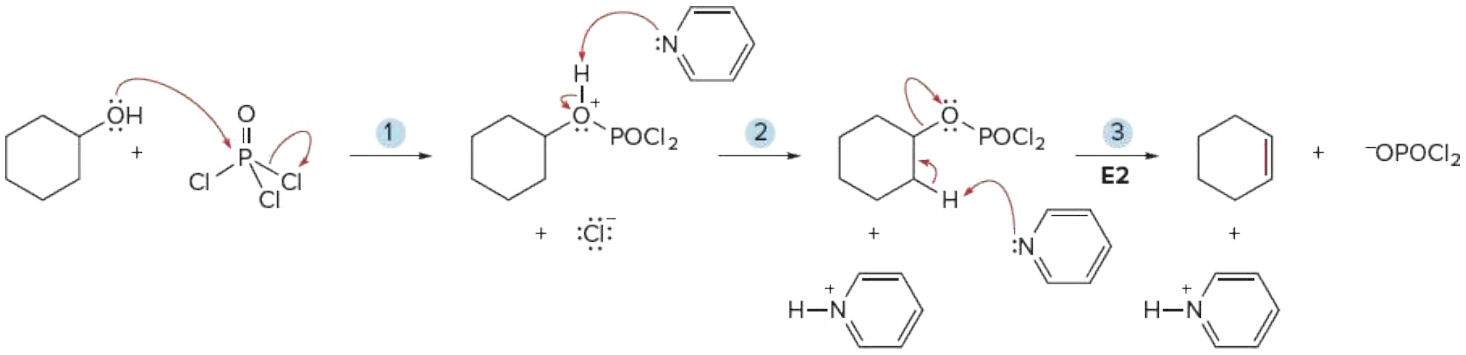
Because some organic compounds decompose in the presence of strong acid, other methods that avoid strong acid have been developed to convert alcohols to alkenes. A common method uses phosphorus oxychloride ($POCl_3$) and pyridine (an amine base) in place of H_2SO_4 or TsOH. For example, the treatment of cyclohexanol with POCl3 and pyridine forms cyclohexene in good yield.



$POCl_3$ serves much the same role as strong acid does in acid-catalyzed dehydration. It converts a poor leaving group (^{-}OH) into a good leaving group. Dehydration then proceeds by an E2 mechanism, as shown in Mechanism 9.4. Pyridine is the base that removes a β proton during elimination.

No rearrangements occur during dehydration with $POCl_3$, suggesting that carbocations are *not* formed as intermediates in this reaction. Steps [1] and [2] of the mechanism convert the OH group into a good leaving group. In Step [3], the C—H and C—O bonds are broken and the π bond is formed.

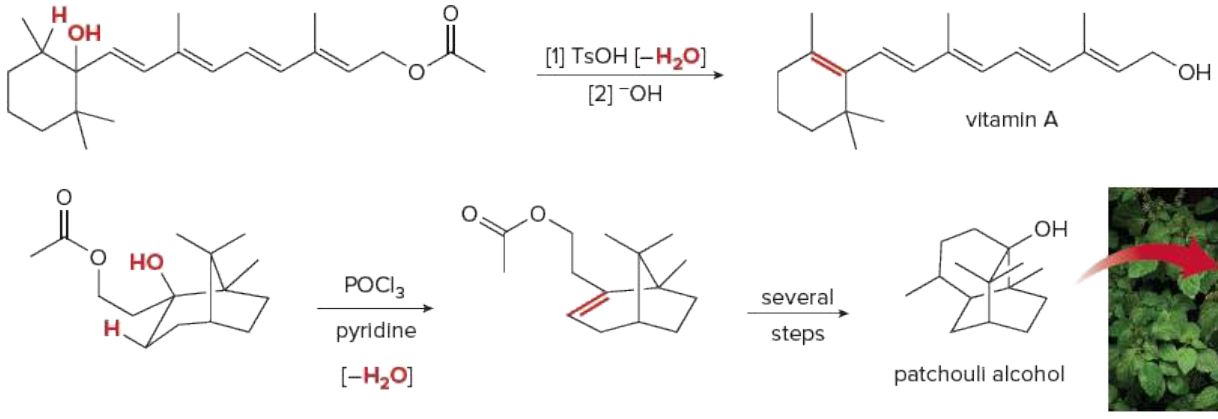
Mechanism 9.4 Dehydration Using $POCl_3$ + Pyridine—An E2 Mechanism



1 – 2 **Reaction of the OH with $POCl_3$ followed by loss of a proton converts a poor leaving group (^-OH) into a good leaving group ($^-OPOCl_2$).**

3 **Two bonds are broken and two bonds are formed. The base (pyridine) removes a proton; the electron pair in the β C—H bond forms the π bond, and the leaving group ($^-OPOCl_2$) departs.**

We have now learned about two different reagents for alcohol dehydration—strong acid (H_2SO_4 or TsOH) and $POCl_3$ + pyridine. The best dehydration method for a given alcohol is often hard to know ahead of time, and this is why organic chemists develop more than one method for a given type of transformation. Two examples of dehydration reactions used in the synthesis of natural products are given in Figure 9.7.



patchouli plant

©Stephen Orsillo/Shutterstock

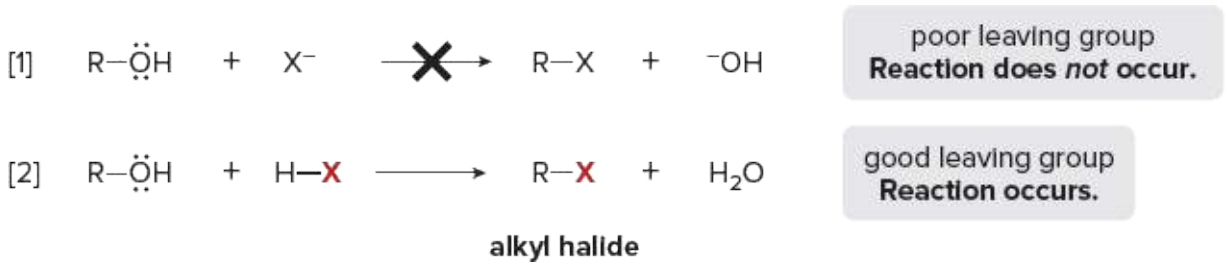
- New double bonds formed by dehydration are shown in red.
- **Patchouli alcohol,** obtained from the patchouli plant native to Malaysia, has been used in perfumery because of its exotic fragrance. In the 1800s, shawls imported from India were often packed with patchouli leaves to ward off insects, thus permeating the clothing with the distinctive odor.

Figure 9.7 **Dehydration reactions in the synthesis of two natural products**

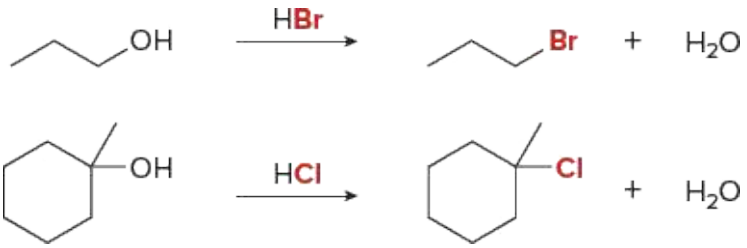
9.11 Conversion of Alcohols to Alkyl Halides with HX

Alcohols undergo nucleophilic substitution reactions only if the OH group is converted to a better leaving group before nucleophilic attack. Thus, substitution does *not* occur

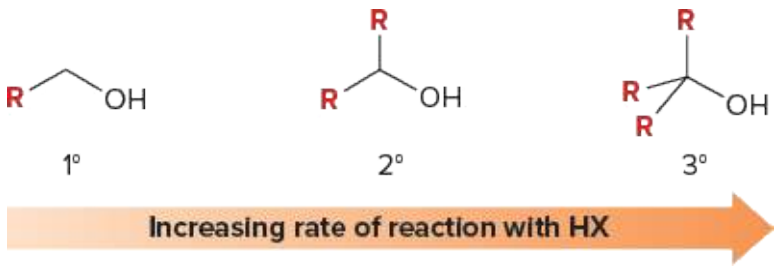
when an alcohol is treated with X^- because ^-OH is a poor leaving group (Reaction [1]), but substitution *does* occur on treatment of an alcohol with HX because H_2O is now the leaving group (Reaction [2]).



- **The reaction of alcohols with HX (X = Cl, Br, I) is a general method to prepare 1°, 2°, and 3° alkyl halides.**

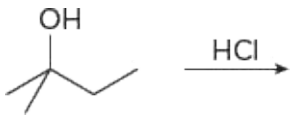


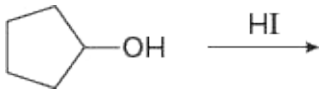
More substituted alcohols usually react more rapidly with HX:

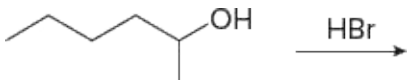


Problem 9.16

Draw the products of each reaction.

a. 

b. 

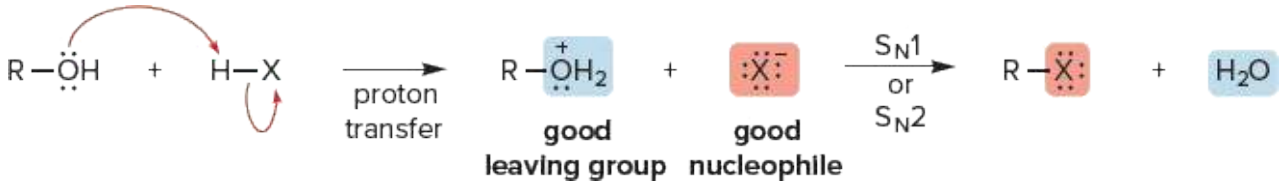
c. 

9.11A Two Mechanisms for the Reaction of ROH with HX

How does the reaction of ROH with HX occur? Acid–base reactions are very fast, so the strong acid HX protonates the OH group of the alcohol, forming a good leaving

group (H_2O) and a good nucleophile (the conjugate base, X^-). Both components are needed for nucleophilic substitution. The mechanism of substitution of X^- for H_2O then depends on the structure of the R group.

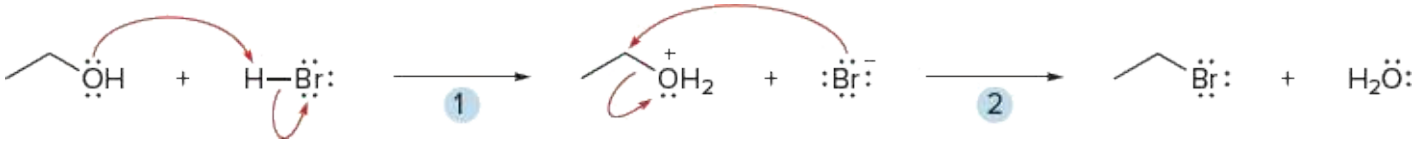
When there is an oxygen-containing reactant and a strong acid, generally the first step in the mechanism is protonation of the oxygen atom.



- **Methyl and 1° ROH form RX by an S_N2 mechanism.**
- **Secondary (2°) and 3° ROH form RX by an S_N1 mechanism.**

The reaction of CH_3CH_2OH with HBr illustrates the S_N2 mechanism of a 1° alcohol (Mechanism 9.5). Nucleophilic attack on the protonated alcohol occurs in one step: the bond to the nucleophile X^- is formed *as* the bond to the leaving group (H_2O) is broken.

Mechanism 9.5 Reaction of a 1° ROH with HX—An S_N2 Mechanism



1. **Protonation of the OH group forms a good leaving group (H_2O).**
2. **The bond to the nucleophile forms *as* the leaving group departs.**

The reaction of $(CH_3)_3COH$ with HBr illustrates the S_N1 mechanism of a 3° alcohol (Mechanism 9.6). Nucleophilic attack on the protonated alcohol occurs in two steps: the bond to the leaving group (H_2O) is broken *before* the bond to the nucleophile X^- is formed.

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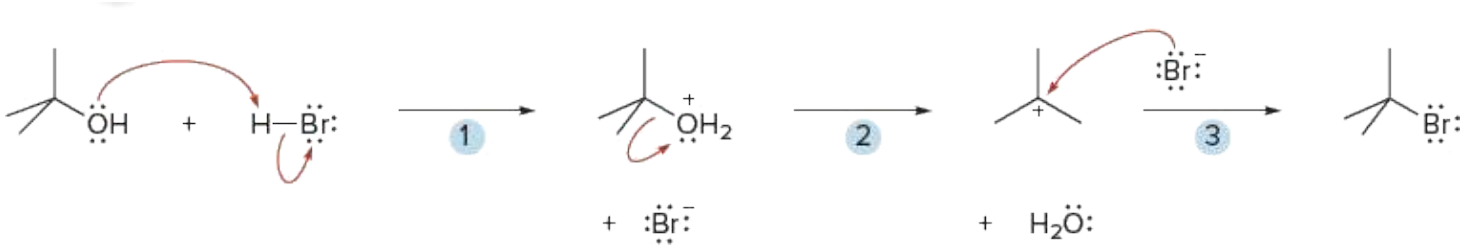
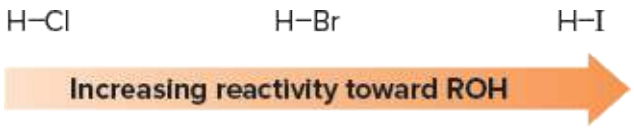
Mechanism 9.6 Reaction of 2° and 3° ROH with HX—An S_N1 Mechanism



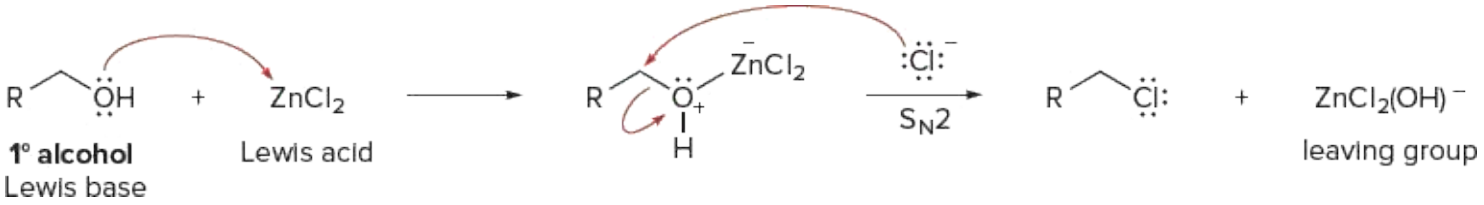
1. **Protonation of the OH group forms a good leaving group (H_2O).**
2. **Loss of the leaving group forms a carbocation.**
3. **Nucleophilic attack of Br^- forms the substitution product.**

Both mechanisms begin with the same first step—protonation of the O atom to form a good leaving group—and both mechanisms give an alkyl halide (RX) as product. The mechanisms differ only in the *timing* of bond breaking and bond making.

The reactivity of hydrogen halides increases with increasing acidity:



Because Cl^- is a poorer nucleophile than Br^- or I^-, the reaction of 1° alcohols with HCl occurs only when an additional Lewis acid catalyst, usually $ZnCl_2$, is added. $ZnCl_2$ complexes with the O atom of the alcohol in a Lewis acid–base reaction, making a leaving group and facilitating the S_N2 reaction.



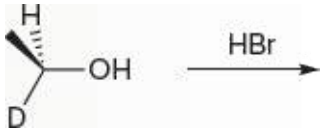
Knowing the mechanism allows us to predict the stereochemistry of the products when reaction occurs at a stereogenic center.

- **Primary (1°) alcohols react by an S_N2 mechanism, so *inversion* occurs at a stereogenic center.**
- **Secondary (2°) and 3° alcohols react by an S_N1 mechanism, so *racemization* occurs at a stereogenic center.**

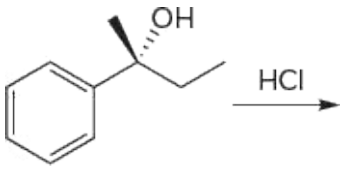
Sample Problem 9.4 Predicting the Stereochemistry When an Alcohol Reacts with a Hydrogen Halide

Draw the products and stereochemistry for each reaction.

a.

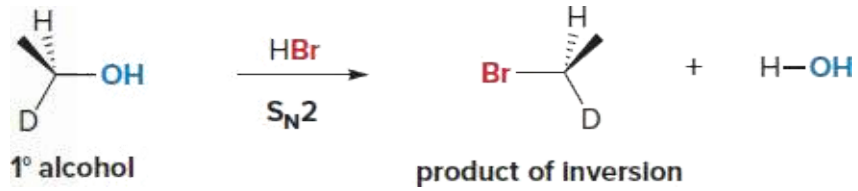


b.

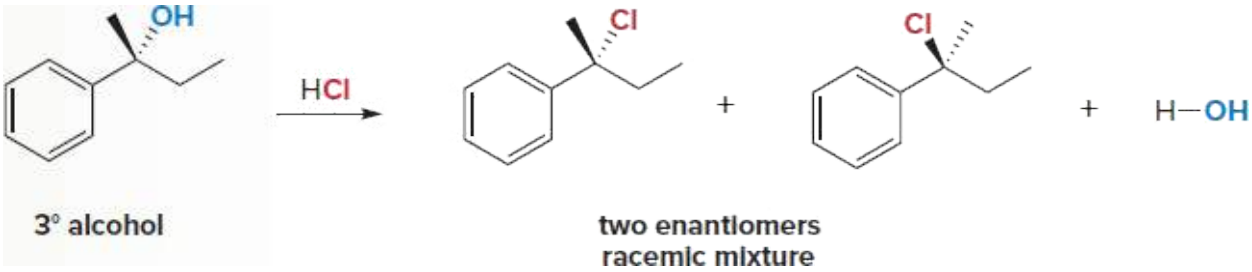


Solution

a. The alcohol is 1°, so the mechanism of substitution is S_N2. Because the leaving group OH (which is protonated to form H_2O) is drawn on the *right* and S_N2 reactions proceed with inversion of stereochemistry at a stereogenic center, the nucleophile approaches from the *left* and a single product is formed.



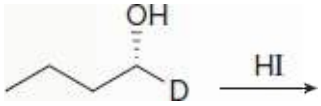
b. The alcohol is 3°, so the mechanism of substitution is S_N1. Because S_N1 reactions form a trigonal planar carbocation, nucleophilic attack of Cl^- occurs from in front and behind to afford a racemic mixture of two enantiomers.



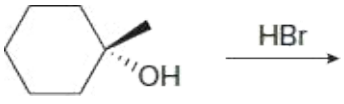
Problem 9.17

Draw the products of each reaction, indicating the stereochemistry around any stereogenic centers.

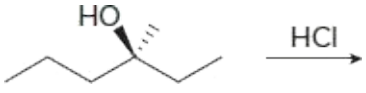
a.



b.



c.



More Practice:

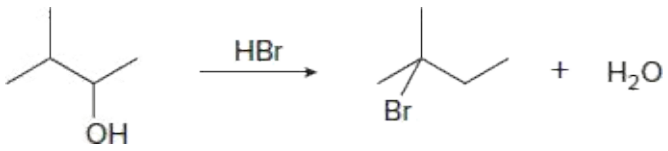
Try Problems 9.38a, c; 9.45; 9.64b.

9.11B Carbocation Rearrangement in the S_N1 Reaction

Because carbocations are formed in the S_N1 reaction of 2° and 3° alcohols with HX, carbocation rearrangements are possible, as illustrated in Sample Problem 9.5.

Sample Problem 9.5 Drawing an S_N1 Mechanism That Involves a Rearrangement

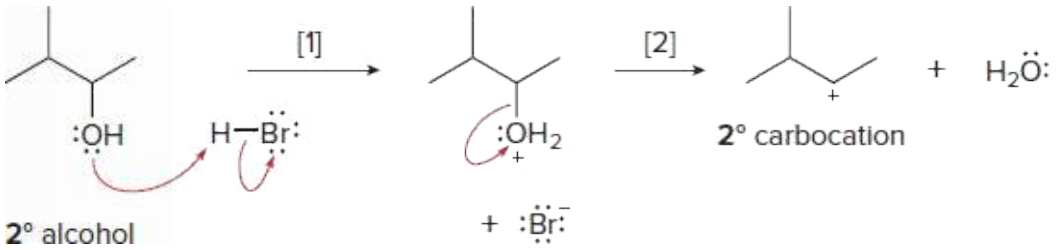
Draw a stepwise mechanism for the following reaction.



Solution

A 2° alcohol reacts with HBr by an S_N1 mechanism. Because substitution converts a 2° alcohol to a 3° alkyl halide in this example, a carbocation rearrangement must occur.

Steps [1] and [2] Protonation of the O atom and then loss of H2O form a 2° carbocation.



Steps [3] and [4] Rearrangement of the 2° carbocation by a 1,2-hydride shift forms a more stable 3° carbocation. Nucleophilic attack forms the substitution product.

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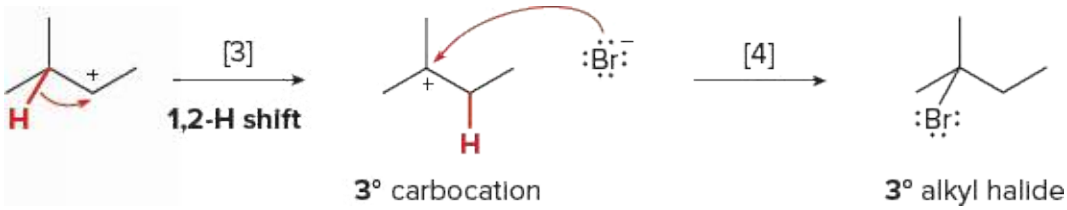
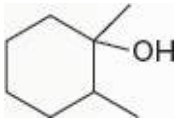
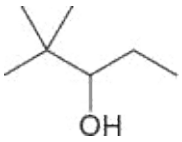
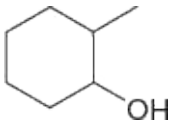


Problem 9.18

What is the major product formed when each alcohol is treated with HCl?

a. 

b. 

c. 

More Practice:

Try Problem 9.48.

9.12 Conversion of Alcohols to Alkyl Halides with $SOCl_2$ and PBr_3

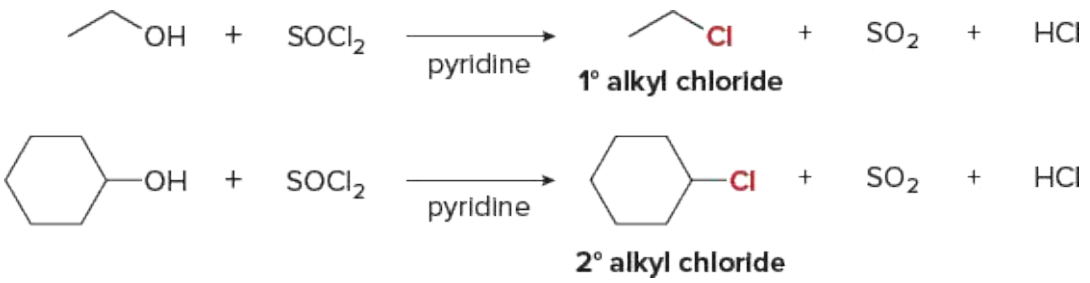
Primary (1°) and 2° alcohols can be converted to alkyl halides using $SOCl_2$ and PBr_3.

- **$SOCl_2$ (thionyl chloride) converts alcohols into alkyl chlorides.**
- **PBr_3 (phosphorus tribromide) converts alcohols into alkyl bromides.**

Both reagents convert ^{-}OH into a good leaving group *in situ*—that is, directly in the reaction mixture—as well as provide the nucleophile, either Cl^- or Br^-, to displace the leaving group.

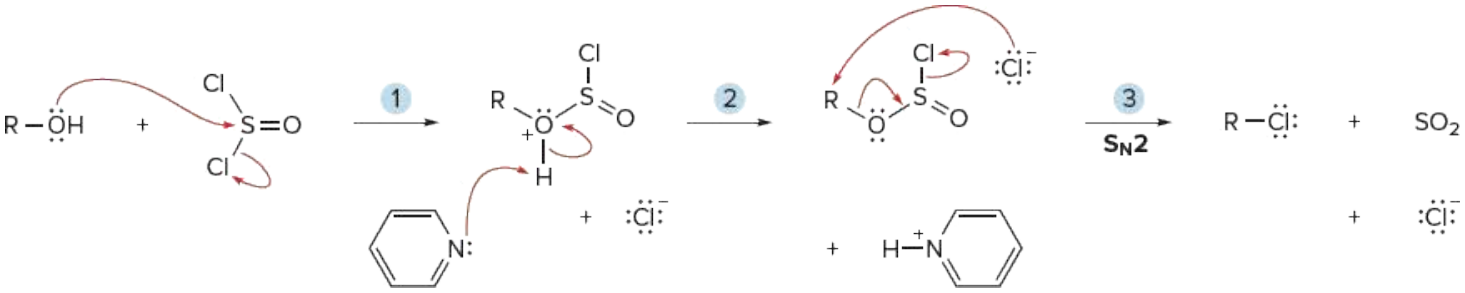
9.12A Reaction of ROH with $SOCl_2$

The treatment of a 1° or 2° alcohol with thionyl chloride, SOCl2, and pyridine forms an alkyl chloride, with SO_2 and HCl as by-products.



The mechanism for this reaction consists of two parts: conversion of the OH group into a better leaving group, and nucleophilic attack by Cl^- via an S_N2 reaction, as shown in Mechanism 9.7.

Mechanism 9.7 Reaction of ROH with $SOCl_2$ + Pyridine—An S_N2 Mechanism



1 – 2 Reaction of the alcohol with $SOCl_2$ and loss of a proton convert the OH group to OSOCl, a good leaving group.

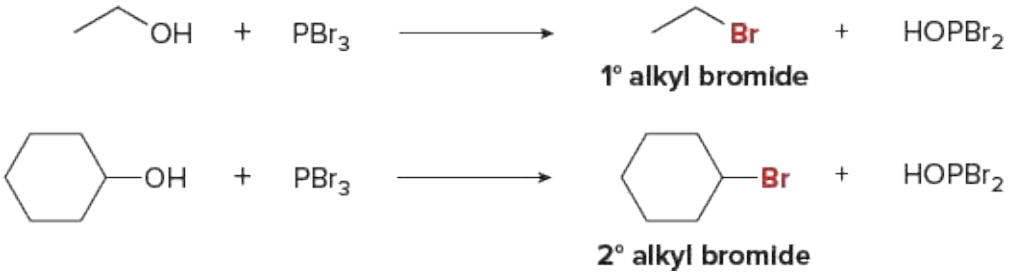
3 Nucleophilic attack of chloride and loss of the leaving group (SO_2 and Cl^-) form RCl in a single step.

Problem 9.19

If the reaction of an alcohol with $SOCl_2$ and pyridine follows an S_N2 mechanism, what is the stereochemistry of the alkyl chloride formed from (*R*)-butan-2-ol?

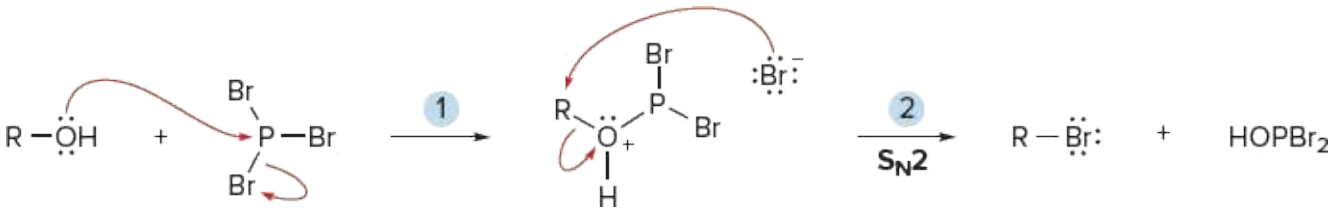
9.12B Reaction of ROH with PBr_3

In a similar fashion, the treatment of a 1° or 2° alcohol with phosphorus tribromide, PBr3, forms an alkyl bromide.



The mechanism for this reaction also consists of two parts: conversion of the OH group into a better leaving group, and nucleophilic attack by Br^- via an S_N2 reaction, as shown in Mechanism 9.8.

Mechanism 9.8 Reaction of ROH with PBr_3—An S_N2 Mechanism



1 **Reaction of the alcohol with PBr_3 converts the OH group to $OPBr_2$, a good leaving group, and generates the nucleophile, Br^-.**

2 **Nucleophilic attack of bromide and loss of the leaving group form RBr in a single step.**

Table 9.2 summarizes the methods for converting an alcohol to an alkyl halide presented in Sections 9.11 and 9.12.

Table 9.2 Summary of Methods for ROH → RX

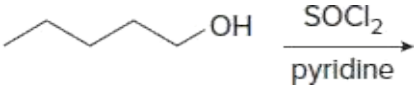
Overall reaction	Reagent	Comment
ROH → RCl	**HCl**	• Useful for all ROH • An S_N1 mechanism for 2° and 3° ROH; an S_N2 mechanism for CH_3OH and 1° ROH
	$SOCl_2$	• Best for CH_3OH, and 1° and 2° ROH • An S_N2 mechanism
ROH → RBr	**HBr**	• Useful for all ROH • An S_N1 mechanism for 2° and 3° ROH; an S_N2 mechanism for CH_3OH and 1° ROH
	PBr_3	• Best for CH_3OH, and 1° and 2° ROH • An S_N2 mechanism
ROH → RI	**HI**	• Useful for all ROH • An S_N1 mechanism for 2° and 3° ROH; an S_N2 mechanism for CH_3OH and 1° ROH

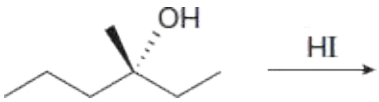
Problem 9.20

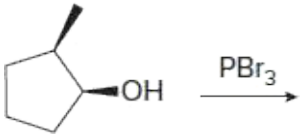
If the reaction of an alcohol with PBr_3 follows an S_N2 mechanism, what is the stereochemistry of the alkyl bromide formed from (*R*)-butan-2-ol?

Problem 9.21

Draw the organic products formed in each reaction, and indicate the stereochemistry of products that contain stereogenic centers.

a. 

b. 

c. 

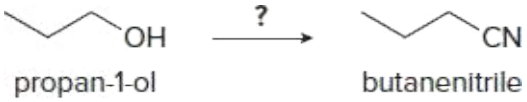
9.12C The Importance of Making RX from ROH

We have now learned two methods to prepare an alkyl chloride and two methods to prepare an alkyl bromide from an alcohol. If there is one good way to carry out a reaction, why search for more? A particular reagent might work well for one starting material, but not so well for another, so organic chemists try to devise several different ways to perform the same overall reaction.

Why are there so many ways to convert an alcohol to an alkyl halide? Alkyl halides are versatile starting materials in organic synthesis, as shown in Sample Problem 9.6.

Sample Problem 9.6 Converting an Alcohol to an S_N2 Product in Two Steps

Convert propan-1-ol to butanenitrile (A).

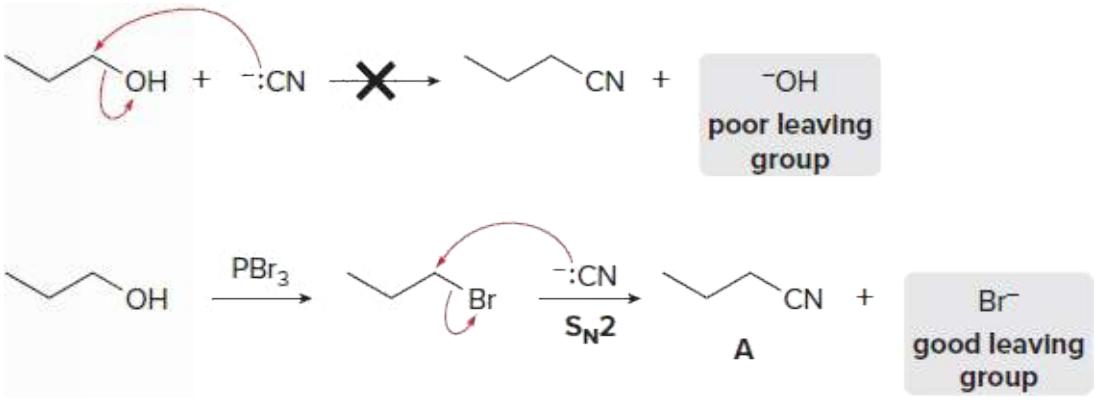


propan-1-ol — butanenitrile **A**

Solution

Direct conversion of propan-1-ol to A using ^-CN as a nucleophile is not possible because ^-OH is a poor leaving group. However, conversion of the OH group to a Br atom forms a good leaving group, which can then readily undergo an S_N2 reaction with ^-CN to yield A. The overall result of this two-

step sequence is the substitution of $^-$OH by $^-$CN.



Problem 9.22

Draw two steps to convert $(CH_3)_2CHOH$ to each of the following compounds: $(CH_3)_2CHN_3$ and $(CH_3)_2CHOCH_2CH_3$.

More Practice:

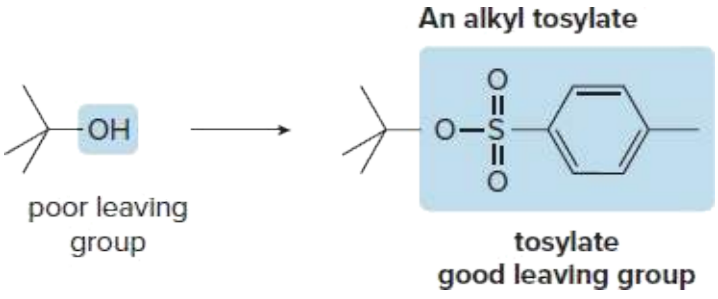
Try Problem 9.66.

9.13 Tosylate—Another Good Leaving Group

We have now learned two methods to convert the OH group of an alcohol to a better leaving group: treatment with strong acids (Section 9.8A), and conversion to an alkyl halide (Sections 9.11–9.12). Alcohols can also be converted to alkyl tosylates.

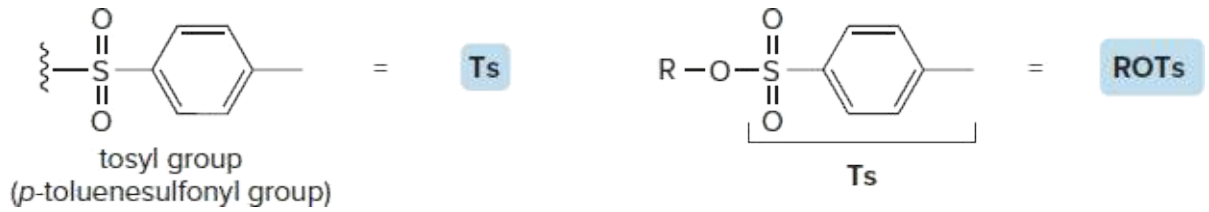
Recall from Section 1.5 that a third-row element like sulfur can have 10 or 12 electrons around it in a valid Lewis structure.

An alkyl tosylate is often called simply a tosylate.



An alkyl tosylate is composed of two parts: the alkyl group R, derived from an alcohol; and the tosylate (short for *p*-toluenesulfonate), which is a good leaving group. A tosyl

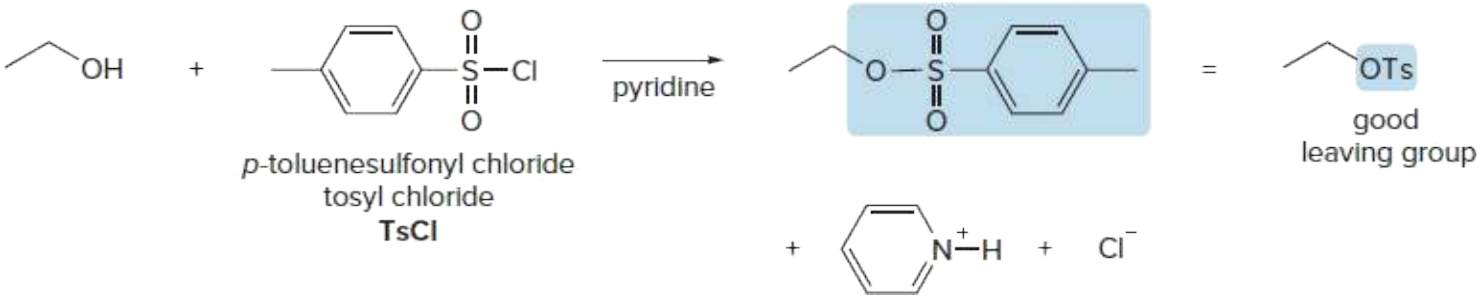
group, $CH_3C_6H_4SO_2-$, is abbreviated as Ts, so an alkyl tosylate becomes ROTs.



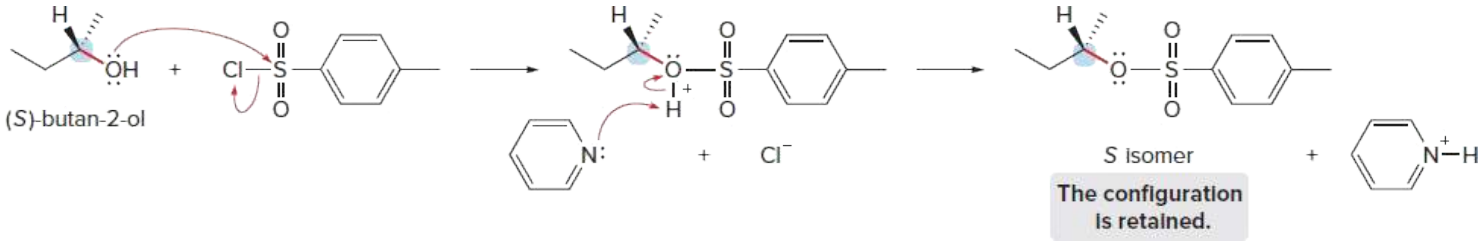
9.13A Conversion of Alcohols to Alkyl Tosylates

A tosylate (TsO^-) is similar to I^- in leaving group ability.

Alcohols are converted to alkyl tosylates by treatment with *p*-toluenesulfonyl chloride (TsCl) in the presence of pyridine. This overall process converts a poor leaving group (^-OH) into a good one (^-OTs). A tosylate is a good leaving group because its conjugate acid, *p*-toluenesulfonic acid ($CH_3C_6H_4SO_3H$, TsOH), is a strong acid (pK_a = −7, Section 2.6).



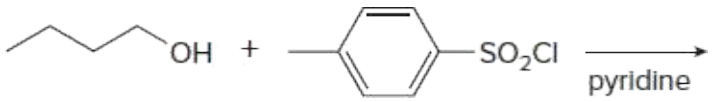
(*S*)-Butan-2-ol is converted to its tosylate with retention of configuration at the stereogenic center. Thus, the C—O bond of the alcohol must *not* be broken when the tosylate is formed.

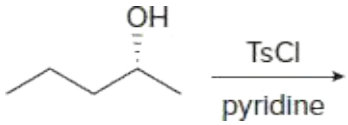


Problem 9.23

Draw the products of each reaction, and indicate the stereochemistry at any stereogenic center.

a.

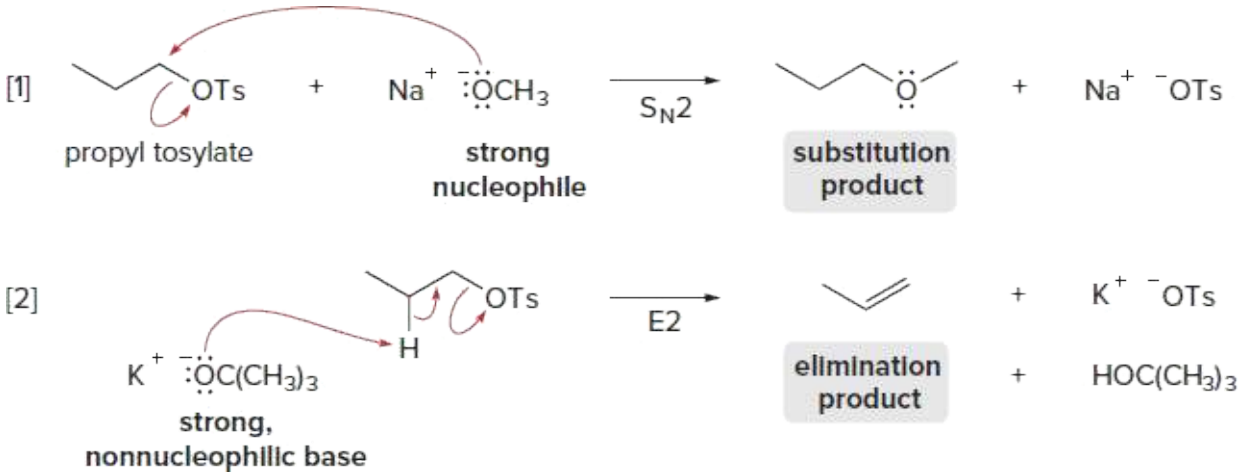


b. 

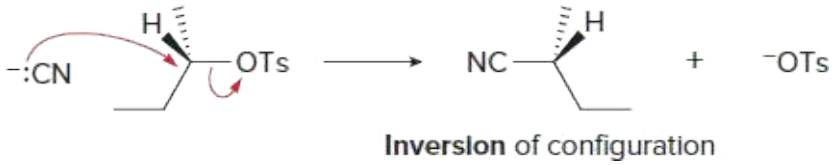
9.13B Reactions of Alkyl Tosylates

Because alkyl tosylates have good leaving groups, they undergo both nucleophilic substitution and β elimination, exactly as alkyl halides do. Generally, alkyl tosylates are treated with strong nucleophiles and bases, so that the mechanism of substitution is S_N2 and the mechanism of elimination is E2.

For example, propyl tosylate, which has the leaving group on a 1° carbon, reacts with $NaOCH_3$ to yield methyl propyl ether, the product of nucleophilic substitution by an S_N2 mechanism. Propyl tosylate reacts with $KOC(CH_3)_3$, a strong bulky base, to yield propene by an E2 mechanism.

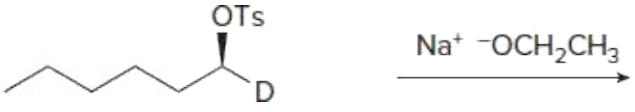


Because substitution occurs via an S_N2 mechanism, inversion of configuration results when the leaving group is bonded to a stereogenic center.



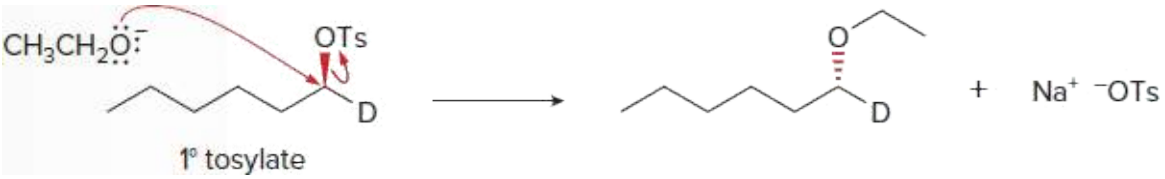
Sample Problem 9.7 Drawing the Substitution Product from an Alkyl Tosylate

Draw the product of the following reaction, including stereochemistry.



Solution

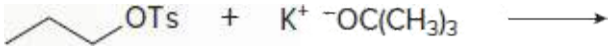
The 1° alkyl tosylate and the strong nucleophile both favor substitution by an S_N2 mechanism, which proceeds by backside attack, resulting in inversion of configuration at the stereogenic center. The leaving group is drawn in front (on a wedge), so the nucleophile approaches from behind, ending up on a dashed wedge.



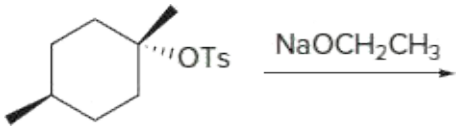
Problem 9.24

Draw the products of each reaction, and include the stereochemistry at any stereogenic center in the products.

a.

b. 

c.

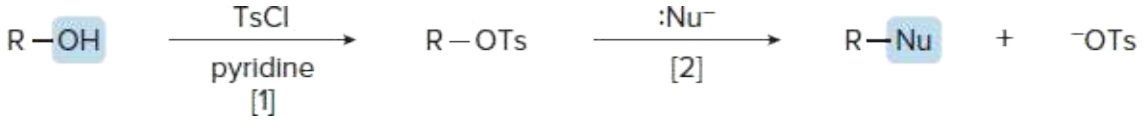
d. 

More Practice:

Try Problems 9.45d; 9.46b; 9.64d, f.

9.13C The Two-Step Conversion of an Alcohol to a Substitution Product

We now have another two-step method to convert an alcohol to a substitution product: reaction of an alcohol with TsCl and pyridine to form an alkyl tosylate (Step [1]), followed by nucleophilic attack on the tosylate (Step [2]).

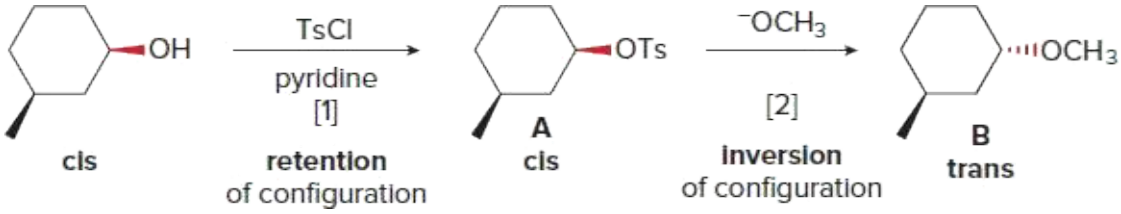


Let's look at the stereochemistry of this two-step process.

- Step [1], formation of the tosylate, proceeds with retention of configuration at a stereogenic center because the C—O bond remains intact.

- Step [2] is an S_N2 reaction, so it proceeds with inversion of configuration because the nucleophile attacks from the back side.
- Overall there is a net inversion of configuration at a stereogenic center.

For example, the treatment of *cis*-3-methylcyclohexanol with *p*-toluenesulfonyl chloride and pyridine forms a cis tosylate A, which undergoes backside attack by the nucleophile $^{-}OCH_3$ to yield the trans ether B.



Problem 9.25

Draw the products formed when (*S*)-butan-2-ol is treated with TsCl and pyridine, followed by NaOH. Label the stereogenic center in each compound as *R* or *S*. What is the stereochemical relationship between the starting alcohol and the final product?

9.13D A Summary of Substitution and Elimination Reactions of Alcohols

The reactions of alcohols in Sections 9.8–9.13C share two similarities:

- **The OH group is converted into a better leaving group by treatment with acid or another reagent.**
- **The resulting product undergoes either elimination or substitution, depending on the reaction conditions.**

Figure 9.8 summarizes these reactions with cyclohexanol as starting material.

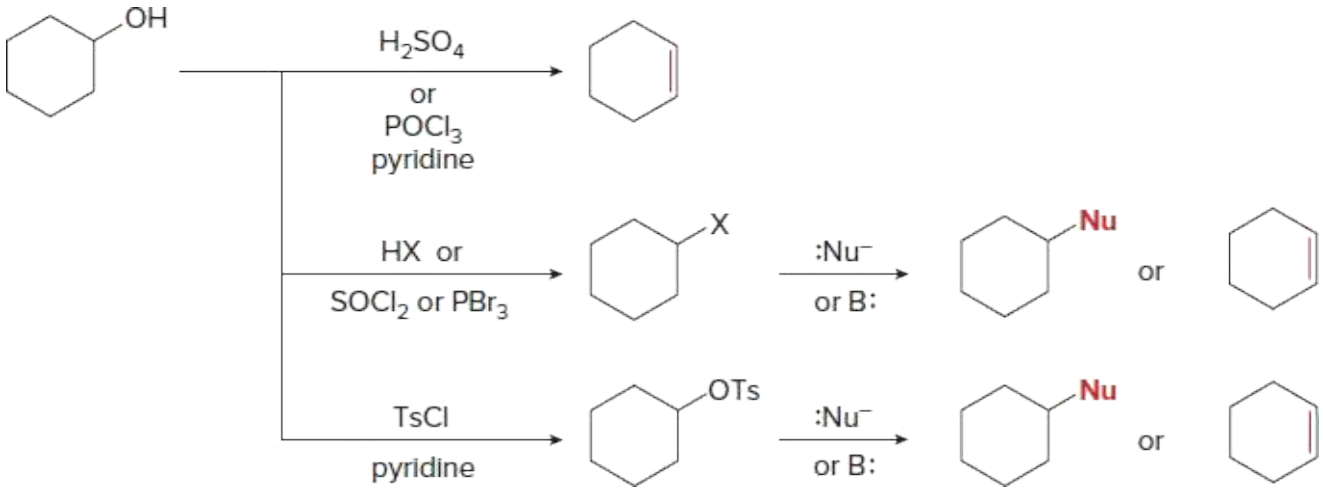


Figure 9.8 **Summary: Nucleophilic substitution and β elimination reactions of alcohols**

Problem 9.26

Draw the product formed when $(CH_3)_2CHOH$ is treated with each reagent.

a. $SOCl_2$, pyridine

b. TsCl, pyridine

c. H_2SO_4

d. HBr

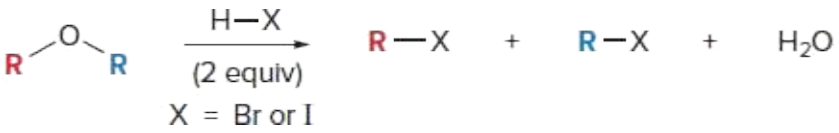
e. PBr_3, then NaCN

f. $POCl_3$, pyridine

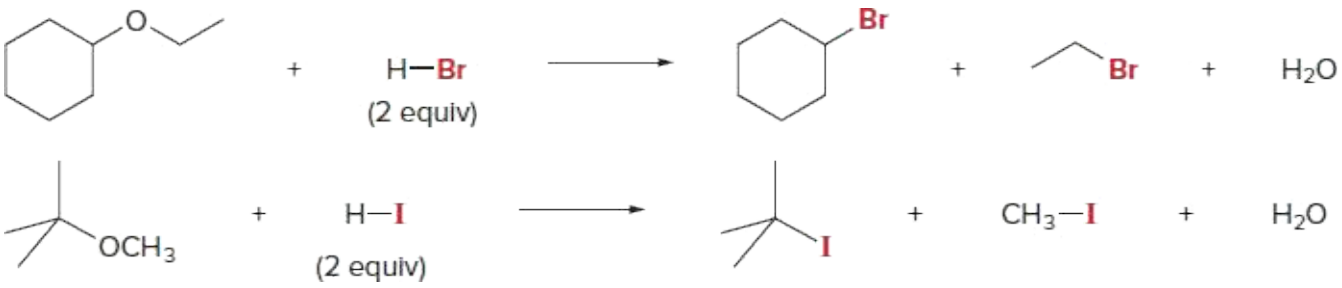
9.14 Reaction of Ethers with Strong Acid

Because ethers are so unreactive, diethyl ether and tetrahydrofuran (THF) are often used as solvents for organic reactions.

Recall from Section 9.7B that ethers have a poor leaving group, so they cannot undergo nucleophilic substitution or β elimination reactions directly. Instead, they must first be converted into a good leaving group by reaction with strong acids. Only HBr and HI can be used, though, because they are strong acids that are also sources of good nucleophiles (Br^- and I^-, respectively). When ethers react with HBr or HI, both C—O bonds are cleaved and two alkyl halides are formed as products.

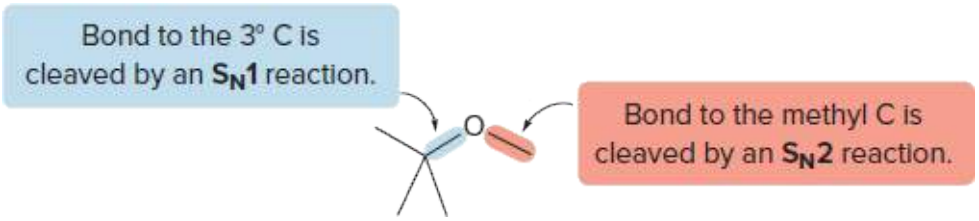


HBr or HI serves as a strong acid that both protonates the O atom of the ether and is the source of a good nucleophile (Br^- or I^-). Because both C—O bonds in the ether are broken, two successive nucleophilic substitution reactions occur.



- **The mechanism of ether cleavage is S_N1 or S_N2, depending on the identity of R.**
- **With 2° or 3° alkyl groups bonded to the ether oxygen, the C—O bond is cleaved by an S_N1 mechanism involving a carbocation; with methyl or 1° R groups, the C—O bond is cleaved by an S_N2 mechanism.**

For example, cleavage of $(CH_3)_3COCH_3$ with HI occurs at two bonds, as shown in Mechanism 9.9. The 3° alkyl group undergoes nucleophilic substitution by an S_N1 mechanism, resulting in the cleavage of one C—O bond. The methyl group undergoes nucleophilic substitution by an S_N2 mechanism, resulting in the cleavage of the second C—O bond.

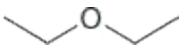


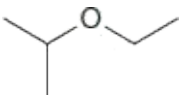
The mechanism illustrates the central role of HX in the reaction:

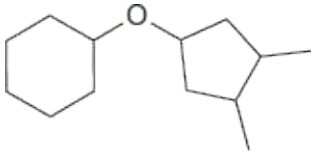
- **HX protonates the ether oxygen, thus making a good leaving group.**
- **HX provides a source of X^- for nucleophilic attack.**

Problem 9.27

What alkyl halides are formed when each ether is treated with HBr?

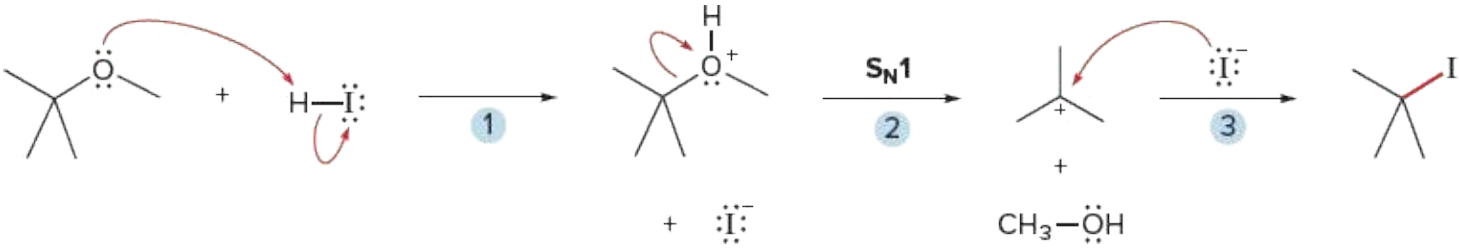
a. 

b. 

c. 

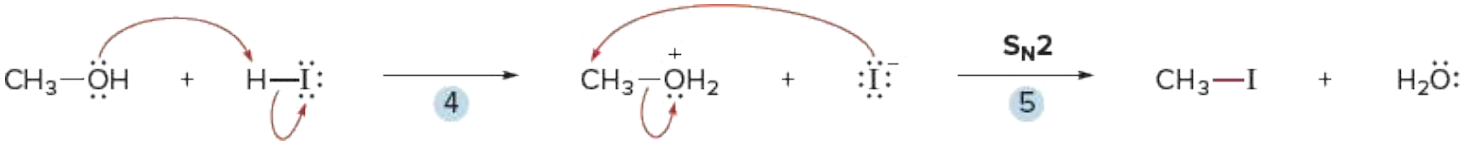
Mechanism 9.9 Mechanism of Ether Cleavage in Strong Acid—$(CH_3)_3COCH_3 + HI \rightarrow (CH_3)_3CI + CH_3I + H_2O$

Part [1] Cleavage of the 3° C—O bond by an S_N1 mechanism



1. **Protonation of the ether O atom forms a good leaving group.**
2. **Cleavage of the C—O bond to the 3° carbon forms a 3° carbocation and CH_3OH.**
3. **Nucleophilic attack of I^- forms the substitution product.**

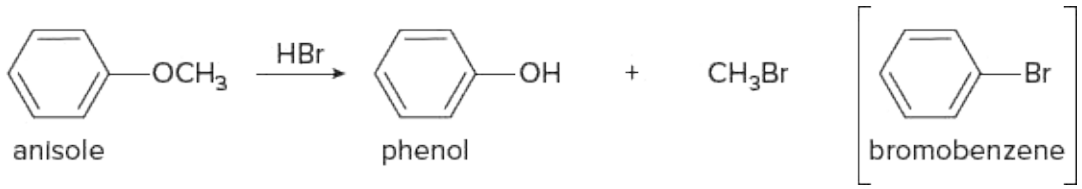
Part [2] Cleavage of the CH_3—O bond by an S_N2 mechanism



4. **Protonation of the OH group forms a good leaving group (H_2O).**
5. **Nucleophilic attack of iodide forms the second alkyl halide, CH_3I. Because the mechanism is S_N2, the C—O bond is broken as the C—I bond (in red) is formed.**

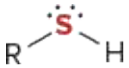
Problem 9.28

Explain why the treatment of anisole with HBr yields phenol and CH_3Br, but not bromobenzene.

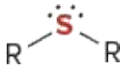


9.15 Thiols and Sulfides

Thiols and sulfides are sulfur analogues of alcohols and ethers, respectively.



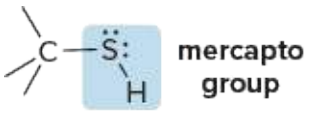
thiol



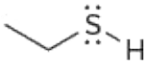
sulfide

9.15A Thiols

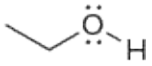
Thiols, also called mercaptans, contain a mercapto group (SH) bonded to a carbon atom. Because sulfur is below oxygen in the periodic table, the sulfur atom is surrounded by two atoms and two lone pairs, giving thiols a bent shape. Unlike alcohols, however, thiols are incapable of intermolecular hydrogen bonds, so thiols have *lower* boiling points and melting points than alcohols with a similar number of carbons.



thiol



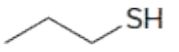
ethanethiol
bp 35 °C



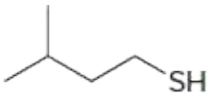
ethanol
bp 78 °C

Many simple thiols have pungent and disagreeable odors. Skunks, onions, and human sweat all contain thiols.

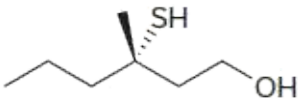
Page 377



propane-1-thiol
onion odor



3-methylbutane-1-thiol
skunk odor

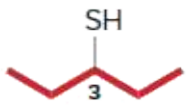


(*S*)-3-methyl-3-sulfanylhexan-1-ol
onion-like odor in human sweat

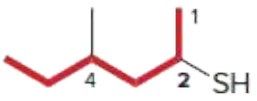
Thiols are named in a similar method to alcohols, using the suffix *-thiol* instead of the suffix *-ol*. To name a thiol in the IUPAC system:

- **Name the parent carbon chain and add the suffix *-thiol.***
- **Number the carbon chain to give the SH group the lower number and apply the other rules of nomenclature.**

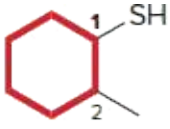
Examples of thiol nomenclature are given in Figure 9.9.



pentane-3-thiol



4-methylhexane-2-thiol



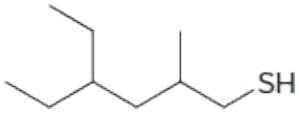
2-methylcyclohexanethiol

Figure 9.9 **Naming thiols**

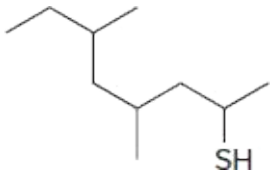
Problem 9.29

Name each thiol.

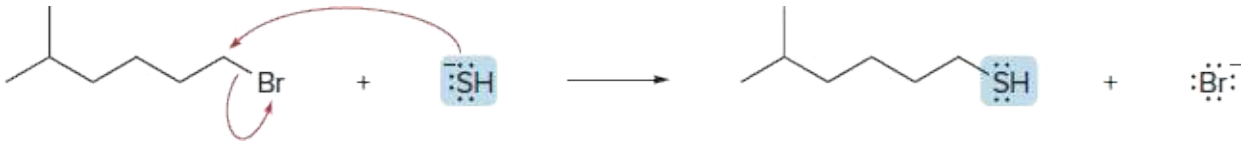
a.



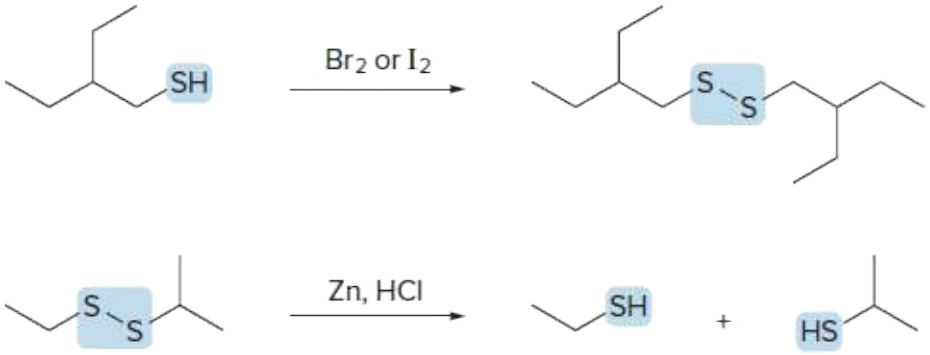
b.



Thiols are prepared by S_N2 reactions of alkyl halides with ^-SH, a good nucleophile.



Thiols are easily oxidized with Br_2 or I_2 to disulfides (RSSR), compounds that contain a sulfur–sulfur bond. This reaction is an oxidation (Section 4.14) because H atoms are removed from the thiol in forming the disulfide. Disulfides are reduced to thiols with Zn and acid.

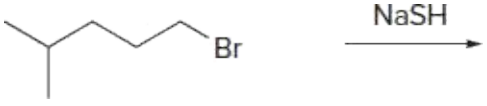


Disulfide formation is especially important in determining the shape and properties of some proteins that contain the amino acid cysteine, as we will learn in Chapter 27.

Problem 9.30

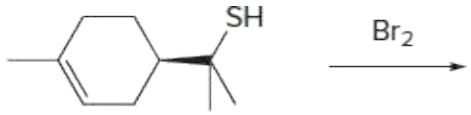
Draw the product of each reaction.

a.

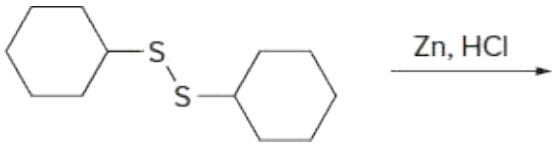


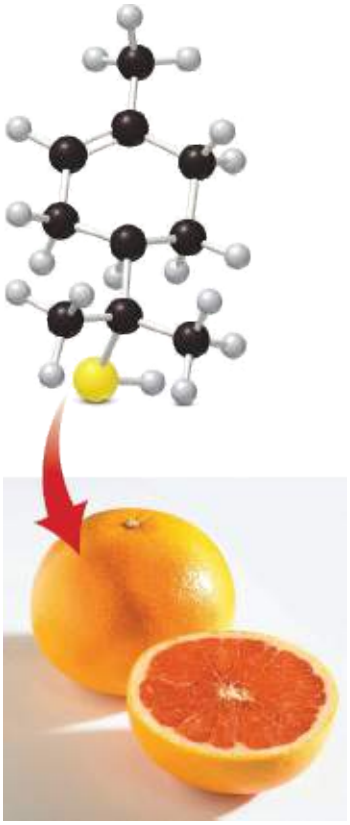
b.

c.



grapefruit mercaptan

d. 



The potent odor of grapefruit mercaptan (Problem 9.30c) contributes to the characteristic aroma of grapefruit.

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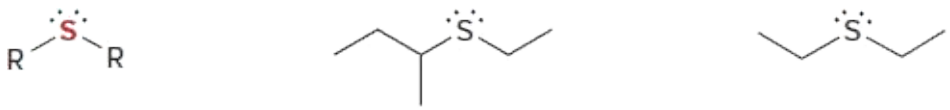
9.15B Sulfides

Sulfides contain two alkyl groups bonded to a sulfur atom. Sulfides are named with the same rules used to name ethers. The suffix *sulfide* is used instead of *ether* for simple compounds.



sulfide

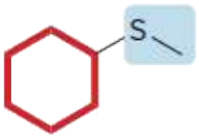
sec-butyl ethyl sulfide

diethyl sulfide

To name more complex sulfides using the IUPAC system, one alkyl group is named as a parent chain and the other is named as part of a substituent bonded to that chain.

- **Name the simpler alkyl group + S atom as an *alkylthio* substituent.**
- **Name the remaining alkyl group as an alkane with an alkylthio**

substituent using the usual rules of nomenclature.



methyl**thio**cyclohexane

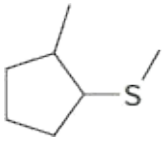
3-ethyl**thio**-5-methyloctane

Problem 9.31

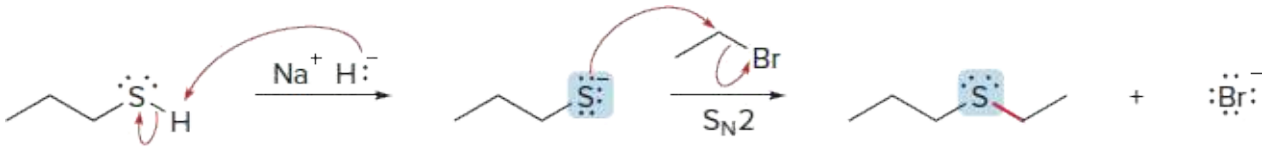
Give the IUPAC name for each sulfide.

a.

b.



Sulfides are prepared from thiols by an S_N2 reaction that is analogous to the Williamson ether synthesis.

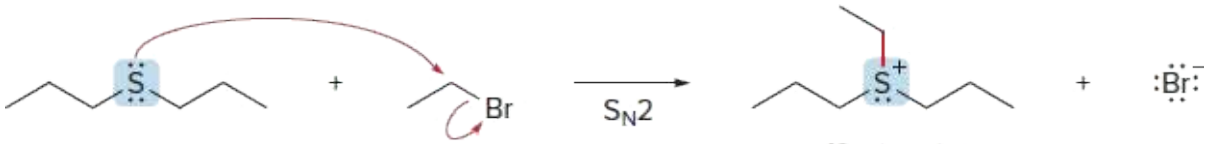


propane-1-thiol

sulfur nucleophile + H_2

ethyl propyl sulfide

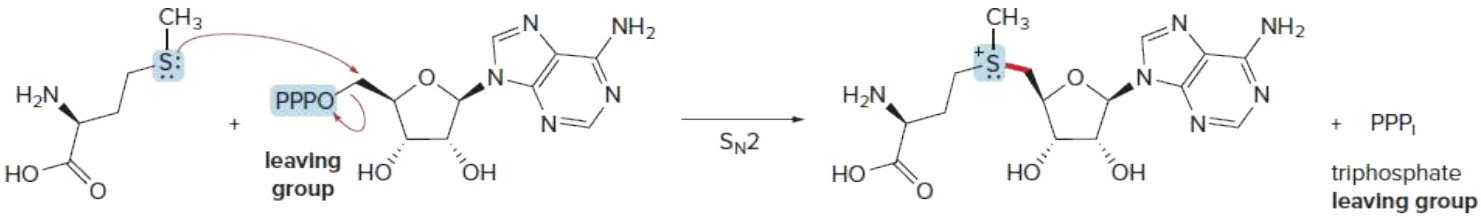
Sulfides contain a nucleophilic sulfur atom that reacts readily with unhindered alkyl halides to form sulfonium ions.



sulfonium ion

S-Adenosylmethionine (SAM), a biological sulfonium ion that was introduced in Section 7.16, is synthesized from the amino acid methionine, which contains a nucleophilic sulfide, and adenosine triphosphate (ATP), which contains a triphosphate leaving group (Section 7.16).

Page 379



methionine

adenosine triphosphate ATP

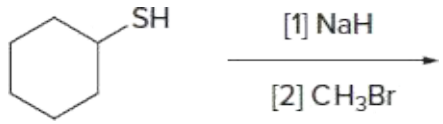
S-adenosylmethionine

triphosphate **leaving group**

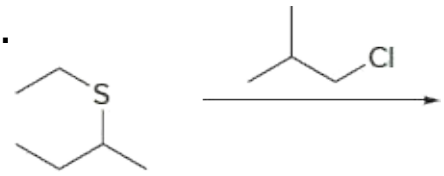
Problem 9.32

Draw the product of each reaction.

a.

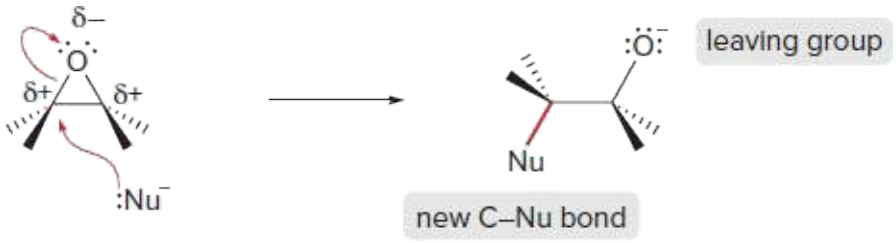


b.

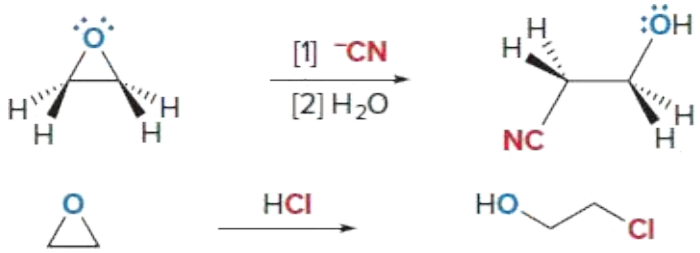


9.16 Reactions of Epoxides

Although epoxides do not contain a good leaving group, they contain a strained three-membered ring with two polar bonds. Nucleophilic attack opens the strained three-membered ring, making it a favorable process even with the poor leaving group.

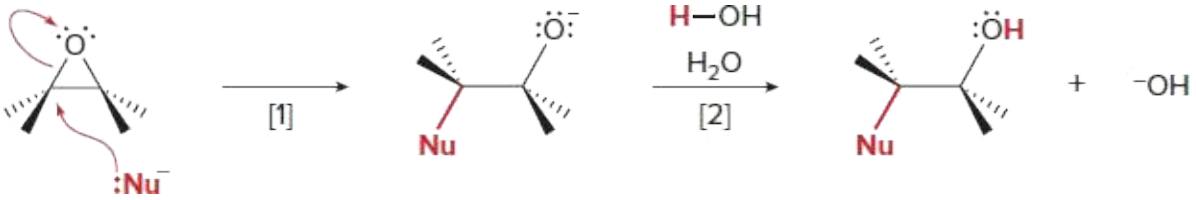


This reaction occurs readily with strong nucleophiles like ⁻CN, and with acids like HZ, where Z is a nucleophilic atom.



9.16A Opening of Epoxide Rings with Strong Nucleophiles

Virtually all strong nucleophiles open an epoxide ring by a two-step reaction sequence.

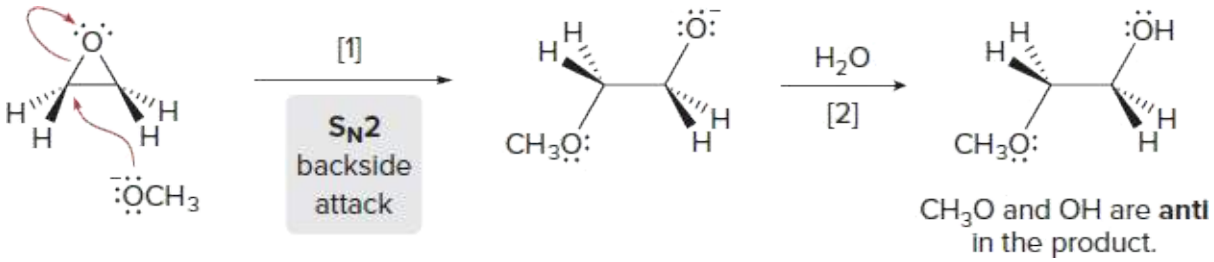


- Step [1]: The nucleophile attacks an electron-deficient carbon of the epoxide, cleaving a C—O bond and relieving the strain of the three-membered ring.
- Step [2]: Protonation of the alkoxide with water generates a neutral product with

two functional groups on adjacent atoms.

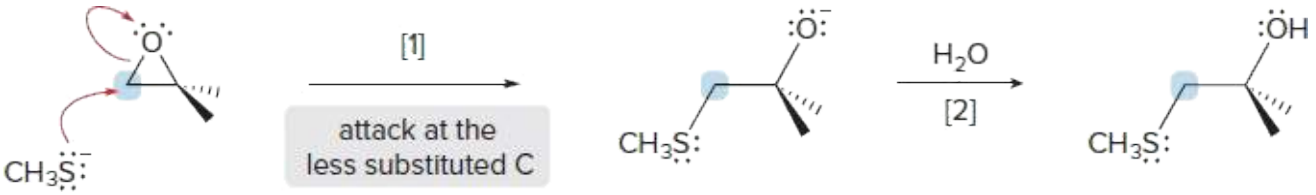
Common nucleophiles that open epoxide rings include ^-OH, ^-OR, ^-CN, ^-SR, and NH_3. With these strong nucleophiles, the reaction occurs via an S_N2 mechanism, resulting in two consequences:

- **The nucleophile opens the epoxide ring from the back side.**



Other examples of the nucleophilic opening of epoxide rings are presented in Sections 12.6 and 17.14.

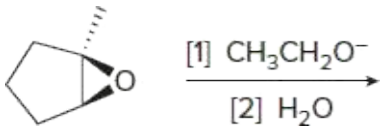
- **In an unsymmetrical epoxide, the nucleophile attacks at the *less* substituted carbon atom.**



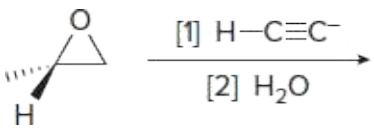
Problem 9.33

Draw the product of each reaction, and indicate the stereochemistry at any stereogenic center.

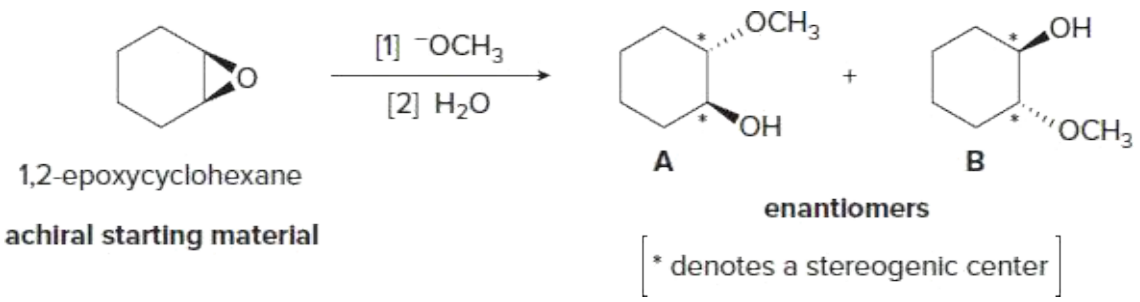
a.



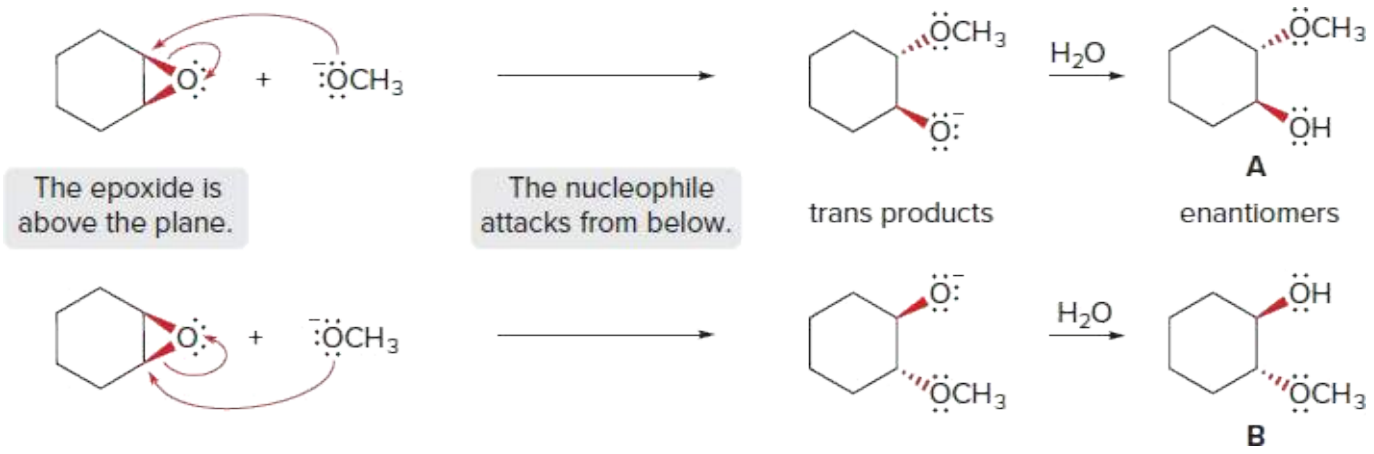
b.



1,2-Epoxycyclohexane, an achiral epoxide with a plane of symmetry, reacts with $^-OCH_3$ to yield two *trans*-1,2-disubstituted cyclohexanes, A and B, which are enantiomers; each has two stereogenic centers.



Nucleophilic attack of $^{-}OCH_3$ occurs from the back side at *either* C—O bond, because both ends are equally substituted. Because attack at either side occurs with equal probability, an equal amount of the two enantiomers is formed—a racemic mixture. This is a specific example of a general rule concerning the stereochemistry of products obtained from an achiral reactant.



- **Whenever an achiral reactant yields a product with stereogenic centers, the product must be achiral (meso) or racemic.**

This general rule can be restated in terms of optical activity. Recall from Section 5.12 that achiral compounds and racemic mixtures are optically inactive.

- **Optically *inactive* starting materials give optically *inactive* products.**

Problem 9.34

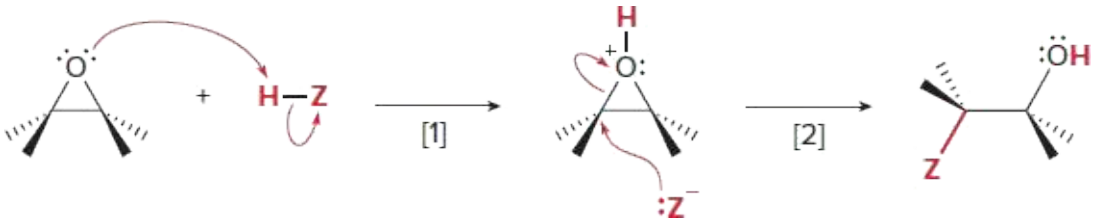
The cis and trans isomers of 2,3-dimethyloxirane both react with ^{-}OH to give butane-2,3-diol. One stereoisomer gives a single achiral product, and one gives two chiral enantiomers. Which epoxide gives one product and which gives two?

cis-2,3-dimethyloxirane

one enantiomer of *trans*-2,3-dimethyloxirane

9.16B Reaction with Acids HZ

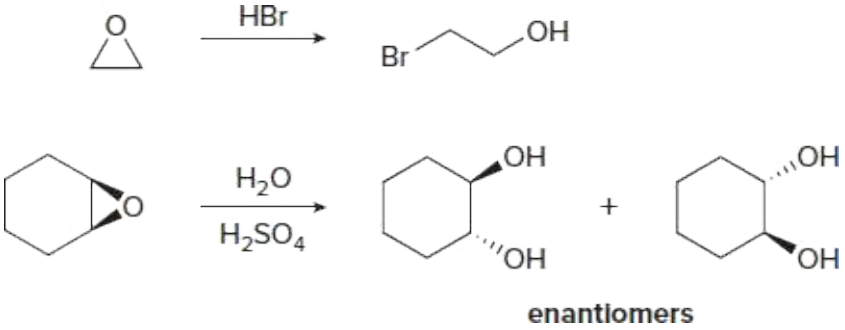
Acids HZ that contain a nucleophile Z also open epoxide rings by a two-step reaction sequence.



- Step [1]: Protonation of the epoxide oxygen with HZ makes the epoxide oxygen into a good leaving group (OH). It also provides a source of a good nucleophile (Z^-) to open the epoxide ring.
- Step [2]: The nucleophile Z^- then opens the protonated epoxide ring by backside attack.

These two steps—protonation followed by nucleophilic attack—are the exact reverse of the opening of epoxide rings with strong nucleophiles, where nucleophilic attack precedes protonation.

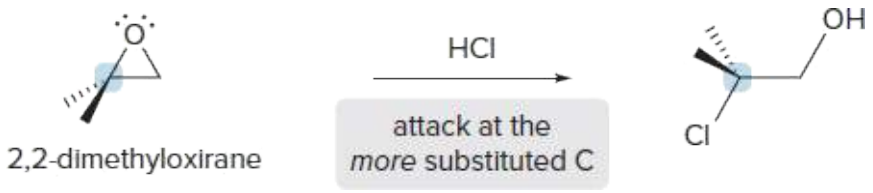
HCl, HBr, and HI all open an epoxide ring in this manner. H_2O and ROH can, too, but acid must also be added. Regardless of the reaction, the product has an OH group from the epoxide on one carbon and a new functional group Z from the nucleophile on the adjacent carbon. With epoxides fused to rings, *trans*-1,2-disubstituted cycloalkanes are formed.



Although backside attack of the nucleophile suggests that this reaction follows an S_N2 mechanism, the regioselectivity of the reaction with unsymmetrical epoxides does not.

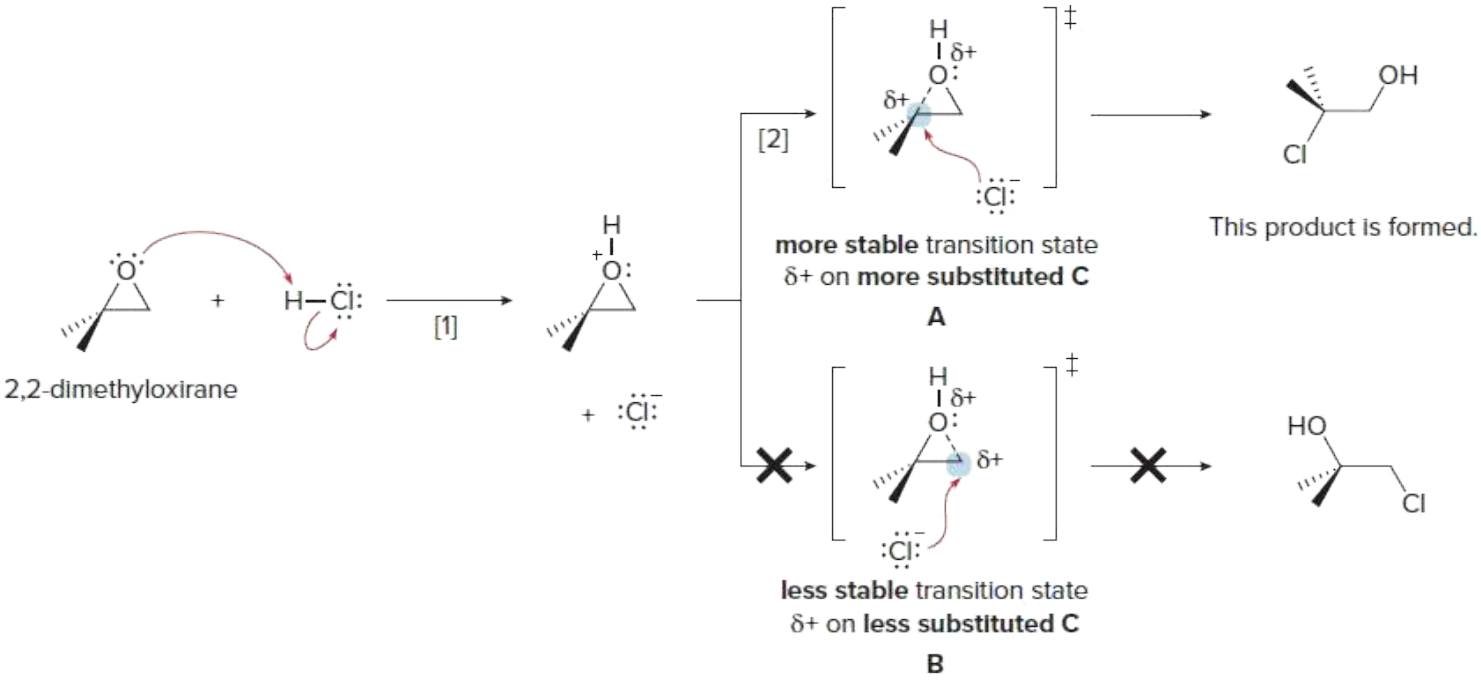
- **With unsymmetrical epoxides, nucleophilic attack occurs at the *more* substituted carbon atom.**

For example, the treatment of 2,2-dimethyloxirane with HCl results in Page 382 nucleophilic attack at the carbon with two methyl groups.



Backside attack of the nucleophile suggests an S_N2 mechanism, but attack at the more substituted carbon suggests an S_N1 mechanism. To explain these results, the mechanism of nucleophilic attack is thought to be somewhere in between S_N1 and S_N2.

Figure 9.10 illustrates two possible pathways for the reaction of 2,2-dimethyloxirane with HCl. Backside attack of Cl^- at the more substituted carbon proceeds via transition state A, whereas backside attack of Cl^- at the less substituted carbon proceeds via transition state B. Transition state A has a partial positive charge on a more substituted carbon, making it more stable. Thus, the preferred reaction path takes place by way of the lower-energy transition state A.



- Transition state **A** is lower in energy because the partial positive charge (δ+) is located on the *more* substituted carbon. In this case, therefore, nucleophilic attack occurs from the back side (an S_N2 characteristic) at the *more* substituted carbon (an S_N1 characteristic).

Figure 9.10 **Opening of an unsymmetrical epoxide ring with HCl**

Opening of an epoxide ring with either a strong nucleophile $:Nu^-$ or an acid HZ is regioselective, because one constitutional isomer is the major or exclusive product. The site selectivity of these two reactions, however, is *exactly the opposite*.

- **With a strong nucleophile, $:Nu^-$ attacks at the *less* substituted carbon.**
- **With an acid HZ, the nucleophile attacks at the *more* substituted**

carbon.

Sample Problem 9.8 Determining the Regioselectivity of Opening an Epoxide Ring

What product is formed when 2,2-dimethyloxirane is treated with each set of reagents: $^{-}OCH_3$ followed by H_2O, or CH_3OH and H_2SO_4?

Solution

All nucleophiles open an epoxide ring from the back side. Classify the nucleophile to determine if nucleophilic attack occurs at the *more* or *less* substituted carbon. With strong, negatively charged nucleophiles, attack occurs at the *less* substituted carbon, whereas with acids HZ, nucleophilic attack occurs at the *more* substituted carbon.

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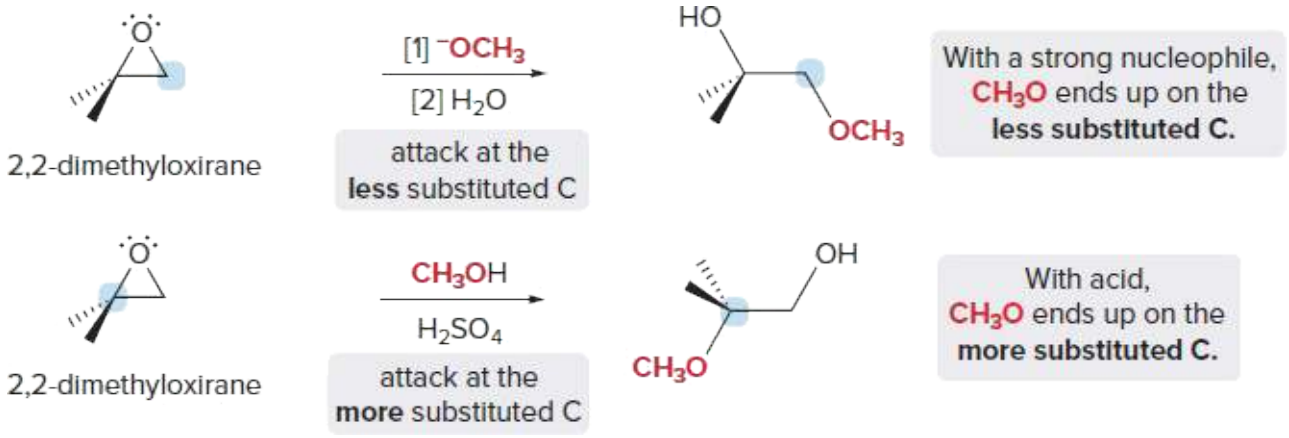
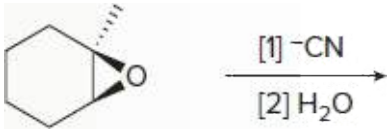


Problem 9.35

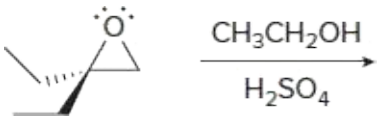
Draw the product of each reaction.

a.

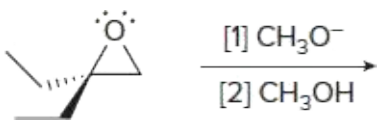
b.



c.



d.



More Practice:

Try Problems 9.60; 9.62; 9.64g, h.

The reaction of epoxide rings with nucleophiles is important for the synthesis of many biologically active compounds, including salmeterol and albuterol, two bronchodilators used in the treatment of asthma (Figure 9.11).

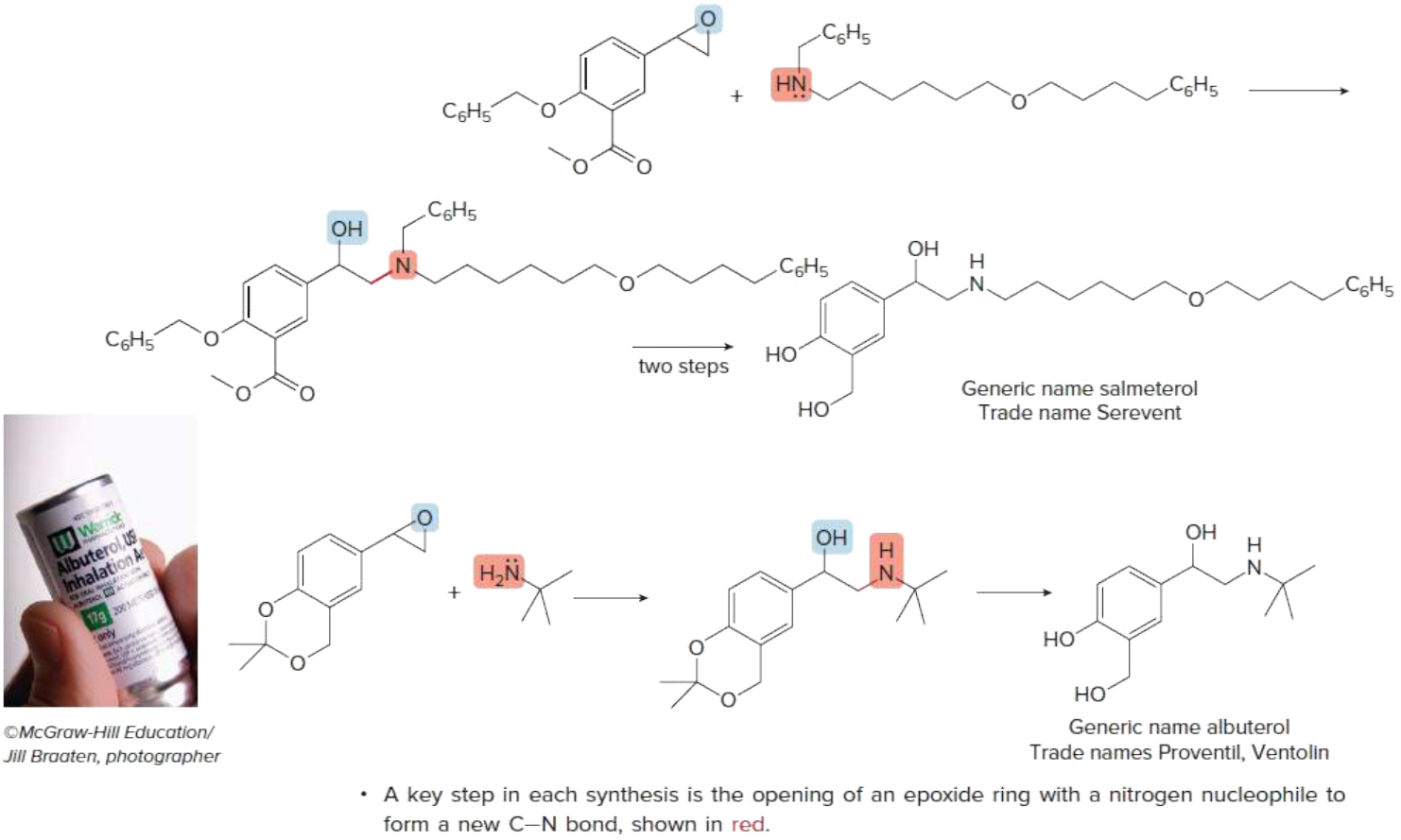


Figure 9.11 **The synthesis of two bronchodilators uses the opening of an epoxide ring.**

9.17 Application: Epoxides, Leukotrienes, and Asthma

The opening of epoxide rings with nucleophiles is a key step in some important biological processes.

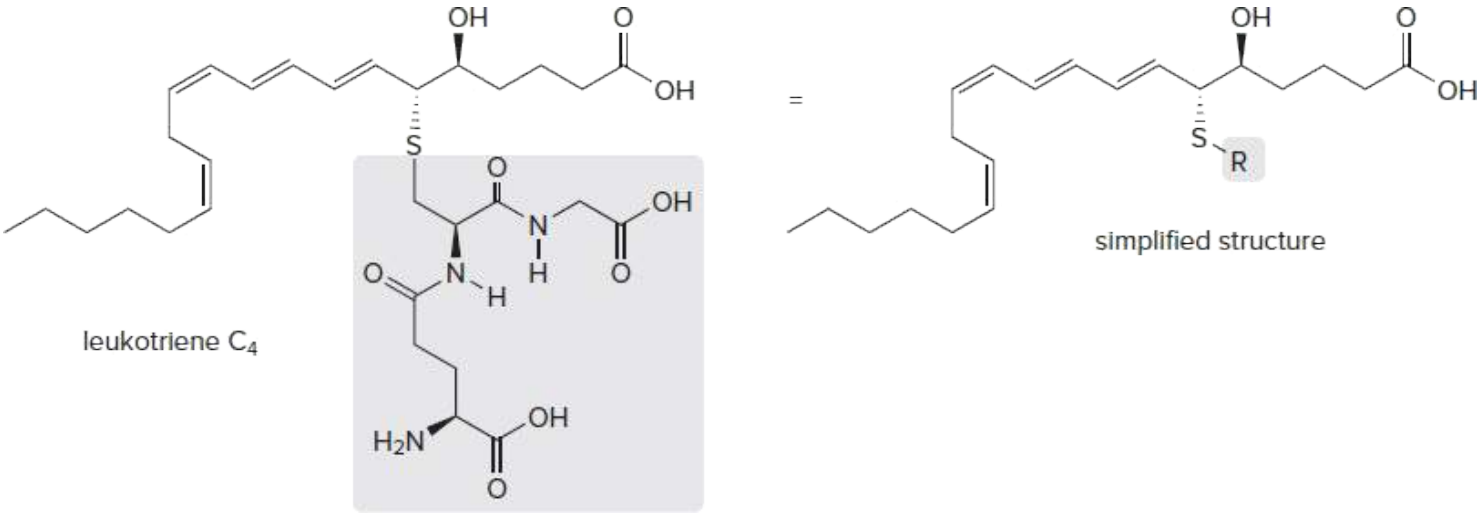
9.17A Asthma and Leukotrienes

Asthma is an obstructive lung disease that affects millions of Americans. Because it involves episodic constriction of small airways, bronchodilators such as albuterol (Figure 9.11) are used to treat symptoms by widening airways. Because asthma is also characterized by chronic inflammation, inhaled steroids that reduce inflammation are

also commonly used.

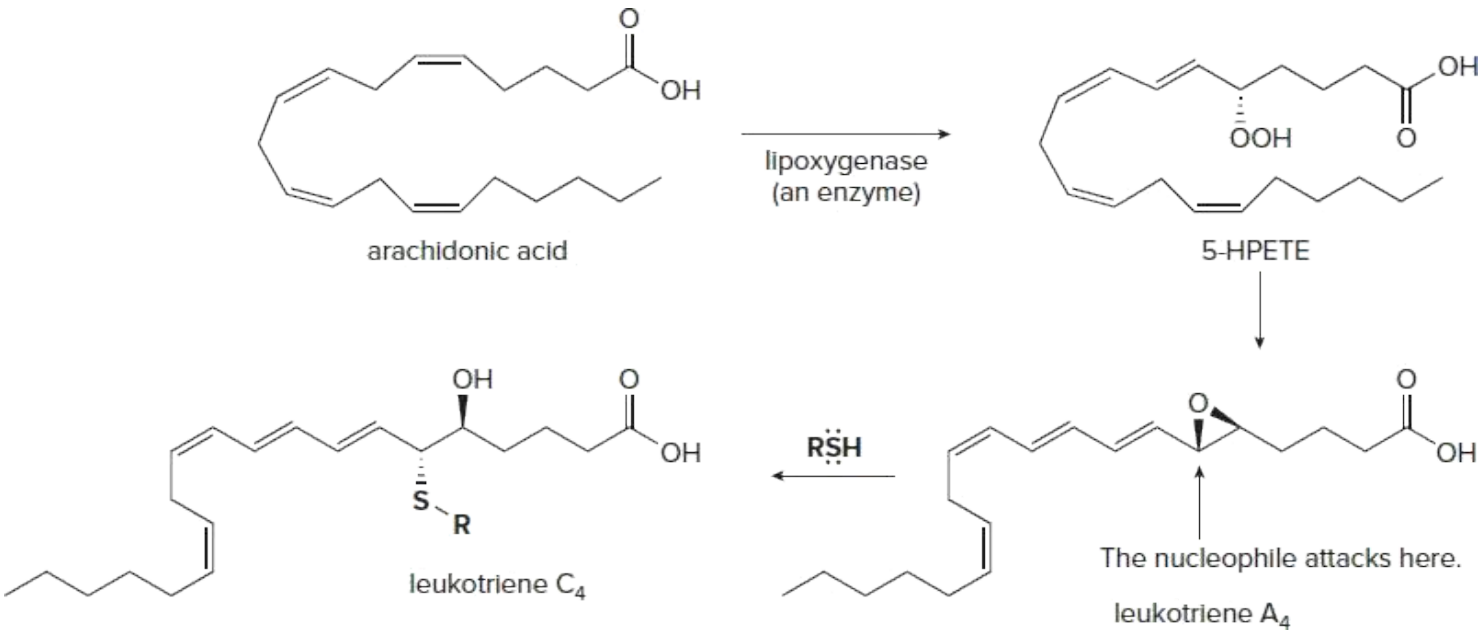
Leukotrienes were first synthesized in 1980 in the laboratory of Professor E. J. Corey, the 1990 recipient of the Nobel Prize in Chemistry.

Leukotrienes are molecules that contribute to the asthmatic response. A typical example, leukotriene C_4, is shown. Although its biological activity was first observed in the 1930s, the chemical structure of leukotriene C_4 was not determined until 1979. Structure determination and chemical synthesis were difficult because leukotrienes are highly unstable and extremely potent, and are therefore present in tissues in exceedingly small amounts.



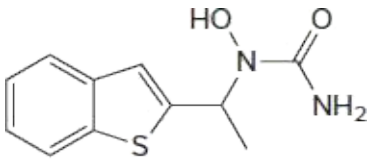
9.17B Leukotriene Synthesis and Asthma Drugs

Leukotrienes are synthesized in cells by the oxidation of arachidonic acid to 5-HPETE, which is then converted to an epoxide, leukotriene A_4. Opening of the epoxide ring with a sulfur nucleophile RSH yields leukotriene C_4.



New asthma drugs act by blocking the synthesis of leukotriene C_4 from arachidonic acid. For example, zileuton (trade name Zyflo CR) inhibits the enzyme (called a lipoxygenase) needed for the first step of this process. By blocking the synthesis of leukotriene C_4, a compound responsible for the disease, zileuton treats the cause of asthma, not just its symptoms.

Page 385

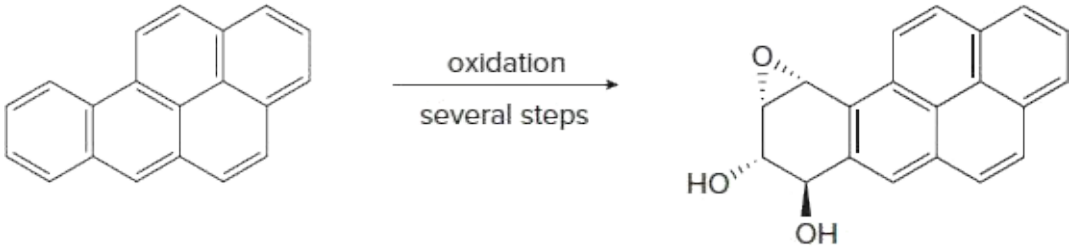


Generic name zileuton
Trade name Zyflo CR
anti-asthma drug

9.18 Application: Benzo[*a*]pyrene, Epoxides, and Cancer

The sooty exhaust from trucks and buses contains PAHs such as benzo[a]pyrene. ***©McGraw-Hill Education/John Thoeming, photographer***

Benzo[*a*]pyrene is a widespread environmental pollutant, produced during the combustion of all types of organic material—gasoline, fuel oil, wood, garbage, and cigarettes. It is a polycyclic aromatic hydrocarbon (PAH), a class of compounds that is discussed further in Chapter 15.



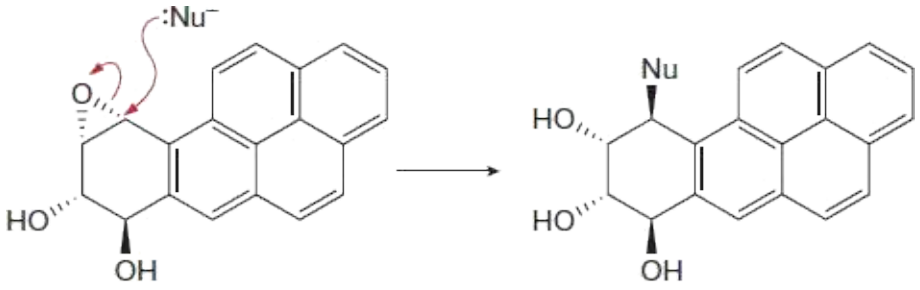
benzo[*a*]pyrene

water insoluble

a diol epoxide

more water soluble

After this nonpolar and water-insoluble hydrocarbon is inhaled or ingested, it is oxidized in the liver to a diol epoxide. Oxidation is a common fate of foreign substances that are not useful nutrients for the body. The oxidation product has three oxygen-containing functional groups, making it much more water soluble, and more readily excreted in urine. It is also a potent carcinogen. The strained three-membered ring of the epoxide reacts readily with biological nucleophiles $:Nu^-$ (such as DNA or an enzyme), leading to ring-opened products that often disrupt normal cell function, causing cancer or cell death.



carcinogen

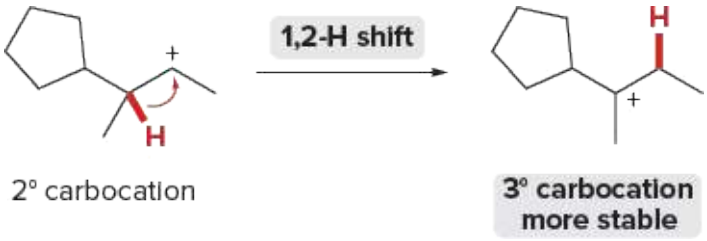
These examples illustrate the central role of the nucleophilic opening of epoxide rings in two well-defined cellular processes.

Chapter 9 REVIEW

KEY CONCEPTS

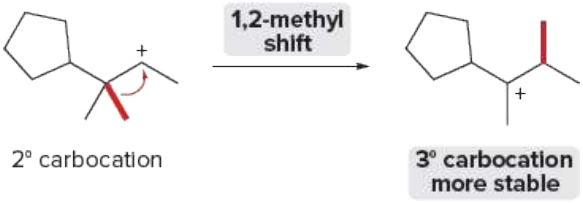
Carbocation rearrangements (9.9)

1 Hydride shift



- ***Less* stable carbocations rearrange to *more* stable carbocations by the shift of a hydrogen atom.**

2 Alkyl shift

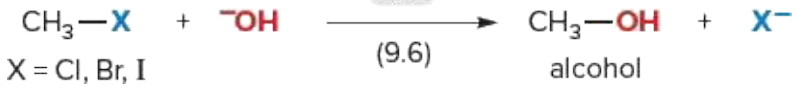


- ***Less* stable carbocations rearrange to *more* stable carbocations by the shift of alkyl group.**

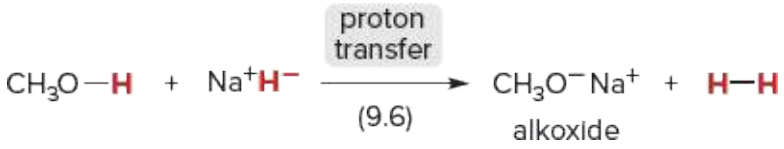
KEY REACTIONS

[1] Preparation of alcohols, alkoxides, ethers, epoxides, thiols, and sulfides

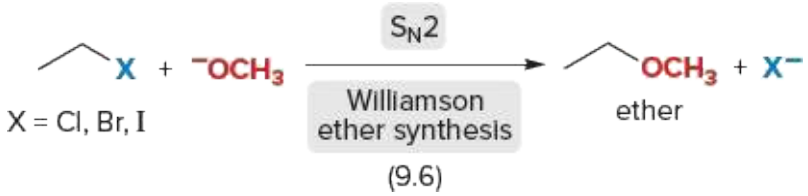
1



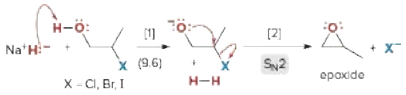
2



3



4



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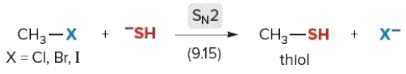

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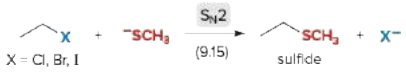

Try Problems 9.43; 9.54; 9.61; 9.64c, d, k.

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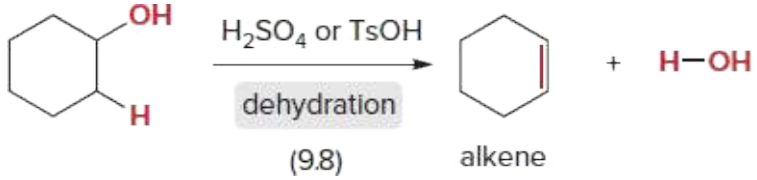
[2] Reactions of alcohols

1



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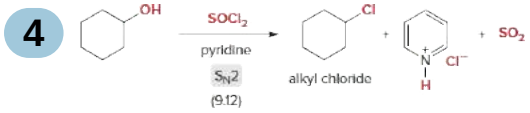
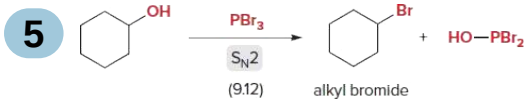
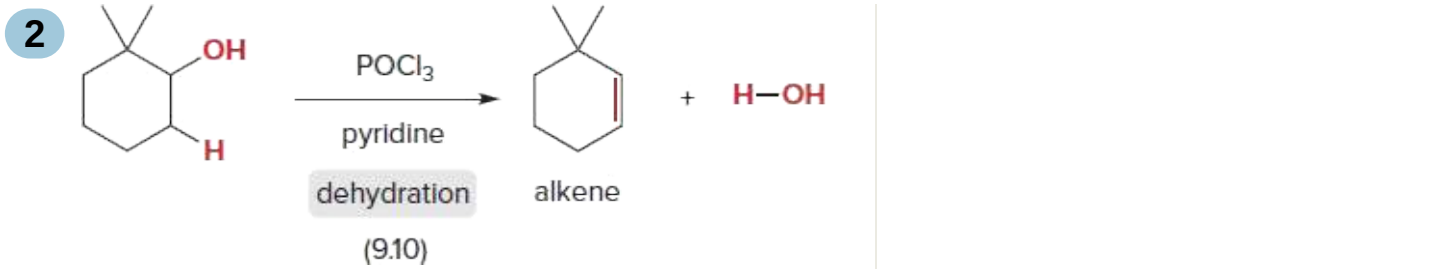


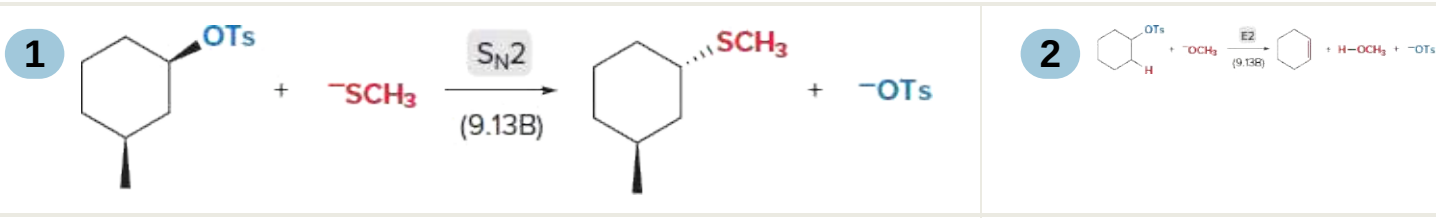
5





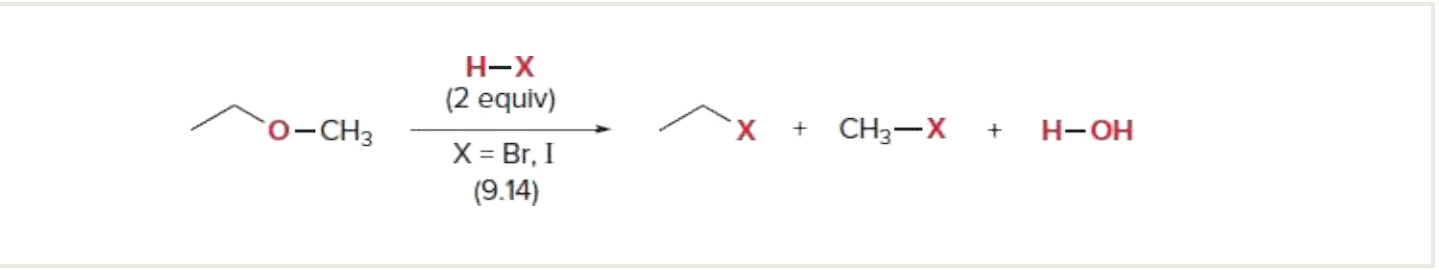
See Table 9.2, Figure 9.8. Try Problems 9.37f, 9.38, 9.43, 9.44.

[3] Reactions of alkyl tosylates



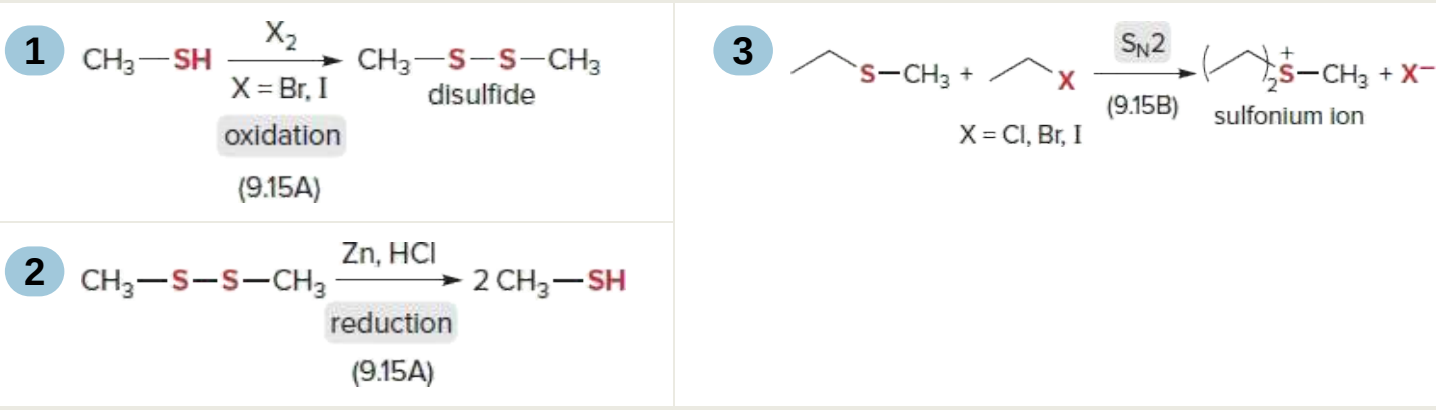
See Sample Problem 9.7. Try Problems 9.45d, 9.46b, 9.64f.

[4] Reactions of ethers



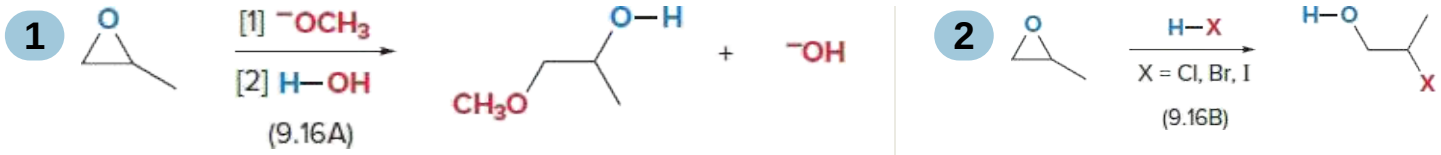
Try Problems 9.56, 9.64j.

[5] Reactions involving thiols and sulfides



Try Problems 9.64c, k, l; 9.65.

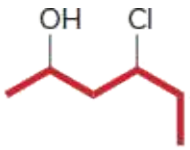
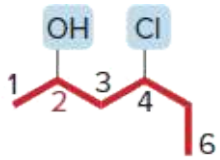
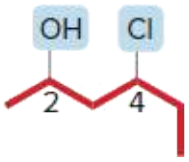
[6] Reactions of epoxides



See Sample Problem 9.8, Figure 9.10. Try Problems 9.59; 9.60; 9.62; 9.64g, h.

KEY SKILLS

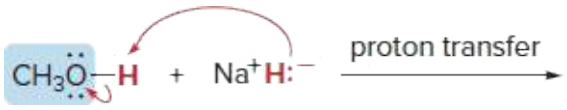
[1] Naming an acyclic alcohol using the IUPAC system (9.3A)

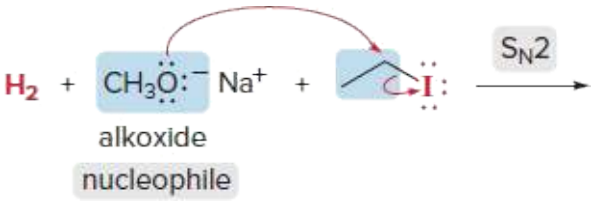
1 Name the parent.	2 Number the chain.	3 Name and number the substituents.
• Count the number of carbons in the longest chain containing the carbon bonded to the OH group. • Change the *-e* ending of the parent alkane to the suffix *-ol*.  **6** C's in the longest chain **hexanol** • parent + suffix	• Number the carbon chain to give the OH group the lower number.  **OH** substituent at **C2** **hexan-2-ol** • Insert the number for the OH group before the suffix *-ol*.	• Name the substituents and combine the parts. hydroxy at C2 chloro at C4  **Answer: 4-chlorohexan-2-ol**

See *How To*, p. 348; Figure 9.2. Try Problems 9.37a, 9.39.

[2] Using the Williamson ether synthesis to convert an alcohol to an ether (9.6)

1 Remove a proton to form an alkoxide.	2 React the alkoxide with an alkyl halide.

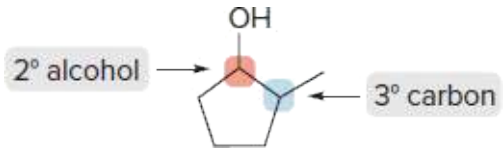
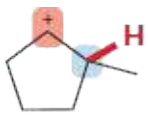
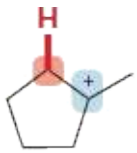




- **The reaction works best for CH_3X and 1° RX.**

See Sample Problem 9.2. Try Problems 9.54, 9.64i.

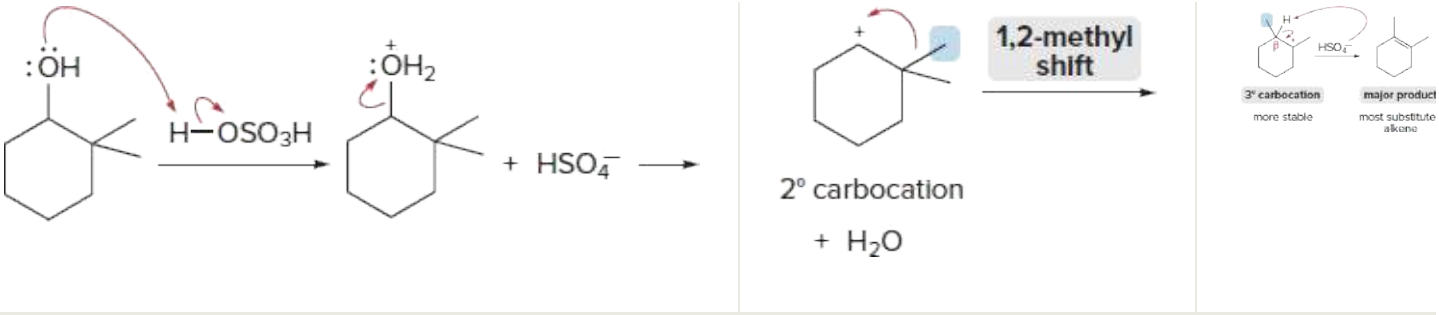
[3] Determining when a carbocation rearrangement might occur (9.9)

1 Classify the alcohol.	**2** Draw the carbocation.	**3** Shift a hydride (or R group) and see if a more stable carbocation results.
 • **The 2° alcohol is adjacent to a 3° carbon.**	 2° carbocation • **A H atom is on a 3° carbon adjacent to the 2° carbocation.**	 3° carbocation • **The hydride shifts to form a more stable 3° carbocation, so rearrangement occurs.**

Try Problems 9.47, 9.48, 9.49.

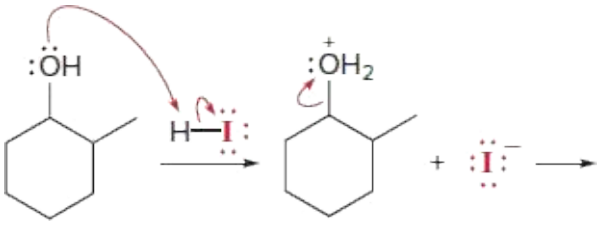
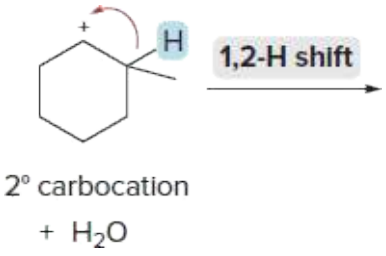
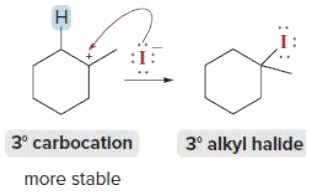
[4] Drawing the products of a dehydration reaction when a 1,2-methyl shift occurs (9.9)

1 Protonation of ROH, and loss of H_2O	**2** Shift of methyl	**3** Loss of a proton



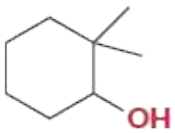
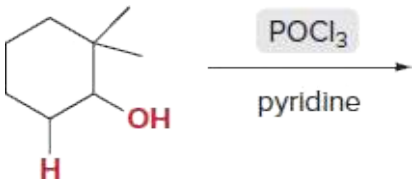
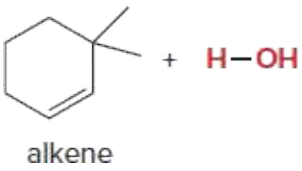
See Sample Problem 9.3. Try Problem 9.44d.

[5] Drawing the products of an S_N1 reaction when a 1,2-hydride shift occurs (9.11B)

1 Protonation of ROH, and loss of H_2O	2 Shift of hydride	3 Nucleophilic attack
		

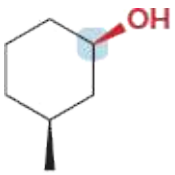
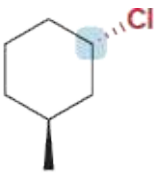
See Sample Problem 9.5. Try Problems 9.47a, 9.48.

[6] Deciding if an alcohol reacts by substitution or elimination (9.10)

1 Classify the alcohol	2 Look at the reagents.	3 Draw the products.
 2° alcohol	 • $POCl_3$ dehydrates ROH.	 alkene • The alkene forms by an E2 mechanism without carbocation rearrangements.

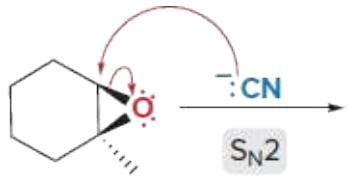
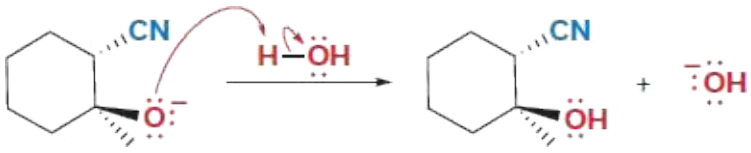
Try Problem 9.43.

[7] Determining the stereochemistry in the conversion of ROH to RCl (9.12)

1 Classify the alcohol.	2 Look at the reagents.	3 Know the mechanism to predict the stereochemistry.
 2° alcohol	$SOCl_2$ → pyridine • $SOCl_2$ converts ROH to RCl by an S_N2 reaction.	 inversion of configuration by an S_N2 mechanism

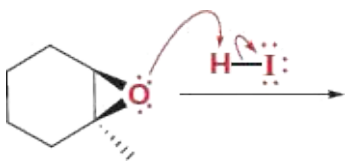
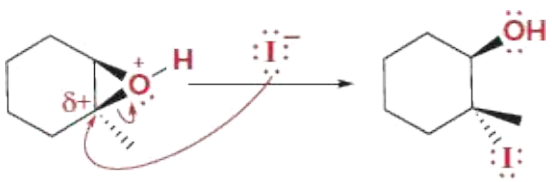
See Sample Problem 9.4. Try Problems 9.38a, c; 9.45.

[8] Drawing the product of an epoxide ring opening with a strong nucleophile (9.16A)

1 Draw the curved arrows for the nucleophilic attack.	2 Protonate the alkoxide.
 backside attack at *less* substituted carbon	 • The CN group and OH group are trans.

See Sample Problem 9.8. Try Problems 9.60b, d; 9.62; 9.64h.

[9] Drawing the product of an epoxide ring opening with an acid (9.16B)

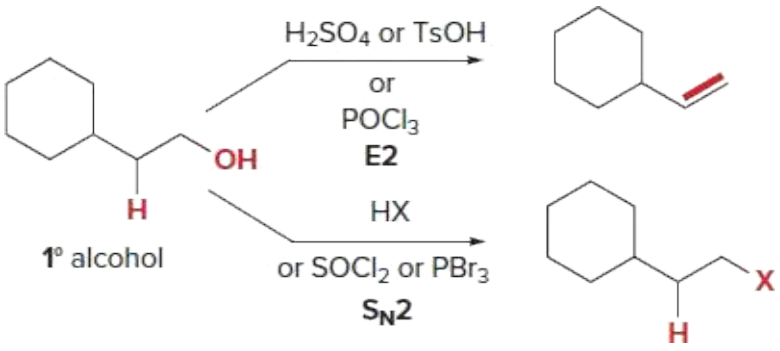
1 Protonate the epoxide.	2 Draw the curved arrows for the nucleophilic attack.
	 backside attack at *more* substituted carbon

- The mechanism is between S_N1 and S_N2.
- The I atom and OH group are trans.

See Sample Problem 9.8, Figure 9.10. Try Problems 9.60a, c; 9.64g.

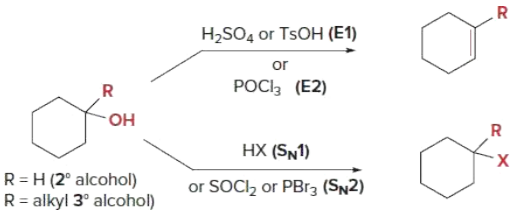
KEY MECHANISM CONCEPTS IN REACTIONS OF ALCOHOLS

1 Reactions of 1 ° ROH



- Dehydration with acid—E2 mechanism
- Dehydration with $POCl_3$ and pyridine—E2 mechanism
- Substitution with HX—S_N2 mechanism
- Substitution with $SOCl_2$ and PBr_3—S_N2 mechanism
- No carbocation intermediates
- See Mechanisms 9.2, 9.4, 9.5, 9.7, 9.8.

2 Reactions of 2° and 3° ROH



- Dehydration with acid—mechanism
- Dehydration with $POCl_3$ and pyridine—E2 mechanism
- Substitution with HX—S mechanism
- Substitution with $SOCl_2$ and PBr_3 (2° ROH only) —S_N2 mechanism
- Carbocation intermedia in both S_N1 and E1 reactions
- Carbocation

	• rearrangements possibl • See Mechanisms 9.1, 9. 9.4, 9.6, 9.7, 9.8.

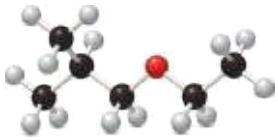
PROBLEMS

Problems Using Three-Dimensional Models

9.36 Name each compound depicted in the ball-and-stick models.

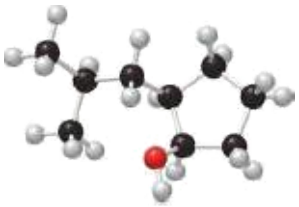
a.

b.



c.

9.37 Answer each question using the ball-and-stick model of compound A.



A

a. Give the IUPAC name for A, including *R,S* designations for stereogenic centers.

b. Classify A as a 1°, 2°, or 3° alcohol.

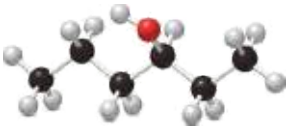
c. Draw a stereoisomer for A and give its IUPAC name.

d. Draw a constitutional isomer that contains an OH group and give its IUPAC name.

e. Draw a constitutional isomer that contains an ether and give its IUPAC name.

f. Draw the products formed (including stereochemistry) when A is treated with each reagent: [1] NaH; [2] H_2SO_4; [3] $POCl_3$, pyridine; [4] HCl; [5] $SOCl_2$, pyridine; [6] TsCl, pyridine.

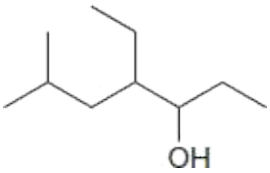
9.38 Draw the product and indicate the stereochemistry when the given alcohol is treated with each reagent: (a) HBr; (b) PBr_3; (c) HCl; (d) $SOCl_2$ and pyridine.



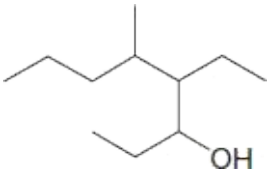
Nomenclature

9.39 Give the IUPAC name for each alcohol.

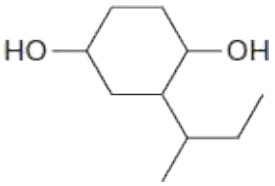
a.



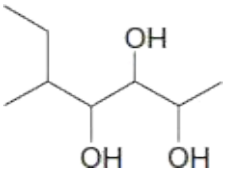
b.



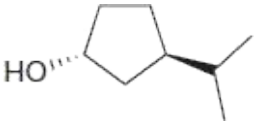
c.



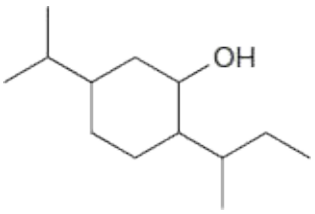
d.



e.

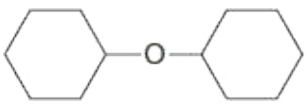


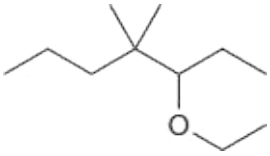
f.

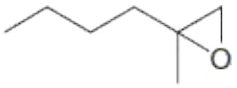


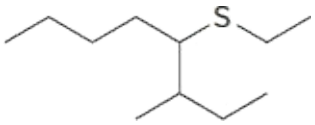
9.40 Name each ether, epoxide, thiol, and sulfide.

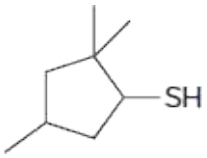
a.

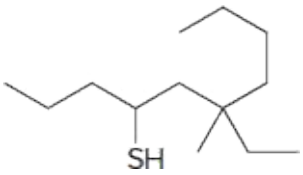


b. 

c. 

d. 

e. 

f. 

9.41 **Give the structure corresponding to each name.**

a. *trans*-2-methylcyclohexanol

b. 2,3,3-trimethylbutan-2-ol

c. 6-*sec*-butyl-7,7-diethyldecan-4-ol

d. 3-chloropropane-1,2-diol

e. 1,2-epoxy-1,3,3-trimethylcyclohexane

f. 1-ethoxy-3-ethylheptane

g. (2*R*,3*S*)-3-isopropylhexan-2-ol

h. (*S*)-2-ethoxy-1,1-dimethylcyclopentane

i. 4-ethylheptane-3-thiol

j. 1-isopropylthio-2-methylcyclohexane

Physical Properties

9.42 **Why is the boiling point of propane-1,3-diol ($HOCH_2CH_2CH_2OH$) higher than the boiling point of propane-1,2-diol [$HOCH_2CH(OH)CH_3$] (215 °C vs. 187 °C)? Why do both diols have a higher boiling point than butan-1-ol ($CH_3CH_2CH_2CH_2OH$, 118 °C)?**

Alcohols

9.43 **Draw the organic product(s) formed when $CH_3CH_2CH_2OH$ is treated with each reagent.**

a. H_2SO_4

b. NaH

c. HCl + $ZnCl_2$

d. HBr

e. $SOCl_2$, pyridine

f. PBr_3

g. TsCl, pyridine

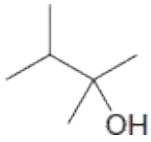
h. [1] NaH; [2] CH_3CH_2Br

i. [1] TsCl, pyridine; [2] NaSH

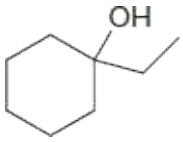
j. $POCl_3$, pyridine

9.44 **What alkenes are formed when each alcohol is dehydrated with TsOH? Label the major product when a mixture results.**

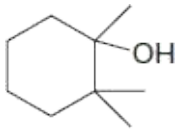
a.



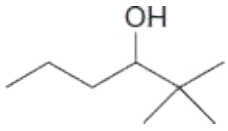
b.



c.

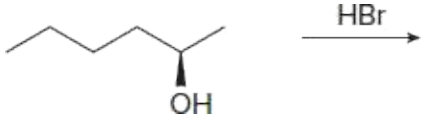


d.

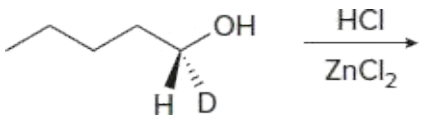


9.45 **Draw the products of each reaction and indicate stereochemistry around stereogenic centers.**

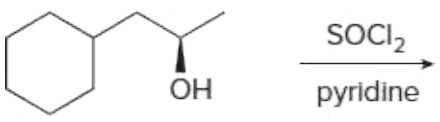
a.



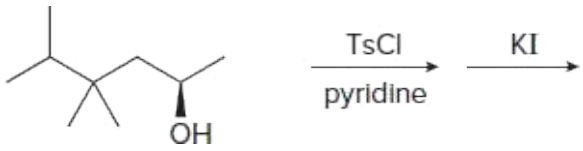
b.



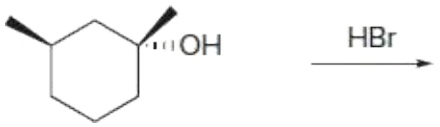
c.



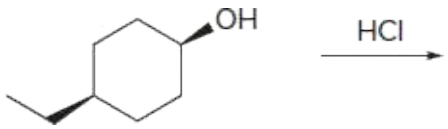
d.



e.



f.



9.46 **Draw the substitution product formed (including stereochemistry) when (*R*)-hexan-2-ol is treated with each series of reagents: (a) NaH, followed by CH_3I; (b) TsCl and pyridine, followed by $NaOCH_3$; (c) PBr_3, followed by $NaOCH_3$. Which two routes produce identical products?**

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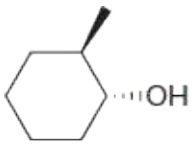
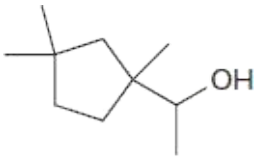
9.47 **(a) What is the major alkene formed when A is dehydrated with H_2SO_4? (b) What is the major alkene formed when A is treated with $POCl_3$ and pyridine? Explain why the major product is different in these reactions.**



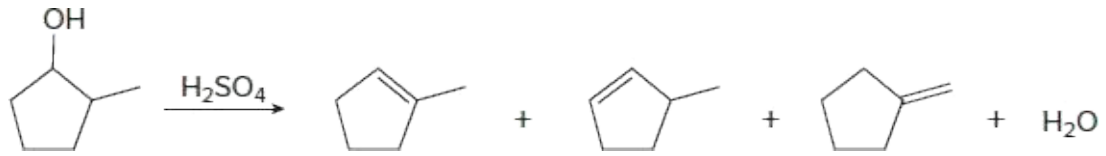
A

9.48 **Reaction of 2° alcohol A with HCl forms three alkyl chlorides, all of which result from rearrangement of the 2° carbocation initially formed. Draw the structures of these products and a mechanism that illustrates how each is formed.**

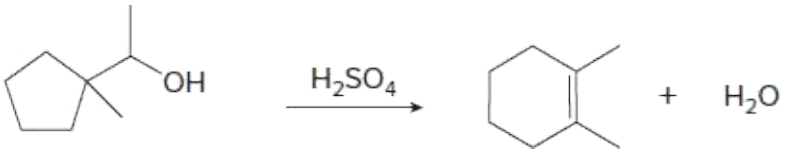


A

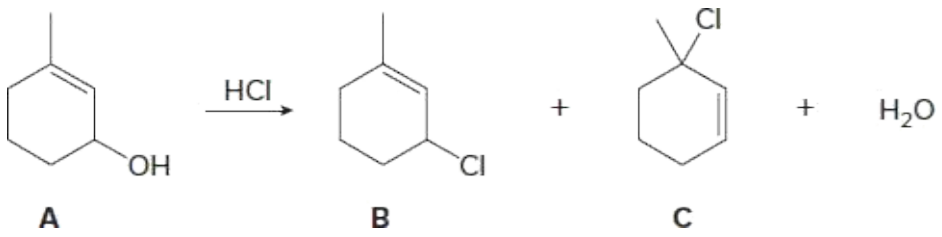
9.49 **Draw a stepwise mechanism for the following reaction.**



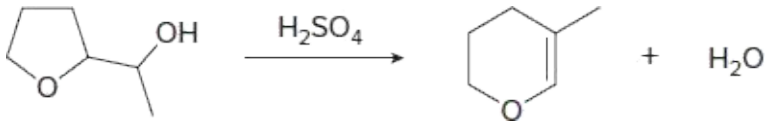
9.50 **Sometimes carbocation rearrangements can change the size of a ring. Draw a stepwise, detailed mechanism for the following reaction.**



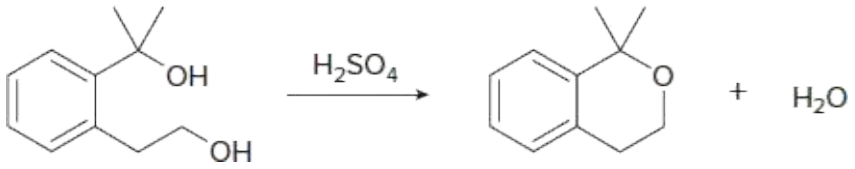
9.51 **An allylic alcohol contains an OH group on a carbon atom adjacent to a C—C double bond. Treatment of allylic alcohol A with HCl forms a mixture of two allylic chlorides, B and C. Draw a stepwise mechanism that illustrates how both products are formed.**



9.52 **Draw a stepwise, detailed mechanism for the following reaction.**



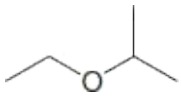
9.53 **Draw a stepwise, detailed mechanism for the following intramolecular reaction that forms a cyclic ether.**



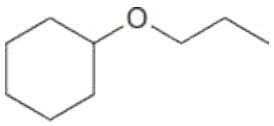
Ethers

9.54 **Draw two different routes to each of the following ethers using a Williamson ether synthesis. Indicate the preferred route (if there is one).**

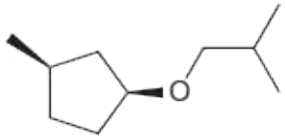
a.



b.



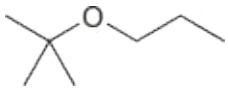
c.



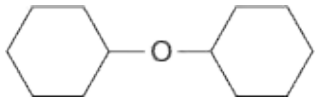
9.55 **Explain why it is not possible to prepare *tert*-butyl phenyl ether using a Williamson ether synthesis.**

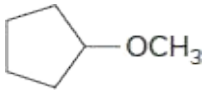
9.56 **Draw the products formed when each ether is treated with two equivalents of HBr.**

a.

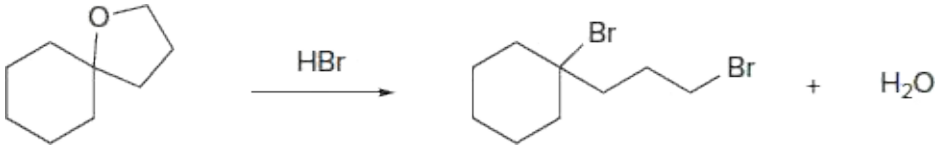


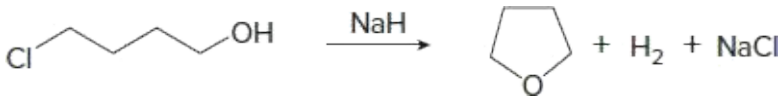
b.



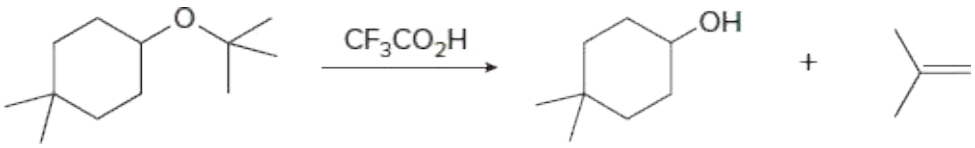
c. 

9.57 Draw a stepwise mechanism for each reaction.

a. 

b. 

9.58 Draw a stepwise mechanism for the following reaction.



Epoxides

9.59 Draw the products formed when ethylene oxide is treated with each reagent.

a. HBr

b. H_2O (H_2SO_4)

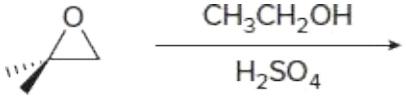
c. [1] $CH_3CH_2O^-$; [2] H_2O

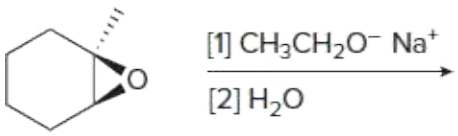
d. [1] $HC{\equiv}C^-$; [2] H_2O

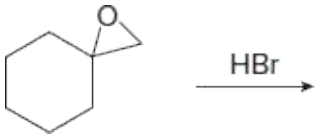
e. [1] ^-OH; [2] H_2O

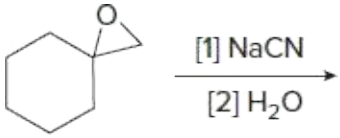
f. [1] CH_3S^-; [2] H_2O

9.60 Draw the products of each reaction.

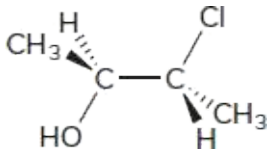
a. 

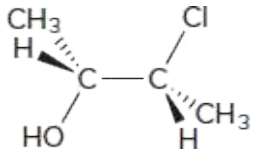
b. 

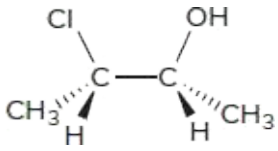
c. 

d. 

9.61 **When each halohydrin is treated with NaH, a product of molecular formula C_4H_8O is formed. Draw the structure of the product and indicate its stereochemistry.**

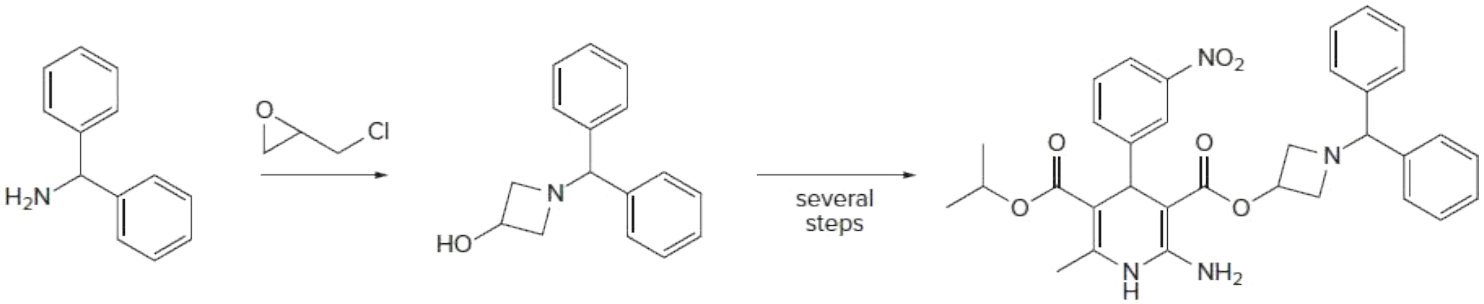
a. 

b. 

c. 

9.62 **(a) What reaction conditions are needed to convert (*R*)-2-ethyl-2-methyloxirane to (*R*)-2-methylbutane-1,2-diol? (b) What reaction conditions are needed to convert (*R*)-2-ethyl-2-methyloxirane to (*S*)-2-methylbutane-1,2-diol?**

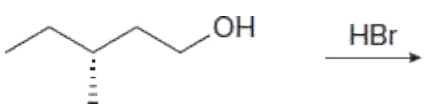
9.63 **Draw a stepwise mechanism for the following reaction, which forms the four-membered ring in azelnidipine, a drug used as a calcium channel blocker sold in Japan.**

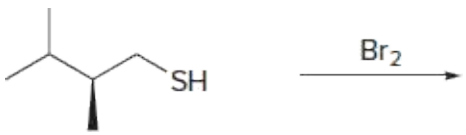


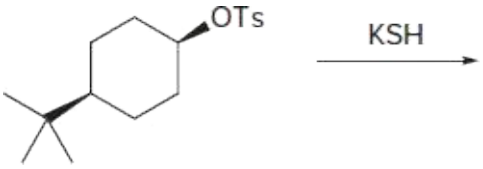
General Problems

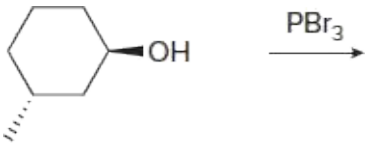
9.64 **Draw the products of each reaction, and indicate the stereochemistry where appropriate.**

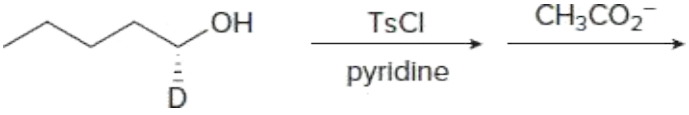
a.

b. 

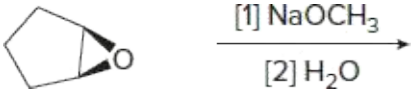
c. 

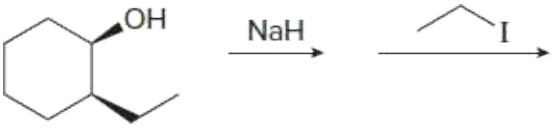
d. 

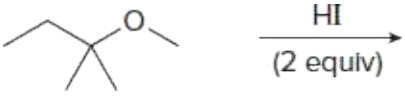
e. 

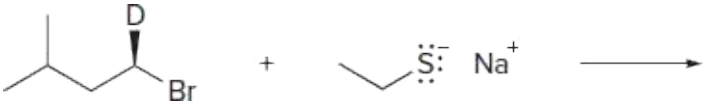
f. 

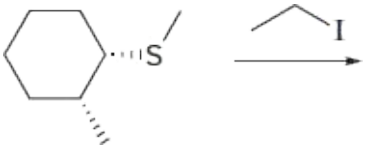
g.

h. 

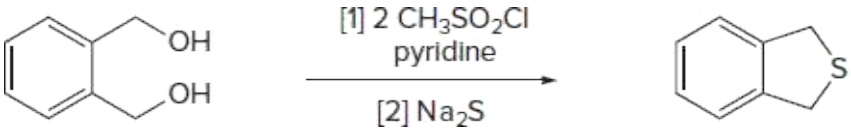
i. 

j. 

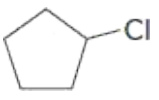
k. 

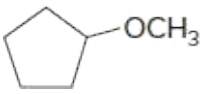
l. 

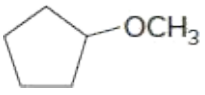
9.65 The following two-step procedure was used to prepare a sulfide from a diol. Draw the intermediate formed in Reaction [1] and draw a mechanism for Reaction [2].

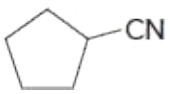


9.66 Prepare each compound from cyclopentanol. More than one step may be needed.

a. 

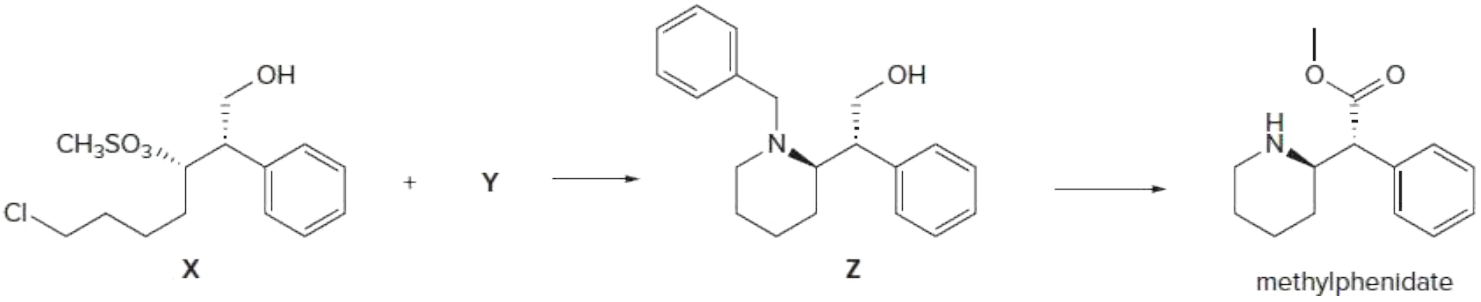
b. 

c. 

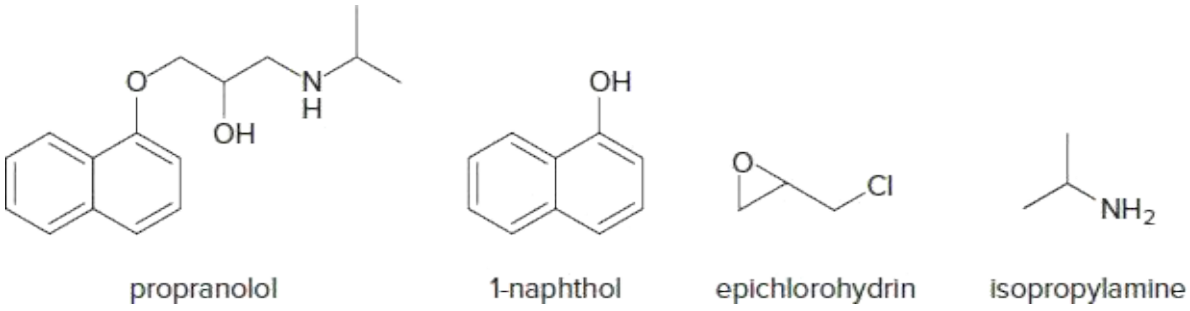
d. 

9.67 Identify Y in the following reaction, one step in the synthesis of

methylphenidate, a drug used to treat attention deficit hyperactivity disorder (ADHD).



9.68 Propranolol, an antihypertensive agent used in the treatment of high blood pressure, can be prepared from 1-naphthol, epichlorohydrin, and isopropylamine using two successive nucleophilic substitution reactions. Devise a stepwise synthesis of propranolol from these starting materials.



Spectroscopy

Problems 9.69–9.72 are intended for students who have already learned about spectroscopy in Chapters A–C.

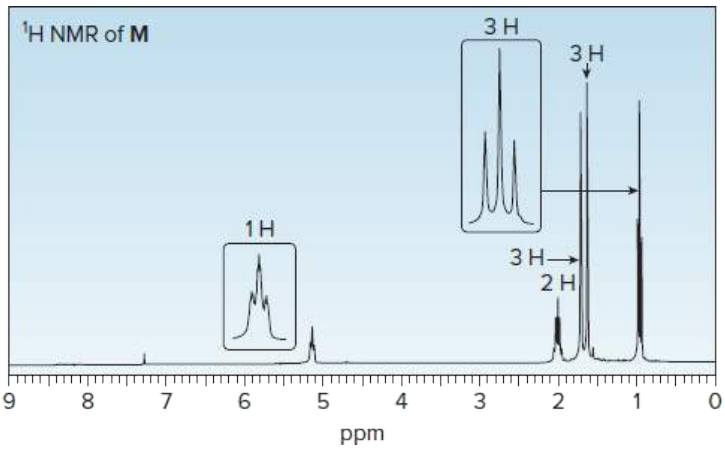
9.69 Propose a structure consistent with each set of spectral data:

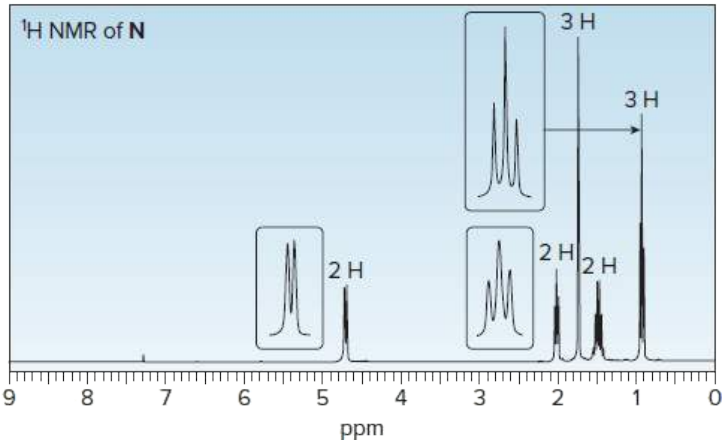
a. $C_6H_{14}O$: IR peak at 3600−3200 cm^{-1}; NMR (ppm):
0.8 (triplet, 6 H) 1.5 (quartet, 4 H)
1.0 (singlet, 3 H) 1.6 (singlet, 1 H)

b. $C_6H_{14}O$: IR peak at 3000−2850 cm^{-1}; NMR (ppm):
1.10 (doublet, relative area = 6)
3.60 (septet, relative area = 1)

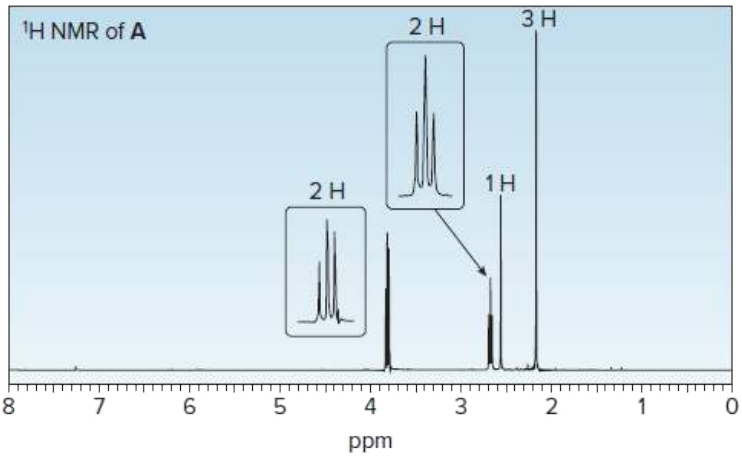
9.70 As we will learn in Chapter 17, reaction of $(CH_3)_2CO$ with LIC≡CH followed by H_2O affords compound D, which has a molecular ion in its mass spectrum at 84 and prominent absorptions in its IR spectrum at 3600−3200, 3303, 2938, and 2120 cm^{-1}. D shows the following ^1H NMR spectral data: 1.53 (singlet, 6 H), 2.37 (singlet, 1 H), and 2.43 (singlet, 1 H) ppm. What is the structure of D?

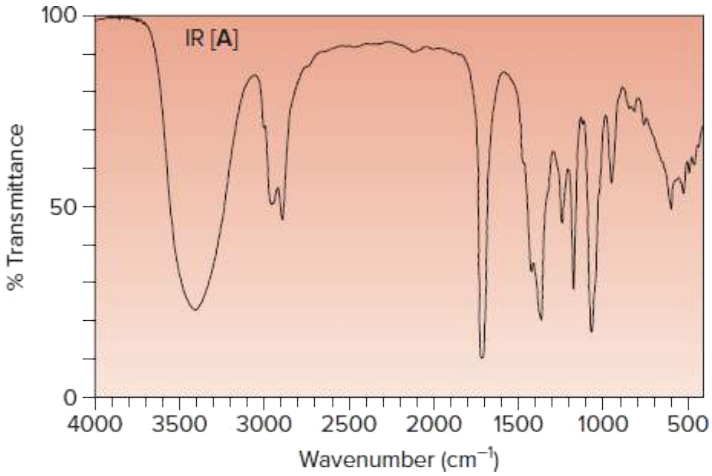
9.71 **Treatment of $(CH_3)_2CHCH(OH)CH_2CH_3$ with TsOH affords two products (M and N) with molecular formula C_6H_{12}. The ^1H NMR spectra of M and N are given below. Propose structures for M and N, and draw a mechanism to explain their formation.**





9.72 Use the ^1H NMR and IR spectra given below to identify compound A, having molecular formula $C_4H_8O_2$.





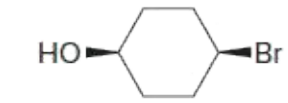
Additional spectroscopy problems involving alcohols, ethers, and epoxides are given in Chapters A–C:

- **Mass spectrometry: A.4, A.26, A.27a, A.28, A.30, A.32, A.33**
- **Infrared spectroscopy: B.11, B.12b, B.16b, B.17, B.19b, B.22, B.26d, B.27(A), (D), B.28c**
- **Nuclear magnetic resonance spectroscopy: C.23; C.25b; C.27; C.29c; C.33a; C.38b, e, g, h; C.42b, c; C.43c, e, f; C.49b, e; C.51a, c; C.55; C.69; C.70b; C.77; C.80**

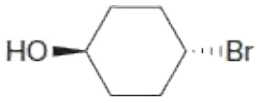
Challenge Problems

9.73 **Treatment of *cis*-4-bromocyclohexanol with HO^- affords compound A and cyclohex-3-en-1-ol. Treatment of *trans*-4-bromocyclohexanol under**

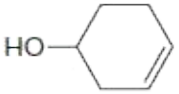
the same conditions forms compound B and cyclohex-3-en-1-ol. A and B contain different functional groups and are not isomers of each other. Propose structures for A and B and offer an explanation for their formation.



cis-4-bromocyclohexanol

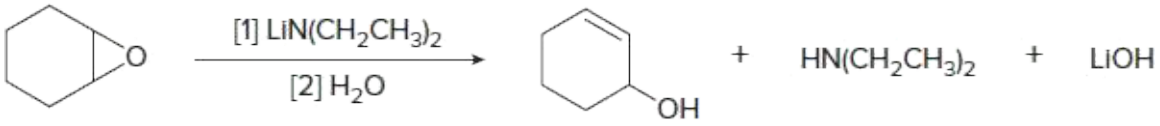


trans-4-bromocyclohexanol



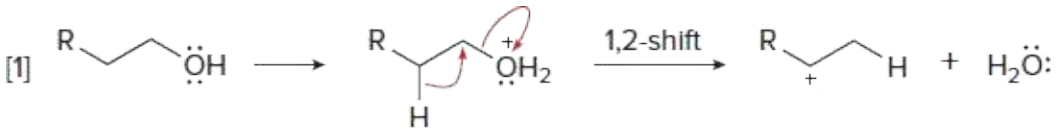
cyclohex-3-en-1-ol

9.74 Epoxides are converted to allylic alcohols with nonnucleophilic bases such as lithium diethylamide [$LiN(CH_2CH_3)_2$]. Draw a stepwise mechanism for the conversion of 1,2-epoxycyclohexane to cyclohex-2-en-1-ol with this base. Explain why a strong bulky base must be used in this reaction.

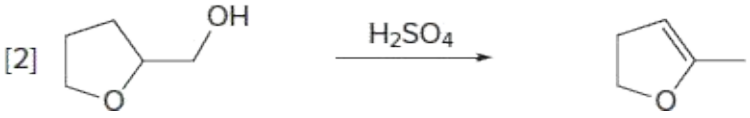


cyclohex-2-en-1-ol

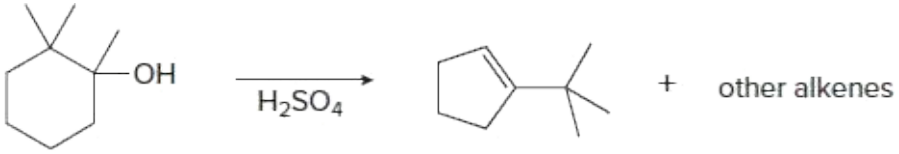
9.75 Rearrangements can occur during the dehydration of 1° alcohols even though no 1° carbocation is formed—that is, a 1,2-shift occurs as the C—OH_2^+ bond is broken, forming a more stable 2° or 3° carbocation, as shown in Equation [1]. Using this information, draw a stepwise mechanism for the reaction shown in Equation [2]. We will see another example of this type of rearrangement in Section 16.5C.



1° alcohol | no 1° carbocation at this step | 2° carbocation

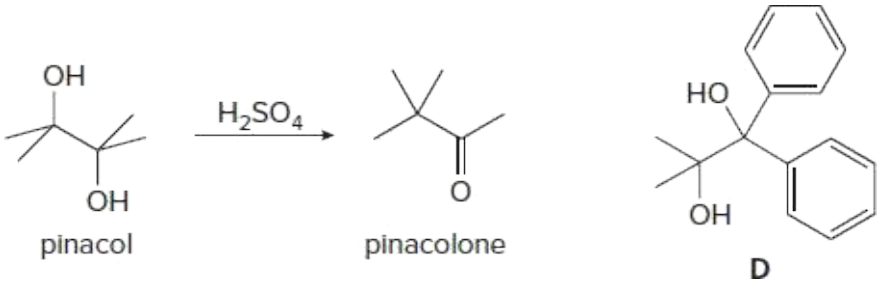


9.76 Dehydration of 1,2,2-trimethylcyclohexanol with H_2SO_4 affords 1-*tert*-butylcyclopentene as a minor product. (a) Draw a stepwise mechanism that shows how this alkene is formed. (b) Draw other alkenes formed in this dehydration. At least one must contain a five-membered ring.

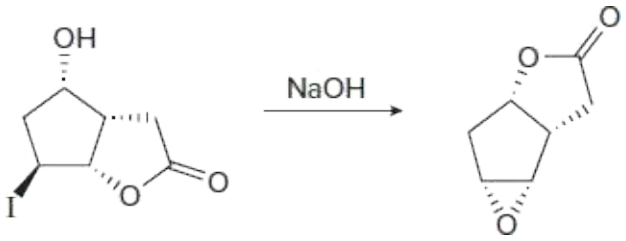


1,2,2-trimethylcyclohexanol | 1-*tert*-butylcyclopentene

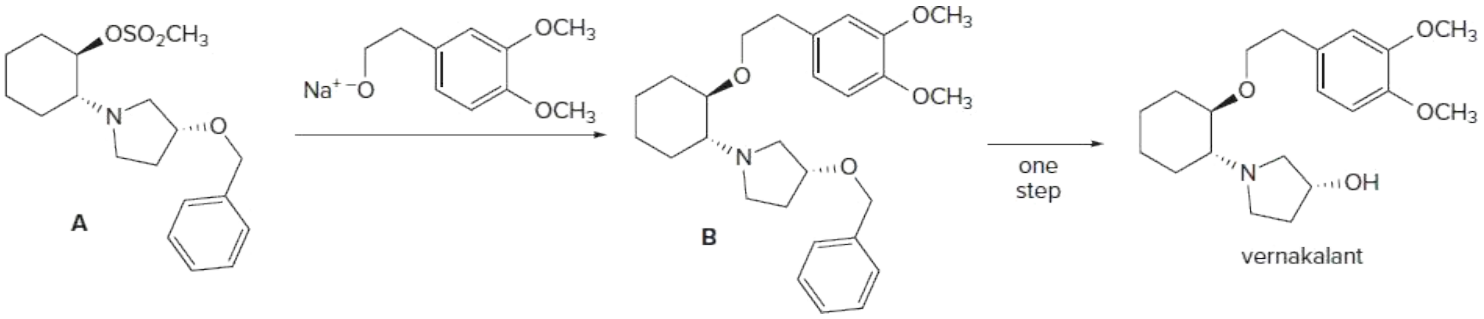
9.77 **1,2-Diols are converted to carbonyl compounds when treated with strong acids, in a reaction called the *pinacol rearrangement.* (a) Draw a stepwise mechanism for this reaction. (Hint: The reaction proceeds by way of carbocation intermediates.) (b) Assuming that the pinacol rearrangement occurs via the more stable carbocation, draw the rearrangement product formed from diol D.**



9.78 **Draw a stepwise mechanism for the following reaction.**

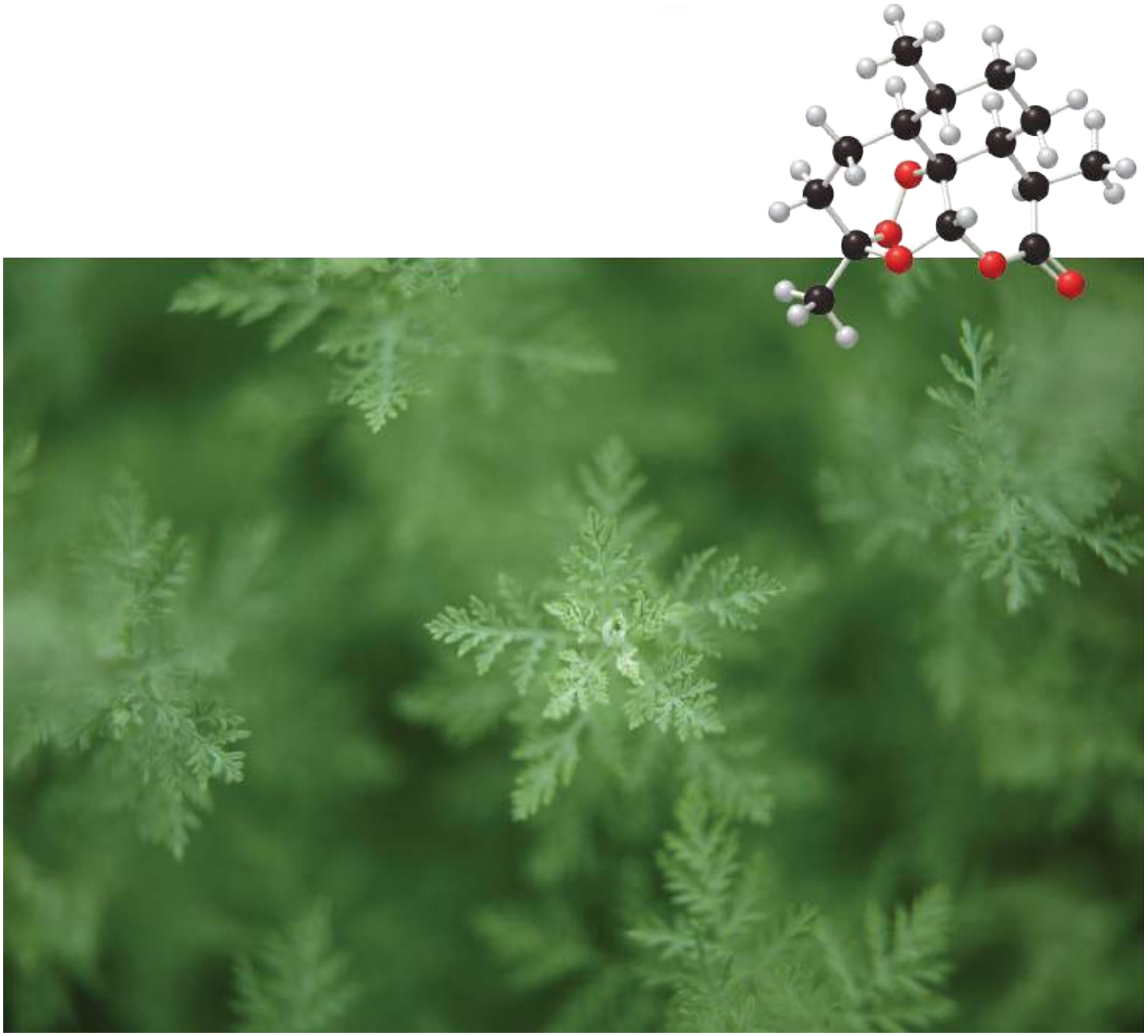


9.79 **Draw a stepwise mechanism for the following reaction, a key step in the synthesis of vernakalant, a drug approved in Europe in 2010 for the treatment of atrial fibrillation. Pure B was separated from a mixture of diastereomers. Your mechanism must explain the trans stereochemistry of the two substituents on the six-membered ring.**



Alkenes and Addition Reactions

10



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10.1 Introduction

10.2 Calculating degrees of unsaturation

10.3 Nomenclature

10.4 Properties of alkenes
10.5 Interesting alkenes
10.6 Lipids—Part 2
10.7 Preparation of alkenes
10.8 Introduction to addition reactions
10.9 Hydrohalogenation—Electrophilic addition of HX
10.10 Markovnikov's rule
10.11 Stereochemistry of electrophilic addition of HX
10.12 Hydration—Electrophilic addition of water
10.13 Halogenation—Addition of halogen
10.14 Stereochemistry of halogenation
10.15 Halohydrin formation
10.16 Hydroboration–oxidation
10.17 Keeping track of reactions
10.18 Alkenes in organic synthesis

Artemisinin is a complex compound isolated from sweet wormwood, *Artemisia annua*, a plant used for hundreds of years in traditional Chinese medicine. A combination of artemisinin (or a related compound) with other drugs constitutes the currently recommended treatment of malaria. Although artemisinin can be obtained by extracting the active drug from the dried leaves of *Artemisia annua*, this process does not meet the worldwide demand. As a result, artemisinin can now be obtained using genetic engineering and fermentation processes. One step in a laboratory synthesis of artemisinin involves an addition reaction of an alkene, the topic of Chapter 10.

Why Study…

Alkenes?

In **Chapters 10** and **11**, we turn our attention to alkenes and alkynes, compounds that contain one and two π bonds, respectively. Because π bonds are easily broken, alkenes

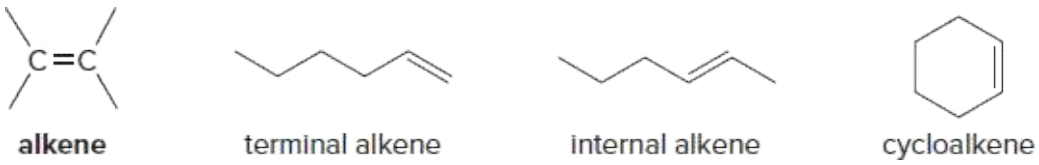
and alkynes undergo addition, the third general type of organic reaction. These multiple bonds also make carbon atoms electron rich, so alkenes and alkynes react with a wide variety of electrophilic reagents in addition reactions that are very versatile in organic synthesis.

In Chapter 10, we review the properties and synthesis of alkenes first, and then concentrate on reactions. Every new reaction in Chapter 10 is an *addition reaction*. The most challenging part is learning the reagents, mechanism, and stereochemistry that characterize each individual reaction.

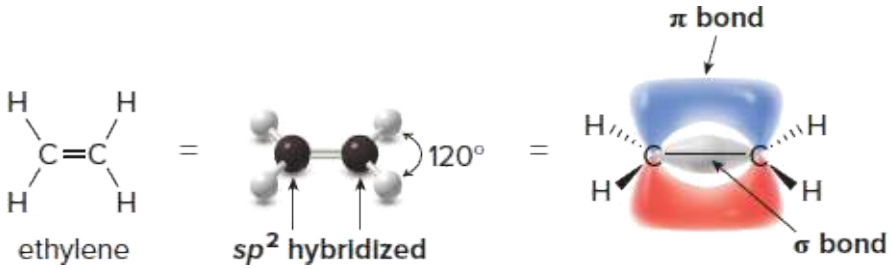
10.1 Introduction

Alkenes are also called olefins.

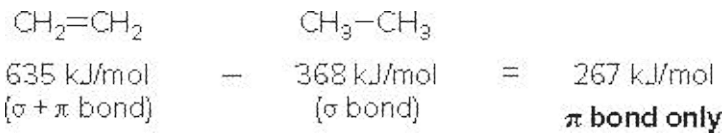
Alkenes are compounds that contain a carbon–carbon double bond. Terminal alkenes have the double bond at the end of the carbon chain, whereas internal alkenes have at least one carbon atom bonded to each end of the double bond. Cycloalkenes contain a double bond in a ring.



The double bond of an alkene consists of one σ bond and one π bond. Each carbon is sp^2 hybridized and trigonal planar, and all bond angles are approximately 120° (Section 8.2A).



Bond dissociation energies of the C–C bonds in ethane (a σ bond only) and ethylene (one σ and one π bond) can be used to estimate the strength of the π component of the double bond. If we assume that the σ bond in ethylene is similar in strength to the σ bond in ethane (368 kJ/mol), then the π bond is worth 267 kJ/mol.



- **The π bond is much *weaker* than the σ bond of a C–C double bond, making it much more easily broken. As a result, alkenes undergo many reactions that alkanes do not.**

Other features of the carbon–carbon double bond, which were presented in Chapter 8, are summarized in Table 10.1.

Cycloalkenes having fewer than eight carbon atoms have a cis geometry. A trans cycloalkene must have a carbon chain long enough to connect the ends of the double bond without introducing too much strain. *trans*-Cyclooctene is the smallest, isolable trans cycloalkene, but it is considerably less stable than *cis*-cyclooctene, making it one of the few alkenes having a higher-energy trans isomer.

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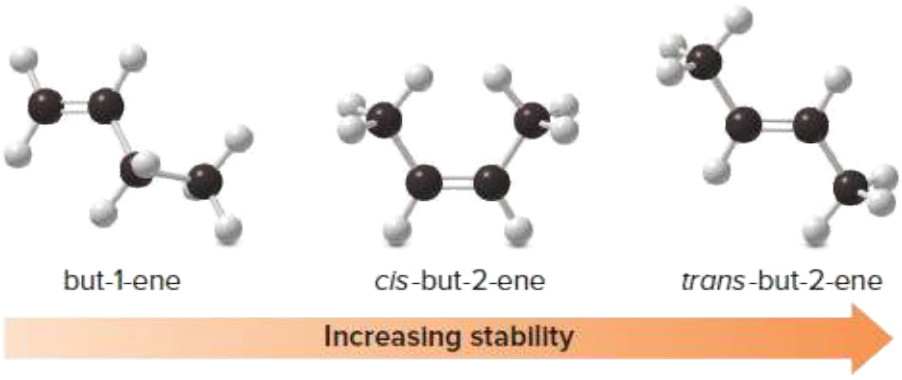
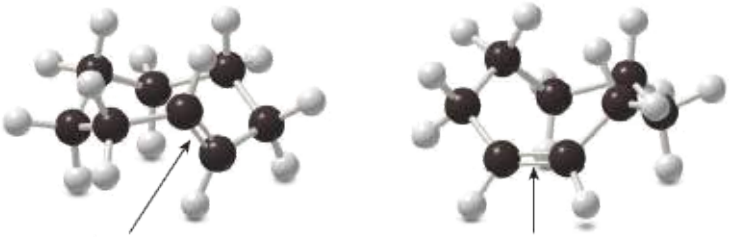
Table 10.1 Properties of the Carbon–Carbon Double Bond

Property	Result
Restricted rotation	• **The rotation around the C–C double bond is restricted.** Rotation can occur only if the π bond breaks and then re-forms, a process that is unfavorable (Section 8.2B).
Stereoisomerism	• Whenever the two groups on each end of a C=C are different from each other, two diastereomers are possible. *Cis*- and *trans*-but-2-ene (drawn at the bottom of Table 10.1) are diastereomers (Section 8.2B).
Stability	• Trans alkenes are generally more stable than cis alkenes. • The stability of an alkene increases as the number of R groups on the C=C increases (Section 8.2C). 



Problem 10.1

Draw the six alkenes of molecular formula C_5H_{10}. Label one pair of diastereomers.

10.2 Calculating Degrees of Unsaturation

An acyclic alkene has the general molecular formula C_nH_{2n}, giving it two fewer hydrogens than an acyclic alkane with the same number of carbons.

In Chapter 12, we will learn how to use the hydrogenation of π bonds to determine how many degrees of unsaturation result from π bonds and how many result from rings.

- **Alkenes are *unsaturated hydrocarbons* because they have fewer than the maximum number of hydrogen atoms per carbon.**

Cycloalkanes also have the general molecular formula C_nH_{2n}. Thus, each π bond or ring removes two hydrogen atoms from a molecule, and this introduces one *degree of unsaturation*. The number of degrees of unsaturation for a given molecular formula can be calculated by comparing the *actual* number of H atoms in a compound and the *maximum* number of H atoms possible. Remember that for n carbons, the maximum number of H atoms is $2n + 2$ (Section 4.1). This procedure gives the total number of rings and π bonds in a molecule.

Sample Problem 10.1 Calculating the Number of Degrees of Unsaturation in a Hydrocarbon

Calculate the number of degrees of unsaturation in a compound of molecular formula C_4H_6, and propose possible structures.

Solution

[1] Calculate the maximum number of H's possible.

- For *n* carbons, the maximum number of H's is *2n* + 2; in this example, 2*n* + 2 = 2(4) + 2 = 10.

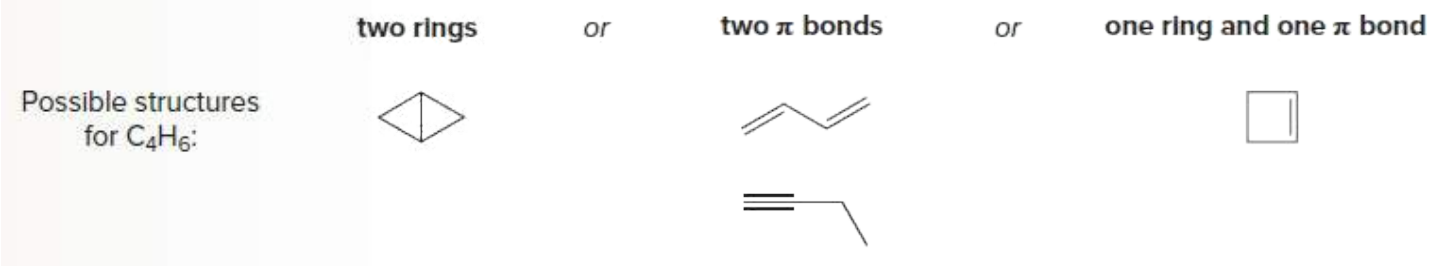
[2] Subtract the actual number of H's from the maximum number and divide by two.

- 10 H's (maximum) − 6 H's (actual) = 4 H's fewer than the maximum number.

$$\frac{\text{4 H's fewer than the maximum}}{\text{2 H's removed for each degree of unsaturation}} =$$

Answer: two degrees of unsaturation

A compound with two degrees of unsaturation has:



Problem 10.2

Calculate the number of degrees of unsaturation for each molecular formula, and propose two possible structures: (a) C_8H_{12}; (b) $C_{10}H_{10}$.

More Practice:

Try Problems 10.35a, b; 10.36.

This procedure can be extended to compounds that contain heteroatoms such as oxygen, nitrogen, and halogen, as illustrated in Sample Problem 10.2.

Sample Problem 10.2 Calculating the Number of Degrees of Unsaturation in Compounds with O, X, or N

Calculate the number of degrees of unsaturation for each molecular formula: (a) C_5H_8O; (b) $C_6H_{11}Cl$; (c) C_8H_9N. Propose one possible structure for each compound.

Solution

a. **When a compound contains an oxygen atom, use the given number of C's and H's and *ignore the O atom* in the calculation; that is, C_5H_8O is**

equivalent to C_5H_8 when calculating degrees of unsaturation.

[1] For 5 C's, the maximum number of H's = 2*n* + 2 = 2(5) + 2 = 12.

[2] Because the compound contains only 8 H's, it has 12 − 8 = 4 H's fewer than the maximum number.

[3] Each degree of unsaturation removes 2 H's, so the answer in Step [2] must be divided by 2.

Answer: two degrees of unsaturation

b. A compound with a halogen atom is equivalent to a hydrocarbon having one *more* H; that is, $C_6H_{11}Cl$ is equivalent to C_6H_{12} when calculating degrees of unsaturation.

[1] For 6 C's, the maximum number of H's = 2*n* + 2 = 2(6) + 2 = 14.

[2] Because the compound contains only 12 H's, it has 14 − 12 = 2 H's fewer than the maximum number.

[3] Each degree of unsaturation removes 2 H's, so the answer in Step [2] must be divided by 2.

Answer: one degree of unsaturation

c. A compound with a nitrogen atom is equivalent to a hydrocarbon having one *fewer* H; that is, C_8H_9N is equivalent to C_8H_8 when calculating degrees of unsaturation.

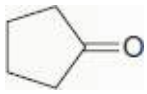
[1] For 8 C's, the maximum number of H's = 2*n* + 2 = 2(8) + 2 = 18.

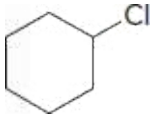
[2] Because the compound contains only 8 H's, it has 18 − 8 = 10 H's fewer than the maximum number.

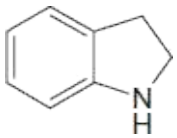
[3] Each degree of unsaturation removes 2 H's, so the answer in Step [2] must be divided by 2.

Answer: five degrees of unsaturation

Possible structures:

a. 

b. 

c. 

Problem 10.3

How many degrees of unsaturation are present in each compound?

a. C_6H_6

b. C_8H_{18}

c. C_7H_8O

d. $C_7H_{11}Br$

e. C_5H_9N

More Practice:

Try Problem 10.35c–h.

Problem 10.4

How many degrees of unsaturation does each of the following drugs contain?

a. zolpidem (sleep aid sold as Ambien), $C_{19}H_{21}N_3O$

b. mefloquine (antimalarial drug), $C_{17}H_{16}F_6N_2O$

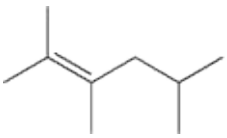
10.3 Nomenclature

- **In the IUPAC system, an alkene is identified by the suffix *-ene.***

10.3A General IUPAC Rules

How To Name an Alkene

Example Give the IUPAC name of the following alkene:



Step [1] Find the longest chain that contains *both* carbon atoms of the double bond.

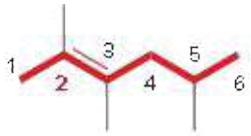
6 C's in the longest chain

hexane ----→ hexene

- Change the ***-ane*** ending of the parent alkane to ***-ene***.

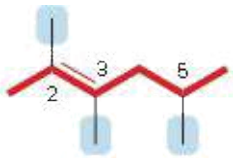
Step [2] Number the carbon chain to give the double bond the lower number, and apply all other rules of nomenclature.

a. Number the chain, and name using the *first* number assigned to the C=C.



- Number the chain to put the C=C at C2, not C4.

b. Name and number the substituents.



three methyl groups at C2, C3, and C5

Answer: 2,3,5-trimethylhex-2-ene

Compounds with two double bonds are named as dienes by changing the -*ane* ending of the parent alkane to the suffix *-adiene*. Compounds with three double bonds are named as trienes, and so forth. Always choose the longest chain that contains *both* atoms of the double bond. In Figure 10.1, the alkene is named as a derivative of heptene because the seven-carbon chain contains both atoms of the double bond, but the eight-carbon chain does not.

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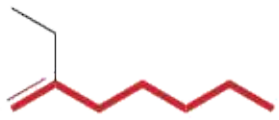
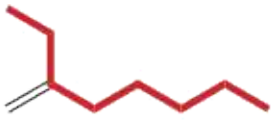


7 C's ----→ heptene

Both C's of the C=C are contained in this long chain.

Correct: 2-ethylhept-1-ene



8 C's

Both C's of the C=C are NOT contained in this long chain.

Incorrect

Figure 10.1 Naming an alkene in which the longest carbon chain does not contain both atoms of the double bond

In naming cycloalkenes, the double bond is located between C1 and C2, and the "1" is usually omitted in the name. The ring is numbered clockwise or counterclockwise to give the first substituent the lower number. Representative examples are given in Figure 10.2.

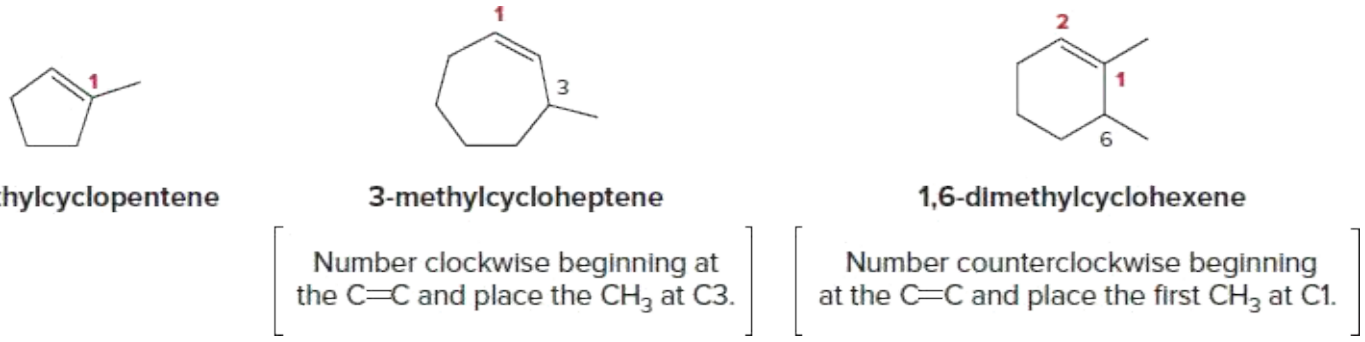


Figure 10.2 **Examples of cycloalkene nomenclature**

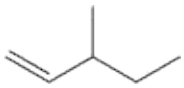
$CH_3CH_2CH{=}CH_2$ is named as 1-butene using the 1979 IUPAC recommendations and but-1-ene using the 1993 IUPAC recommendations.

Compounds that contain both a double bond and a hydroxy group are named as alkenols, and the chain (or ring) is numbered to give the OH group the lower number.

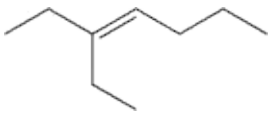
Problem 10.5

Give the IUPAC name for each alkene.

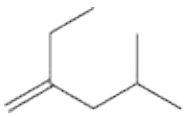
a.



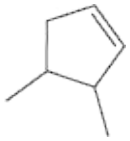
b.



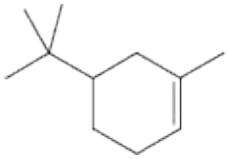
c.



d.

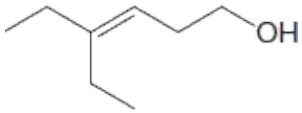


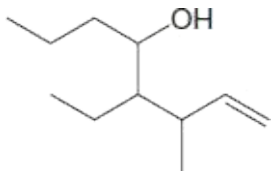
e.

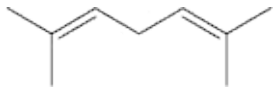


Problem 10.6

Give the IUPAC name for each polyfunctional compound.

a. 

b. 

c. 

10.3B Naming Stereoisomers

A prefix is needed to distinguish two alkenes when diastereomers are possible.

Using Cis and Trans as Prefixes

An alkene having one alkyl group bonded to each carbon atom can be named using the prefixes cis and trans to designate the relative location of the two alkyl groups. For example, *cis*-hex-3-ene has two ethyl groups on the same side of the double bond, whereas *trans*-hex-3-ene has two ethyl groups on opposite sides of the double bond.

2 R's on the **same** side
cis-hex-3-ene

2 R's on **opposite** sides
trans-hex-3-ene

Using the Prefixes *E* and *Z*

***E* stands for the German word *entgegen* meaning "opposite." Z stands for the German word *zusammen*, meaning "together." Using E,Z nomenclature, a cis isomer has the Z configuration and a trans isomer has the *E* configuration.**

Although the prefixes cis and trans can be used to distinguish diastereomers when two alkyl groups are bonded to the C=C, they cannot be used when there are three or four alkyl groups bonded to the C=C.

A
3-methylpent-2-ene

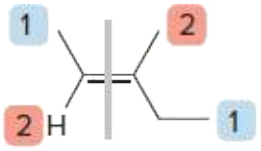
B
3-methylpent-2-ene

For example, alkenes A and B are two *different* compounds that are both called 3-methylpent-2-ene. In A the two CH_3 groups are cis, whereas in B the CH_3 and CH_2CH_3 groups are cis. The *E,Z* system of nomenclature has been devised to unambiguously name these kinds of alkenes.

How To Assign the Prefixes *E* and *Z* to an Alkene

Step [1] **Assign priorities to the two substituents on each end of the C=C by using the priority rules for *R,S* nomenclature (Section 5.6).**

- **Divide the double bond in half, and assign the numbers 1 and 2 to indicate the relative priority of the two groups on each end—the higher-priority group is labeled 1, and the lower-priority group is labeled 2.**



Assign priorities to each side separately.

Step [2] **Assign *E* or *Z* based on the location of the two higher-priority groups (1).**

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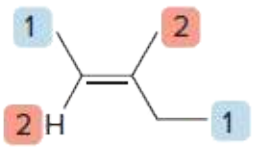
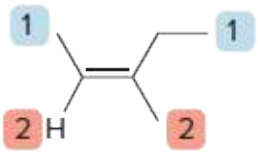
Two higher-priority groups on **opposite sides**



***E* isomer**

(*E*)-3-methylpent-2-ene

Two higher-priority groups on the **same side**



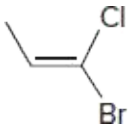
***Z* isomer**

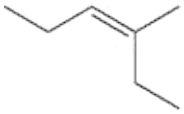
(*Z*)-3-methylpent-2-ene

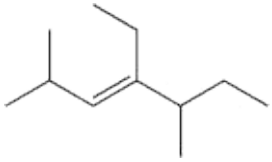
- **The *E* isomer has the two higher-priority groups on the opposite sides.**
- **The *Z* isomer has the two higher-priority groups on the same side.**

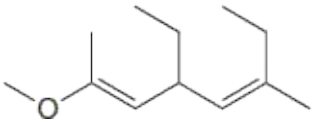
Problem 10.7

Label each C–C double bond as *E* or *Z*.

a. 

b. 

c. 

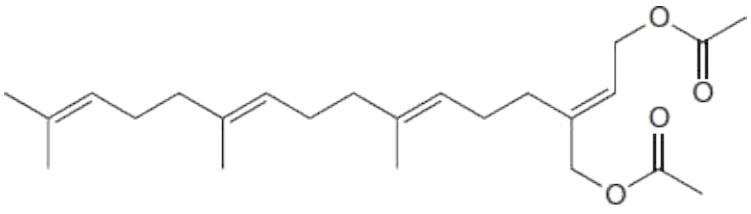
d. 

In response to a chemical distress signal from the coral *Acropora nasuta*, the goby fish protects the coral by eating the poisonous and invasive seaweed *Chlorodesmis fastigiata* (Problem 10.8).

©Danielle Dixson

Problem 10.8

A is a toxin produced by the poisonous seaweed *Chlorodesmis fastigiata.* (a) Label each alkene that exhibits stereoisomerism as *E* or *Z.* (b) Draw a stereoisomer of A that has all *Z* double bonds.



A

Problem 10.9

Draw the structure corresponding to each IUPAC name.

a. (*Z*)-4-ethylhept-3-ene

b. (E)-3,5,6-trimethyloct-2-ene

c. (Z)-2-bromo-1-iodohex-1-ene

10.3C Common Names

The simplest alkene, $CH_2=CH_2$, named in the IUPAC system as ethene, is often called ethylene, its common name. The common names for three alkyl groups derived from alkenes are also used. Three examples of naming organic molecules using these common names are shown in Figure 10.3.

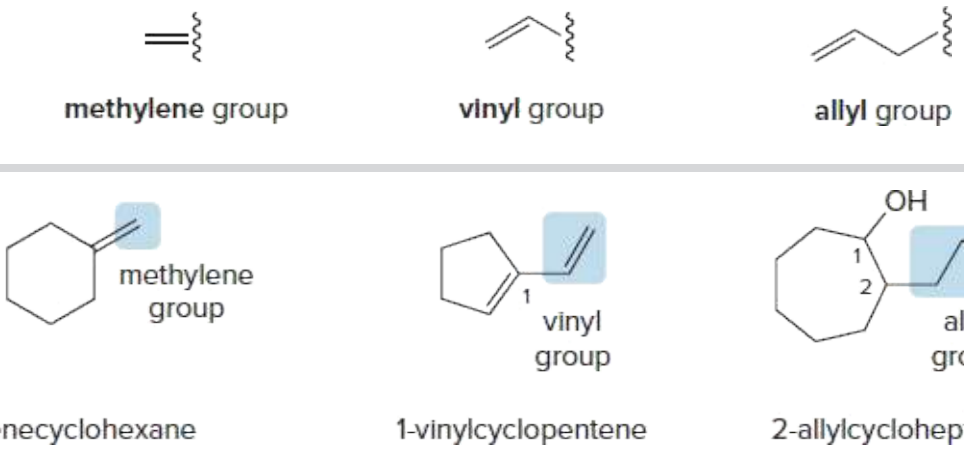


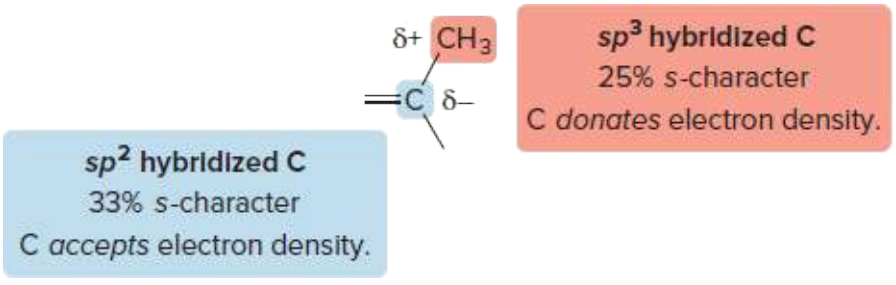
Figure 10.3 **Naming alkenes with common substituent names**

10.4 Properties of Alkenes

Most alkenes exhibit only weak van der Waals interactions, so their physical properties are similar to those of alkanes of comparable molecular weight.

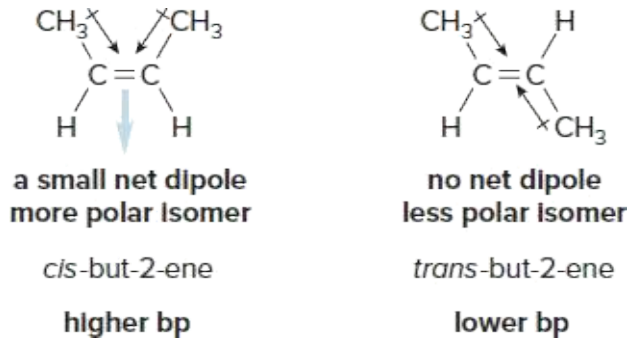
- **Alkenes have low melting points and boiling points.**
- **Melting points and boiling points increase as the number of carbons increases because of increased surface area.**
- **Alkenes are soluble in organic solvents and insoluble in water.**

Cis and trans alkenes often have somewhat different physical properties. For example, *cis*-but-2-ene has a higher boiling point (4 °C) than *trans-but-2-ene* (1 °C). This difference arises because the C–C single bond between an alkyl group and one of the double bond carbons of an alkene is slightly polar. The sp^3 hybridized alkyl carbon donates electron density to the sp^2 hybridized alkenyl carbon.



Related arguments involving $C_{sp^3}-C_{sp^2}$ bonds were used in Section 8.2C to explain why the stability of an alkene increases with increasing alkyl substitution.

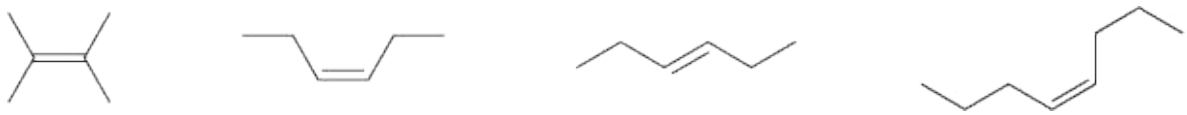
The bond dipole places a partial negative charge on the alkenyl carbon (sp^2) relative to the alkyl carbon (sp^3) because an sp^2 hybridized orbital has greater percent *s*-character (33%) than an sp^3 hybridized orbital (25%). In a cis isomer, the two $C_{sp^3}-C_{sp^2}$ bond dipoles reinforce each other, yielding a small net molecular dipole. In a trans isomer, the two bond dipoles cancel.



- **A cis alkene is more polar than a trans alkene, giving it a slightly higher boiling point and making it more soluble in polar solvents.**

Problem 10.10

Rank the following isomers in order of increasing boiling point.



Students who have already been exposed to spectroscopy or who would like to learn about the spectroscopic properties of alkenes are referred to the following sections:

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- Infrared spectroscopy: Sections B.3A, B.3D, B.4A; Tables B.1, B.2
- Nuclear magnetic resonance spectroscopy: Section C.8; Tables C.1, C.2, C.4, C.5; Sample Problems C.7c, C.9c

10.5 Interesting Alkenes

Ethylene is prepared from petroleum by a process called cracking. Ethylene is the most widely produced organic chemical, serving as the starting material not only for the polymer polyethylene, a widely used plastic, but also for many other useful organic

compounds, as shown in Figure 10.4.

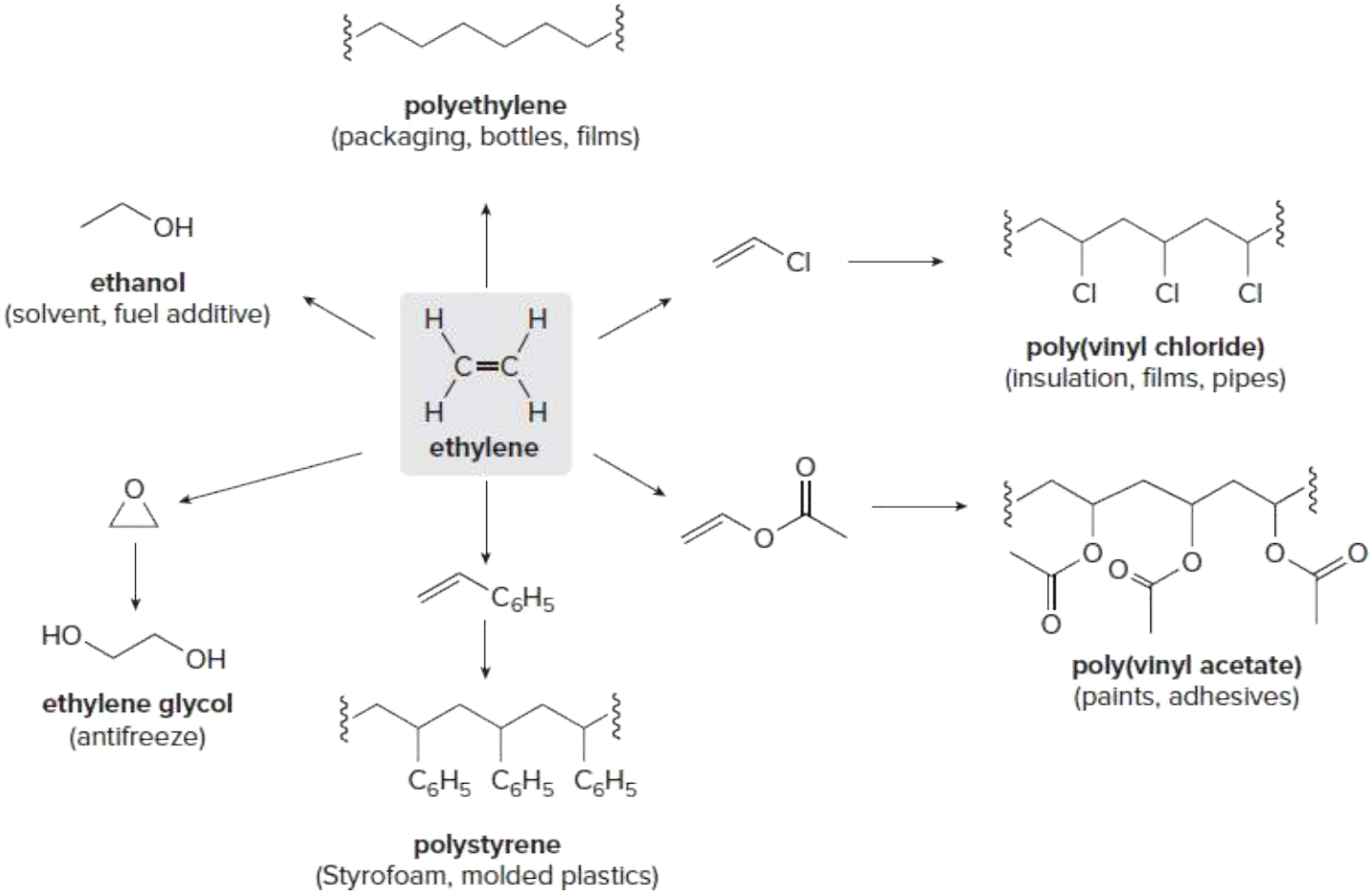
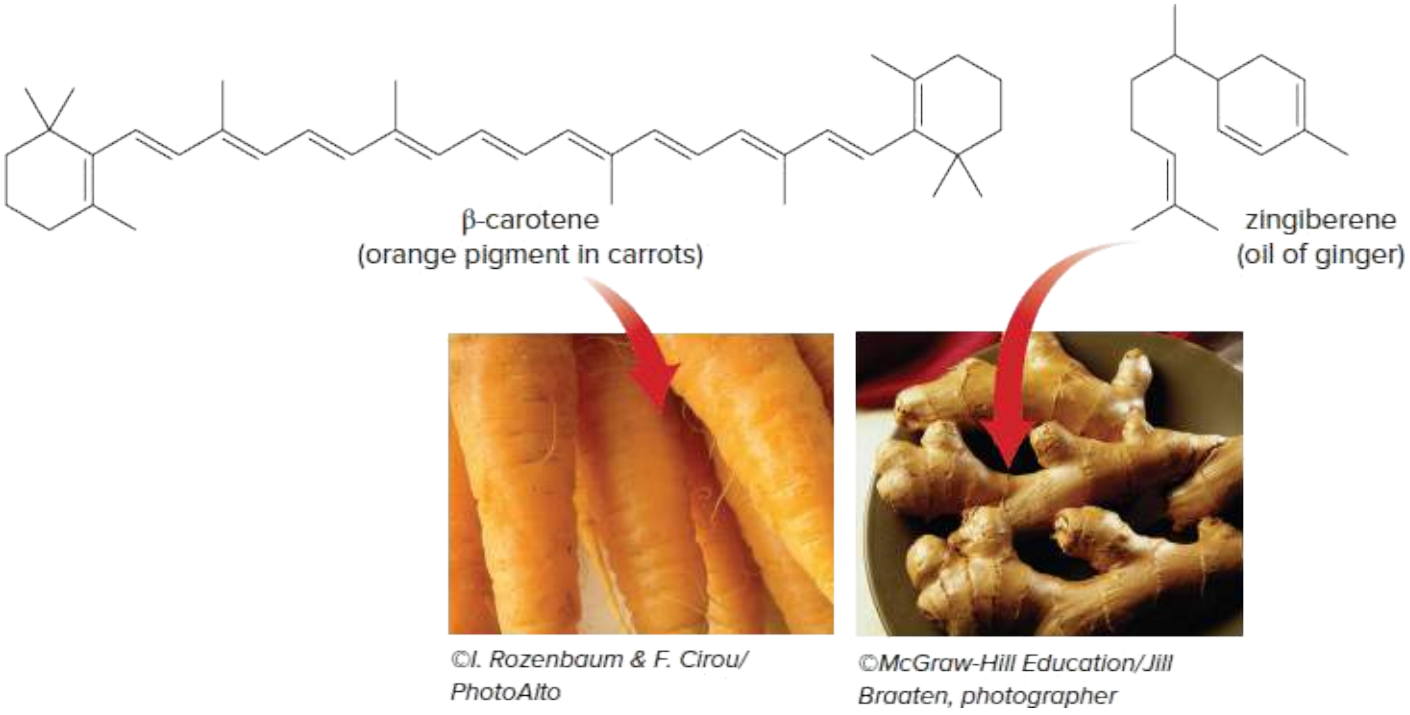


Figure 10.4 **Ethylene, an industrial starting material for many useful products**

Numerous organic compounds containing carbon–carbon double bonds have been isolated from natural sources, including β-carotene, the orange pigment in carrots (Section 3.5A), and zingiberene, a triene in the oil of ginger.

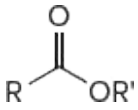


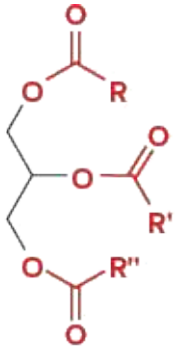
10.6 Lipids—Part 2

Understanding the geometry of C–C double bonds provides an insight into the properties of triacylglycerols, the most abundant lipids. Triacylglycerols contain three ester groups, each having a long carbon chain (abbreviated as R, R′, and R″) bonded to a carbonyl group (C=O).

Lipids are water-insoluble biomolecules composed largely of nonpolar C–C and C–H bonds (Section 4.15).

General structure of an ester:





R groups have 11–19 C's.

Three ester groups are labeled in red.

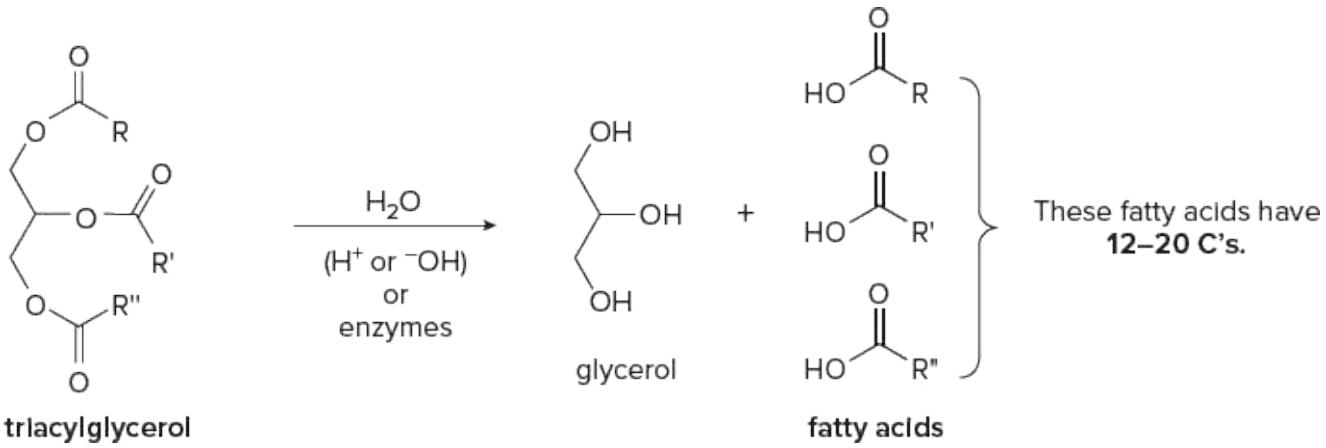
triacylglycerol

10.6A Fatty Acids

Triacylglycerols are hydrolyzed to glycerol (a triol) and three fatty acids of general structure RCO_2H. Naturally occurring fatty acids contain 12–20 carbon atoms, with a carboxy group (CO_2H) at one end.

Candlenuts, known as kukui nuts in Hawai'i, are rich in linoleic and linolenic acids, two essential fatty acids that cannot be

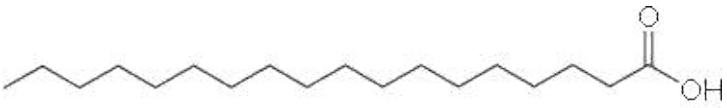
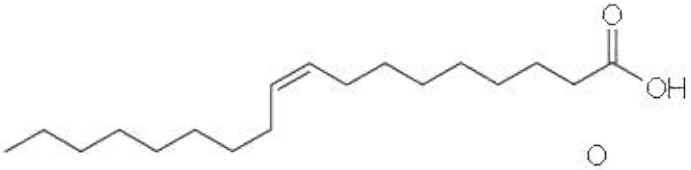
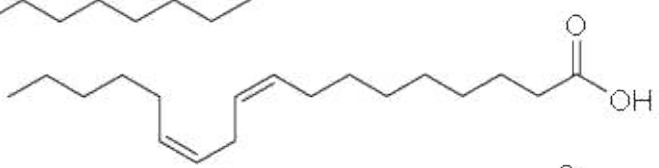
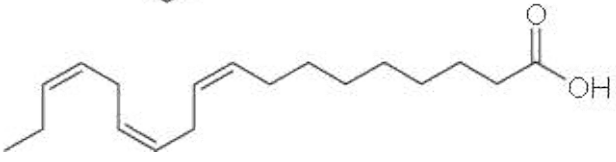
synthesized in the body and must therefore be obtained in the diet. ©*Inga Spence/Science Source*



- **Saturated fatty acids have no double bonds in their long hydrocarbon chains, and unsaturated fatty acids have one or more double bonds in their hydrocarbon chains.**
- **Double bonds in naturally occurring fatty acids have the *Z* configuration.**

Table 10.2 lists the structure and melting point of four fatty acids containing 18 carbon atoms. Stearic acid is one of the two most common saturated fatty acids, and oleic and linoleic acids are the most common unsaturated ones. The data show the effect of *Z* double bonds on the melting point of fatty acids.

Table 10.2 The Effect of Double Bonds on the Melting Point of Fatty Acids

Name	Structure	Mp (°C)
Stearic acid (0 C=C)		69
Oleic acid (1 C=C)		4
Linoleic acid (2 C=C)		−5
Linolenic acid (3 C=C)		−11

- **As the number of double bonds in the fatty acid *increases*, the melting point *decreases*.**

The three-dimensional structures of the fatty acids in Figure 10.5 illustrate how *Z* double bonds introduce kinks in the long hydrocarbon chain, decreasing the ability of the fatty acid to pack well in a crystalline lattice. The *larger* the number of *Z* double bonds, the more kinks in the hydrocarbon chain, and the *lower* the melting point.

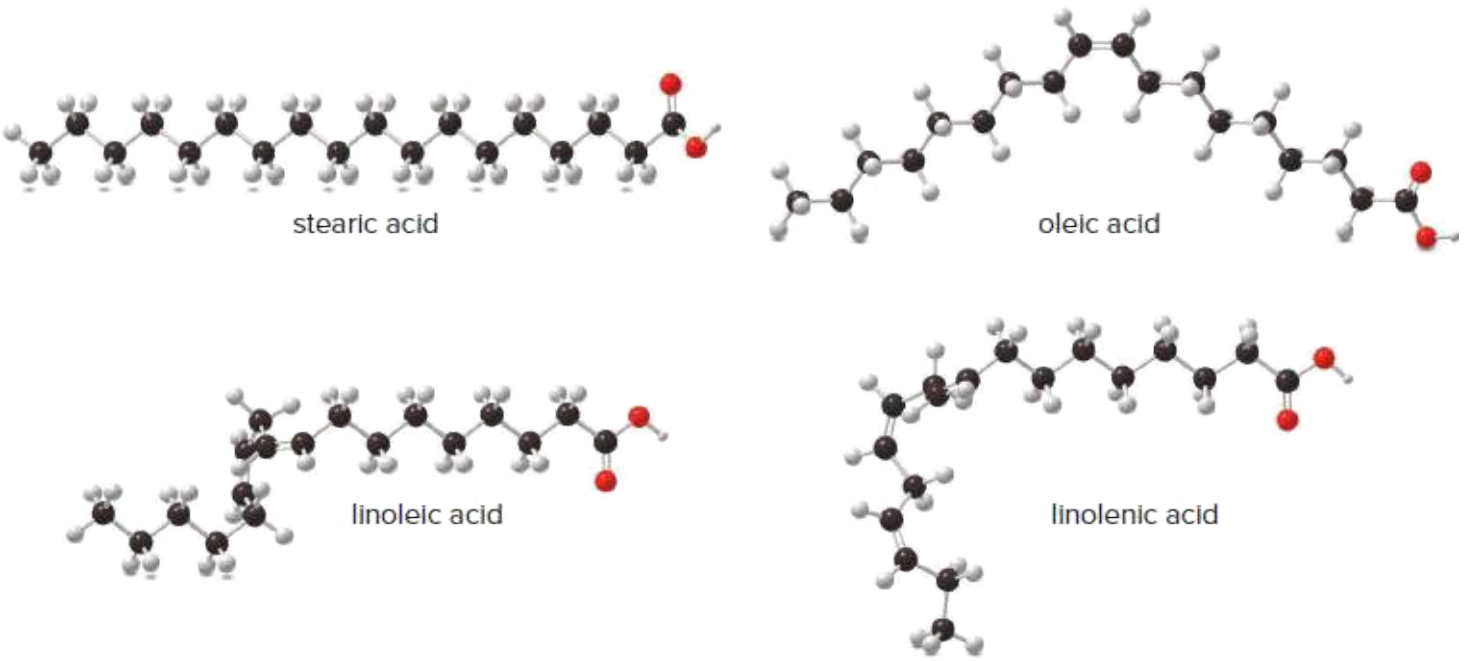
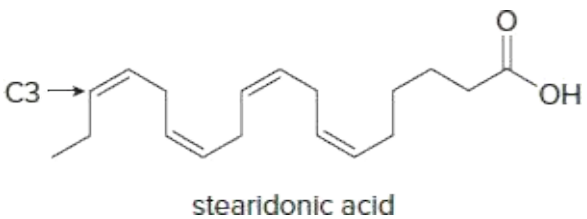


Figure 10.5 **Three-dimensional structure of four C_{18} fatty acids**

Problem 10.11

Linolenic acid (Table 10.2) and stearidonic acid are omega-3 fatty acids, unsaturated fatty acids that contain the first double bond located at C3, when numbering begins at the methyl end of the chain. Predict how the melting point of stearidonic acid compares with the melting points of linolenic and stearic acids. A current avenue of research is examining the use of soybean oil enriched in stearidonic acid as a healthier alternative to vegetable oils that contain fewer degrees of unsaturation.



stearidonic acid

Canola, soybeans, and flaxseed are excellent dietary sources of linolenic acid, an essential fatty acid. Oils derived from omega-3 fatty acids (Problem 10.11) are currently thought to be especially beneficial for individuals at risk of developing coronary artery disease. ©*Jill Braaten*

10.6B Fats and Oils

Fats and oils are triacylglycerols with different physical properties.

- **Fats have higher melting points—they are *solids* at room temperature.**
- **Oils have lower melting points—they are *liquids* at room temperature.**

The identity of the three fatty acids in the triacylglycerol determines whether it is a fat or an oil. Increasing the number of double bonds in the fatty acid side chains decreases the melting point of the triacylglycerol.

- **Fats are derived from fatty acids having few double bonds.**
- **Oils are derived from fatty acids having a larger number of double bonds.**

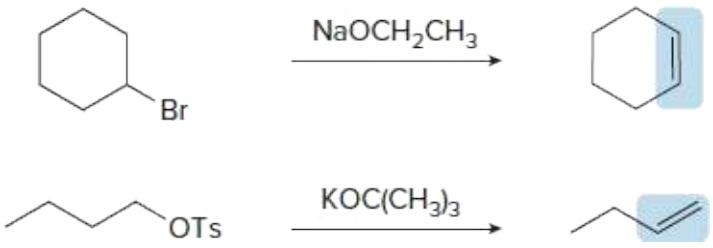
Saturated fats are typically obtained from animal sources, whereas unsaturated oils are common in vegetable sources. Thus, butter and lard are high in saturated triacylglycerols, and olive oil and safflower oil are high in unsaturated triacylglycerols. An exception to this generalization is coconut oil, which is composed largely of saturated alkyl side chains.

Considerable evidence suggests that an elevated cholesterol level is linked to an increased risk of heart disease. Saturated fats stimulate cholesterol synthesis in the liver, thus increasing the cholesterol concentration in the blood.

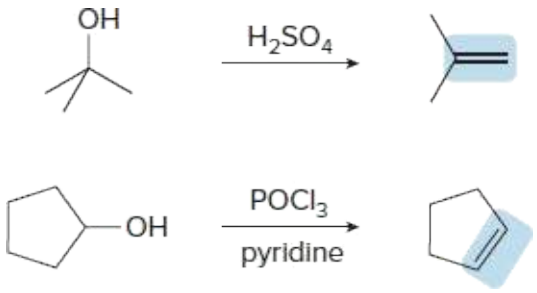
10.7 Preparation of Alkenes

Recall from Chapters 8 and 9 that alkenes can be prepared from alkyl halides and alcohols via elimination reactions. For example, dehydrohalogenation of alkyl halides with strong base yields alkenes via an E2 mechanism (Sections 8.4 and 8.5).

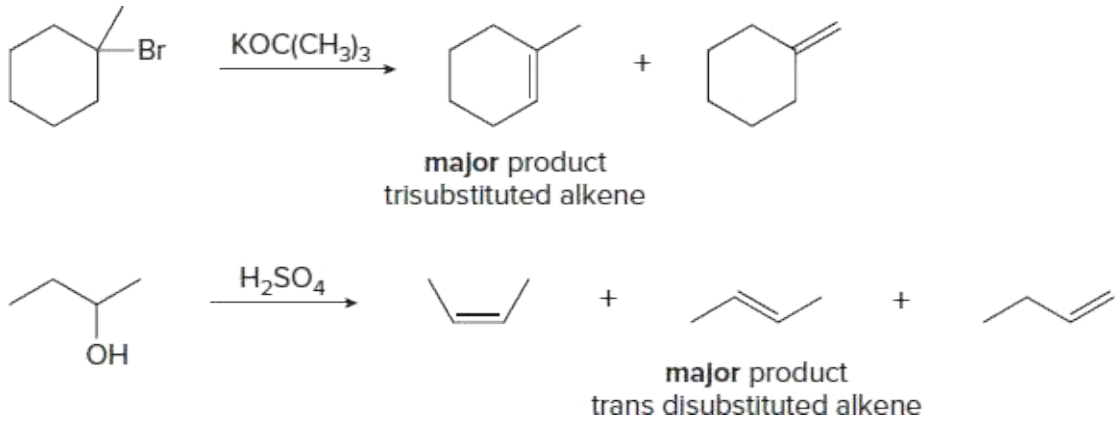
- Typical bases include ^{-}OH and ^{-}OR [especially $^{-}OC(CH_3)_3$], and nonnucleophilic bases such as DBU and DBN.
- Alkyl tosylates can also be used as starting materials under similar reaction conditions (Section 9.13).



The acid-catalyzed dehydration of alcohols with H_2SO_4 or TsOH yields alkenes, too (Sections 9.8 and 9.9). The reaction occurs via an E1 mechanism for 2° and 3° alcohols, and an E2 mechanism for 1° alcohols. E1 reactions involve carbocation intermediates, so rearrangements are possible. Dehydration can also be carried out with $POCl_3$ and pyridine by an E2 mechanism (Section 9.10).

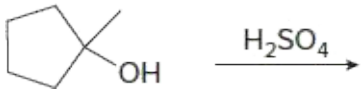


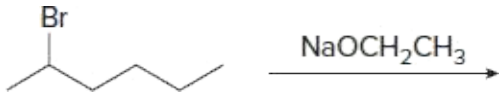
These elimination reactions are stereoselective and regioselective, so the most stable alkene is usually formed as the major product.



Problem 10.12

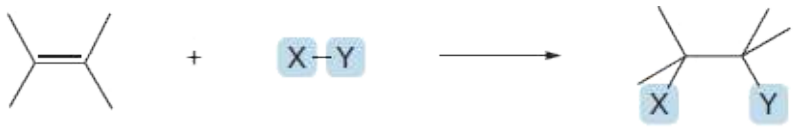
Draw the products of each elimination reaction.

a. 

b. 

10.8 Introduction to Addition Reactions

Because the C–C π bond of an alkene is much *weaker* than a C–C σ bond, the characteristic reaction of alkenes is addition: the π bond is broken and two new σ bonds are formed.



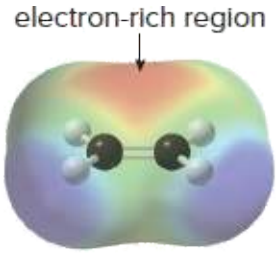
A π bond is broken. Two σ bonds are formed.

Alkenes are electron rich, as seen in the electrostatic potential plot in Figure 10.6. The electron density of the π bond is concentrated above and below the plane of the molecule, making the π bond more exposed than the σ bond.

What kinds of reagents add to the weak, electron-rich π bond of alkenes? There are many of them, and that can make alkene chemistry challenging. To help you organize this information, keep in mind the following:

The addition reactions of alkenes are discussed in Sections 10.9–10.16 and in Chapter 12 (Oxidation and Reduction).

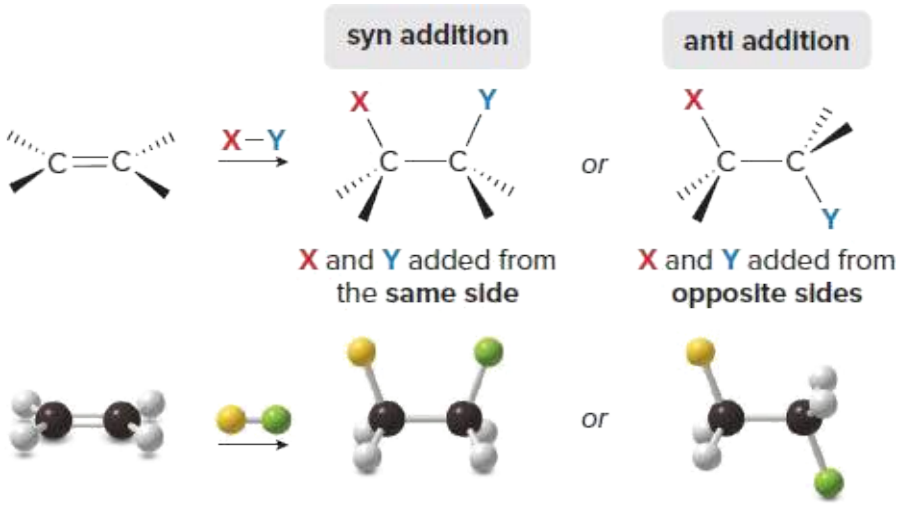
- **Every reaction of alkenes involves *addition:* the π bond is always broken.**
- **Because alkenes are electron rich, simple alkenes do *not* react with nucleophiles or bases, reagents that are themselves electron rich. Alkenes react with *electrophiles.***



- The red electron-rich region of the π bond is located above and below the plane of the molecule. Because the plane of the alkene depicted in this electrostatic potential plot is tipped, only the red region above the molecule is visible.

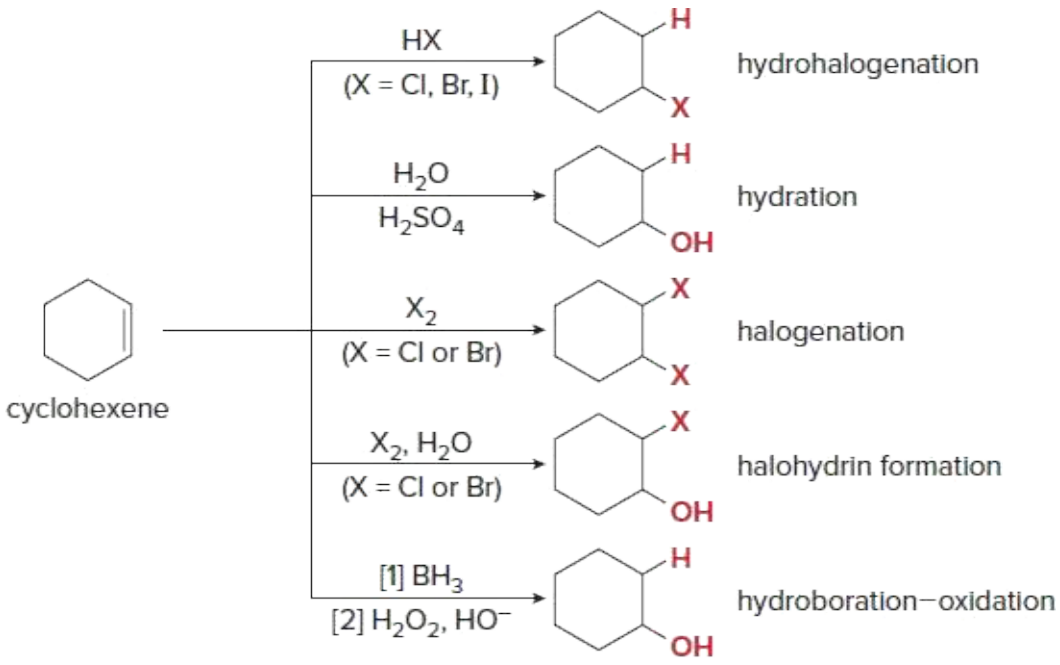
Figure 10.6 **Electrostatic potential plot of ethylene**

The stereochemistry of addition is often important in delineating a reaction's mechanism. Because the carbon atoms of a double bond are both trigonal planar, the elements of X and Y can be added to them from the same side or from opposite sides.



- ***Syn addition*** **takes place when both X and Y are added from the *same* side.**
- ***Anti addition*** **takes place when X and Y are added from *opposite* sides.**

Five reactions of alkenes are discussed in Chapter 10 and each is illustrated in Figure 10.7, using cyclohexene as the starting material.



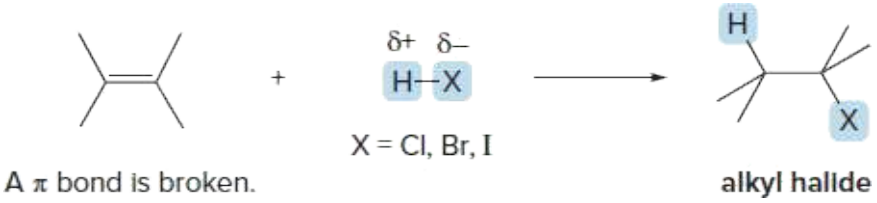
- In each reaction, the π bond is broken and two new σ bonds are formed.

Figure 10.7 **Five addition reactions of cyclohexene**

10.9 Hydrohalogenation—Electrophilic Addition of HX

Hydrohalogenation results in the addition of hydrogen halides HX (X = Cl, Br, and I) to alkenes to form alkyl halides.

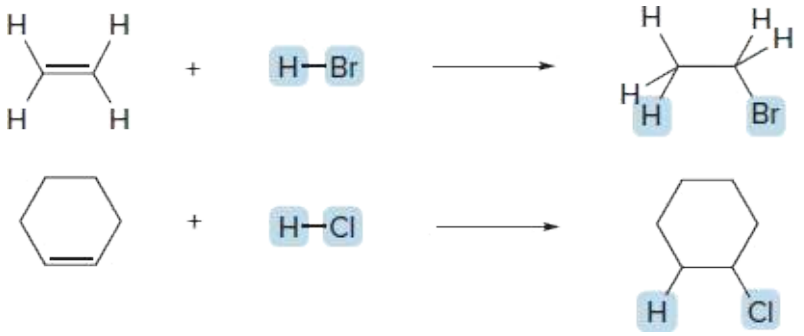
Hydrohalogenation of an alkene to form an alkyl halide is the reverse of the dehydrohalogenation of an alkyl halide to form an alkene, a reaction discussed in detail in Sections 8.4 and 8.5.



Two bonds are broken in this reaction—the weak π bond of the alkene and the HX bond—and two new σ bonds are formed—one to H and one to X. Because X is more electronegative than H, the H–X bond is polarized, with a partial positive charge on H. Because the electrophilic (H) end of HX is attracted to the electron-rich double bond, these reactions are called electrophilic additions.

To draw the products of an addition reaction:

- **Locate the C–C double bond.**
- **Identify the σ bond of the reagent that breaks—namely, the H–X bond in hydrohalogenation.**
- **Break the π bond of the alkene and the σ bond of the reagent, and form two new σ bonds to the C atoms of the double bond.**



Addition reactions are exothermic because the two σ bonds formed in the product are *stronger* than the σ and π bonds broken in the reactants. For example, ΔH° for the addition of HBr to ethylene is −60 kJ/mol, as illustrated in Figure 10.8.

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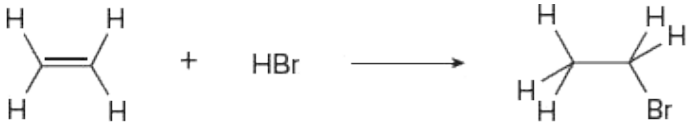


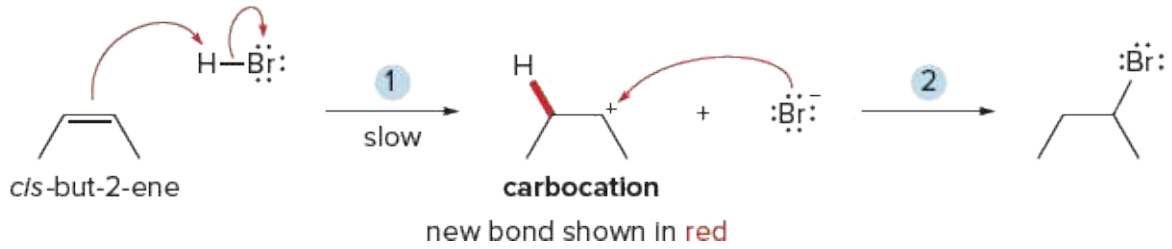
ΔH° calculation:

[1] Bonds broken	ΔH° (kJ/mol)	[2] Bonds formed	ΔH° (kJ/mol)	[3] Overall ΔH° =
$CH_2=CH_2$ π bond	+267	$BrCH_2CH_2$–H	–410	sum in Step [1] + sum in Step [2]
H–Br	+368	CH_3CH_2–Br	–285	
Total	+635 kJ/mol	Total	–695 kJ/mol	+635 kJ/mol –695 kJ/mol
Energy needed to break bonds.		Energy released in forming bonds.		ΔH° = –60 kJ/mol
				The reaction is exothermic.

Figure 10.8 **The addition of HBr to CH_2=CH_2, an exothermic reaction**

The mechanism of electrophilic addition of HX consists of two steps: addition of H^+ to form a carbocation, followed by nucleophilic attack of X^-. The mechanism is illustrated for the reaction of *cis*-but-2-ene with HBr in Mechanism 10.1.

Mechanism 10.1 Electrophilic Addition of HX to an Alkene



1 **The π bond of the alkene attacks the H of HBr to form a new C–H bond and a carbocation in the rate-determining in step.**

2 **Nucleophilic attack of Br^- on the carbocation forms the new C–Br bond.**

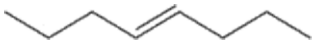
The mechanism of electrophilic addition consists of two successive Lewis acid–base reactions. In Step [1], the alkene is the Lewis base that donates an electron pair to H–Br, the Lewis acid, whereas in Step [2], Br^- is the Lewis base that donates an electron pair to the carbocation, the Lewis acid.

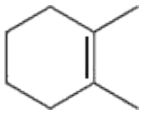
An energy diagram for the reaction of $CH_3CH{=}CHCH_3$ with HBr is given in Figure 10.9. Each step has its own energy barrier with a transition state at each energy maximum. Because Step [1] has a higher-energy transition state, it is rate-determining. $\Delta H°$ for Step [1] is positive because more bonds are broken than formed, whereas $\Delta H°$ for Step [2] is negative because only bond making occurs.

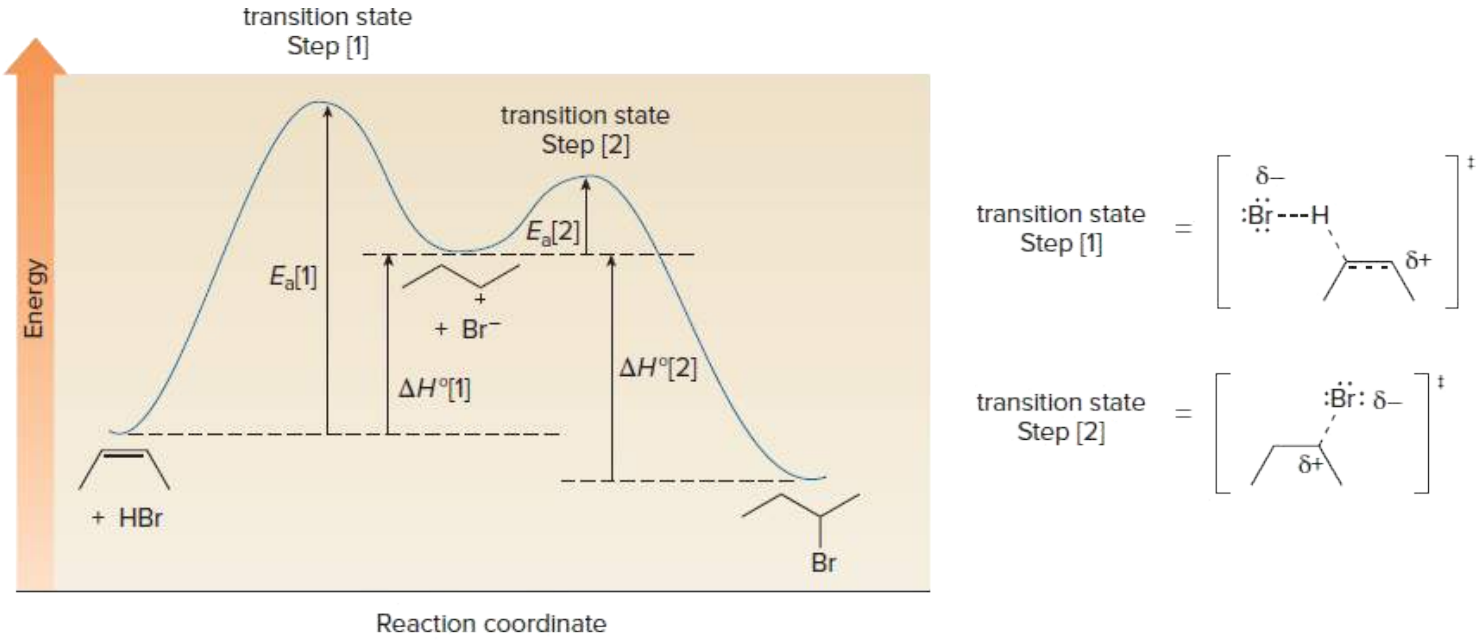
Problem 10.13

What product is formed when each alkene is treated with HCl?

a.

b. 

c. 

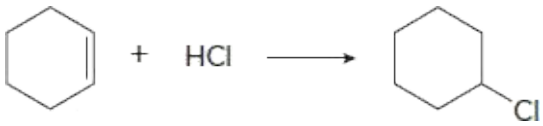


- The mechanism has two steps, so there are two energy barriers.
- Step [1] is **rate-determining.**

Figure 10.9 **Energy diagram for electrophilic addition: $CH_3CH{=}CHCH_3$ + HBr → $CH_3CH_2CH(Br)CH_3$**

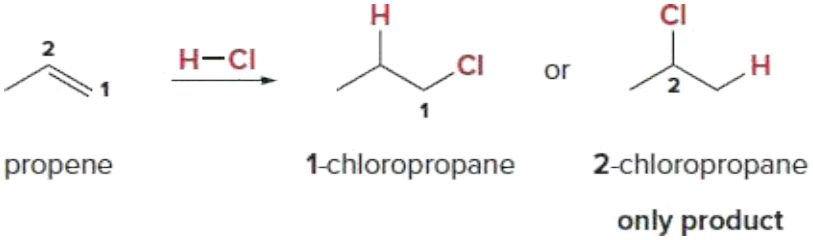
Problem 10.14

Draw a stepwise mechanism for the following reaction. Draw the transition state for each step.



10.10 Markovnikov's Rule

With an unsymmetrical alkene, HX can add to the double bond to give two constitutional isomers.



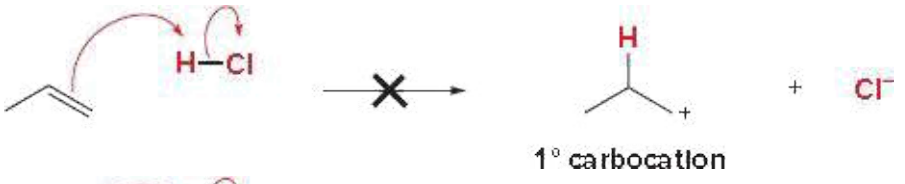
For example, HCl addition to propene could in theory form 1-chloropropane by addition of H and Cl to C2 and C1, respectively, and 2-chloropropane by addition of H and Cl to C1 and C2, respectively. In fact, electrophilic addition forms *only* 2-chloropropane. This is a specific example of a general trend called Markovnikov's rule,

named for the Russian chemist who first determined the regioselectivity of electrophilic addition of HX.

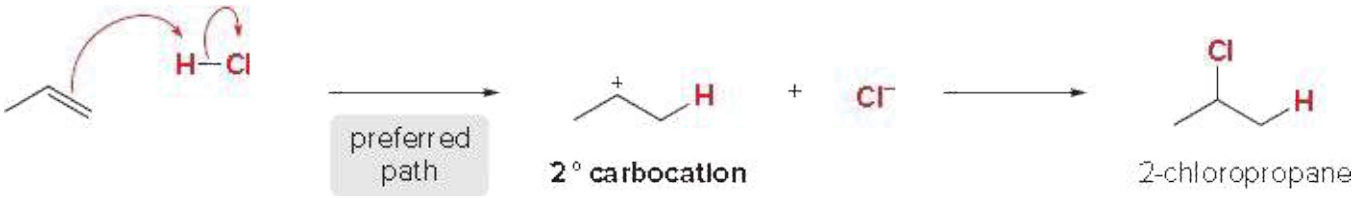
- **Markovnikov's rule: In the addition of HX to an unsymmetrical alkene, the H atom bonds to the *less substituted* carbon atom—that is, the carbon that has more H atoms to begin with.**

The basis of Markovnikov's rule is the formation of a carbocation in the rate-determining step of the mechanism. With propene, there are two possible paths for this first step, depending on which carbon atom of the double bond forms the new bond to hydrogen. Page 414

[1]



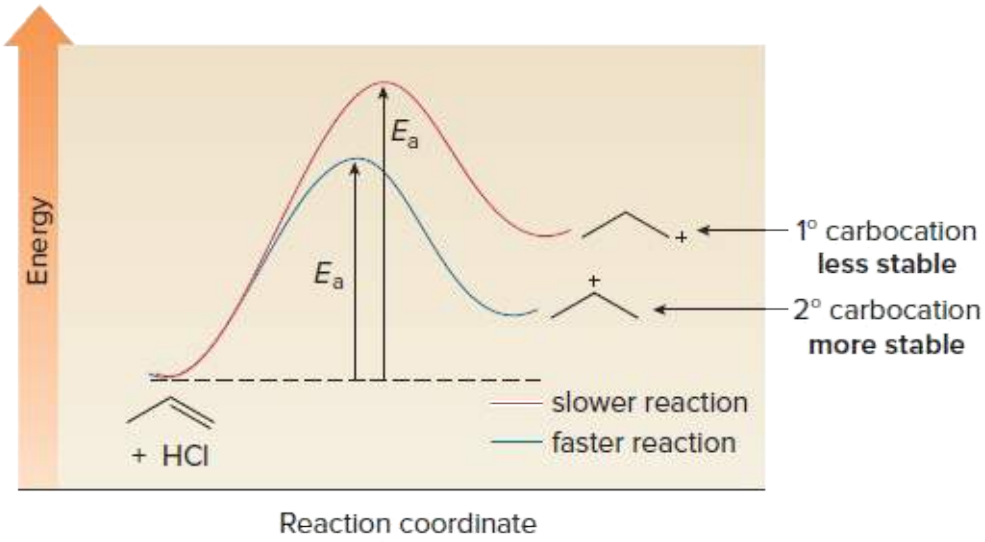
[2]



Path [1] forms a highly unstable 1° carbocation, whereas Path [2] forms a more stable 2° carbocation. According to the Hammond postulate, Path [2] is faster because formation of the carbocation is an endothermic process, so the transition state to form the more stable 2° carbocation is lower in energy (Figure 10.10).

The Hammond postulate was first introduced in Section 7.14 to explain the relative rate of S_N1 reactions with 1°, 2°, and 3° RX.

- **In the addition of HX to an unsymmetrical alkene, the H atom is added to the *less* substituted carbon to form the *more stable, more substituted* carbocation.**



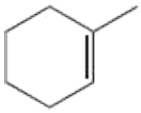
- The E_a for formation of the more stable 2° carbocation is *lower* than the E_a for formation of the 1° carbocation. The 2° carbocation is formed *faster*.

Figure 10.10 **Electrophilic addition and the Hammond postulate**

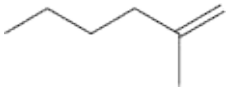
Similar results are seen in any electrophilic addition involving an intermediate carbocation: the more stable, *more* substituted carbocation is formed by addition of the electrophile to the *less* substituted carbon.

Problem 10.15

Draw the products formed when each alkene is treated with HCl.

a. 

b.

c. 

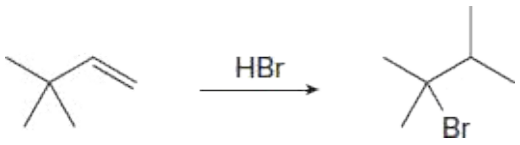
Problem 10.16

Use the Hammond postulate to explain why $(CH_3)_2C{=}CH_2$ reacts faster than $CH_3CH{=}CH_2$ in electrophilic addition of HX.

Because carbocations are formed as intermediates in hydrohalogenation, carbocation rearrangements can occur, as illustrated in Sample Problem 10.3.

Sample Problem 10.3 Drawing Hydrohalogenation with a Carbocation Rearrangement

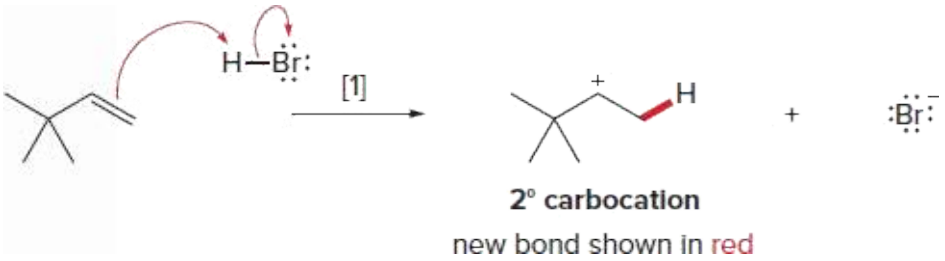
Draw a stepwise mechanism for the following reaction.



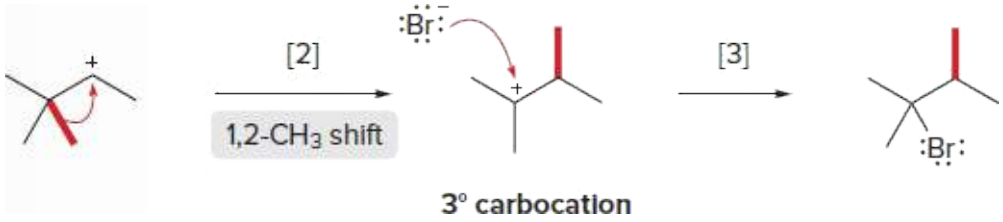
Solution

Because the carbon skeletons of the starting material and product are *different—the* alkene reactant has a 4° carbon and the product alkyl halide does not—a carbocation rearrangement must have occurred.

Markovnikov addition of HBr adds H^+ to the less substituted end of the double bond, forming a 2° carbocation in Step [1].



Rearrangement of the 2° carbocation by a 1,2-methyl shift forms a more stable 3° carbocation in Step [2]. Nucleophilic attack of Br^- forms the product, a 3° alkyl halide, in Step [3].



Problem 10.17

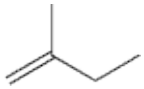
Treatment of 3-methylcyclohexene with HCl yields two products, 1-chloro-3-methylcyclohexane and 1-chloro-1-methylcyclohexane. Draw a mechanism to explain this result.

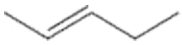
More Practice:

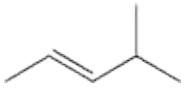
Try Problem 10.55.

Problem 10.18

Addition of HBr to which of the following alkenes will lead to a rearrangement?

a. 

b. 

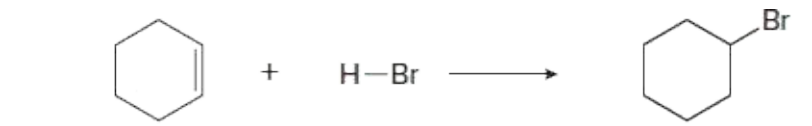
c. 

10.11 Stereochemistry of Electrophilic Addition of HX

To understand the stereochemistry of electrophilic addition, recall two stereochemical principles learned in Chapters 7 and 9.

- **Trigonal planar atoms react with reagents from two directions with equal probability (Section 7.12C).**
- **Achiral starting materials yield achiral or racemic products (Section 9.16).**

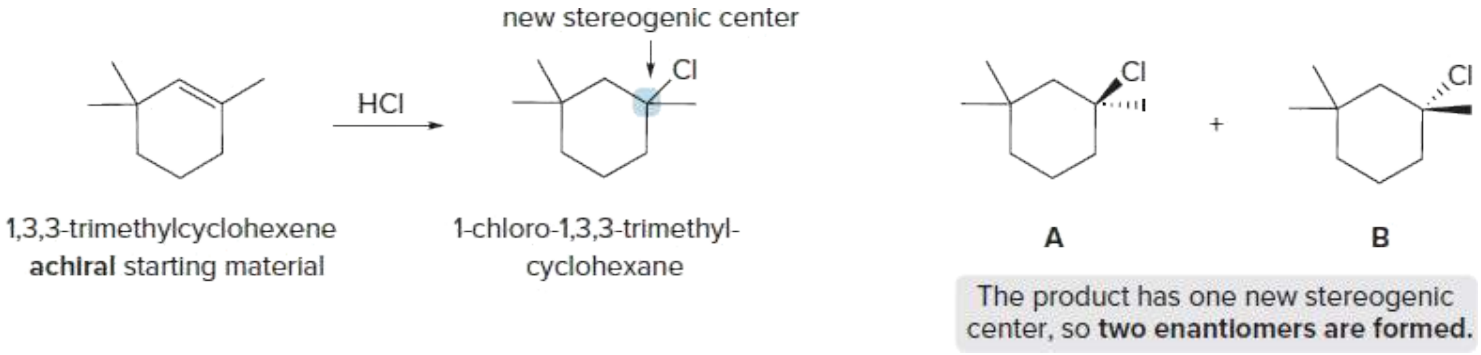
Many hydrohalogenation reactions begin with an achiral reactant and form an achiral product. For example, the addition of HBr to cyclohexene, an achiral alkene, forms bromocyclohexane, an achiral alkyl halide.



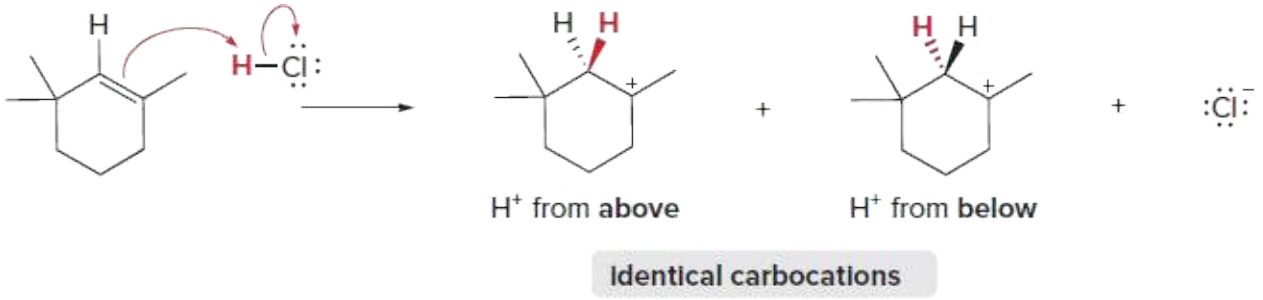
cyclohexene
achiral starting material

bromocyclohexane
achiral product

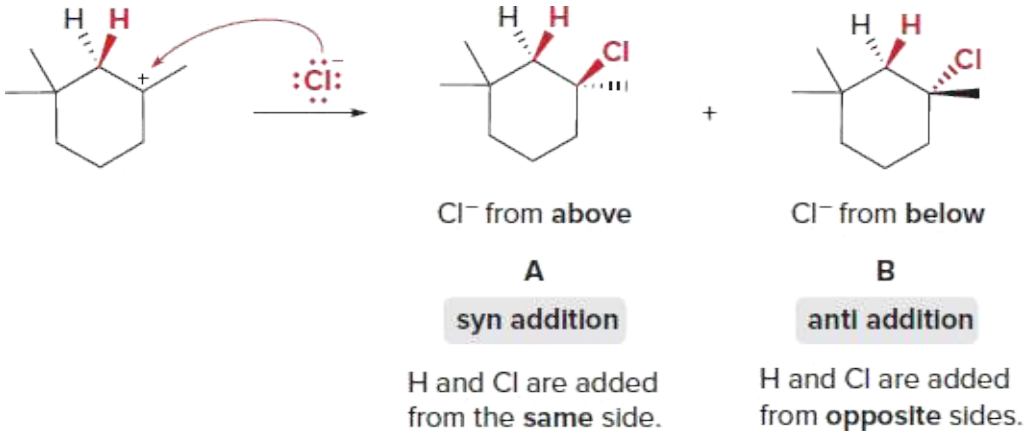
Because addition converts sp^2 hybridized carbons to sp^3 hybridized carbons, Page 416 sometimes new stereogenic centers are formed from hydrohalogenation. Markovnikov addition of HCl to 1,3,3-trimethylcyclohexene, an achiral alkene, forms one constitutional isomer, 1-chloro-1,3,3-trimethylcyclohexane. Because this product now has a stereogenic center at one of the newly formed sp^3 hybridized carbons (labeled in blue), an equal amount of two enantiomers—a racemic mixture—must form.



The mechanism of hydrohalogenation illustrates why two enantiomers are formed. Initial addition of the electrophile H^+ (from HCl) occurs from either side of the planar double bond to form a carbocation. Both modes of addition (from above and below) generate the same achiral carbocation. Either representation of this carbocation can then be used to draw the second step of the mechanism.



Nucleophilic attack of Cl^- on the trigonal planar carbocation also occurs from two different directions, forming two products, A and B, having a new stereogenic center. A and B are not superimposable, so they are enantiomers. Because attack from either direction occurs with equal probability, a racemic mixture of A and B is formed.



The terms cis and trans refer to the arrangement of groups in a particular compound, usually an alkene or a disubstituted cycloalkane. The terms syn and anti describe the stereochemistry of a process—for example, how two groups are added to a double bond.

Because hydrohalogenation begins with a planar double bond and forms a planar carbocation, addition of H and Cl occurs in two different ways. The elements of H and Cl can both be added from the same side of the double bond—that is, syn addition—or they can be added from opposite sides—that is, anti addition. *Both* modes of addition occur in this two-step reaction mechanism.

- **Hydrohalogenation occurs with syn and anti addition of HX.**

Table 10.3 summarizes the characteristics of electrophilic addition of HX to alkenes.

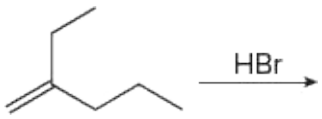
Table 10.3 Summary: Electrophilic Addition of HX to Alkenes

	Observation
Mechanism	• The mechanism involves two steps. • The rate-determining step forms a carbocation. • Rearrangements can occur.
Regioselectivity	• Markovnikov's rule is followed. In unsymmetrical alkenes, H bonds to the less substituted C to form the more stable carbocation.
Stereochemistry	• Syn and anti addition occur.

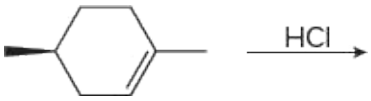
Problem 10.19

Draw the products, including stereochemistry, of each reaction.

a.



b.

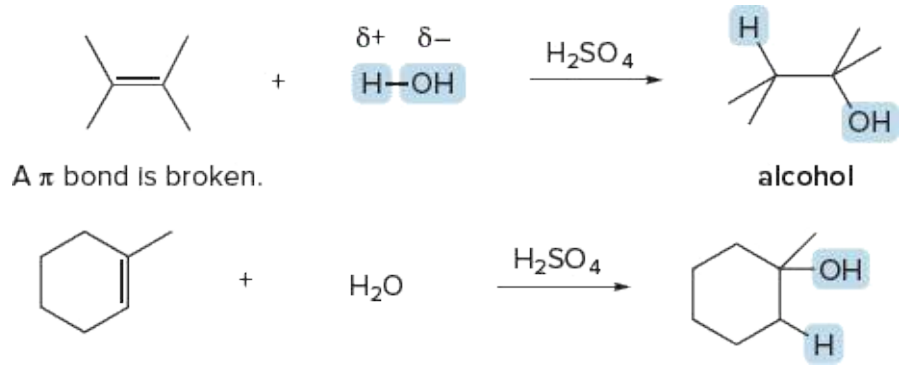


Problem 10.20

Draw all stereoisomers formed when 1,2-dimethylcyclohexene is treated with HCl. Label pairs of enantiomers.

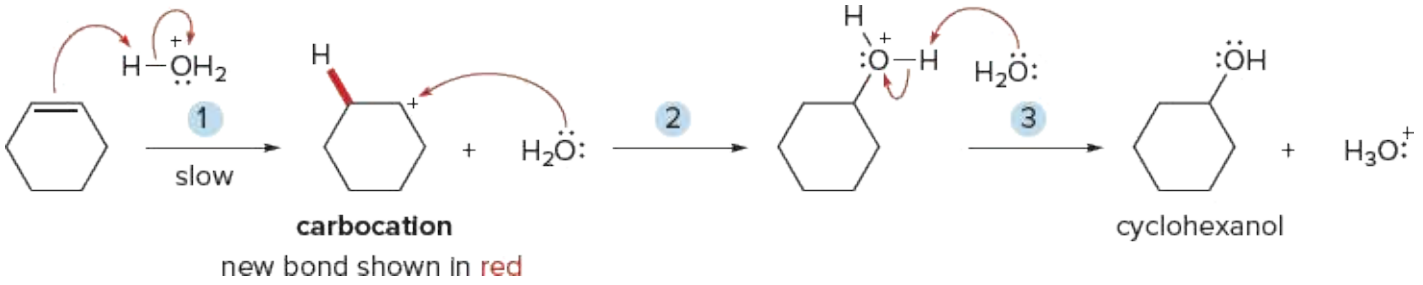
10.12 Hydration—Electrophilic Addition of Water

Hydration results in the addition of water to an alkene to form an alcohol. H2O itself is too weak an acid to protonate an alkene, but with added H_2SO_4, H_3O^+ is formed and addition readily occurs.



Hydration is simply another example of electrophilic addition. The first two steps of the mechanism are similar to those of electrophilic addition of HX—that is, addition of H^+ (from H_3O^+) to generate a carbocation, followed by nucleophilic attack of H_2O. Mechanism 10.2 illustrates the addition of H2O to cyclohexene to form cyclohexanol.

Mechanism 10.2 Electrophilic Addition of H_2O to an Alkene—Hydration



1. **The π bond of the alkene attacks the H of H_3O^+ to form a new C–H bond and a carbocation in the rate-determining step.**
2. **Nucleophilic attack of H_2O on the carbocation forms the new C–O bond.**
3. **Removal of a proton with H_2O forms a neutral alcohol. Because the acid used in Step [1] is regenerated in Step [3], the reaction is acid-catalyzed.**

There are three consequences to the formation of carbocation intermediates: Page 418

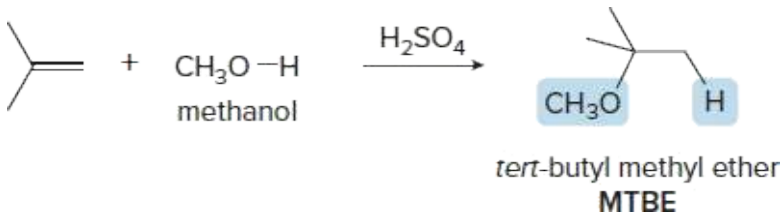
Hydration of an alkene to form an alcohol is the reverse of the dehydration of an alcohol to form an alkene, a reaction discussed in detail in Section 9.8.

- **In unsymmetrical alkenes, H adds to the *less* substituted carbon to**

form the *more* stable carbocation; that is, Markovnikov's rule holds.

- **Addition of H and OH occurs in both a syn and anti fashion.**
- **Carbocation *rearrangements* can occur.**

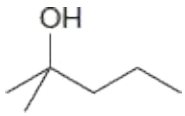
Alcohols add to alkenes, forming ethers, using the same mechanism. Addition of CH_3OH to 2-methylpropene, for example, forms *tert*-butyl methyl ether (MTBE), a high octane fuel additive described in Section 3.4C.

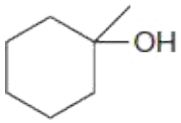


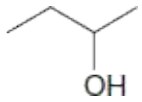
tert-butyl methyl ether
MTBE

Problem 10.21

What two alkenes give rise to each alcohol as the major product of acid-catalyzed hydration?

a. 

b. 

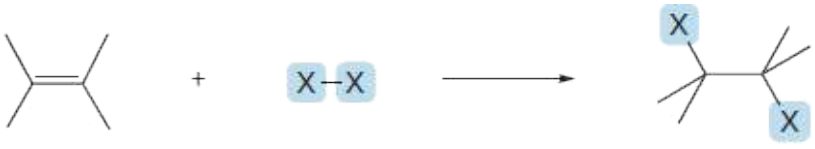
c. 

Problem 10.22

What stereoisomers are formed when pent-1-ene is treated with H_2O and H_2SO_4?

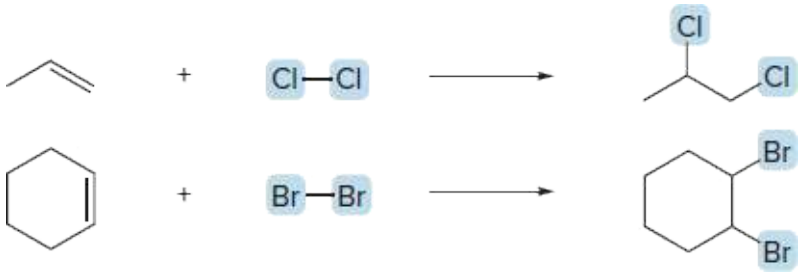
10.13 Halogenation—Addition of Halogen

Halogenation results in the addition of halogen X_2 (X = Cl or Br) to an alkene, forming a vicinal dihalide.



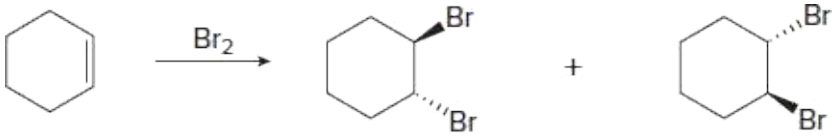
A π bond is broken. vicinal dihalide

Halogenation is synthetically useful only with Cl_2 and Br_2. The dichlorides and dibromides formed in this reaction serve as starting materials for the synthesis of alkynes, as we learned in Section 8.10.



Halogens add to π bonds because halogens are polarizable. The electron-rich double bond induces a dipole in an approaching halogen molecule, making one halogen atom electron deficient and the other electron rich ($X^{\delta+}$–$X^{\delta-}$). The electrophilic halogen atom is then attracted to the nucleophilic double bond, making addition possible.

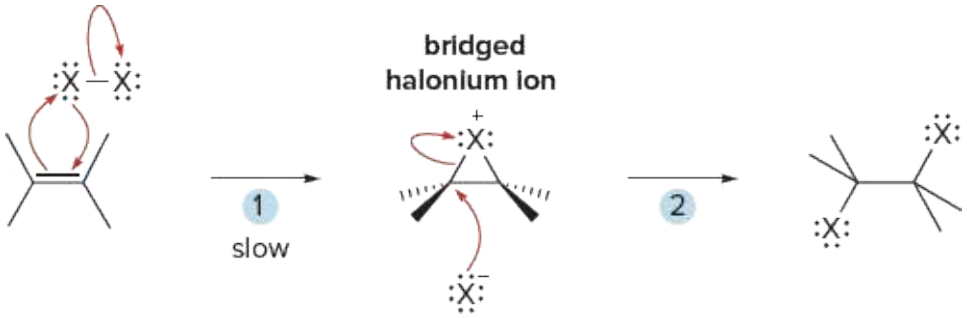
Two facts demonstrate that halogenation follows a different mechanism from that of hydrohalogenation or hydration. First, no rearrangements occur, and second, only anti addition of X2 is observed. For example, treatment of cyclohexene with Br2 yields two trans enantiomers formed by anti addition.



enantiomers

These facts suggest that carbocations are *not* intermediates in halogenation. Page 419 Unstable carbocations rearrange, and both syn and anti addition is possible with carbocation intermediates. The accepted mechanism for halogenation comprises two steps, but it does *not* proceed with formation of a carbocation, as shown in Mechanism 10.3.

Mechanism 10.3 Addition of X_2 to an Alkene—Halogenation



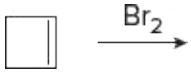
1 **Four bonds are broken or formed to generate an unstable bridged halonium ion that contains a three-membered ring. The electron pair in the π bond and a lone pair on a halogen are used to form two new C–X bonds, and the X–X bond is cleaved.**

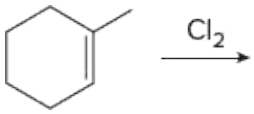
2 **Nucleophilic attack of X^- ring opens the bridged halonim ion and forms a new C–X bond.**

Bridged halonium ions resemble carbocations in that they are short-lived intermediates that react readily with nucleophiles. Carbocations are inherently unstable because only six electrons surround carbon, whereas halonium ions are unstable because they contain a strained three-membered ring with a positively charged halogen atom.

Problem 10.23

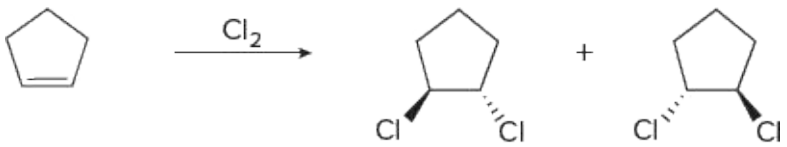
Draw the products of each reaction, including stereochemistry.

a. 

b. 

10.14 Stereochemistry of Halogenation

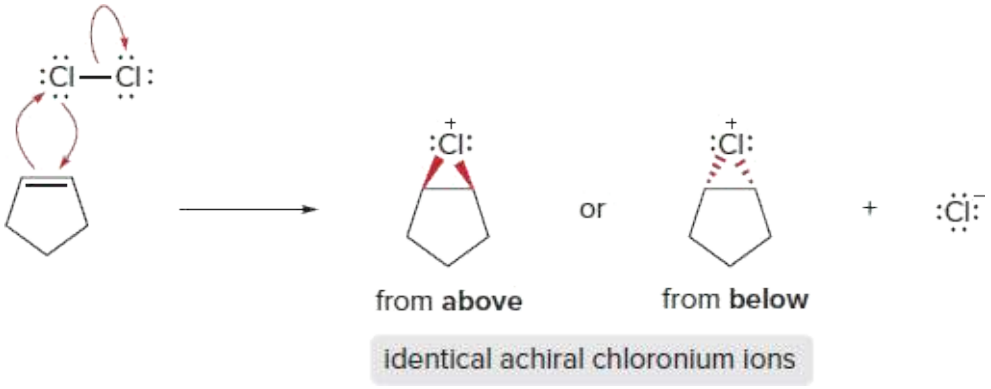
How does the proposed mechanism invoking a bridged halonium ion intermediate explain the observed trans products of halogenation? For example, chlorination of cyclopentene affords both enantiomers of *trans*-1,2-dichlorocyclopentane, with *no* cis products.



trans enantiomers

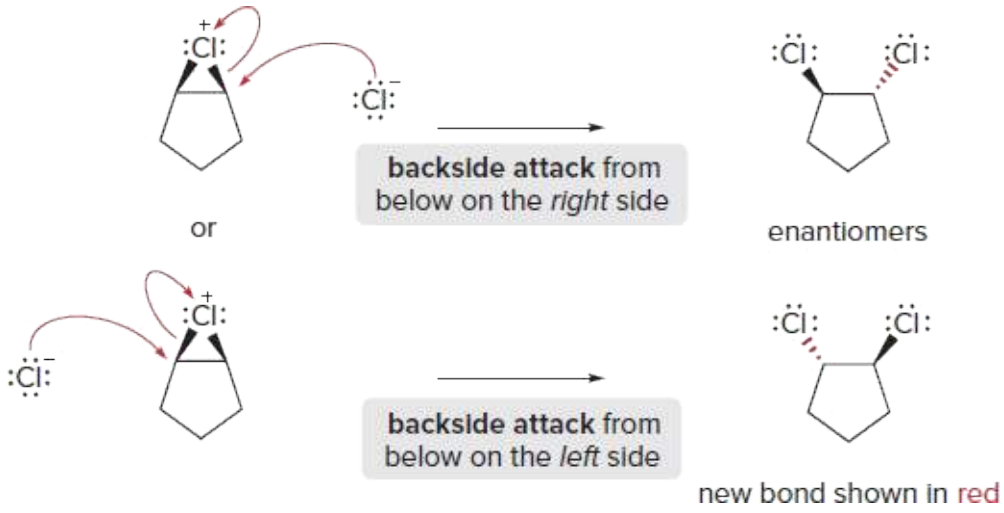
Initial addition of the electrophile Cl^+ (from Cl2) occurs from either side of the planar double bond to form the bridged chloronium ion. In this example, both modes of addition (from above and below) generate the same achiral intermediate, so either representation can be used to draw the second step.

Page 420



In the second step, nucleophilic attack of Cl^- must occur from the back side—that is, from the side of the five-membered ring opposite to the side having the bridged chloronium ion. Because the nucleophile attacks from below in this example and the leaving group departs from above, the two Cl atoms in the product are oriented trans to each other. Backside attack occurs with equal probability at either carbon of the three-membered ring to yield an equal amount of two enantiomers—a racemic mixture.

The opening of bridged halonium ion intermediates resembles the opening of epoxide rings with nucleophiles discussed in Section 9.16.



In summary, the mechanism for halogenation of alkenes occurs in two steps:

- **Addition of X^+ forms an unstable bridged halonium ion in the rate-determining step.**
- **Nucleophilic attack of X^- occurs from the *back side* to form trans products. The overall result is *anti addition* of X_2 across the double bond.**

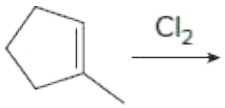
Because halogenation occurs exclusively in an anti fashion, cis and trans alkenes yield different stereoisomers. Halogenation of alkenes is a stereospecific reaction.

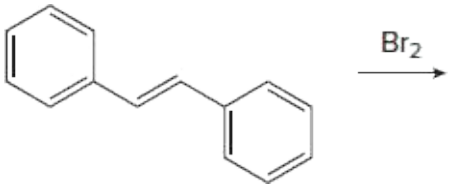
- **A reaction is *stereospecific* when each of two specific stereoisomers of a starting material yields a particular stereoisomer of a product.**

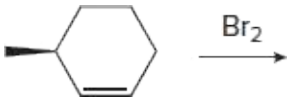
cis-But-2-ene yields two enantiomers, whereas trans-but-2-ene yields a single achiral meso compound, as shown in Figure 10.11.

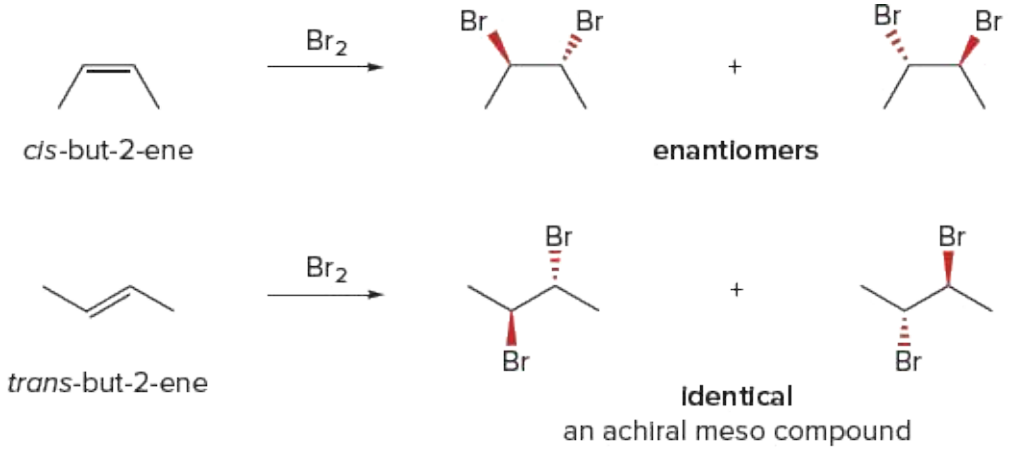
Problem 10.24

Draw all stereoisomers formed in each reaction.

a. 

b. 

c. 



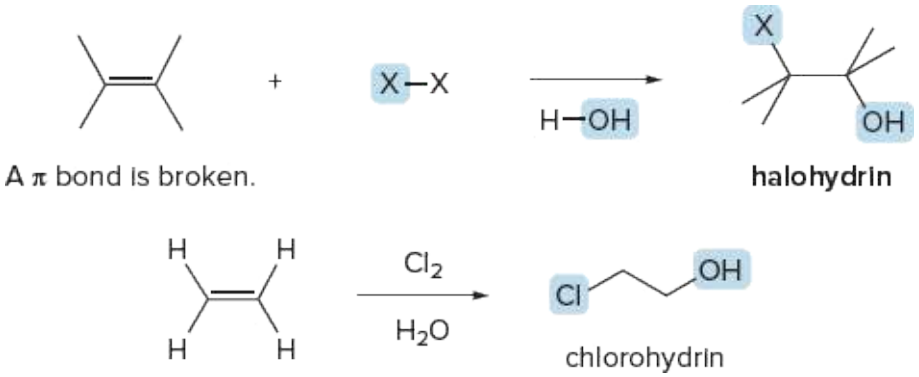
To draw the products of halogenation:

- Add Br_2 in an **anti** fashion across the double bond, leaving all other groups in their original orientations. With the alkene drawn in the plane of the page, **one Br adds from the front (ending up on a wedge), and one Br adds from the back (ending up on a dashed wedge).**
- Sometimes this reaction produces two stereoisomers, as in the case of *cis*-but-2-ene, which forms an equal amount of **two enantiomers.** Sometimes it produces a single compound, as in the case of *trans*-but-2-ene, where a **meso** compound is formed.

Figure 10.11 **Halogenation of *cis*- and *trans*-but-2-ene**

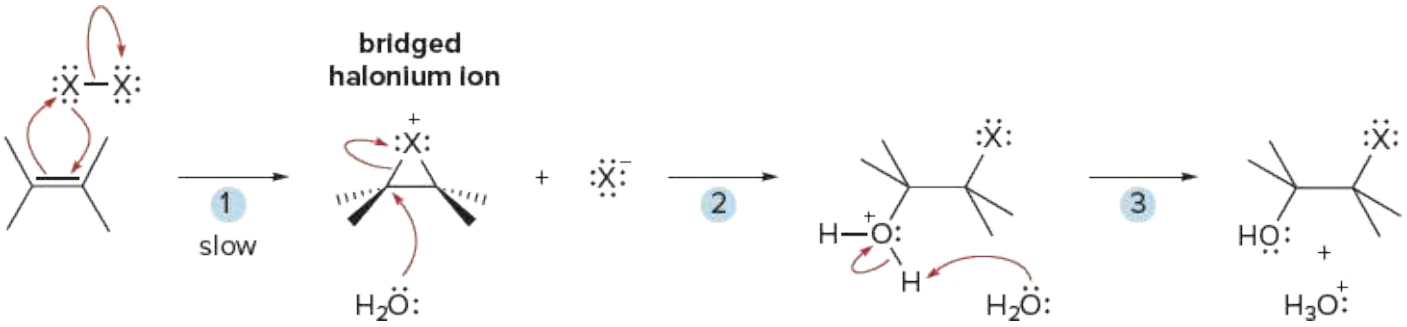
10.15 Halohydrin Formation

Treatment of an alkene with a halogen X_2 and H_2O forms a halohydrin by addition of the elements of X and OH to the double bond.



The mechanism for halohydrin formation is similar to the mechanism for halogenation: addition of the electrophile X^+ (from X_2) to form a bridged halonium ion, followed by nucleophilic attack by H_2O from the back side on the three-membered ring (Mechanism 10.4). Even though X^- is formed in Step [1] of the mechanism, its concentration is small compared to H_2O (often the solvent), so H_2O and *not* X^- is the nucleophile.

Mechanism 10.4 Addition of X and OH—Halohydrin Formation

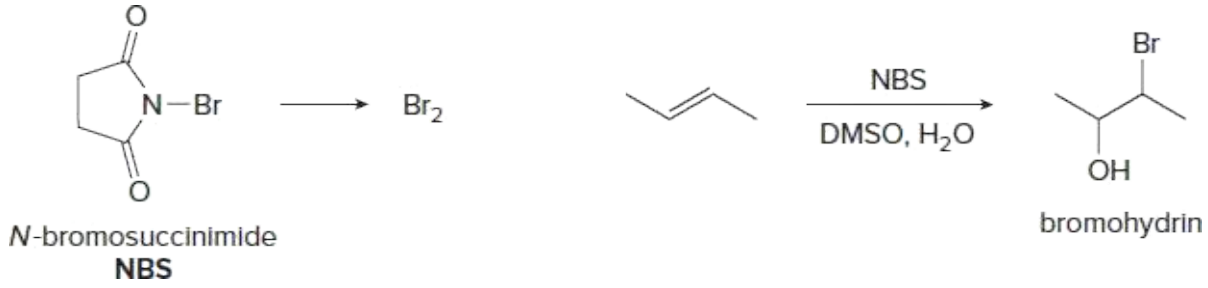


1. **Four bonds are broken or formed to generate an unstable bridged halonium ion that contains a three-membered ring. The electron pair in the π bond and a lone pair on a halogen are used to form two new C–X bonds, and the X–X bond is cleaved.**
2. **Nucleophilic attack of H_2O ring opens the bridged halonium ion and forms a new C–O bond.**
3. **Loss of a proton forms the halohydrin.**

Although the combination of Br_2 and H_2O effectively forms bromohydrins from alkenes, other reagents can also be used. Bromohydrins are also formed with *N*-bromosuccinimide (abbreviated as NBS) in aqueous DMSO [$(CH_3)_2S{=}O$]. NBS

serves as a source of Br_2, which then goes on to form a bromohydrin by the same reaction mechanism.

Recall from Section 7.8C that DMSO (dimethyl sulfoxide) is a polar aprotic solvent.

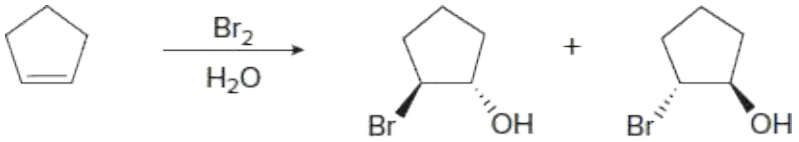


N-bromosuccinimide
NBS

bromohydrin

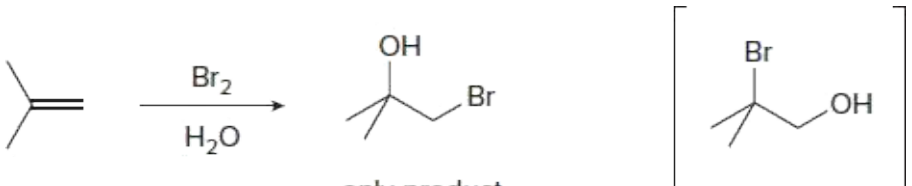
10.15A Stereochemistry and Regioselectivity of Halohydrin Formation

Because the bridged halonium ion ring is opened by backside attack of H_2O, addition of X and OH occurs in an anti fashion and trans products are formed.



trans enantiomers

With unsymmetrical alkenes, two constitutional isomers are possible from addition of X and OH, but only one is formed. The preferred product has the electrophile X^+ bonded to the *less* substituted carbon atom—that is, the carbon that has more H atoms to begin with in the reacting alkene. Thus, the nucleophile (H_2O) bonds to the more substituted carbon.



only product

Br ends up on the *less* substituted C.

not formed

This result is reminiscent of the opening of epoxide rings with acids HZ (Z = a nucleophile), which we encountered in Section 9.16B. As in the opening of an epoxide ring, nucleophilic attack occurs at the *more* substituted carbon end of the bridged halonium ion because that carbon is better able to accommodate a partial positive

charge in the transition state.

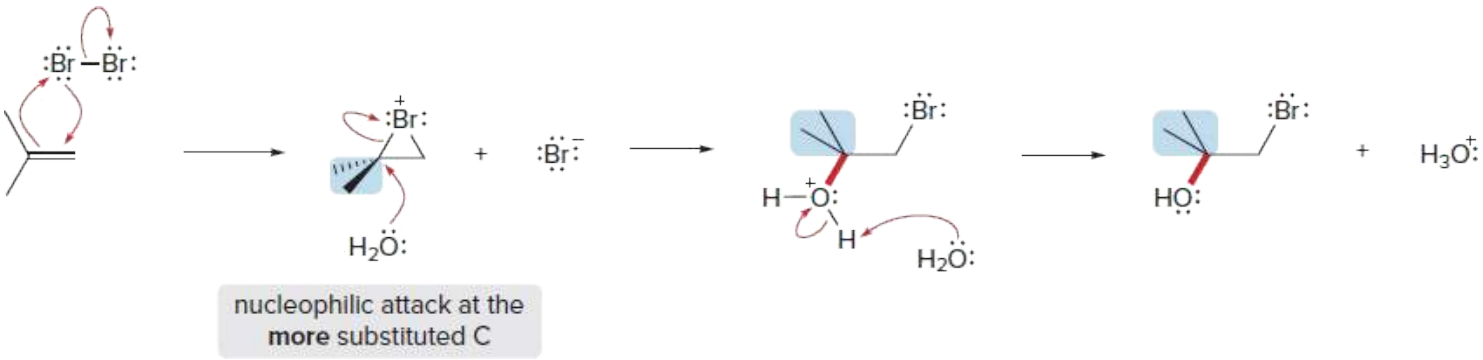


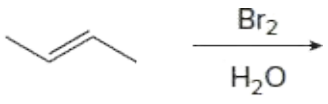
Table 10.4 summarizes the characteristics of halohydrin formation.

Table 10.4 Summary: Conversion of Alkenes to Halohydrins

	Observation
Mechanism	• The mechanism involves three steps. • The rate-determining step forms a bridged halonium ion. • No rearrangements can occur.
Regioselectivity	• The electrophile X^+ bonds to the less substituted carbon.
Stereochemistry	• Anti addition occurs.

Sample Problem 10.4 Drawing the Halohydrin Formed in an Alkene Addition

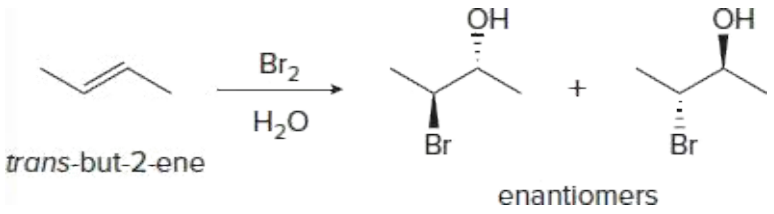
Draw the products of the following reaction, including stereochemistry.



trans-but-2-ene

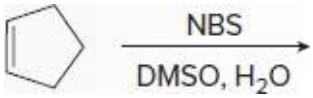
Solution

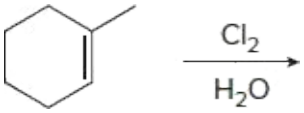
The reagent (Br_2 + H_2O) adds the elements of Br and OH to a double bond in an anti fashion—that is, from opposite sides. To draw two products of anti addition: add Br from above and OH from below in one product; then add Br from below and OH from above in the other product. In this example, the two products are nonsuperimposable mirror images—enantiomers.



Problem 10.25

Draw the products of each reaction and indicate their stereochemistry.

a. 

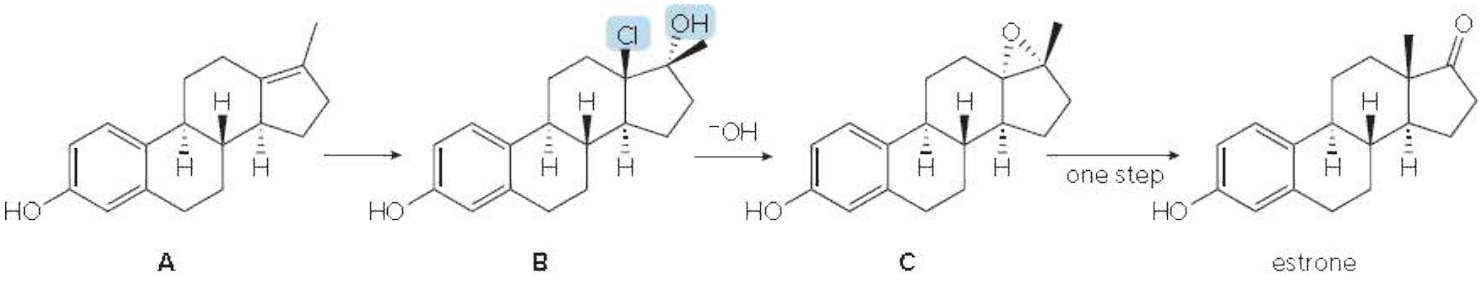
b. 

More Practice:

Try Problems 10.51b, c; 10.52e.

10.15B Halohydrins: Useful Compounds in Organic Synthesis

Because halohydrins are easily converted to epoxides by intramolecular S_N2 reaction (Section 9.6), they have been used in the synthesis of many naturally occurring compounds. Key steps in the synthesis of estrone, a female sex hormone, are illustrated in Figure 10.12.

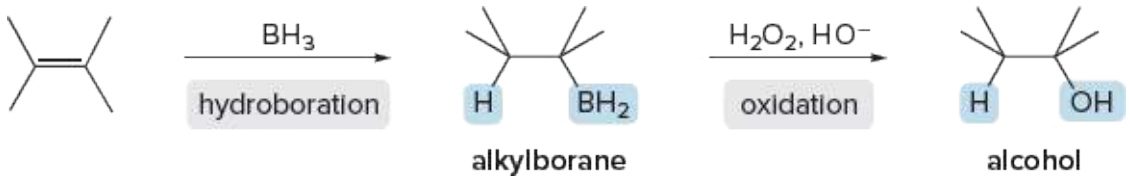


• Chlorohydrin **B**, prepared from alkene **A** by addition of Cl and OH, is converted to epoxide **C** with base. **C** is converted to estrone in one step.

Figure 10.12 **The synthesis of estrone from a chlorohydrin**

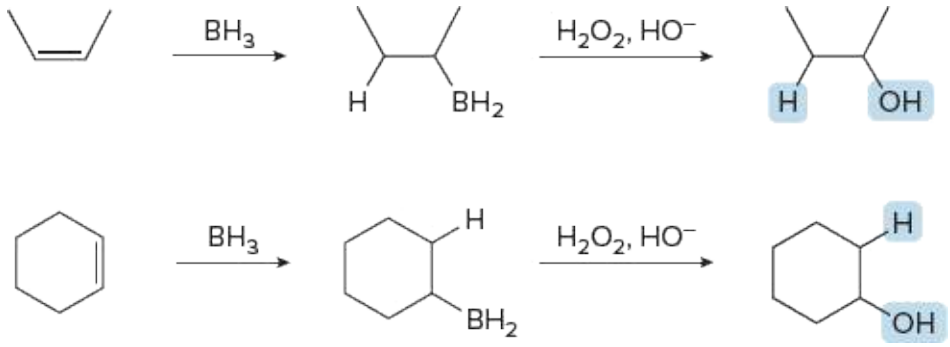
10.16 Hydroboration–Oxidation

Hydroboration–oxidation is a two-step reaction sequence that converts an alkene to an alcohol.

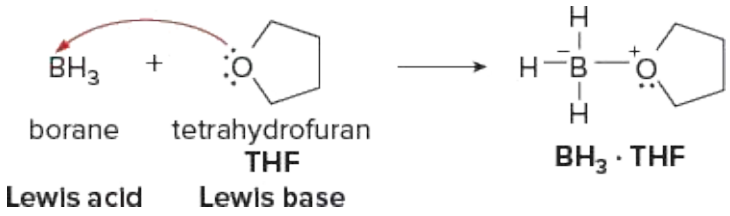


- ***Hydroboration*** **is the addition of borane (BH_3) to an alkene, forming an alkylborane.**
- ***Oxidation*** **converts the C–B bond of the alkylborane to a C–O bond.**

Hydroboration–oxidation results in addition of H_2O to an alkene.

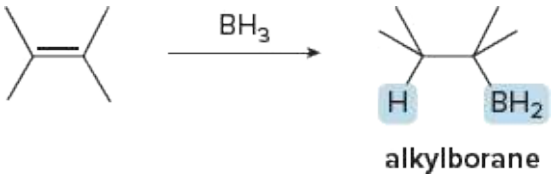


Borane (BH_3) is a reactive gas that exists mostly as the dimer, diborane (B_2H_6). Borane is a strong Lewis acid that reacts readily with Lewis bases. For ease in handling in the laboratory, it is commonly used as a complex with tetrahydrofuran (THF).



10.16A Hydroboration

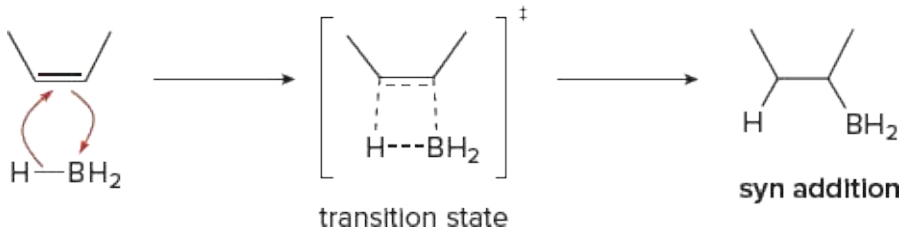
The first step in hydroboration–oxidation is addition of the elements of H and BH_2 to the π bond of the alkene, forming an intermediate alkylborane.



Because syn addition to the double bond occurs and no carbocation rearrangements are observed, carbocations are *not* formed during hydroboration, as shown in Mechanism 10.5.

Mechanism 10.5 Addition of H and BH_2—Hydroboration

One step The π bond and H–BH_2 bonds break as the C–H and C–B bonds form.



The proposed mechanism involves a concerted addition of H and BH_2 from the same side of the planar double bond: the π bond and H–BH_2 bond are broken as two new σ bonds are formed. Because four atoms are involved, the transition state is said to be four-centered.

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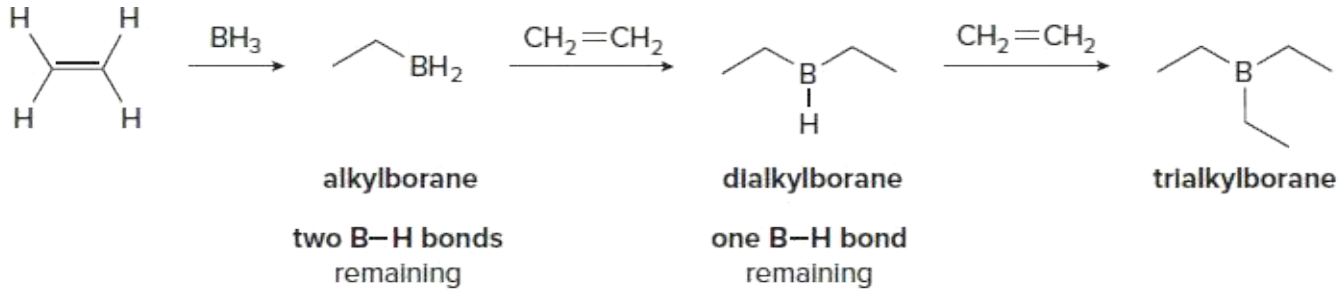
Because the alkylborane formed by reaction with one equivalent of alkene still has two B–H bonds, it can react with two more equivalents of alkene to form a trialkylborane. This is illustrated in Figure 10.13 for the reaction of CH_2=CH_2 with BH_3.



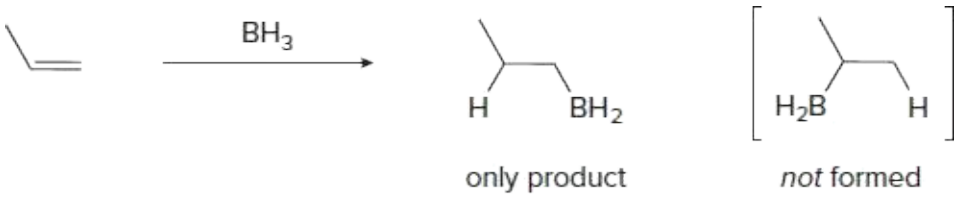
- We often draw hydroboration as if addition stopped after one equivalent of alkene reacts with BH_3. Instead, all three B–H bonds actually react with three equivalents of an alkene to form a trialkylborane. The term **organoborane** is used for any compound with a carbon–boron bond.

Figure 10.13 Conversion of BH_3 to a trialkylborane with three equivalents of CH_2=CH_2

Because only one B–H bond is needed for hydroboration, commercially available dialkylboranes having the general structure R_2BH are sometimes used instead of BH_3. A common example is 9-borabicyclo[3.3.1]nonane (9-BBN). 9-BBN undergoes hydroboration in the same manner as BH_3.

9-borabicyclo[3.3.1]nonane
9-BBN

Hydroboration is regioselective. With unsymmetrical alkenes, the boron atom bonds to the *less* substituted carbon atom. For example, addition of BH_3 to propene forms an alkylborane with the B bonded to the terminal carbon atom.



only product *not* formed

B bonds to the terminal C.

Steric factors explain this regioselectivity. The larger boron atom bonds to the less sterically hindered, more accessible carbon atom.

Because H is more electronegative than B, the B–H bond is polarized to give boron a partial positive charge ($H^{\delta-}$–$B^{\delta+}$), making BH_2 the electrophile in hydroboration.

Electronic factors are also used to explain this regioselectivity. If bond breaking and bond making are not completely symmetrical, boron bears a partial negative charge in the transition state and carbon bears a partial positive charge. Because alkyl groups stabilize a positive charge, the more stable transition state has the partial positive charge on the more substituted carbon, as illustrated in Figure 10.14.

- **In hydroboration, the boron atom bonds to the *less* substituted carbon.**

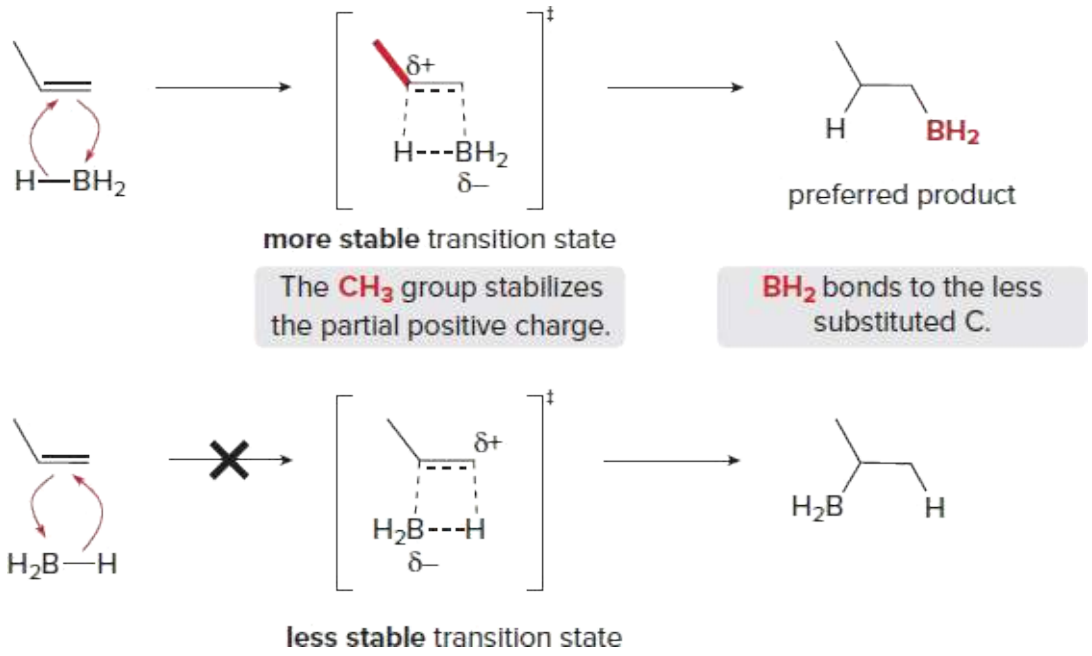


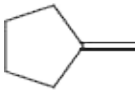
Figure 10.14 **Hydroboration of an unsymmetrical alkene**

Problem 10.26

What alkylborane is formed from hydroboration of each alkene?

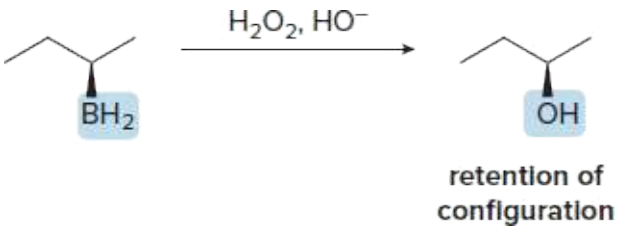
a.

b.

c. 

10.16B Oxidation of the Alkylborane

Because alkylboranes react rapidly with water and spontaneously burn when exposed to the air, they are oxidized, without isolation, with basic hydrogen peroxide (H_2O_2, HO^-). Oxidation replaces the C–B bond with a C–O bond, forming a new OH group with retention of configuration; that is, the OH group replaces the BH_2 group in the same position relative to the other three groups on carbon.



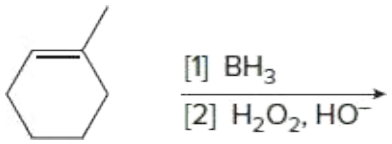
Thus, to draw the product of a hydroboration–oxidation reaction, keep in mind two stereo-chemical facts:

- **Hydroboration occurs with syn addition.**
- **Oxidation occurs with retention of configuration.**

The overall result of this two-step sequence is syn addition of the elements of H and OH to a double bond, as illustrated in Sample Problem 10.5. The OH group bonds to the *less* substituted carbon.

Sample Problem 10.5 Drawing the Products of Hydroboration-Oxidation

Draw the product of the following reaction sequence, including stereochemistry.



Solution

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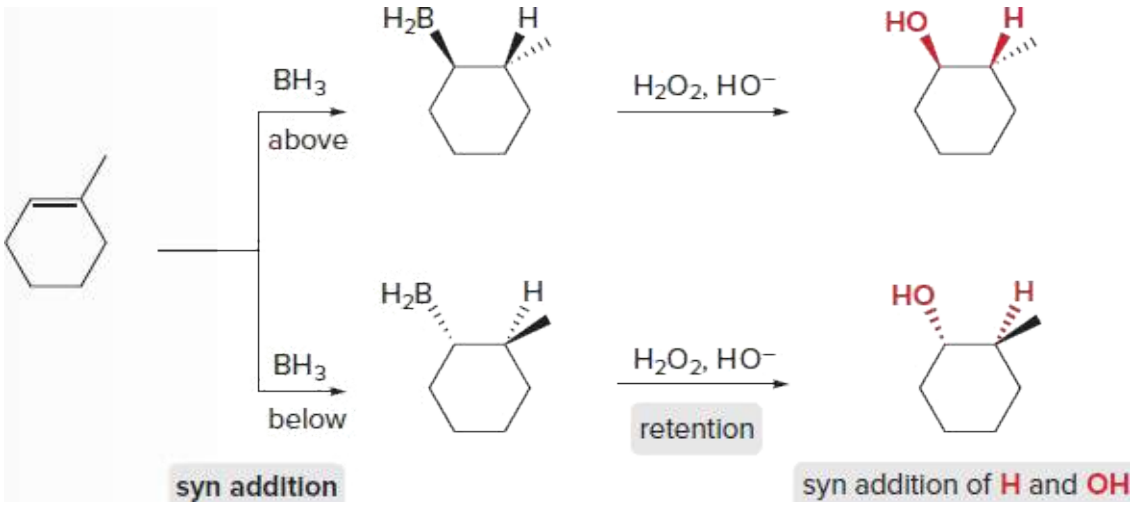
In Step [1], syn addition of BH_3 to the unsymmetrical alkene adds the BH_2 group to the *less* substituted carbon from above and below the planar double bond. Two enantiomeric alkylboranes are formed. In Step [2], oxidation replaces the BH2 group with OH in each enantiomer with retention of configuration to yield two alcohols that are also enantiomers.



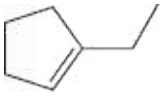
Hydroboration–oxidation results in the addition of H and OH in a syn fashion across the double bond. The achiral alkene is converted to an equal mixture of two enantiomers—that is, a racemic mixture of alcohols.

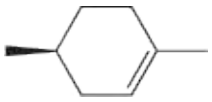
Problem 10.27

Draw the products formed when each alkene is treated with BH_3 followed by H_2O_2,

HO^-. Include the stereochemistry at all stereogenic centers.

a.

b. 

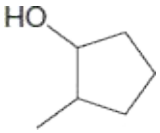
c. 

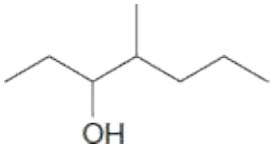
More Practice:

Try Problem 10.52d.

Problem 10.28

What alkene can be used to prepare each alcohol as the exclusive product of a two-step hydroboration–oxidation sequence?

a. 

b. 

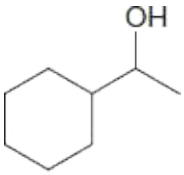
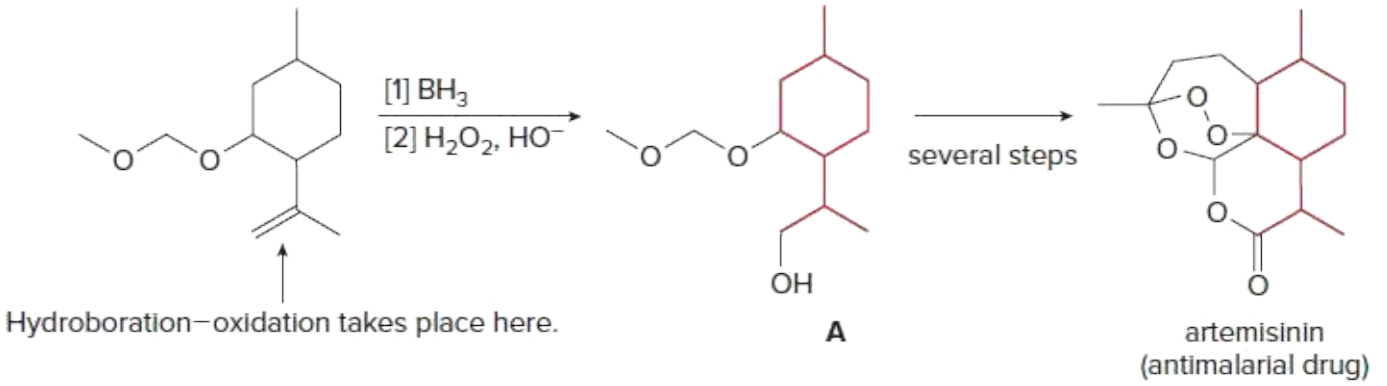
c. 

Table 10.5 summarizes the features of hydroboration–oxidation.

Table 10.5 Summary: Hydroboration–Oxidation of Alkenes

	Observation
Mechanism	• The addition of H and BH_2 occurs in one step. • No rearrangements can occur.
Regioselectivity	• The OH group bonds to the less substituted carbon atom.
Stereochemistry	• Syn addition occurs. • OH replaces BH_2 with retention of configuration.

Hydroboration–oxidation is a very common method for adding H_2O across a double bond. One example is shown in the synthesis of artemisinin (or qinghaosu), the active component of qing-hao, a Chinese herbal remedy used for the treatment of malaria (Figure 10.15) mentioned in the chapter opener.



• The carbon atoms of artemisinin that come from alcohol **A** are indicated in red.

Figure 10.15 **An example of hydroboration–oxidation in synthesis**

10.16C A Comparison of Hydration Methods

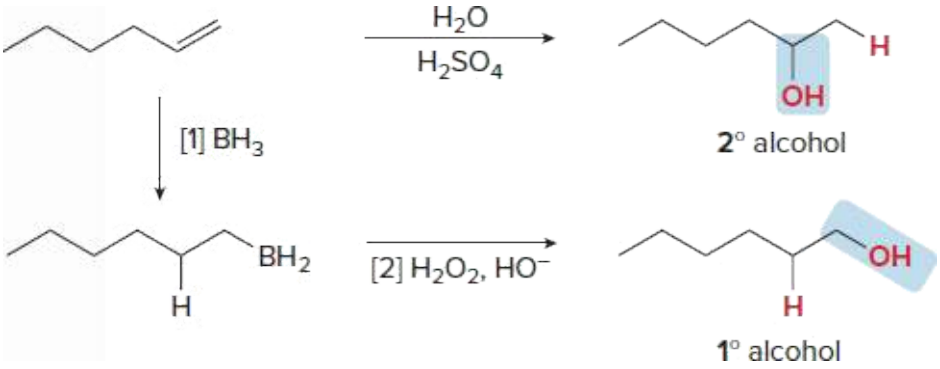
Hydration (H_2O, H^+) and hydroboration–oxidation (BH_3 followed by H_2O_2, HO^-) both add the elements of H_2O across a double bond. Despite their similarities, these reactions often form different constitutional isomers, as shown in Sample Problem 10.6.

Sample Problem 10.6 Comparing Two Different Methods of Hydration of an Alkene

Draw the product formed when $CH_3CH_2CH_2CH_2CH{=}CH_2$ is treated with either (a) H_2O, H_2SO_4; or (b) BH_3 followed by H_2O_2, HO^-.

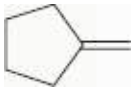
Solution

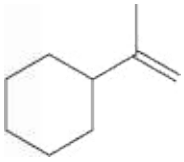
With H_2O + H_2SO_4, electrophilic addition of H and OH places the H atom on the *less* substituted carbon of the alkene to yield a 2° alcohol. In contrast, addition of BH_3 gives an alkylborane with the BH_2 group on the *less* substituted terminal carbon of the alkene. Oxidation replaces BH_2 by OH to yield a 1° alcohol.

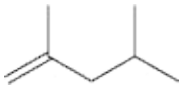


Problem 10.29

Draw the constitutional isomer formed when the following alkenes are treated with each set of reagents: [1] H_2O, H_2SO_4; or [2] BH_3 followed by H_2O_2, ^-OH.

a. 

b. 

c. 

More Practice:

Try Problem 10.48.

10.17 Keeping Track of Reactions

Chapters 7–10 have introduced three basic kinds of organic reactions: nucleophilic substitution, β elimination, and addition. In the process, many specific reagents have been discussed and the stereochemistry that results from many different mechanisms has been examined. How can we keep track of all the reactions?

To make the process easier, remember that most organic molecules undergo only one or two different kinds of reactions. For example:

- **Alkyl halides undergo substitution and elimination because they have good leaving groups.**
- **Alcohols also undergo substitution and elimination, but can do so only when OH is made into a good leaving group.**
- **Alkenes undergo addition because they have easily broken π bonds.**

You must still learn many reaction details, and in truth, there is no one method to

learn them. *You must practice these reactions over and over again, not by merely looking at them, but by writing them.* Some students do this by making a list of specific reactions for each functional group, and then rewriting them with different starting materials. Others make flash cards: index cards that have the starting material and reagent on one side and the product on the other. Whatever method you choose, the details must become second nature, much like the answers to simple addition problems, such as, what is the sum of 2 + 2?

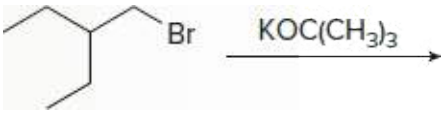
Learning reactions is really a two-step process:

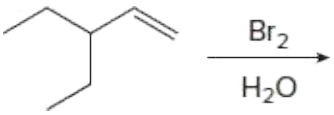
- **First, learn the basic type of reaction for a functional group. This provides an overall organization to the reactions.**
- **Then, learn the specific reagents for each reaction. It helps to classify the reagent according to its properties. Is it an acid or a base? Is it a nucleophile or an electrophile? Is it an oxidizing agent or a reducing agent?**

Sample Problem 10.7 illustrates this process.

Sample Problem 10.7 Using the Functional Group and Reagent to Identity the Type of Reaction

Draw the product of each reaction.

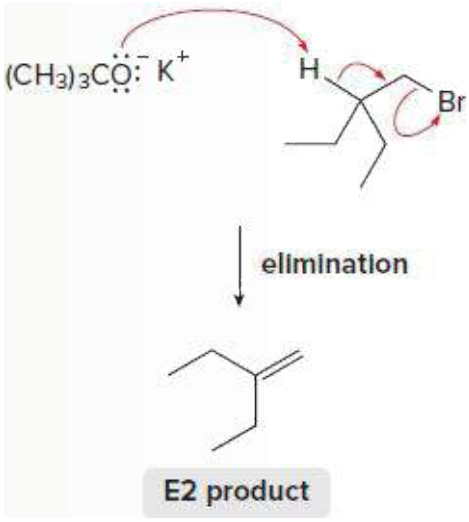
a. 

b. 

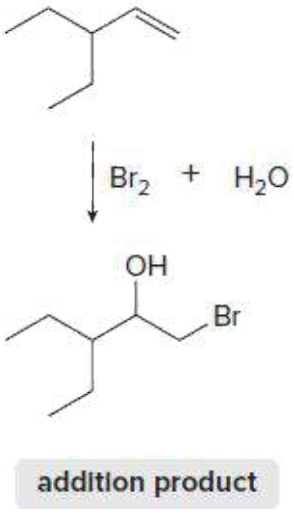
Solution

In each problem, identify the functional group to determine the general reaction type—substitution, elimination, or addition. Then, determine if the reagent is an electrophile, nucleophile, acid, base, and so forth.

a. The reactant is a 1° alkyl halide, which can undergo substitution and elimination. The reagent [$KOC(CH_3)_3$] is a strong nonnucleophilic base, favoring elimination by an E2 mechanism.



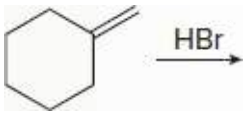
b. The reactant is an alkene, which undergoes addition reactions to its π bond. The reagent (Br_2 + H_2O) serves as the source of the electrophile Br^+, resulting in addition of Br and OH to the double bond (Section 10.15).



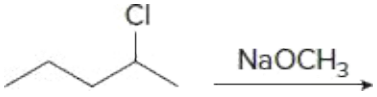
Problem 10.30

Draw the products of each reaction using the two-part strategy from Sample Problem 10.7.

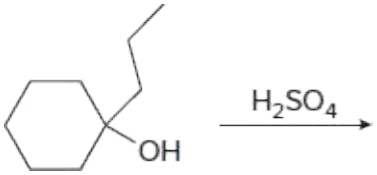
a.



b.



c.



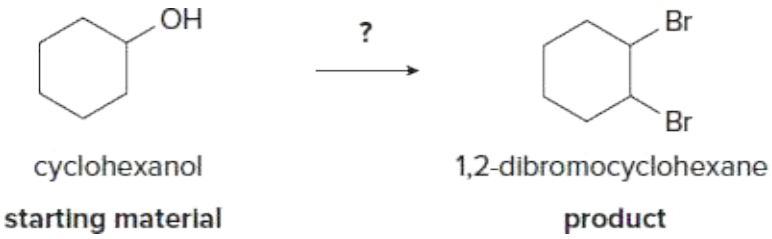
More Practice:

Try Problems 10.33b, 10.34, 10.46, 10.49.

10.18 Alkenes in Organic Synthesis

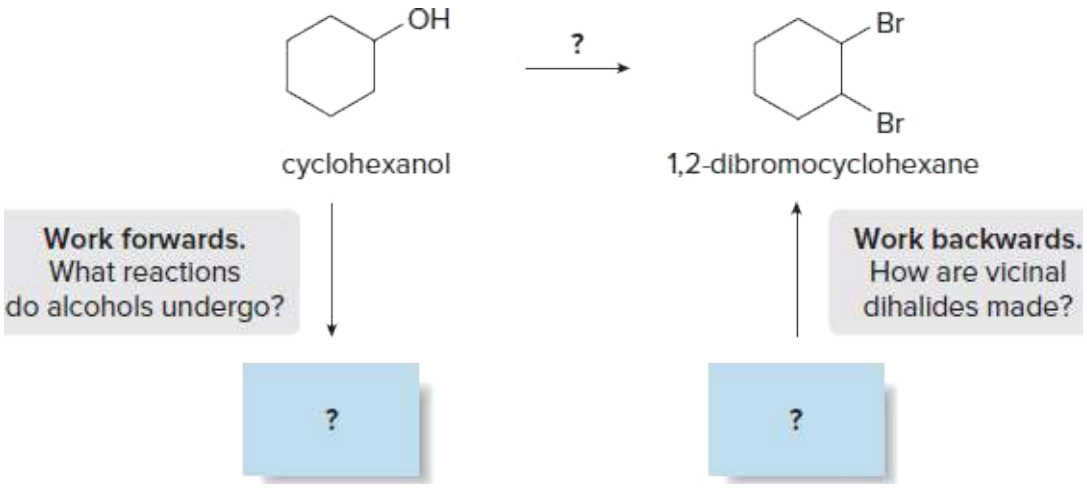
Alkenes are a central functional group in organic chemistry. Alkenes are easily prepared by elimination reactions such as dehydrohalogenation and dehydration. Because their π bond is easily broken, they undergo many addition reactions to prepare a variety of useful compounds.

Suppose, for example, that we must synthesize 1,2-dibromocyclohexane from cyclohexanol, a cheap and readily available starting material. Because there is no way to accomplish this transformation in one step, this synthesis must have at least two steps.



To solve this problem we must:

- **Work backwards from the product by asking: What type of reactions introduce the functional groups in the product?**
- **Work forwards from the starting material by asking: What type of reactions does the starting material undergo?**



Working backwards from the product to determine the starting material from which it is made is called *retrosynthetic analysis*.

In Chapter 11, we will learn about retrosynthetic analysis in more detail.

We know reactions that answer each of these questions.

Working backwards:

[1] 1,2-Dibromocyclohexane, a vicinal dibromide, can be prepared by the addition of Br2 to cyclohexene.

Working forwards:

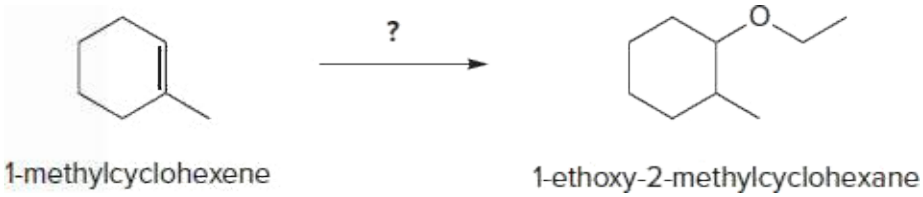
[2] Cyclohexanol can undergo acid-catalyzed dehydration to form cyclohexene.

Cyclohexene is called a synthetic intermediate, or simply an intermediate, because it is the product of one step and the starting material of another. We now have a two-step sequence to convert cyclohexanol to 1,2-dibromocyclohexane, and the synthesis is complete. Take note of the central role of the alkene in this synthesis.

A reactive intermediate is an unstable intermediate like a carbocation, which is formed during the conversion of a stable starting material to a stable product. A synthetic intermediate is a stable compound that is the product of one step and the starting material of another in a multistep synthesis.

Sample Problem 10.8 Devising a Synthesis from an Alkene

Devise a synthesis of 1-ethoxy-2-methylcyclohexane from 1-methylcyclohexene.



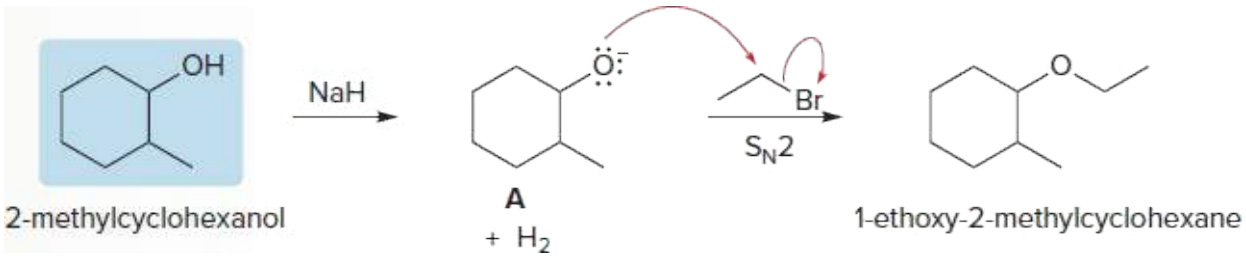
Solution

Work backwards from the product and forwards from the starting material

until a common intermediate is reached.

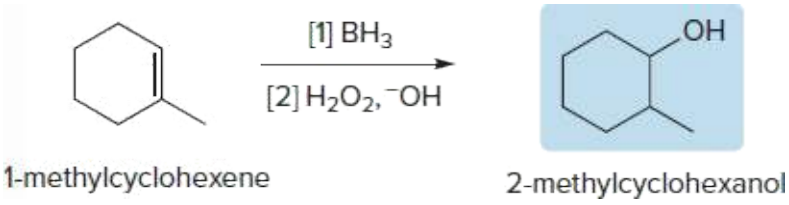
Working backwards:

[1] Williamson ether synthesis converts 2-methylcyclohexanol to 1-ethoxy-2-methylcyclohexanol by a two-step process: reaction with the base NaH to generate alkoxide A, followed by S_N2 reaction with CH_3CH_2Br to generate the ether.



Working forwards:

Hydroboration–oxidation of 1-methylcyclohexene forms 2-methylcyclohexanol, with the OH group on the *less* substituted carbon.



2-Methylcyclohexanol is a synthetic intermediate, and the synthesis is complete by combining both operations.

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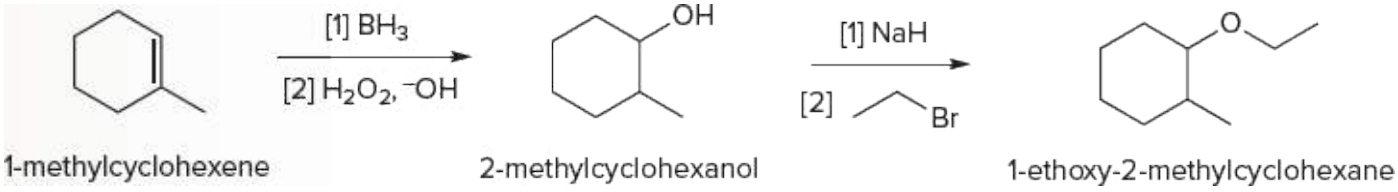
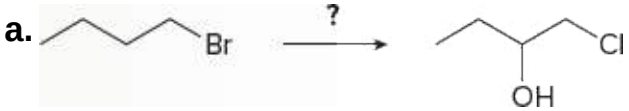
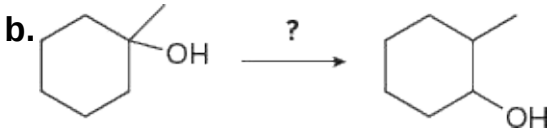


Problem 10.31

Devise a synthesis of each compound from the indicated starting material.





More Practice:

Try Problems 10.63, 10.64.

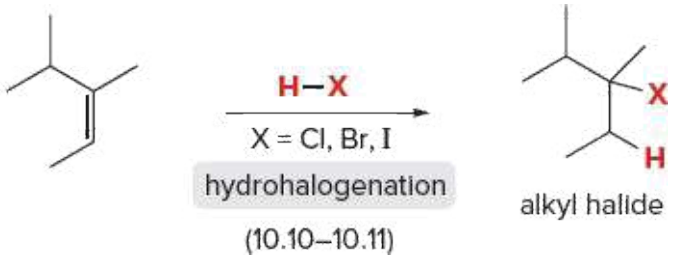
Chapter 10 REVIEW

KEY CONCEPTS

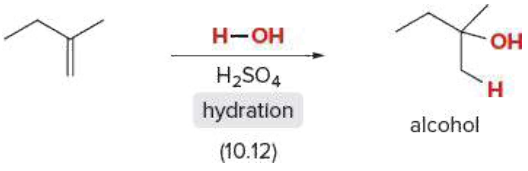
Markovnikov's Rule (10.10, 10.12)

In the addition of HX to an unsymmetrical alkene, the H atom bonds to the *less* substituted carbon.

1



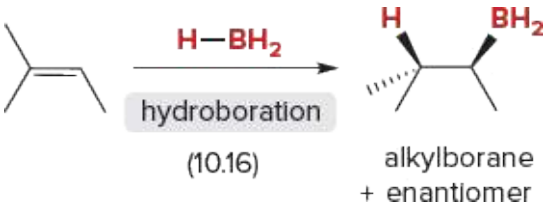
2



Try Problems 10.33b; 10.46a–c; 10.49a, b.

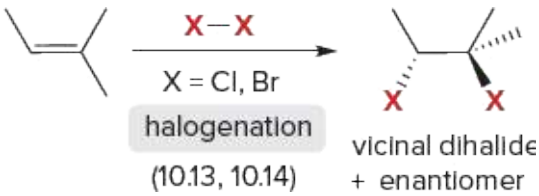
Stereochemistry of Alkene Addition (10.8)

1 Syn addition



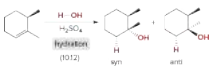
- **H and BH_2 are added from the *same* side.**

2 Anti addition



- **X and X are added from *opposite* sides.**
- **Halohydrin formation also involves *anti* addition. X and OH are added from *opposite* sides.**

3 Syn an additio



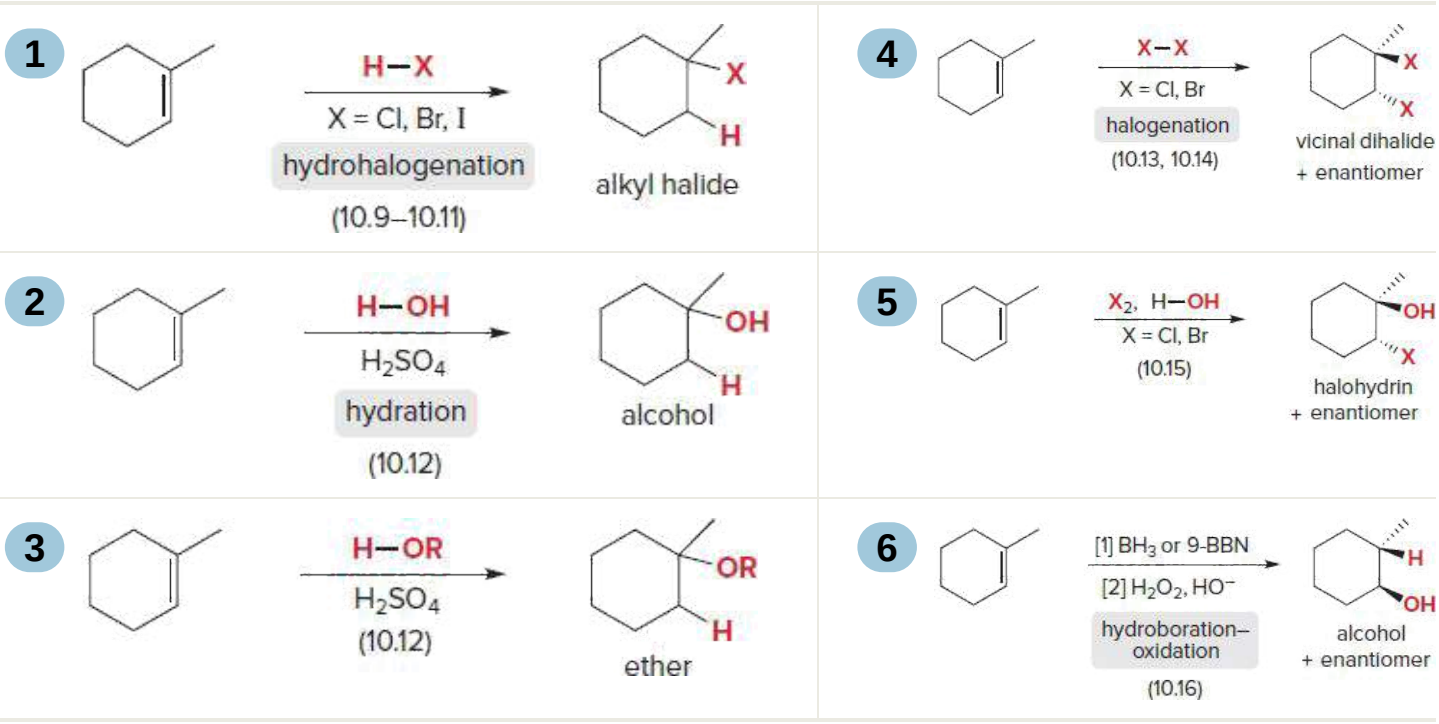
- ***Syn* a additi when are fo**
- **H and added *same* sides.**
- **Hydro also i**

		syn* ar** **additi** **are ad** ***same **sides.**

Try Problems 10.51, 10.52.

KEY CONCEPTS

All reactions of alkenes involve addition—the weak π bond is broken and two new σ bonds are formed.



See Sample Problems 10.3, 10.4, 10.5. Try Problems 10.33b, 10.34, 10.46, 10.49, 10.51, 10.52.

KEY SKILLS

[1] Calculating degrees of unsaturation (10.2)

1 Calculate the maximum number of H's possible.	**2 Subtract the actual number from the maximum number and divide by two.**

Example: C_5H_{10}

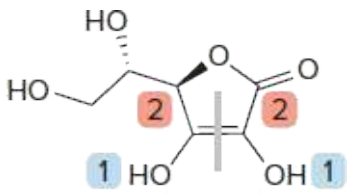
- **For *n* carbons, the maximum number of H's is $2n + 2$; in this example, $2n + 2 = 2(5) + 2 = 12$.**
- **12 H's (maximum) − 10 H's (actual) = 2 H's fewer than the maximum number.**

$$\frac{\text{2 H's fewer than the maximum}}{\text{2 H's removed for each degree unsaturation}} =$$

Answer: one degree of unsaturation

See Sample Problem 10.1. Try Problems 10.35, 10.36.

[2] Assigning *E,Z* in naming an alkene (10.3)

1 Assign priorities to the substituents on each end of the C=C.	**2** Assign *E* or *Z* based on the location of the two higher-priority groups.
 vitamin C ascorbic acid	• **Two higher-priority groups on *opposite* sides → *E* isomer.** • **Two higher-priority groups on the *same* side → *Z* isomer.** **Answer: Vitamin C is a *Z* alkene because the two higher-priority groups are on the *same* side of the C=C.**

See *How To*, p. 403. Try Problems 10.33a, 10.37.

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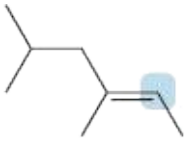
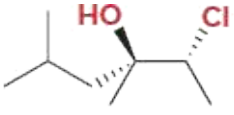
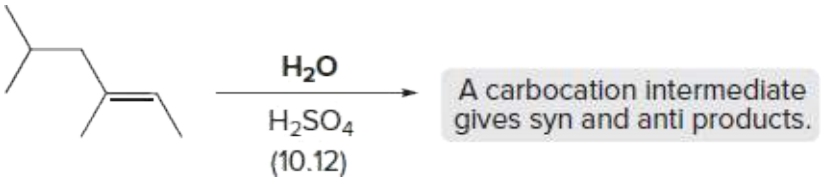
[3] Drawing the products of an addition reaction (10.8–10.16)

1 Use the reagents to identify the two groups added to the C=C.	**2** In an unsymmetrical alkene, determine the regioselectivity.	**3** Use the mechanism to determine the stereochemistry.
Cl_2, H_2O → (10.15) Cl and OH are added.	 Cl ends up on the *less* substituted C.	 anti chlorohydrin + enantiomer

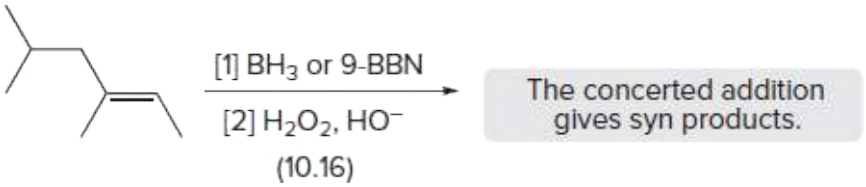
Try Problems 10.33b, 10.34, 10.46, 10.49, 10.51, 10.52.

[4] Comparing the products of hydration of an alkene (10.12, 10.16)

1 **Use the reagents to determine the stereochemistry of H_2O addition.**

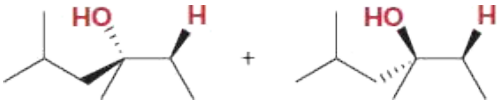


- **H and OH are added from the *same* and *opposite* sides.**

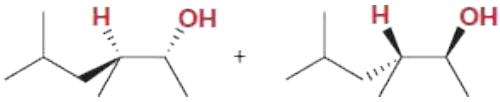


- **H and BH_2 are added from the *same* side, and OH replaces BH_2 with retention of configuration.**

2 **Draw the products.**



- **H bonds to the *less* substituted C.**

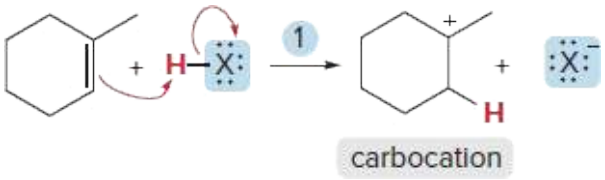


- **H bonds to the *more* substituted C.**

See Sample Problem 10.6. Try Problem 10.48.

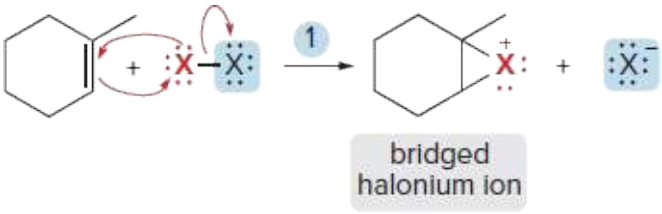
KEY MECHANISM CONCEPTS

1 **Addition of HX and H_2O—Carbocation intermediate**



- **See Mechanisms 10.1 and 10.2.**
- **Carbocation rearrangements are possible.**
- **Markovnikov's rule is**

2 **Addition of X_2 and X, OH—Halonium ion intermediate**



- **See Mechanisms 10.3 and 10.4.**
- **No rearrangements are possible.**
- **Anti addition occurs.**

followed. • Syn and anti addition occur.	In the addition of X and OH, X • bonds to the *less* substituted C.

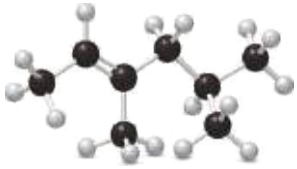
See Tables 10.3, 10.4, 10.5. Try Problems 10.55–10.58.

PROBLEMS

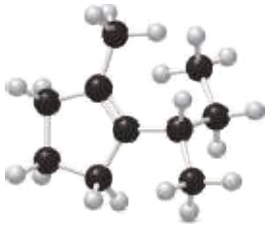
Problems Using Three-Dimensional Models

10.32 Give the IUPAC name for each compound.

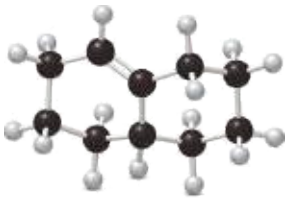
a.



b.



10.33 (a) Label the carbon–carbon double bond in A as *E* or *Z*. (b) Draw the products (including stereoisomers) formed when A is treated with H_2O in the presence of H_2SO_4.



A

10.34 Name the alkene depicted in the ball-and-stick model, and draw the constitutional isomers formed when the alkene is treated with each reagent: (a) Br_2; (b) Br_2 in H_2O; (c) Br_2 in CH_3OH.

Degrees of Unsaturation

10.35 Calculate the number of degrees of unsaturation for each molecular

formula.

a. C_6H_8

b. $C_{40}H_{56}$

c. $C_{10}H_{16}O_2$

d. C_8H_9Br

e. C_8H_9ClO

f. $C_7H_{11}N$

g. C_4H_8BrN

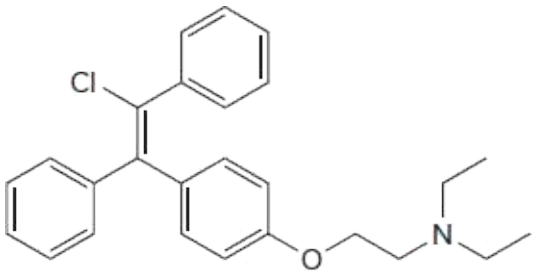
h. $C_{10}H_{18}ClNO$

10.36 **How many rings and π bonds does a compound with molecular formula $C_{10}H_{14}$ possess? List all possibilities.**

Nomenclature and Stereochemistry

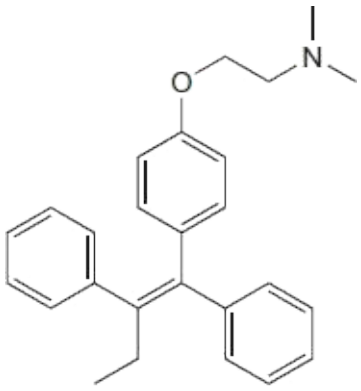
10.37 **Label the alkene in each drug as *E* or *Z*. Enclomiphene is one component of the fertility drug Clomid. Tamoxifen is an anticancer drug. Clavulanic acid is sold in combination with the antibiotic amoxicillin under the trade name Augmentin.**

a.



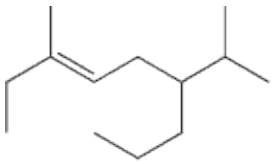
enclomiphene

b.



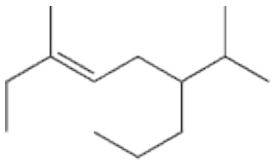
tamoxifen

c.



10.38 Give the IUPAC name for each compound.

a.



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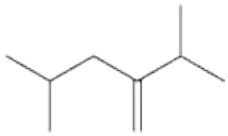

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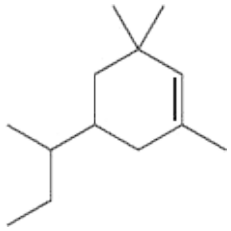

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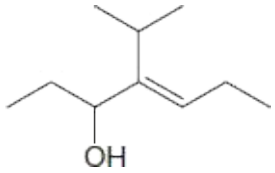
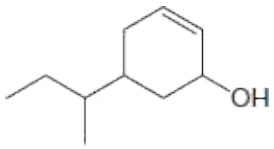


e.



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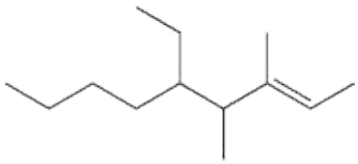


10.39 Give the structure corresponding to each name.

a. (*E*)-4-ethylhept-3-ene

b. 3,3-dimethylcyclopentene

c. 4-vinylcyclopentene

d. (*Z*)-3-isopropylhept-2-ene

e. *cis*-3,4-dimethylcyclopentene

f. 1-isopropyl-4-propylcyclohexene

g. 3,4-dimethylcyclohex-2-enol

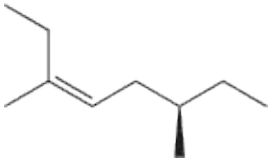
h. 3,5-diethylhex-5-en-3-ol

10.40 (a) Draw all possible stereoisomers of 4-methylnon-2-ene, and name

each isomer, including its *E,Z* and *R,S* prefixes. (b) Label two pairs of enantiomers. (c) Label four pairs of diastereomers.

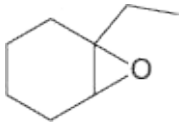
10.41 (a) Draw the structure of (1*E*,4*R*)-1,4-dimethylcyclodecene. (b) Draw the enantiomer and name it, including its *E,Z* and *R,S* prefixes. (c) Draw two diastereomers and name them, including the *E,Z* and *R,S* prefixes.

10.42 (a) Name the following compound including *E,Z* and *R,S* designations. (b) Draw a stereoisomer at the carbon–carbon double bond. (c) Draw a stereoisomer at the stereogenic center.

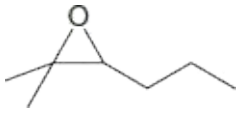


10.43 Now that you have learned how to name alkenes in Section 10.3, name each of the following epoxides as an alkene oxide, as described in Section 9.3.

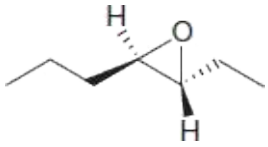
a.



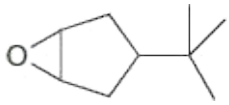
b.



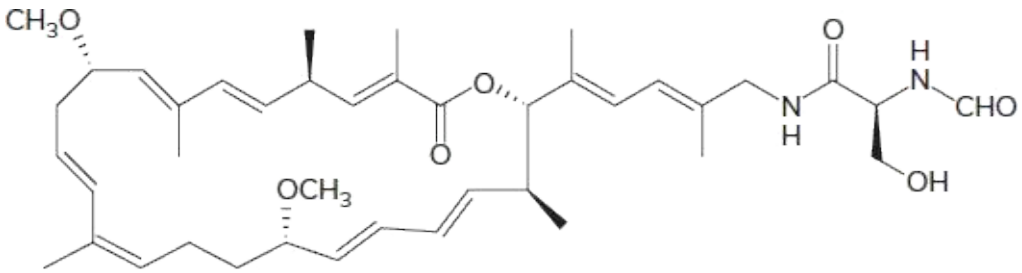
c.



d.



10.44 Iejimalide B, an anticancer agent with a 24-membered ring, is isolated from a tunicate found off Ie Island in Okinawa. (a) Label each double bond in iejimalide B as *E* or *Z*. (b) Label each tetrahedral stereogenic center as *R* or *S*. (c) How many stereoisomers are possible for iejimalide B?

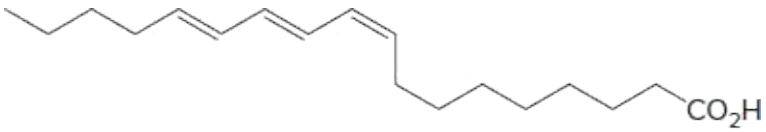


Iejimalide B

Lipids

10.45 Eleostearic acid is an unsaturated fatty acid obtained from the seeds of

the tung oil tree (*Aleurites fordii*), a deciduous tree native to China. (a) Draw the structure of a stereoisomer that has a higher melting point than eleostearic acid. (b) Draw the structure of a stereoisomer that has a lower melting point.



eleostearic acid

Reactions of Alkenes

10.46 Draw the products formed when $(CH_3)_2C{=}CH_2$ is treated with each reagent.

a. HBr

b. H2O, H_2SO_4

c. CH_3CH_2OH, H_2SO_4

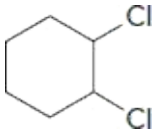
d. Cl_2

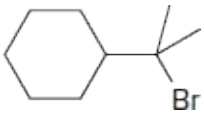
e. Br_2, H_2O

f. NBS (aqueous DMSO)

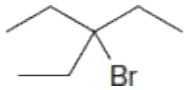
g. [1] BH_3; [2] H_2O_2, HO^-

10.47 What alkene can be used to prepare each alkyl halide or dihalide as the exclusive or major product of an addition reaction?

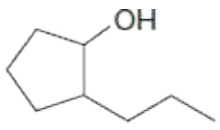
a. 

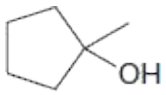
b. 

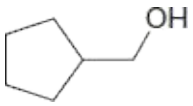
c.

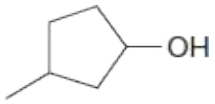
d. 

10.48 Which alcohols can be prepared as a single product by hydroboration–oxidation of an alkene? Which alcohols can be prepared as a single product by the acid-catalyzed addition of H_2O to an alkene?

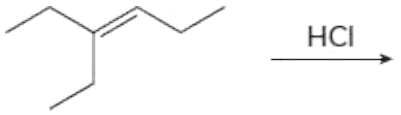
a. 

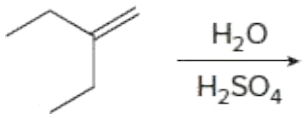
b. 

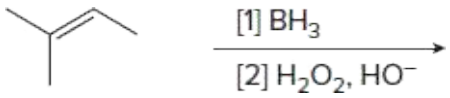
c. 

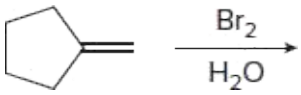
d. 

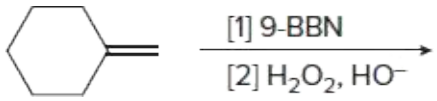
10.49 Draw the constitutional isomer formed in each reaction.

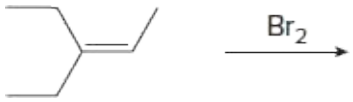
a. 

b. 

c. 

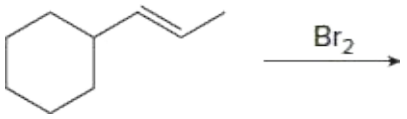
d. 

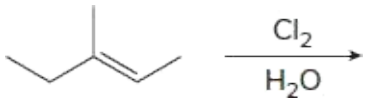
e. 

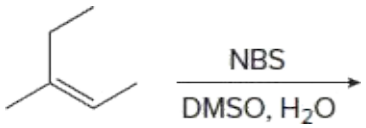
f. 

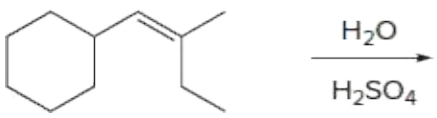
10.50 What three alkenes (excluding stereoisomers) can be used to prepare 3-chloro-3-methylhexane by addition of HCl?

10.51 Draw all stereoisomers formed in each reaction.

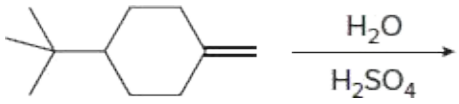
a. 

b. 

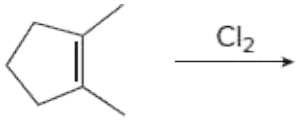
c. 

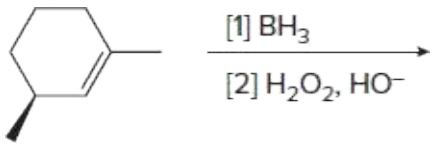
d. 

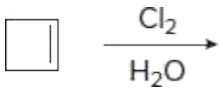
10.52 Draw the products of each reaction, including stereoisomers.

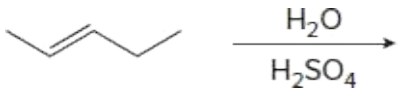
a. 

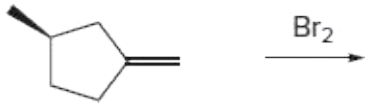
b.

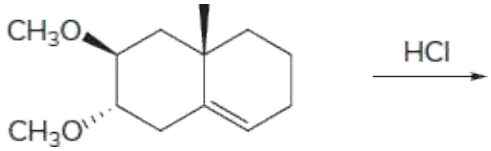
c. 

d. 

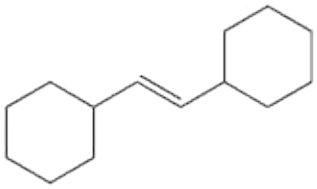
e. 

f. 

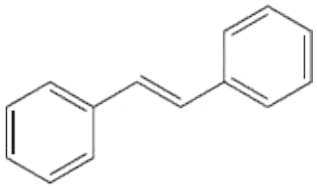
g. 

h. 

10.53 Which alkene reacts faster with HBr? Explain your choice.

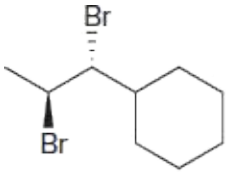


A

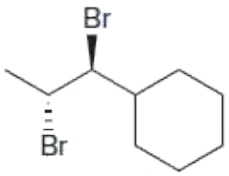


B

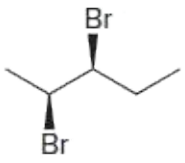
10.54 (a) What alkene yields A and B when it is treated with Br_2 in CCl_4? (b) What alkene yields C and D under the same conditions?



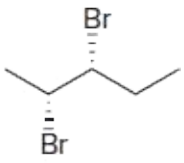
A



B



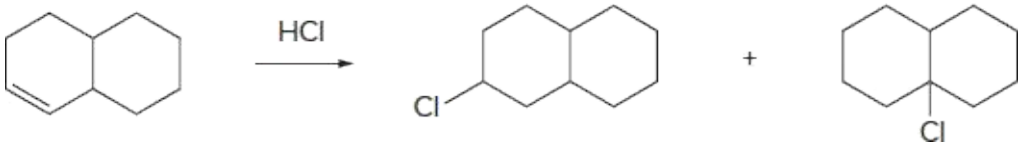
C



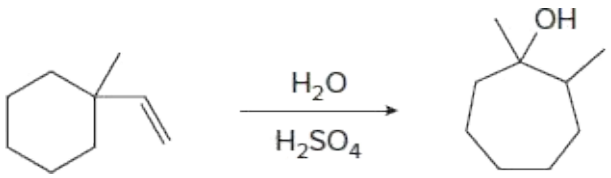
D

Mechanisms

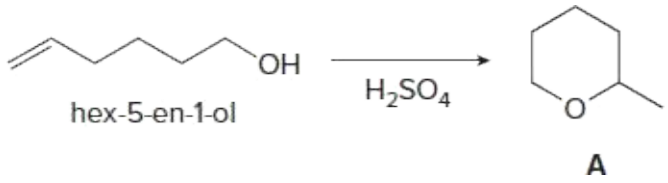
10.55 Draw a stepwise mechanism for the following reaction.



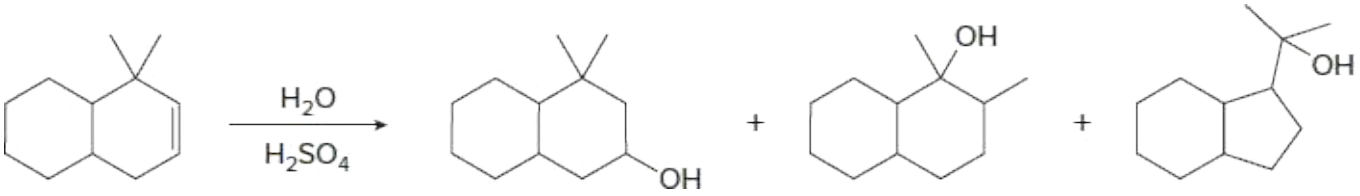
10.56 Draw a stepwise mechanism for the following reaction, which results in ring expansion of a six-membered ring to a seven-membered ring.



10.57 **Draw a stepwise mechanism for the conversion of hex-5-en-1-ol to the cyclic ether A.**



10.58 **Draw a stepwise mechanism that shows how all three alcohols are formed from the bicyclic alkene.**

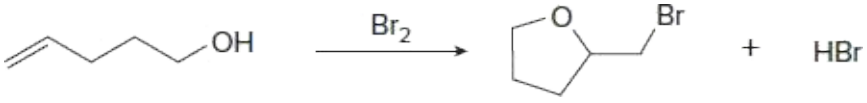


10.59 **Less stable alkenes can be isomerized to more stable alkenes by treatment with strong acid. For example, 2,3-dimethylbut-1-ene is converted to 2,3-dimethylbut-2-ene when treated with H_2SO_4. Draw a stepwise mechanism for this isomerization process.**

10.60 **When buta-1,3-diene (CH_2=CH−CH=CH_2) is treated with HBr, two constitutional isomers are formed, $CH_3CHBrCH=CH_2$ and $BrCH_2CH=CHCH_3$. Draw a stepwise mechanism that accounts for the formation of both products.**

10.61 **Explain why the addition of HBr to alkenes A and C is regioselective, forming addition products B and D, respectively.**

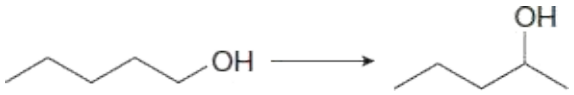
10.62 **Bromoetherification, the addition of the elements of Br and OR to a double bond, is a common method for constructing rings containing oxygen atoms. This reaction has been used in the synthesis of the polyether antibiotic monensin (Problem 18.34). Draw a stepwise mechanism for the following intramolecular bromoetherification reaction.**



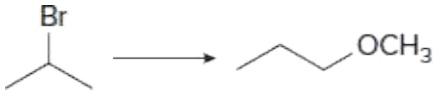
Synthesis

10.63 **Devise a synthesis of each product from the given starting material. More than one step is required.**

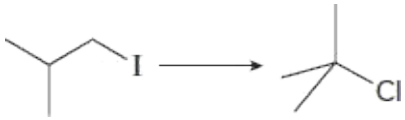
a.



b.

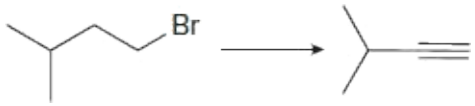


c.



d.

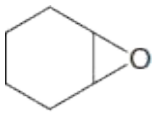
e.



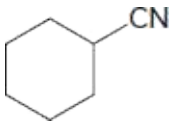
f.

10.64 **Devise a synthesis of each compound from cyclohexene as the starting material. More than one step is needed.**

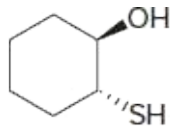
a.



b.



c.



+ enantiomer

Spectroscopy

Problem 10.65 is intended for students who have already learned about spectroscopy in Chapters A–C.

10.65 **When 2-bromo-3,3-dimethylbutane is treated with $K^+ {}^-OC(CH_3)_3$, a single product T having molecular formula C_6H_{12} is formed. When 3,3-dimethylbutan-2-ol is treated with H_2SO_4, the major product U has the same molecular formula. Given the following ^1H NMR data, what are the structures of T and U? Explain in detail the splitting patterns observed for the three split signals in T.**

^1H NMR of T: 1.01 (singlet, 9 H), 4.82 (doublet of doublets, 1 H, *J* = 10, 1.7

Hz), 4.93 (doublet of doublets, 1 H, *J* = 18, 1.7 Hz), and 5.83 (doublet of doublets, 1 H, *J* = 18, 10 Hz) ppm

^{1}H NMR of U: 1.60 (singlet) ppm

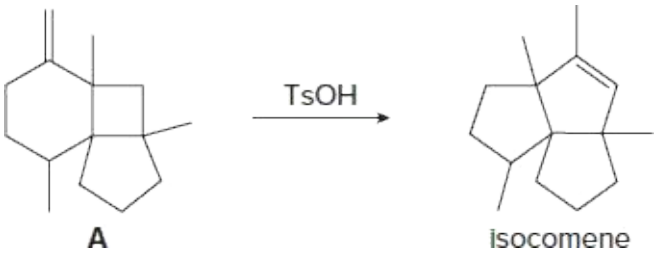
Additional problems on the spectroscopy of alkenes are given in Chapters A–C:

- **Mass spectrometry: A.16b, A.20, A.23**
- **Infrared spectroscopy: B.5, B.7(A), B.12c, B17a, B.18c**
- **Nuclear magnetic resonance spectroscopy: C.12a; C.15d, e; C.29d; C.32d; C.37; C.38d, f; C.43i, j; C.44; C.45; C.49d, f; C.50b; C.51c; C.55**

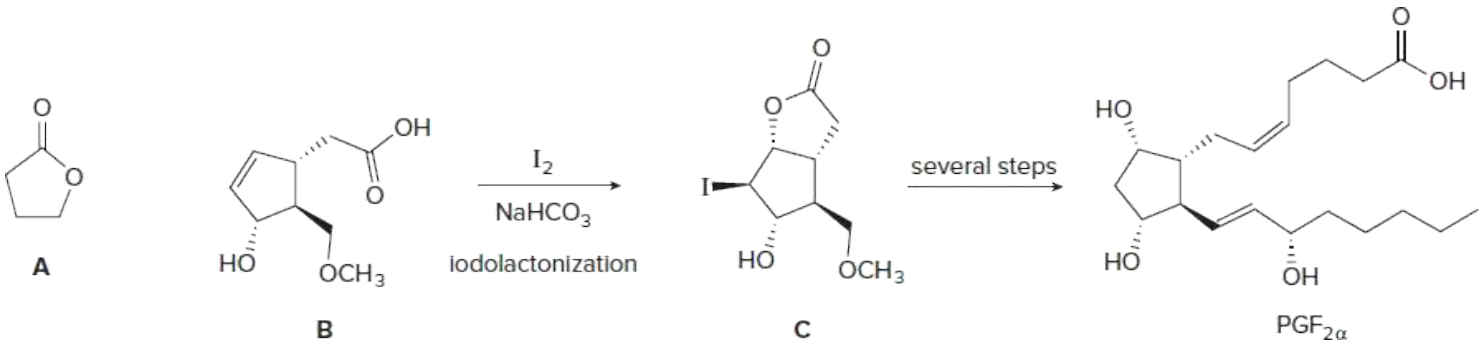
Challenge Problems

10.66 Explain why A is a stable compound but B is not.

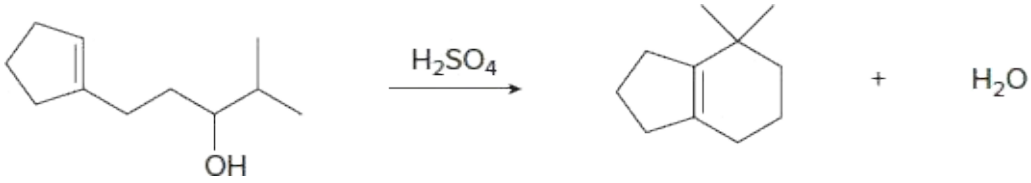
10.67 Alkene A can be isomerized to isocomene, a natural product isolated from goldenrod, by treatment with TsOH. Draw a stepwise mechanism for this conversion. (Hint: Look for a carbocation rearrangement.)



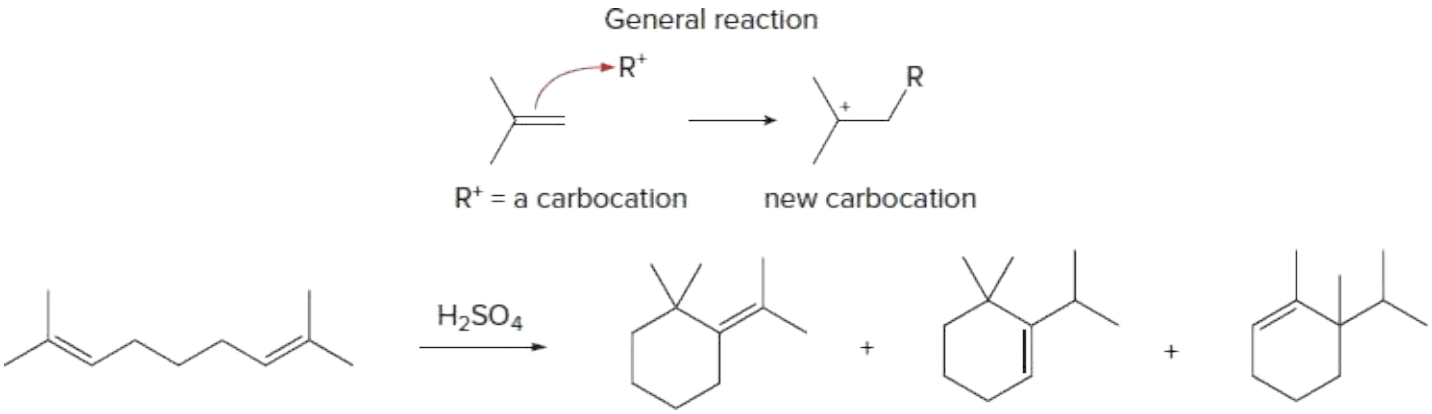
10.68 Lactones, cyclic esters such as compound A, are prepared by halolactonization, an addition reaction to an alkene. For example, iodolactonization of B forms lactone C, a key intermediate in the synthesis of prostaglandin $PGF_{2\alpha}$ (Section 4.15). Draw a stepwise mechanism for this addition reaction.



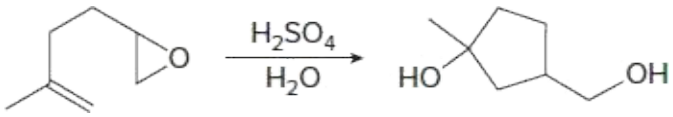
10.69 Draw a stepwise mechanism for the following reaction.



10.70 Like other electrophiles, carbocations add to alkenes to form new carbocations, which can then undergo substitution or elimination reactions depending on the reaction conditions. With this in mind, draw a stepwise mechanism for the following reaction, which involves the addition of an electrophile—a carbocation—to a double bond.

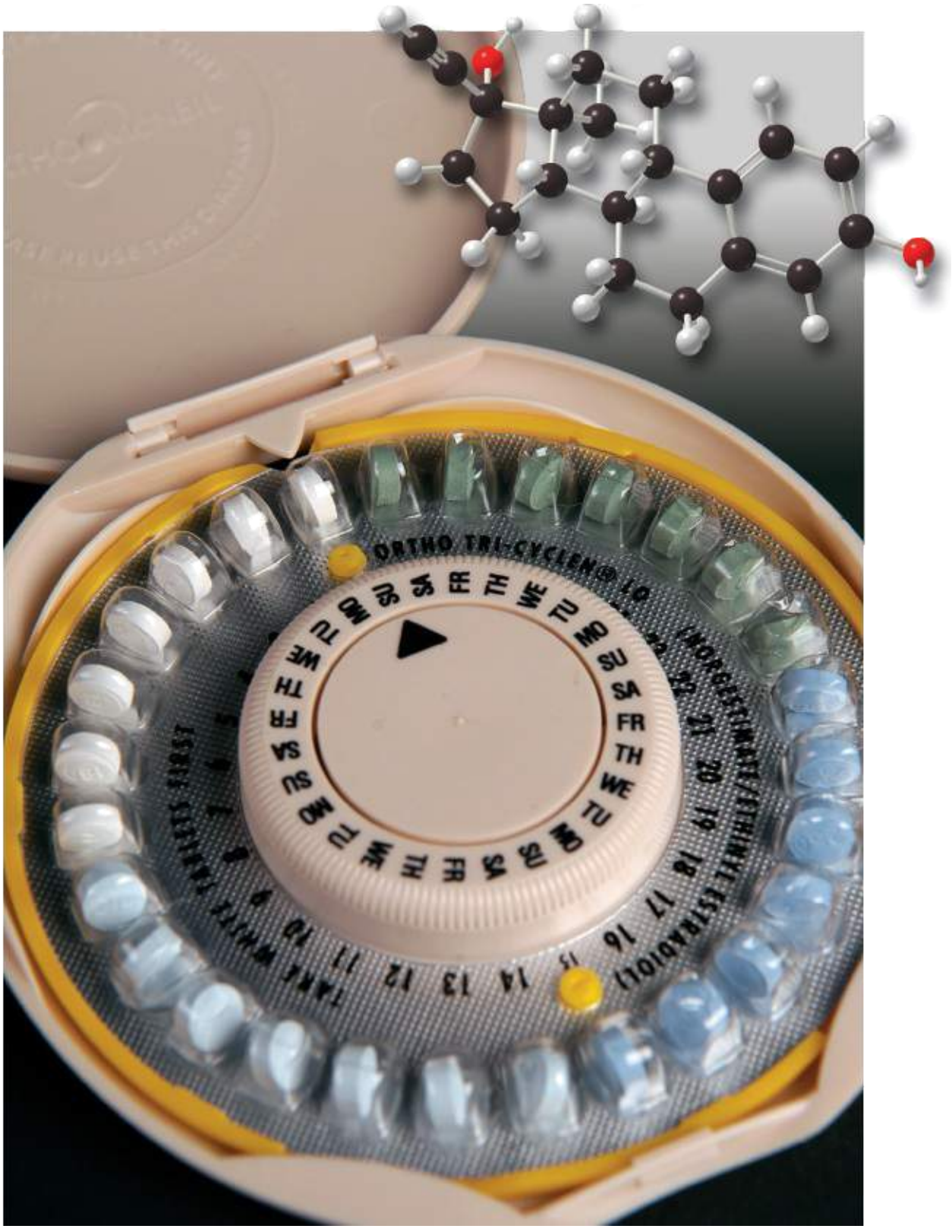


10.71 Draw a stepwise mechanism for the following reaction. This reaction combines two processes: the opening of an epoxide ring with a nucleophile and the addition of an electrophile to a carbon–carbon double bond. (Hint: Begin the mechanism by protonating the epoxide ring.)



11

Alkynes and Synthesis



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11.1 Introduction
11.2 Nomenclature
11.3 Properties of alkynes
11.4 Interesting alkynes
11.5 Preparation of alkynes
11.6 Introduction to alkyne reactions
11.7 Addition of hydrogen halides
11.8 Addition of halogen
11.9 Addition of water
11.10 Hydroboration–oxidation
11.11 Reaction of acetylide anions
11.12 Synthesis

Ethynylestradiol is a synthetic compound whose structure closely resembles the carbon skeleton of female estrogen hormones. Because it is more potent than its naturally occurring analogues, it is a component of several widely used oral contraceptives. Ethynylestradiol and related compounds with similar biological activity contain a carbon–carbon triple bond. In Chapter 11, we learn about alkynes, hydrocarbons that contain triple bonds.

Why Study…

Alkynes?

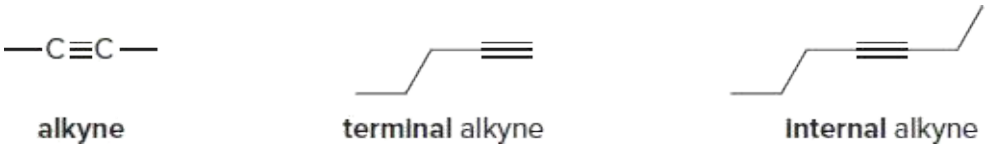
In Chapter 11, we continue our focus on organic molecules with electron-rich functional groups by examining *alkynes*, compounds that contain a carbon–carbon triple bond. Like alkenes, alkynes are nucleophiles with easily broken π bonds, and as such, they undergo addition reactions with electrophilic reagents.

Alkynes also undergo a reaction that has no analogy in alkene chemistry. Because a C–H bond of an alkyne is more acidic than a C–H bond of an alkene or an alkane, alkynes

are readily deprotonated with strong base. The resulting nucleophiles react with electrophiles to form new carbon–carbon a bonds, so that complex molecules can be prepared from simple starting materials. The study of alkynes thus affords an opportunity to learn more about organic synthesis.

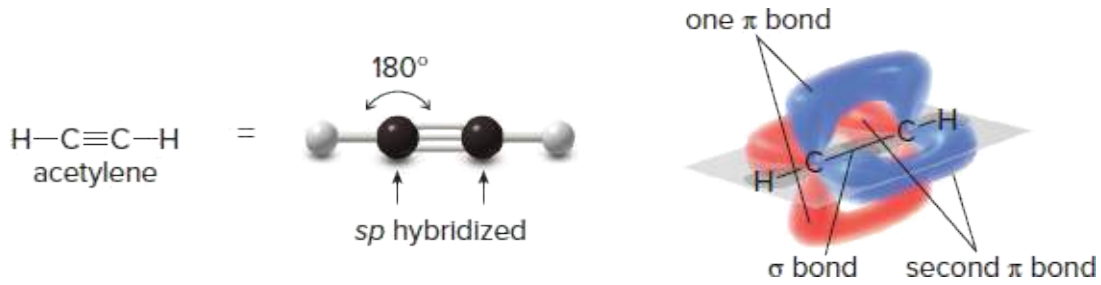
11.1 Introduction

Alkynes contain a carbon–carbon triple bond. A terminal alkyne has the triple bond at the end of the carbon chain, so that a hydrogen atom is bonded directly to a carbon atom of the triple bond. An internal alkyne has a carbon atom bonded to each carbon atom of the triple bond.



An alkyne has the general molecular formula C_nH_{2n-2}, giving it *four* fewer hydrogens than the maximum number possible. Because every degree of unsaturation removes two hydrogens, a triple bond introduces two degrees of unsaturation.

Each carbon of a triple bond is *sp* hybridized and linear, and all bond angles are 180° (Section 1.10C). The triple bond of an alkyne consists of one σ bond and two π bonds.

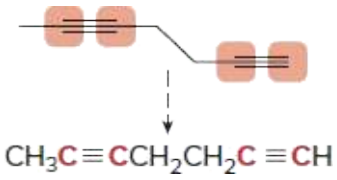


- **The σ bond is formed by end-on overlap of the two *sp* hybrid orbitals.**
- **Each π bond is formed by side-by-side overlap of two 2*p* orbitals.**

Bond dissociation energies of the C–C bonds in ethylene (one σ and one π bond) and acetylene (one σ and two π bonds) can be used to estimate the strength of the second π bond of the triple bond. If we assume that the a bond and first π bond in acetylene are similar in strength to the a and π bonds in ethylene (368 and 267 kJ/mol, respectively), then the second π bond is worth 202 kJ/mol.

Skeletal structures for alkynes may look somewhat unusual, but they follow the customary convention: a carbon atom is

located at the intersection of any two lines and at the end of any line; thus,



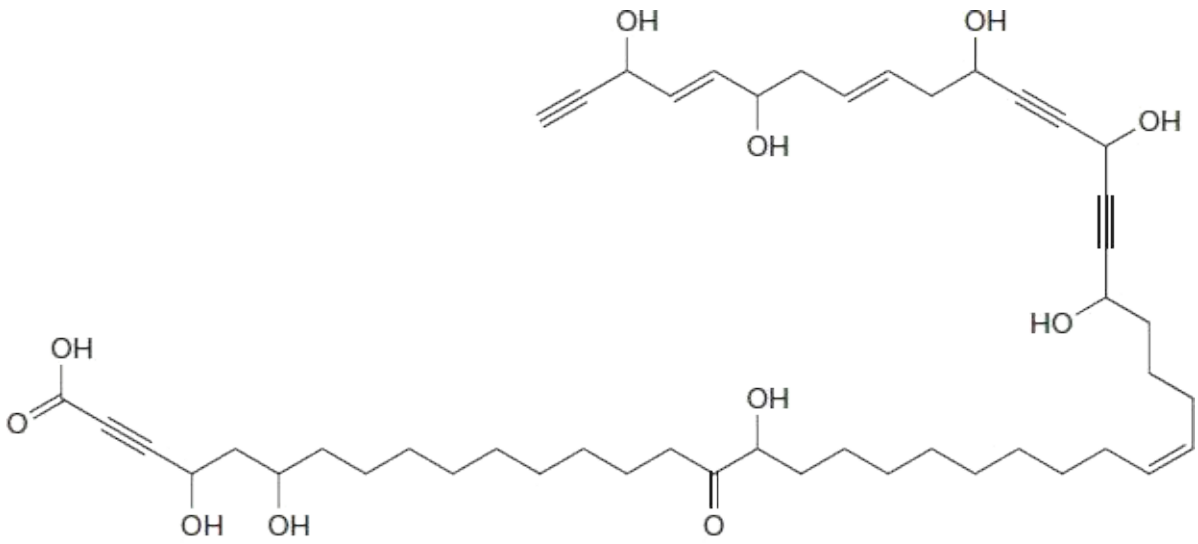
$CH_3C{\equiv}CCH_2CH_2C{\equiv}CH$

$HC{\equiv}CH$		$CH_2{=}CH_2$		
837 kJ/mol	−	635 kJ/mol	=	202 kJ/mol
(σ + two π bonds)		(σ + π bond)		↑ second π bond

- **Both π bonds of a C–C triple bond are weaker than a C–C σ bond, making them much more easily broken. As a result, alkynes undergo many addition reactions.**
- **Alkynes are more polarizable than alkenes because the electrons in their σ bonds are more loosely held.**

Problem 11.1

Nepheliosyne B is a novel acetylenic fatty acid isolated from a New Caledonian marine sponge. (a) Label the most acidic H atom. (b) Which carbon–carbon σ bond is shortest? (c) How many degrees of unsaturation does nepheliosyne B contain? (d) How many bonds are formed from C_{sp}—C_{sp^3}? (e) Label each triple bond as internal or terminal.



nepheliosyne B

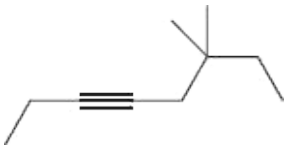
11.2 Nomenclature

Alkynes are named in the same way that alkenes were named in Section 10.3.

- In the IUPAC system, change the *-ane* ending of the parent alkane to the suffix *-yne.*
- Choose the longest carbon chain that contains both atoms of the triple bond and number the chain to give the triple bond the lower number.
- Compounds with two triple bonds are named as *diynes*, those with three are named as *triynes*, and so forth.
- Compounds with both a double and a triple bond are named as *enynes.* The chain is numbered to give the first site of unsaturation (either C=C or C≡C) the lower number.

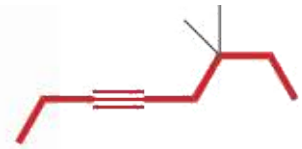
Sample Problem 11.1 Naming an Alkyne

Give the IUPAC name for the following alkyne.



Solution

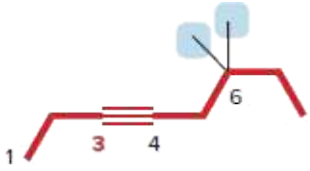
[1] Find the longest chain that contains both carbons of the triple bond.



8 C's in the longest chain

octane ----→ *octyne*

[2] Number the long chain; then name and number the substituents.



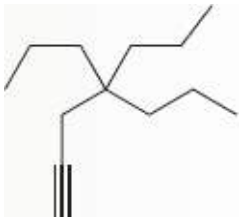
two methyl groups at C6

Answer: 6,6-dimethyloct-3-yne

Problem 11.2

Give the IUPAC name for each compound.

a.



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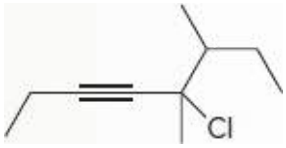
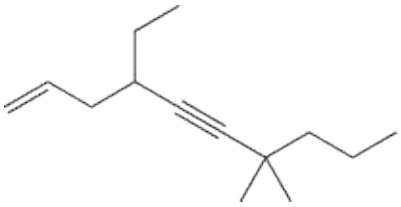
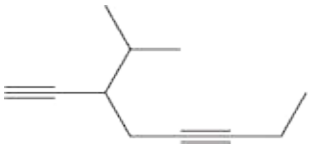


c.



d.



More Practice:

Try Problems 11.24, 11.27.

Problem 11.3

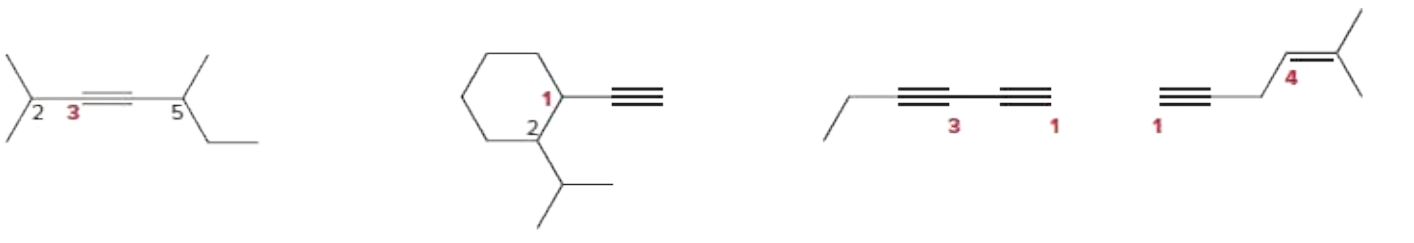
Give the structure corresponding to each of the following names.

a. *trans*-2-ethynylcyclopentanol

b. 4-ferf-butyldec-5-yne

c. 3,3,5-trimethylcyclononyne

The simplest alkyne, HC≡CH, named in the IUPAC system as ethyne, is more often called acetylene, its common name. The two-carbon alkyl group derived from acetylene is called an ethynyl group (HC≡C–). Examples of alkyne nomenclature are shown in Figure 11.1.



2,5-dimethylhept-3-yne 1-ethynyl-2-isopropylcyclohexane hexa-1,3-diyne 5-methylhex-4-en-1-yne

Figure 11.1 Examples of alkyne nomenclature

11.3 Properties of Alkynes

The physical properties of alkynes resemble those of hydrocarbons having a similar shape and molecular weight.

- **Alkynes have low melting points and boiling points.**
- **Melting points and boiling points increase as the number of carbons increases.**
- **Alkynes are soluble in organic solvents and insoluble in water.**

Problem 11.4

Explain why an alkyne often has a slightly higher boiling point than an alkene of similar molecular weight. For example, the bp of pent-1-yne is 39°C, and the bp of pent-1-ene is 30°C.

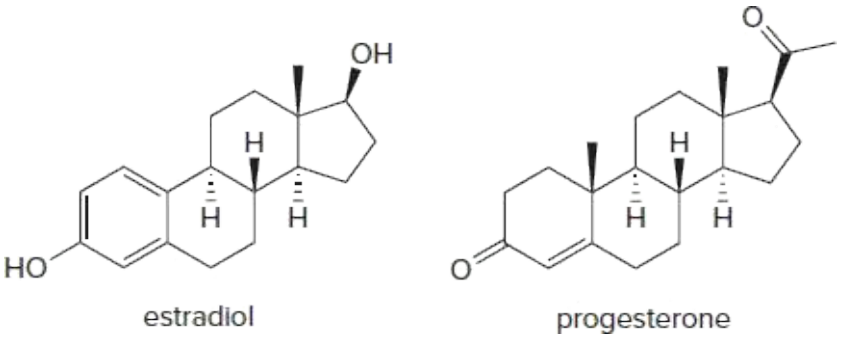
Students who have already been exposed to spectroscopy or who would like to learn about the spectroscopic properties of alkynes are referred to the following sections:

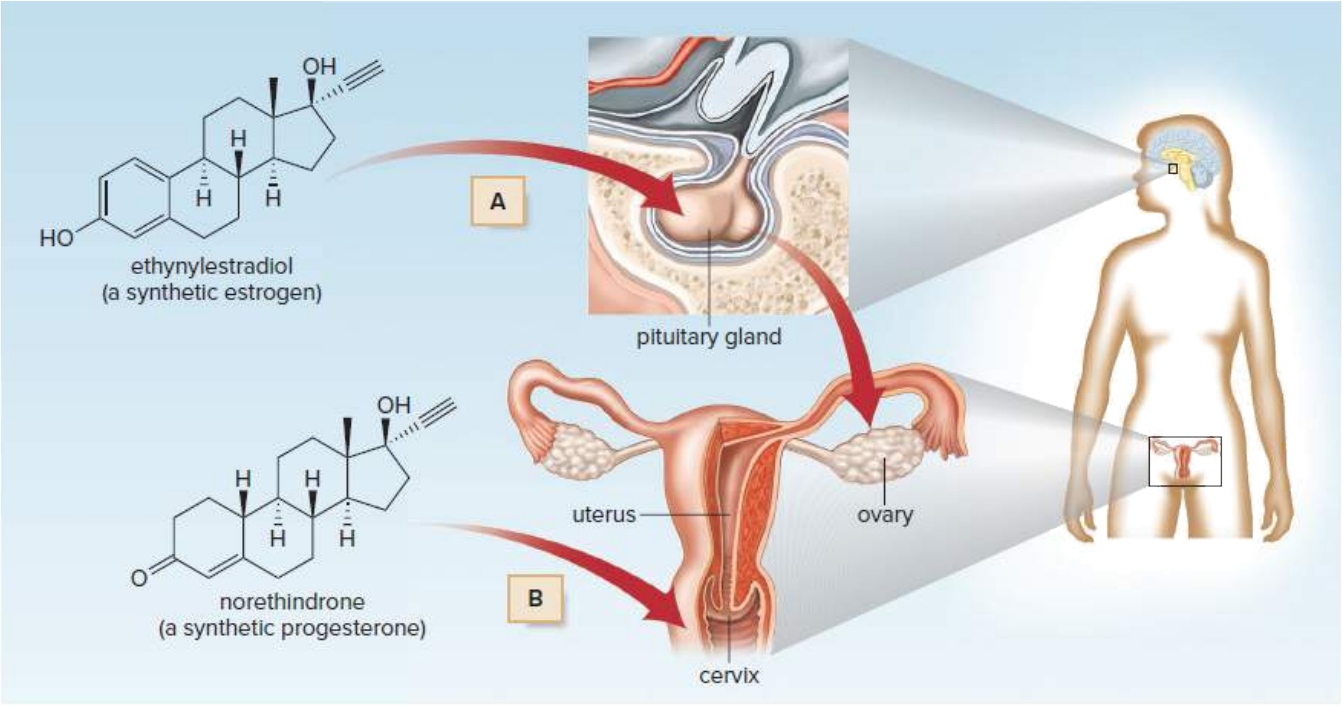
- Infrared spectroscopy: Sections B.3A, B.4A; Tables B.1, B.2; Sample Problem B.2b
- Nuclear magnetic resonance spectroscopy: Section C.4; Tables C.1, C.2, C.5

11.4 Interesting Alkynes

Acetylene, HC≡CH, is a colorless gas with an ethereal odor that burns in oxygen to form CO_2 and H_2O. Because the combustion of acetylene releases more energy per mole of product formed than other hydrocarbons, it burns with a very hot flame, making it an excellent fuel for welding torches.

Ethynylestradiol, the molecule that opened Chapter 11, and norethindrone are two components of oral contraceptives that contain a carbon–carbon triple bond (Figure 11.2). Both molecules are synthetic analogues of the naturally occurring female hormones estradiol and progesterone, but are more potent so they can be administered in lower doses. Most oral contraceptives contain two of these synthetic hormones. They act by artificially elevating hormone levels in a woman, thereby preventing pregnancy.

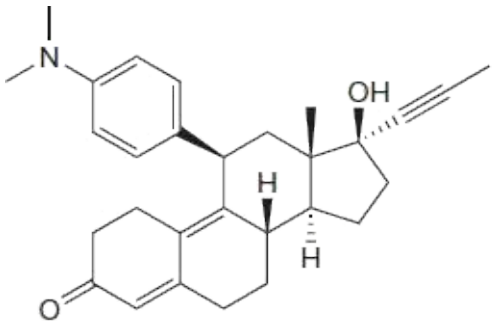




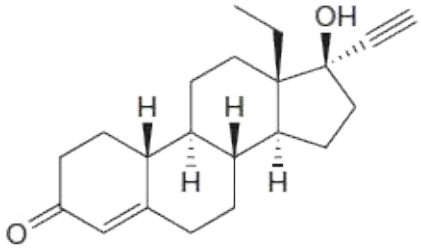
- Monthly cycles of hormones from the pituitary gland cause ovulation, the release of an egg from an ovary. To prevent pregnancy, the two synthetic hormones in many oral contraceptives have different effects on the female reproductive system.
  A: The elevated level of **ethynylestradiol,** a synthetic estrogen, "fools" the pituitary gland into thinking a woman is pregnant, so ovulation does not occur.
  B: The elevated level of **norethindrone,** a synthetic progesterone, stimulates the formation of a thick layer of mucus in the cervix, making it difficult for sperm to reach the uterus.

Figure 11.2 **How oral contraceptives work**

Two other synthetic hormones with alkynyl appendages are RU 486 and levonorgestrel. RU 486 blocks the effects of progesterone and, because of this, prevents implantation of a fertilized egg. RU 486 is used to induce abortions within the first few weeks of pregnancy. Levonorgestrel interferes with ovulation, so it prevents pregnancy if taken within a few days of unprotected sex.

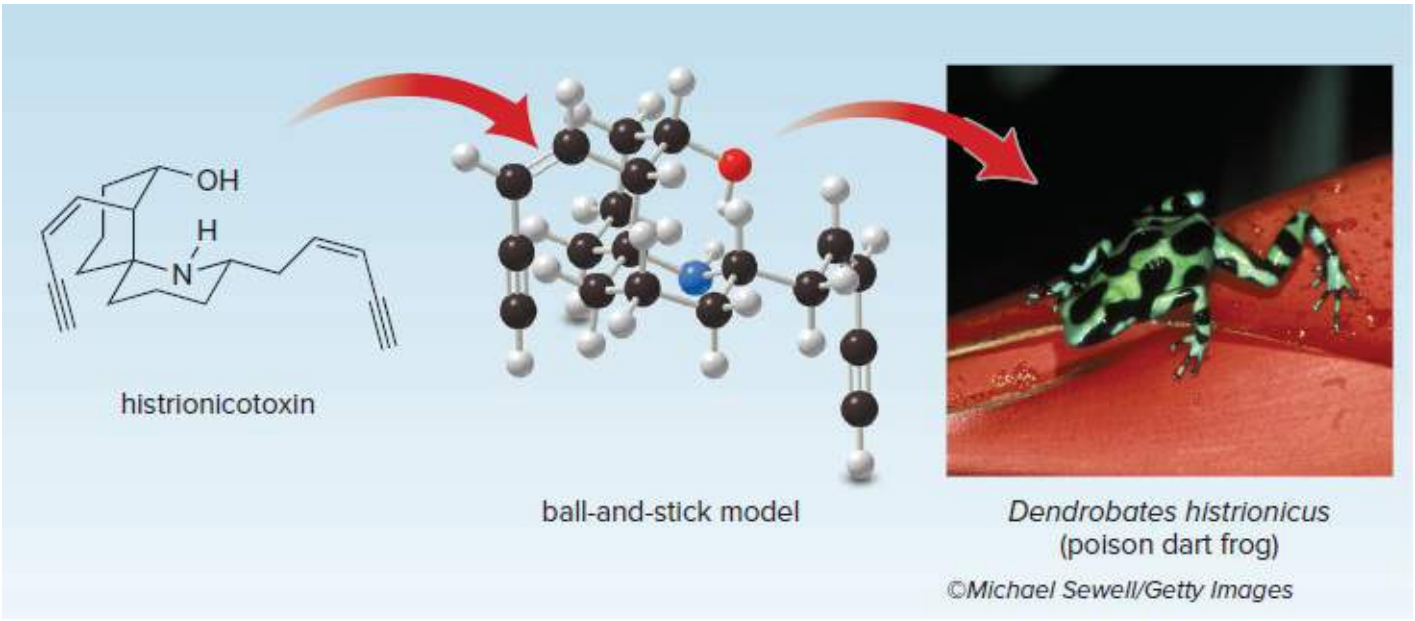


RU 486
(Trade name Mifepristone)



levonorgestrel
(Trade name Plan B)

Histrionicotoxin is a diyne isolated in small quantities from the skin of *Dendrobates histrionicus*, a colorful South American frog (Figure 11.3). This toxin, secreted by the frog as a natural defense mechanism, was used as a poison on arrow tips by the Choco tribe of South America.

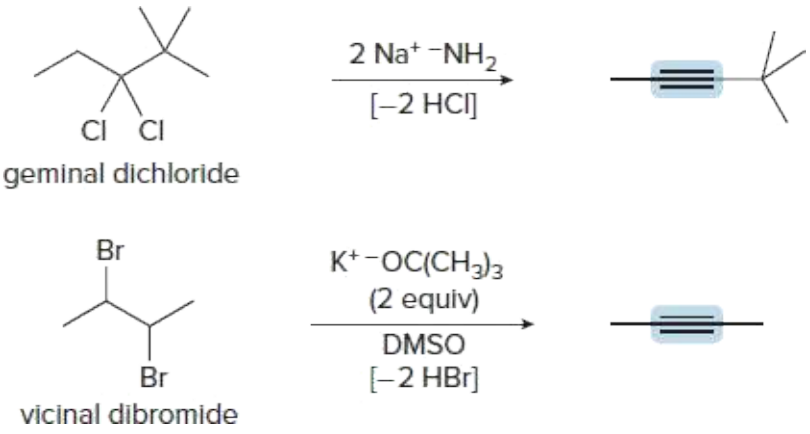


- Histrionicotoxin is a defensive toxin that protects *Dendrobates histrionicus* from potential predators. These small "poison dart" frogs inhabit the moist humid floor of tropical rainforests, and are commonly found in western Ecuador and Colombia. Histrionicotoxin acts by interfering with nerve transmission in mammals, resulting in prolonged muscle contraction.

Figure 11.3 **Histrionicotoxin**

11.5 Preparation of Alkynes

Alkynes are prepared by elimination reactions, as discussed in Section 8.10. A strong base removes two equivalents of HX from a vicinal or geminal dihalide to yield an alkyne by two successive E2 eliminations.



Because vicinal dihalides are synthesized by adding halogens to alkenes, an alkene can be converted to an alkyne by the two-step process illustrated in Sample Problem 11.2.

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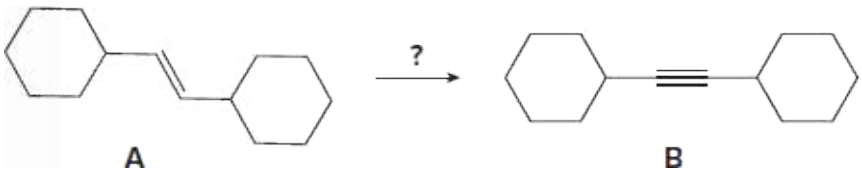
Sample Problem 11.2 Converting an Alkene to an Alkyne

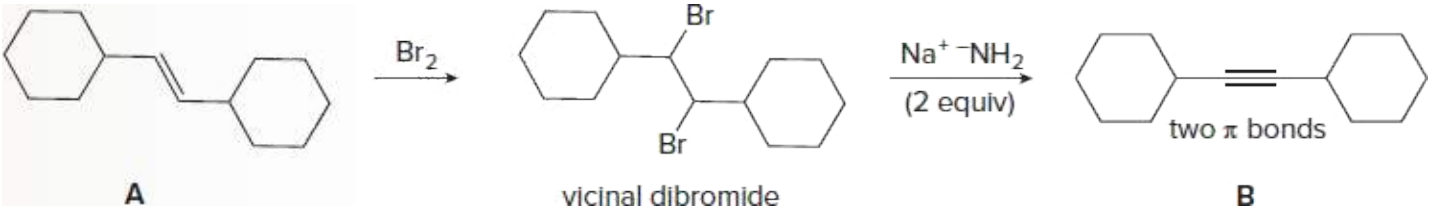
Convert alkene A into alkyne B by a stepwise method.



Solution

A two-step method is needed:

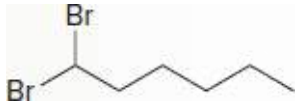
- **Addition of X_2 forms a vicinal dihalide.**
- **Elimination of two equivalents of HX forms two π bonds.**



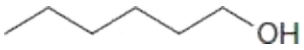
- **This two-step process introduces one degree of unsaturation: an alkene with one π bond is converted to an alkyne with two π bonds.**

Problem 11.5

Convert each compound to hex-1-yne, $HC{\equiv}CCH_2CH_2CH_2CH_3$.

a. 

b.

c. 

More Practice:

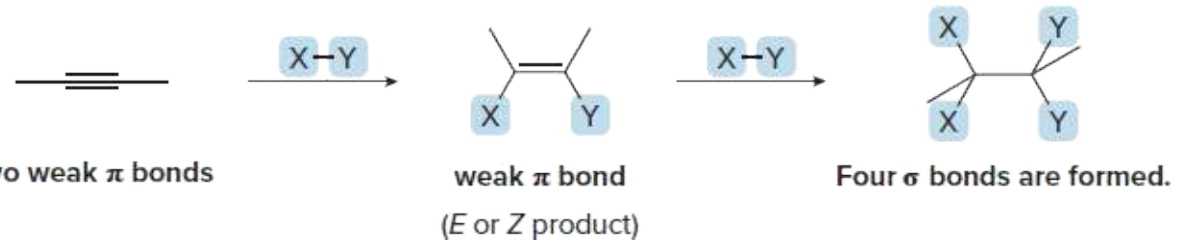
Try Problems 11.38c, 11.49.

11.6 Introduction to Alkyne Reactions

All reactions of alkynes occur because they contain easily broken π bonds or, in the case of terminal alkynes, an acidic, *sp* hybridized C–H bond.

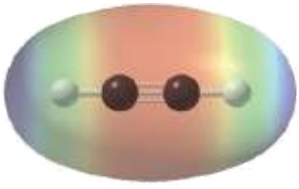
11.6A Addition Reactions

Like alkenes, alkynes undergo addition reactions because they contain weak π bonds. Two sequential reactions take place: addition of one equivalent of reagent forms an alkene, which then adds a second equivalent of reagent to yield a product having four new bonds.



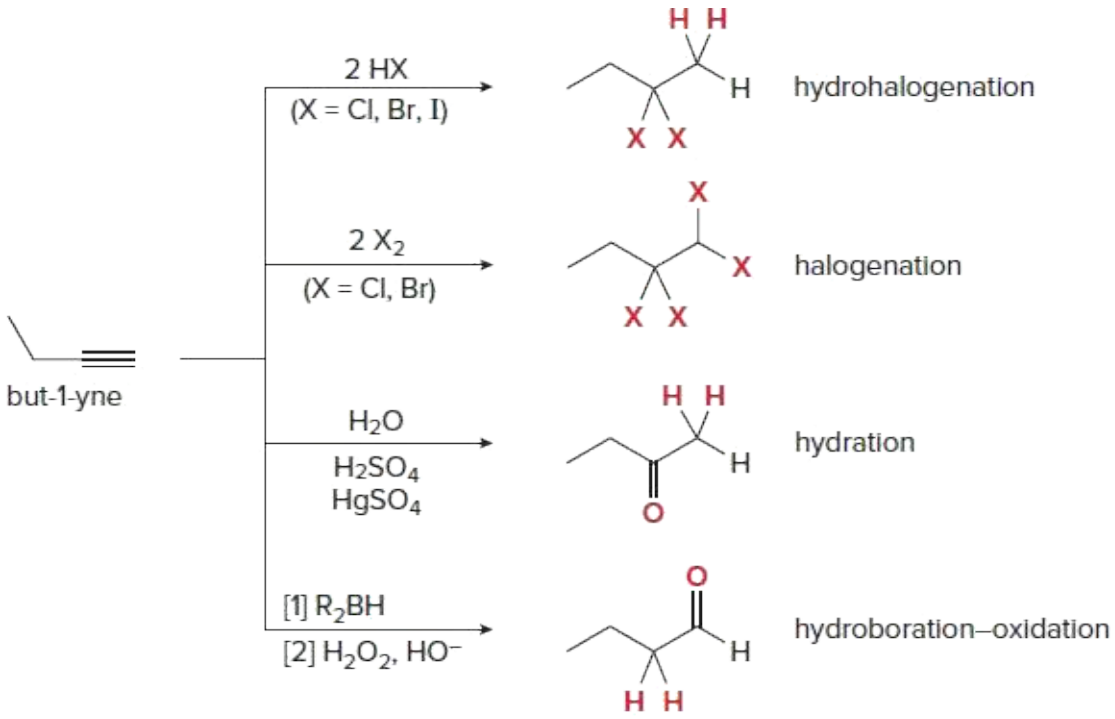
The oxidation and reduction of alkynes, reactions that also involve addition, are discussed in Chapter 12.

Alkynes are electron rich, as shown in the electrostatic potential map of acetylene in Figure 11.4. The two π bonds form a cylinder of electron density between the two *sp* hybridized carbon atoms, and this exposed electron density makes a triple bond nucleophilic. As a result, alkynes react with electrophiles. Four addition reactions are discussed in Chapter 11 and illustrated in Figure 11.5 with but-1-yne as the starting material.



- The red electron-rich region is located between the two carbon atoms, forming a cylinder of electron density.

Figure 11.4 **Electrostatic potential map of acetylene**

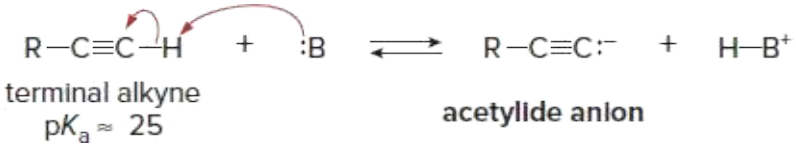


- In each addition, both π bonds of the triple bond are broken, and four new bonds are formed.

Figure 11.5 **Four addition reactions of but-1-yne**

11.6B Terminal Alkynes—Reaction as an Acid

Because *sp* hybridized C–H bonds are more acidic than sp^2 and sp^3 hybridized C–H bonds, terminal alkynes are readily deprotonated with strong base in a Brønsted–Lowry acid–base reaction. The resulting anion is called an acetylide anion.



Recall from Section 2.5D that the acidity of a C–H bond increases as the percent *s*-character of C increases. Thus, the following order of relative acidity results:

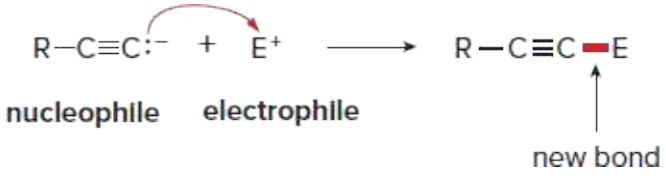
C_{sp^3}–H < C_{sp^2}–H < C_{sp}–H.

What bases can be used for this reaction? Because an acid–base equilibrium favors the weaker acid and base, only bases having conjugate acids with pK_a values *higher* than the terminal alkyne—that is, pK_a values > 25—are strong enough to form a significant concentration of acetylide anion. As shown in Table 11.1, $^-NH_2$ and H^- are strong enough to deprotonate a terminal alkyne, but ^-OH and ^-OR are not.

Table 11.1 A Comparison of Bases for Alkyne Deprotonation

	Base	pK_a of the conjugate acid
These bases are strong enough to deprotonate an alkyne.	$^-NH_2$	38
	H^-	35
These bases are *not* strong enough to deprotonate an alkyne.	^-OH	15.7
	^-OR	15.5–18

Why is this reaction useful? The acetylide anions formed by deprotonating terminal alkynes are strong nucleophiles that can react with a variety of electrophiles, as shown in Section 11.11. Page 449



Problem 11.6

Which bases can deprotonate acetylene? The pK_a values of the conjugate acids are given in parentheses.

a. CH_3NH^- ($pK_a = 40$)

b. CO_3^{2-} ($pK_a = 10.2$)

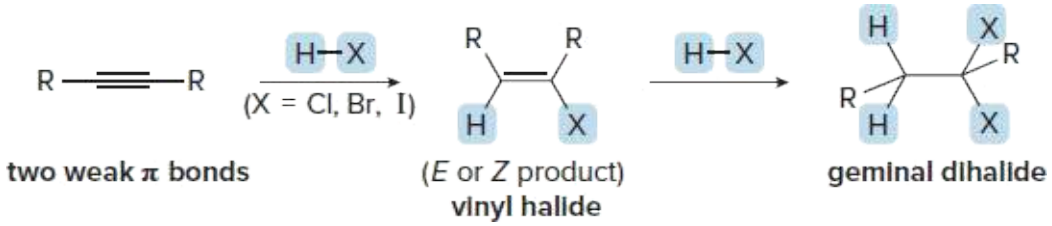
c. $CH_2{=}CH^-$ ($pK_a = 44$)

d. $(CH_3)_3CO^-$ ($pK_a = 18$)

11.7 Addition of Hydrogen Halides

Alkynes undergo hydrohalogenation, the addition of hydrogen halides, HX (X = Cl, Br, I).

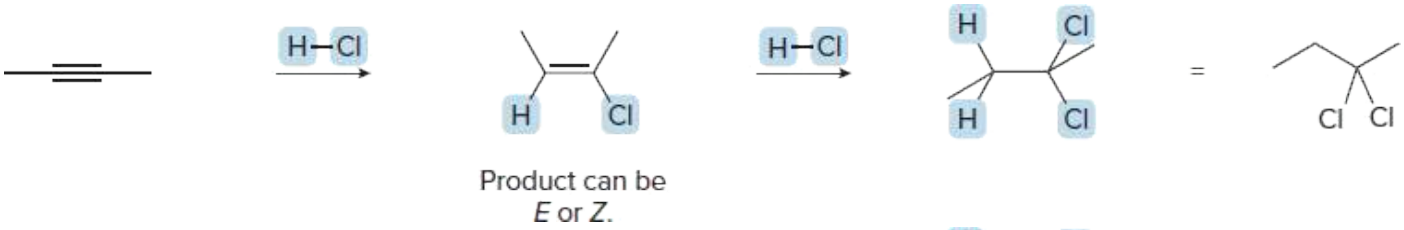
Two equivalents of HX are usually used: addition of one mole forms a vinyl halide, which then reacts with a second mole of HX to form a geminal dihalide.



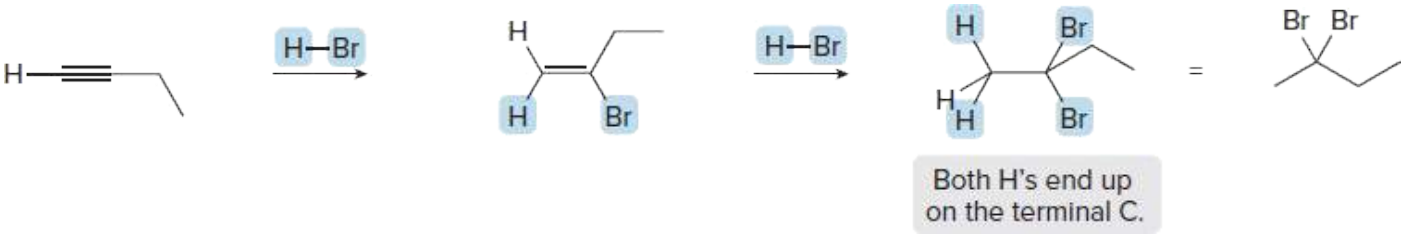
Addition of HX to an alkyne is another example of electrophilic addition, because the electrophilic (H) end of the reagent is attracted to the electron-rich triple bond.

- **With two equivalents of HX, both H atoms bond to the *some* carbon.**
- **With a terminal alkyne, both H atoms bond to the *terminol* carbon; that is, the hydrohalogenation of alkynes follows Markovnikov's rule.**

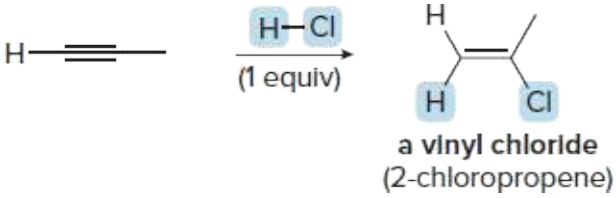
[1]



[2]

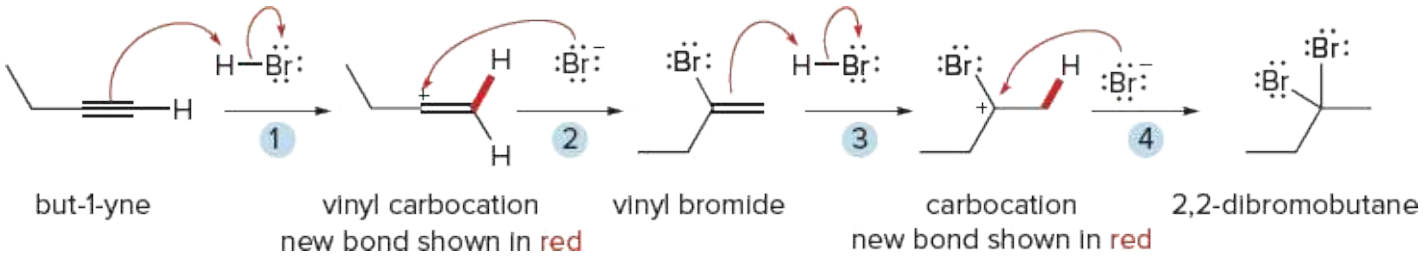


- **With only one equivalent of HX, the reaction stops with formation of the vinyl halide.**



One proposed mechanism for the addition of two equivalents of HX to an alkyne involves two steps for each addition of HX: addition of H^+ (from HX) to form a carbocation, followed by nucleophilic attack of X^-. Mechanism 11.1 illustrates the addition of HBr to but-1-yne to yield 2,2-dibromobutane. Each two-step mechanism is similar to the two-step addition of HBr to *cis*-but-2-ene discussed in Section 10.9.

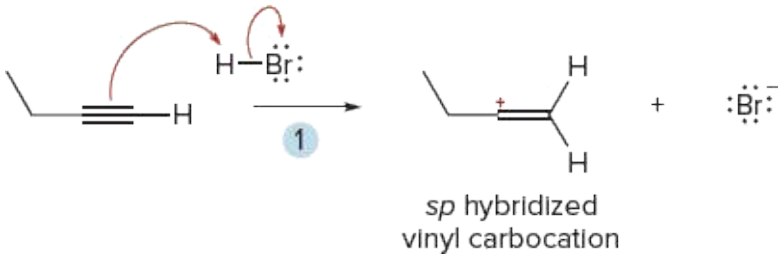
Mechanism 11.1 Electrophilic Addition of HX to an Alkyne



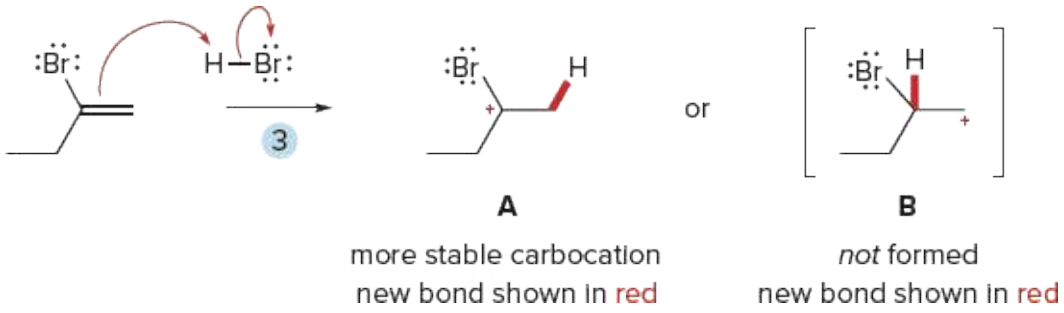
1. **Addition of H^+ forms a vinyl carbocation and follows Markovnikov's rule. The H atom bonds to the terminal C to form the more substituted carbocation.**
2. **Nucleophilic attack of Br^- forms a vinyl bromide. One equivalent of HBr adds in two steps.**
3. **The addition of a second equivalent of HBr follows in the same two-step manner. Addition of H^+ to the vinyl bromide forms a carbocation.**
4. **Nucleophilic attack of Br^- forms a geminal dibromide, 2,2-dibromobutane.**

Because of the instability of a vinyl carbocation, other mechanisms for HX addition that avoid formation of a discrete carbocation have been proposed. It is likely that more than one mechanism occurs, depending in part on the identity of the alkyne substrate.

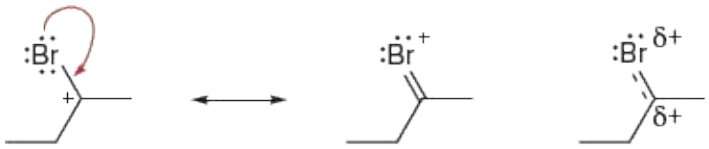
The formation of both carbocations (in Steps [1] and [3]) deserves additional scrutiny. The vinyl carbocation formed in Step [1] is *sp* hybridized and therefore less stable than a 2° sp^2 hybridized carbocation (Section 7.18). This makes electrophilic addition of HX to an alkyne *slower* than electrophilic addition of HX to an alkene, even though alkynes are more polarizable and have more loosely held π electrons than alkenes.



In Step [3], two carbocations are possible but only one is formed. Markovnikov addition in Step [3] places the H on the terminal carbon (C1) to form the more substituted carbocation A, rather than the less substituted carbocation B. Because the more stable carbocation is formed faster—another example of the Hammond postulate—carbocation A must be more stable than carbocation B.



Why is carbocation A, having a positive charge on a carbon that also has a Br atom, more stable? Shouldn't the electronegative Br atom withdraw electron density from the positive charge, and thus destabilize it? It turns out that A is stabilized by resonance but B is not. Two resonance structures can be drawn for carbocation A, but only one Lewis structure can be drawn for carbocation B.



two resonance structures for **A**

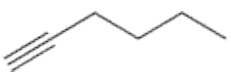
hybrid
The positive charge is delocalized.

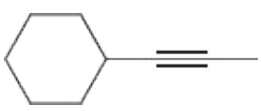
- **Resonance stabilizes a molecule by delocalizing charge and electron density.**
- **Thus, halogens stabilize an adjacent positive charge by resonance.**

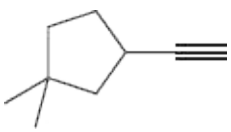
Markovnikov's rule applies to the addition of HX to vinyl halides because addition of H^+ forms a resonance-stabilized carbocation. As a result, addition of each equivalent of HX to a triple bond forms the more stable carbocation, so that both H atoms bond to the less substituted C.

Problem 11.7

Draw the organic products formed when each alkyne is treated with two equivalents of HBr.

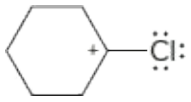
a. 

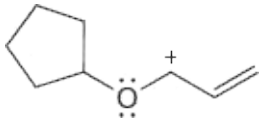
b. 

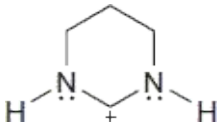
c. 

Problem 11.8

Draw additional resonance structures for each cation.

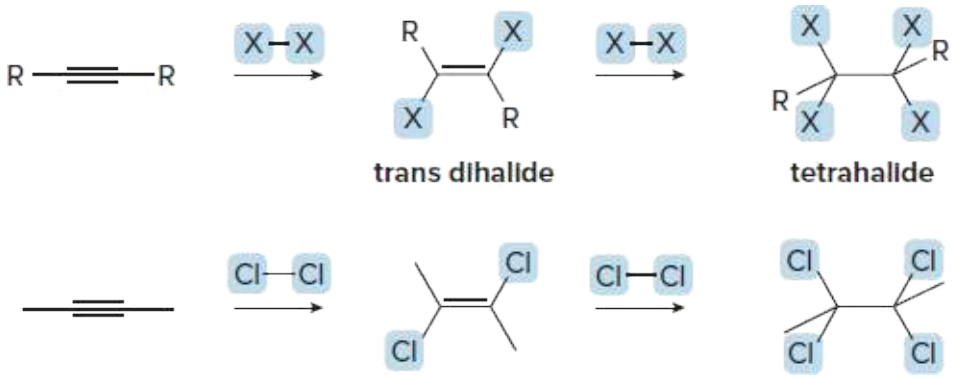
a. 

b. 

c. 

11.8 Addition of Halogen

Halogens, X_2 (X = Cl or Br), add to alkynes in much the same way they add to alkenes (Section 10.13). Addition of one mole of X_2 forms a trans dihalide, which can then react with a second mole of X2 to yield a tetrahalide.



Problem 11.9

Draw the products formed when $CH_3CH_2C{\equiv}CCH_2CH_3$ is treated with each reagent: (a) Br_2 (2 equiv); (b) Cl_2 (1 equiv).

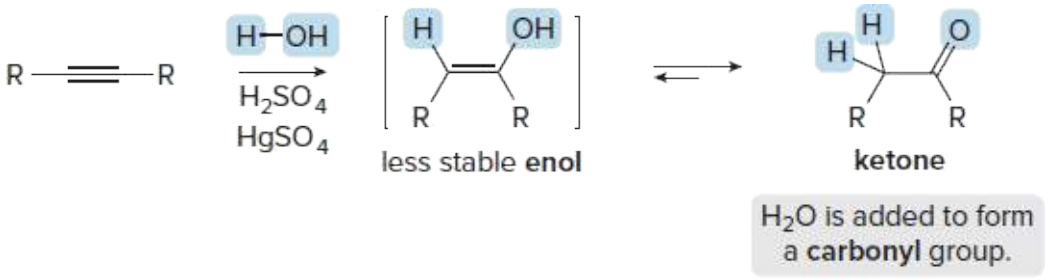
Problem 11.10

Explain the following result. Although alkenes are generally more reactive than alkynes toward electrophiles, the reaction of Cl^2 with but-2-yne can be stopped after one equivalent of Cl^2 has been added.

11.9 Addition of Water

Although the addition of H_2O to an alkyne resembles the acid-catalyzed addition of H_2O to an alkene in some ways, an important difference exists. In the presence of

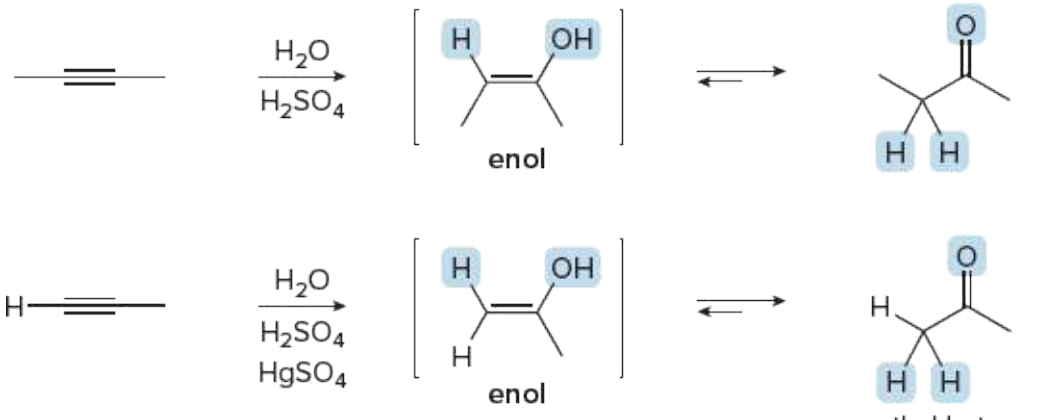
strong acid or Hg^{2+} catalyst, the elements of H_2O add to the triple bond, but the initial addition product, an enol, is unstable and rearranges to a product containing a carbonyl group—that is, a C=O. A carbonyl compound having two alkyl groups bonded to the C=O carbon is called a ketone.



Because an enol contains both a C=C and a hydroxy group, the name enol comes from alkene + alcohol.

$HgSO_4$ is often used in the hydration of internal alkynes as well, because hydration can be carried out under milder reaction conditions.

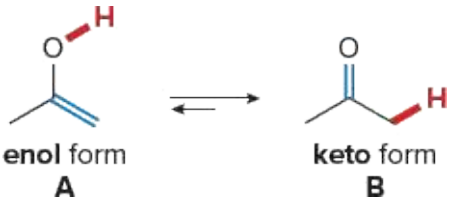
Internal alkynes undergo hydration with concentrated acid, whereas terminal alkynes require the presence of an additional Hg^{2+} catalyst—usually $HgSO_4$—to yield methyl ketones by Markovnikov addition of H_2O.



Markovnikov addition of H_2O
H adds to the terminal C.

Let's first examine the conversion of a general enol A to the carbonyl compound B. A and B are called tautomers: A is the *enol form* and B is the *keto form* of the tautomer.

- ***Tautomers*** **are constitutional isomers that differ in the location of a double bond and a hydrogen atom. Two tautomers are in equilibrium with each other.**

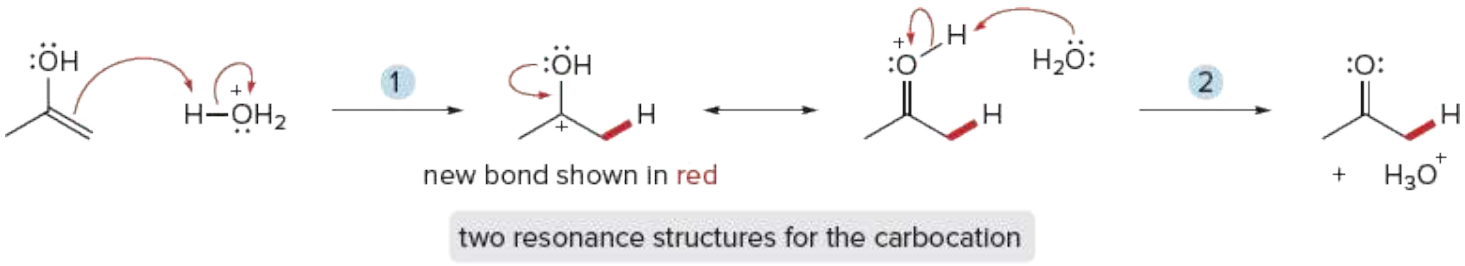


Tautomers differ in the position of a double bond and a hydrogen atom. In Chapter 21 an in-depth discussion of ketoenol tautomers is presented.

- **An enol tautomer has an O–H group bonded to a C=C.**
- **A keto tautomer has a C=O and an additional C–H bond.**

Equilibrium favors the keto form largely because a C=O is much stronger than a C=C. Tautomerization, the process of converting one tautomer into another, is catalyzed by both acid and base. Under the strongly acidic conditions of hydration, tautomerization of the enol to the keto form occurs rapidly by a two-step process: protonation, followed by deprotonation as shown in Mechanism 11.2.

Mechanism 11.2 Tautomerization in Acid



1. **Protonation of the double bond forms a resonance-stabilized carbocation.**
2. **Loss of a proton, which can be drawn with either resonance structure, forms the carbonyl group. Because acid is re-formed in this step, tautomerization is acid-catalyzed.**

Hydration of an internal alkyne with strong acid forms an enol by a mechanism similar to that of the acid-catalyzed hydration of an alkene (Section 10.12). Mechanism 11.3 illustrates the hydration of but-2-yne with H_2O and H_2SO_4. Once formed, the enol then tautomerizes to the more stable keto form by protonation followed by deprotonation.

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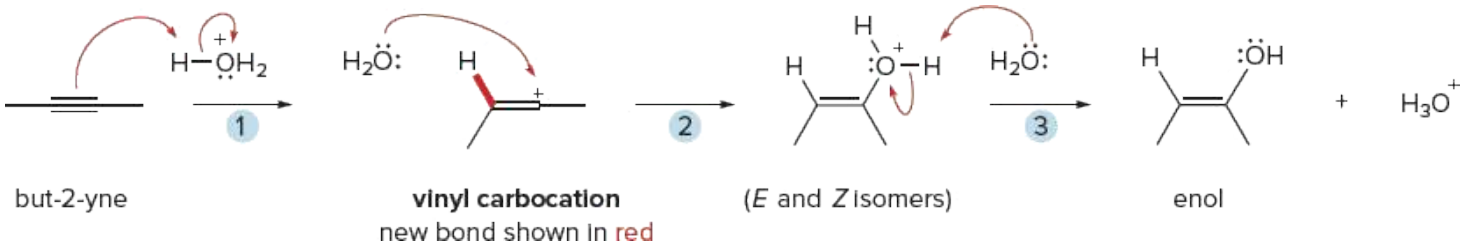
Mechanism 11.3 Hydration of an Alkyne

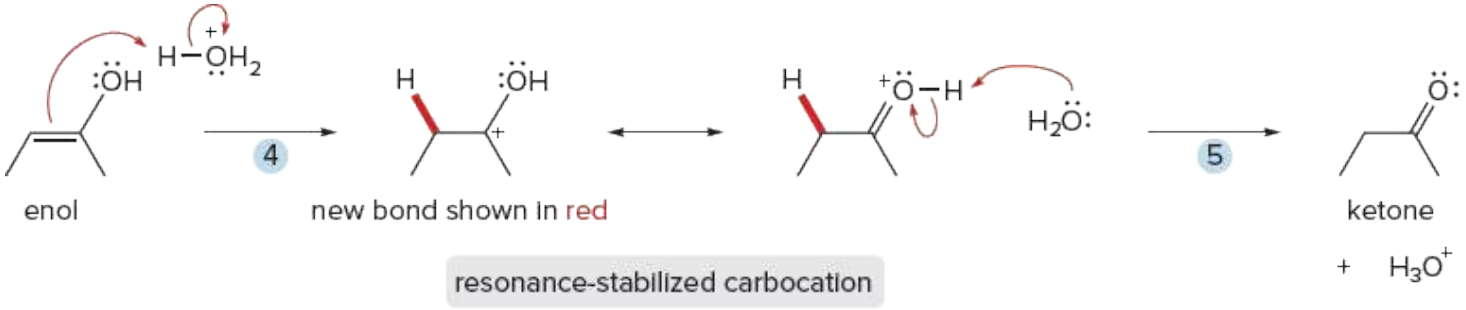
Part [1] Addition of H_2O to form an enol



1 Addition of H^+ forms a vinyl carbocation.

2 – **3** Nucleophilic attack followed by loss of a proton forms the enol.

Part [2] Tautomerization

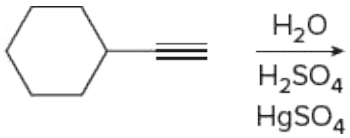


4 Tautomerization of the enol to the keto form begins with protonation of the double bond to form a carbocation.

5 Loss of a proton, which can be drawn with either resonance structure, forms the ketone.

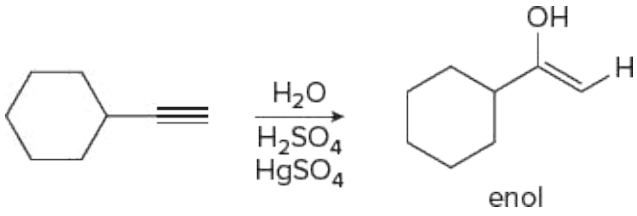
Sample Problem 11.3 Drawing an Enol and a Ketone Formed by Hydration of an Alkyne

Draw the enol intermediate and the ketone product formed in the following reaction.



Solution

First, form the enol by adding H_2O to the triple bond with the H bonded to the less substituted terminal carbon, according to Markovnikov's rule.



To convert the enol to the keto tautomer, add a proton to the C=C and remove a proton from the OH group. In tautomerization, the C–OH bond is converted to a C=O, and a new C–H bond is formed on the other enol carbon.

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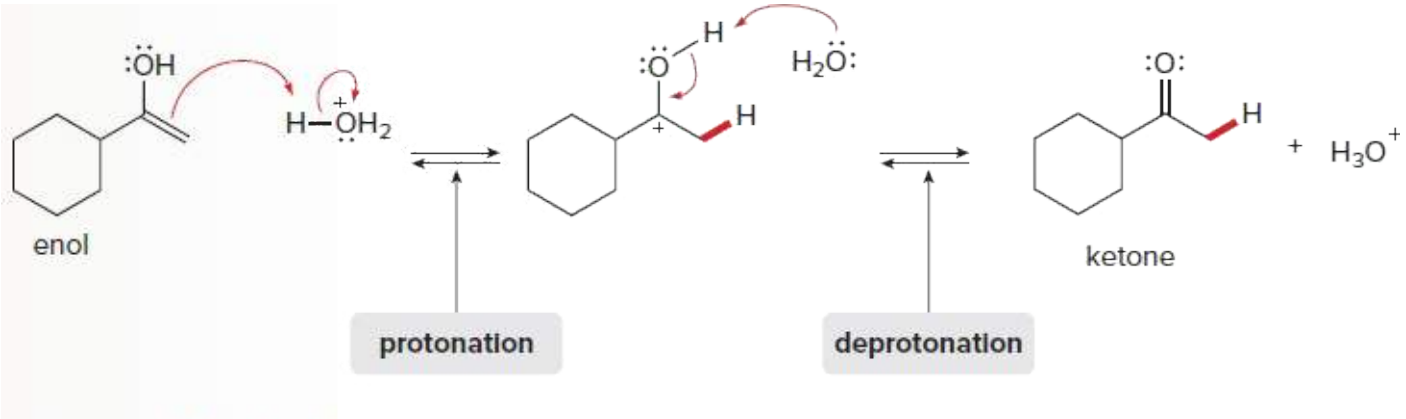


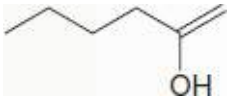
- The overall result is the addition of H_2O to a triple bond to form a ketone.

- **The overall result is the addition of H_2O to a triple bond to form a ketone.**

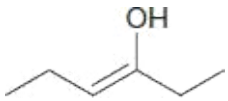
Problem 11.11

Draw the keto tautomer of each enol.

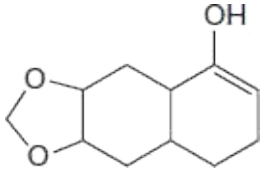
a.



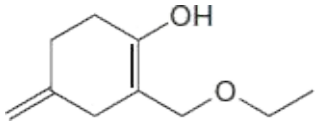
b.



c.



d.



More Practice:

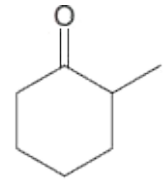
Try Problems 11.25, 11.30, 11.38f.

Problem 11.12

Ignoring *E* and *Z* isomers, what two enols are formed when pent-2-yne is treated with H_2O, H_2SO_4, and $HgSO_4$? Draw the ketones formed from these enols after tautomerization.

Problem 11.13

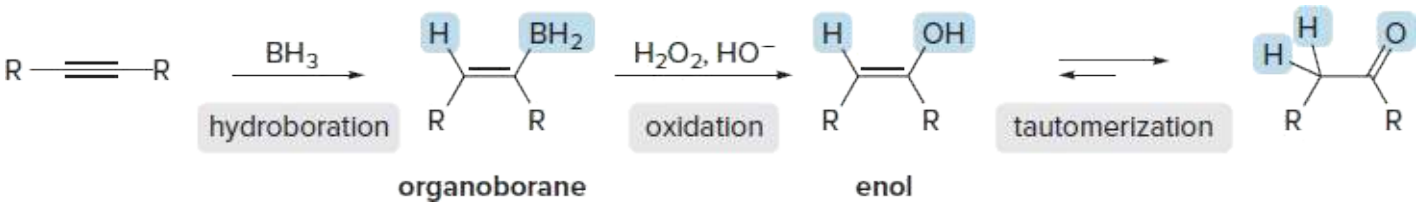
(a) Draw two different enol tautomers of 2-methylcyclohexanone. (b) Draw two constitutional isomers that are not tautomers, but contain a C=C and an OH group.



2-methylcyclohexanone

11.10 Hydroboration–Oxidation

Hydroboration–oxidation is a two-step reaction sequence that converts an alkyne to a carbonyl compound.



- **Addition of borane forms an organoborane.**
- **Oxidation with basic H_2O_2 forms an enol.**
- **Tautomerization of the enol forms a carbonyl compound.**
- **The overall result is addition of H_2O to a triple bond.**

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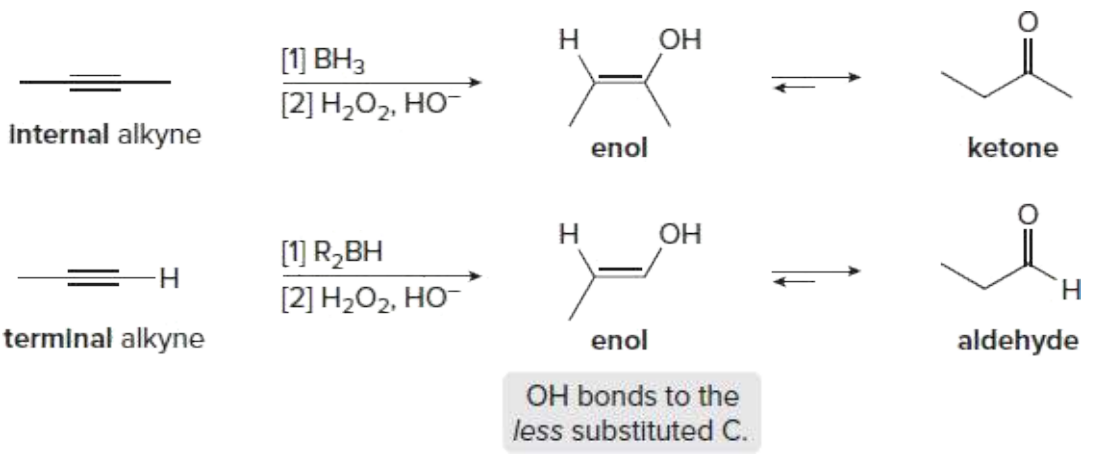
Hydroboration–oxidation of an *internal* alkyne forms a ketone. Hydroboration of a *terminal* alkyne adds boron to the less substituted, terminal carbon. After oxidation to the enol, tautomerization yields an aldehyde, a carbonyl compound having a hydrogen atom bonded to the carbonyl carbon. Hydroboration of a terminal alkyne is generally carried out with a dialkylborane (R_2BH), which has been prepared from BH_3 (Section 10.16).



Hydration (H_2O, H_2SO_4, and $HgSO_4$) and hydroboration–oxidation (BH_3 or R_2BH followed by H_2O_2, HO^-) both add the elements of H_2O across a triple bond. Sample Problem 11.4 shows that different constitutional isomers are formed from terminal alkynes in these two reactions.

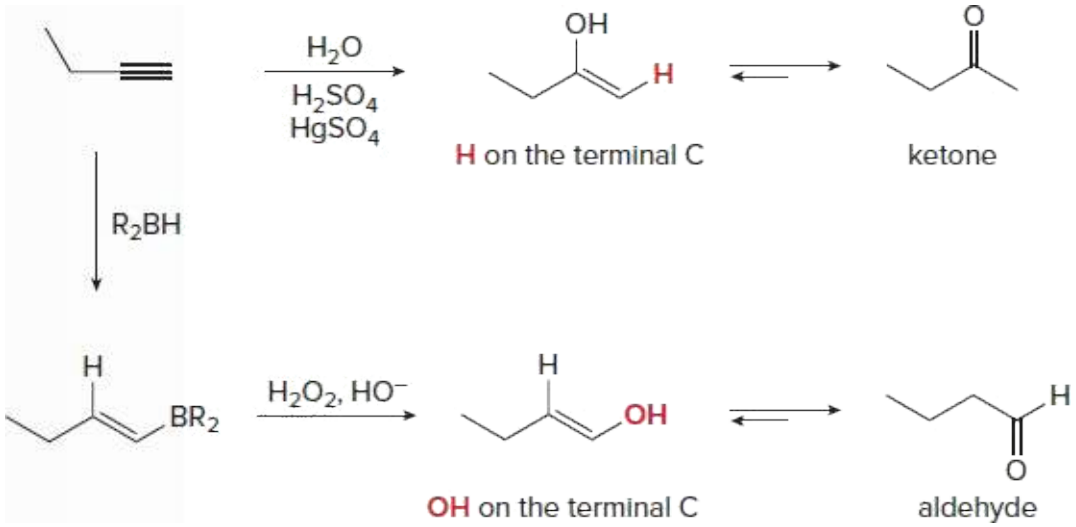
- **Addition of H_2O using H_2O, H_2SO_4, and $HgSO_4$ forms methyl ketones from terminal alkynes.**
- **Addition of H_2O using an organoborane, then H_2O_2, HO^- forms aldehydes from terminal alkynes.**

Sample Problem 11.4 Comparing Hydration Products Using Two Different Methods

Draw the product formed when $CH_3CH_2C{\equiv}CH$ is treated with each of the following sets of reagents: (a) H_2O, H_2SO_4, $HgSO_4$; and (b) R_2BH, followed by H_2O_2, HO^-.

Solution

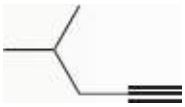
(a) With H_2O + H_2SO_4 + $HgSO_4$, electrophilic addition of H and OH places the H atom on the *less* substituted carbon of the alkyne to form a ketone after tautomerization. (b) In contrast, addition of R2BH places the R2B group on the *less* substituted terminal carbon of the alkyne. Oxidation and tautomerization yield an aldehyde. The ketone and aldehyde formed in these reactions are constitutional isomers.



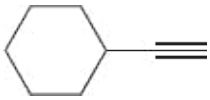
Problem 11.14

Draw the products formed when the following alkynes are treated with each set of reagents: [1] H_2O, H_2SO_4, $HgSO_4$; or [2] R_2BH followed by H_2O_2, ^-OH.

a.



b.



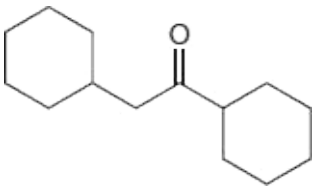
More Practice:

Try Problems 11.33d, e; 11.38d, f.

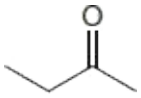
Problem 11.15

What alkyne yields each ketone as the only product both with acid-catalyzed hydration and after hydroboration–oxidation?

a.

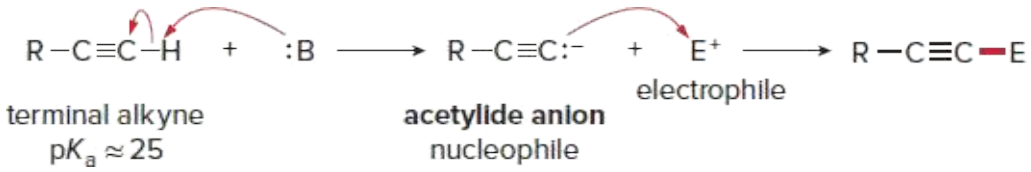


b.



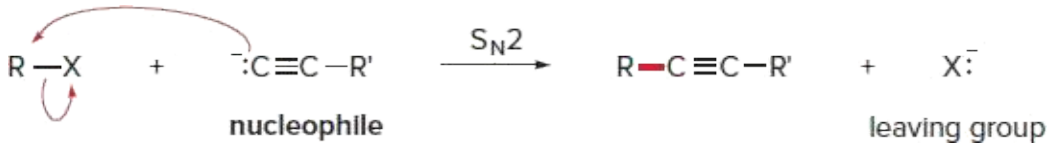
11.11 Reaction of Acetylide Anions

Terminal alkynes are readily converted to acetylide anions with strong bases such as $NaNH_2$ and NaH. These anions are strong nucleophiles, capable of reacting with electrophiles such as alkyl halides and epoxides.



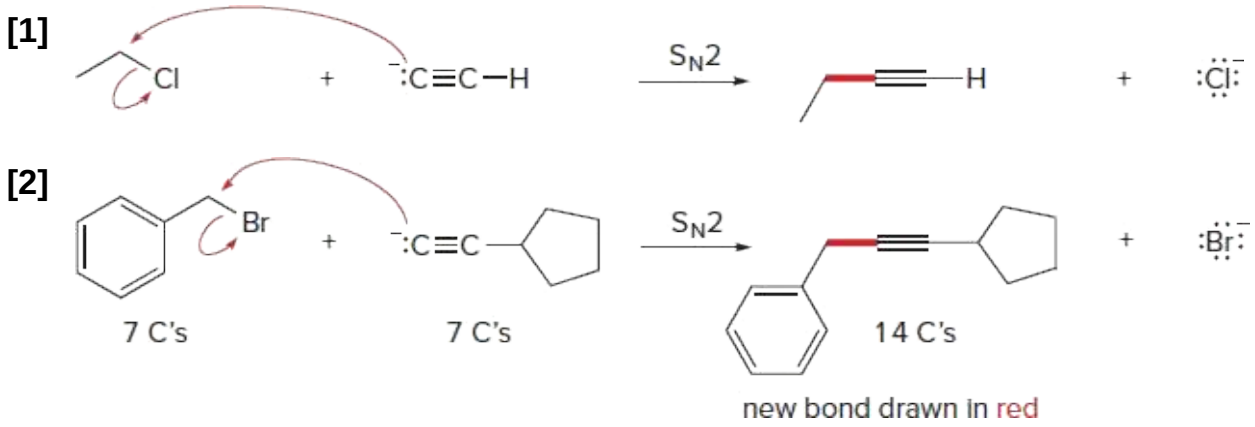
11.11A Reaction of Acetylide Anions with Alkyl Halides

Acetylide anions react with unhindered alkyl halides to yield products of nucleophilic substitution.



Because acetylide anions are strong nucleophiles, the mechanism of nucleophilic

substitution is S_N2, and thus the reaction is fastest with CH_3X and 1° alkyl halides. Terminal alkynes (Reaction [1]) or internal alkynes (Reaction [2]) can be prepared depending on the identity of the acetylide anion.



- **Nucleophilic substitution with acetylide anions forms new carbon~`carbon bonds.**

Because organic compounds consist of a carbon framework, reactions that form carbon–carbon bonds are especially useful. In Reaction [2], for example, nucleophilic attack of a seven-carbon acetylide anion on a seven-carbon alkyl halide yields a 14-carbon alkyne as product.

Although nucleophilic substitution with acetylide anions is a very valuable carbon–carbon bond-forming reaction, it has the same limitations as any S_N2 reaction. Steric hindrance around the leaving group causes 2° and 3° alkyl halides to undergo elimination by an E2 mechanism, as shown with 2-bromo-2-methylpropane. Thus, nucleophilic substitution with acetylide anions forms new carbon–carbon bonds in high yield only with unhindered CH_3X and 1° alkyl halides.

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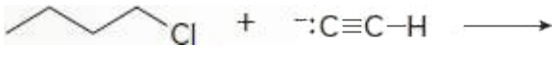
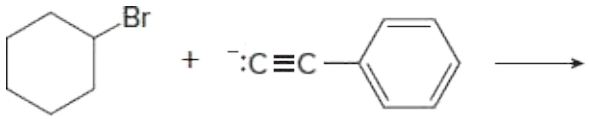
Steric hindrance prevents an S_N2 reaction.

Sample Problem 11.5 Drawing the Products When Acetylide Anions React with Alkyl Halides

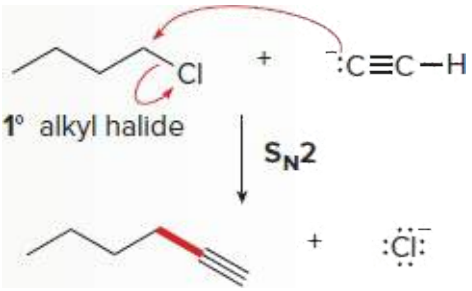
Draw the organic products formed in each reaction.

a. 

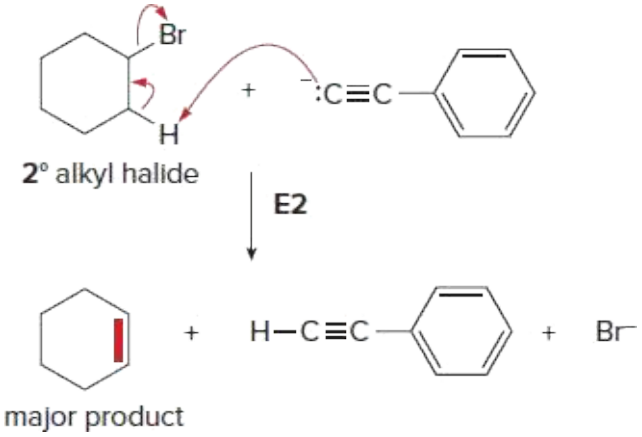
b. 

Solution

a. Because the alkyl halide is 1° and the acetylide anion is a strong nucleophile, substitution occurs by an S_N2 mechanism, resulting in a new C–C bond.

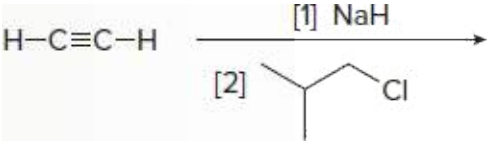


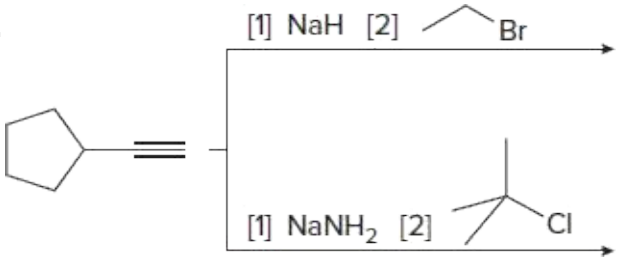
b. Because the alkyl halide is 2°, the major product is formed from elimination by an E2 mechanism.



Problem 11.16

Draw the organic products formed in each reaction.

a. 

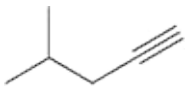
b. 

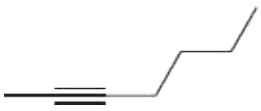
More Practice:

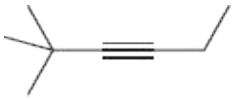
Try Problems 11.33g; 11.38g, i; 11.40a, b.

Problem 11.17

What acetylide anion and alkyl halide can be used to prepare each alkyne? Indicate all possibilities when more than one route will work.

a. 

b. 

c. 

Because acetylene has two *sp* hybridized C–H bonds, two sequential reactions can occur to form two new carbon–carbon bonds, as shown in Sample Problem 11.6.

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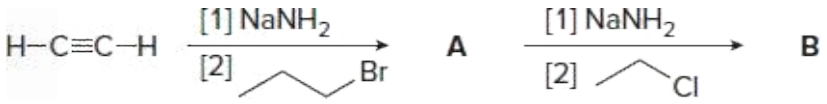
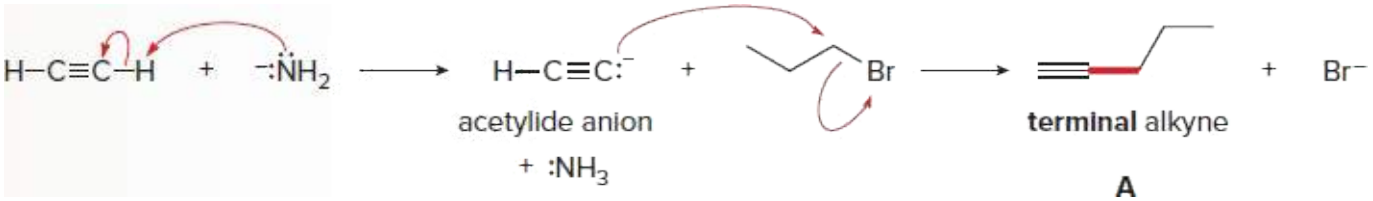
Sample Problem 11.6 Forming an Internal Alkyne by Two Sequential S_N2 Reactions

Identify the terminal alkyne A and the internal alkyne B in the following reaction sequence.

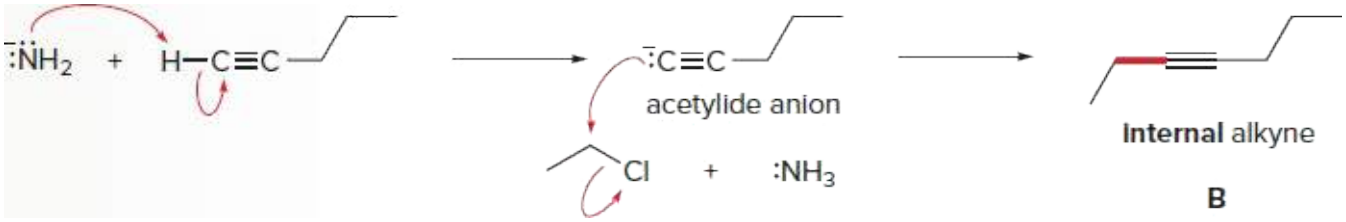


Solution

In each step, the base $^-NH_2$ removes a proton on an *sp* hybridized carbon, and the resulting acetylide anion reacts as a nucleophile with an alkyl halide to yield an S_N2 product. The first two-step reaction sequence forms the terminal alkyne A by nucleophilic attack of the acetylide anion on $CH_3CH_2CH_2Br$.



The second two-step reaction sequence forms the internal alkyne B by nucleophilic attack of the acetylide anion on CH_3CH_2Cl.



Problem 11.18

Show how HC≡CH, CH_3CH_2Br, and $(CH_3)_2CHCH_2CH_2Br$ can be used to prepare

$CH_3CH_2C{\equiv}CCH_2CH_2CH(CH_3)_2$. Show all reagents, and use curved arrows to show movement of electron pairs.

More Practice:

Try Problems 11.33g; 11.38g, i; 11.40a, b; 11.48a; 11.52a.

The soft coral *Capnella imbricata* is the source of the natural product capnellene.

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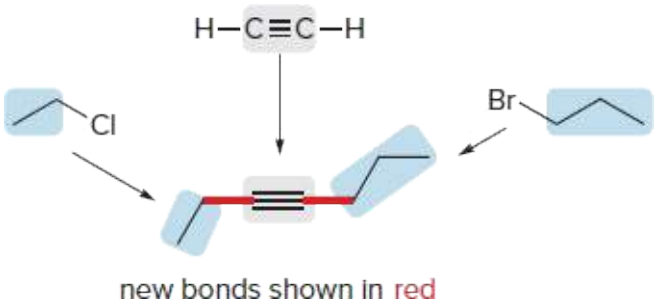
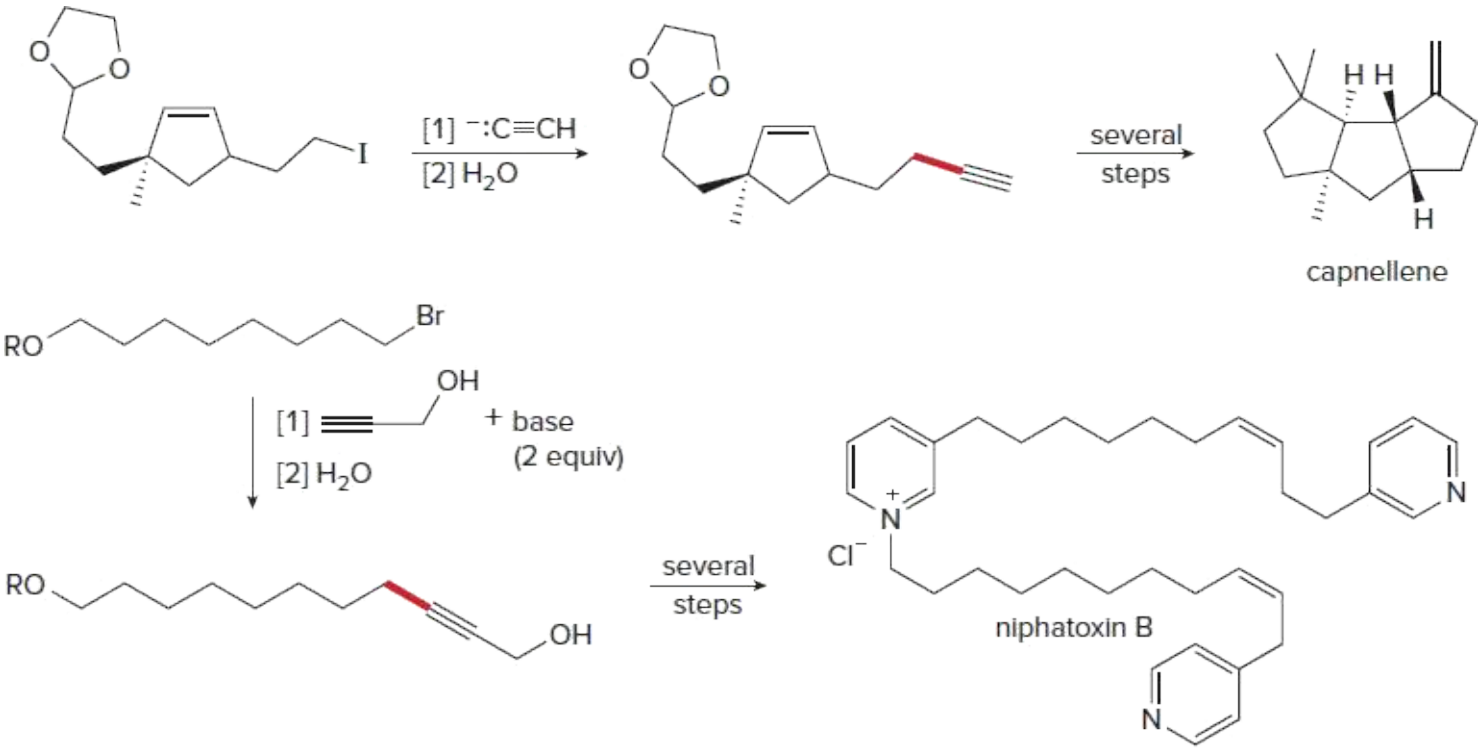
Sample Problem 11.6 illustrates how a seven-carbon product can be prepared from three smaller molecules by forming two new carbon–carbon bonds.



Carbon–carbon bond formation with acetylide anions is a valuable reaction used in the synthesis of numerous natural products. Two examples include capnellene, isolated from the soft coral *Capnella imbricata*, and niphatoxin B, isolated from a red sea sponge, as shown in Figure 11.6.

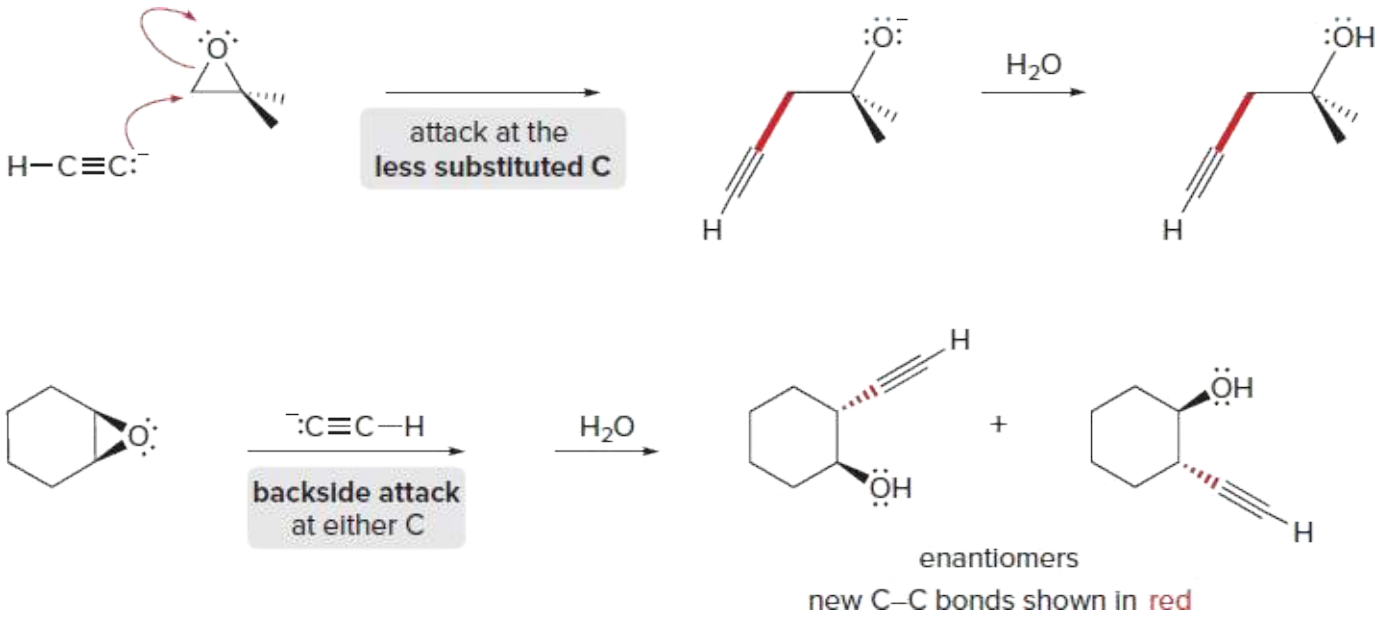


- New carbon–carbon bonds formed from acetylide anions are shown in red.

Figure 11.6 **Use of acetylide anion reactions in the synthesis of two marine natural products**

11.11B Reaction of Acetylide Anions with Epoxides

Acetylide anions are strong nucleophiles that open epoxide rings by an S_N2 mechanism. This reaction also results in the formation of a new carbon–carbon bond. Backside attack occurs at the less substituted end of the epoxide.

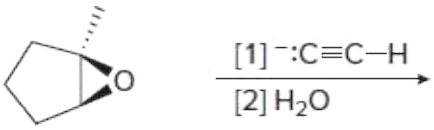


Opening of epoxide rings with strong nucleophiles was first discussed in Section 9.16A.

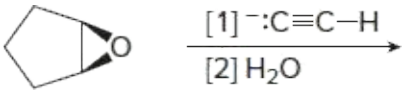
Problem 11.19

Draw the products of each reaction.

a.



b.



Problem 11.20

Draw the products formed when $CH_3CH_2C{\equiv}C\ Na^+$ reacts with each compound.

a. $CH_3CH_2CH_2Br$

b. $(CH_3)_2CHCH_2CH_2Cl$

c. $(CH_3CH_2)_3CCl$

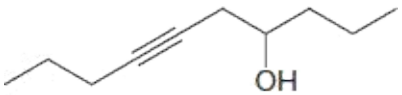
d. $BrCH_2CH_2CH_2CH_2OH$

e. ethylene oxide followed by H_2O

f. propene oxide followed by H_2O

Sample Problem 11.7 Identifying the Acetylide Anion and Epoxide Needed to Synthesize an Alcohol

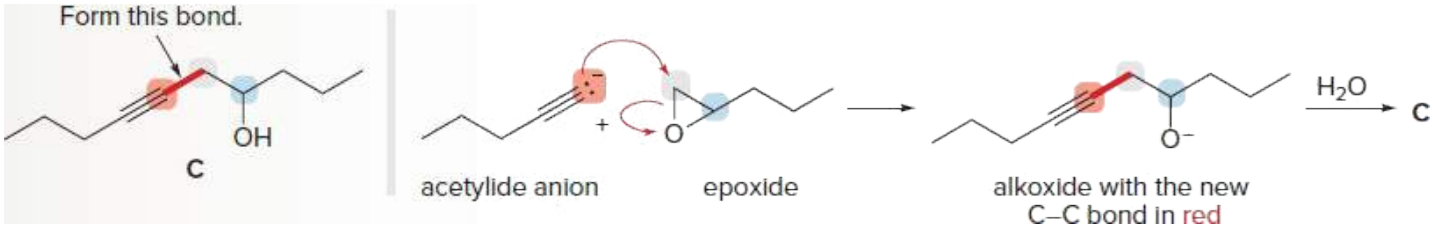
What acetylide anion and epoxide are needed to synthesize C?



C

Solution

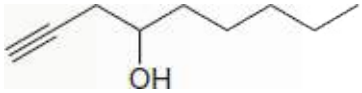
To identify the bond formed when the acetylide anion opens an epoxide ring, locate the carbon bonded to the OH and the adjacent carbon bonded to a C≡C. The new C–C bond results from nucleophilic attack of the acetylide anion with the less substituted end of the epoxide to form an alkoxide that is protonated with water to yield C.



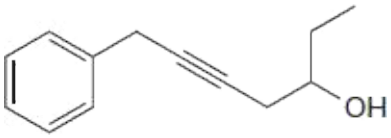
Problem 11.21

What acetylide anion and epoxide are needed to synthesize each compound?

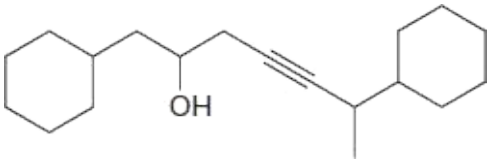
a.



b.



c.



More Practice:

Try Problem 11.47.

11.12 Synthesis

The reactions of acetylide anions give us an opportunity to examine organic synthesis more systematically. Performing a multistep synthesis can be difficult. Not only must you know the reactions for a particular functional group, but you must also put these reactions in a logical order, a process that takes much practice to master.

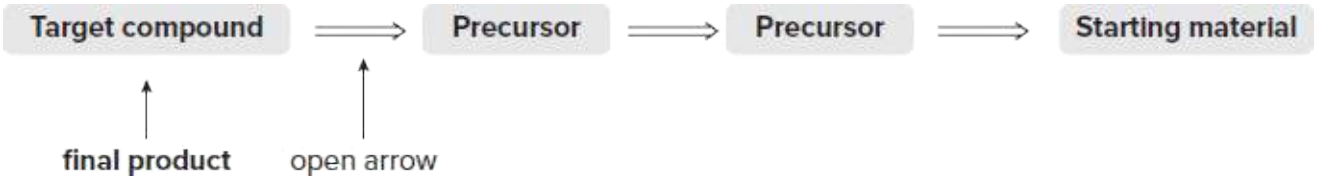
11.12A General Terminology and Conventions

To plan a synthesis of more than one step, we use the process of retrosynthetic analysis—that is, working backwards from the desired product to determine the starting materials from which it is made (Section 10.18). To write a synthesis working backwards from the product to the starting material, an open arrow (⇒) is used to indicate that the product is drawn on the left and the starting material on the right.

Carefully read the directions for each synthesis problem. Sometimes a starting material is specified, whereas at other times you must begin with a compound that meets a particular criterion; for example, you may be asked to synthesize a

compound from alcohols having five or fewer carbon atoms. These limitations are meant to give you some direction in planning a multistep synthesis.

The product of a synthesis is often called the target compound. Using retrosynthetic analysis, we must determine what compound can be converted to the target compound by a single reaction. That is, what is the immediate precursor of the target compound? After an appropriate precursor is identified, this process is continued until we reach a specified starting material. Sometimes multiple retrosynthetic pathways are examined before a particular route is decided upon.



In designing a synthesis, reactions are often divided into two categories:

- **Reactions that form new carbon–carbon bonds.**
- **Reactions that convert one functional group to another—that is, functional group interconversions.**

Appendix F lists the carbon–carbon bond-forming reactions encountered in this text.

Carbon–carbon bond-forming reactions are central to organic synthesis because simpler and less valuable starting materials can be converted to more complex products. Keep in mind that whenever the product of a synthesis has more carbon–carbon bonds than the starting material, the synthesis must contain at least one of these reactions.

How To Develop a Retrosynthetic Analysis

Step [1] Compare the carbon skeletons of the starting material and product.

- **If the product has more carbon–carbon σ bonds than the starting material, the synthesis must form one or more C–C bonds. If not, only functional group interconversion occurs.**
- **Match the carbons in the starting material with those in the product to see where new C–C bonds must be added or where**

functional groups must be changed.

Step [2] Concentrate on the functional groups in the starting material and product and ask:

- What methods introduce the functional groups in the product?
- What kind of reactions does the starting material undergo?

Step [3] Work backwards from the product and forwards from the starting material.

- Ask: What is the immediate precursor of the product?
- Compare each precursor to the starting material to determine if there is a one-step reaction that converts one to the other. Continue this process until the starting material is reached.
- Always generate *simpler* precursors when working backwards.
- Use *fewer* steps when multiple routes are possible.
- Keep in mind that you may need to evaluate several different precursors for a given compound.

Step [4] Check the synthesis by writing it in the synthetic direction.

- To check a retrosynthetic analysis, write out the steps beginning with the starting material, indicating all necessary reagents.

11.12B Examples of Multistep Synthesis

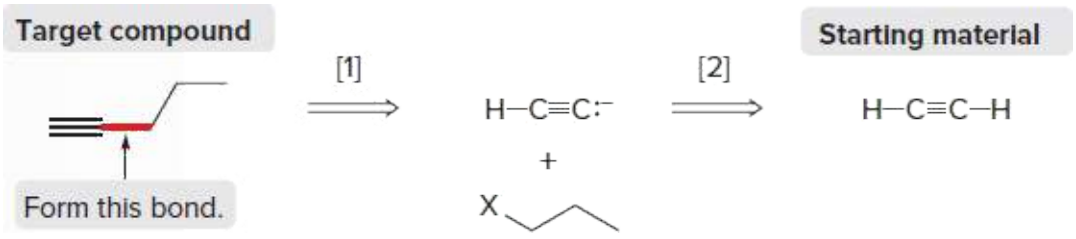
Retrosynthetic analysis with acetylide anions is illustrated in Sample Problems 11.8 and 11.9.

Sample Problem 11.8 Devising a Short Synthesis

Devise a synthesis of $HC{\equiv}CCH_2CH_2CH_3$ from $HC{\equiv}CH$ and any other organic or inorganic reagents.

Retrosynthetic Analysis

The two C's in the starting material match up with the two *sp* hybridized C's in the product, so a three-carbon unit must be added.



Thinking backwards …

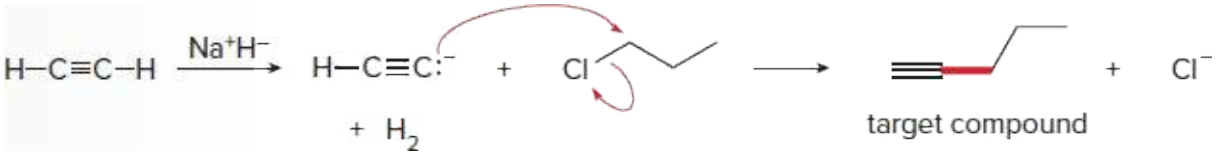
[1] Form a new C–C bond using an acetylide anion and a 1° alkyl halide.

[2] Prepare the acetylide anion from acetylene by treatment with base.

Synthesis

Deprotonation of HC≡CH with NaH forms the acetylide anion, which undergoes S_N2 reaction with an alkyl halide to form the target compound, a five-carbon alkyne.

A two-step process:



Problem 11.22

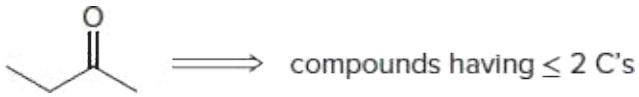
Use retrosynthetic analysis to show how hex-3-yne can be prepared from acetylene and any other organic and inorganic compounds. Then draw the synthesis in the synthetic direction, showing all needed reagents.

More Practice:

Try Problems 11.34d, 11.46a.

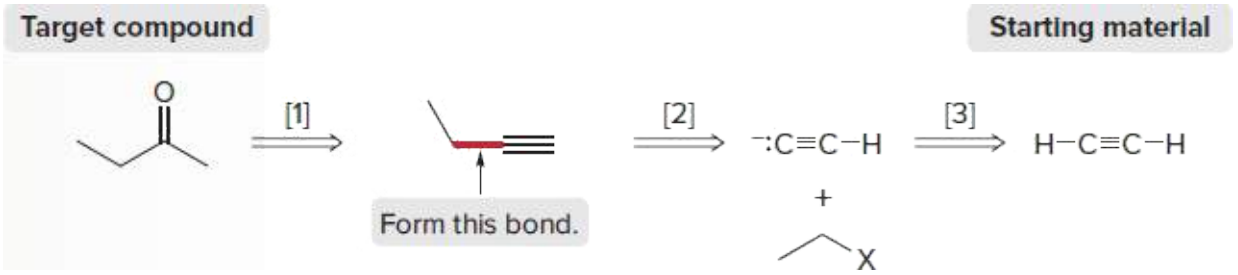
Sample Problem 11.9 Devising a Synthesis with More Than Two Steps

Devise a synthesis of the following compound from starting materials having two or fewer carbons.



Retrosynthetic Analysis

A carbon–carbon bond-forming reaction must be used to convert the two-carbon starting materials to the four-carbon product.



Thinking backwards …

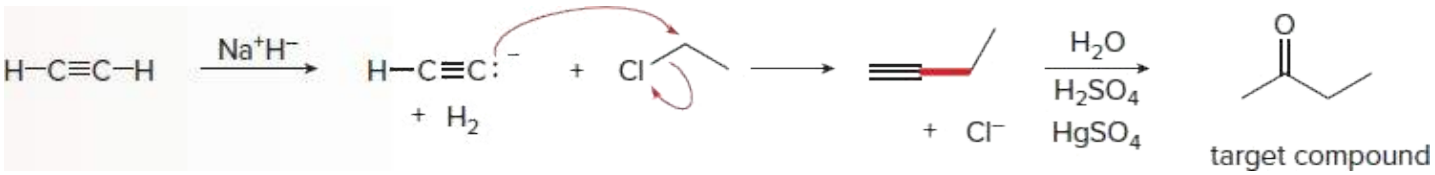
[1] Form the carbonyl group by hydration of a triple bond.

[2] Form a new C–C bond using an acetylide anion and a 1° alkyl halide.

[3] Prepare the acetylide anion from acetylene by treatment with base.

Synthesis

Three steps are needed to complete the synthesis. Treatment of HC=CH with NaH forms the acetylide anion, which undergoes an S_N2 reaction with an alkyl halide to form a four-carbon terminal alkyne. Hydration of the alkyne with H_2O, H_2SO_4, and $HgSO_4$ yields the target compound.



Problem 11.23

Devise a synthesis of $CH_3CH_2CH_2CHO$ from two-carbon starting materials.

More Practice:

Try Problems 11.46b, c; 11.47–11.56.

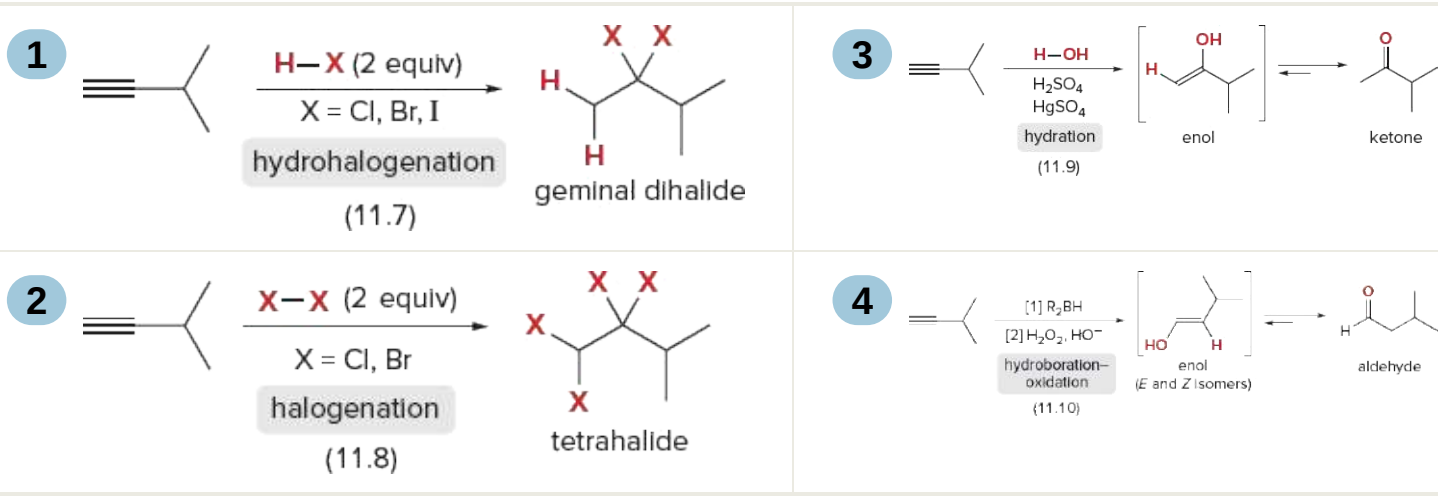
These examples illustrate the synthesis of organic compounds by multistep routes. In Chapter 12, we will learn other useful reactions that expand our capability to do synthesis.

Chapter 11 REVIEW

KEY CONCEPTS

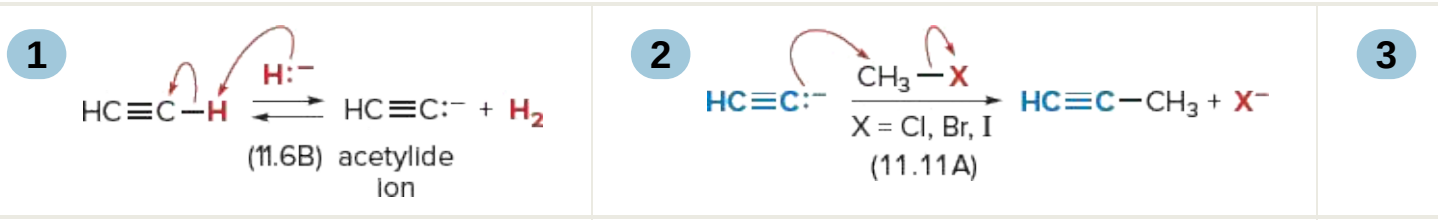
[1] Addition reactions

In each addition, both π bonds of the triple bond are broken, and four new bonds are formed.



See Figure 11.5. Try Problems 11.33a–e; 11.38a, b, d, f.

[2] Reactions involving acetylide anions



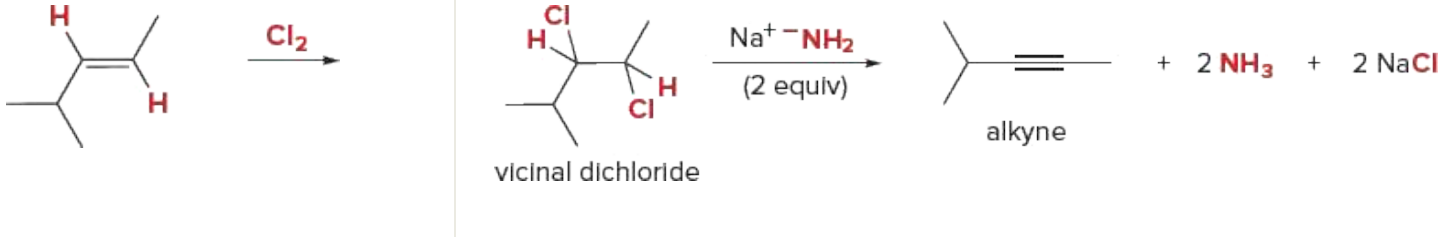
See Table 11.1. Try Problems 11.33f–h; 11.38e, g–j; 11.40; 11.46; 11.47.

KEY SKILLS

[1] Converting an alkene to an alkyne (11.5)

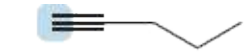
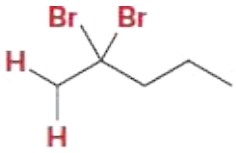
1 **Add halogen (X_2) to an alkene.**

2 **Eliminate two equivalents of HX by treatment wi strong base.**

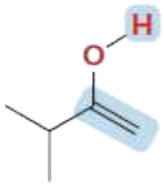
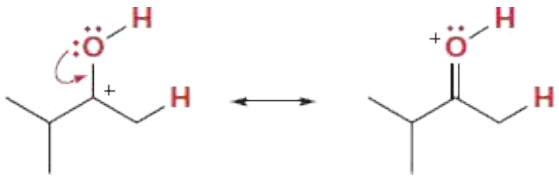
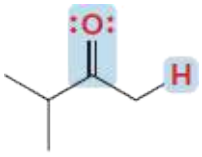


See Sample Problem 11.2. Try Problems 11.38c, 11.49a.

[2] Drawing the product of an addition reaction (11.6–11.10)

1 Use the reagents to identify the two groups added to the C≡C.	2 In an unsymmetrical alkyne, determine the regioselectivity.	3 Draw the product by breaking the π bonds and adding reagents.
H—Br (2 equiv) → (11.7) 2 Br and 2 H are added.	 2 H's end up on the terminal C.	 geminal dibromide

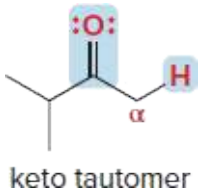
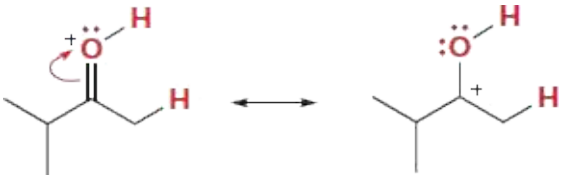
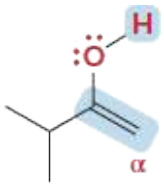
[3] Converting an enol to a keto tautomer in acid (11.9)

1 Locate the C=C and the H atom on the O–H group.	2 Add a proton to the C=C, and draw the two resonance structures.	3 Remove a proton from the OH group.
 enol		 keto tautomer
• An enol tautomer has an O–H group bonded to a C=C.	• The H adds to the C atom that is not attached to the OH group.	• A keto tautomer has a C=O and an additional C–H bond.

See Mechanism 11.2. Try Problem 11.30c, d.

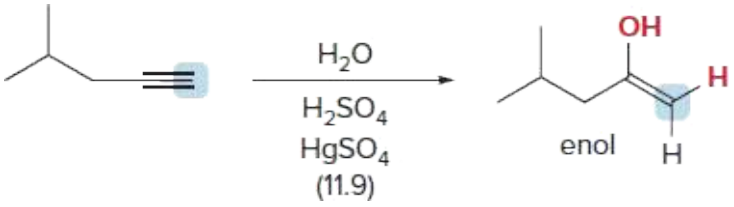
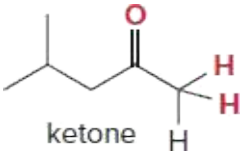
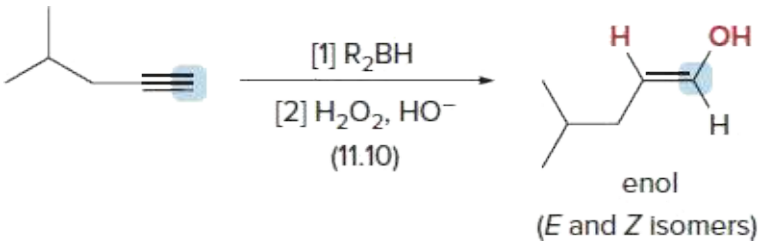
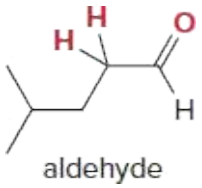
[4] Converting a keto tautomer to an enol in acid (11.9)

1 Locate the C=O and	2 Add a proton to the C=O, and draw the two resonance	3 Remove a proton

the H atom on the a carbon.	**structures.**	**from the a carbon, and draw the C=C.**
 keto tautomer		 enol

Try Problem 11.30a, b.

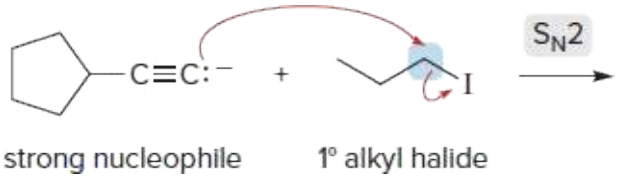
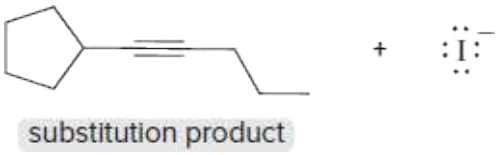
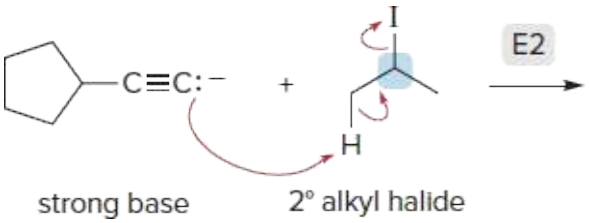
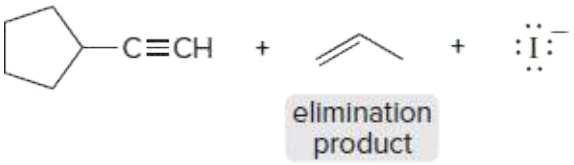
[5] Comparing the products of hydration of an alkyne (11.9, 11.10)

1 Use the reagents to determine the regioselectivity, and add H_2O to form the enol.	**2** Convert the enol to its keto tautomer.
 • H bonds to the terminal C.	 • Addition of H_2O using H_2O, H_2SO_4, and $HgSO_4$ forms methyl ketones from terminal alkynes.
 • OH bonds to the terminal C.	 • Addition of H_2O using hydroboration–oxidation forms aldehydes from

terminal alkynes.

See Sample Problems 11.3, 11.4. Try Problems 11.33d, e; 11.38d, f.

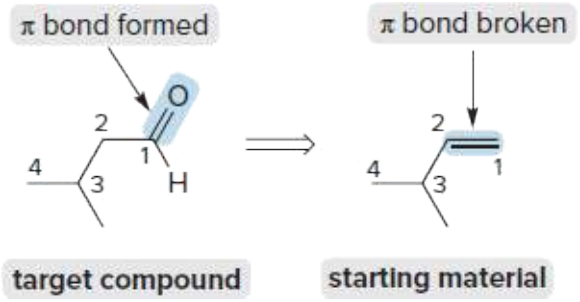
[6] Comparing reactions of acetylide anions (11.11)

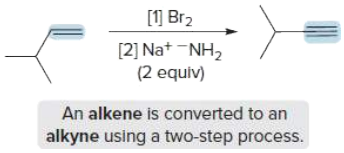
1 Classify the alkyl halide.	2 Draw the products.
	
• 1° Alkyl halides undergo S_N2 reactions. • With a 1° alkyl halide, the acetylide anion acts as a strong nucleophile.	
	
• Alkyl halides that are 2° and 3° undergo E2 reactions. • With a 2° alkyl halide, the acetylide anion acts as a strong base.	

See Sample Problem 11.5. Try Problems 11.33g; 11.38g, i; 11.40a, b.

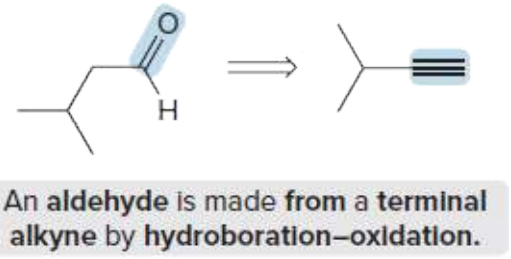
[7] Devising a synthesis (11.12); example: $(CH_3)_2CHCH_2CHO$ from $(CH_3)_2CHCH{=}CH_2$

1 Compare the carbon skeletons and functional groups.	3 Work forwards.

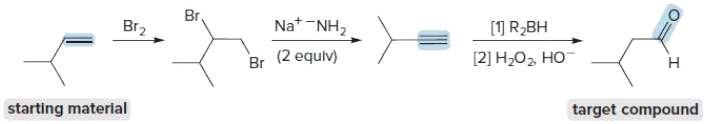




2 **Work backwards.**



4 **Complete the synthesis.**



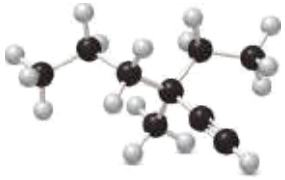
See *How To*, p. 461; Sample Problems 11.8, 11.9. Try Problems 11.46–11.56.

PROBLEMS

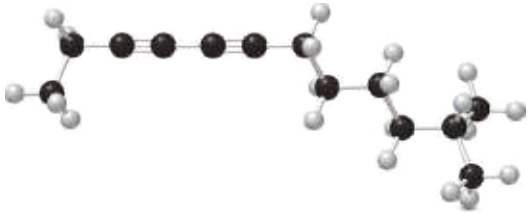
Problems Using Three-Dimensional Models

11.24 **Give the IUPAC name for each compound.**

a.



b.



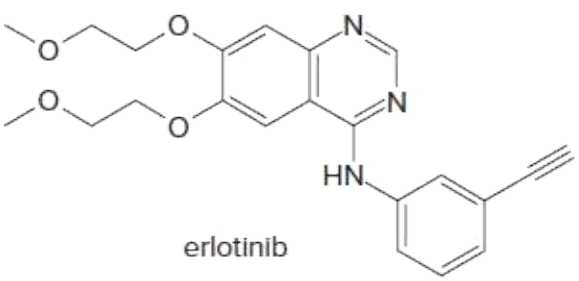
11.25 **Draw the enol tautomer of (a) and the keto tautomer of (b).**

a.

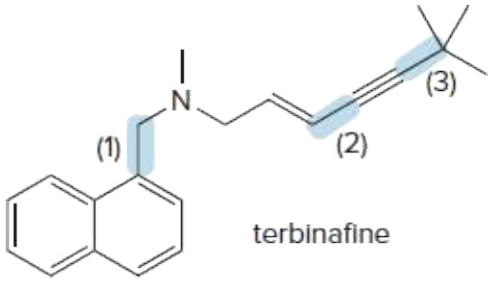
b.

Structure and Nomenclature

11.26 **Answer the following questions about erlotinib and terbinafine. Erlotinib, sold under the trade name Tarceva, was introduced in 2004 for the treatment of lung cancer. Terbinafine is an antifungal medication used to treat ringworm and fungal nail infections.**



erlotinib



terbinafine

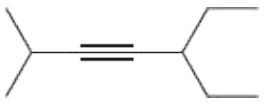
a. Which C–H bond in erlotinib is most acidic?

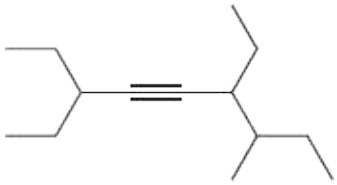
b. What orbitals are used to form the shortest C–C single bond in erlotinib?

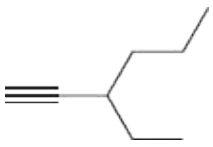
c. Rank the labeled bonds in terbinafine in order of increasing bond strength.

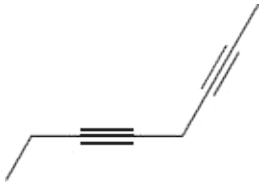
d. Draw two additional resonance structures for terbinafine that contain all uncharged atoms.

11.27 **Give the IUPAC name for each alkyne.**

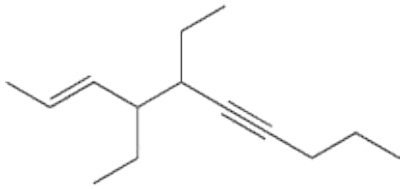
a. 

b. 

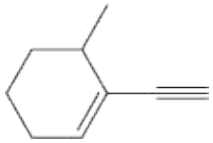
c. 

d. 

e.



f.



11.28 Give the structure corresponding to each name.

a. 5,6-dimethylhept-2-yne

b. 5-*tert*-butyl-6,6-dimethylnon-3-yne

c. (*S*)-4-chloropent-2-yne

d. *cis*-1-ethynyl-2-methylcyclopentane

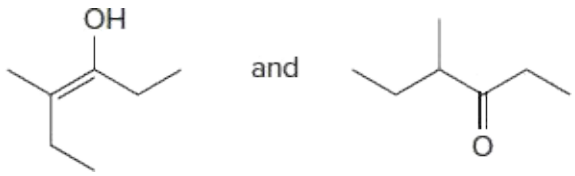
e. 3,4-dimethylocta-1,5-diyne

f. (*Z*)-6-methyloct-6-en-1-yne

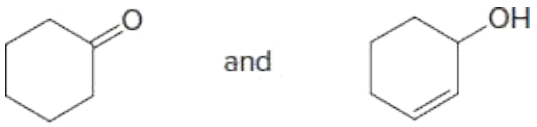
Tautomers

11.29 Label each pair of compounds as keto–enol tautomers or constitutional isomers, but not tautomers.

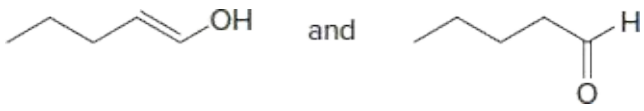
a.



b.



c.



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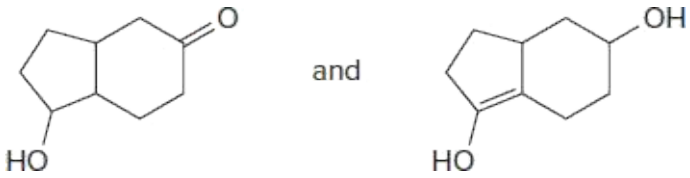
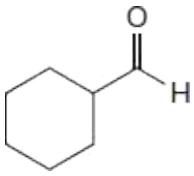
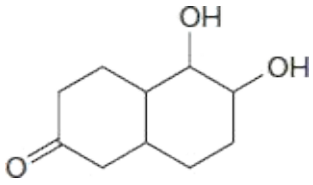


11.30 Draw the enol form of each keto tautomer in parts (a) and (b), and the keto form of each enol tautomer in parts (c) and (d).

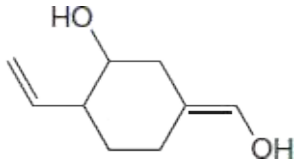
a.



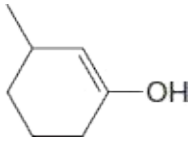
b.



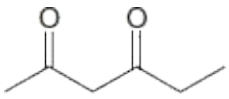
c.



d.

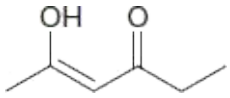


11.31 How is each compound related to A? Choose from tautomers, constitutional isomers but not tautomers, or neither.

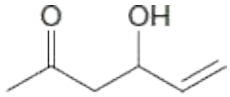


A

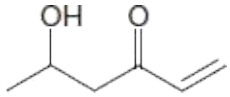
a.



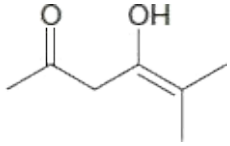
b.



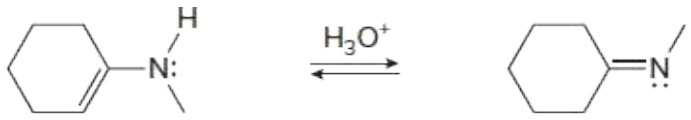
c.



d.



11.32 Enamines and imines are tautomers that contain N atoms. Draw a stepwise mechanism for the acid-catalyzed conversion of enamine X to imine Y.



X
enamine

Y
imine

Reactions

11.33 **Draw the products formed when hex-1-yne is treated with each reagent.**

a. **HCl (2 equiv)**

b. **HBr (2 equiv)**

c. **Cl2 (2 equiv)**

d. **H2O + H_2SO_4 + $HgSO_4$**

e. **[1] R_2BH; [2] H_2O_2, HO^-**

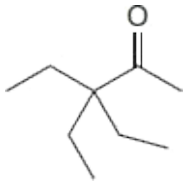
f. **NaH**

g. **[1] $^-NH_2$; [2] CH_3CH_2Br**

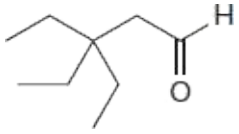
h. [1] $^-NH_2$; [2] ; [3] H_2O

11.34 **What reagents are needed to convert $(CH_3CH_2)_3CC{=}CH$ to each compound?**

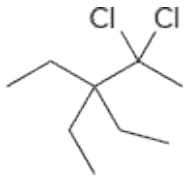
a.



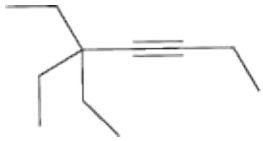
b.



c.



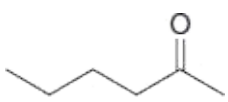
d.



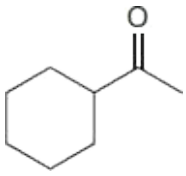
11.35 **Explain the apparent paradox: Although the addition of one equivalent of HX to an alkyne is more exothermic than the addition of HX to an alkene, an alkene reacts faster with HX.**

11.36 **What alkynes give each of the following ketones as the only product after hydration with H_2O, H_2SO_4, and $HgSO_4$?**

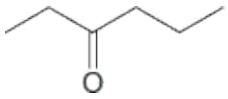
a.



b.

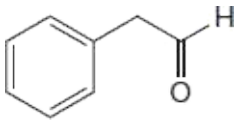


c.

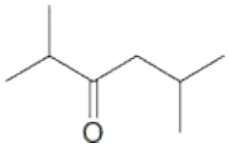


11.37 What alkyne gives each compound as the only product after hydroboration-oxidation?

a.

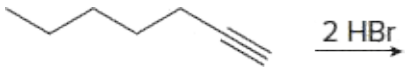


b.

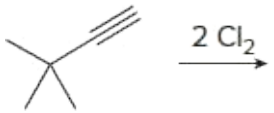


11.38 Draw the organic products formed in each reaction.

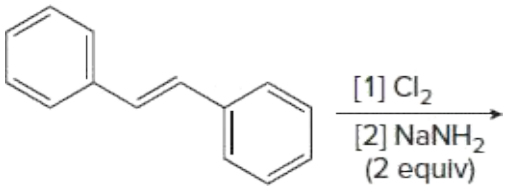
a.



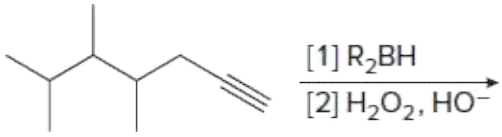
b.



c.

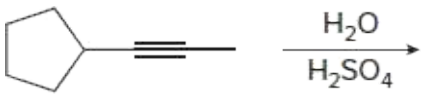


d.

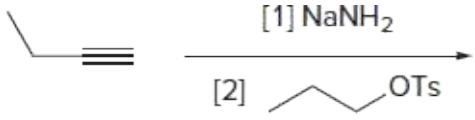


e. $HC{\equiv}C^- + D_2O \longrightarrow$

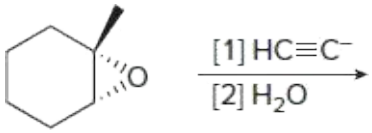
f.



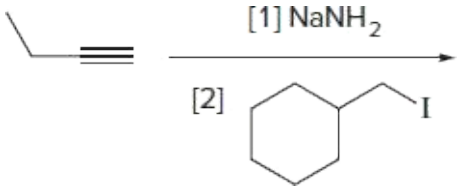
g.



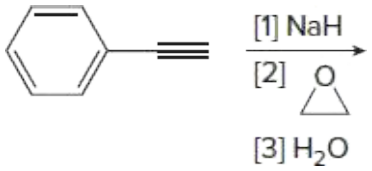
h.



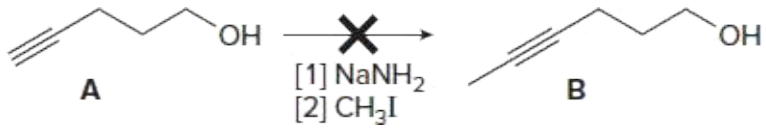
i.



j.

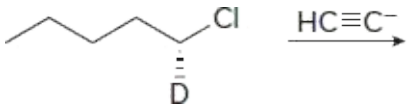


11.39 When alkyne A is treated with $NaNH_2$ followed by CH_3I, a product having molecular formula $C_6H_{10}O$ is formed, but it is *not* compound B. What is the structure of the product, and why is it formed?

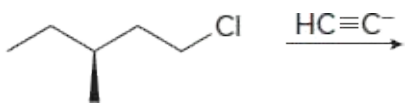


11.40 Draw the products formed in each reaction and indicate stereochemistry.

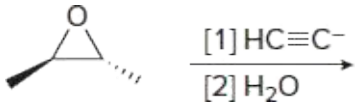
a.



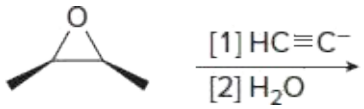
b.



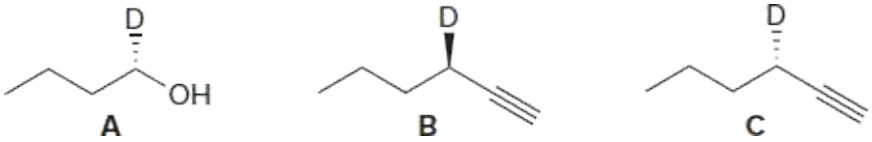
c.



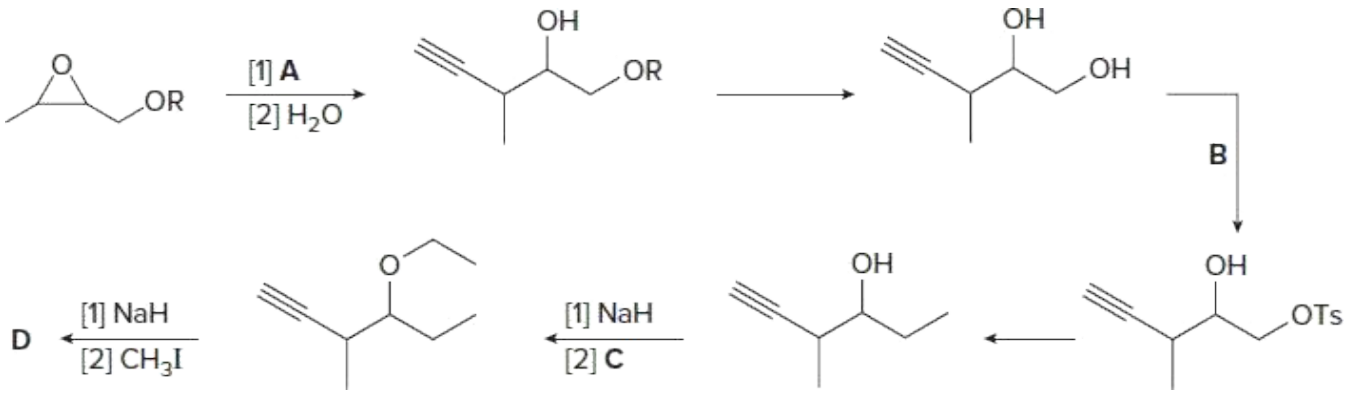
d.



11.41 What reactions are needed to convert alcohol A to either alkyne B or alkyne C?

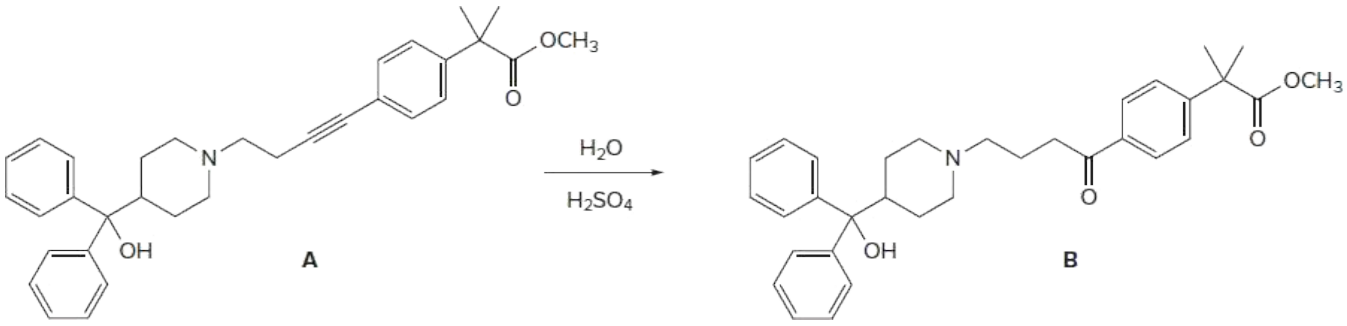


11.42 Identify the lettered compounds in the following reaction scheme.

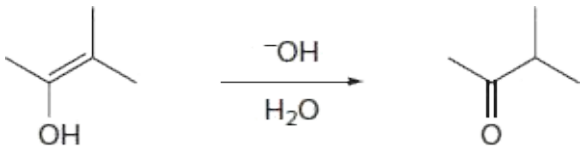


Mechanisms

11.43 One step in the synthesis of the antihistamine fexofenadine (Section 23.5) involves acid-catalyzed hydration of the triple bond in A. Draw a stepwise mechanism for this reaction and explain why only ketone B is formed.



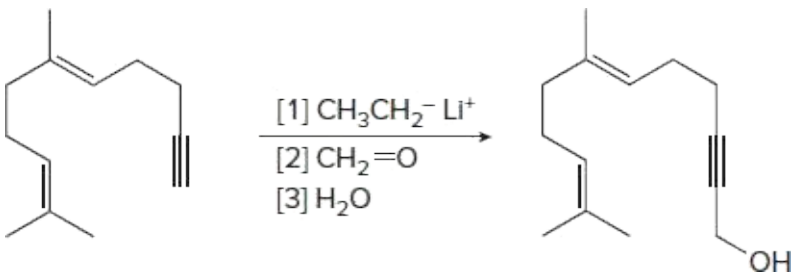
11.44 Tautomerization in base resembles tautomerization in acid, but deprotonation precedes protonation in the two-step mechanism. (a) Draw a stepwise mechanism for the following tautomerization. (b) Then draw a stepwise mechanism for the reverse reaction, the conversion of the keto form to the enol.

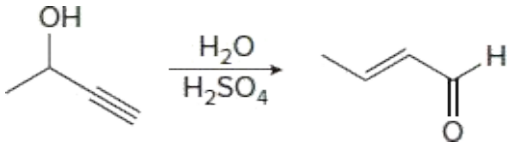


enol form keto form

11.45 Draw a stepwise mechanism for each reaction.

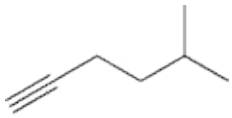
a.

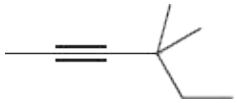


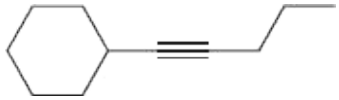
b. 

Synthesis

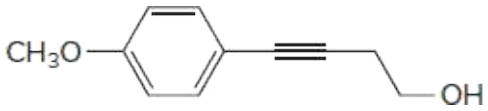
11.46 What acetylide anion and alkyl halide are needed to synthesize each alkyne?

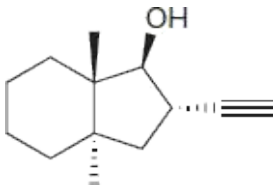
a. 

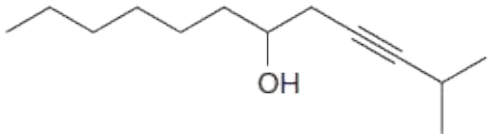
b. 

c. 

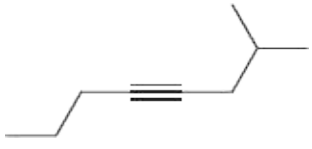
11.47 What acetylide anion and epoxide are needed to synthesize each compound?

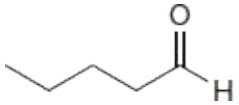
a. 

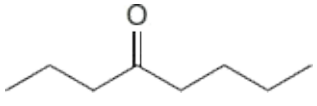
b. 

c. 

11.48 Synthesize each compound from acetylene. You may use any other organic or inorganic reagents.

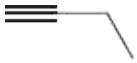
a. 

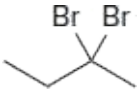
b. 

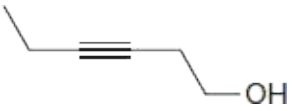
c. 

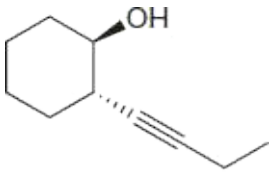
11.49 Devise a synthesis of each compound using $CH_3CH_2CH{=}CH_2$ as the

starting material. You may use any other organic compounds or inorganic reagents.

a. 

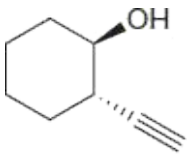
b. 

c. 

d. 

(+ enantiomer)

11.50 Devise a synthesis of the following compound from cyclohexene and acetylene. You may use any other inorganic reagents.

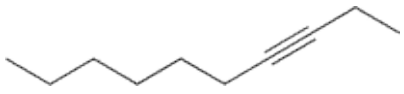


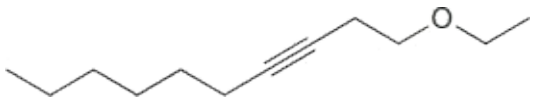
+ enantiomer

11.51 Devise a synthesis of alkyne Y from alkyl bromide X, CH3I, and any needed reagents.

Y X

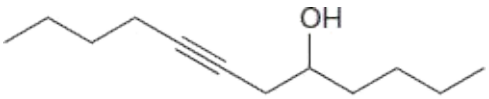
11.52 Devise a synthesis of each compound. You may use HC=CH, ethylene oxide, and alkyl halides as organic starting materials and any inorganic reagents.

a. 

b. 

11.53 Devise a synthesis of the ketone hexan-3-one, $CH_3CH_2COCH_2CH_2CH_3$, from CH_3CH_2Br as the only organic starting material; that is, all the carbon atoms in hexan-3-one must come from CH_3CH_2Br. You may use any other needed reagents.

11.54 **Devise a synthesis of dodec-7-yn-5-ol from hex-1-ene ($CH_3CH_2CH_2CH_2CH{=}CH_2$) as the only organic starting material. You may use any other needed reagents.**



dodec-7-yn-5-ol

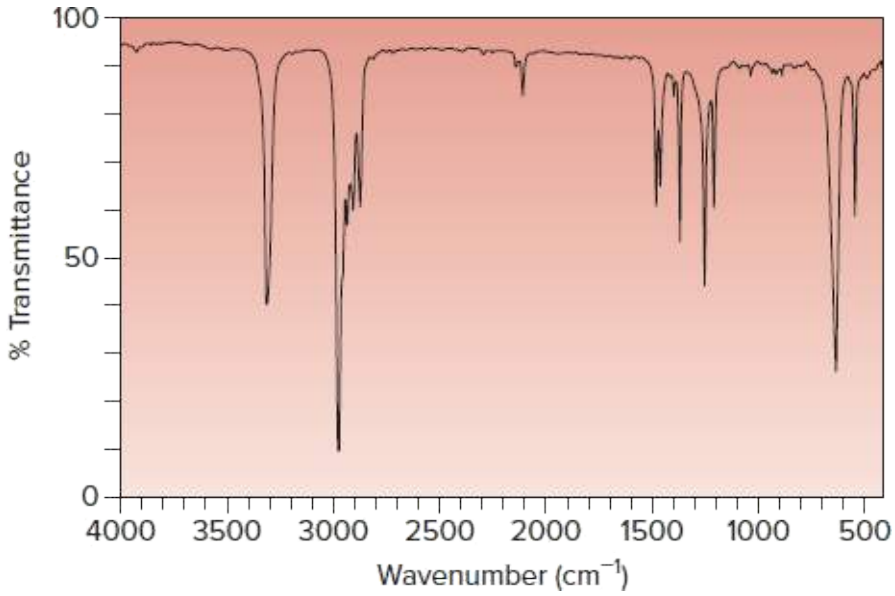
11.55 **Devise a synthesis of each compound using $CH_3CH_2CH_2OH$ as the only organic starting material: (a) $CH_3C{\equiv}CCH_2CH_2CH_3$; (b) $CH_3C{\equiv}CCH_2CH(OH)CH_3$. You may use any other needed inorganic reagents.**

11.56 **Devise a synthesis of $CH_3CH_2C{\equiv}CCH_2CH_2OH$ from CH_3CH_2OH as the only organic starting material. You may use any other needed reagents.**

Spectroscopy

Problem 11.57 is intended for students who have already learned about spectroscopy in Chapters A–C.

11.57 **Compound Y (molecular formula C_6H_{10}) gives four lines in its ^{13}C NMR spectrum (27, 30, 67, and 93 ppm) and the IR spectrum given here. Propose a structure for Y.**



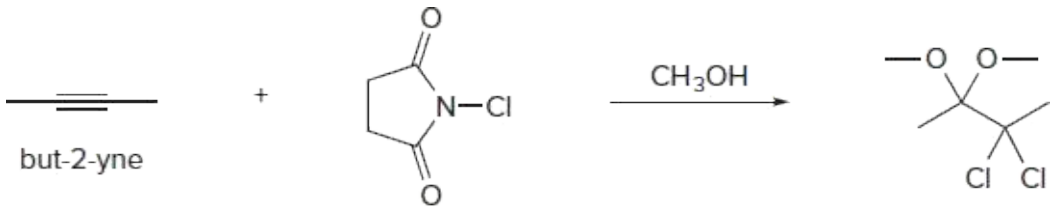
Additional spectroscopy problems on alkynes are given in Chapters B and C:

- **Infrared spectroscopy: B.4a; B.5; B.16a; B.19a; B.21a, d; B.29**
- **Nuclear magnetic resonance spectroscopy: C.12a**

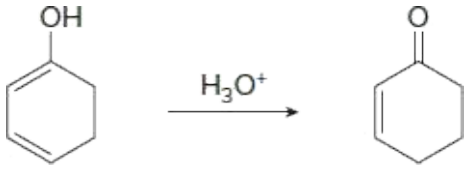
Challenge Problems

11.58 **Explain why the C=C of an enol is more nucleophilic than the C=C of an alkene, despite the fact that the electronegative oxygen atom of the enol inductively withdraws electron density from the carbon–carbon double bond.**

11.59 **N-Chlorosuccinimide (NCS) serves as a source of Cl^+ in electrophilic addition reactions to alkenes and alkynes. Keeping this in mind, draw a stepwise mechanism for the following addition to but-2-yne.**

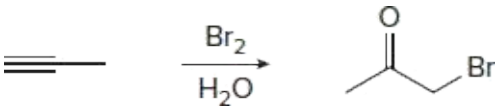


11.60 **Draw a stepwise mechanism for the following reaction.**

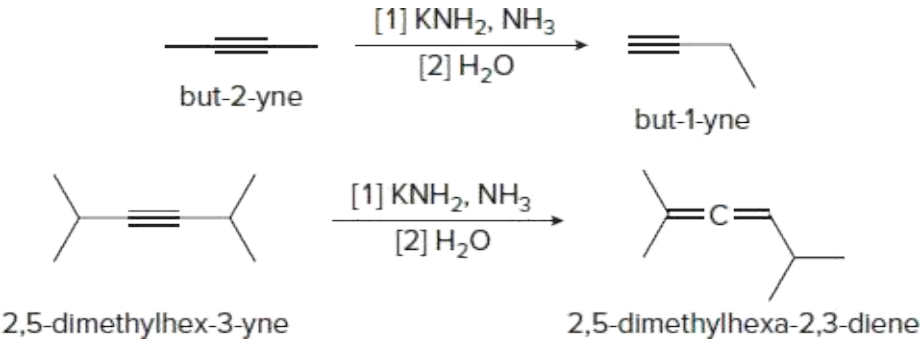


Page 471

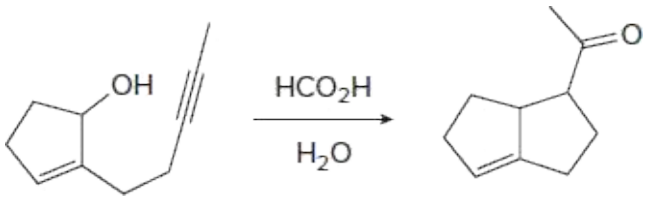
11.61 **Draw a stepwise mechanism for the following reaction.**



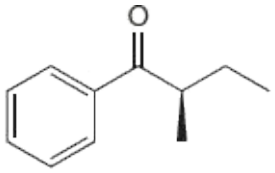
11.62 **Write a stepwise mechanism for each of the following reactions. Explain why a more stable alkyne (but-2-yne) is isomerized to a less stable alkyne (but-1-yne), but under similar conditions, 2,5-dimethylhex-3-yne forms 2,5-dimethylhexa-2,3-diene.**



11.63 **Draw a stepwise mechanism for the following intramolecular reaction.**



11.64 Explain why an optically active solution of (*R*)-α-methylbutyrophenone loses its optical activity when dilute acid is added to the solution.



(*R*)-α-methylbutyrophenone

12 Oxidation and Reduction

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12.1 Introduction

12.2 Reducing agents

12.3 Reduction of alkenes

12.4 Application: Hydrogenation of oils

12.5 Reduction of alkynes

12.6 The reduction of polar C—X σ bonds

12.7 Oxidizing agents

12.8 Epoxidation

12.9 Dihydroxylation

12.10 Oxidative cleavage of alkenes
12.11 Oxidative cleavage of alkynes
12.12 Oxidation of alcohols
12.13 Green chemistry
12.14 Biological oxidation
12.15 Sharpless epoxidation

Soybean oil is rich in oleic and linoleic acids, two unsaturated fatty acids. When a vegetable oil containing unsaturated fatty acids is treated with hydrogen, some or all of the π bonds add hydrogen, decreasing the number of degrees of unsaturation and increasing the melting point. Adding hydrogen to an alkene is a reduction reaction that increases the number of carbon-hydrogen bonds in the product. In Chapter 12, we learn about oxidation and reduction reactions of alkenes and several other functional groups.

Why Study…

Oxidation and Reduction?

In Chapter 12, we discuss the oxidation and reduction of alkenes and alkynes, as well as compounds with polar C—X σ bonds—alcohols, alkyl halides, and epoxides. Although there will be many different reagents and mechanisms, discussing these reactions as a group allows us to more easily compare and contrast them.

The word *mechanism* will often be used loosely here. In contrast to the S_N1 reaction of alkyl halides or the electrophilic addition reactions of alkenes, the details of some of the mechanisms presented in Chapter 12 are known with less certainty. For example, although the identity of a particular intermediate might be confirmed by experiment, other details of the mechanism are suggested by the structure or stereochemistry of the final product.

Oxidation and reduction reactions are very versatile, and knowing them allows us to design many more complex organic syntheses.

12.1 Introduction

Recall from Section 4.14 that the way to determine whether an organic compound has been oxidized or reduced is to compare the relative number of C—H and C—Z bonds (Z = an element *more electronegative* than carbon) in the starting material and product.

Two components are always present in an oxidation or reduction reaction—one component is oxidized and one is reduced. When an organic compound is *oxidized* by a reagent, the reagent itself must be *reduced*. Similarly, when an organic compound is *reduced* by a reagent, the reagent becomes *oxidized*.

- ***Oxidation* results in an *increase* in the number of C—Z bonds (usually C—O bonds) *or* a *decrease* in the number of C—H bonds.**
- ***Reduction* results in a *decrease* in the number of C—Z bonds (usually C—O bonds) *or* an *increase* in the number of C—H bonds.**

Thus, an organic compound such as CH_4 can be oxidized by replacing C—H bonds with C—O bonds, as shown in Figure 12.1. Reduction is the opposite of oxidation, so Figure 12.1 also shows how a compound can be reduced by replacing C—O bonds with C—H bonds. The symbols [O] and [H] indicate oxidation and reduction, respectively.

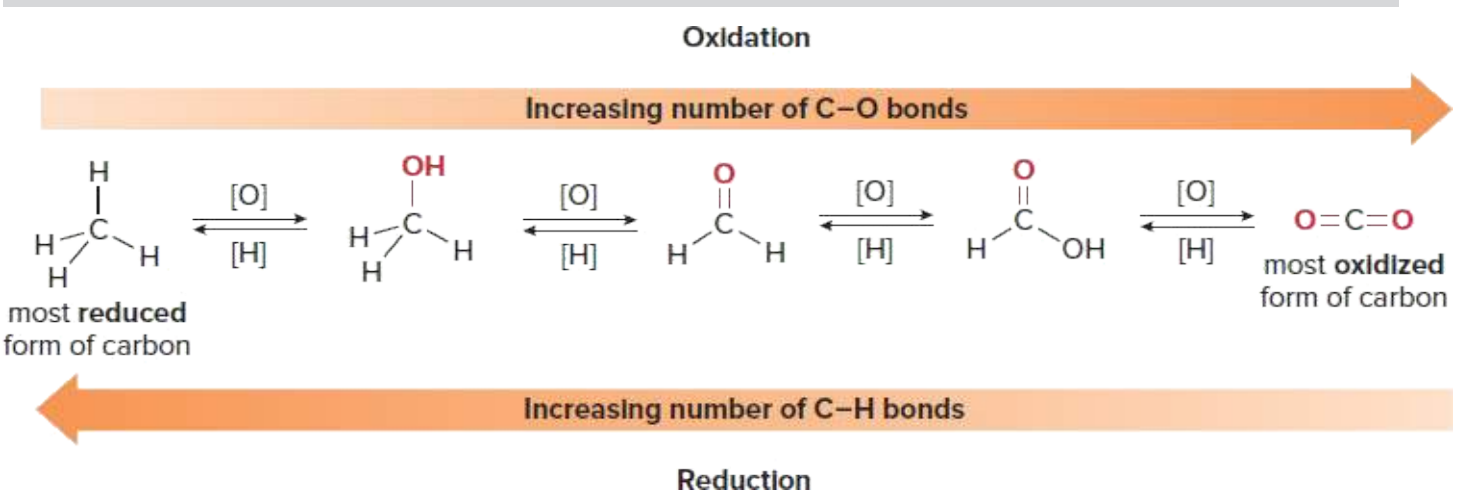


Figure 12.1 **A general scheme for the oxidation and reduction of a carbon compound**

Sometimes two carbon atoms are involved in a single oxidation or reduction reaction, and the net change in the number of C—H or C—Z bonds at *both* atoms must be taken into account. The conversion of an alkyne to an alkene and an alkene to an alkane are examples of reduction, because each process adds two new C—H bonds to the starting

material, as shown in Figure 12.2.

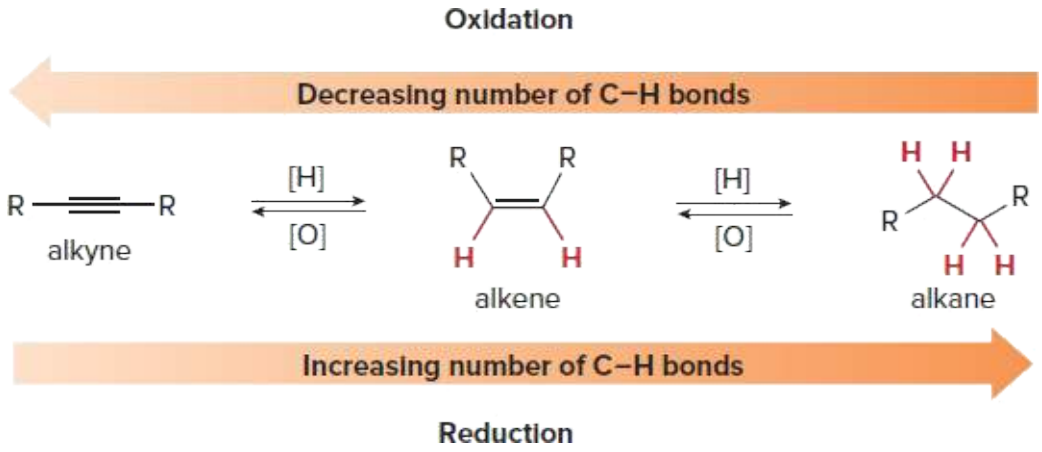


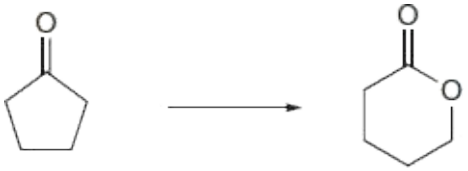
Figure 12.2 **Oxidation and reduction of hydrocarbons**

Problem 12.1

Classify each reaction as oxidation, reduction, or neither.

a.

b.



c.

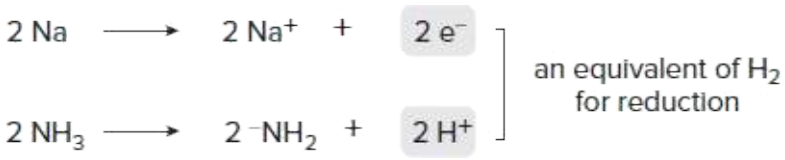
d.

12.2 Reducing Agents

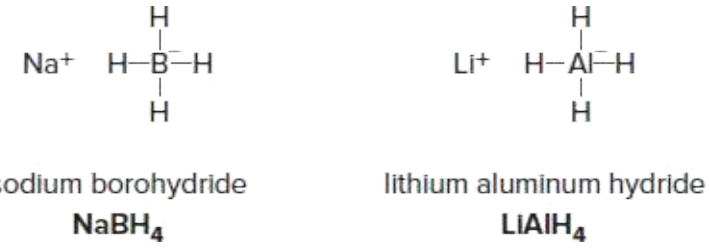
Reducing agents provide the equivalent of two hydrogen atoms, but there are three types of reductions, differing in how H_2 is added. The simplest reducing agent is molecular H_2. Reductions of this sort are carried out in the presence of a metal catalyst that acts as a surface on which the reaction occurs.

The second way to deliver H_2 in a reduction is to add two protons and two electrons to a substrate—that is, $H_2 = 2\ H^+ + 2\ e^-$. Reducing agents of this sort use alkali metals as

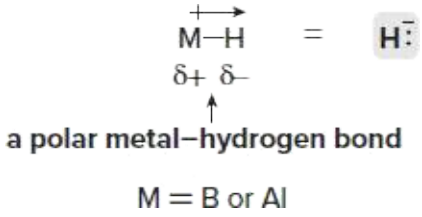
a source of electrons and liquid ammonia (NH_3) as a source of protons. Reductions with Na in NH_3 are called dissolving metal reductions.



The third way to deliver the equivalent of two hydrogen atoms is to add hydride (H^-) and a proton (H^+). The most common hydride reducing agents contain a hydrogen atom bonded to boron or aluminum. Simple examples include sodium borohydride ($NaBH_4$) and lithium aluminum hydride ($LiAlH_4$). These reagents deliver H^- to a substrate, and then a proton is added from H_2O or an alcohol.

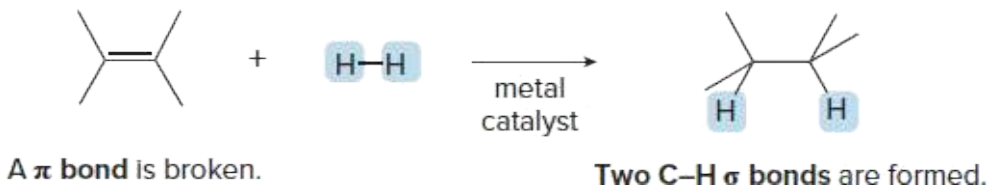


- **Metal hydride reagents act as a source of H^- because they contain polar metal–hydrogen bonds that place a partial negative charge on hydrogen.**



12.3 Reduction of Alkenes

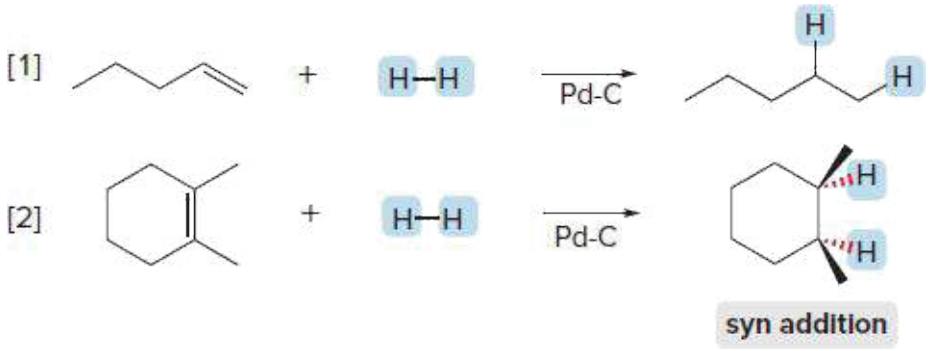
Reduction of an alkene forms an alkane by addition of H_2. Two bonds are broken—the weak π bond of the alkene and the H_2 σ bond—and two new C—H σ bonds are formed.



Hydrogenation catalysts are insoluble in common solvents, thus creating a heterogeneous reaction mixture. This

insolubility has a practical advantage.

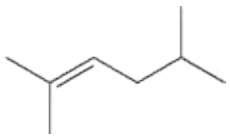
These catalysts contain expensive metals, but they can be filtered away from the other reactants after the reaction is complete, and then reused. The addition of H_2 occurs only in the presence of a metal catalyst, and thus, the reaction is called catalytic hydrogenation. The catalyst consists of a metal—usually Pd, Pt, or Ni—adsorbed onto a finely divided inert solid, such as charcoal. For example, the catalyst 10% Pd on carbon is composed of 10% Pd and 90% carbon, by weight. H_2 adds in a syn fashion, as shown in Equation [2].



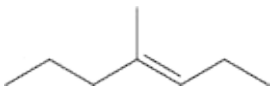
Problem 12.2

What alkane is formed when each alkene is treated with H_2 and a Pd catalyst?

a.



b.



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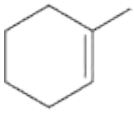
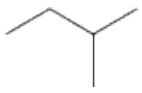


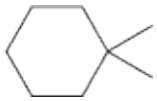
Problem 12.3

Draw all alkenes that react with one equivalent of H_2 in the presence of a palladium catalyst to form each alkane. Consider constitutional isomers only.

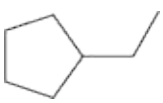
a.



b.



c.

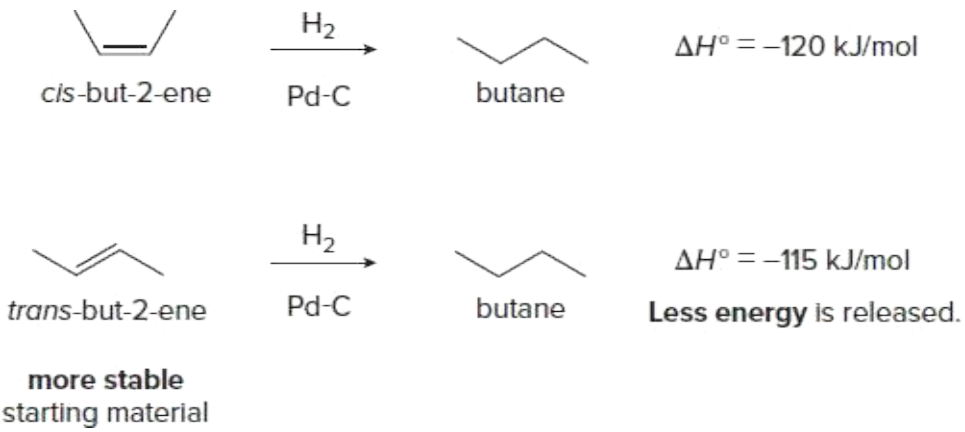


12.3A Hydrogenation and Alkene Stability

Hydrogenation reactions are exothermic because the bonds in the product are stronger than the bonds in the starting materials, making them similar to other alkene addition reactions. The ΔH° for hydrogenation, called the heat of hydrogenation, can be used as a measure of the relative stability of two different alkenes that are hydrogenated to the same alkane.

Recall from Chapter 8 that trans alkenes are generally more stable than cis alkenes.

For example, both *cis*- and *trans*-but-2-ene are hydrogenated to butane, and the heat of hydrogenation for the trans isomer is less than that for the cis isomer. Because less energy is released in converting the trans alkene to butane, it must be *lower* in energy (more stable) to begin with. The relative energies of the butene isomers are illustrated in Figure 12.3.



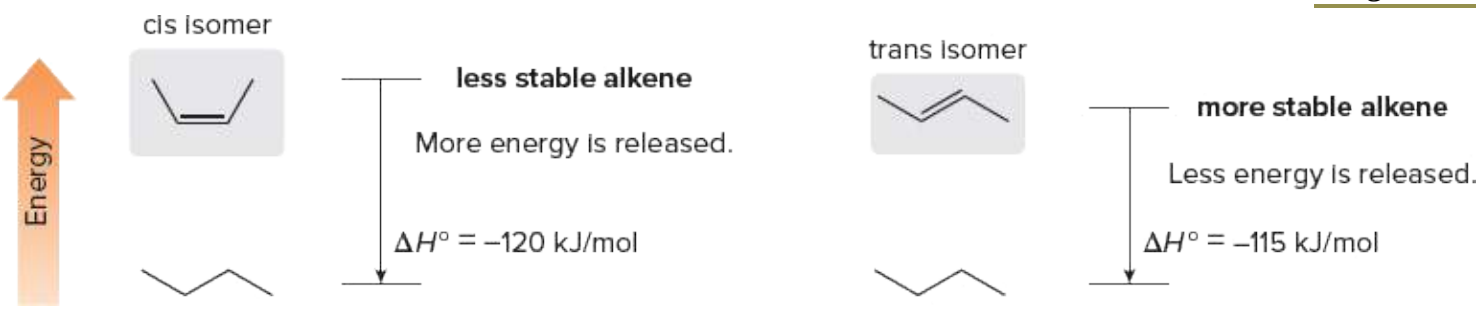
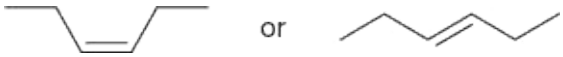


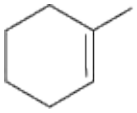
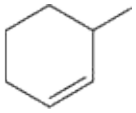
Figure 12.3 **Relative energies of *cis*- and *trans*-but-2-ene**

- **When hydrogenation of two alkenes gives the same alkane, the more stable alkene has the *smaller* heat of hydrogenation.**

Problem 12.4

Which alkene in each pair has the larger heat of hydrogenation?

a.  or

b.  or 

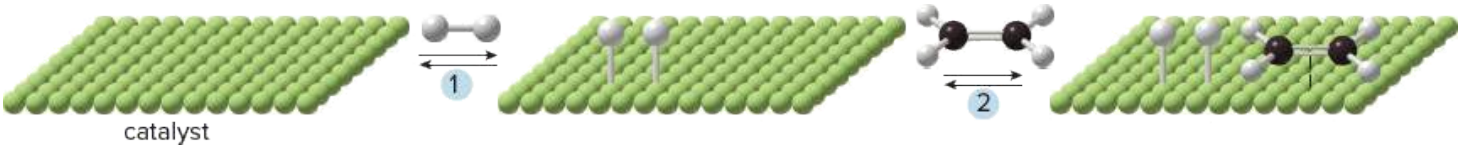
Problem 12.5

Explain why heats of hydrogenation cannot be used to determine the relative stability of 2-methylpent-2-ene and 3-methylpent-1-ene.

12.3B The Mechanism of Catalytic Hydrogenation

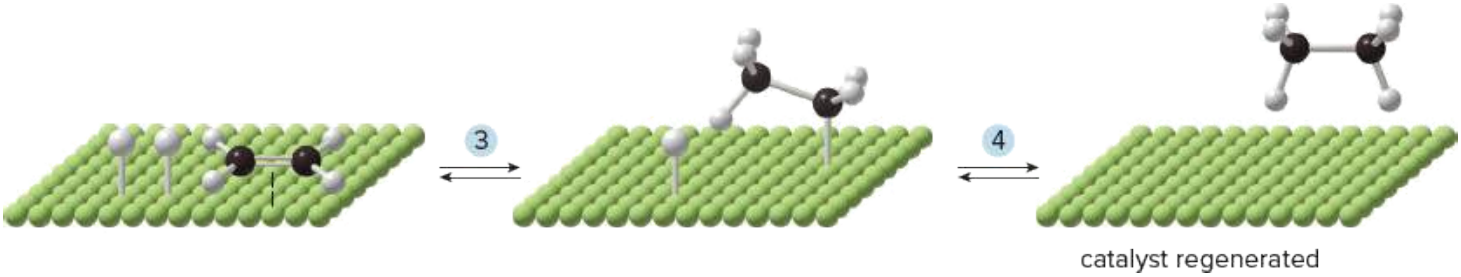
In the generally accepted mechanism for catalytic hydrogenation, the surface of the metal catalyst binds both H_2 and the alkene, and H_2 is transferred to the π bond in a rapid but stepwise process (Mechanism 12.1).

Mechanism 12.1 Addition of H_2 to an Alkene—Hydrogenation



1 **H_2 adsorbs to the catalyst surface with partial or complete cleavage of the H—H bond.**

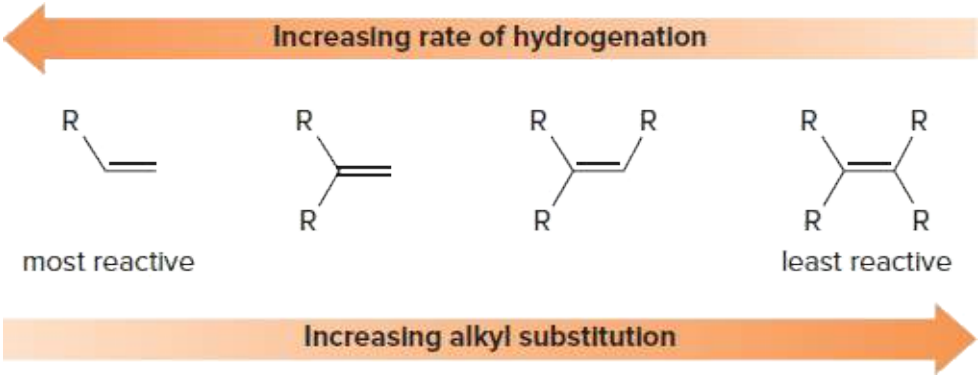
2 **The π bond of the alkene complexes with the metal.**



3–**4** **Two H atoms are transferred sequentially to the π bond in Steps [3] and [4], forming the alkane. Because the product alkane no longer has a π bond with which to complex to the metal, it is released from the catalyst surface.**

The mechanism explains two facts about hydrogenation:

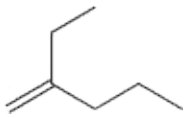
- **Rapid, sequential addition of H_2 occurs from the side of the alkene complexed to the metal surface, resulting in syn addition.**
- **Less crowded double bonds complex more readily to the catalyst surface, resulting in *faster* reaction.**



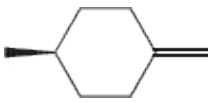
Problem 12.6

Given that syn addition of H_2 occurs from both sides of a trigonal planar double bond, draw all stereoisomers formed when each compound is treated with H_2.

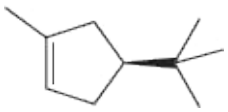
a.



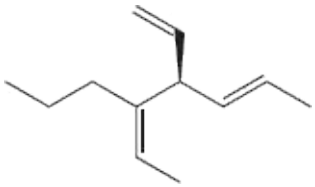
b.



c.



d.



12.3C Hydrogenation Data and Degrees of Unsaturation

Recall from Section 10.2 that the number of degrees of unsaturation gives the *total* number of rings and π bonds in a molecule. Because H_2 adds to π bonds but does *not* add to the C—C σ bonds of rings, hydrogenation allows us to determine how many degrees of unsaturation are due to π bonds and how many are due to rings. This is done by comparing the number of degrees of unsaturation before and after a molecule is treated with H_2, as illustrated in Sample Problem 12.1.

Sample Problem 12.1 Using Hydrogenation Data to Determine the Number of Rings and π Bonds in a Molecule

How many rings and π bonds are contained in a compound of molecular formula C_8H_{12} that is hydrogenated to a compound of molecular formula C_8H_{14}?

Solution

[1] Determine the number of degrees of unsaturation in the compounds before and after hydrogenation.

Before H_2 addition—C_8H_{12}

- **The maximum number of H's possible for *n* C's is 2*n* + 2; in this example, 2*n* + 2 = 2(8) + 2 = 18.**
- **18 H's (maximum) − 12 H's (actual) = 6 H's fewer than the maximum number.**

$$\frac{\text{6 H's fewer than the maximum}}{\text{2 H's removed for each degree of unsaturation}} = \text{three degrees of unsaturation}$$

After H_2 addition—C_8H_{14}

- **The maximum number of H's possible for *n* C's is 2*n* + 2; in this example,**

  2*n* + 2 = 2(8) + 2 = 18.
- **18 H's (maximum) − 14 H's (actual) = 4 H's fewer than the maximum number.**

$$\frac{\text{4 H's fewer than the maximum}}{\text{2 H's removed for each degree of unsaturation}} = \text{two degrees of unsaturation}$$

[2] Assign the number of degrees of unsaturation to rings or π bonds as follows:

- **The number of degrees of unsaturation that remain in the product after H_2 addition = the number of rings in the starting material.**
- **The number of degrees of unsaturation that react with H_2 = the**

number of π bonds.

In this example, two degrees of unsaturation remain after hydrogenation, so the starting material has two rings. Thus:

Before H_2 addition:		After H_2 addition:			
three degrees of unsaturation	–	two degrees of unsaturation	=	one degree of unsaturation that reacted with H_2	
three rings or π bonds in C_8H_{12}	=	two rings	+	one π bond	ANSWER

Problem 12.7

Complete the missing information for compounds A, B, and C, each subjected to hydrogenation.

The number of rings and π bonds refers to the reactant (A, B, or C) prior to hydrogenation.

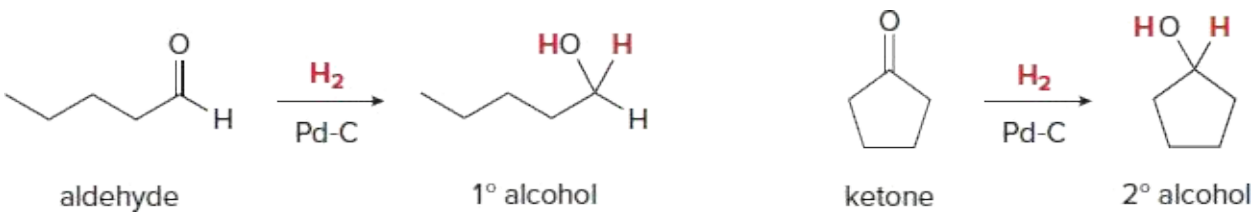
Compound	Molecular formula before hydrogenation	Molecular formula after hydrogenation	Number of rings	Number of π bonds
A	$C_{10}H_{12}$	$C_{10}H_{16}$	?	?
B	?	C_4H_{10}	0	1
C	C_6H_8	?	1	?

More Practice:

Try Problem 12.33.

12.3D Hydrogenation of Other Double Bonds

Compounds that contain a carbonyl group also react with H_2 and a metal catalyst. For example, aldehydes and ketones are reduced to 1° and 2° alcohols, respectively. We return to this reaction in Chapter 17.



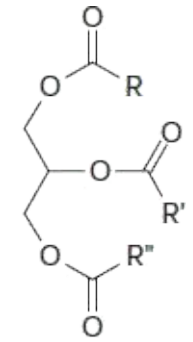
12.4 Application: Hydrogenation of Oils

Many processed foods, such as peanut butter, margarine, and some brands of crackers, contain *partially hydrogenated* vegetable oils. These oils are produced by hydrogenating the long hydrocarbon chains of triacylglycerols.

In Section 10.6 we learned that fats and oils are triacylglycerols that differ in the number of degrees of unsaturation in their long alkyl side chains.

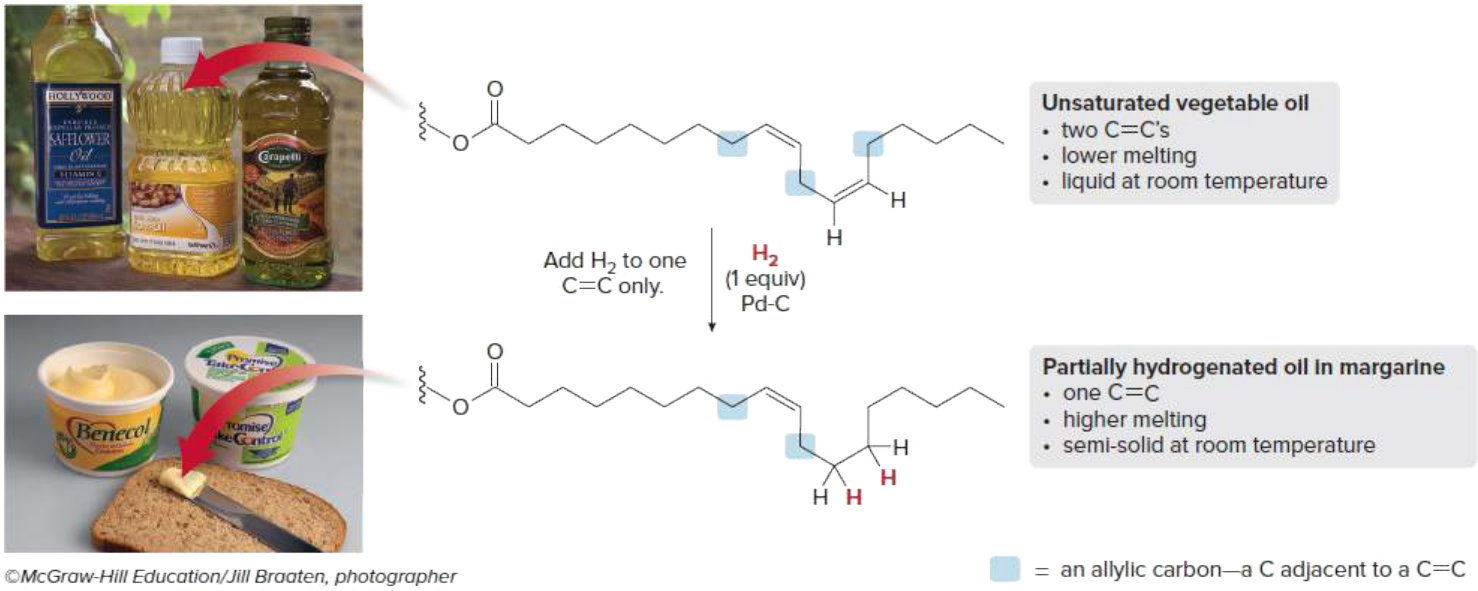
- **Fats—usually animal in origin—are solids with triacylglycerols having few degrees of unsaturation.**
- **Oils—usually vegetable in origin—are liquids with triacylglycerols having a larger number of degrees of unsaturation.**

When an unsaturated vegetable oil is treated with hydrogen, some (or all) of the π bonds add H_2, decreasing the number of degrees of unsaturation (Figure 12.4). This increases the melting point of the oil. For example, margarine is prepared by partially hydrogenating vegetable oil to give a product having a semi-solid consistency that more closely resembles butter. This process is sometimes called *hardening*.



triacylglycerol

The number of double bonds in the R groups of the triacylglycerol determines whether it is a fat or an oil.



©McGraw-Hill Education/Jill Braaten, photographer

- **Decreasing** the number of degrees of unsaturation **increases** the melting point. Only one long chain of the triacylglycerol is drawn.
- When an oil is *partially* hydrogenated, some double bonds react with H_2, whereas some double bonds remain in the product.
- Partial hydrogenation **decreases** the number of allylic sites (shown in blue), making a triacylglycerol **less** susceptible to oxidation, thereby increasing its shelf life.

Figure 12.4 **Partial hydrogenation of the double bonds in a vegetable oil**

Peanut butter is a common consumer product that contains partially hydrogenated vegetable oil. ©*McGraw-Hill Education/Elite Images*

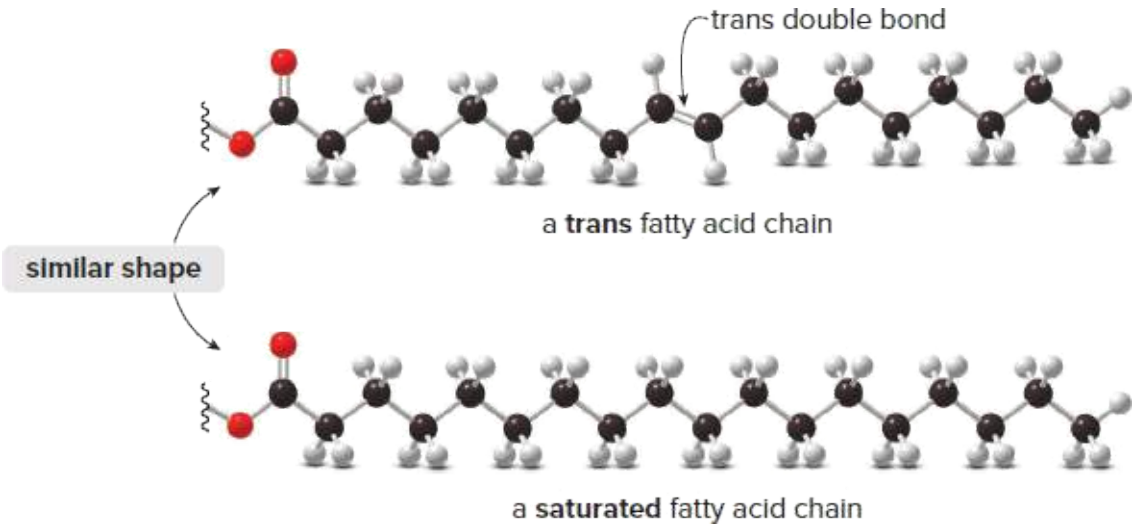
If unsaturated oils are healthier than saturated fats, why does the food industry hydrogenate oils? There are two reasons—aesthetics and shelf life. Consumers prefer the semi-solid consistency of margarine to a liquid oil. Imagine pouring vegetable oil on a piece of toast or pancakes.

Furthermore, unsaturated oils are more susceptible than saturated fats to oxidation at the allylic carbon atoms—the carbons adjacent to the double bond carbons—a process discussed in Chapter 13. Oxidation makes the oil rancid and inedible. Hydrogenating

the double bonds reduces the number of allylic carbons (also illustrated in Figure 12.4), thus reducing the likelihood of oxidation and increasing the shelf life of the food product. This process reflects a delicate balance between providing consumers with healthier food products, while maximizing shelf life to prevent spoilage.

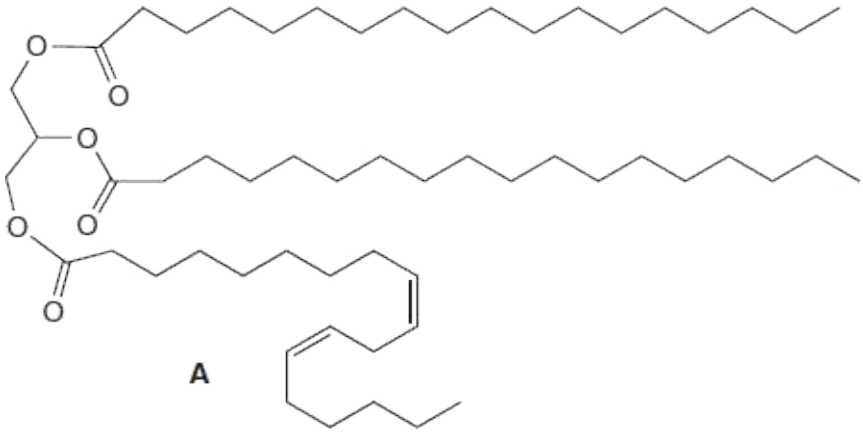
One other fact is worthy of note. Because the steps in hydrogenation are reversible and H atoms are added in a sequential rather than concerted fashion, a cis double bond can be isomerized to a trans double bond. After addition of one H atom (Step [3] in Mechanism 12.1), an intermediate can lose a hydrogen atom to re-form a double bond with either the cis or trans configuration.

As a result, some of the cis double bonds in vegetable oils are converted to trans double bonds during hydrogenation, forming so-called "trans fats." The shape of the resulting fatty acid chain is very different, closely resembling the shape of a *saturated* fatty acid chain. Consequently, trans fats are thought to have the same negative effects on blood cholesterol levels as saturated fats; that is, trans fats stimulate cholesterol synthesis in the liver, thus increasing blood cholesterol levels, a factor linked to increased risk of heart disease.



Problem 12.8

Draw the products formed when triacylglycerol A is treated with each reagent, forming compounds B and C. Rank A, B, and C in order of increasing melting point.

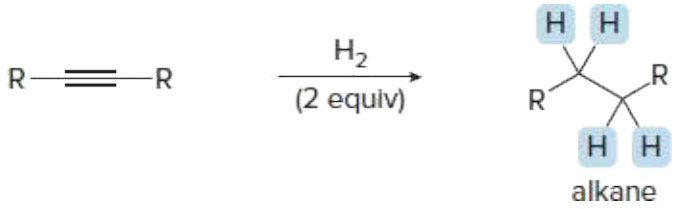


a. H_2 (excess), Pd-C (Compound **B**)
b. H_2 (1 equiv), Pd-C (Compound **C**)

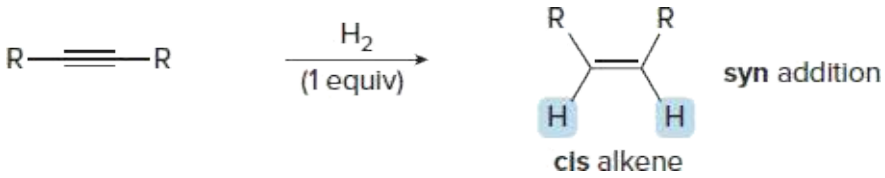
12.5 Reduction of Alkynes

Reduction of an alkyne adds H_2 to one or both of the π bonds. There are three different ways by which the elements of H_2 can be added to a triple bond.

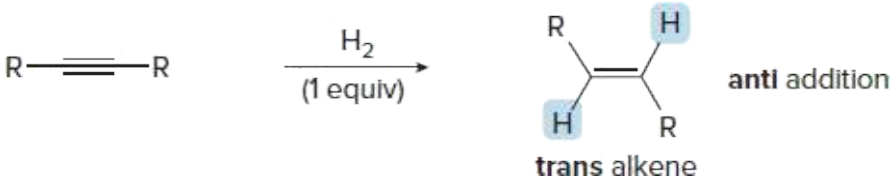
- **Adding two equivalents of H_2 forms an alkane.**



- **Adding one equivalent of H_2 in a syn fashion forms a cis alkene.**



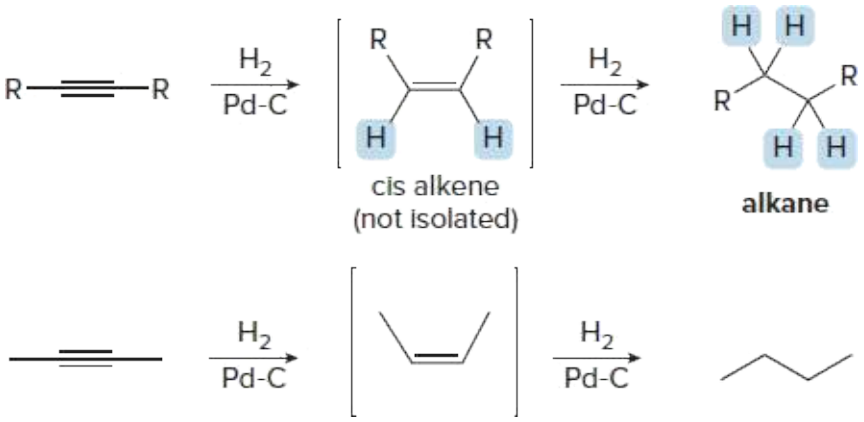
- **Adding one equivalent of H_2 in an anti fashion forms a trans alkene.**



12.5A Reduction of an Alkyne to an Alkane

When an alkyne is treated with two or more equivalents of H_2 and a Pd catalyst, reduction of *both* π bonds occurs. Syn addition of one equivalent of H_2 forms a cis alkene, which adds a second equivalent of H_2 to form an alkane. Four new C—H bonds are formed. By using a Pd-C catalyst, it is not possible to stop the reaction after

addition of only one equivalent of H_2.

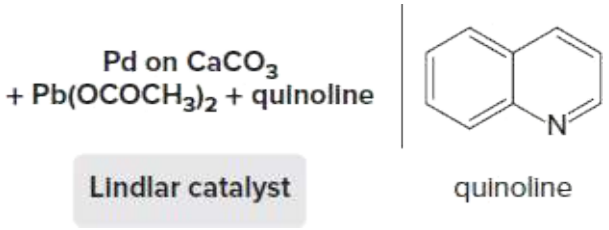


Problem 12.9

Which alkyne has the smaller heat of hydrogenation, $HC{\equiv}CCH_2CH_2OH_3$ or $CH_3C{\equiv}CCH_2CH_3$? Explain your choice.

12.5B Reduction of an Alkyne to a Cis Alkene

Palladium metal is too active a catalyst to allow the hydrogenation of an alkyne to stop after one equivalent of H_2. To prepare a cis alkene from an alkyne and H_2, a less active Pd catalyst is used—Pd adsorbed onto $CaCO_3$ with added lead(II) acetate and quinoline. This catalyst is called the Lindlar catalyst after the chemist who first prepared it. Compared to Pd metal, the Lindlar catalyst is deactivated or "poisoned."

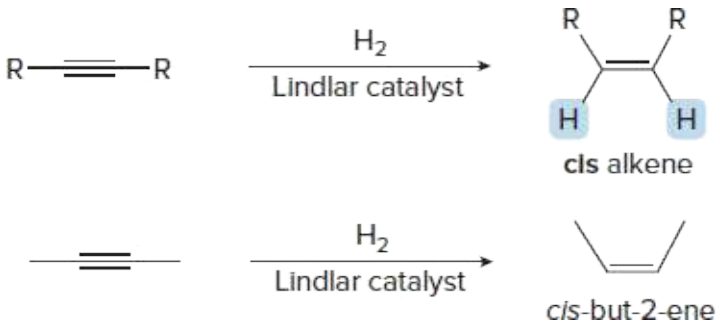


Reduction of an alkyne to a cis alkene is a stereoselective reaction, because only one stereoisomer is formed.

Jasmine flowers are the source of *cis*-jasmone, a perfume component (Problem 12.10).

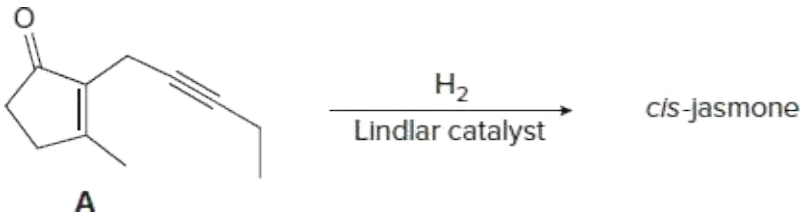
©Charlotte Björnström/EyeEm/Getty Images

With the Lindlar catalyst, one equivalent of H_2 adds to an alkyne, and the cis alkene product is unreactive to further reduction.



Problem 12.10

What is the structure of *cis*-jasmone, a natural product isolated from jasmine flowers, formed by treatment of alkyne A with H_2 in the presence of the Lindlar catalyst?

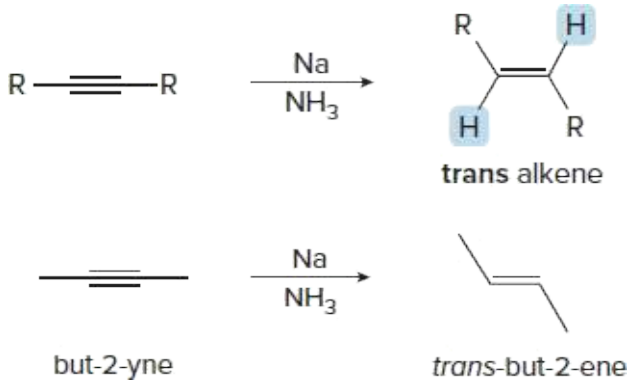


Problem 12.11

(a) Draw the structure of a compound of molecular formula C_6H_{10} that reacts with H_2 in the presence of Pd-C but does not react with H_2 in the presence of Lindlar catalyst. (b) Draw the structure of a compound of molecular formula C_6H_{10} that reacts with H_2 when either catalyst is present.

12.5C Reduction of an Alkyne to a Trans Alkene

Although catalytic hydrogenation is a convenient method for preparing cis alkenes from alkynes, it cannot be used to prepare trans alkenes. With a dissolving metal reduction (such as Na in NH3), however, the elements of H_2 are added in an anti fashion to the triple bond, thus forming a trans alkene. For example, but-2-yne reacts with Na in NH3 to form *trans*-but-2-ene.



The mechanism for the dissolving metal reduction using Na in NH3 features sequential addition of electrons and protons to the triple bond. Half-headed arrows denoting the movement of a single electron must be used in two steps when Na donates *one* electron. The mechanism can be divided conceptually into two parts, each of which consists of two steps: addition of an electron followed by protonation of the resulting negative charge, as shown in Mechanism 12.2.

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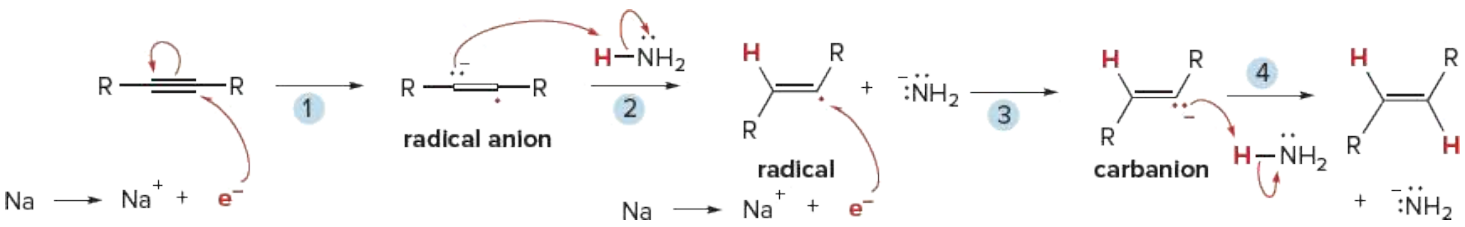
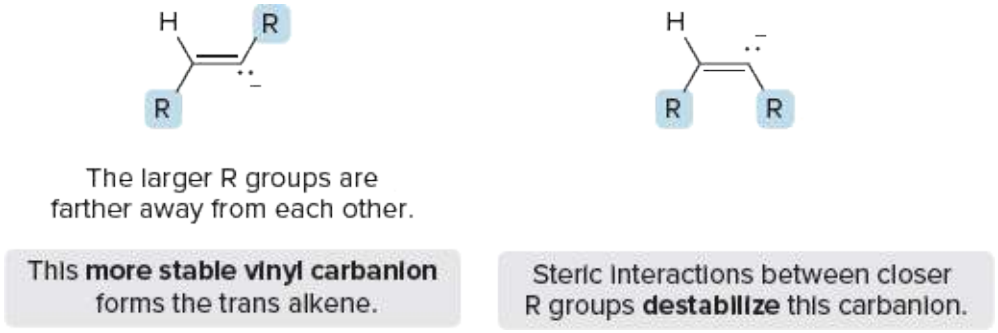
Mechanism 12.2 Dissolving Metal Reduction of an Alkyne to a Trans Alkene



1. **Addition of an electron to the triple bond forms a radical anion, a species that contains *both* a negative charge *and* an unpaired electron.**
2. **Protonation of the anion with the solvent NH_3 yields a radical. The net result of the first two steps is the addition of a H atom.**
3. **Addition of a second electron forms a carbanion.**
4. **Protonation of the carbanion forms the trans alkene. Steps [3] and [4] add the second H atom to the triple bond.**

Although the vinyl carbanion formed in Step [3] could have two different arrangements of its R groups, only the trans alkene is formed from the more stable vinyl carbanion; this carbanion has the larger R groups farther away from each other to avoid steric interactions. Protonation of this anion leads to the more stable trans product.



Dissolving metal reduction of a triple bond with Na in NH_3 is a stereoselective reaction because it forms a trans product exclusively.

- **Dissolving metal reductions always form the more stable trans product preferentially.**

The three methods to reduce a triple bond are summarized in Figure 12.5 using hex-3-yne as starting material.

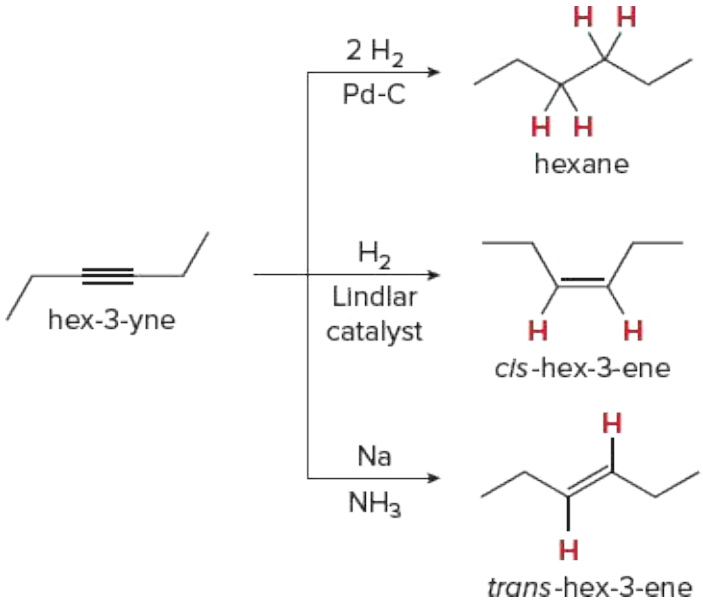


Figure 12.5 **Summary: Three methods to reduce a triple bond**

Problem 12.12

What product is formed when $CH_3OCH_2CH_2C{\equiv}CCH_2CH(CH_3)_2$ is treated with each reagent:

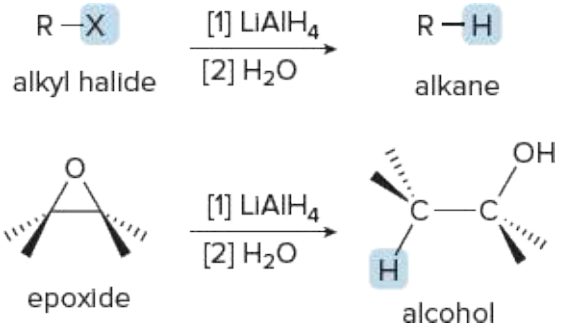
(a) H_2 (excess), Pd-C; (b) H_2 (1 equiv), Lindlar catalyst; (c) H_2 (excess), Lindlar catalyst; (d) Na, NH_3?

Problem 12.13

A chiral alkyne A with molecular formula C_6H_{10} is reduced with H_2 and Lindlar catalyst to B having the *R* configuration at its stereogenic center. What are the structures of A and B?

12.6 The Reduction of Polar C—X σ Bonds

Compounds containing polar C—X σ bonds that react with strong nucleophiles are reduced with metal hydride reagents, most commonly lithium aluminum hydride. Two functional groups possessing both of these characteristics are alkyl halides and epoxides. Alkyl halides are reduced to alkanes with loss of X^- as the leaving group. Epoxide rings are opened to form alcohols.



Reduction of these C—X σ bonds is another example of nucleophilic substitution, in which $LiAlH_4$ serves as a source of a hydride nucleophile (H^-). Because H^- is a strong nucleophile, the reaction follows an S_N2 mechanism, illustrated for the one-step reduction of an alkyl halide in Mechanism 12.3.

Mechanism 12.3 Reduction of RX with $LiAlH_4$

- **The nucleophile H^- replaces the leaving group X in a single step.**

Because the reaction follows an S_N2 mechanism:

- **Unhindered CH_3X and 1° alkyl halides are more easily reduced than more substituted 2° and 3° halides.**
- **In unsymmetrical epoxides, nucleophilic attack of H^- (from $LiAlH_4$)**

occurs at the *less* substituted carbon atom.

Examples are shown in Figure 12.6.

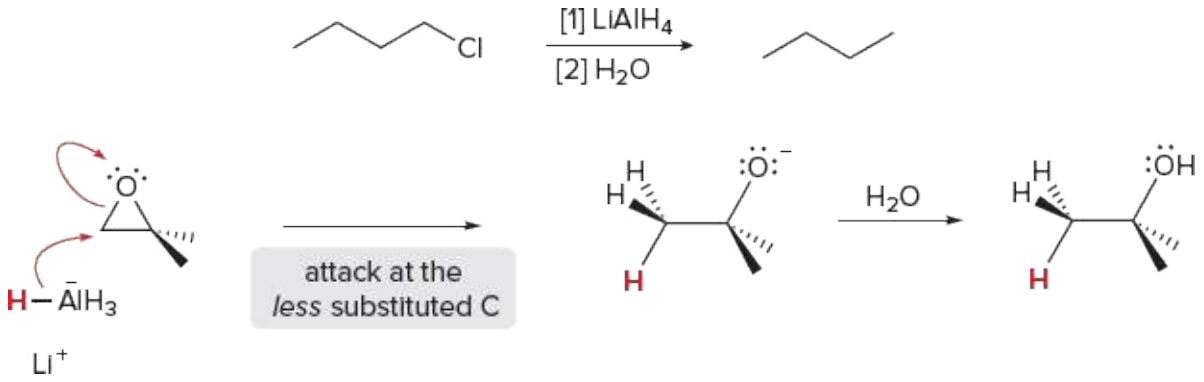
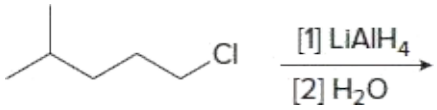


Figure 12.6 **Examples of reduction of C—X σ bonds with $LiAlH_4$**

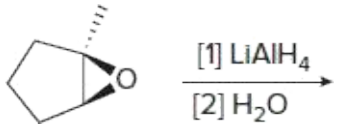
Problem 12.14

Draw the products of each reaction.

a.



b.

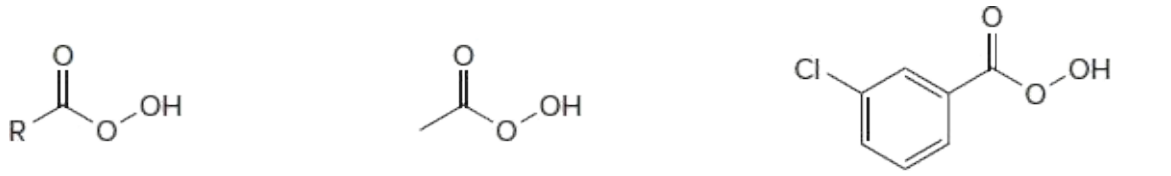


12.7 Oxidizing Agents

Oxidizing agents fall into two main categories:

- Reagents that contain an oxygen–oxygen bond
- Reagents that contain metal–oxygen bonds

Oxidizing agents containing an O—O bond include O_2, O_3 (ozone), H_2O_2 (hydrogen peroxide), $(CH_3)_3COOH$ (*tert*-butyl hydroperoxide), and peroxyacids. Peroxyacids, a group of reagents with the general structure RCO_3H, have one more O atom than carboxylic acids (RCO_2H). Some peroxyacids are commercially available whereas others are prepared and used without isolation. Two common peroxyacids are peroxyacetic acid and *meta*-chloroperoxybenzoic acid, abbreviated as mCPBA.

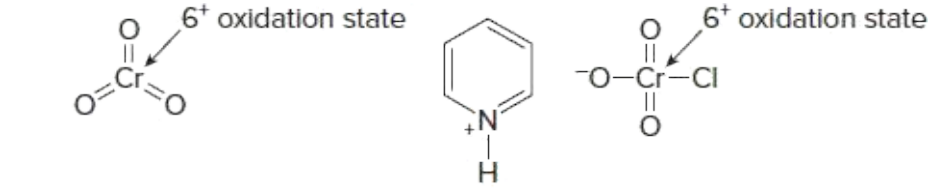


peroxyacid

peroxyacetic acid

meta-chloroperoxybenzoic acid
mCPBA

The most common oxidizing agents with metal–oxygen bonds contain either chromium in the +6 oxidation state (six Cr—O bonds) or manganese in the +7 oxidation state (seven Mn—O bonds). Common Cr^{6+} reagents include chromium(VI) oxide (CrO_3) and sodium or potassium dichromate ($Na_2Cr_2O_7$ and $K_2Cr_2O_7$). These reagents are strong oxidants used in the presence of a strong aqueous acid such as H_2SO_4. Pyridinium chlorochromate (PCC), a Cr^{6+} reagent that is soluble in halogenated organic solvents, can be used without strong acid present. This makes it a more selective Cr^{6+} oxidant, as described in Section 12.12.



chromium(VI) oxide
CrO_3

pyridinium chlorochromate
PCC

The most common Mn^{7+} reagent is $KMnO_4$ (potassium permanganate), a strong, water-soluble oxidant. Other oxidizing agents that contain metals include OsO_4 (osmium tetroxide) and Ag_2O [silver(I) oxide].

In the remainder of Chapter 12, the oxidation of alkenes, alkynes, and alcohols—three functional groups already introduced in this text—is presented (Figure 12.7). Addition reactions to alkenes and alkynes that increase the number of C—O bonds are described in Sections 12.8–12.11. Oxidation of alcohols to carbonyl compounds appears in Sections 12.12–12.14.

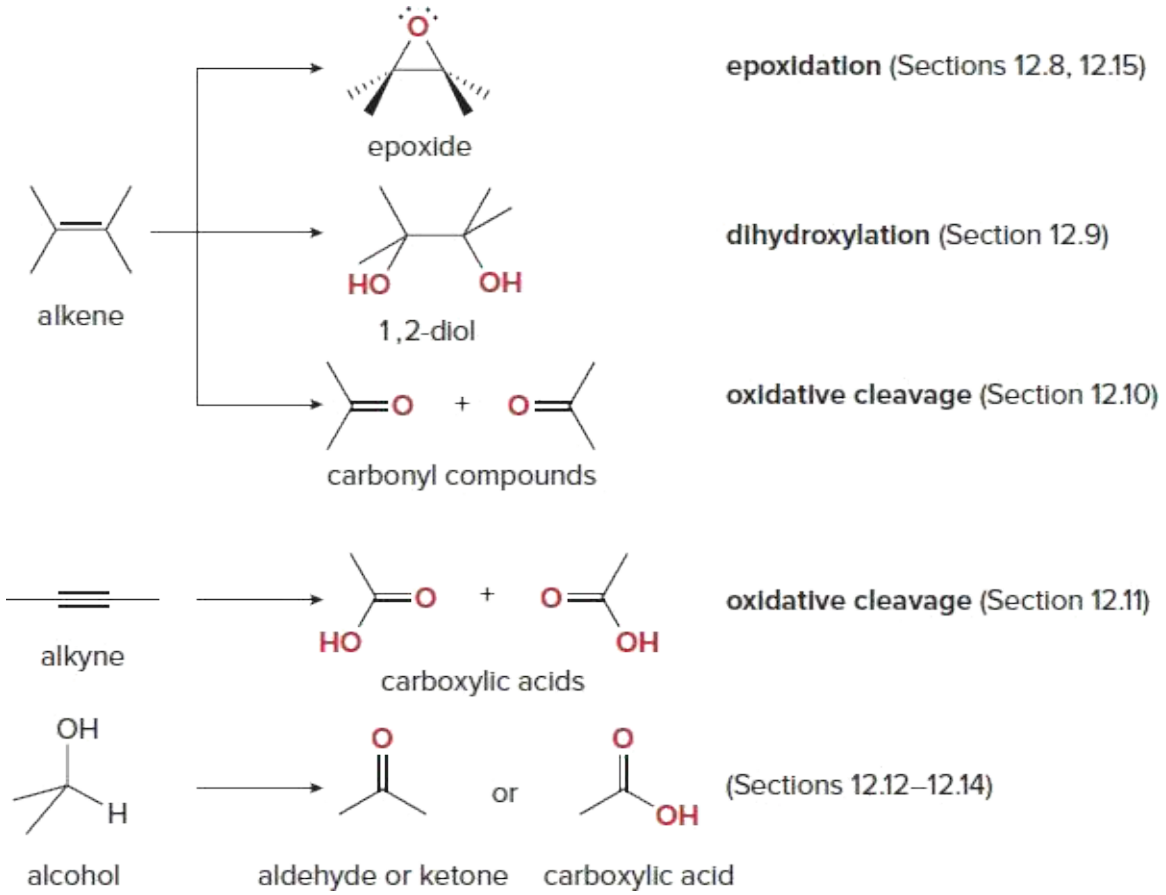
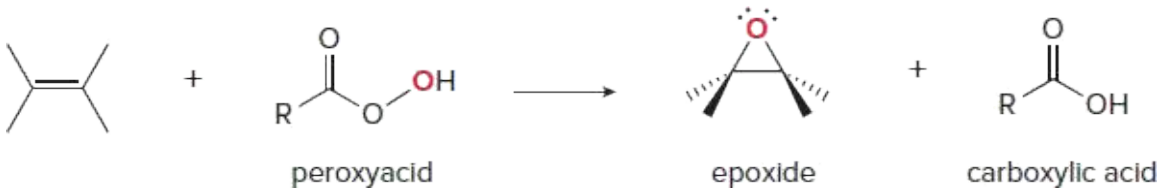


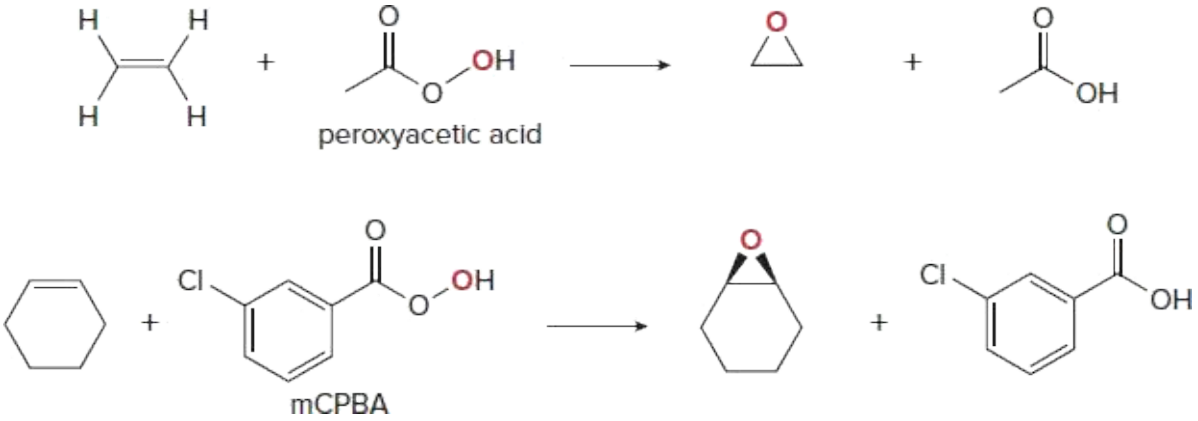
Figure 12.7 **Oxidation reactions of alkenes, alkynes, and alcohols**

12.8 Epoxidation

Epoxidation is the addition of a single oxygen atom to an alkene to form an epoxide.

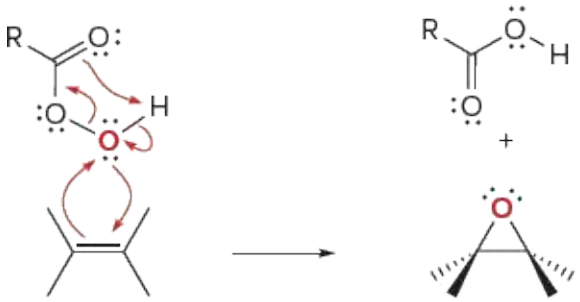


The weak π bond of the alkene is broken and two new C—O σ bonds are formed. Epoxidation is typically carried out with a peroxyacid, resulting in cleavage of the weak O—O bond of the reagent.



Epoxidation occurs via the concerted addition of one oxygen atom of the peroxyacid to the π bond as shown in Mechanism 12.4. Epoxidation resembles the formation of the bridged halonium ion in Section 10.13, in that two bonds in a three-membered ring are formed in one step.

Mechanism 12.4 Epoxidation of an Alkene with a Peroxyacid

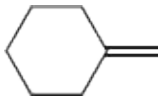


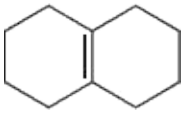
- **All bonds are broken and formed in a single step. The two epoxide C—O bonds are formed from one electron pair of the π bond and one lone pair of the peroxyacid. The weak O—O bond is broken.**

Problem 12.15

What epoxide is formed when each alkene is treated with mCPBA?

a.

b. 

c. 

12.8A The Stereochemistry of Epoxidation

Epoxidation occurs via syn addition of an O atom from either side of the planar double bond, so that both C—O bonds are formed on the same side. The relative position of substituents in the alkene reactant is retained in the epoxide product.

- **A cis alkene gives an epoxide with cis substituents. A trans alkene gives an epoxide with trans substituents.**

Epoxidation is a stereospecific reaction because cis and trans alkenes yield different

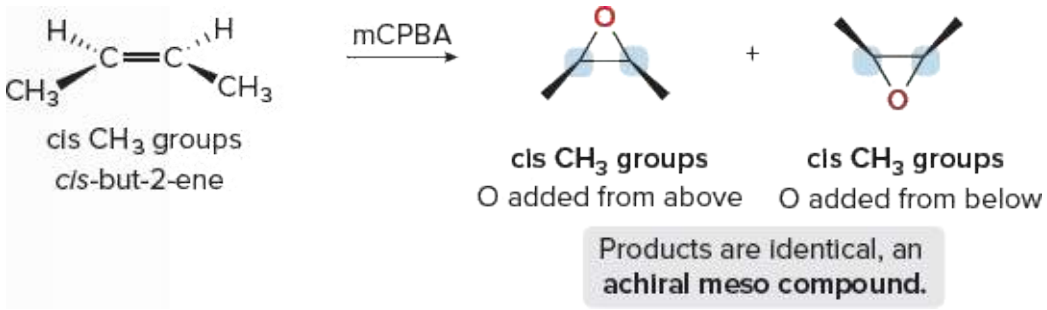
stereoisomers as products, as illustrated in Sample Problem 12.2.

Sample Problem 12.2 Drawing the Stereoisomers Formed in Epoxidation

Draw the stereoisomers formed when *cis*- and *trans*-but-2-ene are epoxidized with mCPBA.

Solution

To draw each product of epoxidation, add an O atom from either side of the alkene, and keep all substituents in their *original* orientations. The cis methyl groups in *cis*-but-2-ene become cis substituents in the epoxide. Addition of an O atom from either side of the trigonal planar alkene leads to the same compound—an achiral meso compound that contains two stereogenic centers, labeled in blue.



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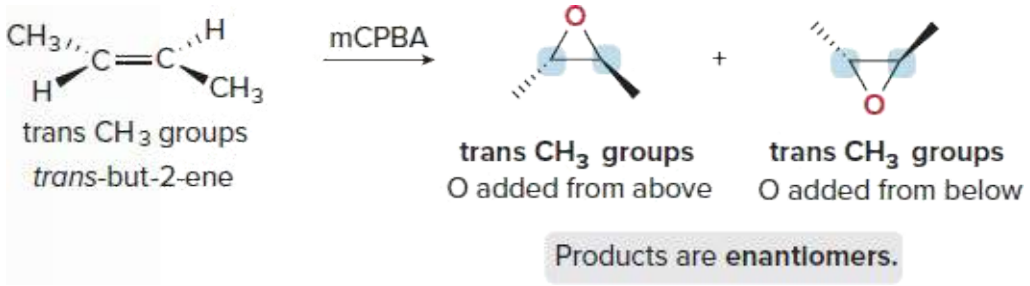
Epoxidation of *cis*- and *trans*-but-2-ene illustrates the general rule about the stereochemistry of reactions: an achiral starting material gives achiral or racemic products.

The trans methyl groups in *trans*-but-2-ene become trans substituents in the epoxide. Addition of an O atom from either side of the trigonal planar alkene yields an equal mixture of two enantiomers—a racemic mixture—with two stereogenic centers labeled in blue.

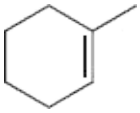


Problem 12.16

Draw all stereoisomers formed when each alkene is treated with mCPBA.

a.

b.

c. 

More Practice:

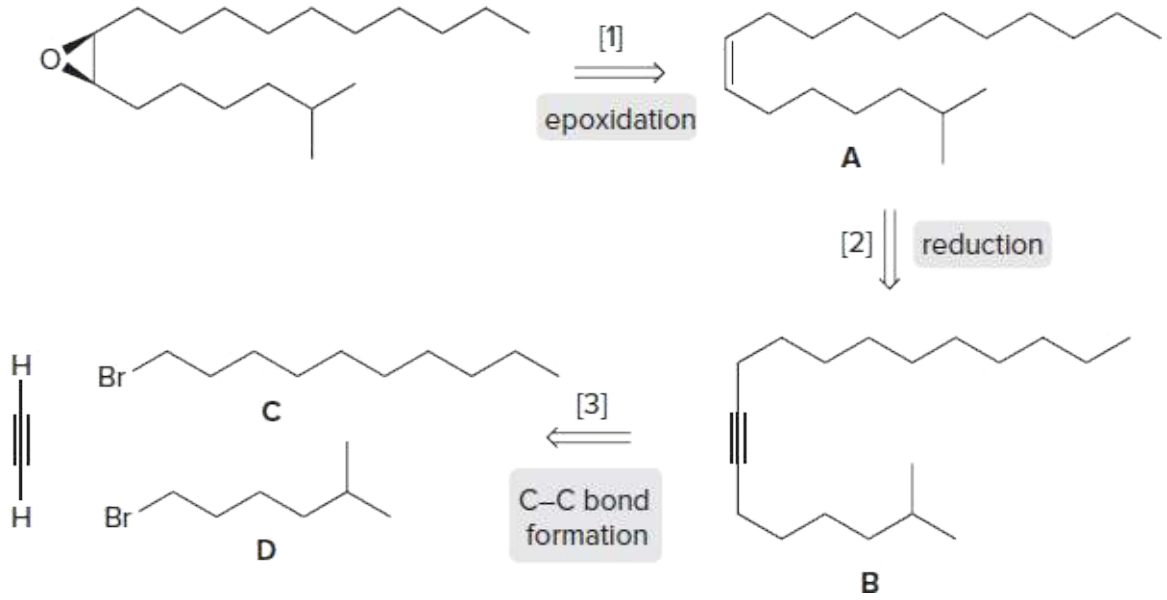
Try Problem s 12.28b; 12.35d, k; 12.36b.

In 1869, the gypsy moth was introduced into New England in an attempt to develop a silk industry. Some moths escaped into the wild and the population flourished. Mature gypsy moth caterpillars eat an average of one square foot of leaf surface per day, defoliating shade trees and entire forests. Many trees die after a single defoliation.

Source: USDA APHIS PPQ, Bugwood.org

12.8B The Synthesis of Disparlure

Disparlure, the sex pheromone of the female gypsy moth, is synthesized by a stepwise reaction sequence that uses an epoxidation reaction as the final step. Retrosynthetic analysis of disparlure illustrates three key operations:

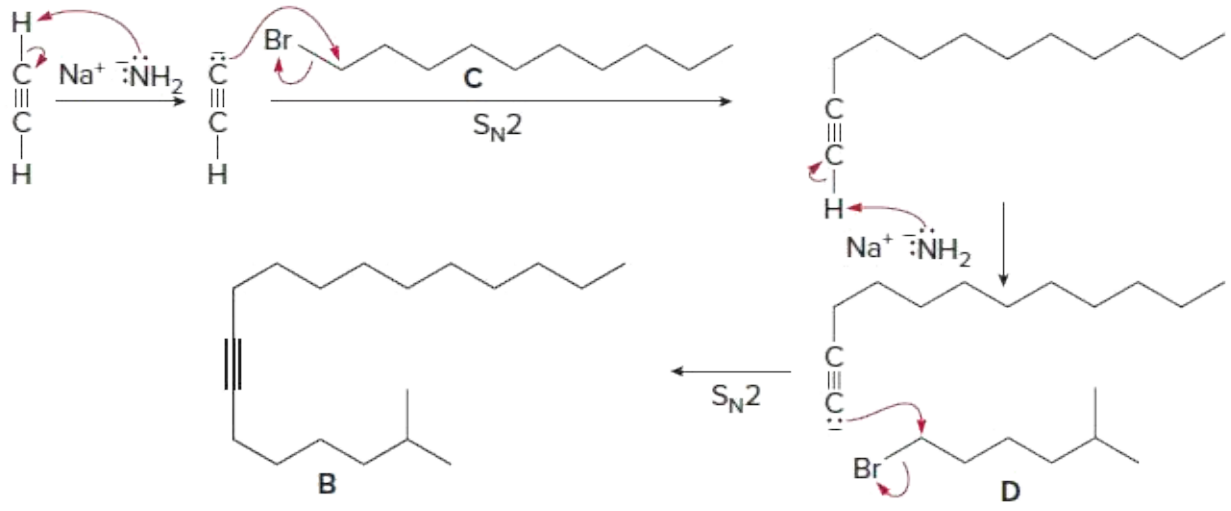


- Step [1] The cis epoxide in disparlure is prepared from a cis alkene A by epoxidation.
- Step [2] A is prepared from an internal alkyne B by reduction.
- Step [3] B is prepared from acetylene and two 1° alkyl halides (C and D) by using S_N2 reactions with acetylide anions.

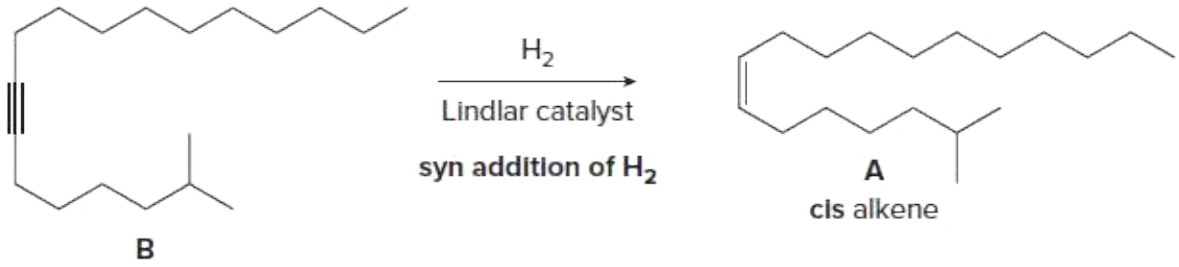
Figure 12.8 illustrates the synthesis of disparlure beginning with acetylene. The synthesis is conceptually divided into three parts:

- Part [1] Acetylene is converted to an internal alkyne B by forming two C—C bonds. Each bond is formed by treating an alkyne with base ($NaNH_2$) to form an acetylide anion, which reacts with an alkyl halide (C or D) in an S_N2 reaction (Section 11.11A).
- Part [2] The internal alkyne B is reduced to a cis alkene A by syn addition of H_2 using the Lindlar catalyst (Section 12.5B).
- Part [3] The cis alkene A is epoxidized to disparlure using a peroxyacid such as mCPBA.

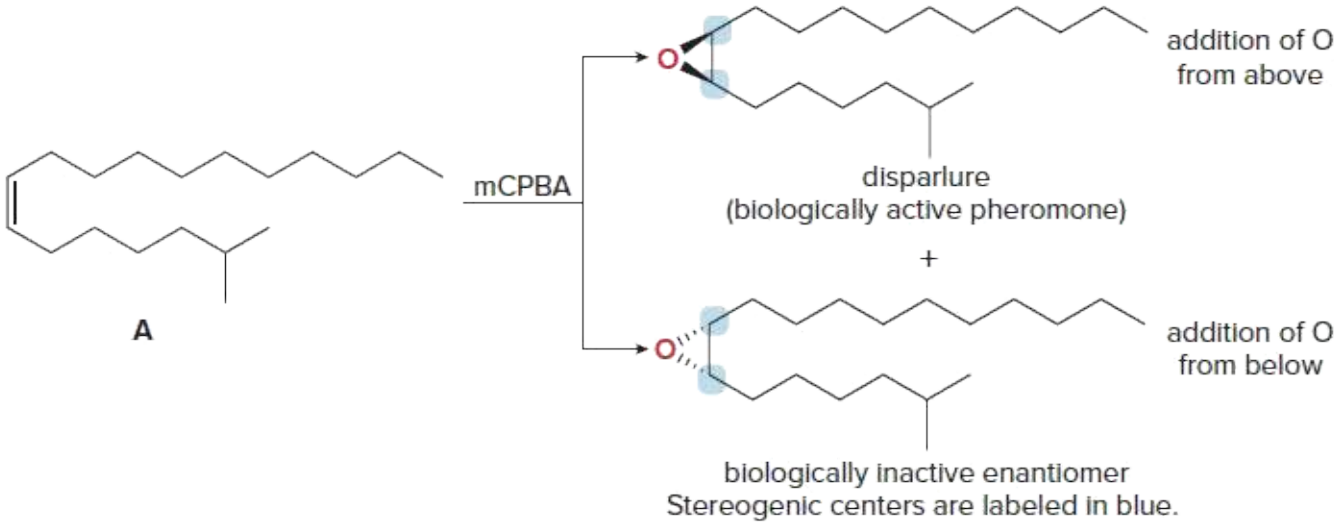
Part [1] Formation of two C—C bonds using acetylide anions (Section 11.11A)



Part [2] Reduction of alkyne **B** to form cis alkene **A** (Section 12.5B)



Part [3] Epoxidation of **A** to form disparlure (Section 12.8)



- Disparlure has been used to control the spread of the gypsy moth caterpillar, a pest that has periodically devastated forests in the northeastern United States by defoliating many shade and fruit-bearing trees. The active pheromone is placed in a trap containing a poison or sticky substance, and the male moth is lured to the trap by the pheromone. Alternatively, thousands of disparlure-baited traps are placed along the edges of infestation. When the pheromone permeates the air, males are confused and can't locate individual females, so that mating is disrupted. Such a species-specific method presents a way of controlling an insect population that avoids the widespread use of harmful, nonspecific pesticides.

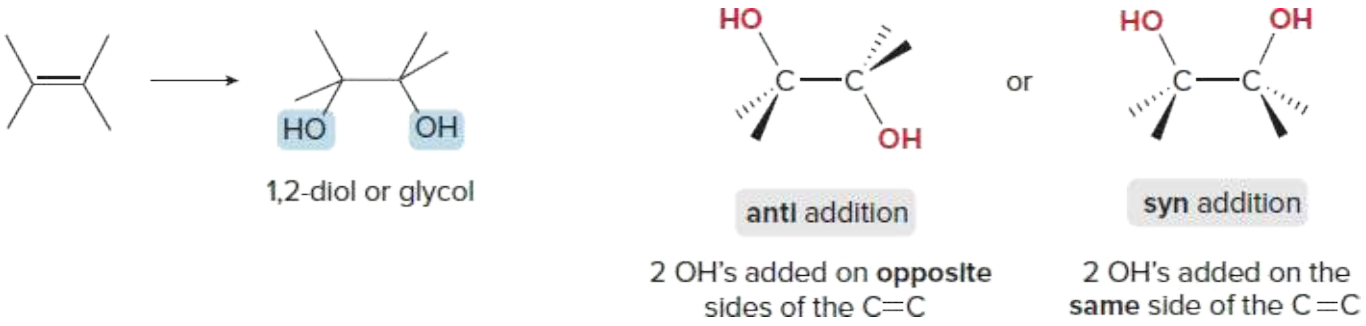
Figure 12.8 **The synthesis of disparlure**

How to separate a racemic mixture into its component enantiomers is discussed in Section 27.3.

Epoxidation of the cis alkene A from two different sides of the double bond affords two cis epoxides in the last step—a racemic mixture of two enantiomers. Thus, half of the product is the desired pheromone disparlure, but the other half is its biologically inactive enantiomer. Separating the desired from the undesired enantiomer is difficult and expensive, because both compounds have identical physical properties. A reaction that affords a chiral epoxide from an achiral precursor without forming a racemic mixture is discussed in Section 12.15.

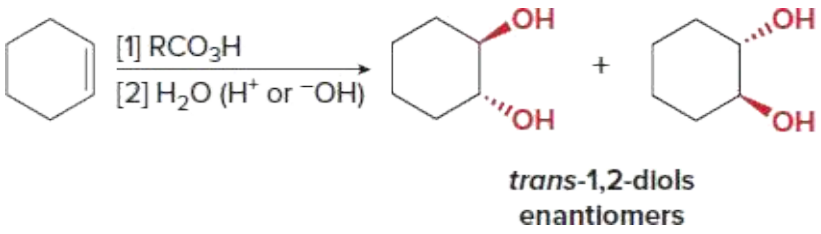
12.9 Dihydroxylation

Dihydroxylation is the addition of two hydroxy groups to a double bond, forming a 1,2-diol or glycol. Depending on the reagent, the two new OH groups can be added to the opposite sides (anti addition) or the same side (syn addition) of the double bond.

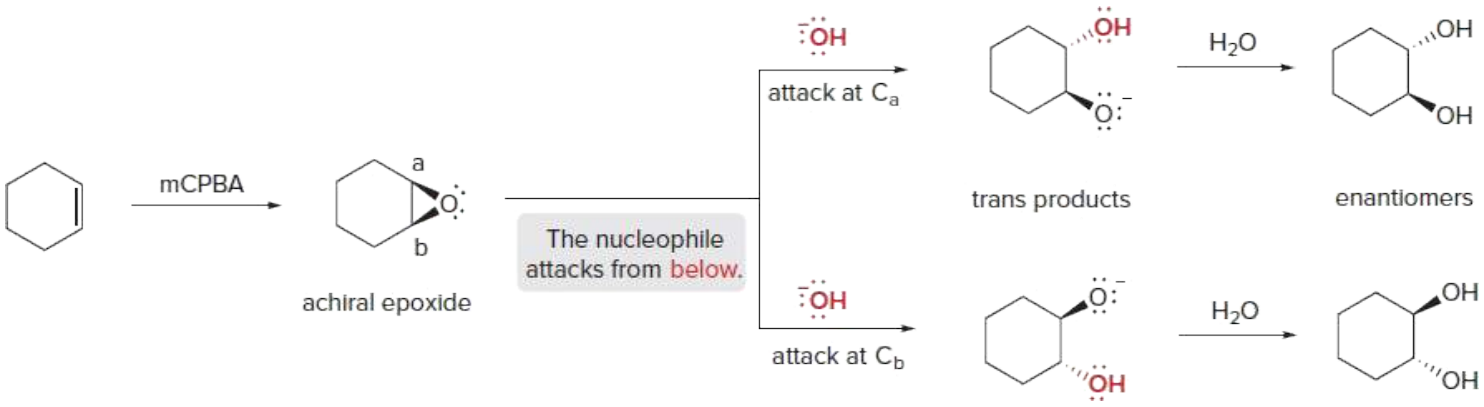


12.9A Anti Dihydroxylation

Anti dihydroxylation is achieved in two steps—epoxidation followed by opening of the ring with ^{-}OH or H_2O. Cyclohexene, for example, is converted to a racemic mixture of two *trans*-cyclohexane-1,2-diols by anti addition of two OH groups.



The stereochemistry of the products can be understood by examining the stereochemistry of each step.



Epoxidation of cyclohexene adds an O atom from either above or below the plane of the double bond to form a single achiral epoxide, so only one representation is shown. Opening of the epoxide ring then occurs with backside attack at either C—O bond. Because the epoxide is drawn above the plane of the six-membered ring, nucleophilic attack occurs from below the plane. This reaction is a specific example of the opening of epoxide rings with strong nucleophiles, first presented in Section 9.16A.

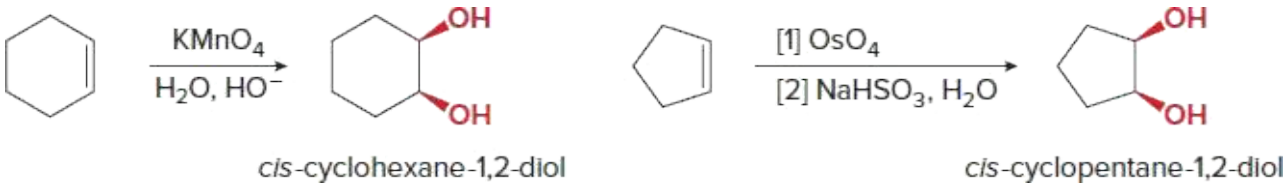
Because one OH group of the 1,2-diol comes from the epoxide and one OH group comes from the nucleophile ($^-$OH), the overall result is anti addition of two OH groups to an alkene.

Problem 12.17

Draw the products formed when both *cis*- and *trans*-but-2-ene are treated with a peroxyacid followed by $^-$OH (in H_2O). Explain how these reactions illustrate that anti dihydroxylation is stereospecific.

12.9B Syn Dihydroxylation

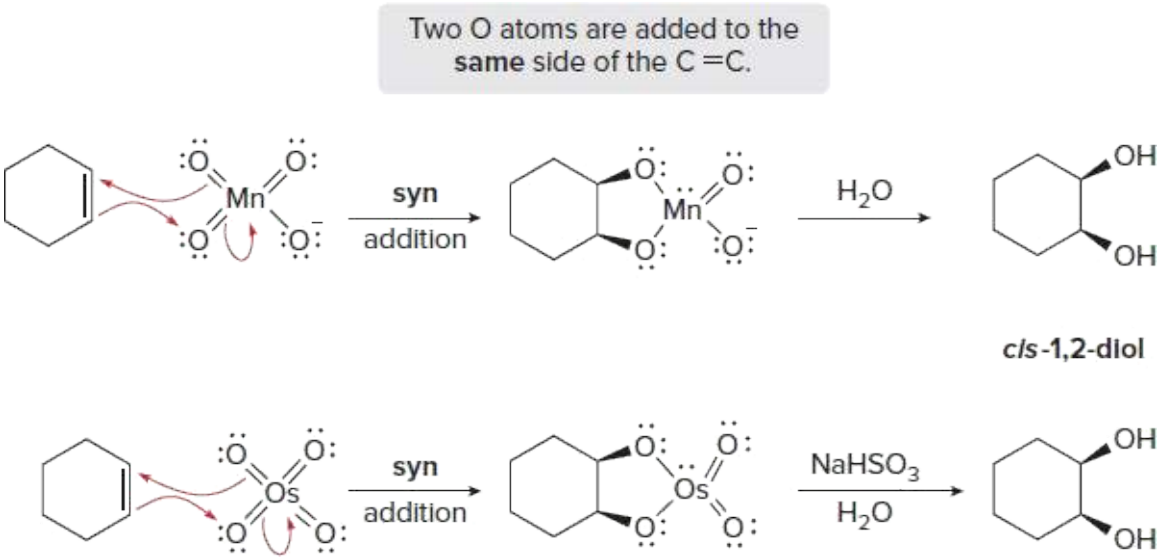
Syn dihydroxylation results when an alkene is treated with either $KMnO_4$ or OsO_4.



cis-cyclohexane-1,2-diol

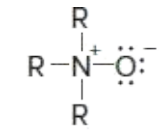
cis-cyclopentane-1,2-diol

Each reagent adds two oxygen atoms to the same side of the double bond—that is, in a syn fashion—to yield a cyclic intermediate. Hydrolysis of the cyclic intermediate cleaves the metal–oxygen bonds, forming the *cis*-1,2-diol. With OsO_4, sodium bisulfite ($NaHSO_3$) is also added in the hydrolysis step.



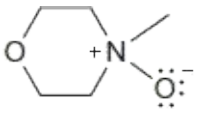
Although $KMnO_4$ is inexpensive and readily available, its use is limited by its insolubility in organic solvents. To prevent further oxidation of the product 1,2-diol, the reaction mixture must be kept basic with added ^-OH.

NMO is an amine oxide. It is not possible to draw a Lewis structure of an amine oxide having only neutral atoms.



amine oxide

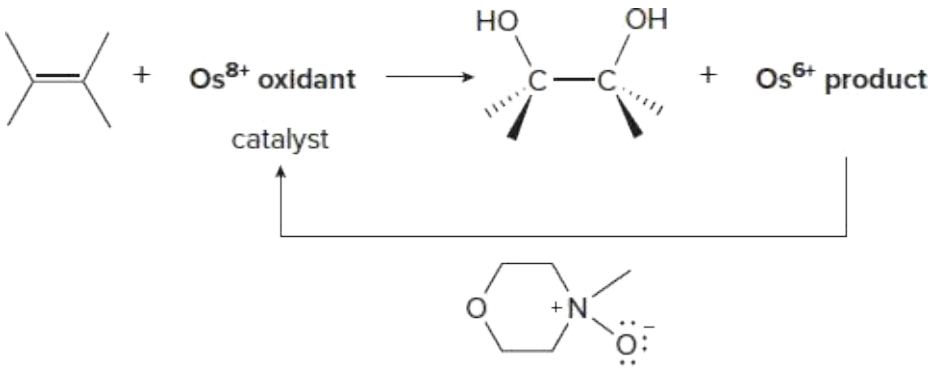
Although OsO_4 is a more selective oxidant than KMnO4 and is soluble in organic solvents, it is toxic and expensive. To overcome these limitations, dihydroxylation can be carried out by using a *catalytic* amount of OsO_4, if the oxidant *N*-methylmorpholine *N*-oxide (NMO) is also added.



N-methylmorpholine *N*-oxide

NMO

In the catalytic process, dihydroxylation of the double bond converts the Os^{8+} oxidant into an Os^{6+} product, which is then re-oxidized by NMO to Os^{8+}. This Os^{8+} reagent can then be used for dihydroxylation once again, and the catalytic cycle continues.



NMO oxidizes the **Os^{6+} product** back to **Os^{8+}** to begin the cycle again.

Problem 12.18

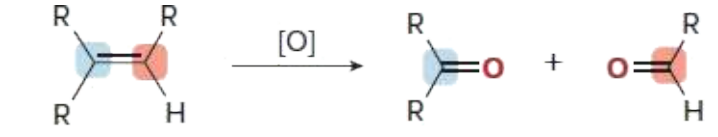
Draw the products formed when both *cis*- and *trans*-but-2-ene are treated with OsO_4, followed by hydrolysis with $NaHSO_3 + H_2O$. Explain how these reactions illustrate that syn dihydroxylation is stereospecific.

Lightning produces O_3 from O_2 during an electrical storm. Moreover, the pungent odor around a heavily used photocopy machine is O_3 produced from O_2 during the process. O_3 at ground level is an unwanted atmospheric pollutant. In the stratosphere, however, it protects us from harmful ultraviolet radiation, as discussed in Chapter 13.

©Balazs Kovacs/Getty Images

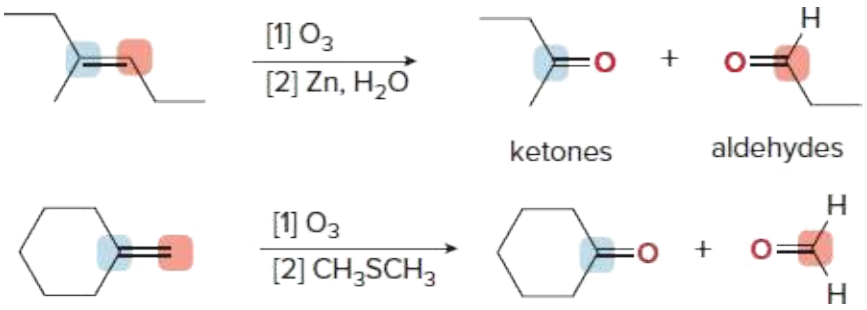
12.10 Oxidative Cleavage of Alkenes

Oxidative cleavage of an alkene breaks both the σ and π bonds of the double bond to form two carbonyl groups. Depending on the number of R groups bonded to the double bond, oxidative cleavage yields either ketones or aldehydes.

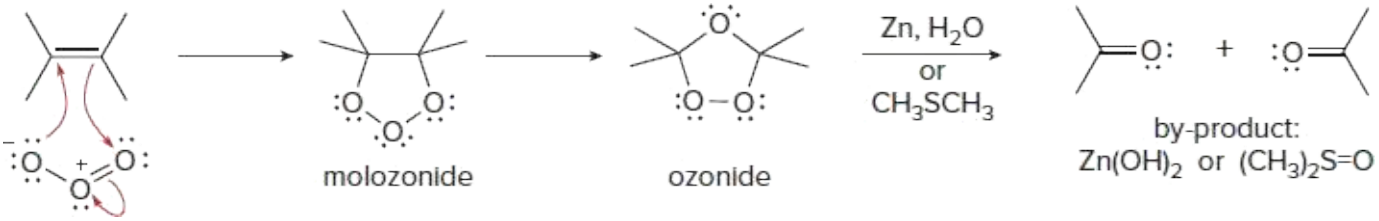


The σ and π bonds are broken. ketone aldehyde

One method of oxidative cleavage relies on a two-step procedure using ozone (O_3) as the oxidant in the first step. Cleavage with ozone is called ozonolysis.



Addition of ozone to the π bond of the alkene forms an unstable intermediate called a molozonide, which then rearranges to an ozonide by a stepwise process. The unstable ozonide is then reduced without isolation to afford carbonyl compounds. Zn (in H_2O) and dimethyl sulfide (CH3SCH3) are two common reagents used to convert the ozonide to carbonyl compounds.

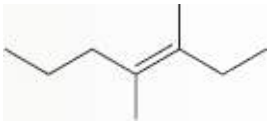


To draw the product of any oxidative cleavage:

- Locate all π bonds in the molecule.
- Replace each C=C by two C=O bonds.

Sample Problem 12.3 Drawing the Oxidative Cleavage Products from an Alkene

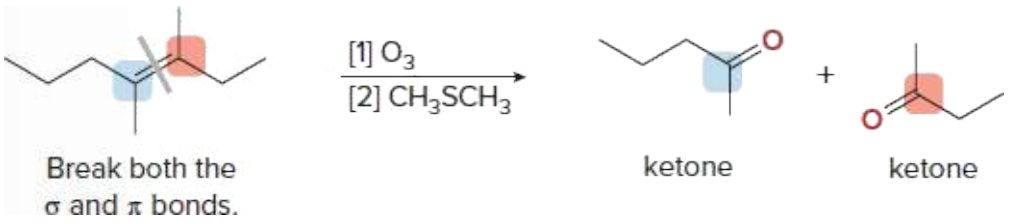
Draw the products when each alkene is treated with O3 followed by CH3SCH3.

a. 

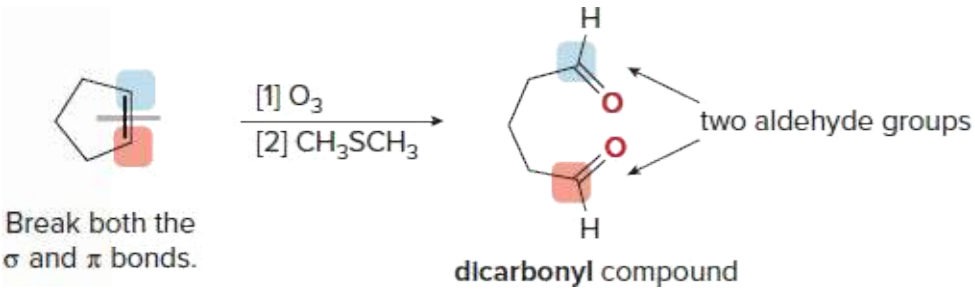
b.

Solution

a. Cleave the double bond and replace it with two carbonyl groups.



b. For a cycloalkene, oxidative cleavage results in a single molecule with two carbonyl groups—a dicarbonyl compound.

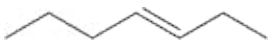


Problem 12.19

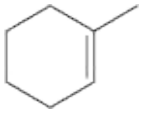
Draw the products formed when each alkene is treated with O_3 followed by Zn, H_2O.

a.

b.



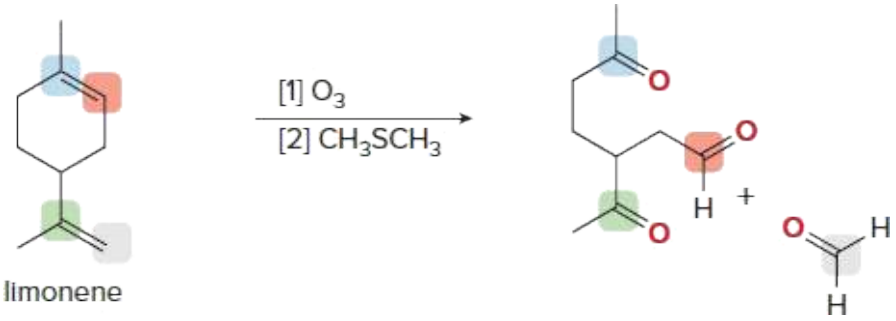
c.



More Practice:

Try Problem s 12.35i; 12.37c; 12.45a, b; 12.48.

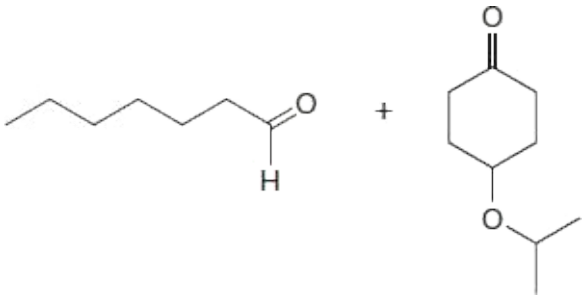
Ozonolysis of dienes (and other polyenes) results in oxidative cleavage of all C=C bonds. The number of carbonyl groups formed in the products is *twice* the number of double bonds in the starting material. The *two* double bonds in limonene are converted to products containing *four* carbonyl groups.



Oxidative cleavage is a valuable tool for structure determination of unknown compounds. The ability to determine what alkene gives rise to a particular set of oxidative cleavage products is thus a useful skill, illustrated in Sample Problem 12.4.

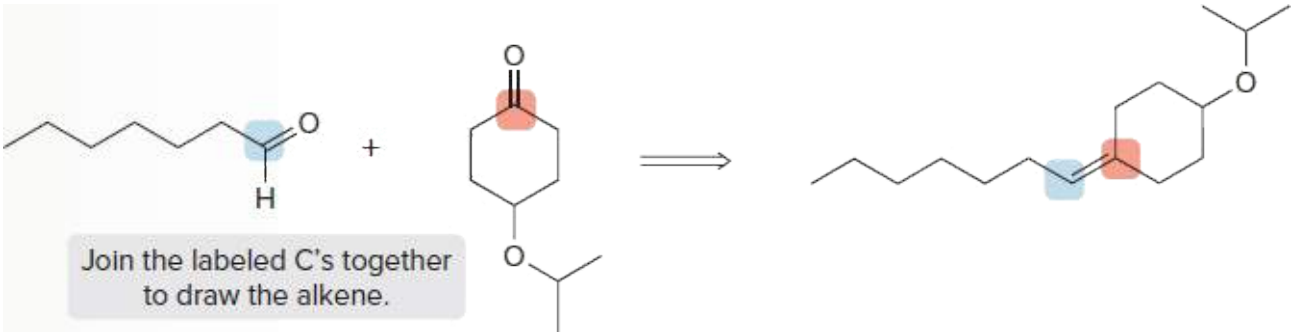
Sample Problem 12.4 Determining the Alkene That Forms a Set of Oxidative Cleavage Products

What alkene forms the following products after reaction with O_3 followed by CH_3SCH_3?



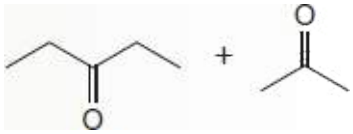
Solution

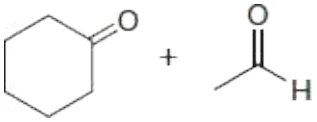
To draw the starting material, ignore the O atoms in the carbonyl groups and join the carbonyl carbons together by a C=C.

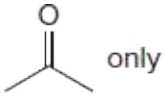


Problem 12.20

What alkene yields each set of oxidative cleavage products?

a. 

b. 

c. 

More Practice:

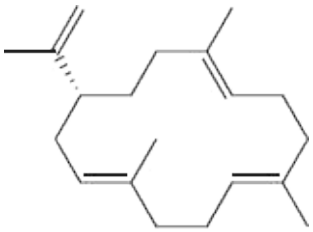
Try Problem s 12.46a, b; 12.47.

Cembrene A (Problem 12.21) is isolated from soft corals of the genus *Naphthea*.

©magnusdeepbelow/Shutterstock

Problem 12.21

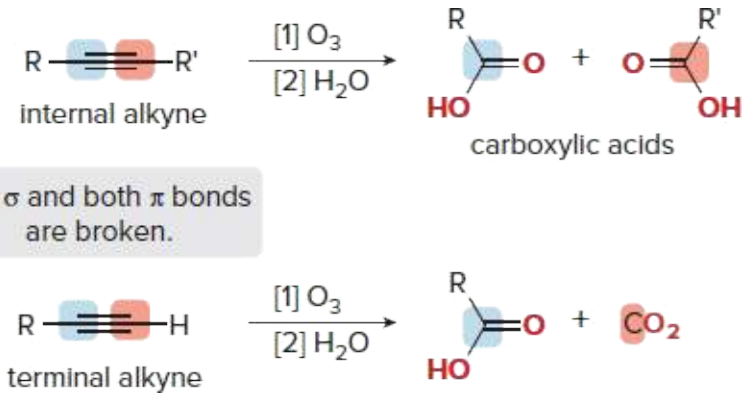
Draw the products formed when cembrene A is treated with O_3 followed by CH_3SCH_3. Label each product as chiral or achiral.



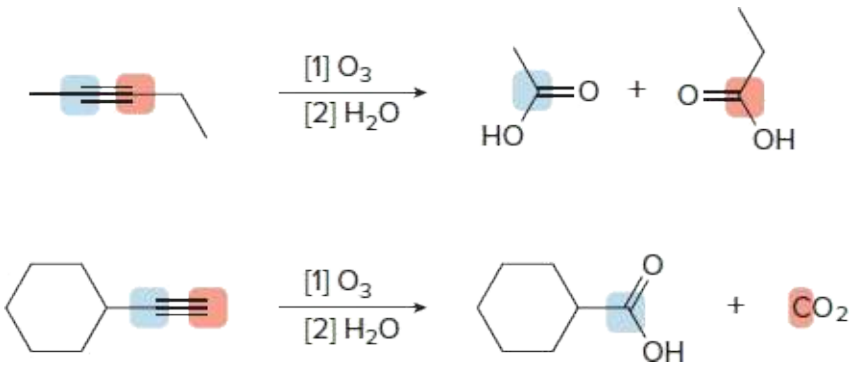
cembrene A

12.11 Oxidative Cleavage of Alkynes

Alkynes also undergo oxidative cleavage of the σ bond and both π bonds of the triple bond. Internal alkynes are oxidized to carboxylic acids (RCOOH), whereas terminal alkynes afford carboxylic acids and CO_2 from the *sp* hybridized C—H bond.



Oxidative cleavage is commonly carried out with O_3, followed by cleavage of the intermediate ozonide with H_2O.

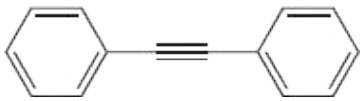


Problem 12.22

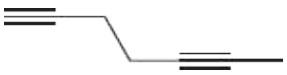
Draw the products formed when each alkyne is treated with O_3 followed by H_2O.

a.

b.



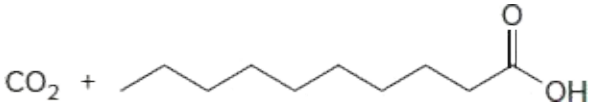
c.



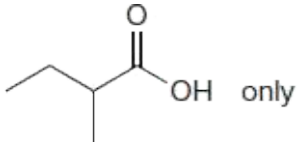
Problem 12.23

What alkyne (or diyne) yields each set of oxidative cleavage products?

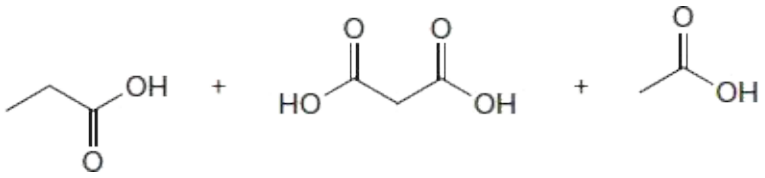
a.



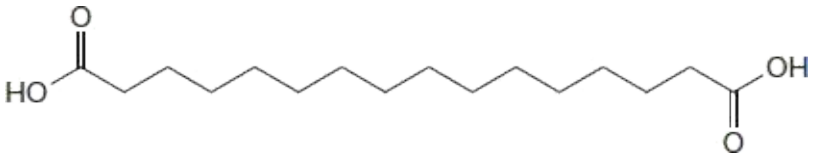
b.



c.



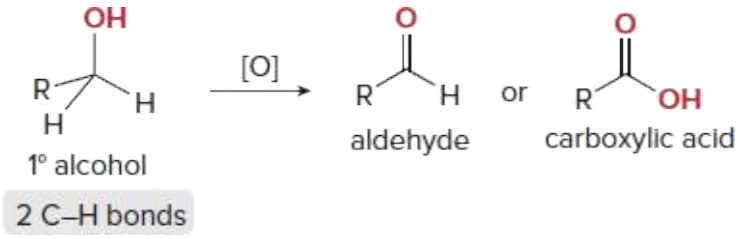
d.



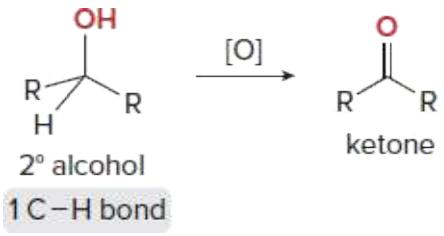
12.12 Oxidation of Alcohols

Alcohols are oxidized to a variety of carbonyl compounds, depending on the type of alcohol and reagent. Oxidation occurs by replacing the C—H bonds *on the carbon bearing the OH group* by C—O bonds.

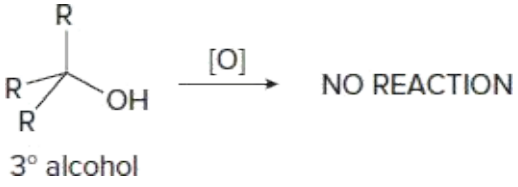
- **1° Alcohols are oxidized to either aldehydes or carboxylic acids by replacing either one or two C—H bonds by C—O bonds.**



- **2° Alcohols are oxidized to ketones by replacing the one C—H bond by a C—O bond.**

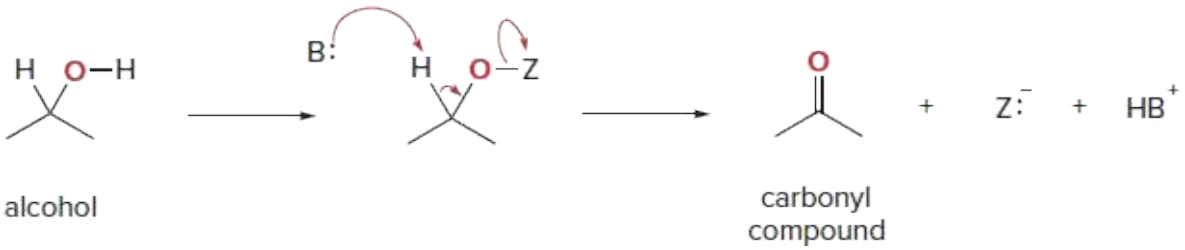


- **3° Alcohols have no H atoms on the carbon with the OH group, so they are *not* easily oxidized.**



Alcohol oxidations often occur by a pathway that involves bonding a leaving group Z to the oxygen, where Z is typically a metal in a high oxidation state. Elimination with a

base then forms a C=O and a metal in a lower oxidation state.

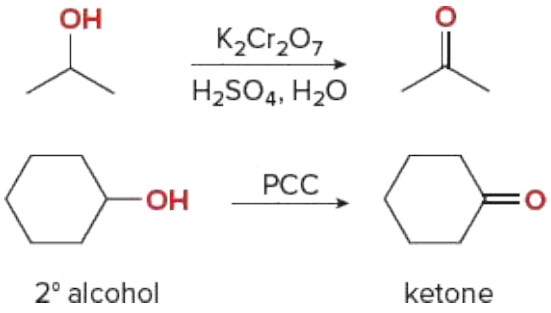


The oxidation of alcohols to carbonyl compounds is typically carried out with Cr^{6+} oxidants, which are reduced to Cr^{3+} products.

- CrO_3, $Na_2Cr_2O_7$, and $K_2Cr_2O_7$ are strong, nonselective oxidants used in aqueous acid (H_2SO_4 + H_2O).
- PCC (Section 12.7) is soluble in CH_2Cl_2 (dichloromethane), and can be used without strong acid present, making it a more selective, milder oxidant.

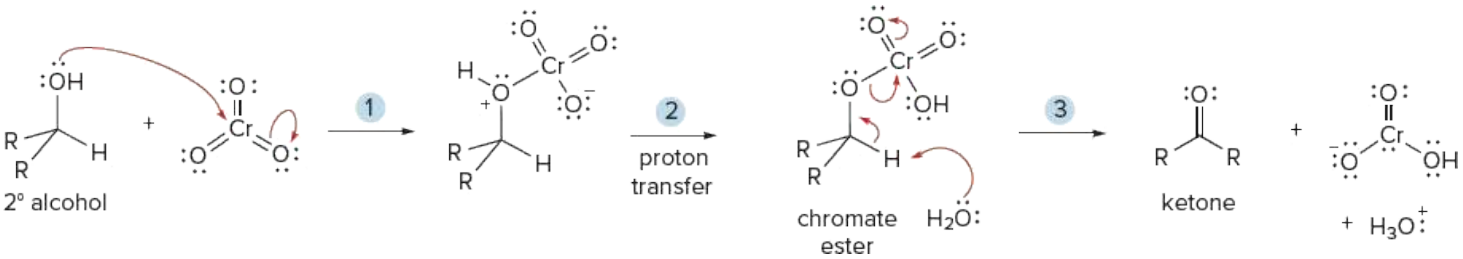
12.12A Oxidation of 2° Alcohols

Any of the Cr^{6+} oxidants effectively oxidizes 2° alcohols to ketones.



The mechanism for alcohol oxidation has two key parts: formation of a chromate ester and loss of a proton. Mechanism 12.5 is drawn for the oxidation of a general 2° alcohol with CrO_3.

Mechanism 12.5 Oxidation of an Alcohol with CrO_3



1 – 2 Nucleophilic attack of the alcohol on the electrophilic metal (Cr^{6+} oxidation state) followed by proton transfer forms a chromate ester.

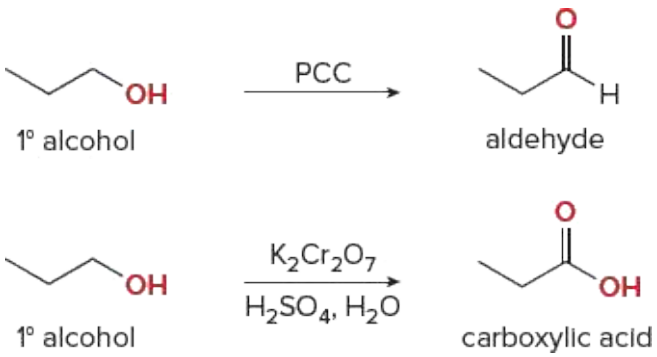
3 **A base removes a proton and the electron pair in the C—H bond forms the new π bond of the C=O. Carbon is oxidized because the number of C—O bonds increases, and Cr^{6+} is reduced to Cr^{4+}.**

These three steps convert the Cr^{6+} oxidant to a Cr^{4+} product, which is then further reduced to a Cr^{3+} product by a series of steps.

12.12B Oxidation of 1° Alcohols

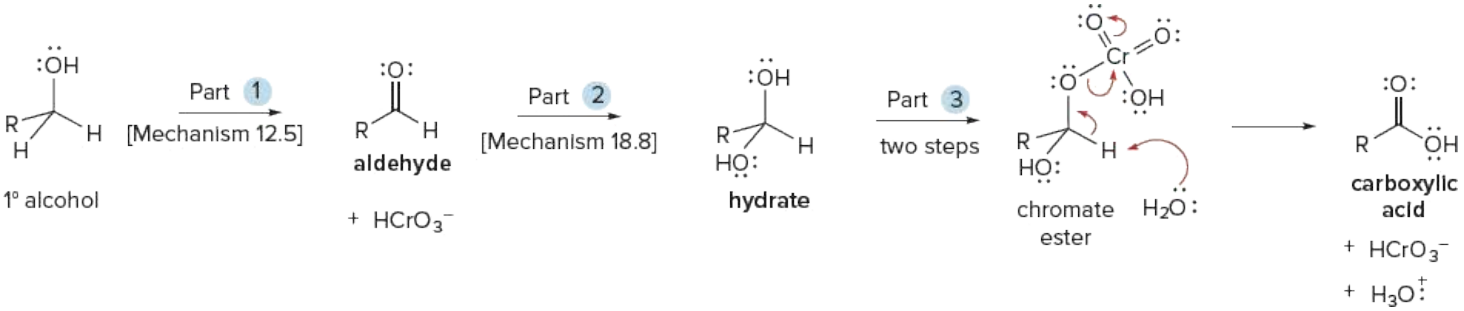
1° Alcohols are oxidized to either aldehydes or carboxylic acids, depending on the reagent.

- **1° Alcohols are oxidized to aldehydes (RCHO) under mild reaction conditions—using PCC in CH_2Cl_2.**
- **1° Alcohols are oxidized to carboxylic acids (RCOOH) under harsher reaction conditions: $Na_2Cr_2O_7$, $K_2Cr_2O_7$, or CrO_3 in the presence of H_2O and H_2SO_4.**



The mechanism for the oxidation of 1° alcohols to aldehydes parallels the oxidation of 2° alcohols to ketones detailed in Section 12.12A. Oxidation of a 1° alcohol to a carboxylic acid requires three operations: oxidation first to the aldehyde, reaction with water, and then further oxidation to the carboxylic acid, as shown in Mechanism 12.6.

Mechanism 12.6 Oxidation of a 1° Alcohol to a Carboxylic Acid



Part 1 **The 1° alcohol is oxidized to an aldehyde by the three-step sequence in Mechanism 12.5.**

Part 2 **Water adds to the C=O to form a hydrate, a compound with two OH groups bonded to the same carbon, by a mechanism discussed in Section 18.12.**

Part 3 **Oxidation of the C—H bond of the hydrate follows Mechanism 12.5—formation of a chromate ester and loss of a proton.**

Cr^{6+} oxidations are characterized by a color change, as the red-orange Cr^{6+} reagent is reduced to green Cr^{3+}. The first devices used to measure blood alcohol content in individuals suspected of "driving under the influence" made use of this color change. Oxidation of CH_3CH_2OH, the 1° alcohol in alcoholic beverages, with orange $K_2Cr_2O_7$ forms CH_3COOH and green Cr^{3+}.

Blood alcohol level can be determined by having an individual blow into a tube containing $K_2Cr_2O_7$, H_2SO_4, and an inert solid. The alcohol in the exhaled breath is oxidized by the Cr^{6+} reagent, which turns green in the tube (Figure 12.9). The higher the concentration of CH_3CH_2OH in the breath, the more Cr^{6+} is reduced, and the farther the green Cr^{3+} color extends down the length of the sample tube. This value is then correlated with blood alcohol content to determine if an individual has surpassed the legal blood alcohol limit.

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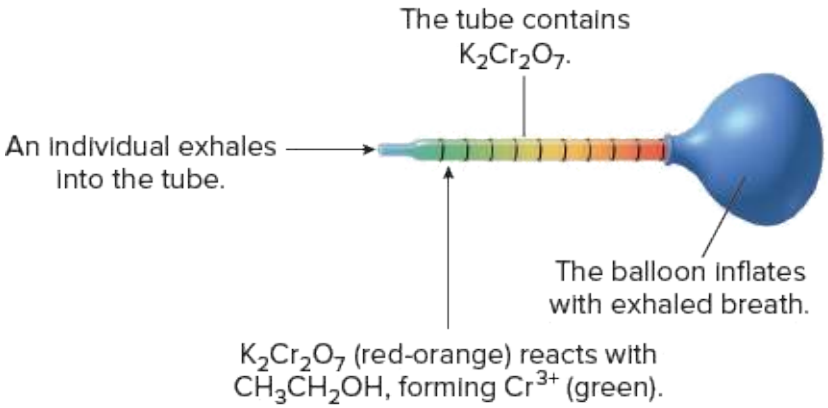
a. Schematic of an alcohol testing device



b. Consumer product

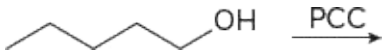
©McGraw-Hill Education/Elite Images

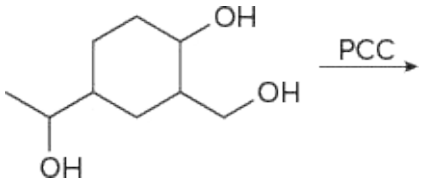
- The oxidation of CH_3CH_2OH with $K_2Cr_2O_7$ to form CH_3COOH and Cr^{3+} was the first available method for the routine testing of alcohol concentration in exhaled breath. Some consumer products for alcohol screening are still based on this technology.

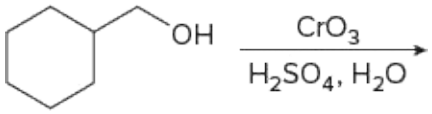
Figure 12.9 **Blood alcohol screening**

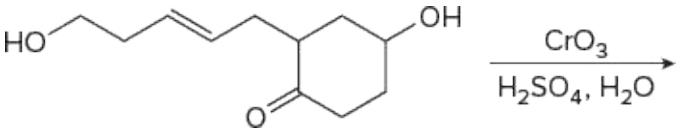
Problem 12.24

Draw the organic products in each of the following reactions.

a. 

b. 

c. 

d. 

12.13 Green Chemistry

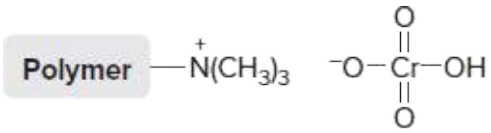
Several new methods of oxidation are based on green chemistry. *Green chemistry* is the use of environmentally benign methods to synthesize compounds. Its purpose is to use safer reagents and less solvent, and develop reactions that form fewer by-products and generate less waste.

Green polymer synthesis using starting materials derived from renewable resources (rather than petroleum) is discussed in Chapter 28.

Since many oxidation methods use toxic reagents (such as OsO_4 and O_3) and corrosive acids (such as H_2SO_4), or they generate carcinogenic by-products (such as Cr^{3+}), alternative reactions have been developed. One method uses a polymer-supported Cr^{6+} reagent—$HCrO_4^-$–Amberlyst A-26 resin—that avoids the use of strong acid, and forms a Cr^{3+} by-product that can be easily removed from the product by filtration.

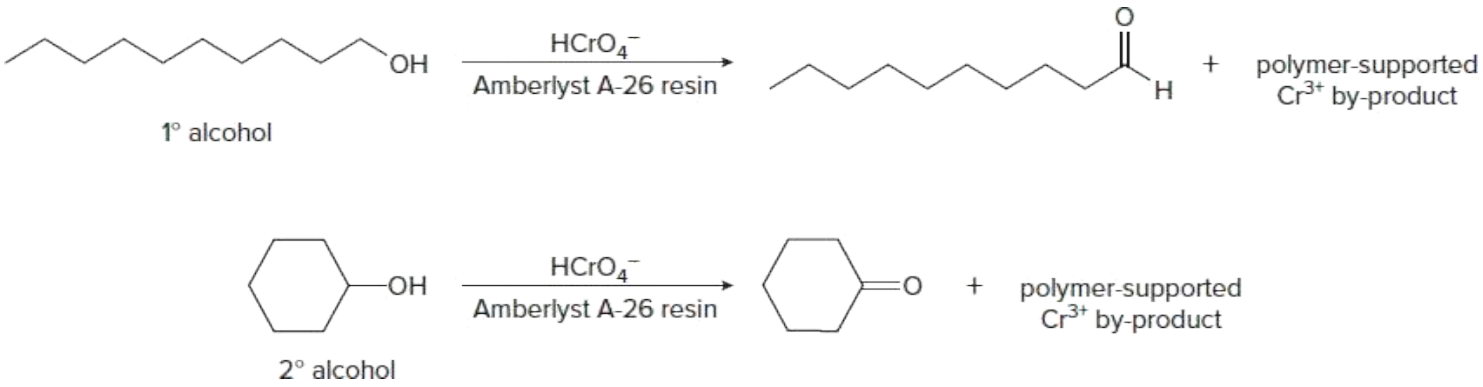
The Amberlyst A-26 resin consists of a complex hydrocarbon network with cationic ammonium ion appendages that serve as counterions to the anionic chromium oxidant, $HCrO_4^-$. Heating the insoluble polymeric reagent with an alcohol results in

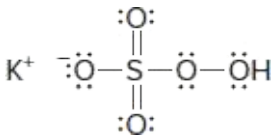
oxidation to a carbonyl compound, with formation of an insoluble Cr^{3+} by-product. Not only can the metal by-product be removed by filtration without added solvent, it can also be regenerated and reused in a subsequent reaction.



Amberlyst A-26 resin Cr^{6+} oxidant

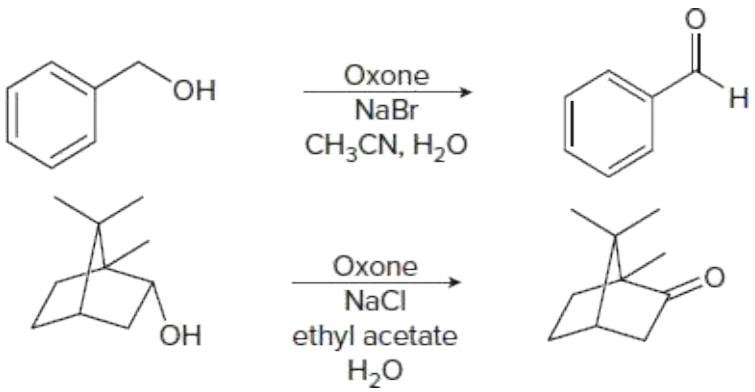
With $HCrO_4^-$–Amberlyst A-26 resin, 1° alcohols are oxidized to aldehydes and 2° alcohols are oxidized to ketones.





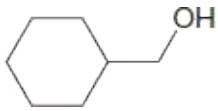
potassium peroxymonosulfate

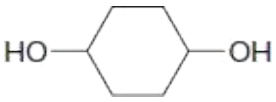
Many other green approaches to oxidation that avoid the generation of metal by-products entirely are also under active investigation. For example, potassium peroxymonosulfate, $KHSO_5$, is a sulfate derivative of hydrogen peroxide, sold as a triple salt ($2\ KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) under the trade name of Oxone. Oxone oxidizes a variety of substrates without the presence of a heavy metal like chromium or manganese, and in some cases, oxidation reactions can be carried out in water or aqueous solutions. The weak oxygen–oxygen bond of the reagent is cleaved during oxidation, and a sulfate salt (K_2SO_4) is formed as by-product. Two examples of oxidations of alcohols are shown.

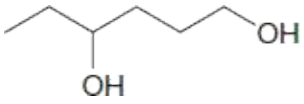


Problem 12.25

What carbonyl compound is formed when each alcohol is treated with $HCrO_4^-$–Amberlyst A-26 resin?

a. 

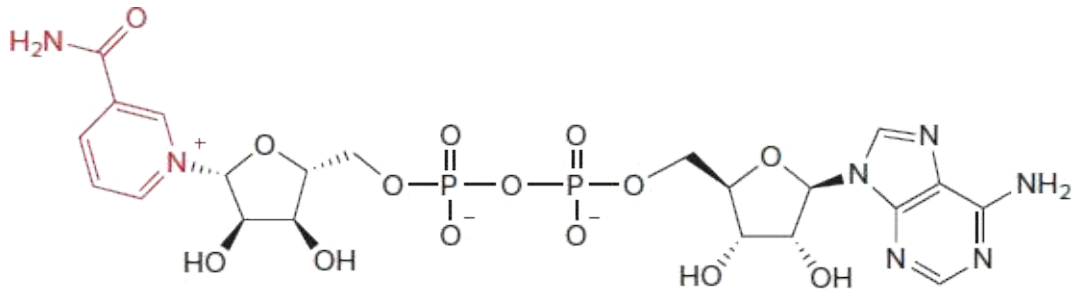
b. 

c. 

12.14 Biological Oxidation

Many reactions in biological systems involve oxidation or reduction. Instead of using Cr^{6+} reagents for oxidation, cells use two organic compounds—a high-molecular-weight enzyme and a simpler coenzyme that serves as the oxidizing agent.

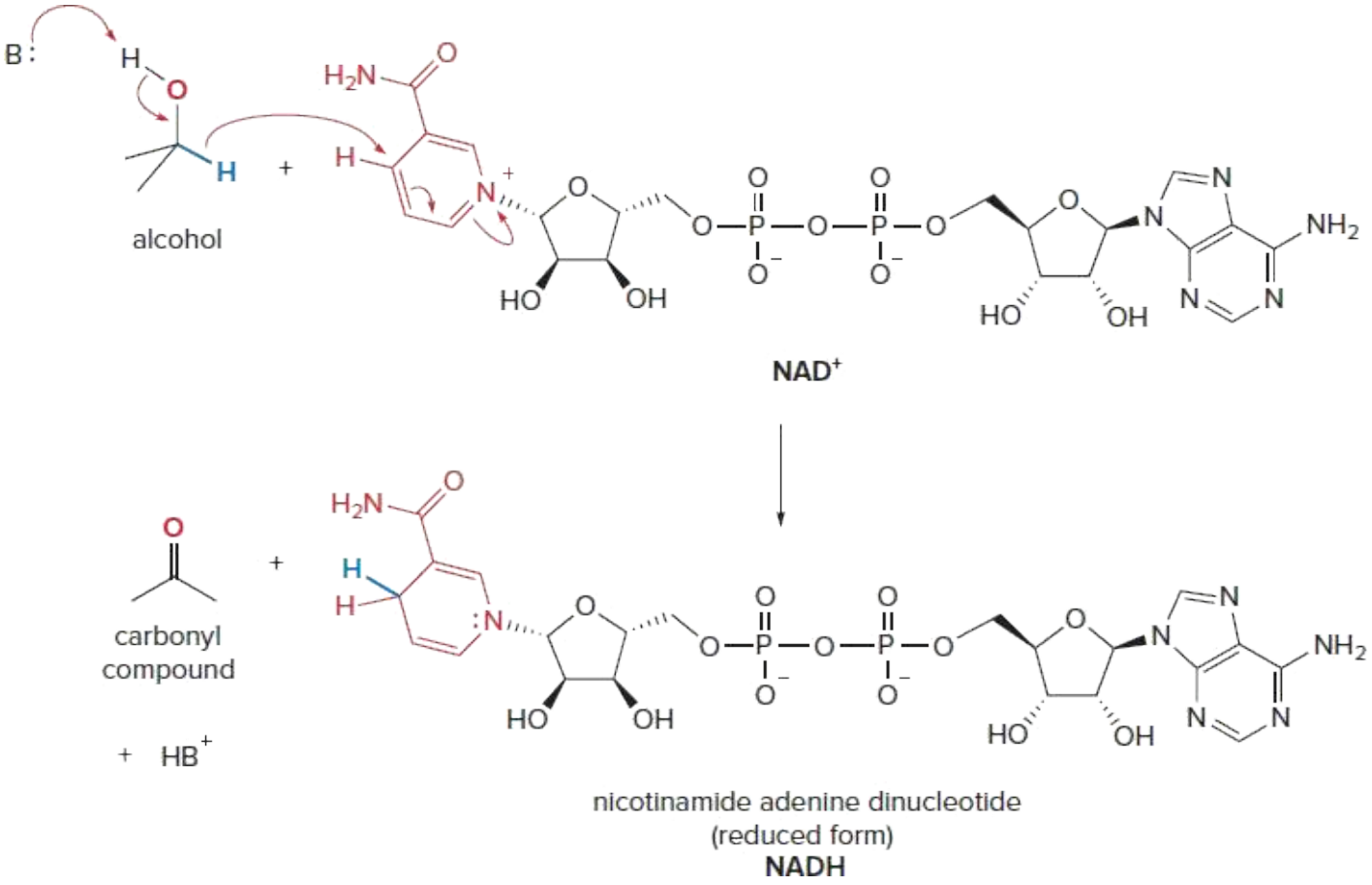
The coenzyme often used to oxidize alcohols in biological systems is nicotinamide adenine dinucleotide, abbreviated as NAD^+. Although the structure is complex, only a portion of the molecule, drawn in red, participates in redox reactions.



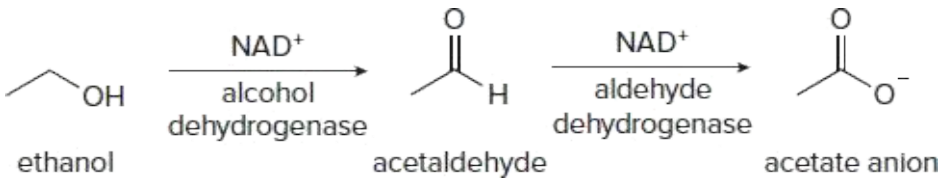
nicotinamide adenine dinucleotide
NAD^+

Biological oxidation of an alcohol occurs by transferring a hydride, a hydrogen atom

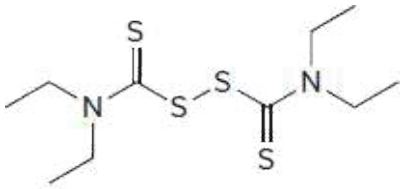
with two electrons, from the alcohol to NAD^+ to form a carbonyl group. In the process, NAD^+ is reduced to nicotinamide adenine dinucleotide (reduced form), abbreviated as NADH. NADH is a biological reducing agent that converts carbonyl compounds to alcohols, as discussed in Section 17.6.



For example, when CH_3CH_2OH (ethanol) is ingested, it is oxidized in the liver by NAD^+ to CH_3CHO (acetaldehyde), and then to CH_3COO^- (acetate anion, the conjugate base of acetic acid). Acetate is the starting material for the synthesis of fatty acids and cholesterol. Both oxidations are catalyzed by a dehydrogenase enzyme.



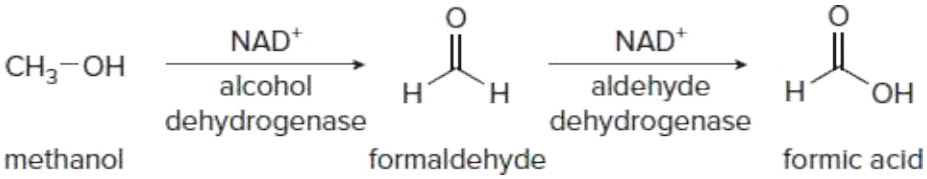
If more ethanol is ingested than can be metabolized in a given time, the concentration of acetaldehyde builds up. This toxic compound is responsible for the feelings associated with a hangover.



Antabuse

Antabuse, a drug given to alcoholics to prevent them from consuming alcoholic beverages, acts by interfering with the normal oxidation of ethanol. Antabuse inhibits the oxidation of acetaldehyde to the acetate anion. Because the first step in ethanol metabolism occurs but the second does not, the concentration of acetaldehyde rises, causing an individual to become violently ill.

Like ethanol, methanol is oxidized by the same enzymes to give an aldehyde and an acid: formaldehyde and formic acid. These oxidation products are extremely toxic because they cannot be used by the body. As a result, the pH of the blood decreases, and blindness and death can follow.

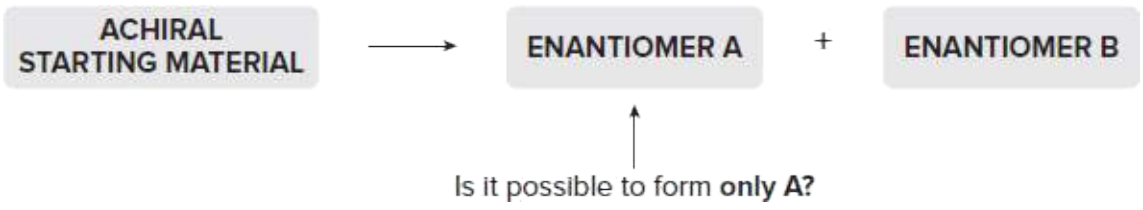


methanol formaldehyde formic acid

Because the enzymes have a higher affinity for ethanol than methanol, methanol poisoning is treated by giving ethanol to the afflicted individual. With both methanol and ethanol in the patient's system, the enzymes react more readily with ethanol, allowing the methanol to be excreted unchanged without the formation of methanol's toxic oxidation products.

12.15 Sharpless Epoxidation

In all of the reactions discussed so far, an achiral starting material has reacted with an achiral reagent to give either an achiral product or a racemic mixture of two enantiomers. If you are trying to make a chiral product, this means that only half of the product mixture is the desired enantiomer and the other half is the undesired one. The synthesis of disparlure, outlined in Figure 12.8, exemplifies this dilemma.



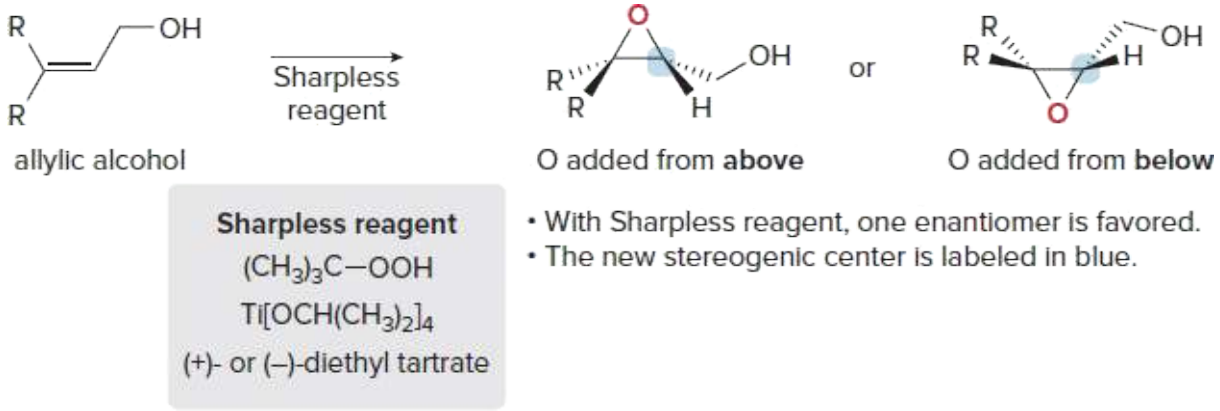
K. Barry Sharpless, of The Scripps Research Institute, reasoned that using a chiral

reagent might make it possible to favor the formation of one enantiomer over the other.

K. Barry Sharpless shared the 2001 Nobel Prize in Chemistry for his work on chiral oxidation reactions.

- **An *enantioselective* reaction affords predominantly or exclusively one enantiomer.**
- **A reaction that converts an achiral starting material into predominantly one enantiomer is also called an *asymmetric reaction*.**

The Sharpless asymmetric epoxidation is an enantioselective reaction that oxidizes alkenes to epoxides. Only the double bonds of allylic alcohols—that is, alcohols having a hydroxy group on the carbon adjacent to a C=C—are oxidized in this reaction.



The Sharpless reagent consists of three components: *tert*-butyl hydroperoxide, $(CH_3)_3COOH$; a titanium catalyst—usually titanium(IV) isopropoxide, $Ti[OCH(CH_3)_2]_4$; and diethyl tartrate (DET). There are two different chiral diethyl tartrate isomers, labeled as (+)-DET or (–)-DET to indicate the direction in which they rotate polarized light.

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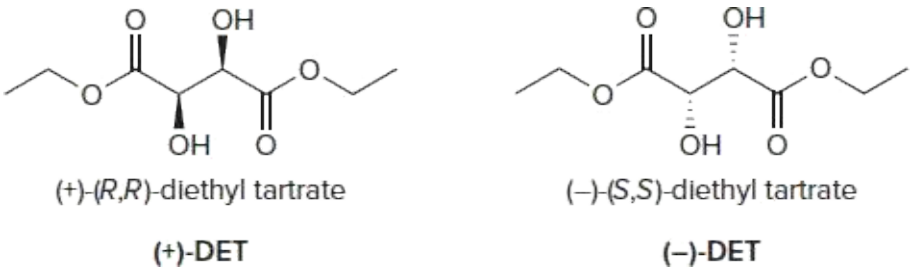


(+)-DET is prepared from

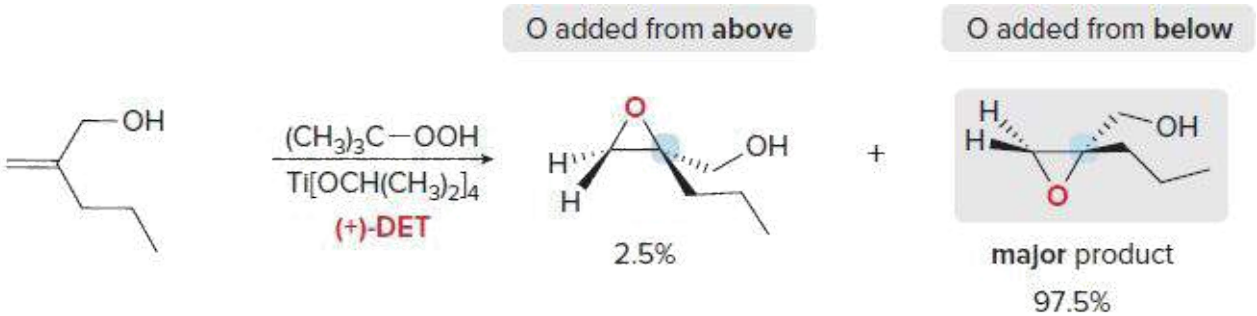
(+)-(*R*,*R*)-tartaric acid

[$HO_2CCH(OH)CH(OH)CO_2H$], a naturally occurring carboxylic acid found in grapes and sold as a by-product of the wine industry. ©*Image Source*

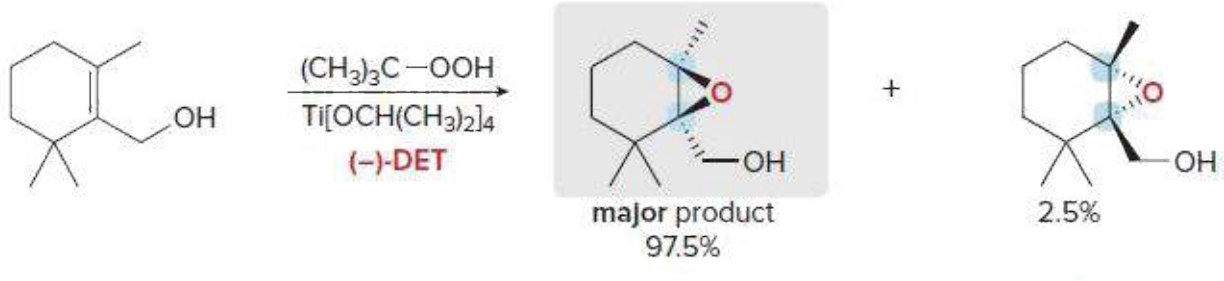
Enantiomeric excess = *ee* = % of one enantiomer − % of the other enantiomer.

The identity of the DET isomer determines which enantiomer is the major product obtained in the epoxidation of an allylic alcohol with the Sharpless reagent.

[1]



[2]

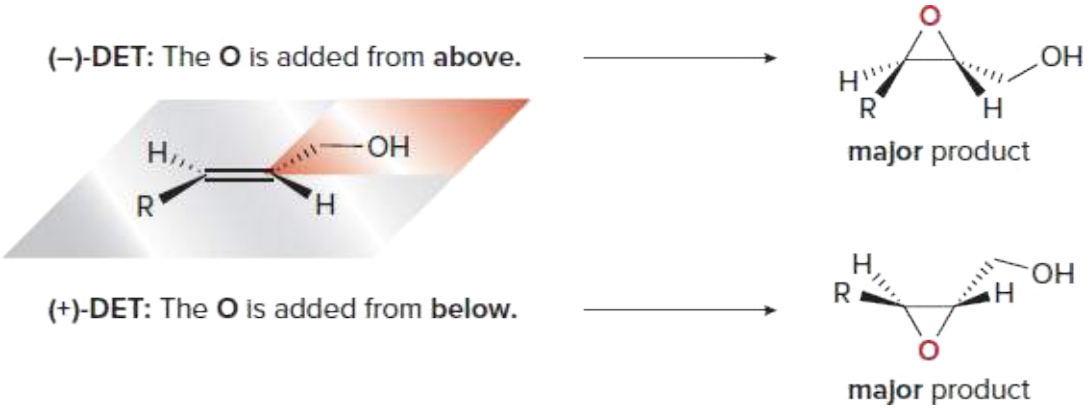


Stereogenic centers are labeled in blue.

The degree of enantioselectivity of a reaction is measured by its enantiomeric excess (*ee*) (Section 5.12D). Reactions [1] and [2] are highly enantioselective because each has an enantiomeric excess of 95% (97.5% of the major enantiomer –2.5% of the minor enantiomer).

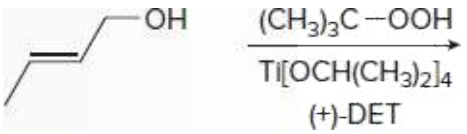
To determine which enantiomer is formed for a given isomer of DET, draw the allylic alcohol in a plane, with the C=C horizontal and the OH group in the upper right corner; then:

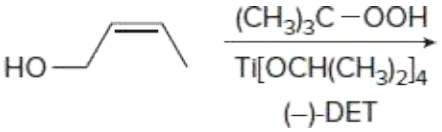
- **Epoxidation with (−)-DET adds an oxygen atom from *above* the plane.**
- **Epoxidation with (+)-DET adds an oxygen atom from *below* the plane.**



Sample Problem 12.5 Drawing the Product of a Sharpless Epoxidation

Predict the major product in each epoxidation.

a. 

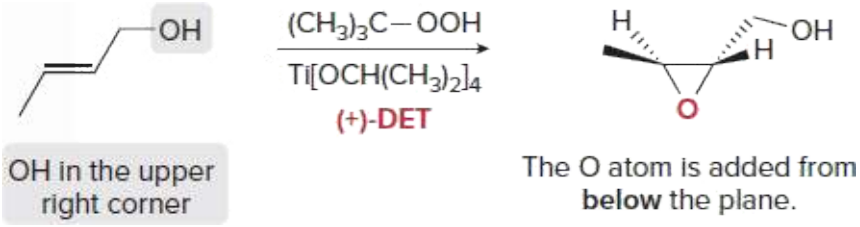
b. 

Solution

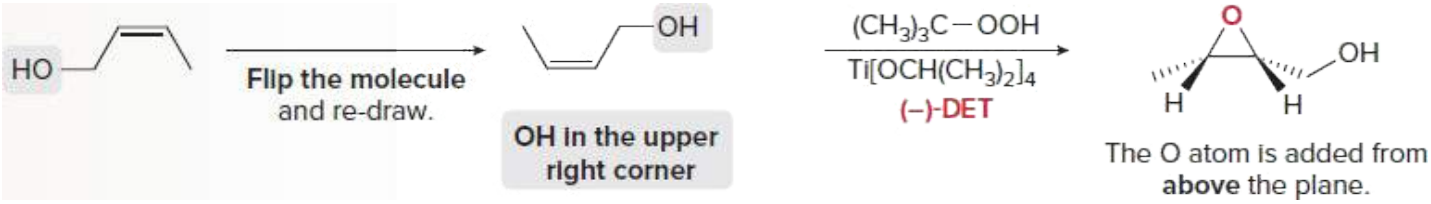
To draw an epoxidation product:

- **Draw the allylic alcohol with the C=C horizontal and the OH group in the upper right corner of the alkene. Re-draw the alkene if necessary.**
- **(+)-DET adds the O atom from below, and (−)-DET adds the O atom from above.**

a. **Because the C=C is drawn horizontal with the OH group in the upper right corner, it is not necessary to re-draw the alkene. With (+)-DET, the O atom is added from below.**



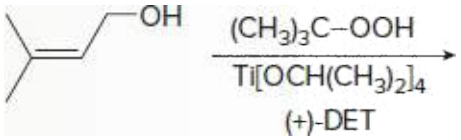
b. **The allylic alcohol must be re-drawn with the C=C horizontal and the OH group in the upper right corner. Because (−)-DET is used, the O atom is then added from above.**



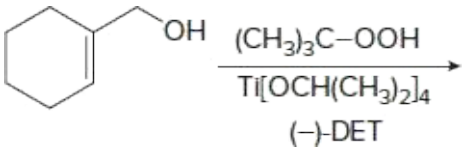
Problem 12.26

Draw the products of each Sharpless epoxidation.

a.



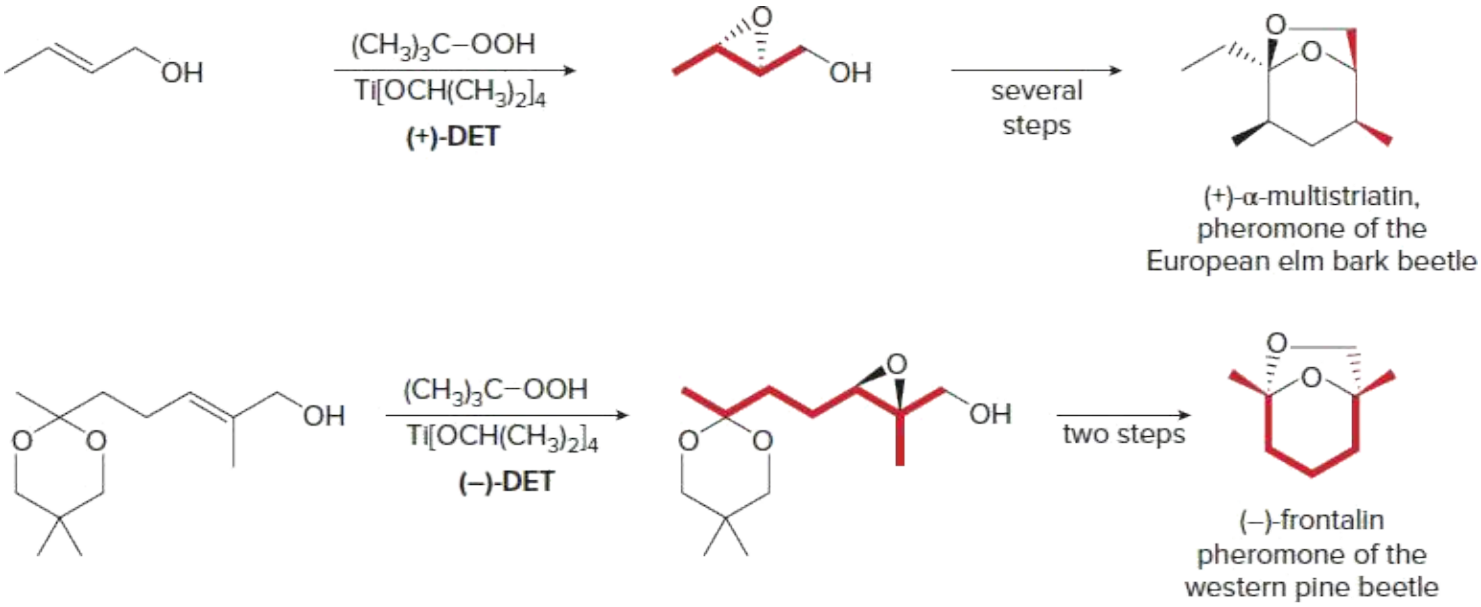
b.



More Practice:

Try Problem s 12.28e; 12.35j; 12.36e, f; 12.54; 12.55.

The Sharpless epoxidation has been used to synthesize many chiral natural products, including two insect pheromones—(+)-α-multistriatin and (–)-frontalin, as shown in Figure 12.10.

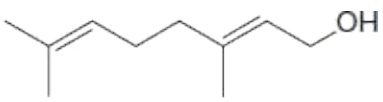


- The bonds in the products that originate from the epoxide intermediate are indicated in red.

Figure 12.10 **The synthesis of chiral insect pheromones using asymmetric epoxidation**

Problem 12.27

Explain why only one C=C of geraniol is epoxidized with the Sharpless reagent.



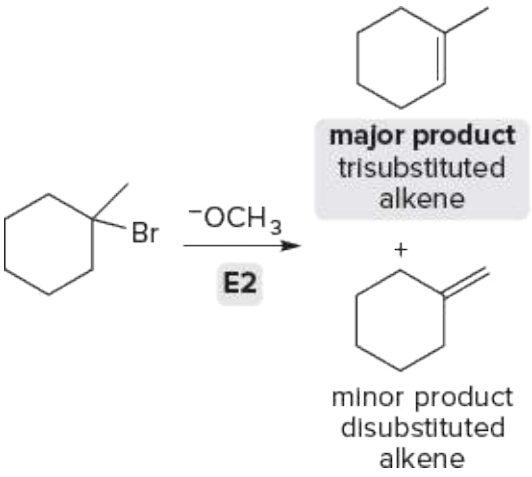
geraniol

Chapter 4 REVIEW

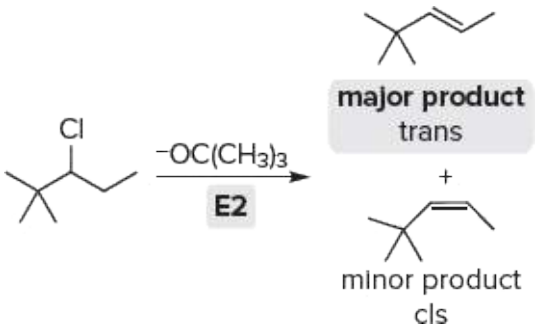
KEY CONCEPTS

Reaction Selectivity

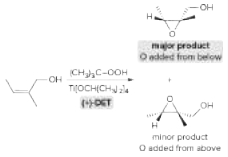
1 **Regioselective reaction (8.5)**	2 **Stereoselective reaction (8.5)**	3 **Enantio reactior**



- **one constitutional isomer formed predominantly or exclusively**



- **one stereoisomer formed predominantly or exclusively**

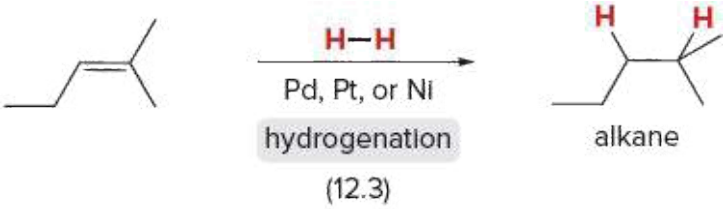


- **one ena formed predom or exclu**

KEY REACTIONS

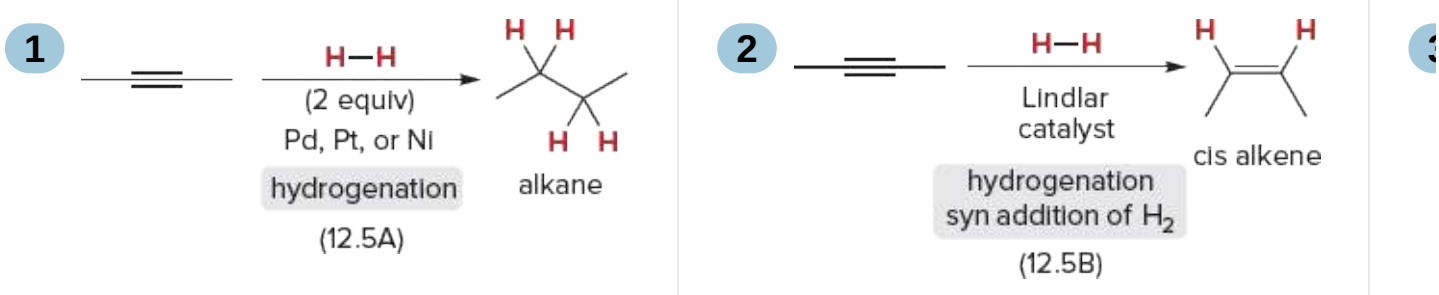
Reduction Reactions

[1] Reduction of alkenes



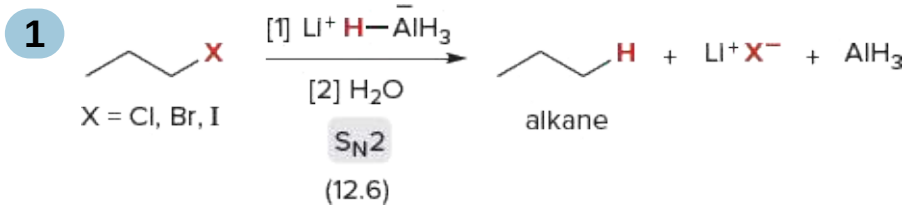
Try Problem s 12.28a, 12.31, 12.35a, 12.36a.

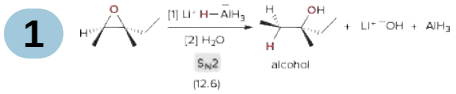
[2] Reduction of alkynes



See Figure 12.5. Try Problem 12.38d.

[3] Reduction of alkyl halides and epoxides

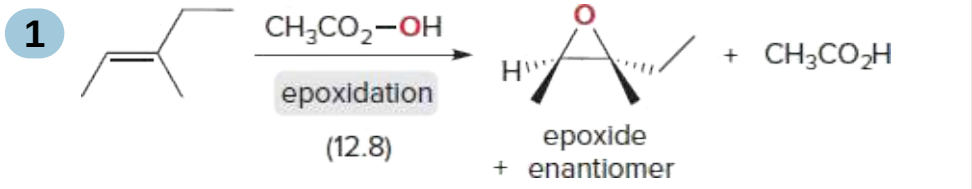


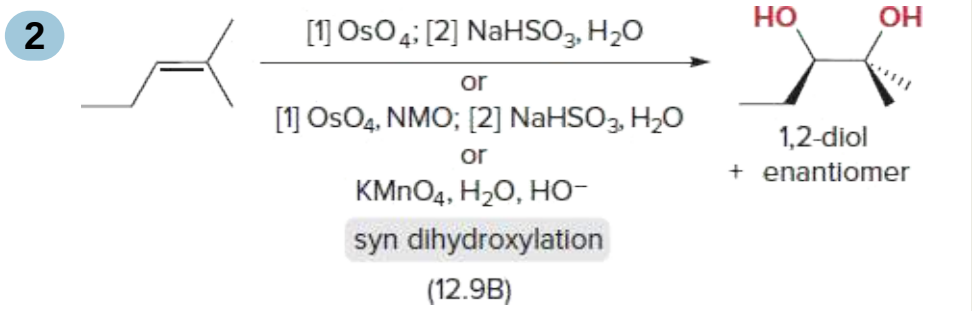


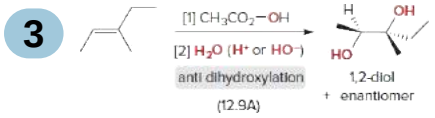
See Figure 12.6. Try Problems 12.35l; 12.36g; 12.38a, c.

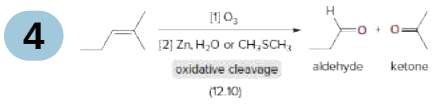
Oxidation Reactions

[1] Oxidation of alkenes



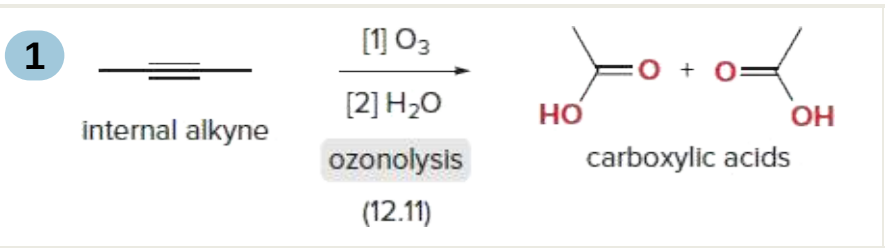


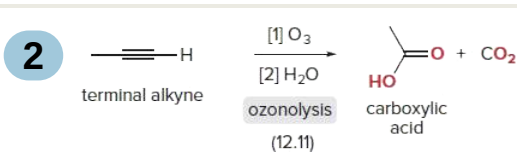




See Sample Problems 12.2, 12.3, Figure 12.7. Try Problems 12.28; 12.35d–g; i, k; 12.36b; 12.37c; 12.38b; 12.45a, b.

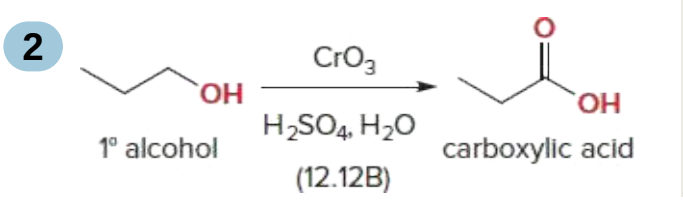
[2] Oxidative cleavage of alkynes



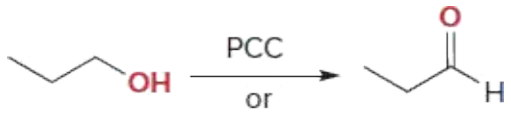


Try Problem 12.45c, d.

[3] Oxidation of alcohols



1



1° alcohol — aldehyde

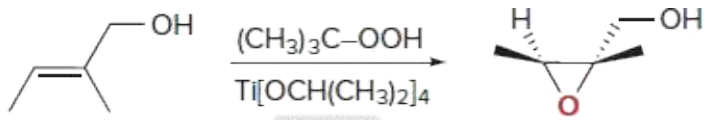
(12.12B, 12.13)

3

Try Problem s 12.28c, d; 12.36c, d, h.

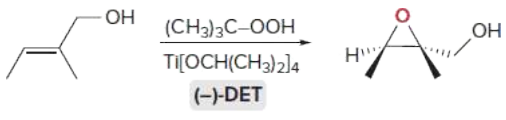
[4] Asymmetric epoxidation of allylic alcohols (12.15)

1



(12.15)

2



(12.15)

See Sample Problem 12.5, Figure 12.10.

Try Problem s 12.28e; 12.35j; 12.36e, f; 12.54; 12.55.

KEY SKILLS

[1] Determining the number of rings and π bonds in a compound ($C_{14}H_{20}$) hydrogenated to a compound of molecular formula $C_{14}H_{26}$ (12.3C)

1 Determine the degrees of unsaturation before and after hydrogenation.

Before H_2 addition—$C_{14}H_{20}$

- **The maximum number of H's possible for *n* C's is 2*n* + 2; in this example, 2*n* + 2 = 2(14) + 2 = 30.**
- **30 H's (maximum) − 20 H's (actual) = 10 H's fewer than the maximum number.**

$$\frac{\text{10 H's fewer than the maximum}}{\text{2 H's removed for each degree of unsaturation}} =$$

five degrees of unsaturation

After H_2 addition—$C_{14}H_{26}$

- **The maximum number of H's possible for *n* C's is 2*n* + 2; in this example, 2*n* + 2 = 2(14) + 30.**
- **30 H's (maximum) – 26 H's (actual) = 4 H's fewer than the maximum number.**

$$\frac{\text{4 H's fewer than the maximum}}{\text{2 H's removed for each degree of unsaturation}} =$$

two degrees of unsaturation

2 **Assign degrees of unsaturation.**

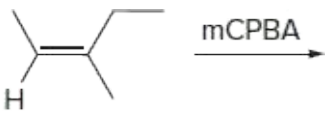
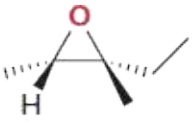
Before H_2 addition: **After H_2 addition:**

five degrees of unsaturation — two degrees of unsaturation = three degrees of unsaturation that reacted with H_2

five rings or π bonds in $C_{14}H_{20}$ = two rings + three π bonds Answer

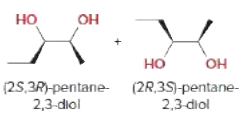
See Sample Problem 12.1. Try Problem 12.33.

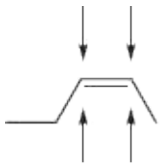
[2] Drawing the stereoisomers from alkene epoxidation with mCPBA (12.8A); example: (*Z*)-3-methylpent-2-ene

1 Draw the starting materials.	**2** Add an O atom from above the alkene.	**3** Add an O atom from below the alkene.
 (*Z*)-3-methylpent-2-ene	 (2*R*,3*S*)-2-ethyl-2,3-dimethyl-oxirane	(2*S*,3*R*)-2-ethyl-2,3-dimethyl-oxirane

See Sample Problem 12.2. Try Problems 12.28b; 12.35d, k; 12.36b.

[3] Drawing the products of dihydroxylation of an alkene (12.9)

1 Use the reagents to identify the two groups added to the C=C.	**2** Use the mechanism to determine the stereochemistry.	**3** Draw the product(s
$KMnO_4$, H_2O, HO^- (12.9B) → 2 OH's are added.		 (2*S*,3*R*)-pentane-2,3-diol (2*R*,3*S*)-pentane-2,3-diol



2 OH's add to the top or bottom of the C=C.

syn dihydroxylation

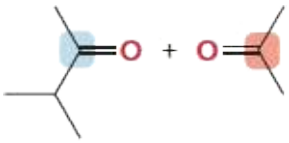
Try Problem s 12.35e–g, 12.38b.

[4] Drawing the products of an ozonolysis reaction (12.10)

1 **Cleave the double bond.**

Break both the σ and π bonds.

2 **Replace the double bond with two carbonyl groups.**



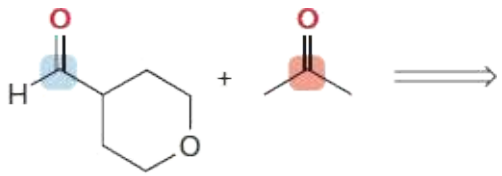
ketone ketone

See Sample Problem 12.3. Try Problems 12.35i; 12.37c; 12.45a, b; 12.48.

Page 505

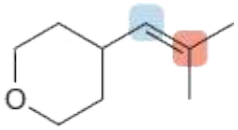
[5] Identifying an alkene from ozonolysis products (12.10)

1 **Identify the C atoms in the carbonyl groups.**



Join the labeled C's together to draw the alkene.

2 **Ignore the O atoms in the C=O's, and join the carbonyl carbons together by a C=C.**

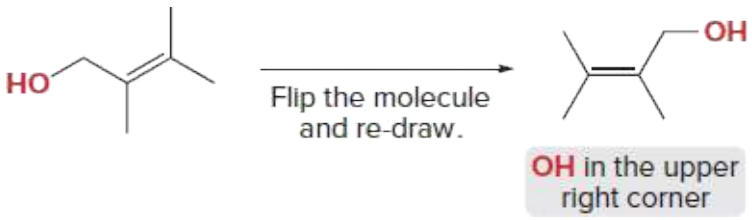


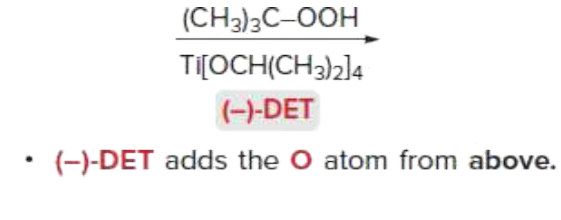
See Sample Problem 12.4. Try Problems 12.46a, b; 12.47.

[6] Predicting the product of a Sharpless reaction (12.15)

1 **Draw the allylic alcohol with the C=C horizontal and the OH group in the upper right corner of the alkene.**

2 **Use the reagents to determine how to add the atom to the C=C.**



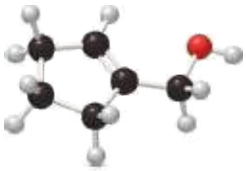


See Sample Problem 12.5. Try Problems 12.28e; 12.35j; 12.36e, f; 12.54; 12.55.

PROBLEMS

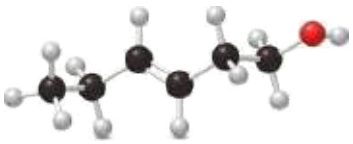
Problems Using Three-Dimensional Models

12.28 **Draw the products formed when A is treated with each reagent: (a) H_2 + Pd-C; (b) mCPBA; (c) PCC; (d) CrO_3, H_2SO_4, H_2O; (e) Sharpless reagent with (+)-DET.**



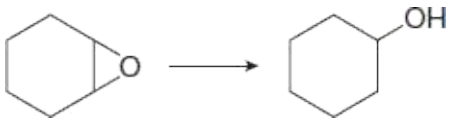
A

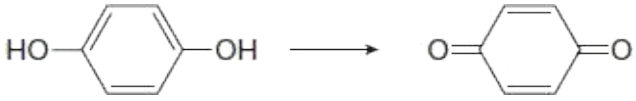
12.29 **Devise a synthesis of the following compound from acetylene and organic compounds containing two or fewer carbons. You may use any other required reagents.**



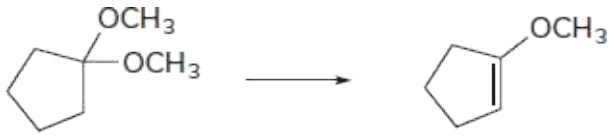
Classifying Reactions as Oxidation or Reduction

12.30 **Label each reaction as oxidation, reduction, or neither.**

a. 

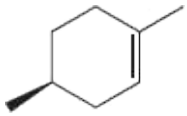
b. 

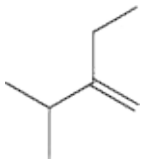
c.

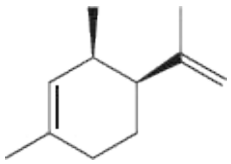
d. 

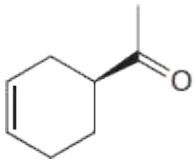
Hydrogenation

12.31 **Draw the organic products formed when each compound is treated with H_2, Pd-C. Indicate the three-dimensional structure of all stereoisomers formed.**

a. 

b. 

c. 

d. 

12.32 **Match each alkene to its heat of hydrogenation.**

Alkenes: 3-methylbut-1-ene, 2-methylbut-1-ene, 2-methylbut-2-ene

$\Delta H°$ (hydrogenation) kJ/mol: −119, −127, −112

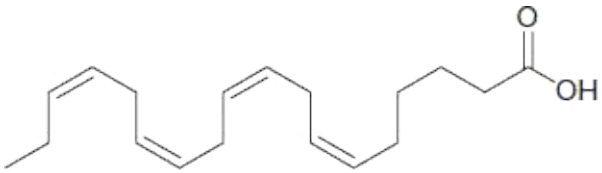
12.33 **How many rings and π bonds are contained in compounds A—C? Draw one possible structure for each compound.**

a. Compound A has molecular formula C_5H_8 and is hydrogenated to a compound having molecular formula C_5H_{10}.

b. Compound B has molecular formula $C_{10}H_{16}$ and is hydrogenated to a compound having molecular formula $C_{10}H_{18}$.

c. Compound C has molecular formula C_8H_8 and is hydrogenated to a compound having molecular formula C_8H_{16}.

12.34 Stearidonic acid ($C_{18}H_{28}O_2$) is an unsaturated fatty acid obtained from oils isolated from hemp and blackcurrant (see also Problem 10.11).



stearidonic acid

a. What fatty acid is formed when stearidonic acid is hydrogenated with excess H_2 and a Pd catalyst?

b. What fatty acids are formed when stearidonic acid is hydrogenated with one equivalent of H_2 and a Pd catalyst?

c. Draw the structure of a possible product formed when stearidonic acid is hydrogenated with one equivalent of H_2 and a Pd catalyst, and one double bond is isomerized to a trans isomer.

d. How do the melting points of the following fatty acids compare: stearidonic acid; one of the products formed in part (b); the product drawn in part (c)?

Reactions—General

12.35 Draw the organic products formed when cyclopentene is treated with each reagent. With some reagents, no reaction occurs.

a. H_2 + Pd-C

b. H_2 + Lindlar catalyst

c. Na, NH_3

d. CH_3CO_3H

e. [1] CH_3CO_3H; [2] H_2O, HO^-

f. [1] OsO_4 + NMO; [2] $NaHSO_3$, H_2O

g. $KMnO_4$, H_2O, HO^-

h. [1] $LiAlH_4$; [2] H_2O

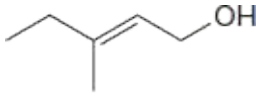
i. [1] O_3; [2] CH_3SCH_3

j. $(CH_3)_3COOH$, $Ti[OCH(CH_3)_2]_4$, (−)-DET

k. mCPBA

l. Product in (k); then [1] $LiAlH_4$; [2] H_2O

12.36 Draw the organic products formed when allylic alcohol A is treated with each reagent.



A

a. H_2 + Pd-C

b. mCPBA

c. PCC

d. CrO_3, H_2SO_4, H_2O

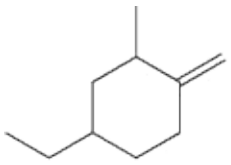
e. $(CH_3)_3COOH$, $Ti[OCH(CH_3)_2]_4$, (+)-DET

f. $(CH_3)_3COOH$, $Ti[OCH(CH_3)_2]_4$, (−)-DET

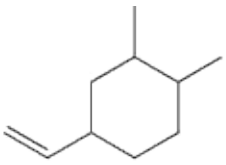
g. [1] PBr_3; [2] $LiAlH_4$; [3] H_2O

h. $HCrO_4^-$–Amberlyst A-26 resin

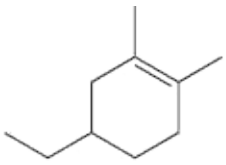
12.37 For alkenes A, B, C, and D: (a) Rank A—D in order of increasing heat of hydrogenation; (b) rank A—D in order of increasing rate of reaction with H_2, Pd-C; (c) draw the products formed when each alkene is treated with ozone, followed by Zn, H_2O.



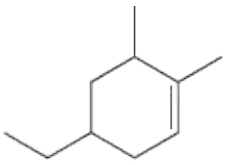
A



B



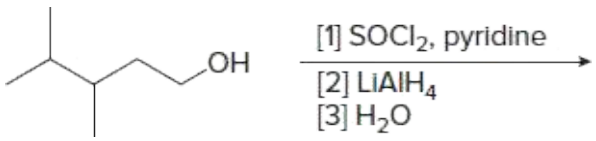
C



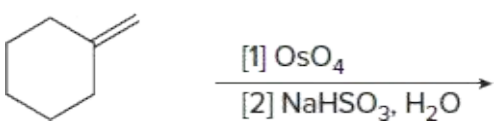
D

12.38 Draw the organic products formed in each reaction.

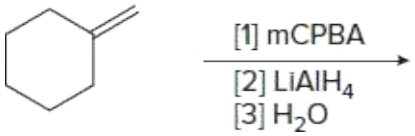
a.



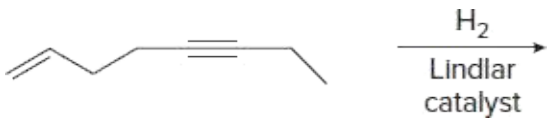
b.



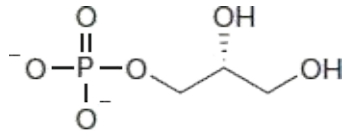
c.



d.



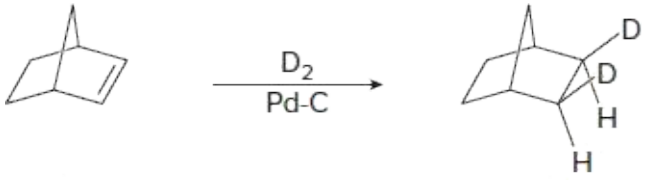
12.39 **One step in the degradation of fats involves the reaction of (*R*)-glycerol phosphate with NAD^+ in the presence of the enzyme glycerol phosphate dehydrogenase. What products are formed if reaction occurs at only the 2° alcohol?**



(*R*)-glycerol phosphate

12.40 **Draw the structure of two different epoxides that would yield 2-methylpentan-2-ol [$(CH_3)_2C(OH)CH_2CH_2CH_3$] when reduced with $LiAlH_4$.**

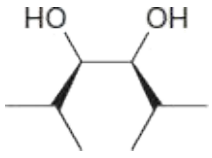
12.41 **Hydrogenation of alkene A with D_2 in the presence of Pd-C affords a single product B. Keeping this result in mind, what compound is formed when A is treated with each reagent: (a) mCPBA; (b) Br_2, H_2O followed by base? Explain these results.**



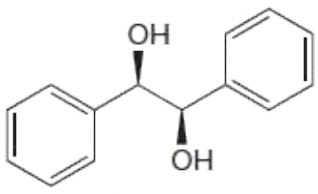
A B

12.42 **What alkene is needed to synthesize each 1,2-diol using [1] OsO_4 followed by $NaHSO_3$ in H_2O; or [2] CH_3CO_3H followed by ^-OH in H_2O?**

a.

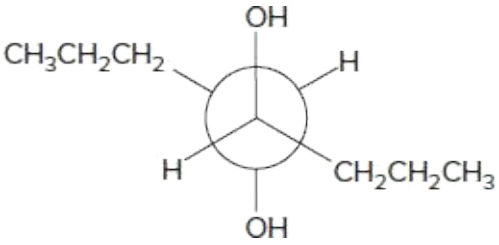


b.

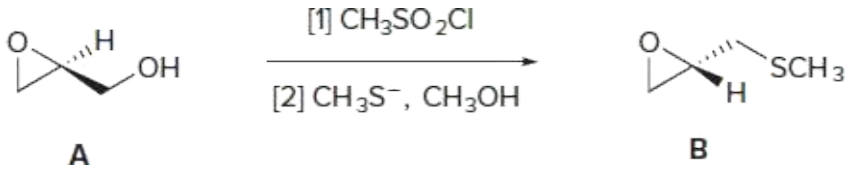


+ enantiomer

c.

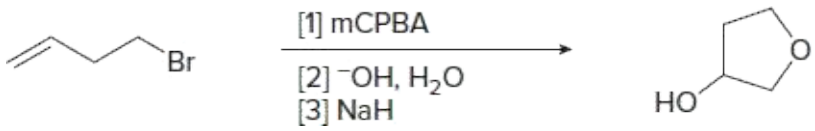


12.43 (a) What product is formed in Step [1] of the following reaction sequence? (b) Draw a mechanism for Step [2] that accounts for the observed stereochemistry. (c) What reaction conditions are necessary to form chiral A from prop-2-en-1-ol (CH_2=$CHCH_2OH$)?



A B

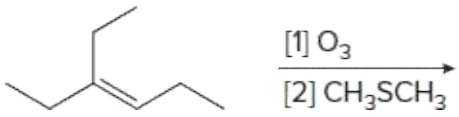
12.44 Draw the products formed after Steps [1] and [2] in the following three-step sequence. Then draw stepwise mechanisms for each step.



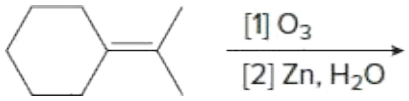
Oxidative Cleavage

12.45 Draw the products formed in each oxidative cleavage.

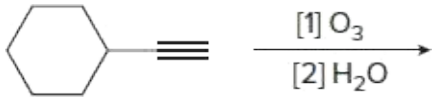
a.



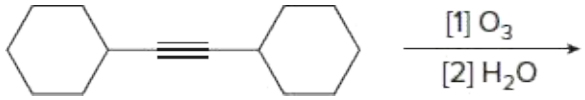
b.



c.

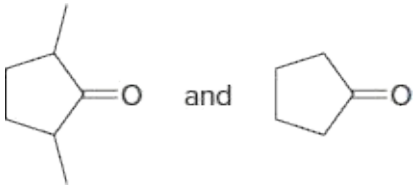


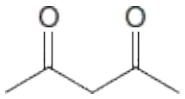
d.

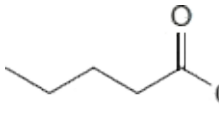


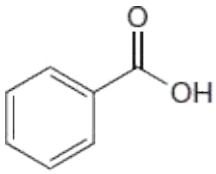
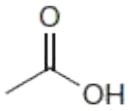
12.46 What alkene or alkyne yields each set of products after oxidative cleavage with ozone?

a.

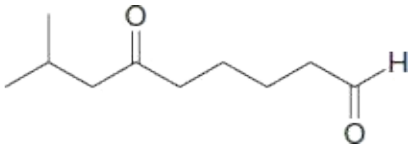


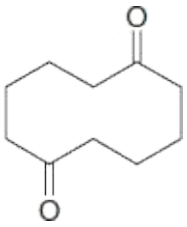
b.  and two equivalents of $CH_2{=}O$

c.  and CO_2

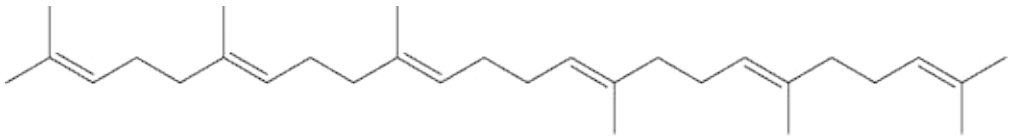
d.  and 

12.47 Identify the starting material in each reaction.

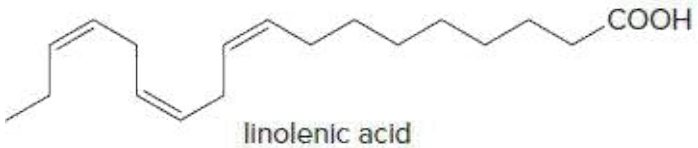
a. $C_{10}H_{18}$ $\xrightarrow[\text{[2] } CH_3SCH_3]{\text{[1] } O_3}$ 

b. $C_{10}H_{16}$ $\xrightarrow[\text{[2] } CH_3SCH_3]{\text{[1] } O_3}$ 

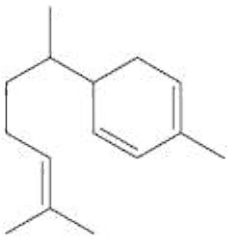
12.48 Draw the products formed when each naturally occurring compound is treated with O_3 followed by Zn, H_2O.

a. 

squalene

b. 

linolenic acid

c. 

zingiberene

Identifying Compounds from Reactions

12.49 Identify compounds A, B, and C.

a. Compound A has molecular formula C8H12 and reacts with two

equivalents of H_2. A gives $HCOCH_2CH_2CHO$ as the only product of oxidative cleavage with O_3 followed by CH_3SCH_3.

b. Compound B has molecular formula C_6H_{10} and gives $(CH_3)_2CHCH_2CH_2CH_3$ when treated with excess H_2 in the presence of Pd. B reacts with $NaNH_2$ and CH_3I to form compound C (molecular formula C_7H_{12}).

12.50 Oximene and myrcene, two hydrocarbons isolated from alfalfa that have the molecular formula $C_{10}H_{16}$, both yield 2,6-dimethyloctane when treated with H_2 and a Pd catalyst. Ozonolysis of oximene forms $(CH_3)_2C{=}O$, $CH_2{=}O$, $CH_2(CHO)_2$, and CH_3COCHO. Ozonolysis of myrcene yields $(CH_3)_2C{=}O$, $CH_2{=}O$ (two equiv), and $HCOCH_2CH_2COCHO$. Identify the structures of oximene and myrcene.

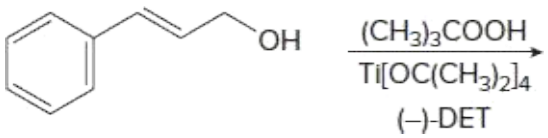
12.51 DHA is a fatty acid derived from fish oil and an abundant fatty acid in vertebrate brains. Hydrogenation of DHA forms docosanoic acid $[CH_3(CH_2)_{20}CO_2H]$, and ozonolysis forms CH_3CH_2CHO, $CH_2(CHO)_2$ (five equivalents), and $HCOCH_2CH_2CO_2H$. What is the structure of DHA if all double bonds have the *Z* configuration?

12.52 One compound that contributes to the "seashore smell" at beaches in Hawai'i is dictyopterene D', a component of a brown edible seaweed called limu lipoa. Hydrogenation of dictyopterene D' with excess H_2 in the presence of a Pd catalyst forms butylcycloheptane. Ozonolysis with O_3 followed by $(CH_3)_2S$ forms $CH_2(CHO)_2$, $HCOCH_2CH(CHO)_2$, and CH_3CH_2CHO. What are possible structures of dictyopterene D'?

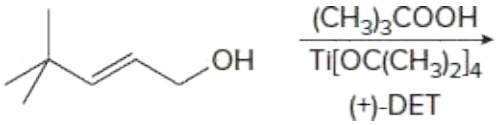
12.53 Treatment of compound A ($C_8H_{17}Br$) with $NaOCH_2CH_3$ affords two constitutional isomers B and C. Ozonolysis of B affords $CH_2{=}O$ and $(CH_3CH_2CH_2)_2C{=}O$. Ozonolysis of C affords $CH_3CH_2CH_2COCH_3$ and CH_3CH_2CHO. What is the structure of A?

Sharpless Asymmetric Epoxidation

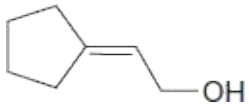
12.54 Draw the product of each asymmetric epoxidation reaction.

a. 

b.



12.55 Epoxidation of the following allylic alcohol using the Sharpless reagent with (−)-DET gives two epoxy alcohols in a ratio of 87:13.

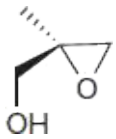


a. Assign structures to the major and minor product.

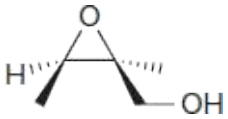
b. What is the enantiomeric excess in this reaction?

12.56 What allylic alcohol and DET isomer are needed to make each chiral epoxide using a Sharpless asymmetric epoxidation reaction?

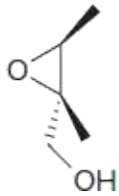
a.



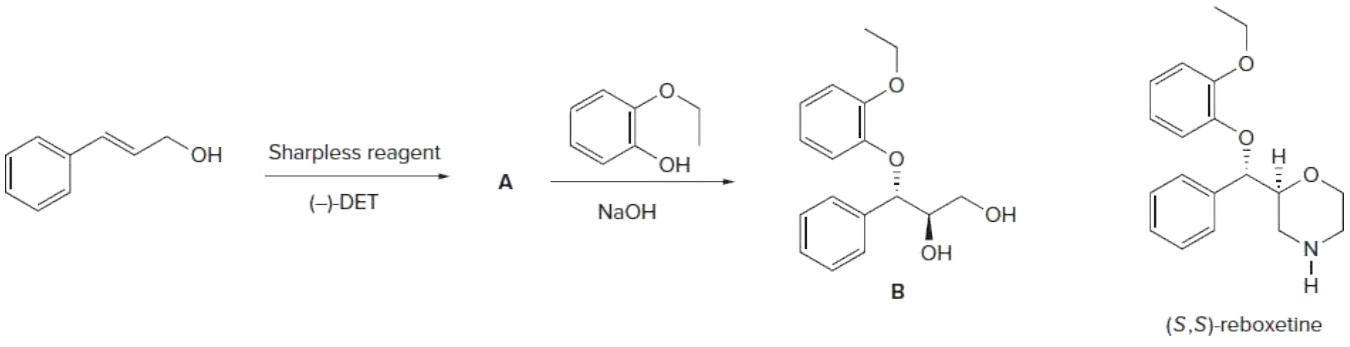
b.



c.

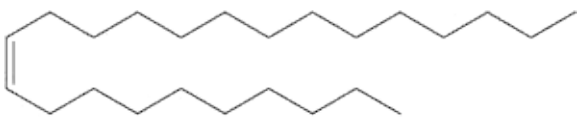


12.57 Identify A in the following reaction sequence, and draw a mechanism for the conversion of A to B. B has been converted to (*S,S*)-reboxetine, an antidepressant marketed outside the United States.



Synthesis

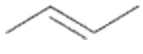
12.58 Devise a synthesis of muscalure, the sex pheromone of the common housefly, from acetylene and any other required reagents.

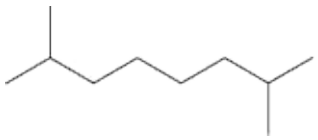


muscalure

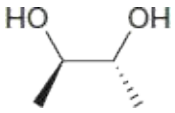
12.59 **It is sometimes necessary to isomerize a cis alkene to a trans alkene in a synthesis, a process that cannot be accomplished in a single step. Using the reactions you have learned in Chapters 8–12, devise a stepwise method to convert *cis*-but-2-ene to *trans*-but-2-ene.**

12.60 **Devise a synthesis of each compound from acetylene and any other required reagents.**

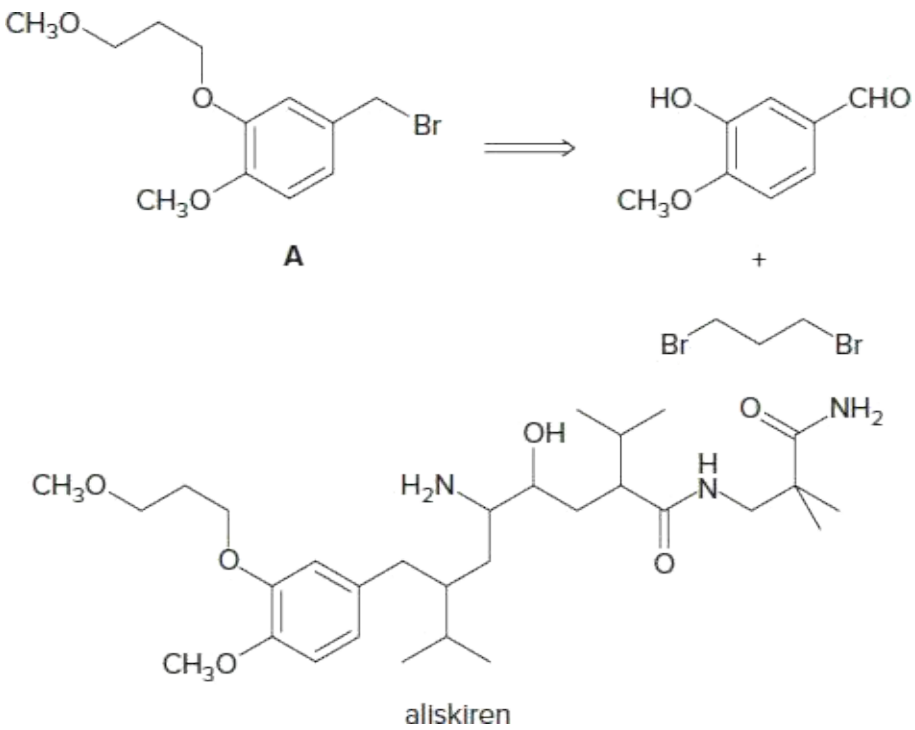
a. 

b. 

c.

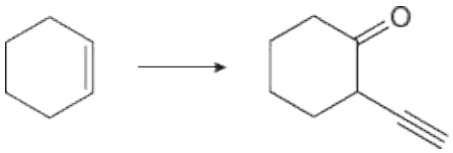
d. 

12.61 **Devise a synthesis of compound A from the given starting materials. You may use any other inorganic reagents or organic alcohols. A was used to prepare aliskiren, a drug used to treat hypertension (see also Problem 5.7).**



12.62 **Devise a synthesis of each compound from the indicated starting material, organic compounds containing one or two carbons, and any other required reagents.**

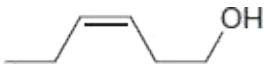
a.



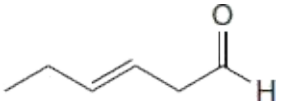
b.

(+ enantiomer)

c. H−C≡C−H ⟶

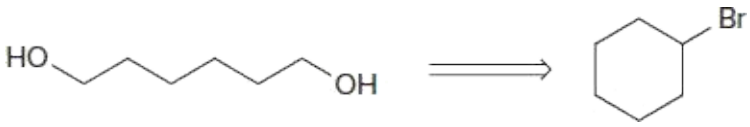


d. H−C≡C−H ⟶



12.63 Devise a synthesis of each compound from the indicated starting material. You may use any other needed organic or inorganic reagents.

a.



b.

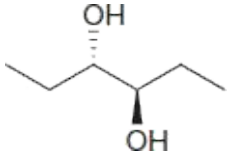
12.64 Devise a synthesis of (3*R*,4*S*)-3,4-dichlorohexane from acetylene and any needed organic compounds or inorganic reagents.

12.65 Devise a synthesis of each compound from CH_3CH_2OH as the only organic starting material; that is, every carbon in the product must come from a molecule of ethanol. You may use any other needed inorganic reagents.

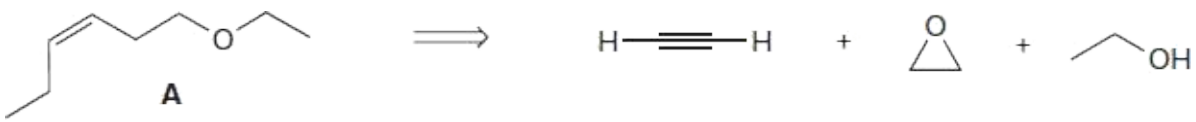
a.

b.

c.



12.66 Devise a synthesis of A from the three starting materials given. You may use any other needed organic or inorganic reagents.



Spectroscopy

Problems 12.67 and 12.68 are intended for students who have already learned about spectroscopy in Chapters A—C.

12.67 **Treatment of alcohol A (molecular formula $C_5H_{12}O$) with CrO_3, H_2SO_4, and H_2O affords B with molecular formula $C_5H_{10}O$, which gives an IR absorption at 1718 cm^{-1}. The ^1H NMR spectrum of B contains the following signals: 1.10 (doublet, 6 H), 2.14 (singlet, 3 H), and 2.58 (septet, 1 H) ppm. What are the structures of A and B?**

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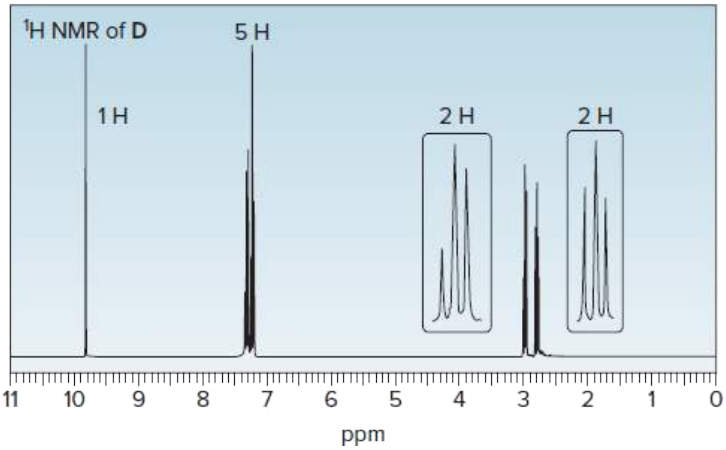
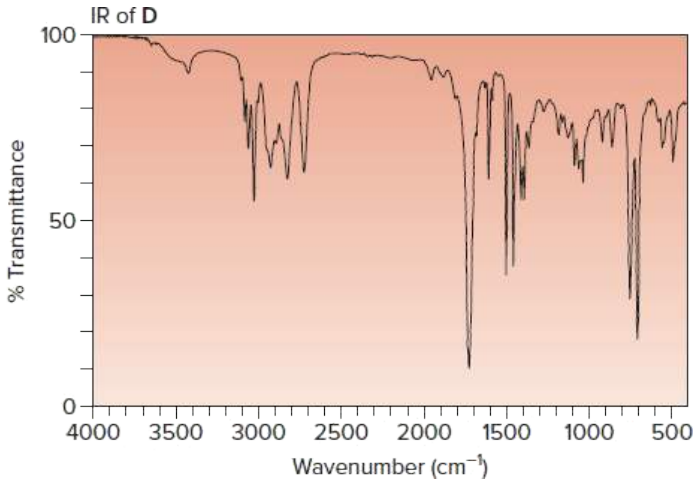
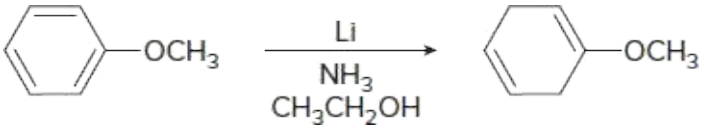
12.68 **Treatment of compound C (molecular formula $C_9H_{12}O$) with PCC affords D (molecular formula $C_9H_{10}O$). Use the ^1H NMR and IR spectra of D to determine the structures of both C and D.**



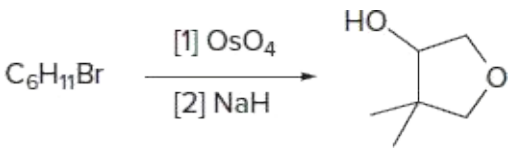


Challenge Problems

12.69 **The Birch reduction is a dissolving metal reaction that converts substituted benzenes to cyclohexa-1,4-dienes using Li and liquid ammonia in the presence of an alcohol. Draw a stepwise mechanism for the following Birch reduction.**



12.70 **Identify the starting material in the following reaction sequence.**

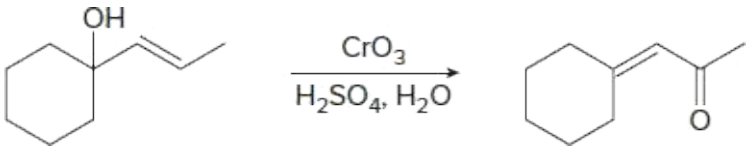


12.71 **In the Cr^{6+} oxidation of cyclohexanols, it is generally true that sterically hindered alcohols react faster than unhindered alcohols. Which of the**

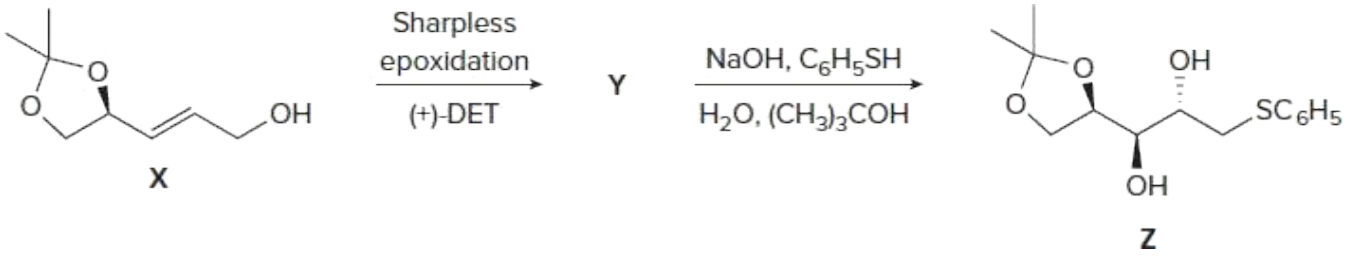
following alcohols should be oxidized more rapidly?

12.72 Dihydroxylation of an alkene can be carried out with H_2O_2 in HCO_2H. In this reaction, *trans*-but-2-ene affords (2*R*,3*S*)-butane-2,3-diol, whereas *cis*-but-2-ene affords a mixture of (2*R*,3*R*)-butane-2,3-diol and (2*S*,3*S*)-butane-2,3-diol. Does dihydroxylation by this method occur with syn or anti addition?

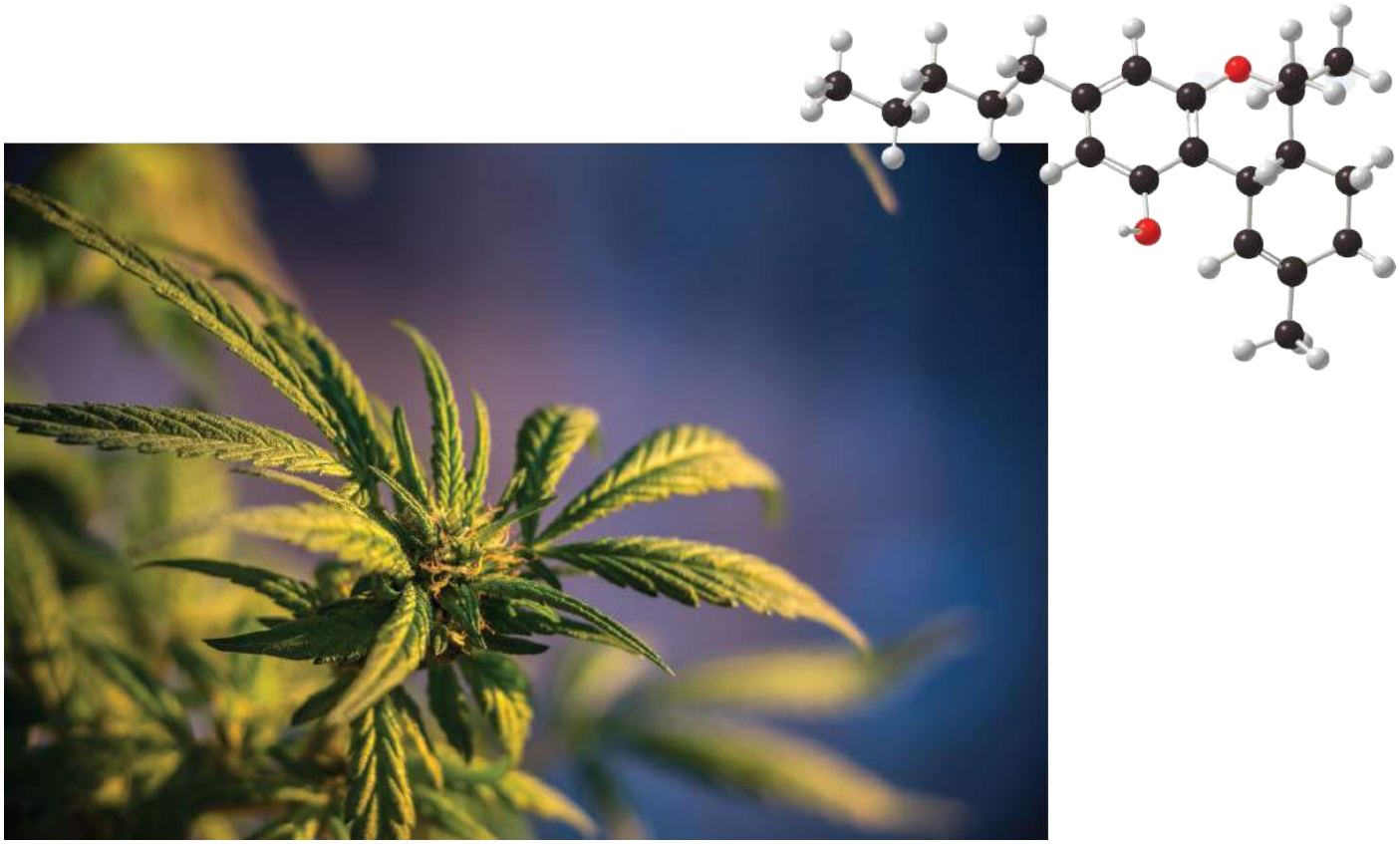
12.73 Draw a stepwise mechanism for the following reaction.



12.74 Sharpless epoxidation of allylic alcohol X forms compound Y. Treatment of Y with NaOH and C_6H_5SH in an alcohol–water mixture forms Z. Identify the structure of Y and draw a mechanism for the conversion of Y to Z. Account for the stereochemistry of the stereogenic centers in Z. Z has been used as an intermediate in the synthesis of chiral carbohydrates.



A Mass Spectrometry



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A.1 Mass spectrometry and the molecular ion

A.2 Alkyl halides and the M + 2 peak

A.3 Fragmentation

A.4 Fragmentation patterns of some common functional groups

A.5 Other types of mass spectrometry

Tetrahydrocannabinol (THC), first isolated from Indian hemp, is the primary active constituent of cannabis. The recreational use of cannabis has been legalized in several parts of the United States, and the medical use of THC as an

anti-nausea agent for chemotherapy patients and as an appetite stimulant for AIDS-related anorexia is well documented. Like other controlled substances, THC can be detected in minute amounts using modern instrumental methods. In Spectroscopy Part A, we examine mass spectrometry, a method to determine the molecular weight of an organic compound.

Why Study…

Spectroscopy?

Whether a compound is prepared in the laboratory or isolated from a natural source, a chemist must determine its identity. Seventy years ago, determining the structure of an organic compound involved a series of time-consuming operations: measuring physical properties (melting point, boiling point, solubility, and density), identifying the functional groups using a series of chemical tests, and converting an unknown compound into another compound whose physical and chemical properties were then characterized as well.

Although still a challenging task, structure determination has been greatly simplified by modern instrumental methods. These techniques have both decreased the time needed for compound characterization, and increased the complexity of compounds whose structures can be completely determined.

In Spectroscopy A, we are introduced to mass spectrometry (MS), which is used to determine the molecular weight and molecular formula of a compound. In Spectroscopy B, we learn how infrared (IR) spectroscopy is used to identify a compound's functional groups. Spectroscopy C is devoted to nuclear magnetic resonance (NMR) spectroscopy, which is used to identify the carbon–hydrogen framework in a compound, making it the most powerful spectroscopic tool for organic structure analysis. Each method provides valuable information for determining the structure of an organic compound. We examine three methods that rely on the interaction of an energy source with a molecule to produce a change that is recorded in a spectrum.

A.1 Mass Spectrometry and the Molecular Ion

Mass spectrometry is a technique used for measuring the molecular weight and determining the molecular formula of an organic molecule.

A.1A General Features

In the most common type of mass spectrometer, a molecule is vaporized and ionized, usually by bombardment with a beam of high-energy electrons, as shown in Figure A.1. The energy of these electrons is typically about 6400 kJ, or 70 electron volts (eV). This electron beam ionizes a molecule by causing it to eject an electron.

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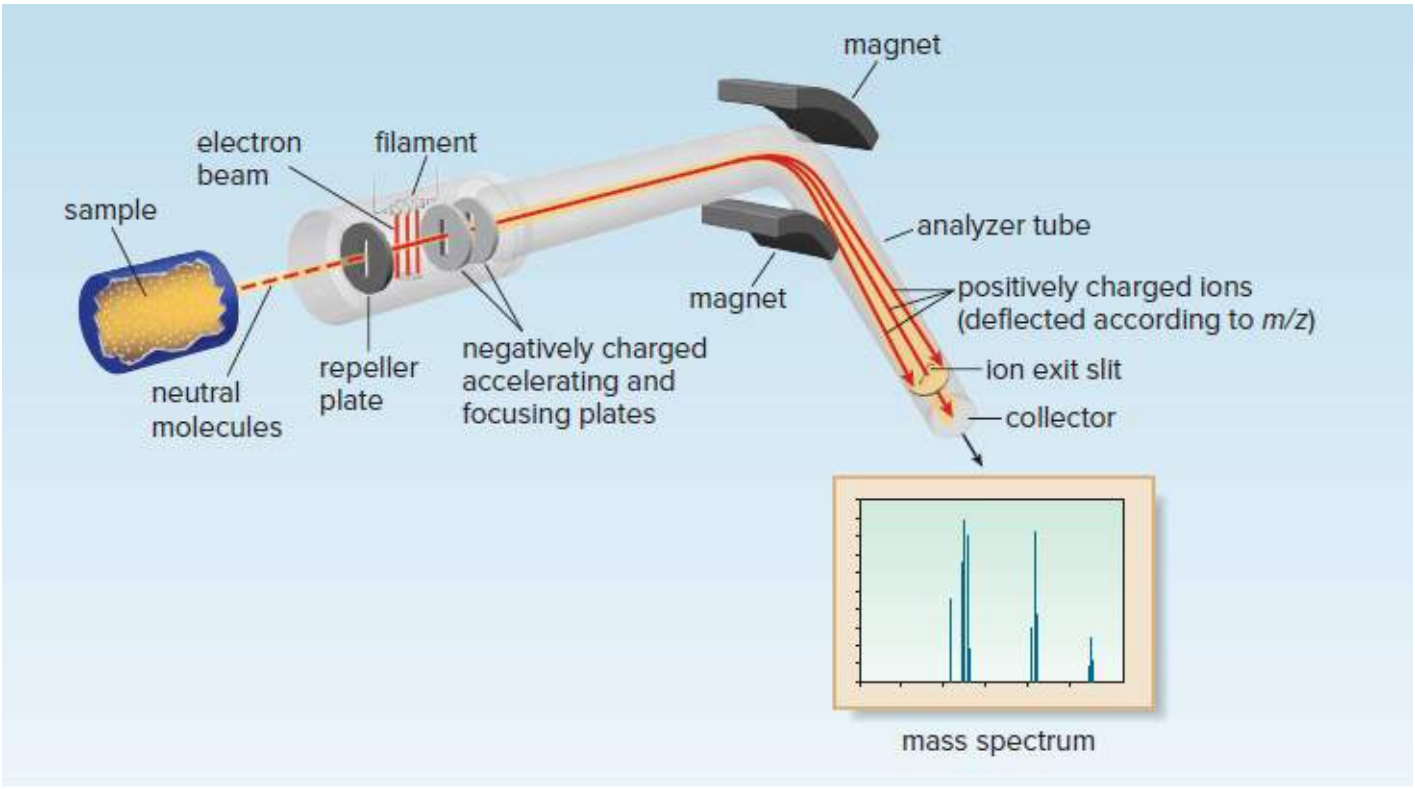
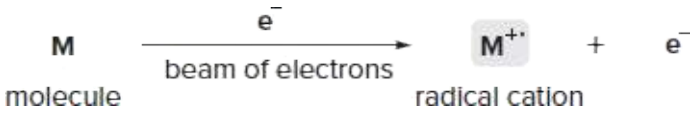


- In a mass spectrometer, a sample is vaporized and bombarded by a beam of electrons to form an unstable radical cation, which then decomposes to smaller fragments. The positively charged ions are accelerated toward a negatively charged plate, and then passed through a curved analyzer tube in a magnetic field, where they are deflected by different amounts depending on their ratio of mass to charge (m/z). A mass spectrum plots the intensity of each ion versus its m/z ratio.

Figure A.1 **Schematic of a mass spectrometer**

The term spectroscopy is usually used for techniques that use electromagnetic radiation as an energy source. Because the energy source in MS is a beam of electrons, the term mass spectrometry is used instead.

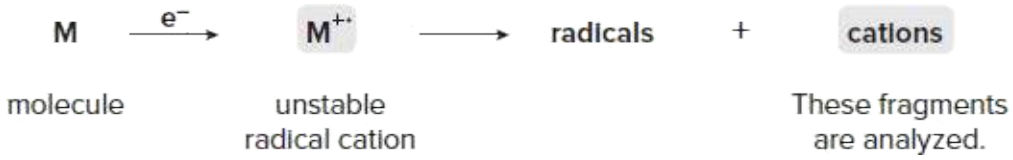


The species formed is a radical cation, symbolized $M^{+\cdot}$. It is a radical because it has an unpaired electron, and it is a cation because it has one fewer electron than it started

with.

- **The radical cation $M^{+\cdot}$ is called the *molecular ion* or the *parent ion*.**

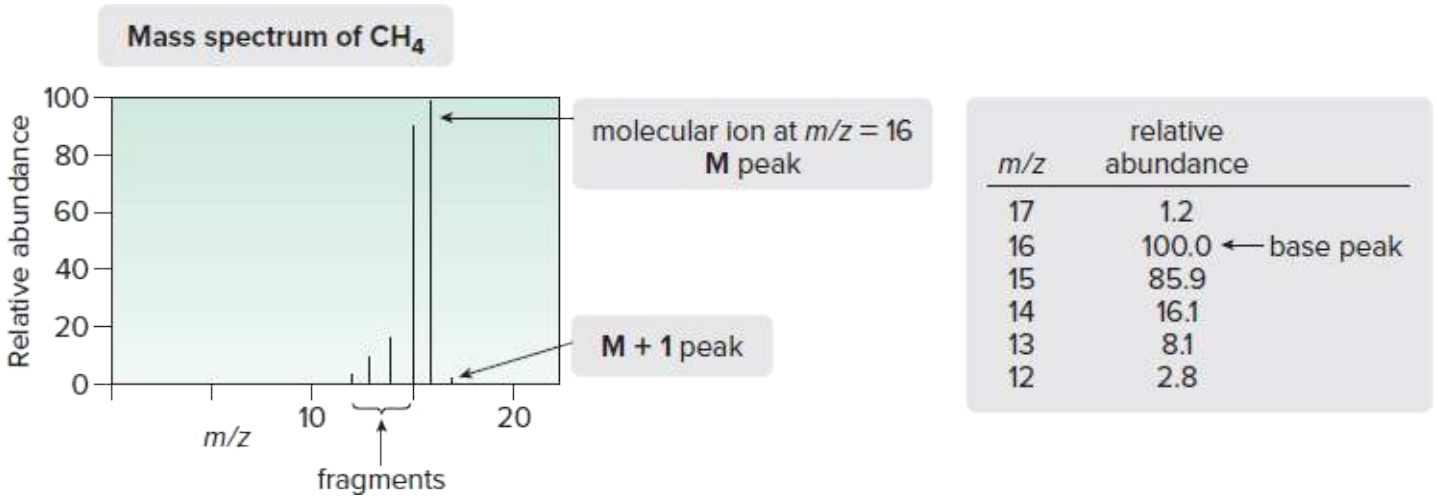
A single electron has a negligible mass, so the mass of $M^{+\cdot}$ represents the molecular weight of M. Because the molecular ion $M^{+\cdot}$ is inherently unstable, it decomposes. Single bonds break to form *fragments*, radicals and cations having a lower molecular weight than the molecular ion. A mass spectrometer analyzes the masses of cations only. The cations are accelerated in an electric field and deflected in a curved path in a magnetic field, thus sorting the molecular ion and its fragments by their mass-to-charge (m/z) ratio. Because z is almost always +1, m/z actually measures the mass (m) of the individual ions.



- **A *mass spectrum* plots the amount of each cation (its relative abundance) versus its mass.**

The whole-number mass of CH_4 is (1 C × 12 amu) + (4 H × 1 amu) = 16 amu; amu = atomic mass unit.

A mass spectrometer analyzes the masses of *individual* molecules, not the weighted average mass of a group of molecules, so the whole-number masses of the most common individual isotopes must be used to calculate the mass of the molecular ion. Thus, the mass of the molecular ion for CH_4 should be 16. As a result, the mass spectrum of CH_4 shows a line for the molecular ion—the parent peak or M peak—at $m/z = 16$.



The tallest peak in a mass spectrum is called the base peak. For CH_4, the base peak is also the M peak, although this may *not* always be the case for all organic compounds.

The mass spectrum of CH_4 consists of more peaks than just the M peak. What is responsible for the peaks at $m/z < 16$? Because the molecular ion is unstable, it fragments into other cations and radical cations containing one, two, three, or four fewer hydrogen atoms than methane itself. Thus, the peaks at m/z = 15, 14, 13, and 12, are due to these lower-molecular-weight fragments. The decomposition of a molecular ion into lower-molecular-weight fragments is called fragmentation.

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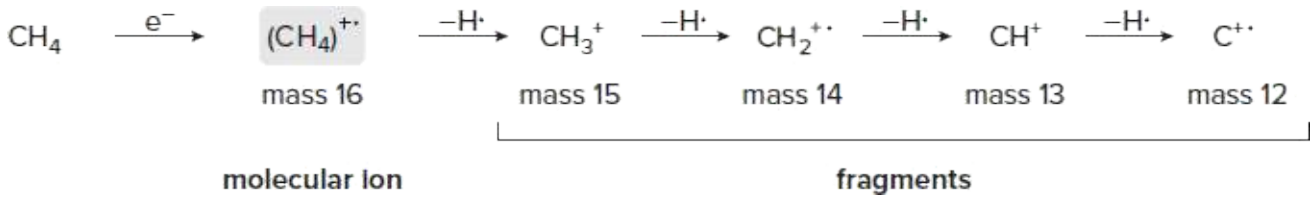
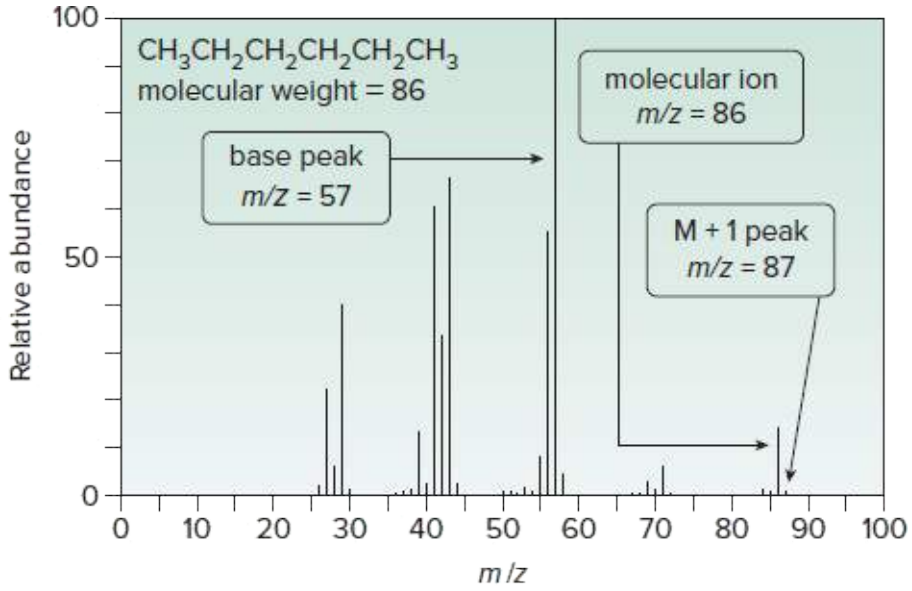


What is responsible for the small peak at m/z = 17 in the mass spectrum of CH_4? Although most carbon atoms have an atomic mass of 12, 1.1% of them have an additional neutron in the nucleus, giving them an atomic mass of 13. When one of these carbon-13 isotopes forms methane, it gives a molecular ion peak at m/z = 17 in the mass spectrum. This peak is called the M + 1 peak.

These key features—the molecular ion, the base peak, and the M + 1 peak—are illustrated in the mass spectrum of hexane in Figure A.2.

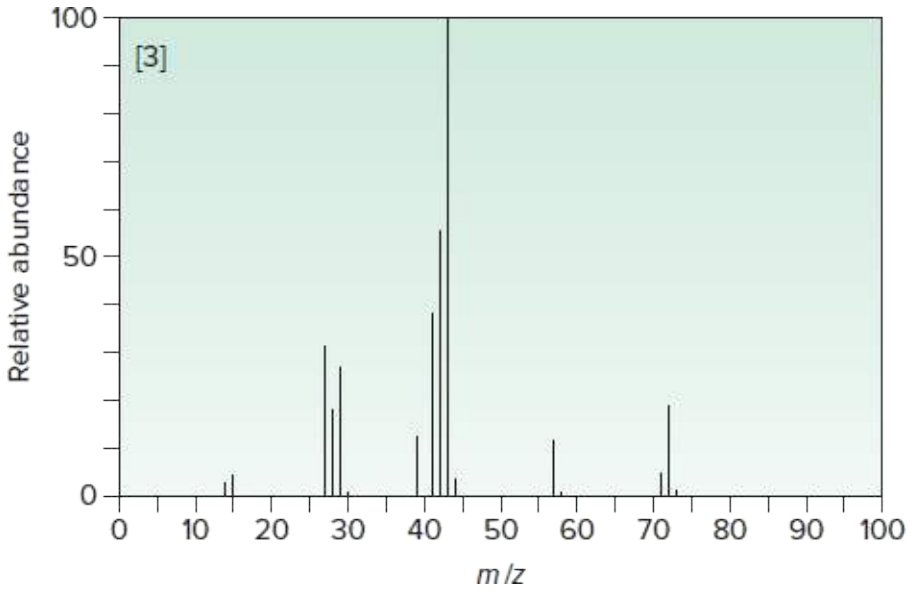


- The molecular ion for hexane (molecular formula C_6H_{14}) is at $m/z = 86$.
- The base peak (relative abundance = 100) occurs at $m/z = 57$.
- A small M + 1 peak occurs at $m/z = 87$.

Figure A.2 **Mass spectrum of hexane ($CH_3CH_2CH_2CH_2CH_2CH_3$)**

Problem A.1

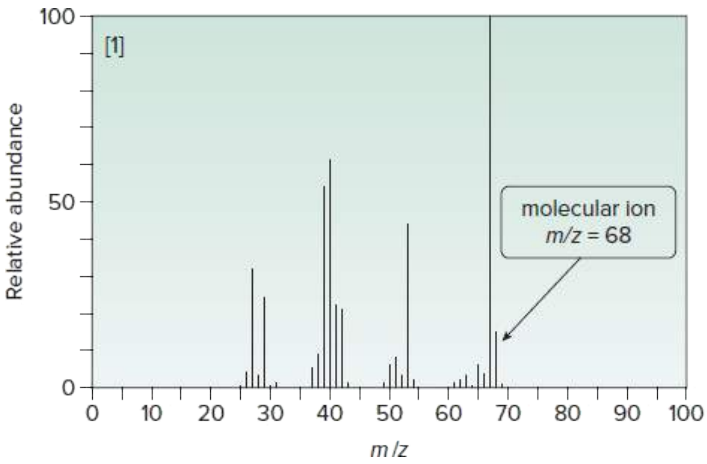
Label the molecular ion, the base peak, and the M + 1 peak in the mass spectrum of pentane (C_5H_{12}).

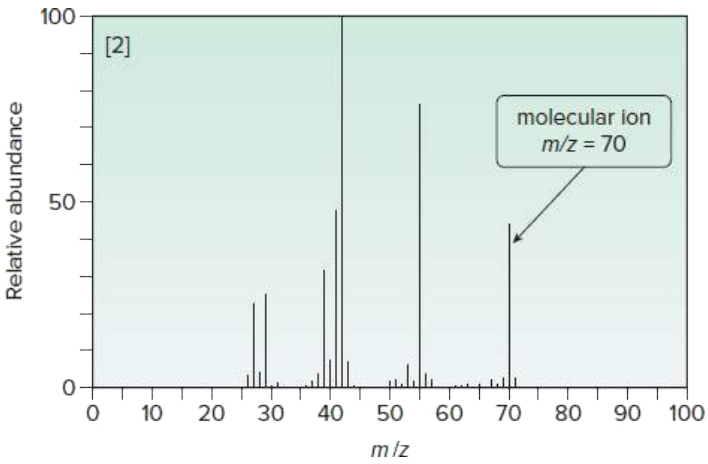


A.1B Analyzing Unknowns Using the Molecular Ion

Because the mass of the molecular ion equals the molecular weight of a compound, a mass spectrum can be used to distinguish between compounds that have similar physical properties but different molecular weights, as illustrated in Sample Problem A.1.

Pent-1-ene and pent-1-yne are low-boiling hydrocarbons that have different molecular ions in their mass spectra. Match each hydrocarbon to its mass spectrum.





Solution

To solve this problem, first determine the molecular formula and molecular weight of each compound. Then, because the molecular weight of the compound equals the mass of the molecular ion, match the molecular weight to *m/z* for the molecular ion:

Compound	Molecular formula	Molecular weight = *m/z* of molecular ion	Spectrum
pent-1-ene	C_5H_{10}	70	[2]
pent-1-yne	C_5H_8	68	[1]

Problem A.2

What is the mass of the molecular ion formed from compounds having each molecular formula: (a) C_3H_6O; (b) $C_{10}H_{20}$; (c) $C_8H_8O_2$; (d) methamphetamine ($C_{10}H_{15}N$)?

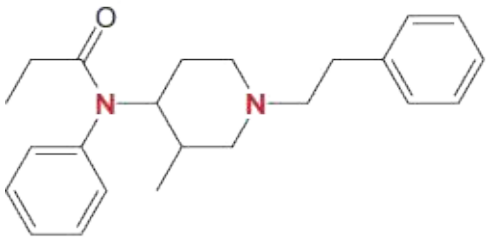
More Practice:

Try Problems A.16, A.17.

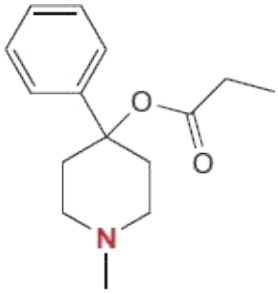
Hydrocarbons like methane (CH_4) and hexane (C_6H_{14}), as well as compounds that contain only C, H, and O atoms, always have a molecular ion with an *even* mass. An

odd molecular ion generally indicates that a compound contains nitrogen.

The effect of N atoms on the mass of the molecular ion in a mass spectrum is called the nitrogen rule: A compound that contains an *odd* number of N atoms gives an odd molecular ion. Conversely, a compound that contains an *even* number of N atoms (including *zero*) gives an *even* molecular ion. Two "street" drugs that mimic the effects of heroin illustrate this principle: 3-methyl-fentanyl (two N atoms, even molecular weight) and MPPP (one N atom, odd molecular weight).



3-methylfentanyl
$C_{23}H_{30}N_2O$
molecular weight = 350



MPPP
(1-methyl-4-phenyl-4-propionoxypiperidine)
$C_{15}H_{21}NO_2$
molecular weight = 247

A.1C Using the Molecular Ion to Propose Molecular Formulas

How to use the molecular ion to propose molecular formulas for an unknown is shown in the stepwise procedure and Sample Problem A.2.

How To Use the Mass of a Molecular Ion to Propose Molecular Formulas for an Unknown

Example Propose possible molecular formulas for a compound with a molecular ion at *m/z* = 154.

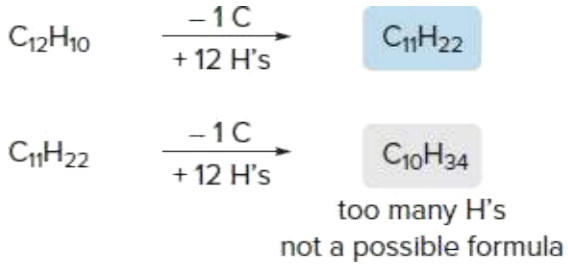
Step [1] **With an even mass of a molecular ion, the compound likely contains C, H, and possibly O atoms. Use the molecular ion to determine the maximum number of C's possible for a hydrocarbon.**

- **Divide 154 by 12, the mass of 1 C atom. The remainder gives the number of H's.**

$$\frac{154}{12} = \text{12 C's maximum (remainder = 10)} \longrightarrow C_{12}H_{10}$$

Step [2] **To determine another possible molecular formula for a hydrocarbon, replace 1 C by 12 H's. Repeat the process until the formula has more**

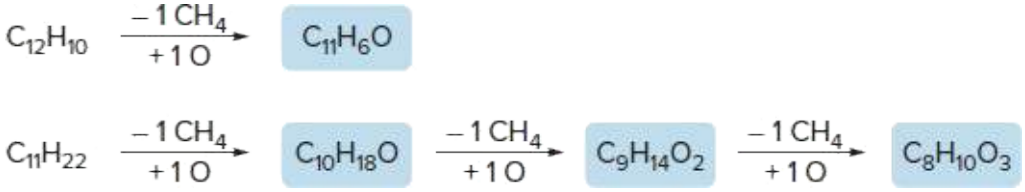
than the maximum number of H's possible.



- Because the maximum number of H's for a compound with 11 C's is 24 ($C_{11}H_{2(11)+2}$), $C_{10}H_{34}$ is not a possible formula.

Step [3] To determine possible molecular formulas for compounds with O atoms, replace CH_4 (mass 16) by O (mass 16) in each formula. Repeat the process to give possible molecular formulas for compounds with two or more O atoms.

- Four possibilities are shown.



Sample Problem A.2 Using the Molecular Ion to Propose a Molecular Formula

Propose possible molecular formulas for a compound with a molecular ion at *m/z* = 86.

Solution

Because the molecular ion has an even mass, the compound likely contains C, H, and possibly O atoms. Begin by determining the molecular formula for a hydrocarbon having a molecular ion at 86. Then, because the mass of an O atom is 16 (the mass of CH_4), replace CH_4 by O to give a molecular formula containing one O atom. Repeat this last step to give possible molecular formulas for compounds with two or more O atoms.

For a molecular ion at *m/z* = 86:

Possible hydrocarbons:

- Divide 86 by 12 (mass of 1 C atom). This gives the maximum number of C's possible.

$$\frac{86}{12} = 7\text{ C's maximum (remainder = 2)} \longrightarrow C_7H_2$$

- **Replace 1 C by 12 H's for another possible molecular formula.**

$$C_6H_{14} \xrightarrow[+\,1\,O]{-\,CH_4} C_5H_{10}O$$

Possible compounds with C, H, and O:

- **Substitute 1 O for CH_4. (This can't be done for C_7H_2.)**

$$C_7H_2 \xrightarrow[+\,12\text{ H's}]{-\,1\,C} C_6H_{14}$$

- **Repeat the process.**

$$C_5H_{10}O \xrightarrow[+\,1\,O]{-\,CH_4} C_4H_6O_2$$

Problem A.3

Propose two molecular formulas for each of the following molecular ions: (a) 72; (b) 100; (c) 73.

More Practice:

Try Problems A.18, A.19.

Sample Problem A.3 Using the Molecular Ion and Degrees of Unsaturation to Propose a Molecular Formula

Propose a molecular formula for nootkatone, a compound that contains the elements C, H, and O, has five degrees of unsaturation, and has a molecular ion in its mass spectrum at *m/z* = 218.

Solution

Determine possible molecular formulas using the procedure in Sample Problem A.2. Because each degree of unsaturation removes 2 H's, the correct molecular formula has 10 fewer H's than the maximum number.

For a molecular ion at $m/z = 218$:

$$\frac{218}{12} = 18 \text{ C's maximum (remainder = 2)} \longrightarrow C_{18}H_2$$

not enough H's

$$C_{18}H_2 \xrightarrow[+12 \text{ H's}]{-1 \text{ C}} C_{17}H_{14} \xrightarrow[+1 \text{ O}]{-1 \text{ CH}_4} C_{16}H_{10}O$$

not enough H's

$$C_{17}H_{14} \xrightarrow[+12 \text{ H's}]{-1 \text{ C}} C_{16}H_{26} \xrightarrow[+1 \text{ O}]{-1 \text{ CH}_4} C_{15}H_{22}O$$

five degrees of unsaturation

Answer

The maximum number of H's for a compound with 15 C's is $2n + 2 = 2(15) + 2 = 32$.

A compound with 22 H's has 10 fewer H's than the maximum number and thus five degrees of unsaturation.

Problem A.4

Propose a molecular formula for cedrol, an alcohol found in cedar oil. Cedrol has three degrees of unsaturation and a molecular ion in its mass spectrum at $m/z = 222$.

More Practice:

Try Problems A.20, A.21.

Nootkatone (Sample Problem A.3) occurs naturally in grapefruits, and has been used for many years as a flavoring in foods and beverages.

©MizC/Getty Images

A.2 Alkyl Halides and the M + 2 Peak

Most of the elements found in organic compounds, such as carbon, hydrogen, oxygen, nitrogen, sulfur, phosphorus, fluorine, and iodine, have one major isotope. Chlorine and bromine, on the other hand, have two, giving characteristic patterns to the mass

spectra of their compounds.

Chlorine has two common isotopes, ^{35}Cl and ^{37}Cl, which occur naturally in a 3:1 ratio. Thus, there are two peaks in a 3:1 ratio for the molecular ion of an alkyl chloride. The larger peak—the M peak—corresponds to the compound containing ^{35}Cl, and the smaller peak—the M + 2 peak—corresponds to the compound containing ^{37}Cl.

- **When the molecular ion consists of two peaks (M and M + 2) in a 3:1 ratio, a Cl atom is present.**

Sample Problem A.4 Determining the Molecular Ions for an Alkyl Chloride

What molecular ions will be present in a mass spectrum of 2-chloropropane, $(CH_3)_2CHCl$?

Solution

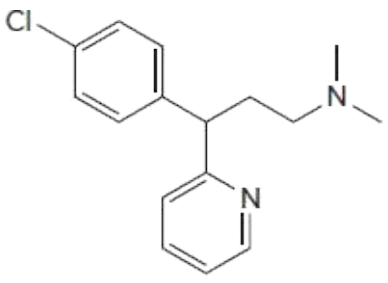
Calculate the molecular weight using each of the common isotopes of Cl.

Molecular formula	Mass of molecular ion (*m/z*)
$C_3H_7{}^{35}Cl$	78 (M peak)
$C_3H_7{}^{37}Cl$	80 (M + 2 peak)

There should be two peaks in a ratio of 3:1, at *m/z* = 78 and 80, as illustrated in the mass spectrum of 2-chloropropane in Figure A.3.

Problem A.5

What molecular ions will be present in the mass spectrum of the antihistamine chlorpheniramine?



chlorpheniramine

More Practice:

Try Problem A.22.

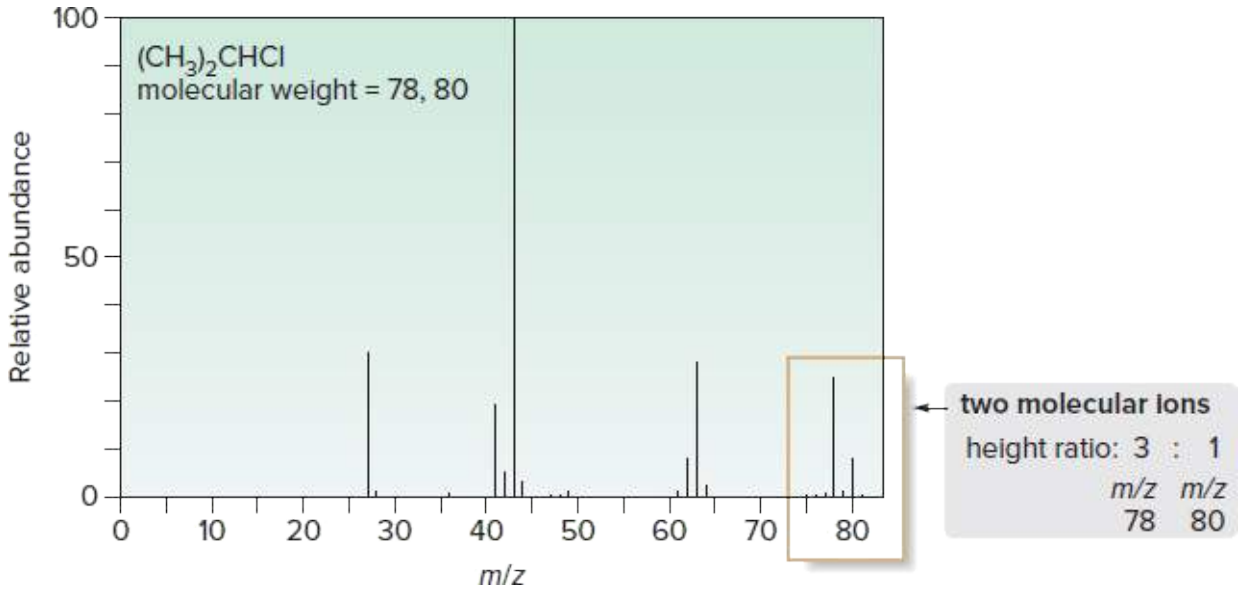


Figure A.3 **Mass spectrum of 2-chloropropane [$(CH_3)_2CHCl$]**

Bromine has two common isotopes, ^{79}Br and ^{81}Br, which occur naturally in a 1:1 ratio. Thus, there are two peaks in a 1:1 ratio for the molecular ion of an alkyl bromide. In the mass spectrum of 2-bromopropane (Figure A.4), for example, there is an M peak at m/z = 122 and an M + 2 peak at m/z = 124.

- **When the molecular ion consists of two peaks (M and M + 2) in a 1:1 ratio, a Br atom is present in the molecule.**

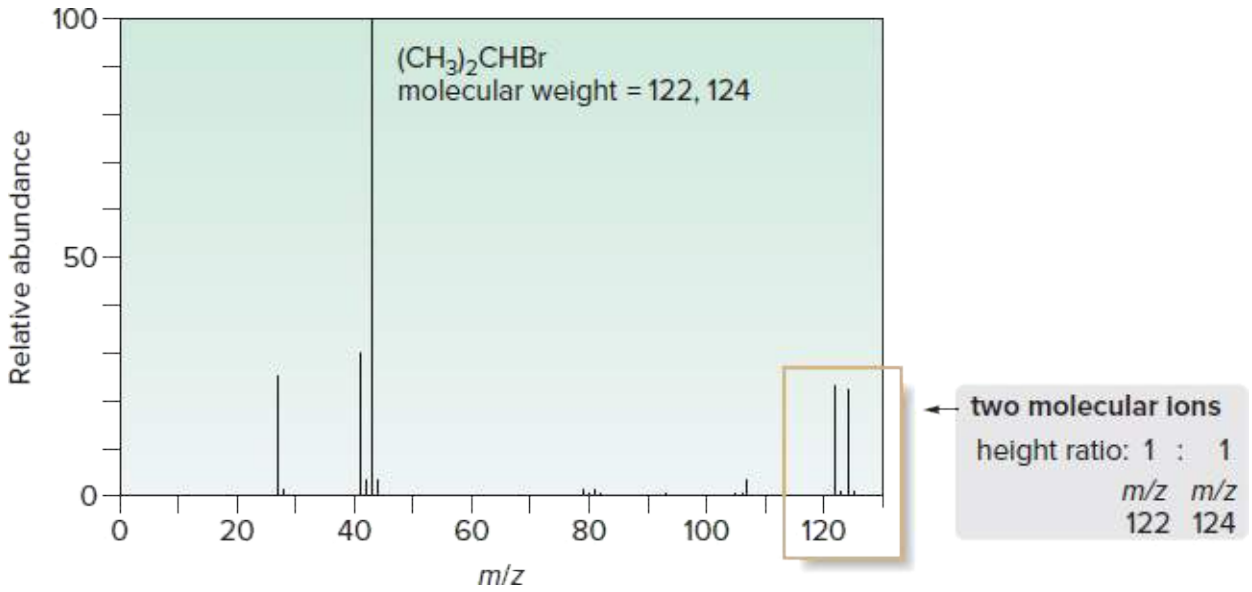


Figure A.4 **Mass spectrum of 2-bromopropane [$(CH_3)_2CHBr$]**

Problem A.6

What molecular ions would you expect for compounds having each of the following molecular formulas: (a) C_4H_9Cl; (b) C_3H_7F; (c) $C_4H_{11}N$; (d) $C_4H_4N_2$?

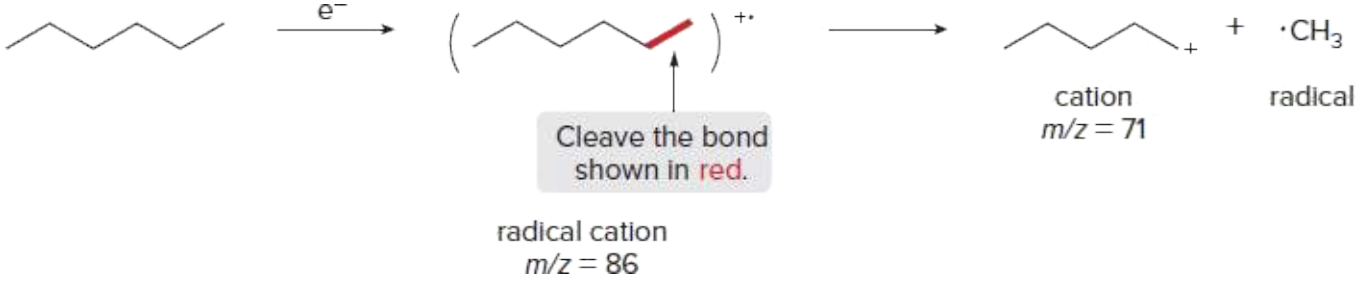
Problem A.7

What molecular ions would you expect for the compound depicted in the ball-and-stick model?

A.3 Fragmentation

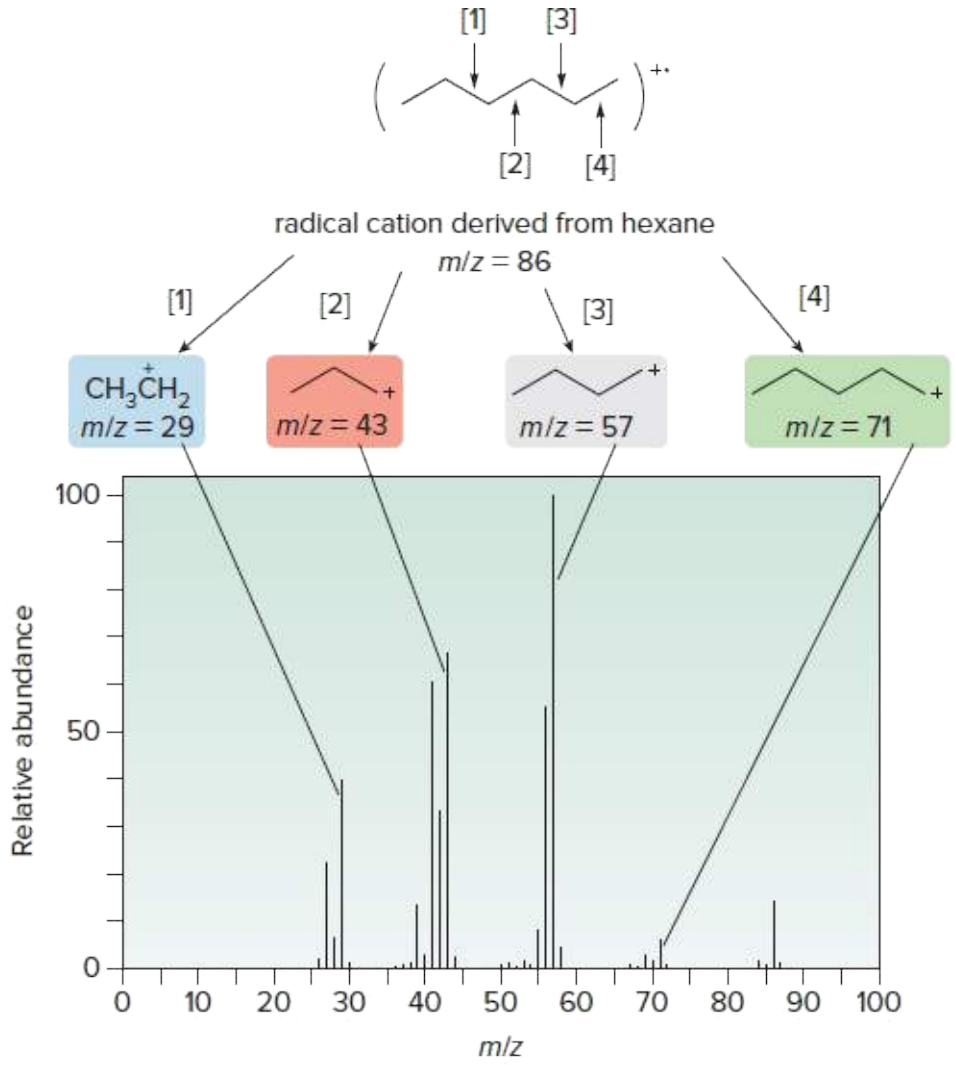
While many chemists use a mass spectrum to determine only a compound's molecular weight and molecular formula, additional useful structural information can be obtained from fragmentation patterns. Although each organic compound fragments in a unique way, a particular functional group exhibits common fragmentation patterns.

As an example, consider hexane, whose mass spectrum was shown in Figure A.2. When hexane is bombarded by an electron beam, it forms a highly unstable radical cation (m/z = 86) that can decompose by cleavage of any of the C—C bonds. Thus, cleavage of the terminal C—C bond forms $CH_3CH_2CH_2CH_2CH_2^+$ and $CH_3\cdot$. Fragmentation generates a cation and a radical, and cleavage generally yields the more stable, more substituted carbocation.



- **Loss of a CH_3 group always forms a fragment with a mass 15 units less than that of the molecular ion.**

As a result, the mass spectrum of hexane shows a peak at m/z = 71 due to $CH_3CH_2CH_2CH_2CH_2^+$. Figure A.5 illustrates how cleavage of other C—C bonds in hexane gives rise to other fragments that correspond to peaks in its mass spectrum.



- Cleavage of C—C bonds (labeled [1]–[4]) in hexane forms lower-molecular-weight fragments that correspond to lines in the mass spectrum. Although the mass spectrum is complex, possible structures can be assigned to some of the fragments, as shown.

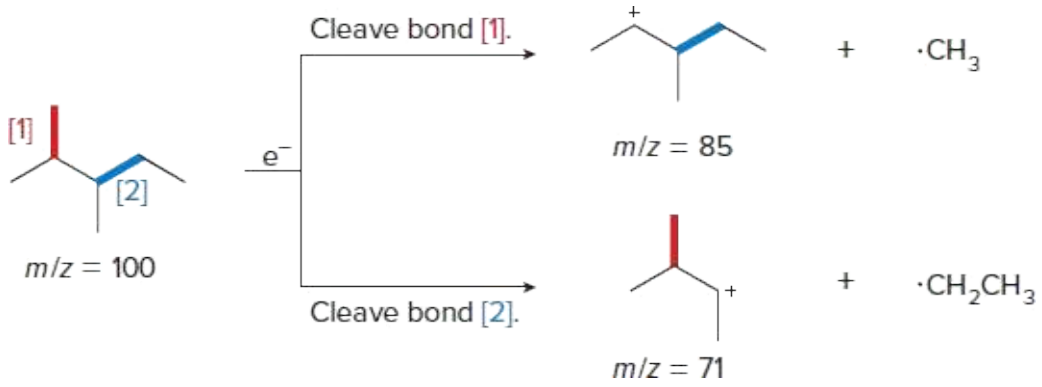
Figure A.5 **Identifying fragments in the mass spectrum of hexane**

Sample Problem A.5 Assigning Possible Structures to Fragments in a Mass Spectrum

The mass spectrum of 2,3-dimethylpentane [$(CH_3)_2CHCH(CH_3)CH_2CH_3$] shows fragments at *m/z* = 85 and 71. Propose possible structures for the ions that give rise to these peaks.

Solution

To solve a problem of this sort, first calculate the mass of the molecular ion. Draw out the structure of the compound, break a C—C bond, and calculate the mass of the resulting fragments. Repeat this process on different C—C bonds until fragments of the desired mass-to-charge ratio are formed.



In this example, 2,3-dimethylpentane has a molecular ion at *m/z* = 100. Cleavage of bond [1] forms a 2° carbocation with *m/z* = 85 and CH_3 ·. Cleavage of bond [2] forms another 2° carbocation with *m/z* = 71 and CH_3CH_2 ·. Thus, the fragments at *m/z* = 85 and 71 are possibly due to the two carbocations drawn.

Problem A.8

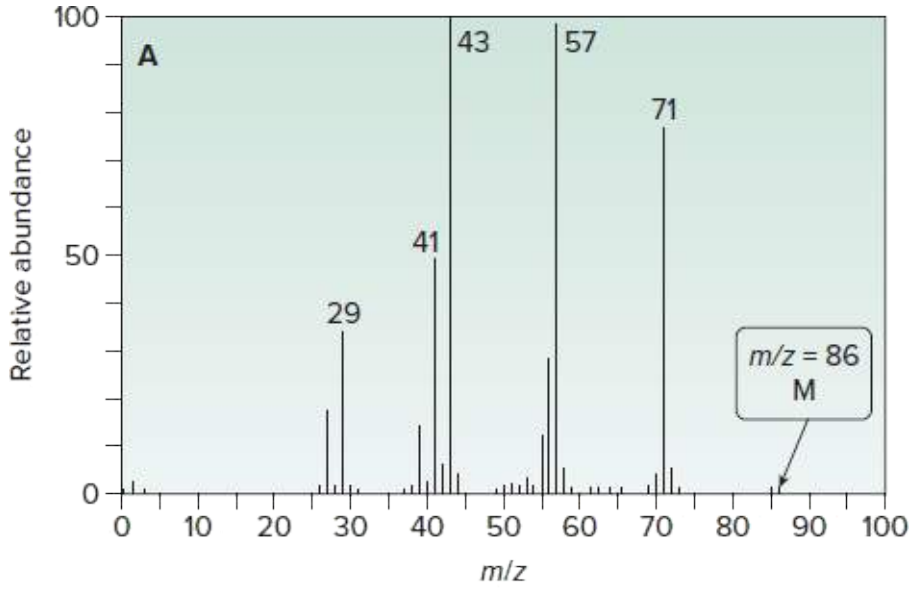
The mass spectrum of 2,3-dimethylpentane also shows peaks at *m/z* = 57 and 43. Propose possible structures for the ions that give rise to these peaks.

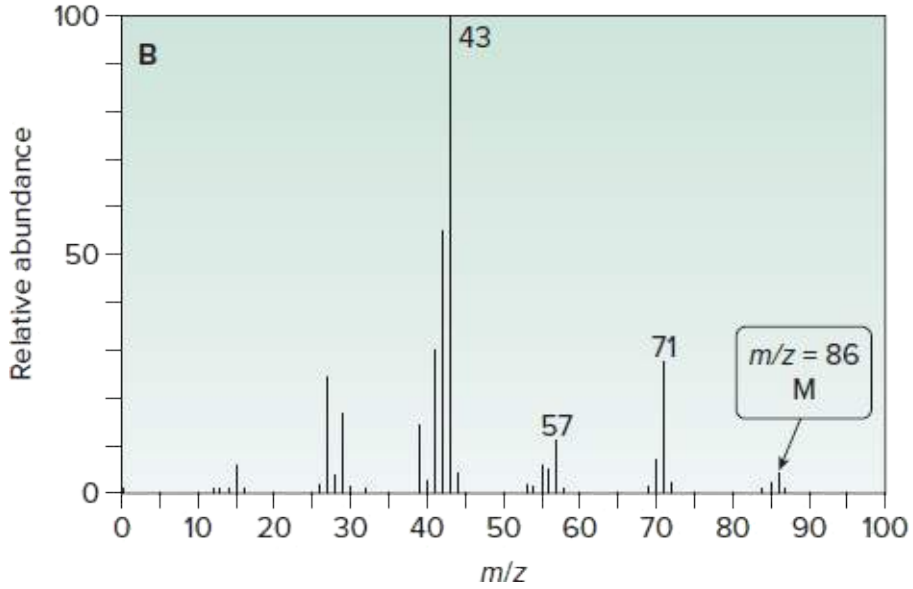
More Practice:

Try Problem A.15.

Sample Problem A.6 Identifying Isomers from Fragmentation Patterns

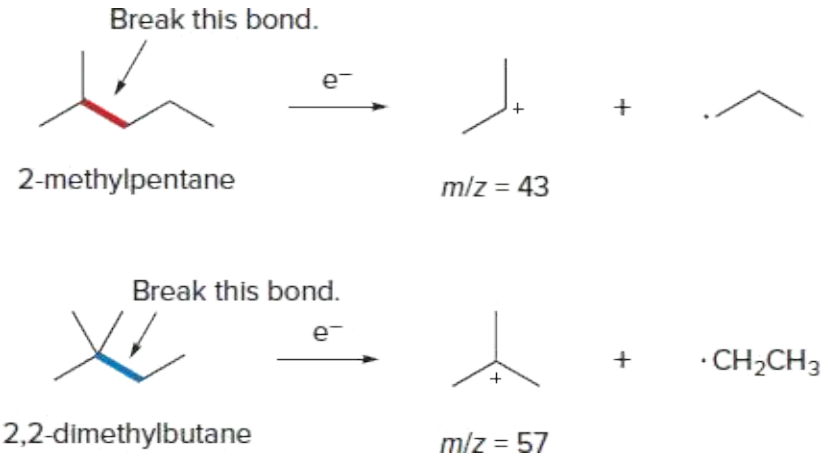
Which mass spectrum (A or B) corresponds to each isomer: 2-methylpentane [$(CH_3)_2CHCH_2CH_2CH_3$] or 2,2-dimethylbutane [$(CH_3)_3CCH_2CH_3$]?





Solution

Because both compounds have the same molecular formula (C_6H_{14}) resulting in the same molecular ion at *m/z* = 86, fragmentation patterns must be used to distinguish the isomers. Look at bond cleavage in each compound that yields fragments that are more abundant in one spectrum than the other.



For example, in 2-methylpentane, cleavage of the bond shown in red forms a fragment at *m/z* = 43 (due to a 2° carbocation), the base peak in spectrum B. In contrast, in 2,2-dimethylbutane, cleavage of the bond shown in blue forms a fragment at *m/z* = 57 (due to a 3° carbocation), a prominent fragment in spectrum A. Using this information, we can assign spectrum B to 2-methylpentane, and spectrum A to 2,2-dimethylbutane.

Problem A.9

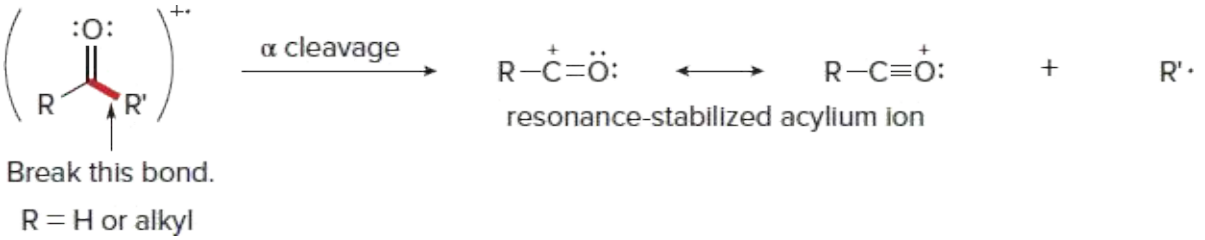
The base peak in the mass spectrum of 2,2,4-trimethylpentane [$(CH_3)_3CCH_2CH(CH_3)_2$] occurs at *m/z* = 57. What ion is responsible for this peak and why is this ion the most abundant fragment?

A.4 Fragmentation Patterns of Some Common Functional Groups

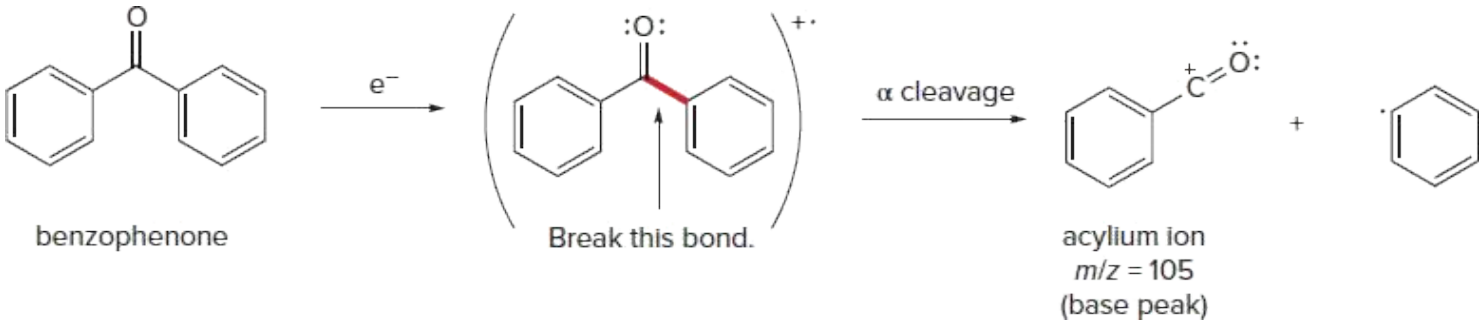
Each functional group exhibits characteristic fragmentation patterns that help to analyze a mass spectrum.

A.4A Aldehydes and Ketones

Aldehydes and ketones often undergo the process of α cleavage, breaking the bond between the carbonyl carbon and the carbon adjacent to it. Cleavage yields a neutral radical and a resonance-stabilized acylium ion.



For example, α cleavage of benzophenone forms a fragment at *m/z* = 105 due to a resonance-stabilized acylium ion.

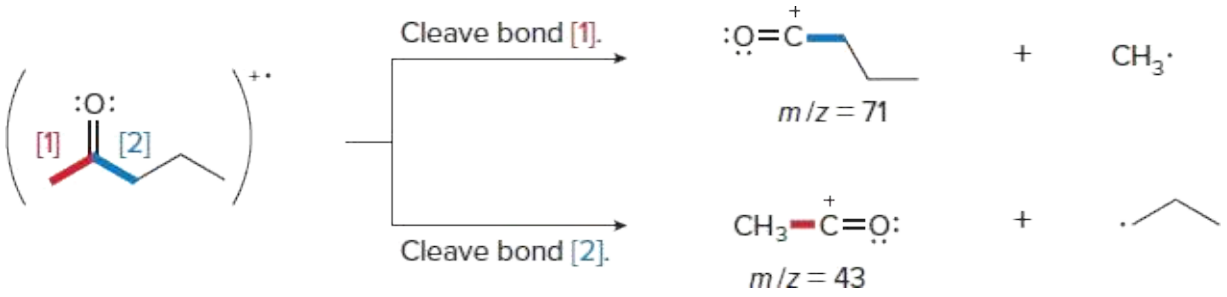


Sample Problem A.7 Drawing the Fragments Formed from α Cleavage

What mass spectral fragments are formed from α cleavage of pentan-2-one, $CH_3COCH_2CH_2CH_3$?

Solution

Alpha (α) cleavage breaks the bond between the carbonyl carbon and the carbon adjacent to it, yielding a neutral radical and a resonance-stabilized acylium ion. A ketone like pentan-2-one with two different alkyl groups bonded to the carbonyl carbon has two different pathways for α cleavage.

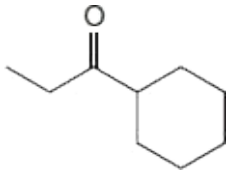


As a result, two fragments are formed by α cleavage of pentan-2-one, giving peaks at *m/z* = 71 and 43.

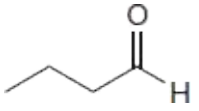
Problem A.10

What cations are formed in the mass spectrometer by α cleavage of each of the following compounds?

a.



b.

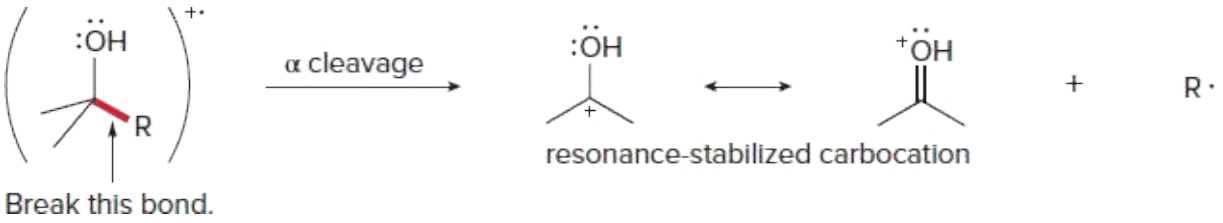


More Practice:

Try Problems A.27b, c; A.31

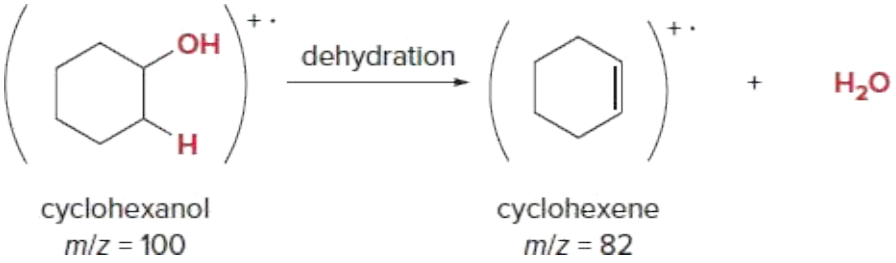
A.4B Alcohols

Alcohols undergo fragmentation in two different ways—α cleavage and dehydration. Alpha (α) cleavage occurs by breaking a bond between an alkyl group and the carbon that bears the OH group, resulting in an alkyl radical and a resonance-stabilized carbocation.



Likewise, alcohols undergo dehydration, the elimination of H_2O, from two adjacent atoms. Unlike fragmentations discussed thus far, dehydration results in the cleavage of two bonds and forms H_2O and the radical cation derived from an alkene.

For example, dehydration of cyclohexanol forms the radical cation of cyclohexene, a fragment with a mass 18 units less than that of the molecular ion, as shown in Figure A.6.



- **Loss of H_2O from an alcohol always forms a fragment with a mass 18 units less than the molecular ion.**

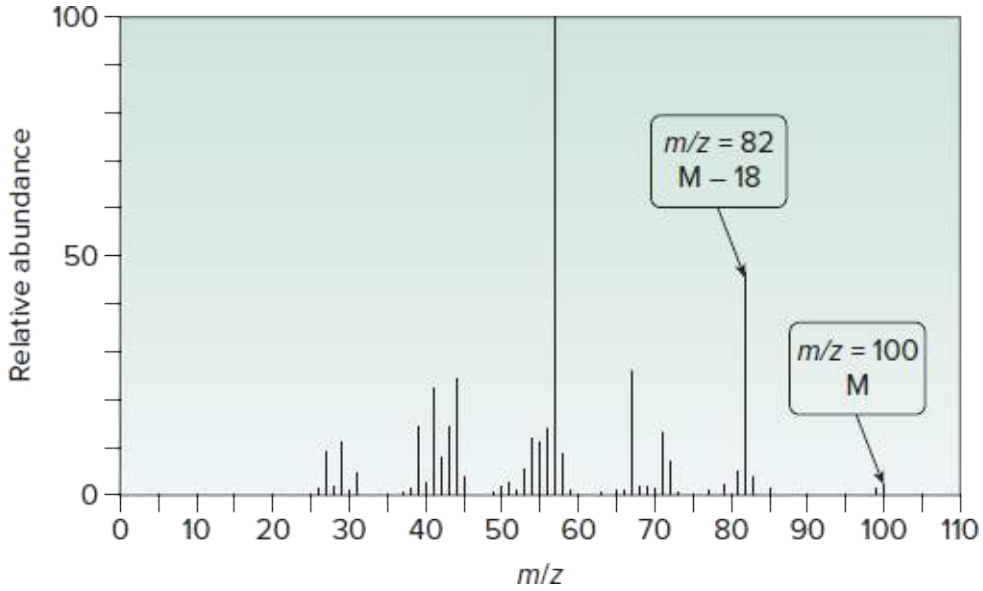


Figure A.6 **The mass spectrum of cyclohexanol**

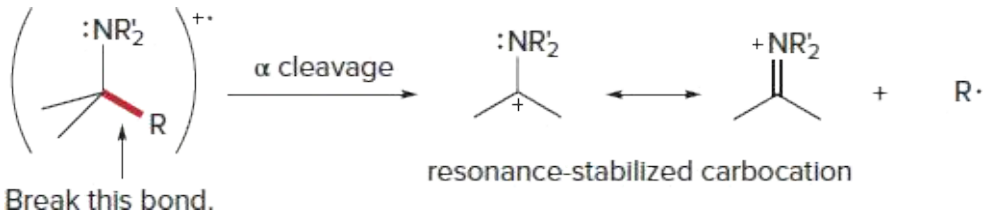
Problem A.11

(a) What mass spectral fragments are formed by α cleavage of butan-2-ol, $CH_3CH(OH)CH_2CH_3$?

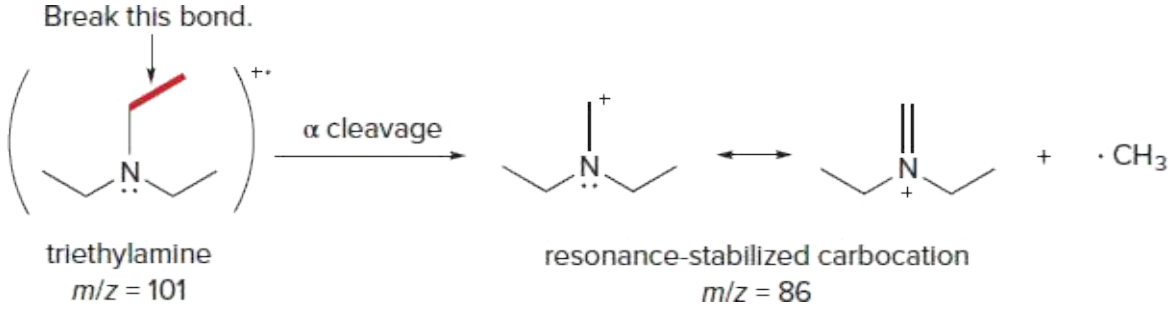
(b) What fragments are formed by dehydration of butan-2-ol?

A.4C Amines

Like alcohols, amines undergo fragmentation by α cleavage. Alpha (α) cleavage occurs by breaking the bond between an alkyl group and the carbon that bears the amine nitrogen, forming an alkyl radical and a resonance-stabilized carbocation.

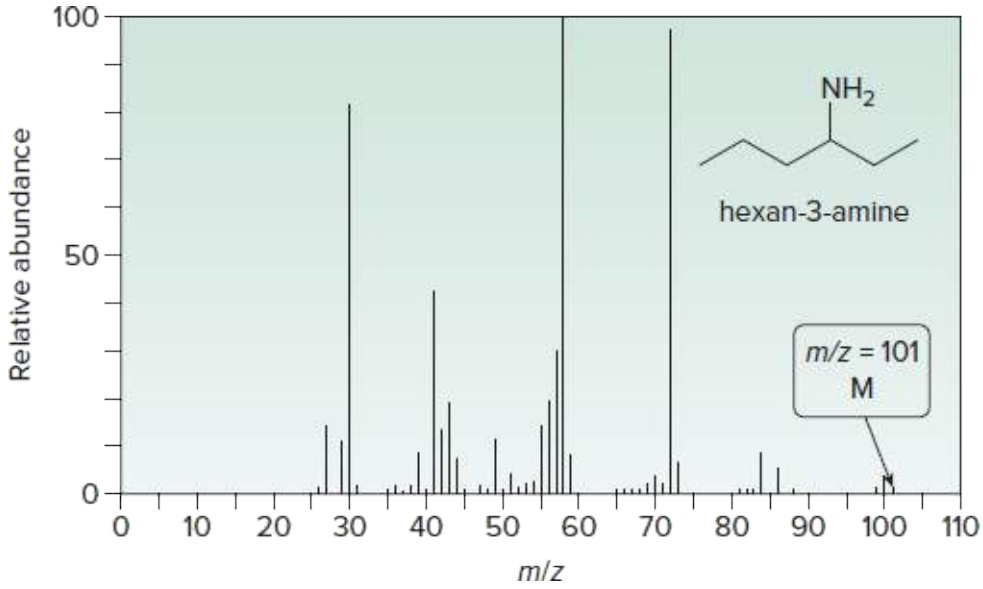


For example, α cleavage of triethylamine (molecular ion at m/z = 101) forms CH_3. and a resonance-stabilized cation at m/z = 86.



Problem A.12

Propose structures for the two fragments of highest abundance in the mass spectrum of hexan-3-amine.



A.5 Other Types of Mass Spectrometry

Recent advances have greatly expanded the information obtained from mass spectrometry.

Table A.1 Exact Masses of Some Common Isotopes

Isotope	Mass
^{12}C	12.0000
^{1}H	1.00783
^{16}O	15.9949
^{14}N	14.0031

A.5A High-Resolution Mass Spectrometry

The mass spectra described thus far have been low-resolution spectra; that is, they report *m/z* values to the nearest whole number. As a result, the mass of a given molecular ion can correspond to many different molecular formulas, as shown in Sample Problem A.2.

High-resolution mass spectrometers measure *m/z* ratios to four (or more) decimal places. This is valuable because except for carbon-12, whose mass is defined as

12.0000, the masses of all other nuclei are very close to—but not exactly—whole numbers. Table A.1 lists the exact mass values of a few common nuclei. Using these values, it is possible to determine the single molecular formula that gives rise to a molecular ion.

For example, a compound having a molecular ion at m/z = 60 using a low-resolution mass spectrometer could have the following molecular formulas:

Formula	Exact mass
C_3H_8O	60.0575
$C_2H_4O_2$	60.0211
$C_2H_8N_2$	60.0688

If the molecular ion had an exact mass of 60.0578, the compound's molecular formula is C_3H_8O, because its mass is closest to the observed value.

Problem A.13

The low-resolution mass spectrum of an unknown analgesic X had a molecular ion of 151. Possible molecular formulas include $C_7H_5NO_3$, $C_8H_9NO_2$, and $C_{10}H_{17}N$. High-resolution mass spectrometry gave an exact mass of 151.0640. What is the molecular formula of X?

A.5B Gas Chromatography–Mass Spectrometry (GC–MS)

Two analytical tools—gas chromatography (GC) and mass spectrometry (MS)—can be combined into a single instrument (GC–MS) to analyze mixtures of compounds (Figure A.7a). The gas chromatograph separates the mixture, and then the mass spectrometer records a spectrum of the individual components.

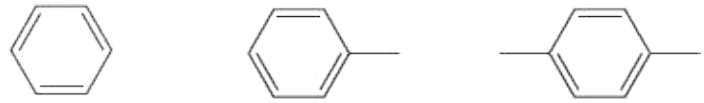
A gas chromatograph consists of a thin capillary column containing a viscous, high-boiling liquid, all housed in an oven. When a sample is injected into the GC, it is vaporized and swept by an inert gas through the column. The components of the mixture travel through the column at different rates, often separated by boiling point, with lower-boiling compounds exiting the column before higher-boiling compounds. Each compound then enters the mass spectrometer, where it is ionized to form its molecular ion and lower-molecular-weight fragments. The GC–MS records a gas chromatogram for the mixture, which plots the amount of each component versus its retention time—that is, the time required to travel through the column. Each component of a mixture is characterized by its retention time in the gas chromatogram and its molecular ion in the mass spectrum (Figure A.7b).

GC–MS is widely used for characterizing mixtures containing environmental pollutants. It is also used to analyze urine and hair samples for the presence of illegal drugs or banned substances thought to improve athletic performance.

To analyze a urine sample for THC (tetrahydrocannabinol), the principal psychoactive component of marijuana that opened this chapter, the organic compounds are extracted from urine, purified, concentrated, and injected into the GC–MS. THC appears as a GC peak with a characteristic retention time (for a given set of experimental parameters), and gives a molecular ion at 314, its molecular weight, as shown in Figure A.8.

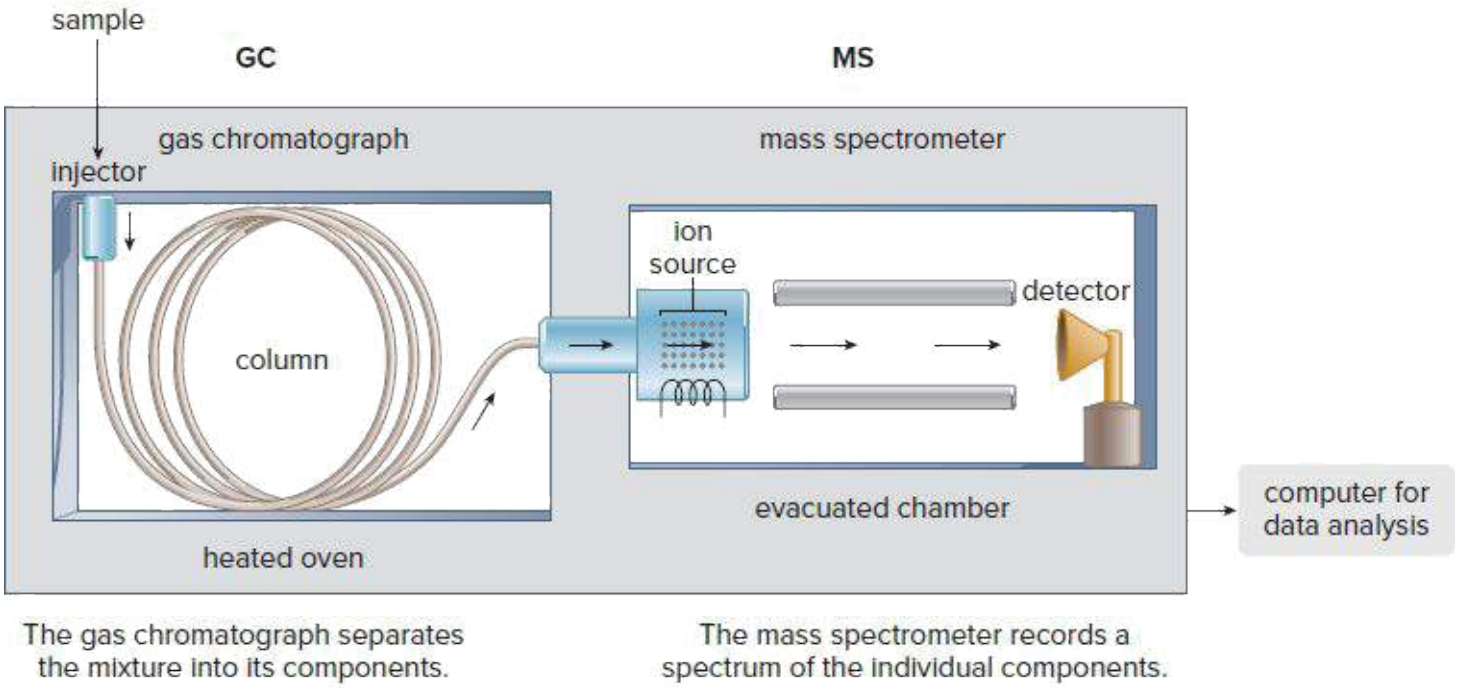
Problem A.14

Benzene, toluene, and *p*-xylene (BTX) are often added to gasoline to boost octane ratings. What would be observed if a mixture of these three compounds were subjected to GC–MS analysis? How many peaks would be present in the gas chromatogram? What would be the relative order of the peaks? What molecular ions would be observed in the mass spectra?



benzene toluene *p*-xylene

a. Schematic of a GC–MS instrument



b. GC trace of a three-component mixture. The mass spectrometer gives a spectrum for each component.

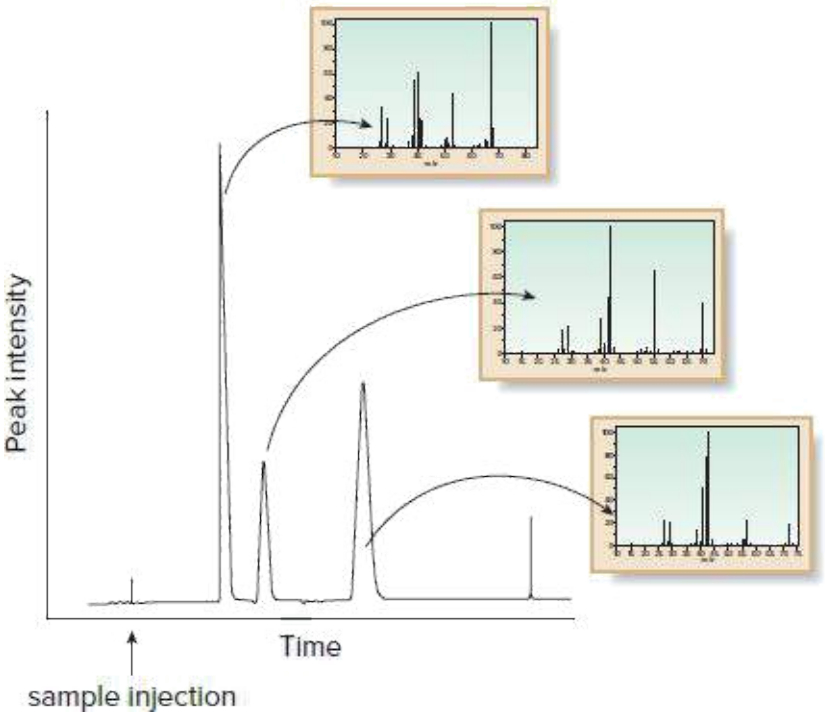


Figure A.7 **Compound analysis using GC–MS**

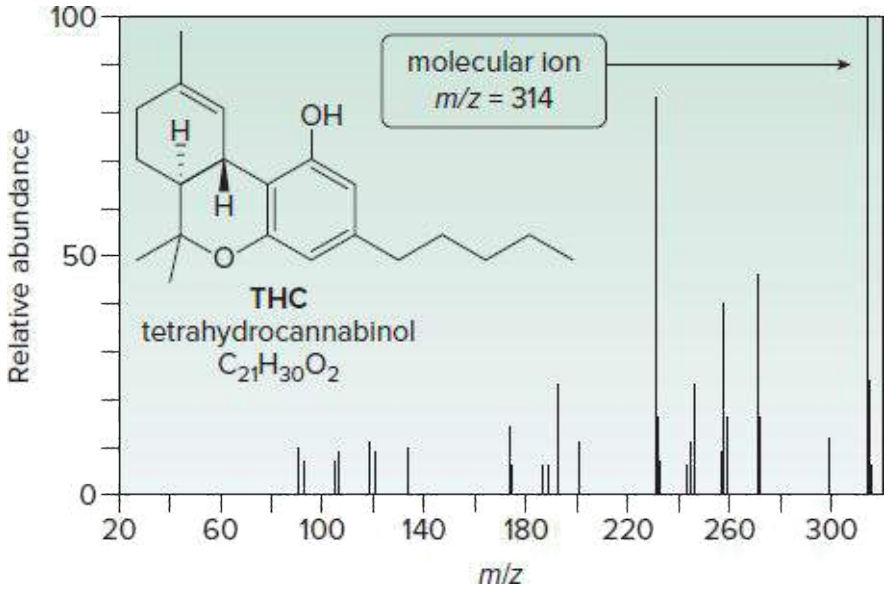


Figure A.8 **Mass spectrum of tetrahydrocannabinol (THC)**

Dr. John Fenn shared the 2002 Nobel Prize in Chemistry for his development of ESI mass spectrometry.

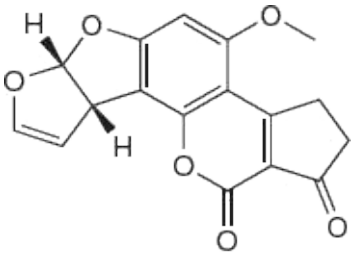
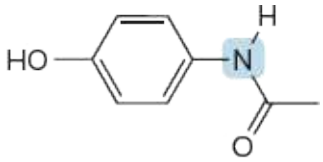
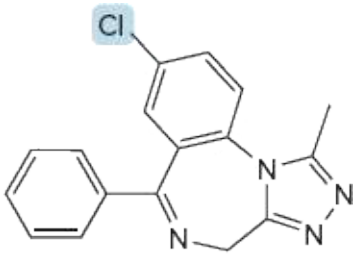
A.5C Mass Spectra of High-Molecular-Weight Biomolecules

Until the 1980s mass spectra were limited to molecules that could be readily vaporized with heat under vacuum, and thus had molecular weights of < 800. In the last 35 years, new methods have been developed to generate gas phase ions of large molecules, allowing mass spectra to be recorded for large biomolecules such as proteins and carbohydrates. Electrospray ionization (ESI), for example, forms ions by creating a fine spray of charged droplets in an electric field. Evaporation of the charged droplets forms gaseous ions that are then analyzed by their *m/z* ratio. ESI and related techniques have extended mass spectrometry into the analysis of nonvolatile compounds with molecular weights greater than 100,000 daltons (atomic mass units).

Spectroscopy A CHAPTER REVIEW

KEY CONCEPTS

Molecular ion (M) in mass spectrometry (A.1, A.2)

1 A compound with C, H, and O atoms	2 A compound with N atoms	3 A compound with a Cl atom
 aflatoxin B1 even molecular ion *m/z* = 312	 acetaminophen (Tylenol) odd molecular ion *m/z* = 151	 alprazolam (Xanax) two molecular ions *m/z* = 308 *m/z* = 310
• mass of the molecular ion (M) = molecular weight of the compound • *m/z* = mass-to-charge ratio	• an odd number of N atoms = odd molecular ion	• 3:1 ratio (M and M + 2)

Try Problems A.16, A.17, A.22, A.24a–c.

KEY SKILLS

[1] Proposing possible molecular formulas for a compound that contains C, H, and perhaps O with a given molecular ion (A.1); example: *m/z* = 100

Possible hydrocarbons		Possible compounds with O	
1 Divide 100 by 12.	2 Replace one C atom by 12 H atoms.	3 Substitute one O atom for CH_4.	4
$\frac{100}{12}$ = 8 C's maximum (remainder = 4) → C_8H_4	C_8H_4 → (− 1 C, + 12 H's) → C_7H_{16}	C_7H_{16} → (− CH_4, + 1 O) → $C_6H_{12}O$	

See *How To* (A.1C), Sample Problems A.2, A.3. Try Problems A.18–A.21.

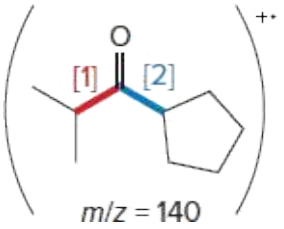
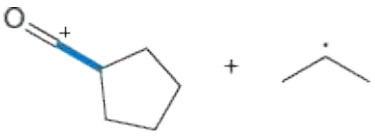
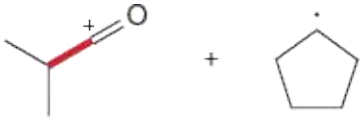
[2] Determining the molecular ions for a compound with Cl or Br (A.2);

example: bromocyclohexane ($C_6H_{11}Br$)

1 Provide the molecular formulas using each of the common isotopes.	2 Calculate the molecular weight from the molecular formulas.
Molecular formula $C_6H_{11}{}^{79}Br$ $C_6H_{11}{}^{81}Br$	Mass of the molecular ion (*m/z*) 162 (M peak) 164 (M + 2 peak)

See Sample Problem A.4, Figures A.3, A.4. Try Problem A.22.

[3] Proposing possible structures for fragmentation by α cleavage (A.3, A.4)

1 Determine which bonds are cleaved in the molecular ion.	2 Cleave bond [1].	3 Cleave bond [2].
 *m/z* = 140	 *m/z* = 97	 *m/z* = 71 • Two cationic fragments are formed by α cleavage of a ketone.

See Sample Problems A.6, A.7, Figure A.5. Try Problems A.26–A.33.

PROBLEMS

Problems that combine mass spectrometry and infrared spectroscopy are located at the end of Spectroscopy B. Problems that combine mass spectrometry, infrared spectroscopy, and nuclear magnetic resonance spectroscopy are found at the end of Spectroscopy C.

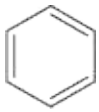
Problem Using a Three-Dimensional Model

A.15 **The mass spectrum of the following compound shows fragments at *m/z* = 127, 113, and 85. Propose structures for the ions that give rise to these peaks.**

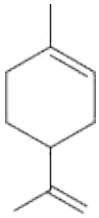
Molecular Ions and Molecular Formulas

A.16 **What molecular ion is expected for each compound?**

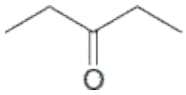
a.



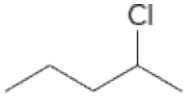
b.



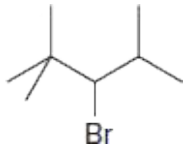
c.



d.



e.



A.17 **Which compound gives a molecular ion at *m/z* = 122: $C_6H_5CH_2CH_2CH_3$, $C_6H_5COCH_2CH_3$, or $C_6H_5OCH_2CH_3$?**

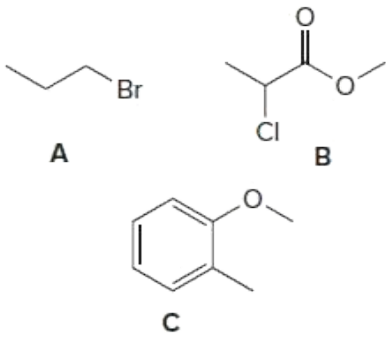
A.18 **Propose two molecular formulas for each molecular ion: (a) 102; (b) 98; (c) 119; (d) 74.**

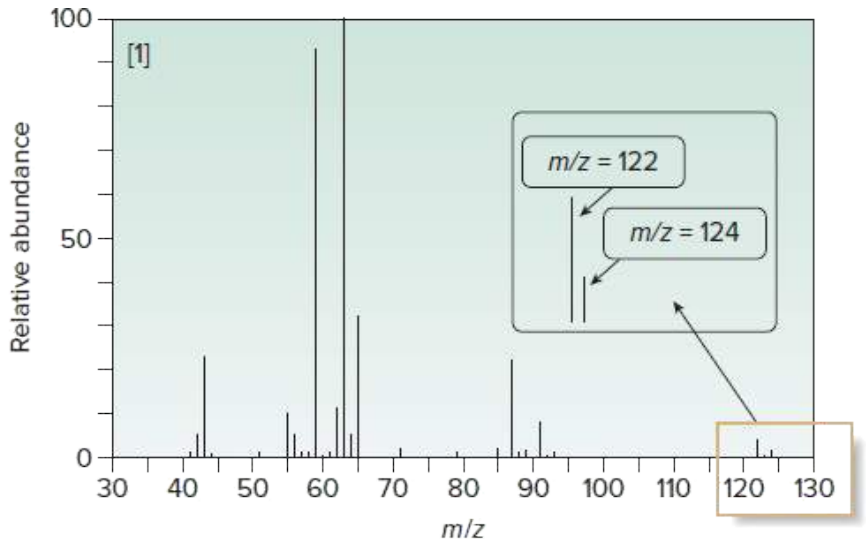
A.19 **Propose four possible structures for a hydrocarbon with a molecular ion at *m/z* = 112.**

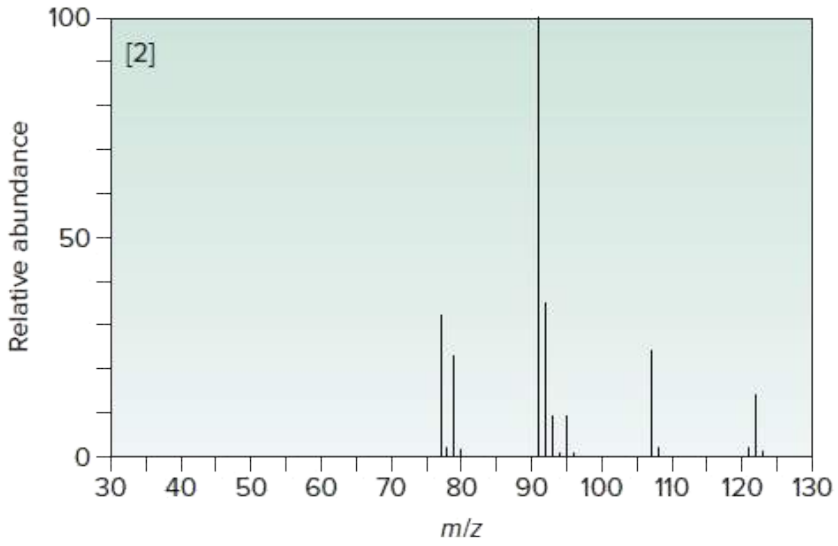
A.20 **What is the molecular formula for α-himachalene, a hydrocarbon obtained from cedar wood, which has four degrees of unsaturation and has a molecular ion in its mass spectrum at *m/z* = 204?**

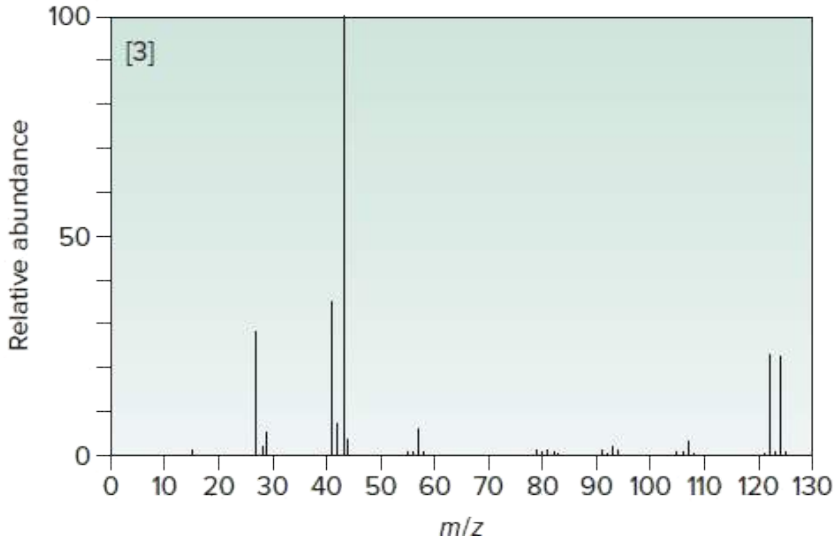
A.21 **Propose a molecular formula for rose oxide, a rose-scented compound isolated from roses and geraniums, which contains the elements of C, H, and O, has two degrees of unsaturation, and has a molecular ion in its mass spectrum at *m/z* = 154.**

A.22 **Match each structure to its mass spectrum.**









A.23 **Propose two possible structures for a hydrocarbon having an exact mass of 96.0939 that forms ethylcyclopentane upon hydrogenation with H_2 and Pd-C.**

A.24 **Propose a structure consistent with each set of data.**

a. a compound that contains a benzene ring and has a molecular ion at *m/z* = 107

b. a hydrocarbon that contains only sp^3 hybridized carbons and a molecular ion at *m/z* = 84

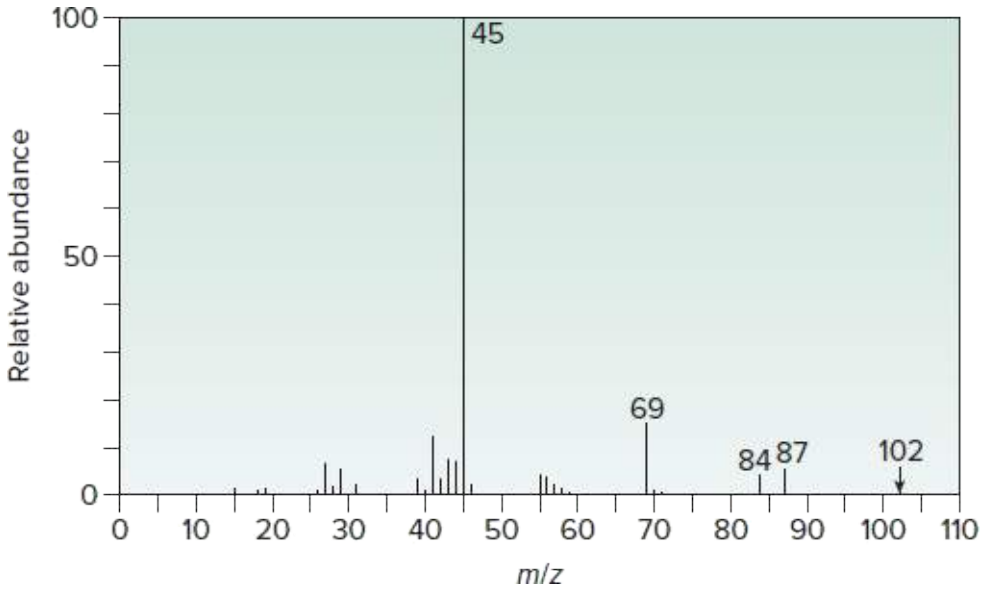
c. a compound that contains a carbonyl group and gives a molecular ion at *m/z* = 114

d. a compound that contains C, H, N, and O and has an exact mass for the molecular ion at 101.0841

A.25 **A low-resolution mass spectrum of the neurotransmitter dopamine gave a molecular ion at *m/z* = 153. Two possible molecular formulas for this molecular ion are $C_8H_{11}NO_2$ and $C_7H_{11}N_3O$. A high-resolution mass spectrum provided an exact mass at 153.0680. Which of the possible molecular formulas is the correct one?**

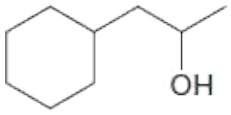
Fragmentation

A.26 **Label each of the following in the mass spectrum of hexan-2-ol [$CH_3CH(OH)CH_2CH_2CH_2CH_3$]: the molecular ion, the base peak, the fragment resulting from the loss of H_2O, and α cleavage fragments.**

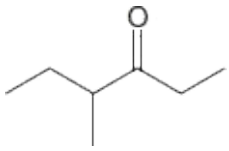


A.27 **What cations are formed in the mass spectrometer by α cleavage of each of the following compounds?**

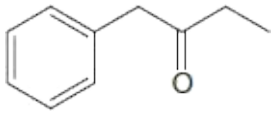
a.



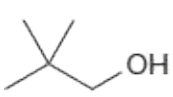
b.



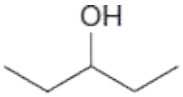
c.



A.28 Consider isomeric alcohols A and B and mass spectra [1] and [2].

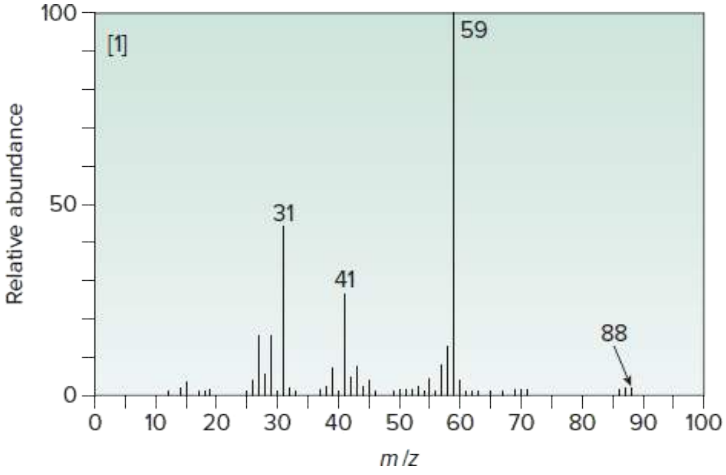


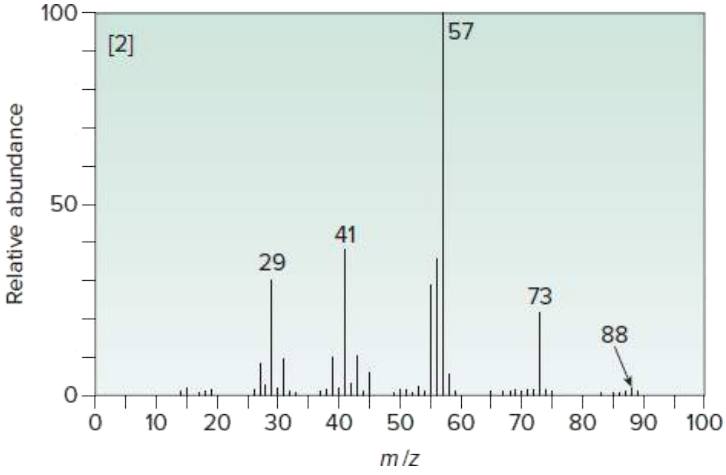
A



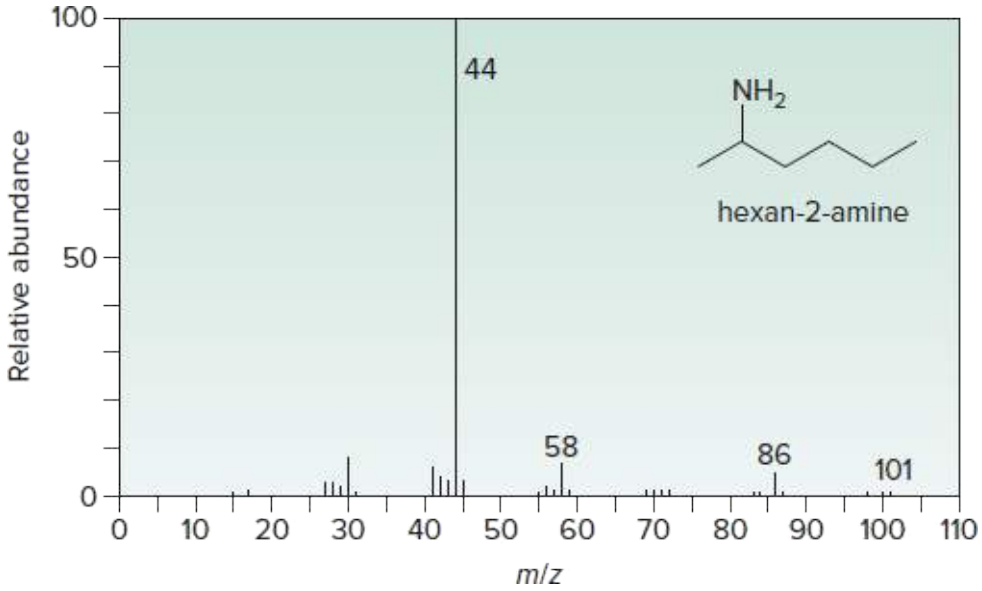
B

(a) Label the molecular ion and base peak in each spectrum. (b) Use the fragmentation patterns to determine which mass spectrum corresponds to isomer A and which corresponds to isomer B.





A.29 Consider the mass spectrum of hexan-2-amine. Label the molecular ion and base peak and propose a structure for the fragment that corresponds to the base peak.



A.30 For each compound, assign likely structures to the fragments at each *m/z* value, and explain how each fragment is formed.

a. $C_6H_5CH_2CH_2OH$: peaks at *m/z* = 104, 91

b. $CH_2=C(CH_3)CH_2CH_2OH$: peaks at *m/z* = 71, 68, 41, 31

A.31 Suppose you have two bottles, labeled ketone A and ketone B. You know that one bottle contains $CH_3CO(CH_2)_5CH_3$ and one contains $CH_3CH_2CO(CH_2)_4CH_3$, but you do not know which ketone is in which bottle. Ketone A gives a fragment at *m/z* = 99 and ketone B gives a fragment at *m/z* = 113. What are the likely structures of ketones A and B from these fragmentation data?

A.32 Primary (1°) alcohols often show a peak in their mass spectra at *m/z* = 31. Suggest a structure for this fragment.

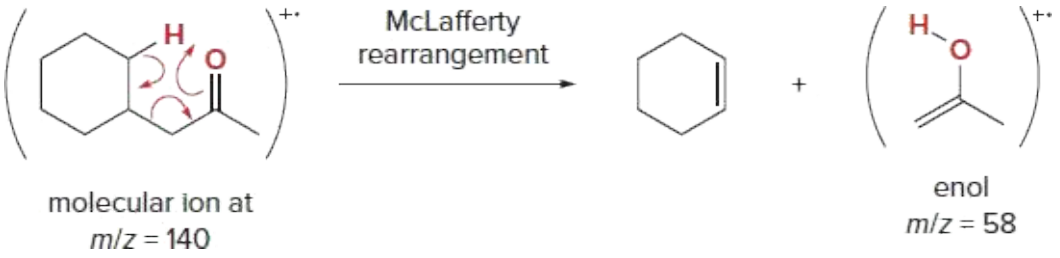
A.33 Like alcohols, ethers undergo α cleavage by breaking a carbon–carbon bond between an alkyl group and the carbon bonded to the ether oxygen atom; that is, the red C—C bond in R—CH_2OR' is broken. With this in mind, propose structures for the fragments formed by α cleavage of $(CH_3)_2CHCH_2OCH_2CH_3$. Suggest a reason why an ether fragments by α cleavage.

Challenge Problems

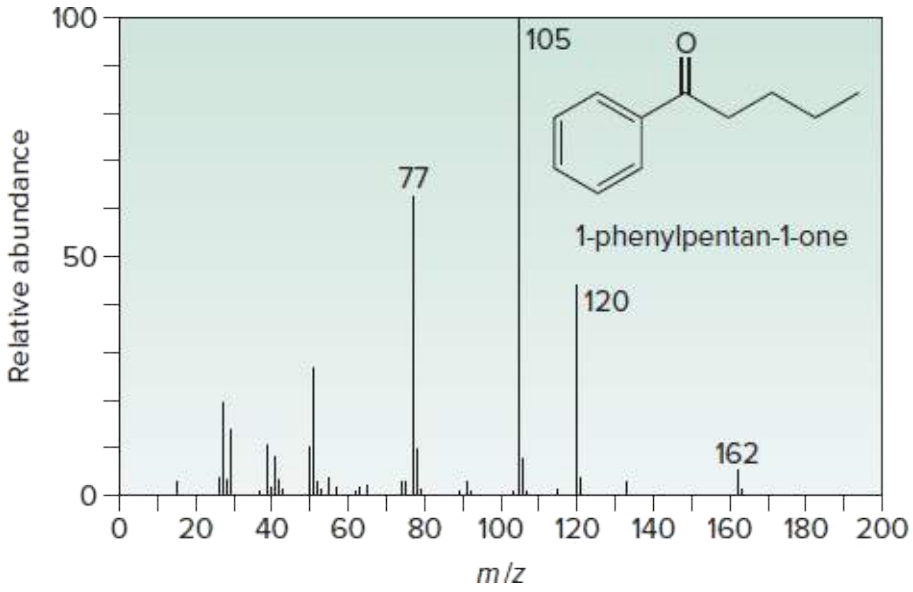
A.34 What molecular ions would be present in the mass spectrum of a compound that contains C, H, and (a) 1 Br and 1 Cl; (b) 3 Br's? Give the relative peak intensities of the molecular ions in each case.

A.35 In addition to α cleavage, some aldehydes and ketones undergo the McLafferty rearrangement. In the McLafferty rearrangement, a hydrogen on a carbon three atoms from the C=O is transferred to the carbonyl

oxygen and a carbon–carbon bond is broken. This process forms an alkene and the radical cation derived from an enol, which appears as a fragment in the mass spectrum.

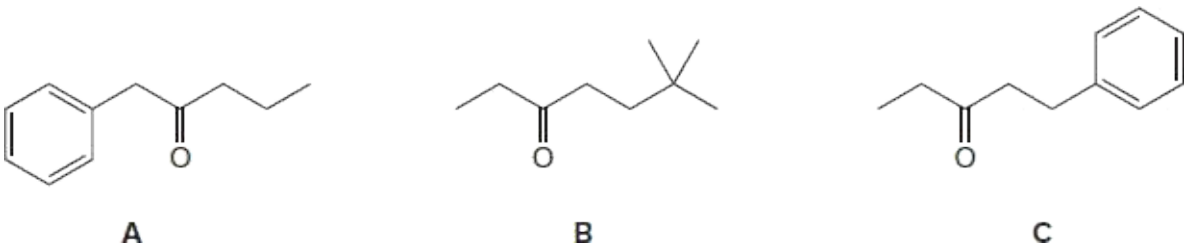


a. Draw the products formed from the McLafferty rearrangement of 1-phenylpentan-1-one, and identify the fragment that results in the given mass spectrum.



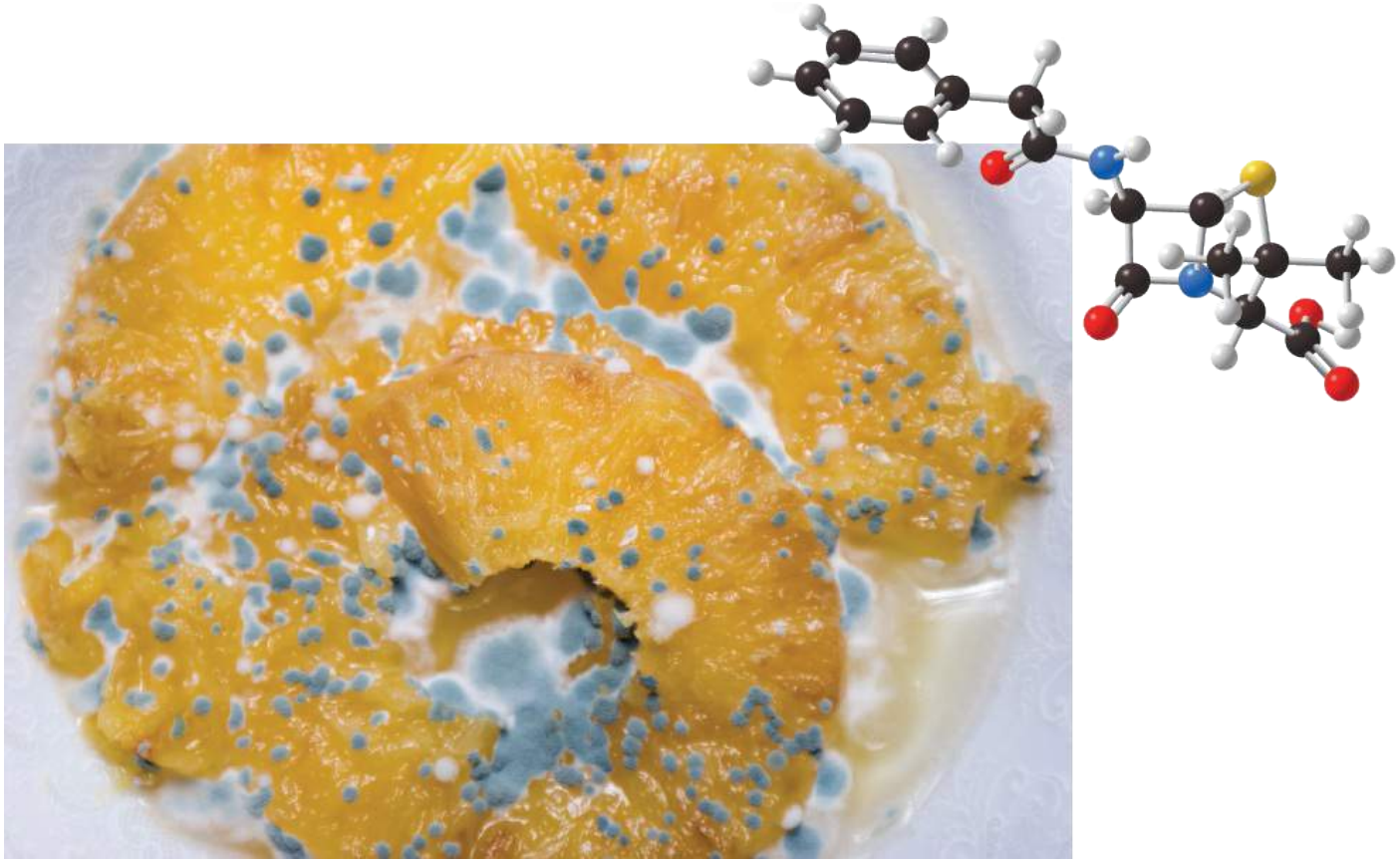
b. If a mass spectrum of the ester ethyl pentanoate ($CH_3CH_2CH_2CH_2CO_2CH_2CH_3$) is recorded, what is the mass of the radical cation formed by the McLafferty rearrangement?

c. Which of the following compounds can undergo a McLafferty rearrangement?



A B C

B Infrared Spectroscopy



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B.1 Electromagnetic radiation

B.2 The general features of infrared spectroscopy

B.3 IR absorptions

B.4 Infrared spectra of common functional groups

B.5 IR and structure determination

The serendipitous discovery of penicillin from a mold of the genus *Penicillium* by Scottish bacteriologist Sir Alexander Fleming in 1928 is considered one of the single most important events in the history of medicine. Penicillin G and

related compounds are members of the β-lactam family of antibiotics, all of which contain a strained four-membered amide ring that is responsible for their biological activity. Penicillin was first used to cure a streptococcal infection in 1942, and by 1944 penicillin production was given high priority by the U.S. government, because it was needed to treat the many injured soldiers in World War II. The unusual structure of penicillin was elucidated by modern instrumental methods in the 1940s. In Spectroscopy Part B, we learn about infrared spectroscopy, which is used to determine the functional groups in organic compounds like penicillin.

Why Study…

Infrared Spectroscopy?

Although mass spectrometry tells us the molecular weight and molecular formula for an organic compound, other forms of spectroscopy must be used to completely delineate the structure of a complex compound. Infrared spectroscopy is a technique that uses infrared light to interact with compounds, causing bonds to bend and vibrate, and giving a spectrum with characteristic absorptions for particular functional groups. Because the properties and reactions of an organic compound are determined in large part by what functional groups it contains, infrared spectroscopy is a valuable method for determining the structure of compounds isolated from natural sources, and for monitoring the progress of reactions that result in the addition or removal of functional groups.

We begin this chapter by learning about infrared light, the energy source used in infrared spectroscopy.

B.1 Electromagnetic Radiation

Infrared (IR) spectroscopy and nuclear magnetic resonance (NMR) spectroscopy (Part C) both use a form of electromagnetic radiation as their energy source. To understand IR and NMR, therefore, you need to understand some of the properties of electromagnetic radiation—radiant energy having dual properties of both waves and particles.

The particles of electromagnetic radiation are called photons, each having a discrete amount of energy called a quantum. Because electromagnetic radiation also has wave

properties, it can be characterized by its wavelength and frequency.

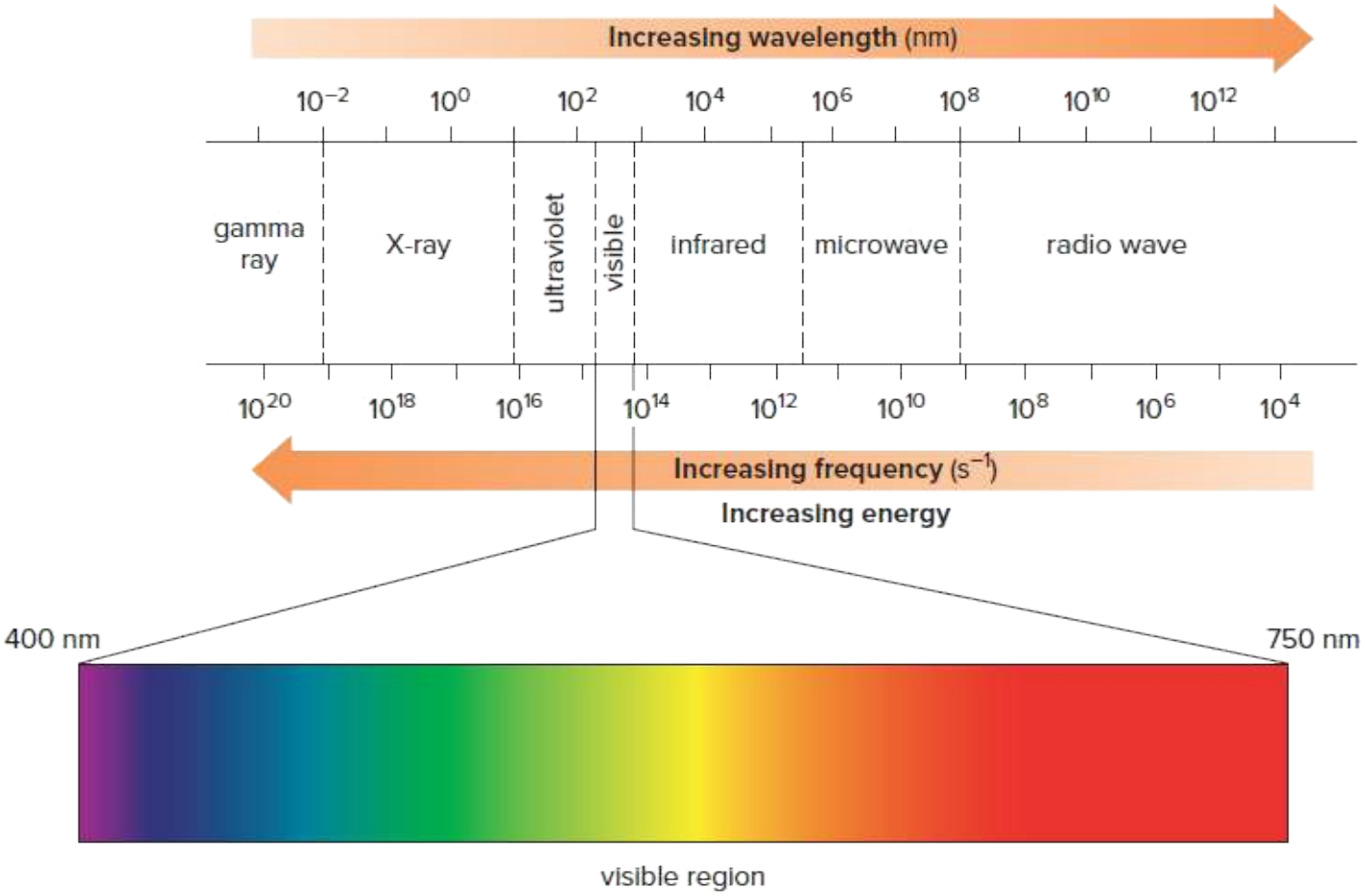
Length units used to report wavelength include:

Unit	Length
meter (m)	1 m
centimeter (cm)	10^{-2} m
micrometer (μm)	10^{-6} m
nanometer (nm)	10^{-9} m
Angstrom (Å)	10^{-10} m

- **Wavelength (λ) is the distance from one point on a wave (e.g., the peak or trough) to the same point on the adjacent wave. A variety of different length units are used for λ, depending on the type of radiation.**
- **Frequency (*ν*) is the number of waves passing a point per unit time. Frequency is reported in cycles per second (s^{-1}), which is also called hertz (Hz).**

You come into contact with many different kinds of electromagnetic radiation in your daily life. You use visible light to see the words on this page, you may cook with microwaves, and you should use sunscreen to protect your skin from the harmful effects of ultraviolet radiation.

The different forms of electromagnetic radiation make up the electromagnetic spectrum. The spectrum is arbitrarily divided into different regions, as shown in Figure B.1. All electromagnetic radiation travels at the speed of light (c), 3.0×10^8 m/s.



- Visible light occupies only a small region of the electromagnetic spectrum.

Figure B.1 **The electromagnetic spectrum**

The speed of electromagnetic radiation (c) is directly proportional to its wavelength and frequency: Page 536

$$c = \lambda\nu$$

The speed of light (c) is a constant, so wavelength and frequency are *inversely* related:

- **$\lambda = c/\nu$: Wavelength increases as frequency decreases.**
- **$\nu = c/\lambda$: Frequency increases as wavelength decreases.**

The energy (E) of a photon is directly proportional to its frequency where h = Planck's constant (6.63×10^{-34} J · s).

$$E = h\nu$$

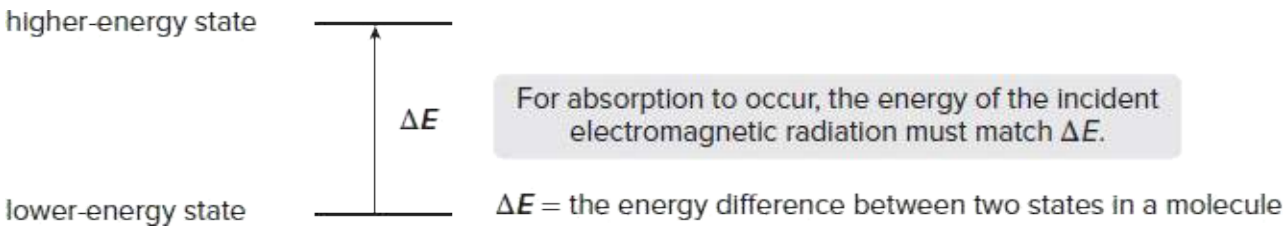
Frequency and wavelength are *inversely* proportional ($\nu = c/\lambda$), however, so energy and wavelength are *inversely* proportional:

$$E = h\nu = \frac{hc}{\lambda}$$

- **The energy of electromagnetic radiation increases as frequency increases and wavelength decreases.**

When electromagnetic radiation strikes a molecule, some wavelengths—but not all—are absorbed. Only some wavelengths are absorbed because molecules have discrete energy levels. The energies of their electronic, vibrational, and nuclear spin states are *quantized*, not *continuous*.

- **For absorption to occur, the energy of the photon must match the difference between two energy states in a molecule.**



- **The *larger* the energy difference between two states, the *higher* the energy of radiation needed for absorption, the *higher* the frequency, and the *shorter* the wavelength.**

Problem B.1

Which of the following has the higher frequency: (a) light having a wavelength of 10^2 or 10^4 nm; (b) light having a wavelength of 100 nm or 100 μm; (c) red light or blue light?

Problem B.2

Which of the following has the higher energy: (a) light having a ν of 10^4 Hz or 10^8 Hz; (b) light having a λ of 10 nm or 1000 nm; (c) red light or blue light?

B.2 The General Features of Infrared Spectroscopy

Organic chemists use infrared (IR) spectroscopy to identify the functional groups in a compound.

B.2A Background

Using the wavenumber scale results in IR values in a numerical range that is easier to report than the corresponding frequencies given in hertz (4000–400 cm^{-1} compared to 1.2×10^{14}–1.2×10^{15} Hz).

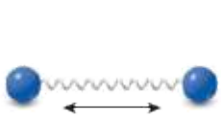
Infrared radiation (λ = 2.5–25 μm) is the energy source in infrared spectroscopy. Infrared light has somewhat longer wavelengths than visible light, making infrared light lower in frequency and lower in energy than visible light. Frequencies in IR spectroscopy are reported using a unit called the wavenumber ($\tilde{\nu}$):

$$\tilde{\nu} = \frac{1}{\lambda}$$

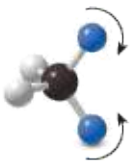
Wavenumber is *inversely* proportional to wavelength and reported in reciprocal centimeters (cm^{-1}). Wavenumber ($\tilde{\nu}$) is *proportional* to frequency (ν). Frequency (and therefore energy) increases as the wavenumber increases. Using the wavenumber scale, IR absorptions occur from 4000 cm^{-1} to 400 cm^{-1}.

- **Absorption of IR light causes changes in the vibrational motions of a molecule.**

Covalent bonds are not static. They are more like springs with weights on each end. When two atoms are bonded to each other, the bond stretches back and forth. When three or more atoms are joined together, bonds can also bend. These bond stretching and bending vibrations represent the different vibrational modes available to a molecule.

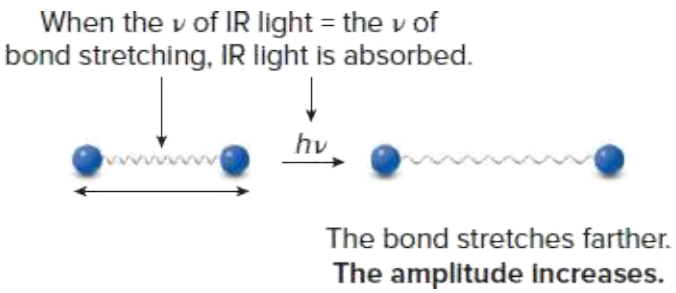


A bond can stretch.



Two bonds can bend.

These vibrations are quantized, so they occur only at specific frequencies, which correspond to the frequency of IR light. When the frequency of IR light matches the frequency of a particular vibrational mode, the IR light is absorbed, causing the amplitude of the particular bond stretch or bond bend to increase.



- **Different kinds of bonds vibrate at different frequencies, so they absorb different frequencies of IR light.**
- **IR spectroscopy distinguishes between the different kinds of bonds in a molecule, so it is possible to determine the functional groups present.**

Problem B.3

Which of the following has higher energy: (a) IR light of 3000 cm^{-1} or 1500 cm^{-1} in wavenumber; (b) IR light having a wavelength of 10 μm or 20 μm?

B.2B Characteristics of an IR Spectrum

In an IR spectrometer, light passes through a sample. Frequencies that match vibrational frequencies are absorbed, and the remaining light is transmitted to a detector. A spectrum plots the amount of transmitted light versus its wavenumber. The IR spectrum of propan-1-ol, $CH_3CH_2CH_2OH$, illustrates several important features of IR spectroscopy.

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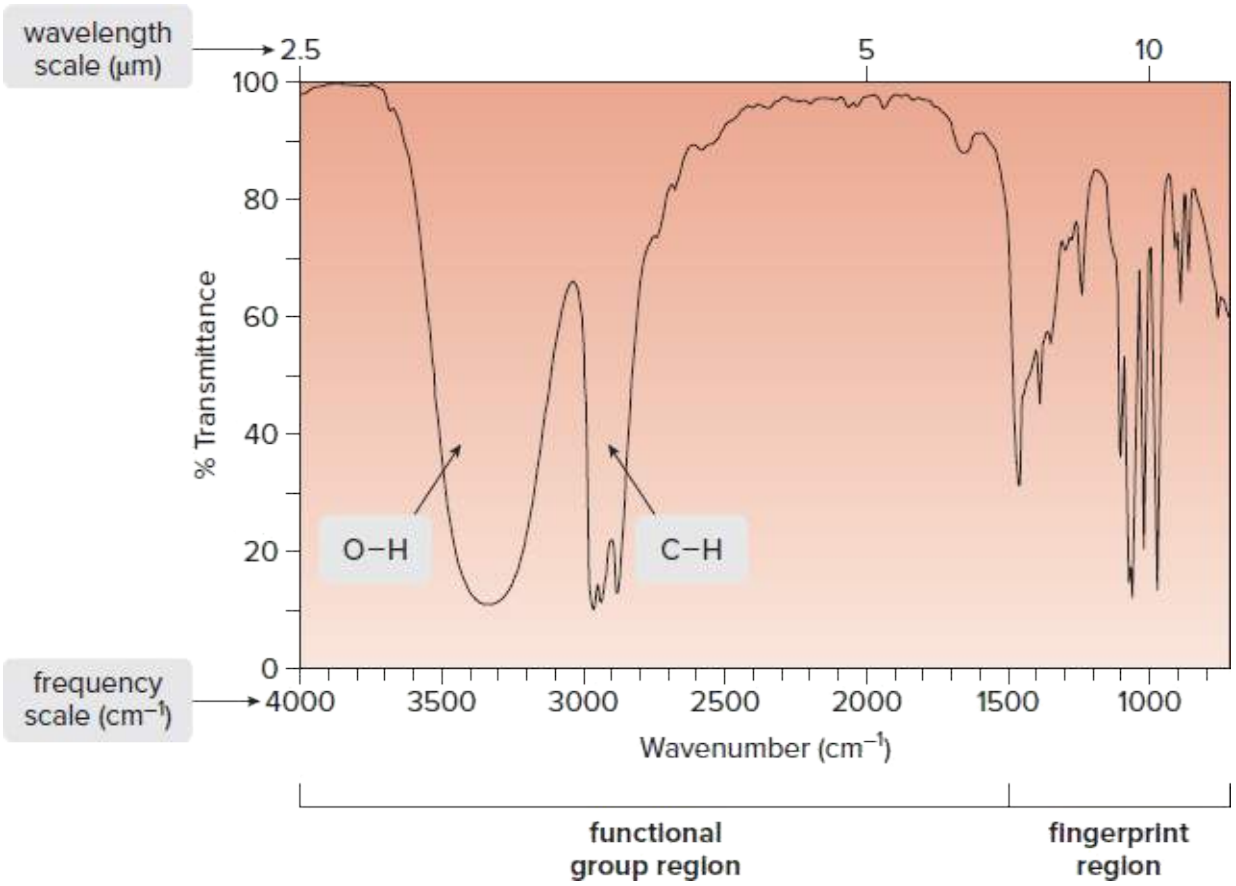
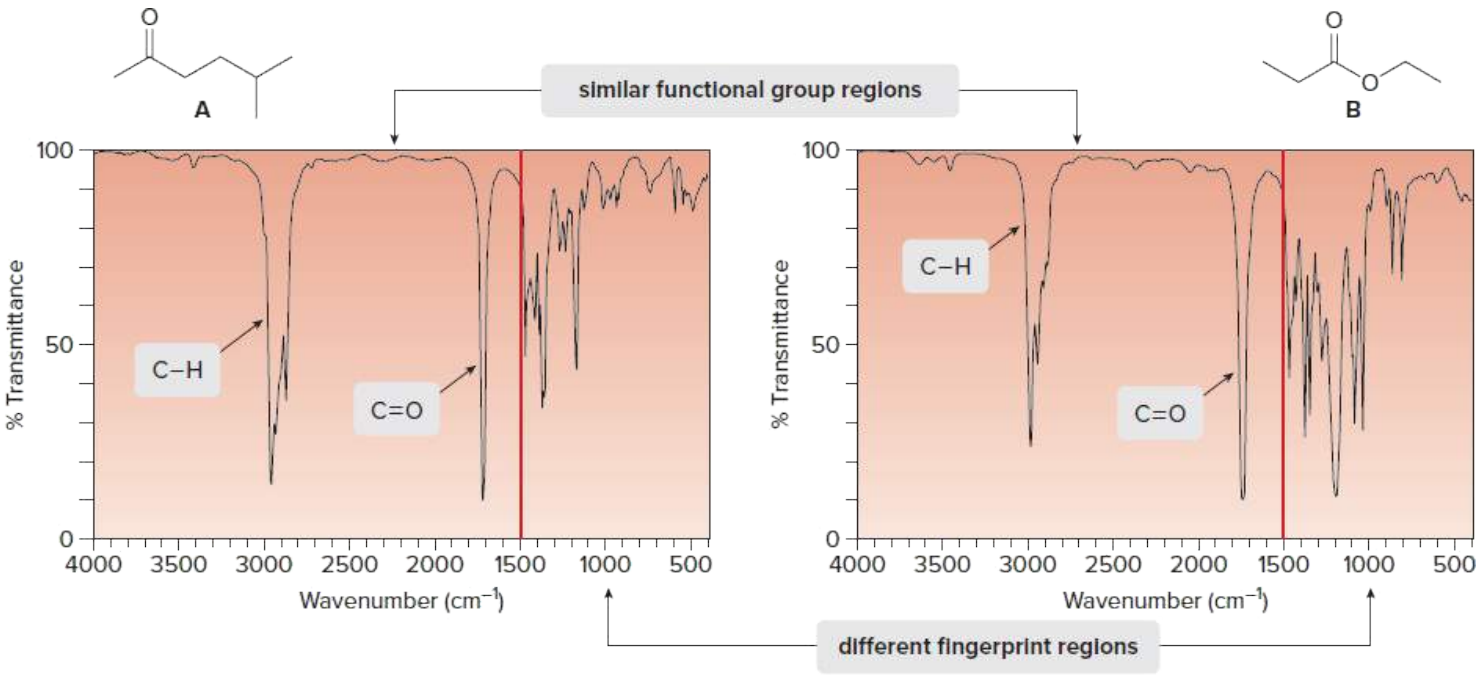
- The absorption peaks go *down* on a page. The *y* axis measures percent transmittance: 100% transmittance means that all the light shone on a sample is transmitted and none is absorbed; 0% transmittance means that none of the light shone on a sample is transmitted and all is absorbed. A strong absorption has a low % transmittance because much light is absorbed.
- Each peak corresponds to a particular kind of bond, and each bond type (such as O—H and C—H) occurs at
- IR spectra have both a wavelength and a wavenumber scale on the *x* axis. Wavelengths are recorded in μm (2.5–25). Wavenumber, frequency, and energy *decrease* from left to right. Where a peak occurs is reported in reciprocal centimeters (cm^{-1}).



Conceptually, the IR spectrum is divided into two regions:

- **The functional group region occurs at ≥ 1500 cm^{-1}. Common functional groups give one or two peaks in this region, at a characteristic frequency.**
- **The fingerprint region occurs at < 1500 cm^{-1}. This region often contains a complex set of peaks and is unique for every compound.**

Compare, for example, the IR spectra of 5-methylhexan-2-one (A) and ethyl propanoate (B) in Figure B.2. The IR spectra look similar in their functional group regions because both compounds contain a carbonyl group (C=O) and several sp^3 hybridized C—H bonds. Because A and B are different compounds, however, their fingerprint regions look very different.



- **A** and **B** show similar absorptions for their C=O group and sp^3 hybridized C–H bonds in the functional group region.
- **A** and **B** are different compounds, so their fingerprint regions are quite different.

Figure B.2 **Comparing the functional group region and fingerprint region of two compounds**

B.3 IR Absorptions

B.3A Where Particular Bonds Absorb in the IR

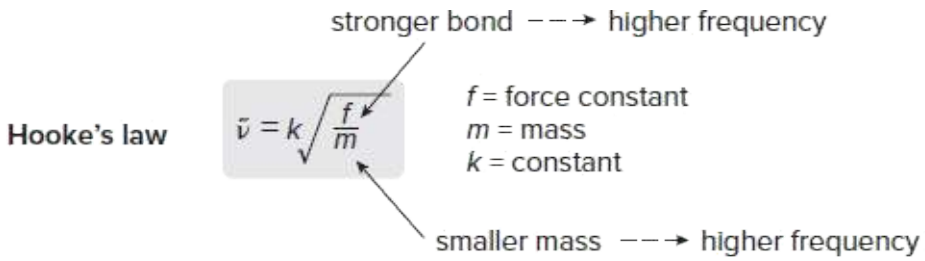
Where a particular bond absorbs in the IR depends on bond strength and atom mass.

- **Bond strength: stronger bonds vibrate at higher frequency, so they absorb at higher $\tilde{\nu}$.**
- **Atom mass: bonds with lighter atoms vibrate at higher frequency, so they absorb at higher $\tilde{\nu}$.**

Thinking of bonds as springs with weights on each end illustrates these trends. The strength of the spring is analogous to bond strength, and the mass of the weights is analogous to atomic mass. For two springs with the same weights on each end, the stronger spring vibrates at a higher frequency. For two springs of the same strength, springs with lighter weights vibrate at higher frequency than those with heavier weights. Hooke's law, as shown in Figure B.3, describes the relationship of frequency to mass and bond strength.

The frequency of bond vibration can be derived from Hooke's law, which

describes the motion of a vibrating spring:



- The force constant (f) is the strength of the bond (or spring). The larger the value of f, the stronger the bond, and the higher the $\tilde{\nu}$ of vibration.
- The mass (m) is the mass of atoms (or weights). The smaller the value of m, the higher the $\tilde{\nu}$ of vibration.

Figure B.3 **Hooke's law: How the frequency of bond vibration depends on atom mass and bond strength**

As a result, bonds absorb in four predictable regions in an IR spectrum. These four regions, and the bonds that absorb there, are summarized in Figure B.4. Remembering the information in this figure will help you analyze the spectra of unknown compounds. To help you remember it, keep in mind these two points:

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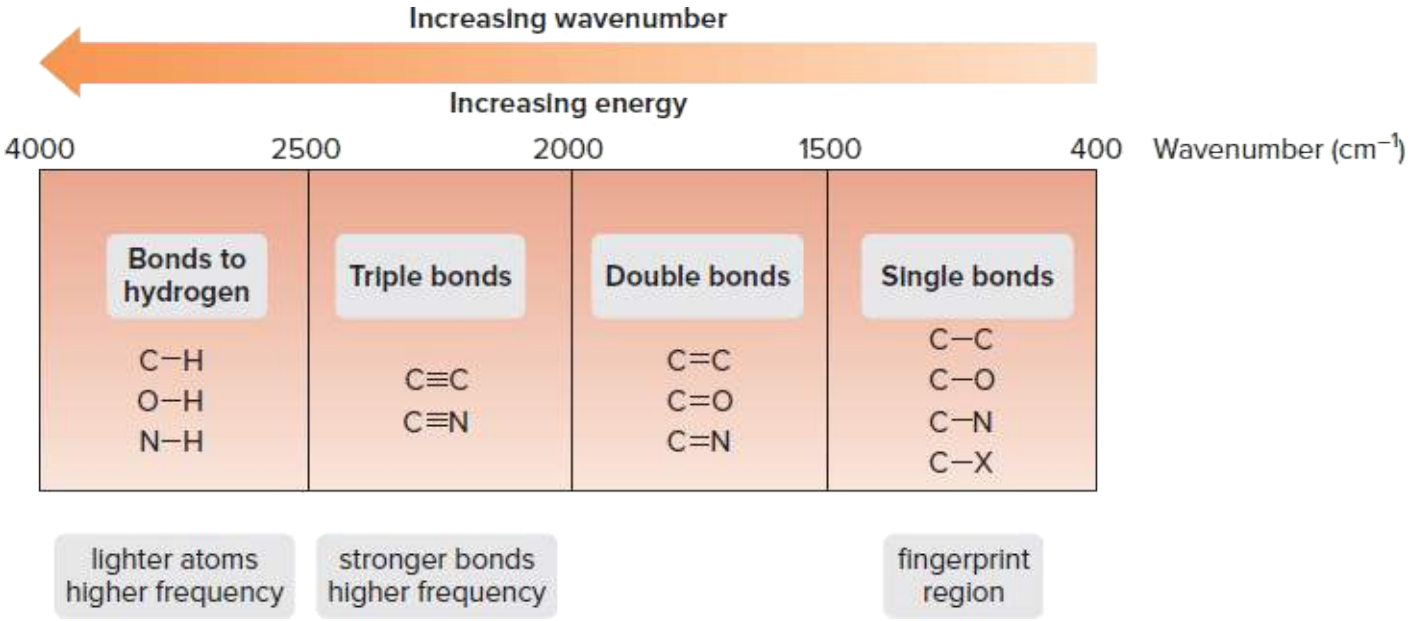


Figure B.4 **Summary: The four regions of the IR spectrum**

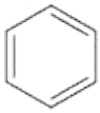
- **Absorptions for bonds to hydrogen always occur on the *left* side of the spectrum (the high wavenumber region). H has so little mass that H—Z bonds (where Z = C, O, and N) vibrate at *high* frequencies.**
- **Bond strength decreases in going from C≡C → C=C → C—C, so the frequency of vibration *decreases*—that is, the absorptions for these**

bonds move farther to the right side of the spectrum.

The functional group region consists of absorptions for single bonds to hydrogen (all H—Z bonds), as well as absorptions for all multiple bonds. Most absorptions in the functional group region are due to bond stretching (rather than bond bending). The fingerprint region consists of absorptions due to all other single bonds (except H—Z bonds), often making it a complex region that is very difficult to analyze.

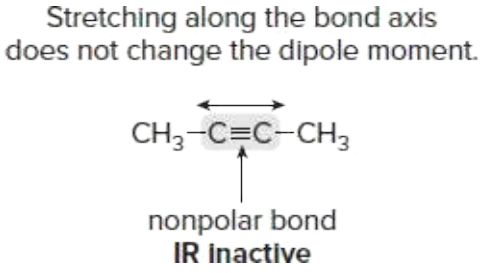
Besides learning the general regions of the IR spectrum, it is useful to learn the specific absorption values for common bonds. Table B.1 lists the most important IR absorptions in the functional group region. Other details of IR absorptions will be presented in later chapters when new functional groups are introduced. Appendix G contains a detailed list of the characteristic IR absorption frequencies for common bonds.

Table B.1 Important IR Absorptions

Bond type	Approximate $\bar{\nu}$ (cm^{-1})	Intensity
O—H	3600–3200	strong, broad
N—H	3500–3200	medium
C—H	~3000	
• C_{sp^3}—H	3000–2850	strong
• C_{sp^2}—H	3150–3000	medium
• C_{sp}—H	3300	medium
C≡C	2250	medium
C≡N	2250	medium
C=O	1800–1650 (often ~1700)	strong
C=C	1650	medium
	1600, 1500	medium

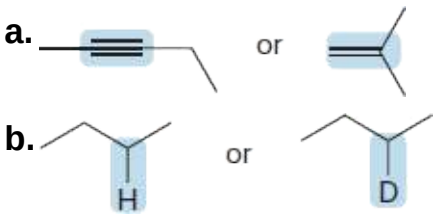
Almost all bonds in a molecule give rise to an absorption peak in an IR spectrum, but a few do not. For a bond to absorb in the IR, there must be a change in dipole moment during the vibration. Thus, symmetrical, nonpolar bonds do *not* absorb in the IR. The

carbon–carbon triple bond of but-2-yne, for example, does not have an IR stretching absorption at 2250 cm^{-1} because the C≡C bond is nonpolar and there is no change in dipole moment when the bond stretches along its axis. This type of vibration is said to be IR inactive.



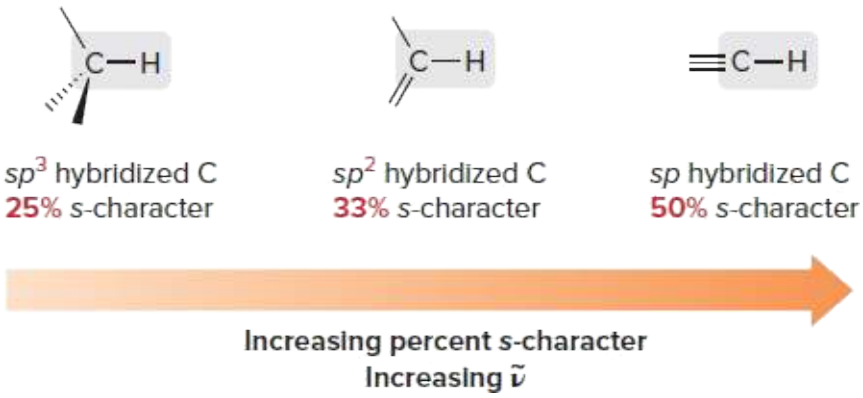
Problem B.4

Which highlighted bond in each pair absorbs at higher wavenumber?



B.3B The Effect of Percent *s*-Character on C—H Absorptions

Any factor that affects bond strength affects the location of an IR absorption. Recall from Section 1.11 that the strength of a C—H bond *increases* as the percent *s*-character of the hybrid orbital on carbon *increases;* thus:

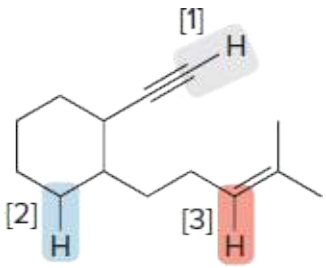


- **The *higher* the percent *s*-character, the *stronger* the bond and the *higher* the wavenumber of the absorption.**

Problem B.5

Rank the indicated bonds in the following compound in order of increasing (a) strength;

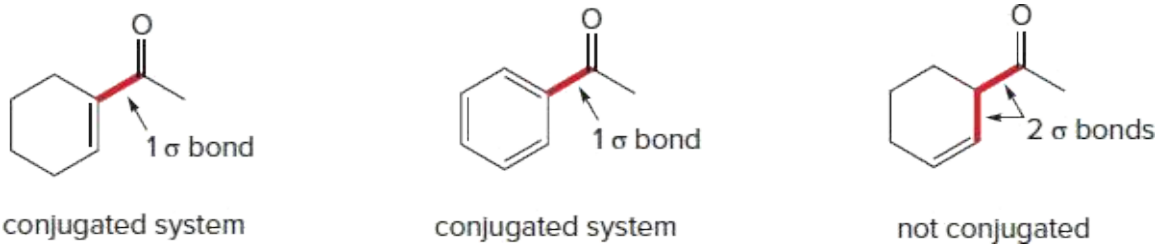
(b) bond length; (c) percent *s*-character; (d) wavenumber of absorption.



B.3C The Effect of Resonance on IR Absorptions

When a compound contains a carbonyl group (C=O), often the carbonyl absorption is the most intense peak in the IR spectrum. The exact location of that absorption depends on what groups are bonded directly to the carbonyl carbon.

When a carbonyl group is bonded to a carbon–carbon double bond or a benzene ring, the two sites of unsaturation are separated by one σ bond and the system is said to be *conjugated*. As we will learn in Chapter 14, conjugation results in many unusual properties of a compound, one of which is reflected in the location of its carbonyl absorption.



- **Conjugation of the carbonyl group with a C=C or a benzene ring shifts the absorption to lower wavenumber by ~30 cm^{-1}.**

The effect of conjugation on the frequency of the C=O absorption is explained by resonance. An α,β-unsaturated carbonyl compound can be written as three resonance structures, two of which place a single bond between the carbon and oxygen atoms of the carbonyl group. Thus, the π bond of the carbonyl group is delocalized, giving the conjugated carbonyl group some single bond character, and making it somewhat weaker than an unconjugated C=O. Weaker bonds absorb at lower frequency (lower wavenumber) in an IR spectrum.

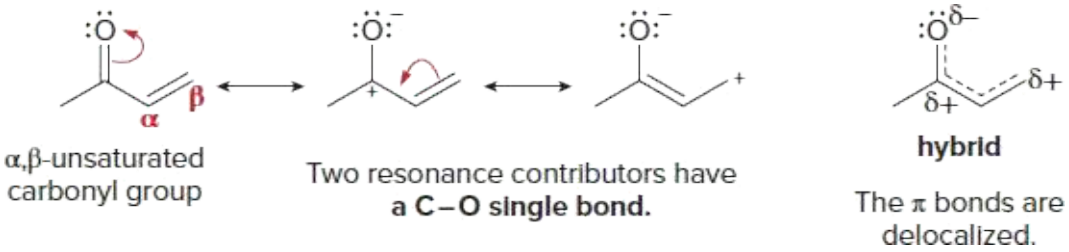


Figure B.5 illustrates the effects of conjugation on the location of the carbonyl absorption in some representative compounds.

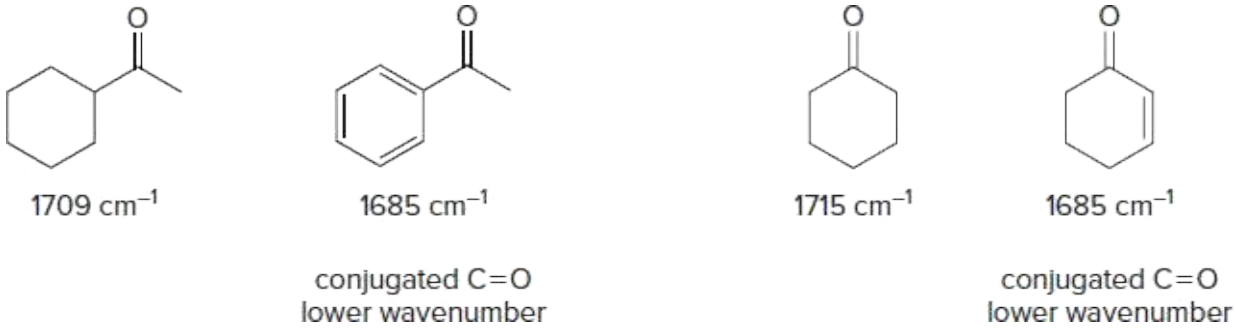
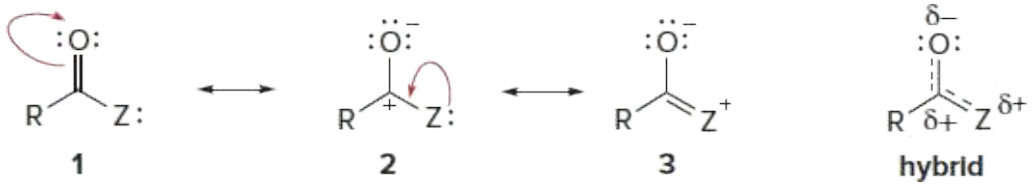


Figure B.5 **The effect of conjugation on the carbonyl absorption in an IR spectrum**

Resonance also affects the relative position of the carbonyl absorptions of compounds RCOZ, when Z contains a nonbonded electron pair. Three resonance structures can be drawn for RCOZ.



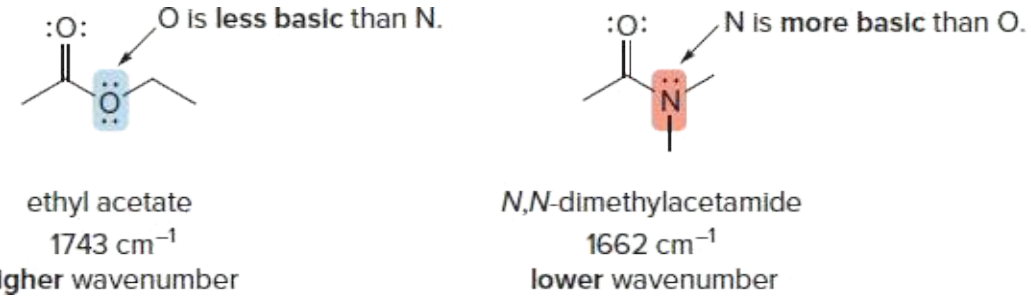
Because resonance structures 2 and 3 contain a carbon–oxygen single bond, the more these structures contribute to the resonance hybrid, the more single bond character the carbonyl group possesses, and the *lower* the frequency of the carbonyl absorption.

- **The more basic Z is, the more it donates its electron pair and the more resonance structure 3 contributes to the hybrid.**
- **As a result, as the basicity of Z *increases*, the frequency of the carbonyl absorption *decreases*.**

To compare the carbonyl absorptions of an ester (RCO_2R') and an amide ($RCONR'_2$), we look at the relative basicity of an $-OR'$ group and an $-NR'_2$ group. Basicity decreases across a row of the periodic table, so an $-NR'_2$ group is more basic than an

–OR′ group. Thus, an amide carbonyl has more single bond character than an ester carbonyl, and the carbonyl absorption occurs at *lower* wavenumber.

For example, the carbonyl absorptions of the ester ethyl acetate and the amide *N,N*-dimethyl-acetamide occur at 1743 and 1662 cm^{-1}, respectively.



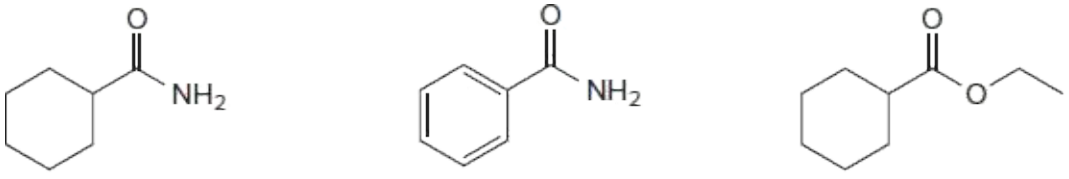
ethyl acetate
1743 cm^{-1}
higher wavenumber

N,N-dimethylacetamide
1662 cm^{-1}
lower wavenumber

Sample Problem B.1 illustrates how resonance affects the position of the carbonyl absorption in three compounds. Page 543

Sample Problem B.1 Predicting the Relative Position of Carbonyl Absorptions

Rank compounds A, B, and C in order of increasing frequency of the carbonyl absorption in their IR spectra.



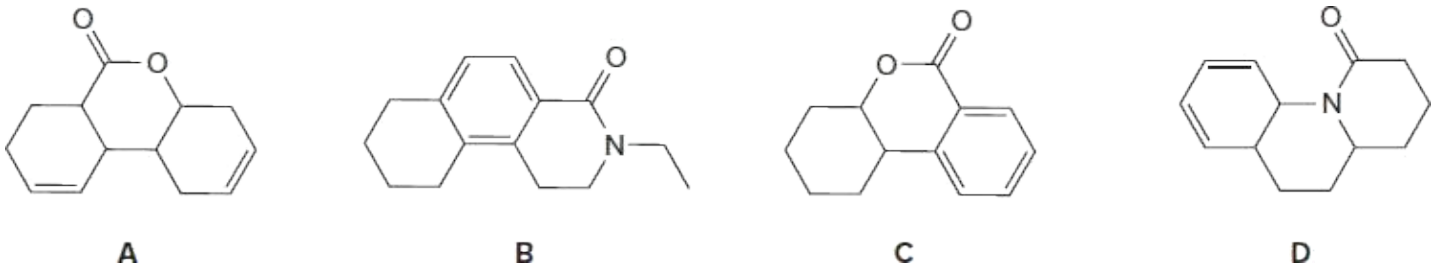
A B C

Solution

Compare pairs of compounds. A and B are both amides, but B contains a carbonyl that is conjugated with a benzene ring. Because conjugation shifts the carbonyl absorption to lower wavenumber, B absorbs at lower wavenumber than A. C is an ester that is not conjugated. In comparing carbonyl absorptions in A and C, the amide A contains a more basic N atom, so the carbonyl absorption of A occurs at lower wavenumber than that of ester C. Thus, in order of increasing frequency (wavenumber): B < A < C.

Problem B.6

(a) Considering compounds A, B, C, and D, which compound has a C=O that absorbs at the *highest* wavenumber? (b) Which compound has a C=O that absorbs at the *lowest* wavenumber?



More Practice:

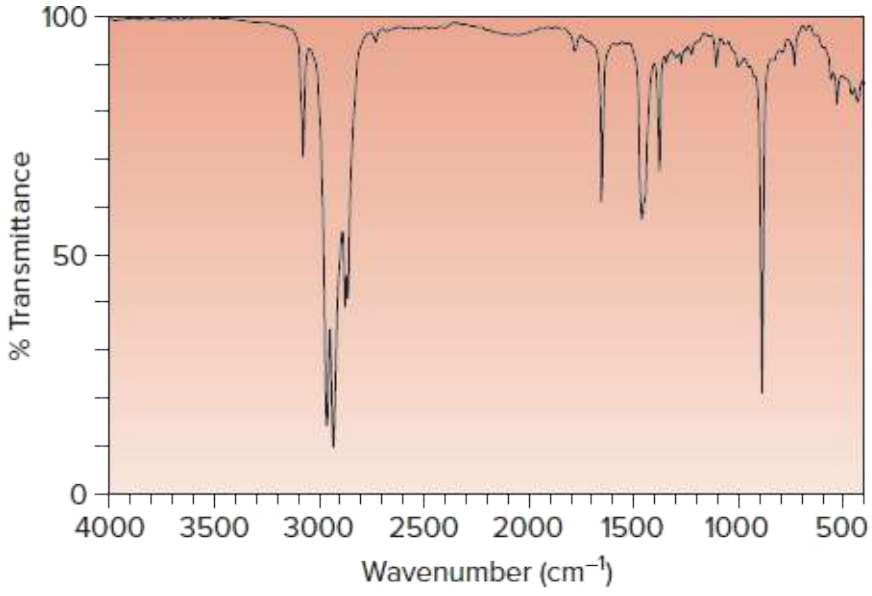
Try Problems B.23, B.24.

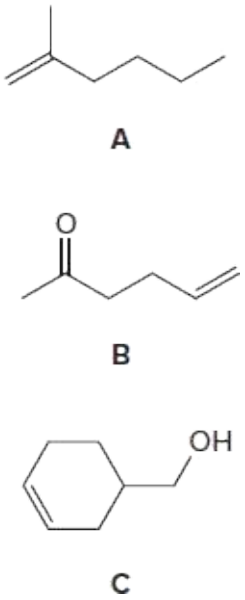
B.3D Analyzing an IR Spectrum

The principles learned in this section can be used to determine what types of bonds are present in a compound, as shown in the stepwise *How To*.

How To Analyze an IR Spectrum

Example **Which compound—A, B, or C—gives rise to the given IR spectrum?**

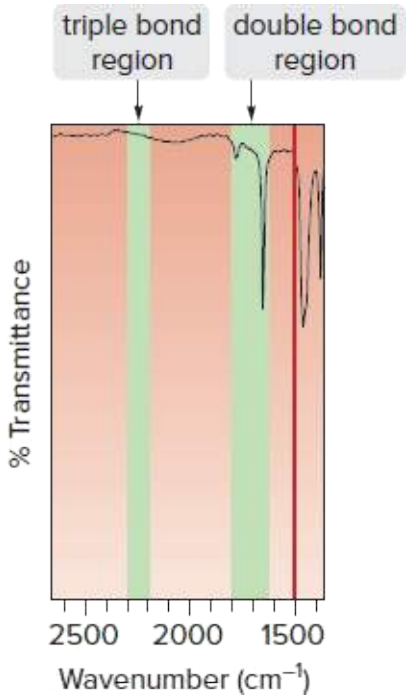




Step [1] **Concentrate on the functional group region above 1500 cm^{-1}, and examine the two sections where double and triple bonds absorb, using the values in Table B.1.**

Page 544

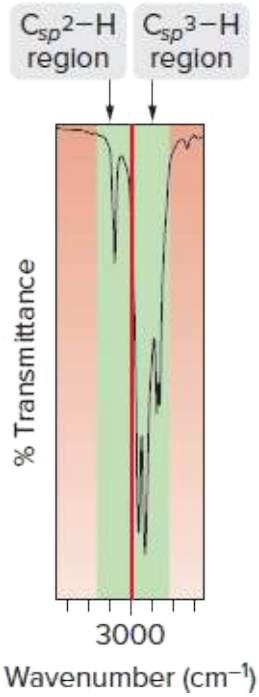
- **A C=C absorbs at ~1650 cm^{-1}.**
- **A C=O absorbs between 1650 and 1800 cm^{-1}, often around 1700 cm^{-1}.**
- **A C≡C or C≡N absorbs at ~2250 cm^{-1}.**



- **In this example, there are no absorptions in the triple bond region and an absorption of medium intensity at 1650 cm^{-1}, suggesting that the compound contains a C=C.**
- **Because there is no strong absorption at ~1700 cm^{-1}, the compound does *not* contain a C=O.**
- **Using these data, we can eliminate B as a possibility because B contains a C=O.**

Step [2] **Examine the C—H region around 3000 cm^{-1}.**

- C_{sp^3}**–H bonds absorb at 3000−2850 cm^{-1}.**
- C_{sp^2}**–H bonds absorb at 3150−3000 cm^{-1}.**
- **C_{sp}—H bonds absorb at 3300 cm^{-1}.**



- **I n addition to C_{sp^3}–H bonds, which are present in almost all organic compounds, the compound contains an absorption in the C_{sp^2}–H region.**
- **Both A and C contain C_{sp^2}–H, so both compounds are still possibilities.**

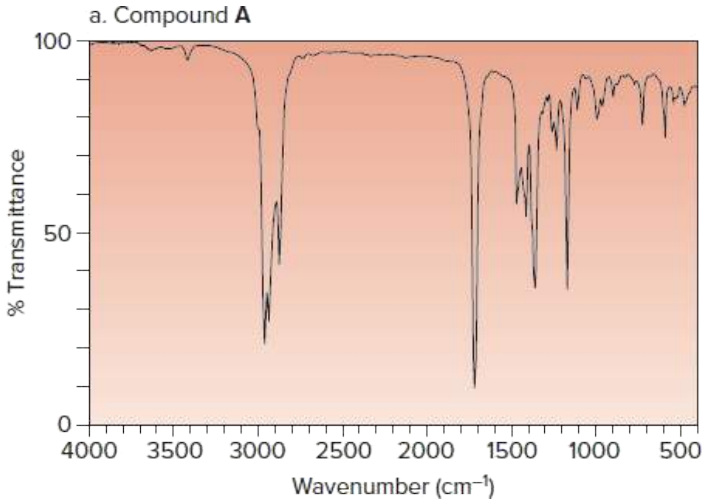
Step [3] **Examine the region above 3000 cm^{-1} for O—H and N—H bonds.**

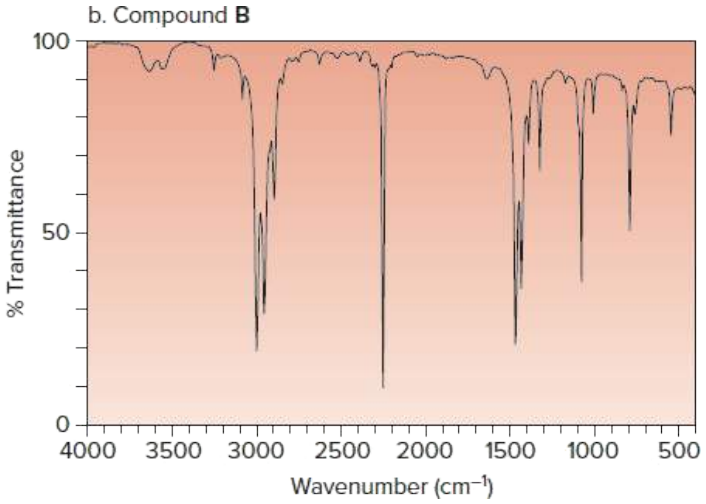
- **O—H bonds appear as strong, broad peaks at at 3600−3200 cm^{-1}.**
- **N—H bonds of amines and amides absorb in the 3500−3200 cm^{-1} region, and are of medium intensity.**

Because the IR shows no absorption at 3600−3200 cm^{-1}, the compound does not contain an OH group. This eliminates C as a possibility, so the IR spectrum is due to A.

Sample Problem B.2 Using IR Spectroscopy to Determine the Types of Bonds in a Compound

What types of bonds are responsible for the absorptions above 1500 cm^{-1} in compounds A and B?





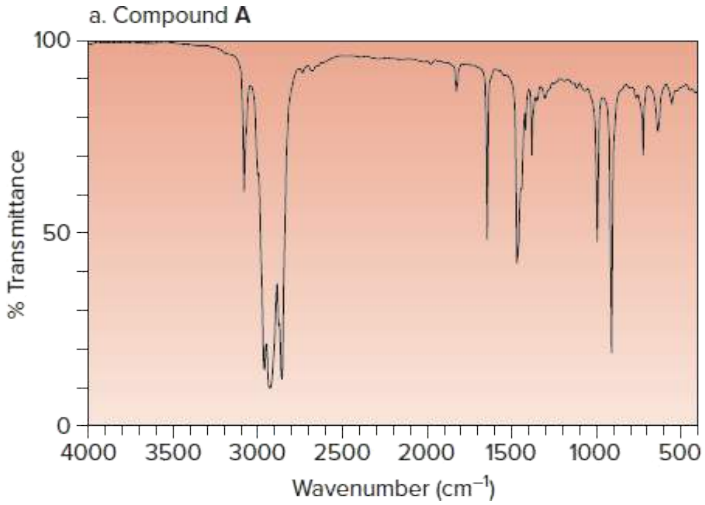
Solution

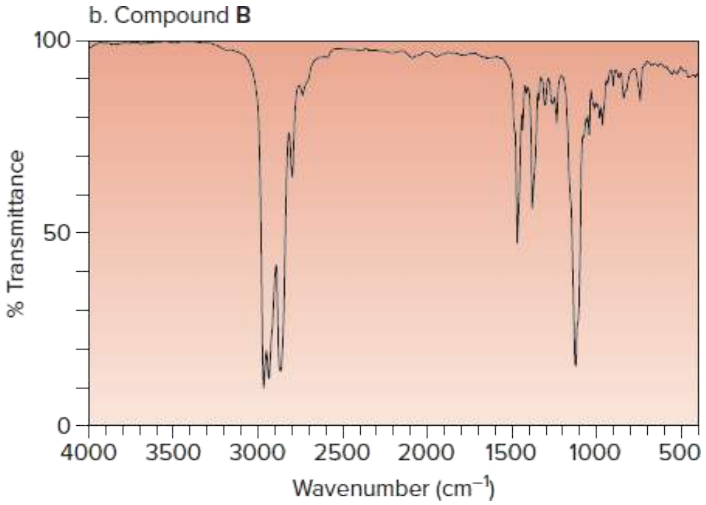
a. Compound A has two major absorptions above 1500 cm^{-1}: The absorption at ~3000 cm^{-1} is due to C—H bonds and the absorption at ~1700 cm^{-1} is due to a C=O group. Because the C—H absorption occurs at < 3000 cm^{-1}, all C—H bonds contain sp^3 hybridized C atoms.

b. Compound B has two major absorptions above 1500 cm^{-1}: The absorption at ~3000 cm^{-1} is due to C_{sp^3}–H bonds and the absorption at ~2250 cm^{-1} is due to a triple bond, either a C≡C or a C≡N.

Problem B.7

What types of bonds are responsible for the absorptions above 1500 cm^{-1} in the IR spectra for compounds A and B?





More Practice:

Try Problems B.17, B.19, B.27.

B.4 Infrared Spectra of Common Functional Groups

Each class of compounds exhibits characteristic absorptions in the infrared.

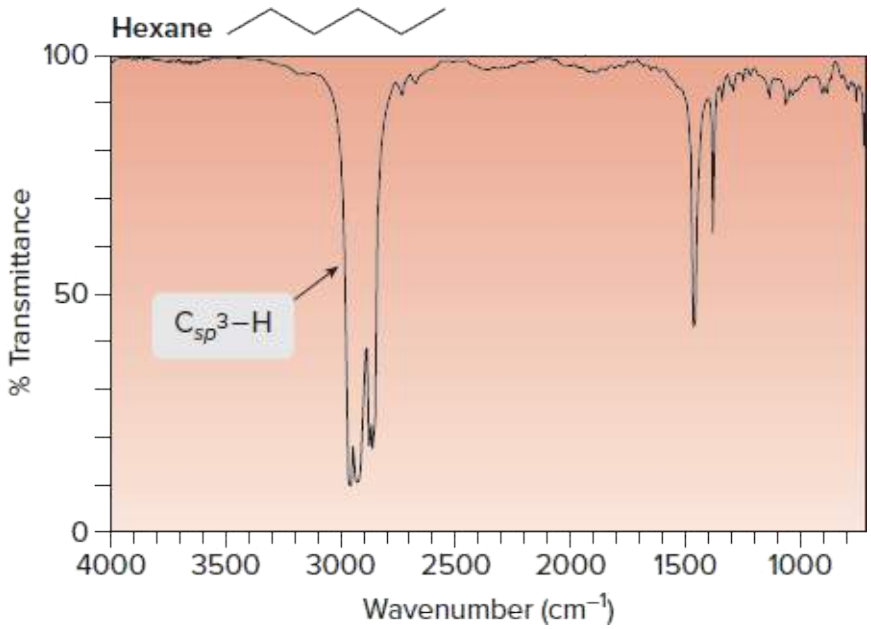
B.4A IR Absorptions in Hydrocarbons

The IR spectra of an alkane, an alkene, an alkyne, and an aromatic compound with a benzene ring illustrate characteristic differences.

Alkanes

An alkane like hexane has only C—C single bonds and sp^3 hybridized C atoms. Therefore, it has only one major absorption above 1500 cm^{-1}:

- C_{sp^3}–H absorption at 3000–2850 cm^{-1}

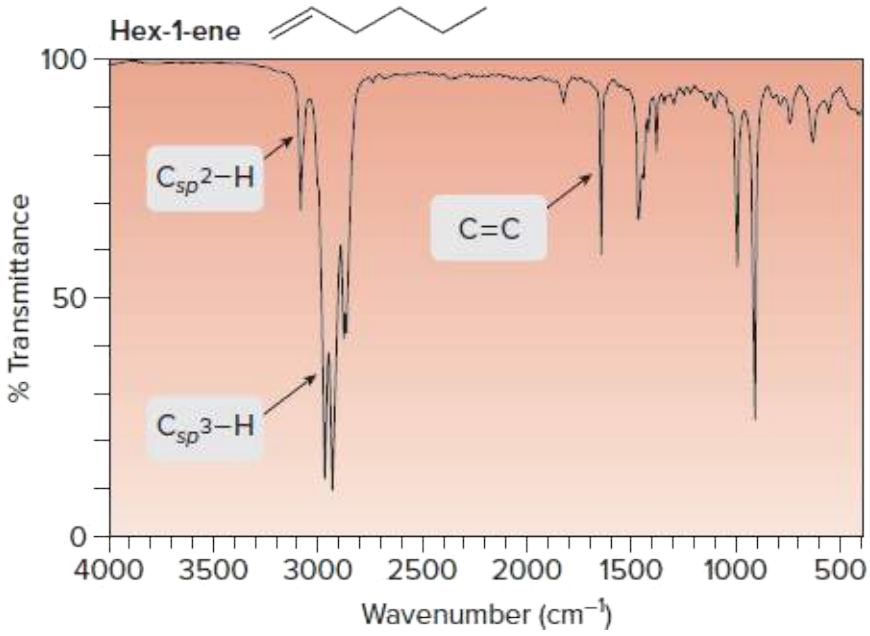


Alkenes

An alkene like hex-1-ene has a C=C and C_{sp^2}–H, in addition to its sp^3 hybridized C atoms.

Therefore, there are three major absorptions above 1500 cm^{-1}:

- C_{sp^2}–H at 3150–3000 cm^{-1}
- C_{sp^3}–H at 3000–2850 cm^{-1}
- C=C at 1650 cm^{-1}

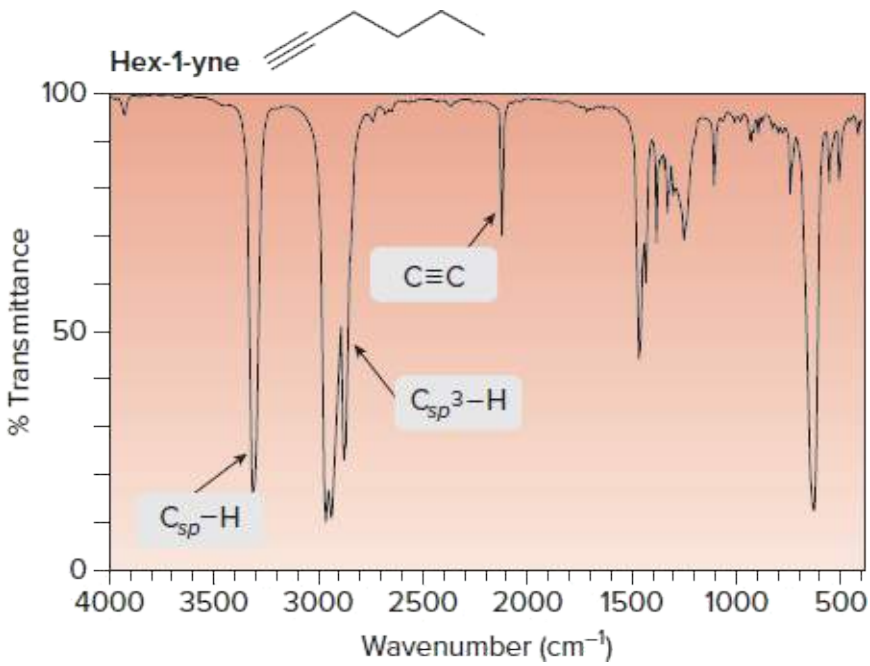


Alkynes

An alkyne like hex-1-yne has a C≡C and C_{sp}—H, in addition to its sp^3 hybridized C atoms.

Therefore, there are three major absorptions:

- C_{sp}—H at 3300 cm^{-1}
- C_{sp^3}–H at 3000–2850 cm^{-1}
- C≡C at ~2250 cm^{-1}



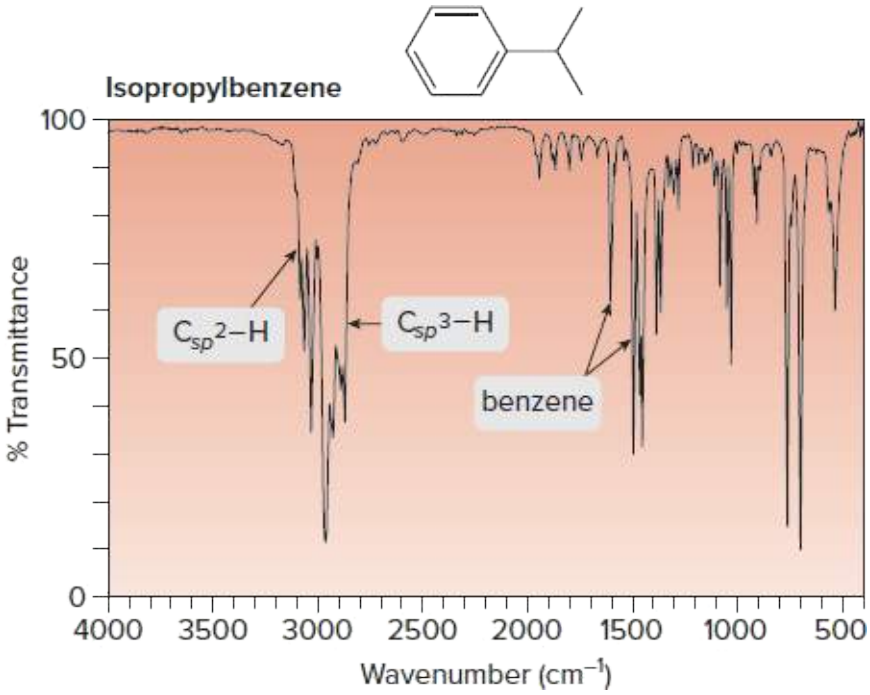
Problem B.8

How do the IR spectra of the isomers cyclopentane and pent-1-ene differ?

Aromatic Compounds with Benzene Rings

An aromatic compound like isopropylbenzene contains a benzene ring and C_{sp^2}–H, in addition to its sp^3 hybridized C atoms. Thus, there are three major absorptions:

- C_{sp^2}–H at 3150–3000 cm^{-1}
- C_{sp^3}–H at 3000–2850 cm^{-1}
- Benzene ring at 1600, 1500 cm^{-1}

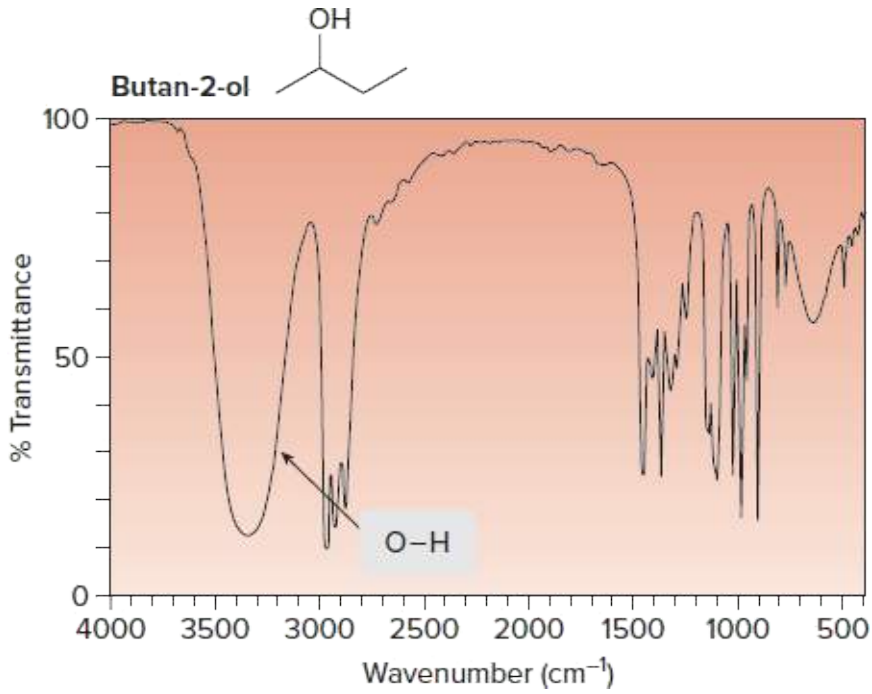


B.4B IR Absorptions in Oxygen-Containing Compounds

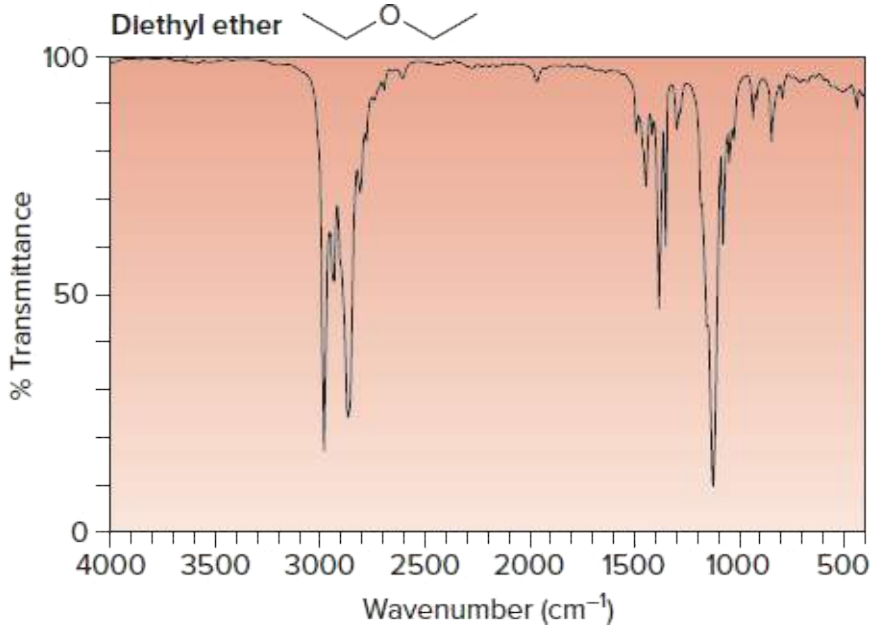
The most important IR absorptions for oxygen-containing compounds occur at 3600–3200 cm^{-1} for an OH group and at approximately 1700 cm^{-1} for a C=O.

Alcohols and Ethers

The most prominent absorption for an alcohol like butan-2-ol is the broad, strong absorption at 3600–3200 cm^{-1} due to the OH group.



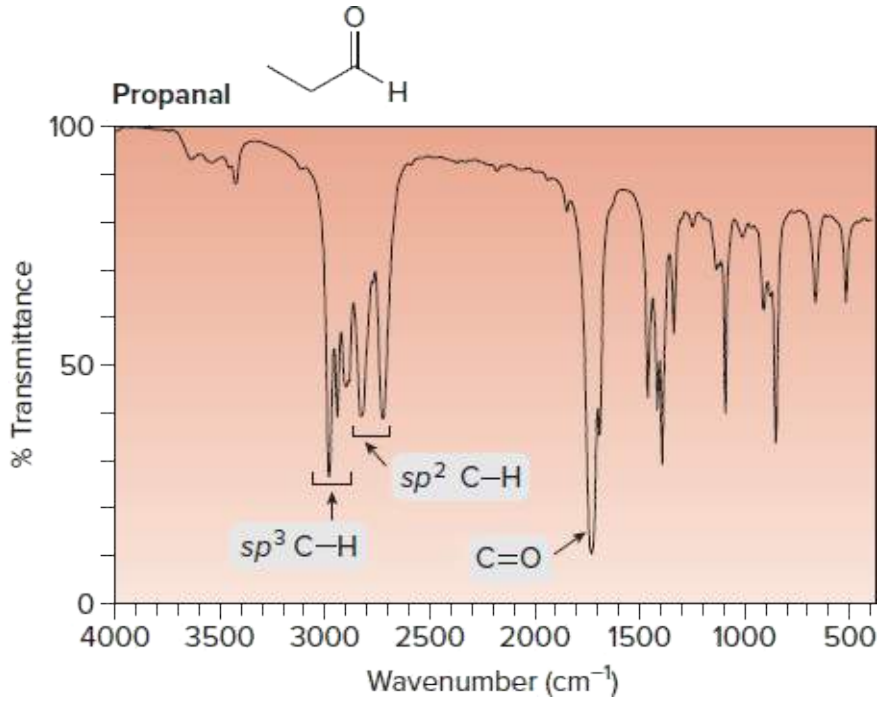
An ether like diethyl ether has neither an OH group nor a C=O, so its only absorption above 1500 cm^{-1} occurs at ~3000 cm^{-1}, due to sp^3 hybridized C—H bonds. Compounds that contain an oxygen atom but do not show an OH or C=O absorption are ethers.



Aldehydes

An aldehyde like propanal has a C=O and C_{sp^2}–H. In addition to the absorption of its C_{sp^3}–H, there are two major absorptions:

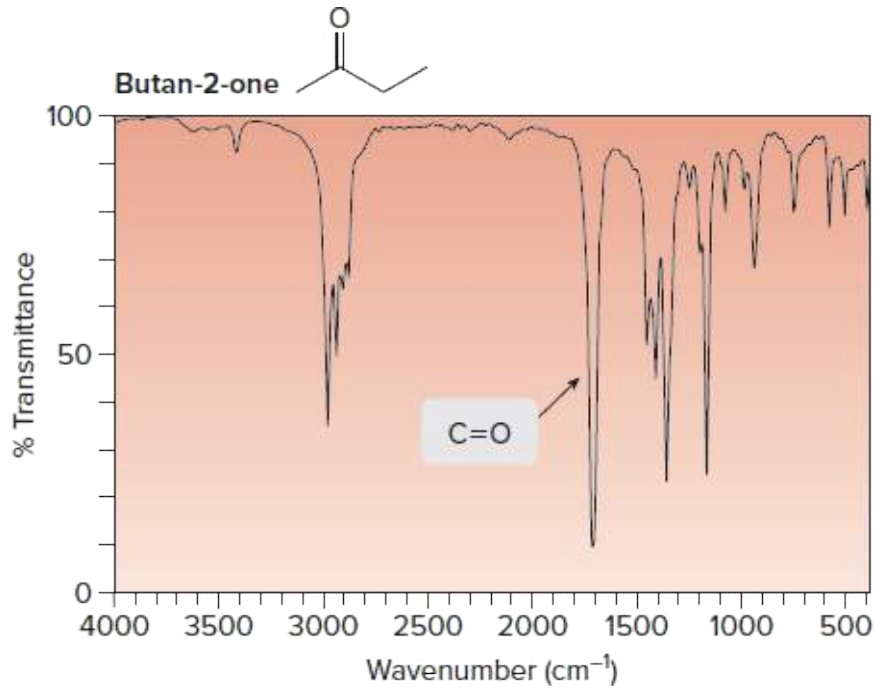
- C_{sp^2}–H of the aldehyde C—H at 2830–2700 cm^{-1} (one or two peaks)
- C=O at ~1700 cm^{-1}



Ketones

In addition to the absorption of its C_{sp^3}–H, a ketone like butan-2-one has one major absorption:

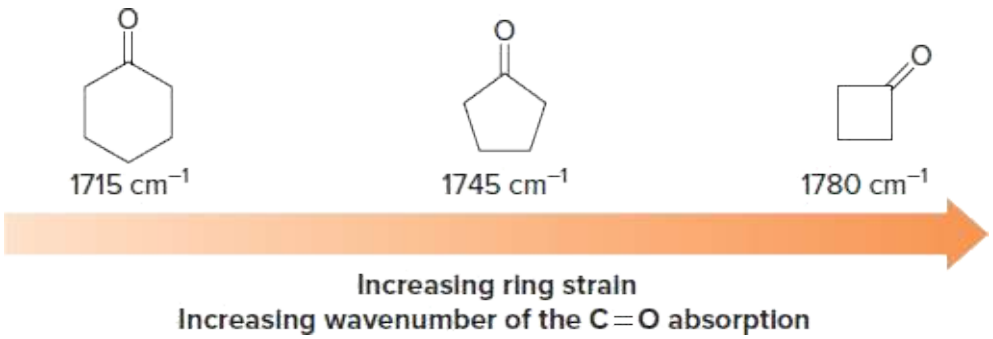
- C=O at ~1700 cm^{-1}



The exact location of the carbonyl absorption provides additional information about a compound. In Section B.3C, we learned that conjugation of the C=O with a C=C or a benzene ring shifts the absorption to lower wavenumber.

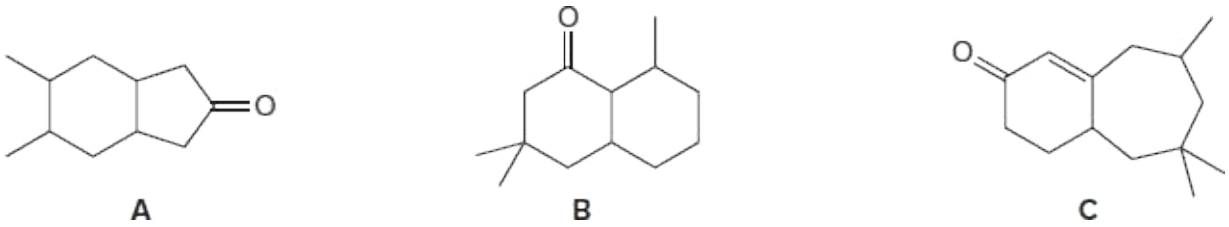
When the carbonyl carbon is located in a ring, ring size also affects the location of the carbonyl absorption.

- **The carbonyl absorption of cyclic ketones shifts to higher wavenumber as the size of the ring decreases and the ring strain increases.**



Problem B.9

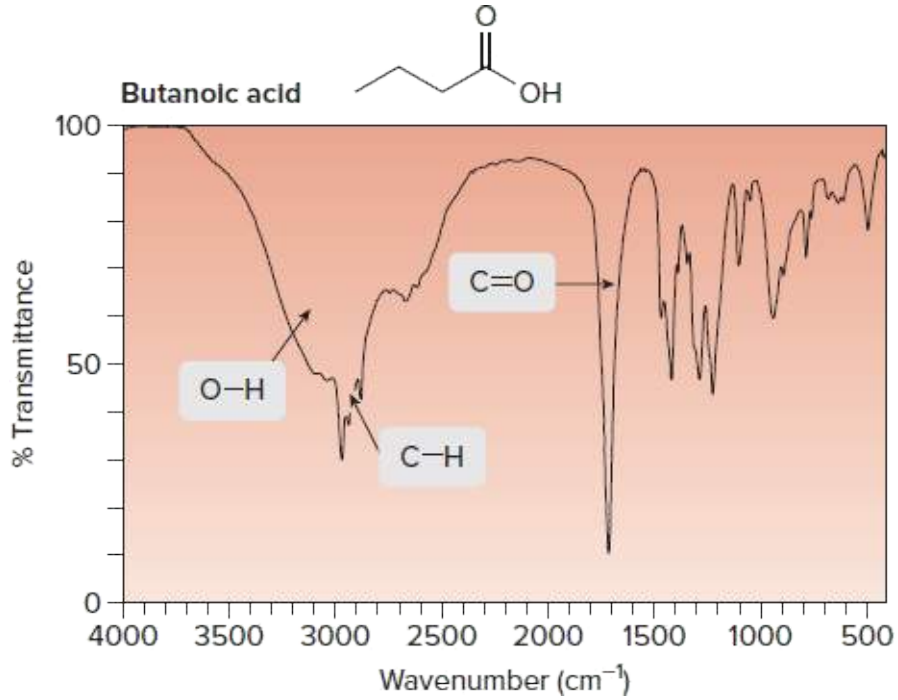
Rank the following compounds in order of increasing frequency of the carbonyl absorption.



Carboxylic Acids

A carboxylic acid like butanoic acid has two characteristic IR absorptions:

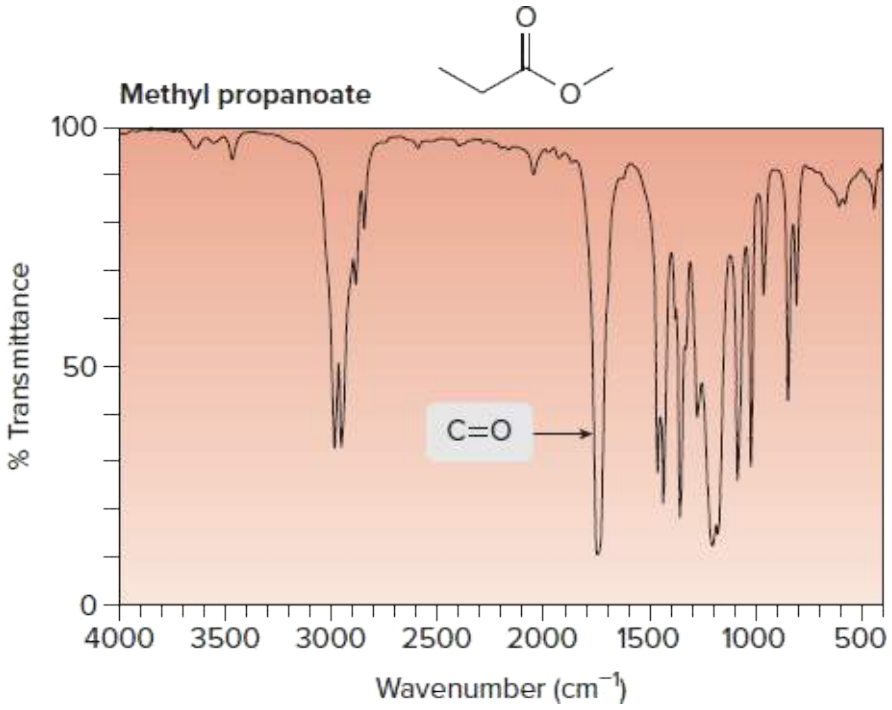
- O—H at 3500–2500 cm^{-1}, a broad, strong absorption that almost obscures the C—H peak at ~3000 cm^{-1}.
- C=O at ~1710 cm^{-1}



Esters and Amides

In addition to the absorption of its C_{sp^3}–H, an ester like methyl propanoate has one major absorption:

- C=O at ~1745–1735 cm^{-1}



An amide like propanamide has three characteristic absorptions:

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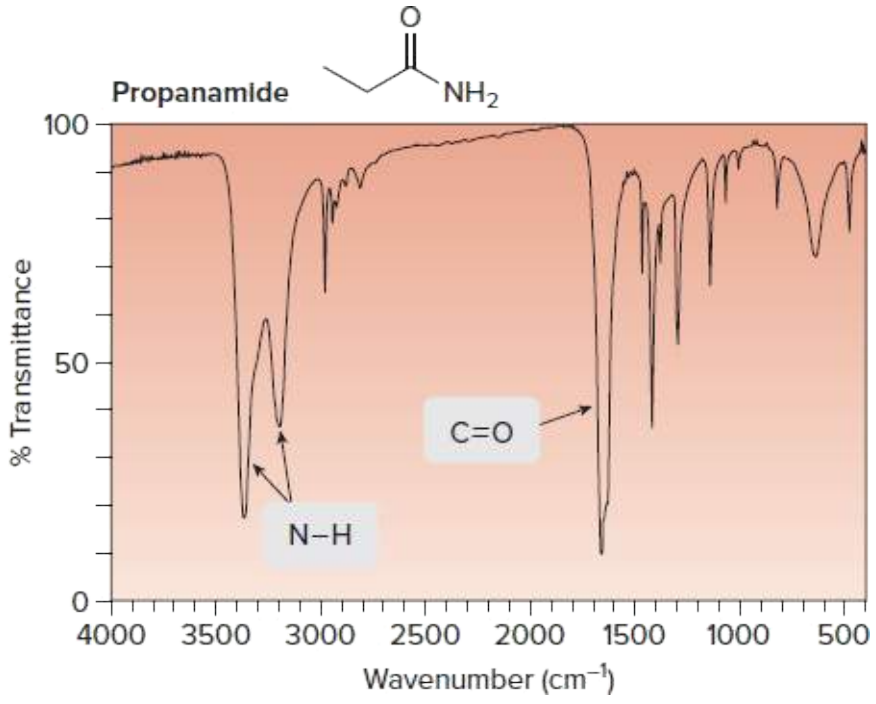
- N—H stretching peaks at 3400–3200 cm^{-1} (one or two peaks)
- C=O at 1680–1630 cm^{-1}
- N—H bending absorption at ~1640 cm^{-1}



Problem B.10

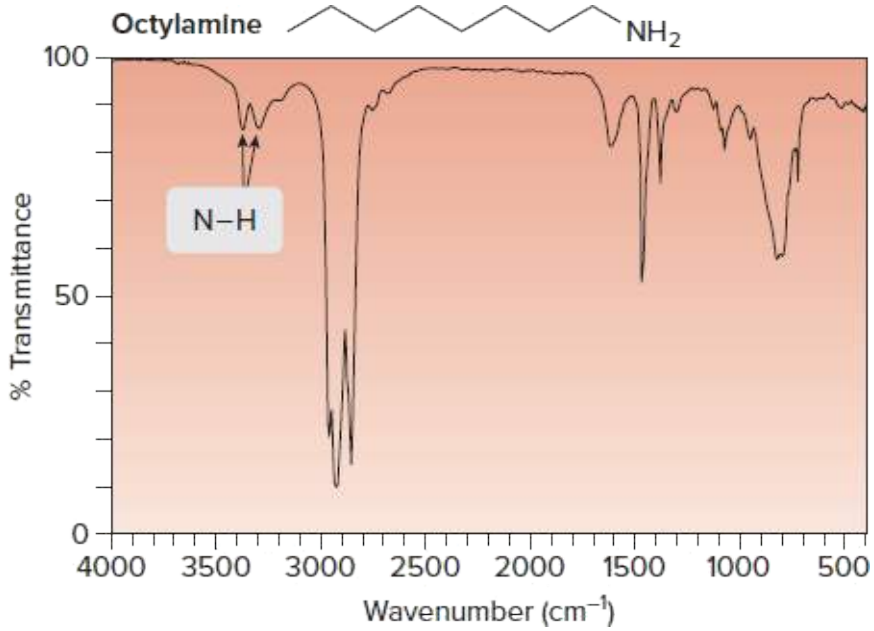
How would compounds X and Y differ in their IR spectra?

X Y

B.4C IR Absorptions in Amines and Nitriles

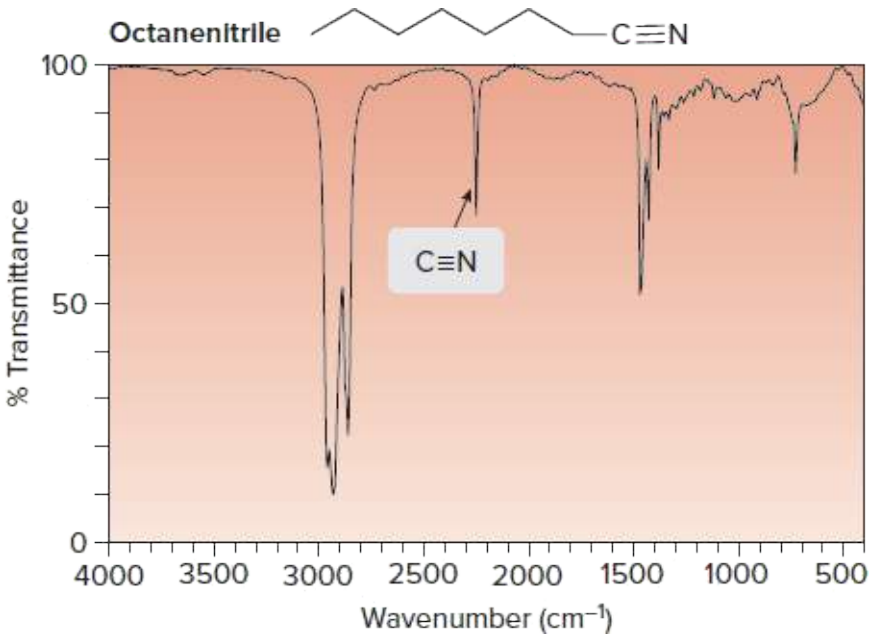
Common functional groups that contain nitrogen atoms are also distinguishable by their IR absorptions above 1500 cm^{-1}.

The N—H bonds in an amine like octylamine give rise to two weak absorptions at 3300 and 3400 cm^{-1}.



The C≡N group of a nitrile like octanenitrile absorbs in the triple bond region at ~2250 cm^{-1}.

Page 552



B.4D Summary of IR Absorptions for Common Functional Groups

Table B.2 summarizes the typical IR peaks for common functional groups.

Table B.2 Characteristic IR Absorptions in the Functional Group Region

Compound type	Absorption (cm^{-1})	Intensity
Alkane		
C_{sp^3}–H	3000–2850	strong
Alkene		
C_{sp^2}–H	3150–3000	medium
C=C	1650	medium
Alkyne		
C_{sp}—H	3300	medium
C≡C	2250	medium
Benzene	1600, 1500	medium
Alcohol		
O—H	3600–3200	strong, broad
Amine		
N—H	3500–3300	medium
Carbonyl compounds		

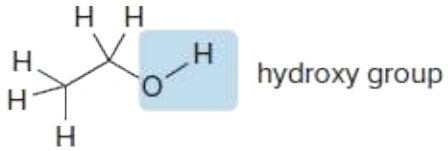
Aldehyde C_{sp^2}—H	2830–2700	medium
Aldehyde C=O	1730	strong
Ketone C=O	1715	strong
Ester C=O	1745–1735	strong
Amide C=O	1680–1630	strong
Amide N—H	3400–3200	medium
Carboxylic acid		
O—H	3500–2500	strong, very broad
C=O	1710	strong
Nitrile		
C≡N	2250	medium

Sample Problem B.3 Using IR Spectroscopy to Distinguish Isomers

How can the two isomers having molecular formula C_2H_6O be distinguished by IR spectroscopy?

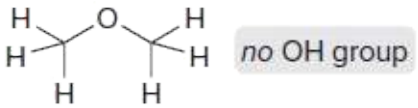
Solution

First, draw the structures of the compounds and then locate the functional groups. One compound is an alcohol and one is an ether.



ethanol

- C–H absorption at ~3000 cm^{-1}
- O–H absorption at 3600–3200 cm^{-1}



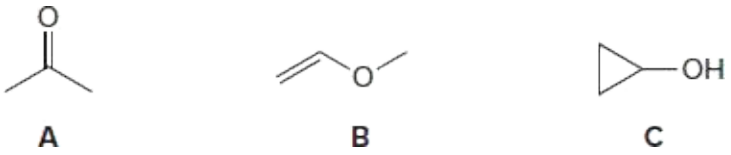
dimethyl ether

- C–H absorption at ~3000 cm^{-1} **only**

Although both compounds have sp^3 hybridized C—H bonds, ethanol has an OH group that gives a strong absorption at 3600–3200 cm^{-1}, and dimethyl ether does not. This feature distinguishes the two isomers.

Problem B.11

How do the three isomers of molecular formula C_3H_6O (A, B, and C) differ in their IR spectra?



A B C

More Practice:

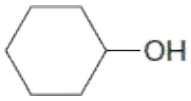
Try Problems B.21, B.22, B.25, B.26.

Problem B.12

What are the major IR absorptions in the functional group region for each compound?

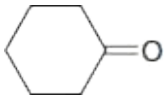
a.

b.

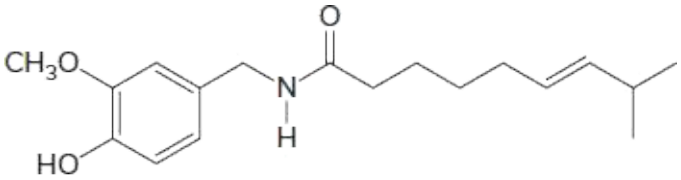


c.

d.



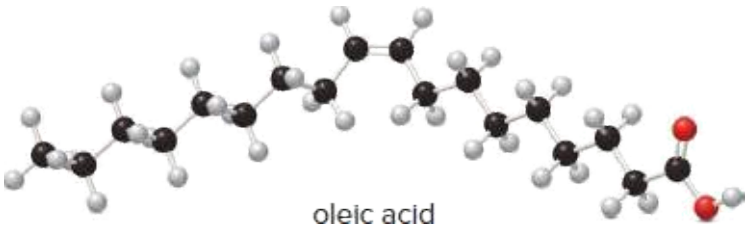
e.



capsaicin
(spicy component of hot peppers)

Problem B.13

What are the major IR absorptions in the functional group region for oleic acid, a common unsaturated fatty acid (Section 10.6A)?



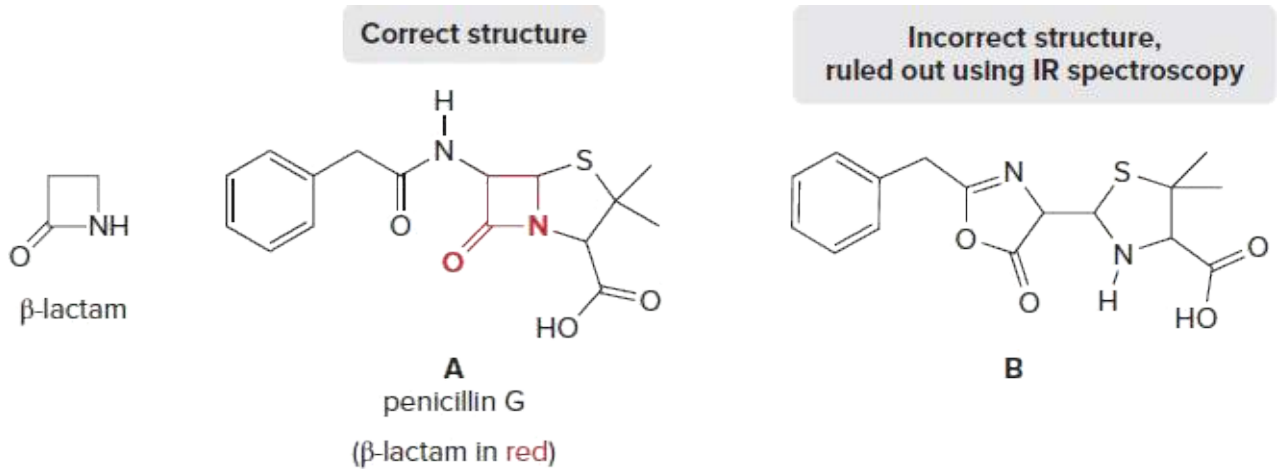
oleic acid

B.5 IR and Structure Determination

Since its introduction, IR spectroscopy has proven to be a valuable tool for determining the functional groups in organic molecules.

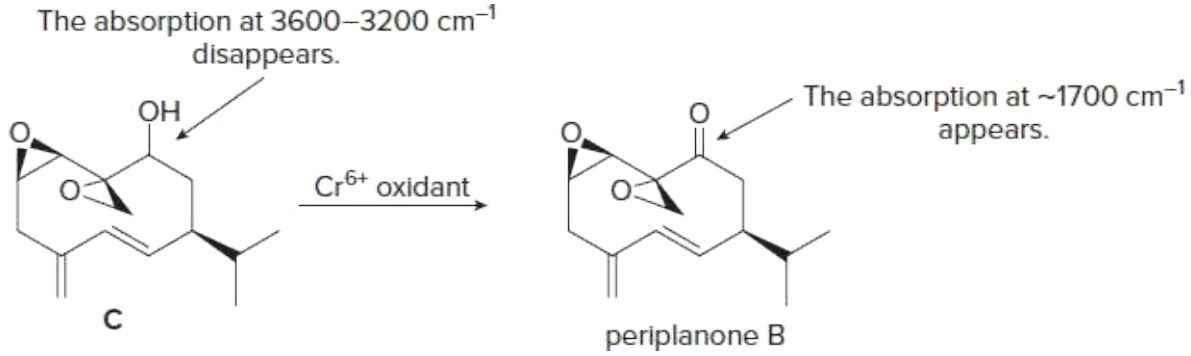
In the 1940s, IR spectroscopy played a key role in elucidating the structure of the antibiotic penicillin G, the chapter-opening molecule. β-Lactams, four-membered

rings that contain an amide, have a carbonyl group that absorbs at ~1760 cm^{-1}, a much higher frequency than that observed for most amides and many other carbonyl groups. Because penicillin G had an IR absorption at this frequency, A became the leading candidate for the structure of penicillin rather than B, a possibility originally considered more likely. Structure A was later confirmed by X-ray analysis.



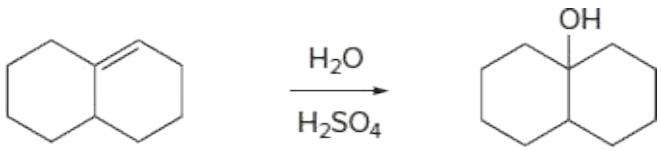
New instruments for determining blood alcohol concentration use IR spectroscopy for analyzing the C—H absorption of CH_3CH_2OH in exhaled air. Figure 12.9 illustrated an earlier method based on oxidation chemistry.

IR spectroscopy is often used to determine the outcome of a chemical reaction. For example, oxidation of the hydroxy group in C to form the carbonyl group in periplanone B is accompanied by the disappearance of the OH absorption (3600–3200 cm^{-1}) and the appearance of a carbonyl absorption near 1700 cm^{-1} in the IR spectrum of the product. Periplanone B is the sex pheromone of the female American cockroach.



Problem B.14

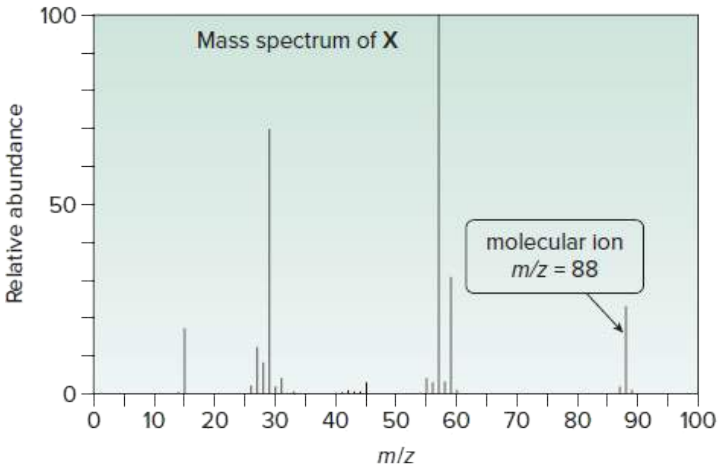
How can IR spectroscopy be used to determine when the following reaction is complete?

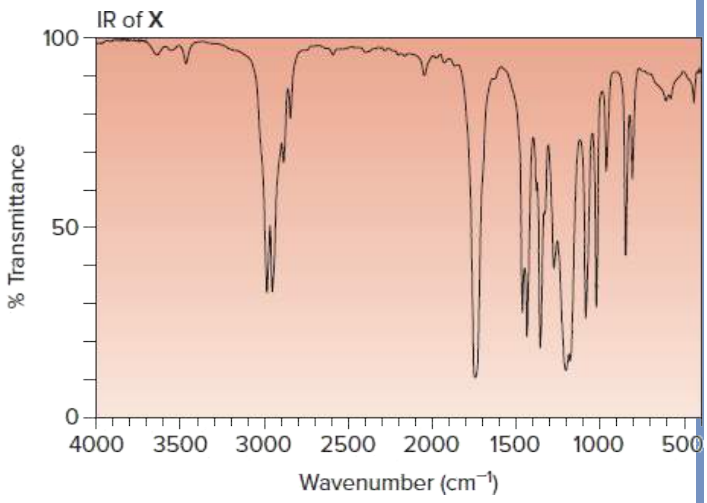


The combination of IR and mass spectral data provides key information on the structure of an unknown compound. The mass spectrum reveals the molecular weight of the unknown (and the molecular formula if an exact mass is available), and the IR spectrum helps to identify the important functional groups.

How To Use MS and IR for Structure Determination

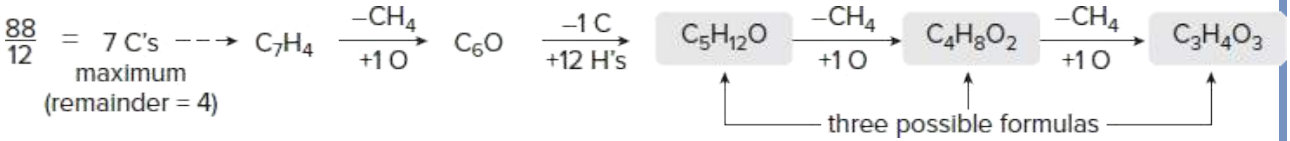
Example **What information is obtained from the mass spectrum and IR spectrum of an unknown compound X? Assume X contains the elements C, H, and O.**





Step [1] **Use the molecular ion to determine possible molecular formulas. Use an exact mass (when available) to determine a molecular formula.**

- **Use the procedure outlined in Sample Problem A.2 to calculate possible molecular formulas. For a molecular ion at *m/z* = 88:**



- **Discounting C_7H_4 (a hydrocarbon) and C_6O (because it contains no H's) gives three possible formulas for X.**
- **If high-resolution mass spectral data are available, the molecular formula can be determined directly. If the molecular ion had an exact mass of 88.0580, the molecular formula of X is $C_4H_8O_2$ (exact mass = 88.0524) rather than $C_5H_{12}O$ (exact mass**

= 88.0888) or $C_3H_4O_3$ (exact mass = 88.0160).

Step [2] Calculate the number of degrees of unsaturation (Section 10.2).

- **For a compound of molecular formula $C_4H_8O_2$, the maximum number of H's = $2n + 2 = 2(4) + 2 = 10$.**
- **Because the compound contains only 8 H's, it has 10 − 8 = 2 H's fewer than the maximum number.**
- **Because each degree of unsaturation removes 2 H's, X has one degree of unsaturation. X has one ring or one π bond.**

Step [3] Determine what functional group is present from the IR spectrum.

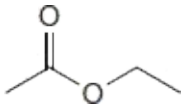
- **The two major absorptions in the IR spectrum above 1500 cm^{-1} are due to sp^3 hybridized C—H bonds (~3000–2850 cm^{-1}) and a C=O group (1740 cm^{-1}). Thus, the one degree of unsaturation in X is due to the presence of the C=O.**

Mass spectrometry and IR spectroscopy give valuable but limited information on the identity of an unknown. Although the mass spectral and IR data reveal that X has a molecular formula of C4H8O2 and contains a carbonyl group, more data are needed to determine its complete structure. In Spectroscopy C, we will learn how other spectroscopic data can be used for that purpose.

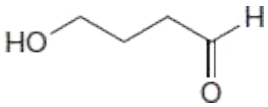
Problem B.15

Which of the following possible structures for X can be excluded on the basis of its IR spectrum?

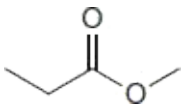
a.



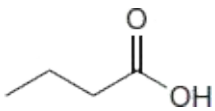
b.



c.



d.



Problem B.16

Propose structures consistent with each set of data: (a) a hydrocarbon with a molecular ion at *m/z* = 68 and IR absorptions at 3310, 3000–2850, and 2120 cm^{-1}; (b) a compound

containing C, H, and O with a molecular ion at *m/z* = 60 and IR absorptions at 3600–3200 and 3000–2850 cm^{-1}.

Spectroscopy B CHAPTER REVIEW

KEY CONCEPTS

[1] Electromagnetic radiation (B.1)

1 Wavelength and frequency

- **The wavelength (*λ*) and frequency (*ν*) of electromagnetic radiation are *inversely* related (*c* = speed of light):**

$$\lambda = c/\nu \quad \text{or} \quad \nu = c/\lambda$$

2 Energy and frequency

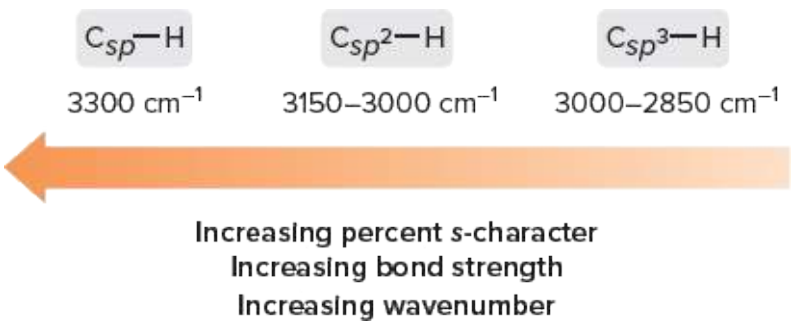
- **The energy (E) of a photon is proportional to its frequency (*ν*); the higher the frequency, the higher the energy [*h* = Planck's constant (6.63×10^{-34} J · s)]:**

$$E = h\nu$$

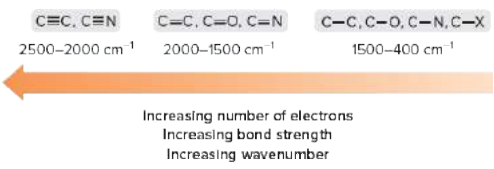
Try Problems B.1–B.3.

[2] Bond strength and IR absorption (B.3)

1 The higher the percent *s*-character, the stronger the bond, and the higher the $\tilde{\nu}$ of absorption.



2 As the number of electrons between two nuclei increases, bond become stronger, and $\tilde{\nu}$ of absorption is high



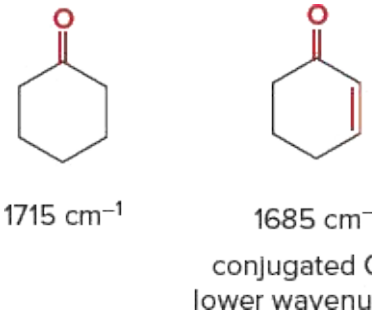
- **Using the wavenumber scale, IR absorptions occur from 4000 to 400**

- IR absorptions are reported in wavenumbers, $\tilde{\nu} = 1/\lambda$. cm^{-1}.

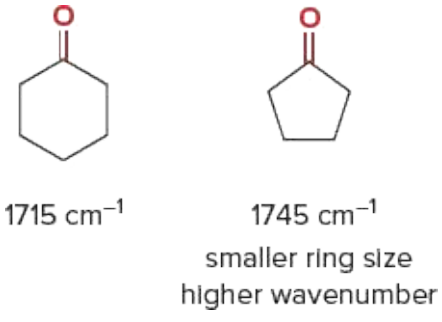
See Table B.1. Try Problem B.18.

[3] Factors affecting the location of a carbonyl absorption (B.3C, B.4B)

1 Conjugation shifts a C=O absorption to lower wavenumber.



2 For cyclic compounds, a smaller ring size shifts a C=O absorption to higher wavenumber.



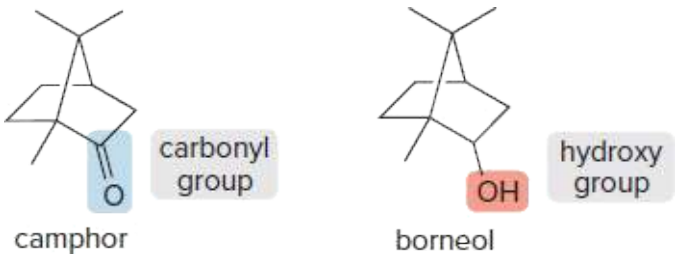
See Sample Problem B.1, Table B.2. Try Problems B.23, B.24.

KEY SKILLS

[1] Using the functional groups to distinguish two compounds by IR spectroscopy (B.4D)

1 Locate the functional groups.

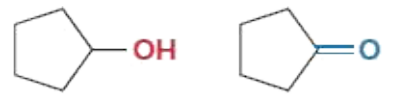
2 Identify the absorptions of the functional groups, and determine the unique absorptions for each compound.



- Both compounds have C_{sp^3}–H bonds at ~2950 cm^{-1}.
- Camphor has a C=O at 1745 cm^{-1}.
- Borneol has an OH group at 3600–3200 cm^{-1}.

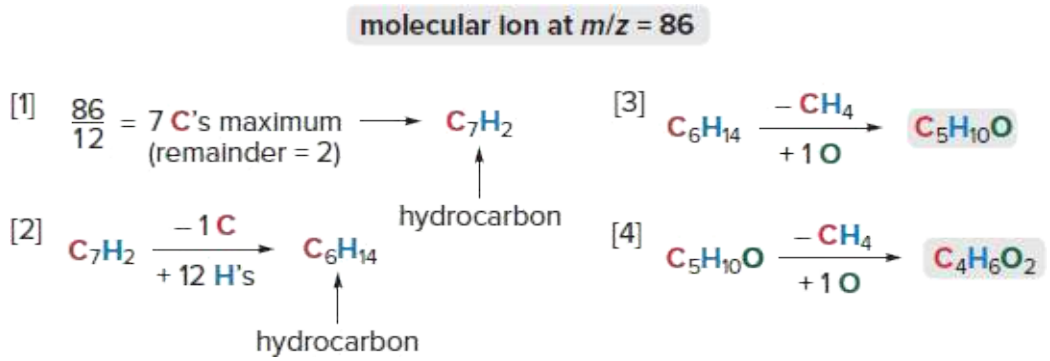
See Sample Problem B.3, Table B.2. Try Problems B.21, B.22, B.25, B.26.

[2] Using IR absorptions to distinguish between two compounds (B.4); example: cyclopentanone and cyclopentanol

1 Evaluate the IR absorptions above 1500 cm^{-1} for both compounds	2 Determine the functional groups.	3 Identify compounds A and B.
• Compound A: 3500–3200, 2961, and 2873 cm^{-1} • Compound B: 2966, 2921, and 1747 cm^{-1}	• O—H bond at 3500–3200 cm^{-1} • C_{sp^3}–H bonds at 2966–2873 cm^{-1} • C=O group at 1747 cm^{-1}	 cyclopentanol compound A cyclopentanone compound B

See Sample Problem B.2. Try Problem B.27.

[3] Using MS and IR to determine possible structures of a compound that contains C, H, and O (B.5); example: *m/z* = 86

1 Use the molecular ion to determine the possible molecular formulas.	3 Use an mass t determ molecu formul
	• High-resolut mass spectr gives t molecu formul compo • If the e

mass is
86.077
molecu
formul
is C_5H_1
(exact
= 86.07
rather
$C_4H_6O_2$
(exact
= 86.03

2 **Calculate the number of degrees of unsaturation (10.2).**

4 **Determ**
the
functio
groups
IR.

$C_5H_{10}O_2$

For n carbons, the maximum number of H's is $2n + 2$; in this example, $2n + 2 = 2(5) + 2 = 12$.

12 H's (maximum) − 10 H's (actual) = 2 H's fewer than the maximum number

$$\frac{\text{2 H's fewer than the maximum}}{\text{2 H's per degree of unsaturation}}$$

Answer: one degree of unsaturation

$C_4H_6O_2$

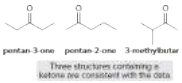
For n carbons, the maximum number of H's is $2n + 2$; in this example, $2n + 2 = 2(4) + 2 = 10$.

10 H's (maximum) − 6 H's (actual) = 4 H's fewer than the maximum number

$$\frac{\text{4 H's fewer than the maximum}}{\text{2 H's per degree of unsaturation}}$$

Answer: two degrees of unsaturation

- C_{sp^3}–H
at 2973
cm^{-1}
- C=O b
(1718 c



See *How To* (B.5), Table B.2. Try Problems B.29–B.38.

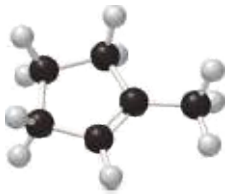
PROBLEMS

Problems that combine mass spectrometry, infrared spectroscopy, and nuclear magnetic resonance spectroscopy are found at the end of Spectroscopy C.

Problem Using Three-Dimensional Models

B.17 **What major IR absorptions are present above 1500 cm^{-1} for each compound?**

a.

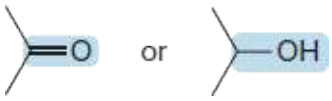


b.

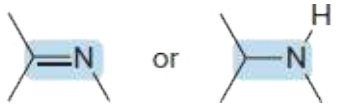
Infrared Spectroscopy

B.18 **Which of the highlighted bonds absorbs at higher $\tilde{\nu}$ in an IR spectrum?**

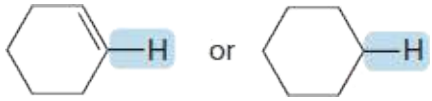
a.



b.

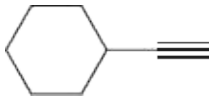


c.

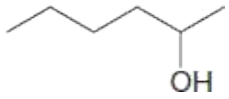


B.19 **What major IR absorptions are present above 1500 cm^{-1} for each compound?**

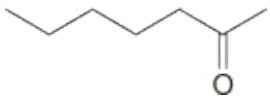
a.



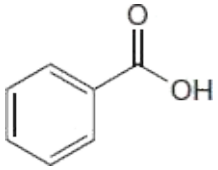
b.



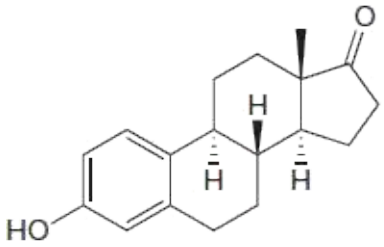
c.



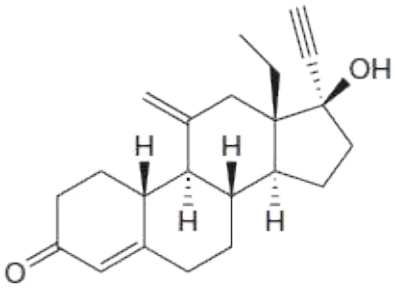
d.



B.20 **Estrone is a female sex hormone, and etonogestrel is a synthetic hormone used in contraceptive implants to prevent pregnancy. (a) Identify the prominent IR absorptions resulting from the functional groups in each compound. (b) How do the locations of the carbonyl absorptions in these two compounds compare? Explain your reasoning.**

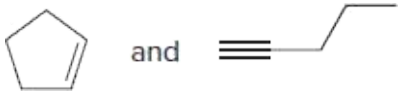


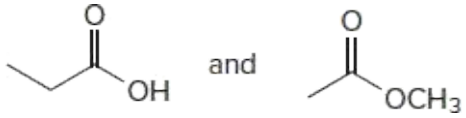
estrone

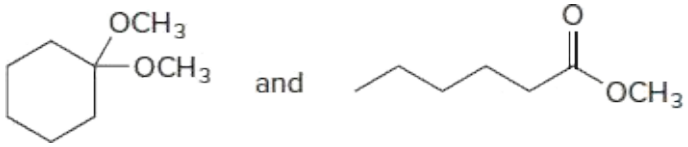


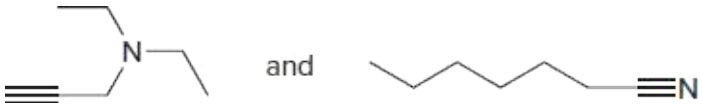
etonogestrel

B.21 How would each of the following pairs of compounds differ in their IR spectra?

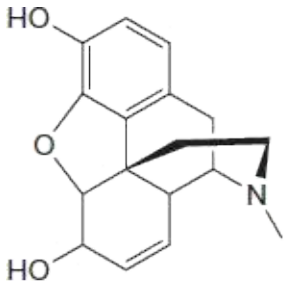
a. 

b. 

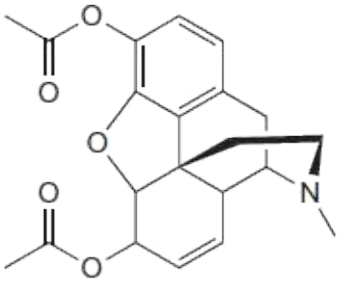
c. 

d. 

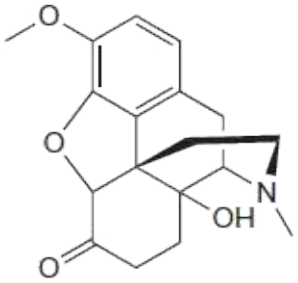
B.22 Morphine, heroin, and oxycodone are three addicting analgesic narcotics. How could IR spectroscopy be used to distinguish these three compounds from each other?



morphine

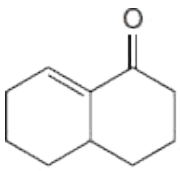


heroin

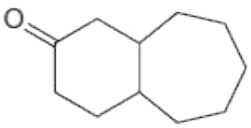


oxycodone

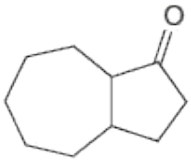
B.23 (a) Which of the following compounds has a C=O that absorbs at the *highest* wavenumber? (b) Which of the following compounds has a C=O that absorbs at the *lowest* wavenumber?



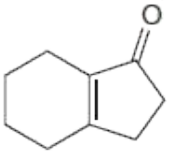
A



B



C



D

B.24 Rank the following compounds in order of increasing wavenumber of the

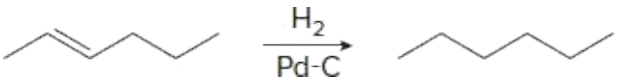
carbonyl absorption in the IR.

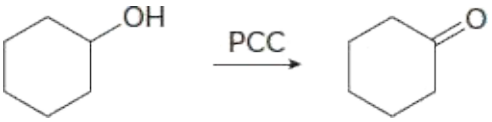
A B C D

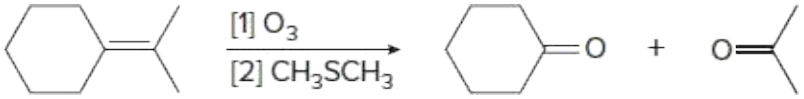
B.25 Reduction of cyclohex-2-enone can yield cyclohexanone, cyclohex-2-enol, or cyclohexanol, depending on the reagent and reaction conditions. How could you use IR spectroscopy to distinguish the three possible products?

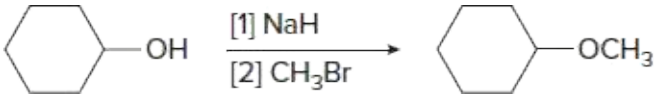
cyclohex-2-enone cyclohexanone cyclohex-2-enol cyclohexanol

B.26 Tell how IR spectroscopy could be used to determine when each reaction is complete.

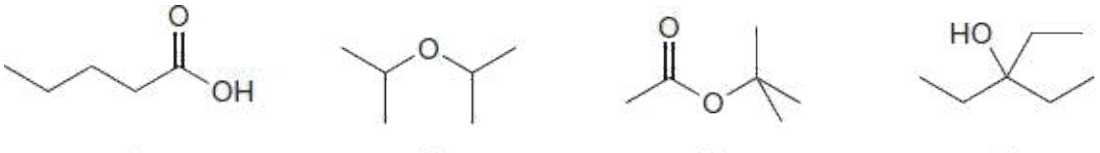
a. 

b. 

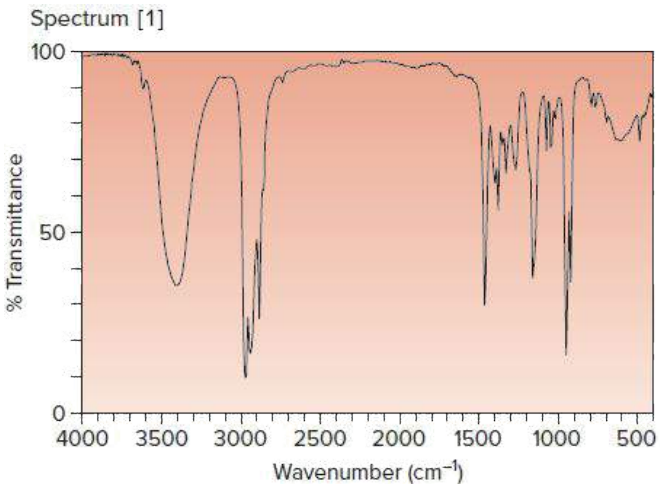
c. 

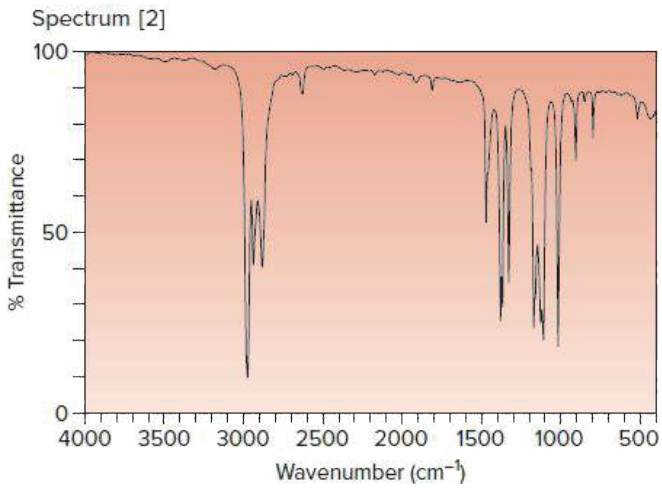
d. 

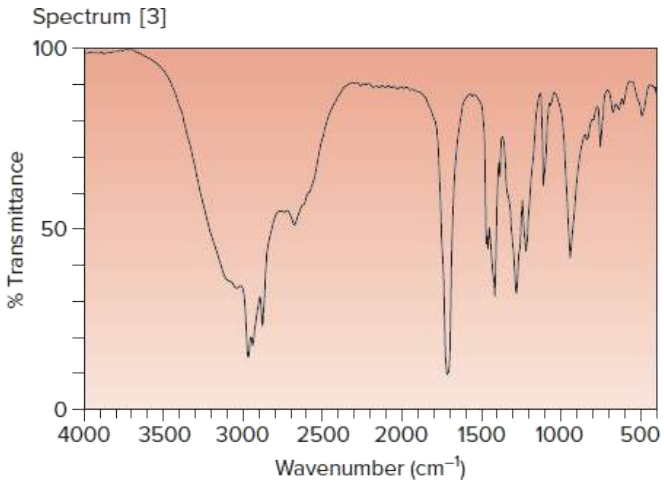
B.27 Match each compound to its IR spectrum.

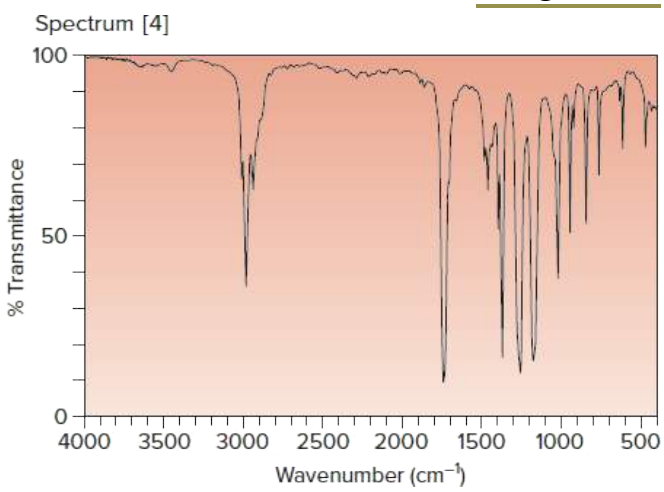


A B C D









Spectroscopy Problems That Combine Mass Spectrometry and Infrared Spectroscopy

B.28 **Propose possible structures consistent with each set of data. Assume each compound has an sp^3 hybridized C—H absorption in its IR spectrum, and that other major IR absorptions above 1500 cm^{-1} are listed.**

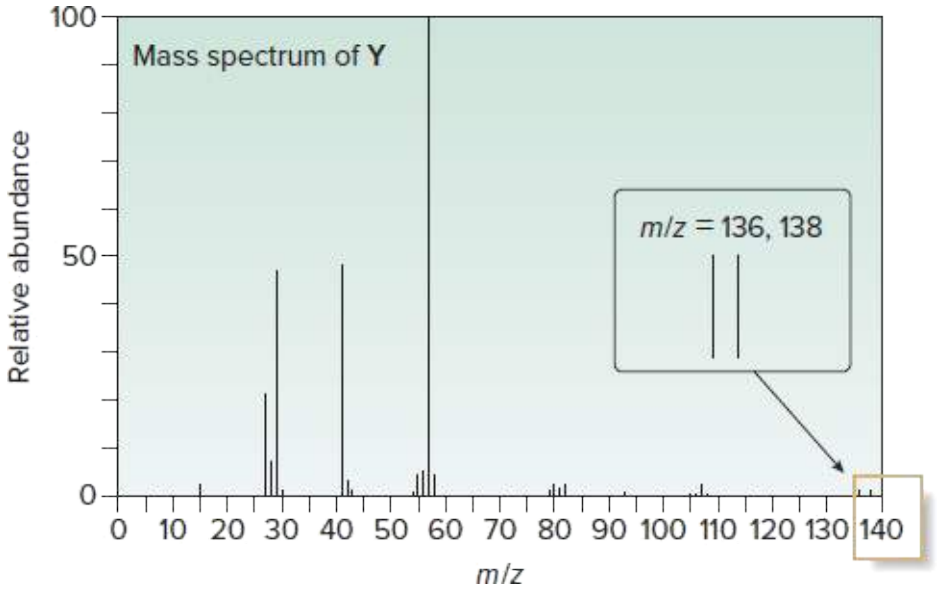
a. a compound having a molecular ion at 72 and an absorption in its IR spectrum at 1725 cm^{-1}

b. a compound having a molecular ion at 55 and an absorption in its IR spectrum at −2250 cm^{-1}

c. a compound having a molecular ion at 74 and an absorption in its IR spectrum at 3600−3200 cm^{-1}

B.29 **A chiral hydrocarbon X exhibits a molecular ion at 82 in its mass spectrum. The IR spectrum of X shows peaks at 3300, 3000−2850, and 2250 cm^{-1}. Propose a structure for X.**

B.30 **A chiral compound Y has a strong absorption at 2970−2840 cm^{-1} in its IR spectrum and gives the following mass spectrum. Propose a structure for Y.**



B.31 Treatment of benzoic acid ($C_6H_5CO_2H$) with NaOH followed by 1-iodo-3-methylbutane forms H. H has a molecular ion at 192 and IR absorptions at 3064, 3035, 2960−2872, and 1721 cm^{-1}. Propose a structure for H.

B.32 Treatment of benzaldehyde (C_6H_5CHO) with Zn(Hg) in aqueous HCl forms a compound Z that has a molecular ion at 92 in its mass spectrum. Z shows absorptions at 3150−2950, 1605, and 1496 cm^{-1} in its IR spectrum. Give a possible structure for Z.

B.33 Reaction of *tert*-butyl pentyl ether [$CH_3CH_2CH_2CH_2CH_2OC(CH_3)_3$] with HBr forms 1-bromopentane ($CH_3CH_2CH_2CH_2CH_2Br$) and compound B. B has a molecular ion in its mass spectrum at 56 and gives peaks in its IR spectrum at 3150−3000, 3000−2850, and 1650 cm^{-1}. Propose a structure for B, and draw a stepwise mechanism that accounts for its formation.

B.34 Reaction of 2-methylpropanoic acid [$(CH_3)_2CHCO_2H$] with $SOCl_2$ followed by 2-methylpropan-1-ol forms X. X has a molecular ion at 144 and IR absorptions at 2965, 2940, and 1739 cm^{-1}. Propose a structure for X.

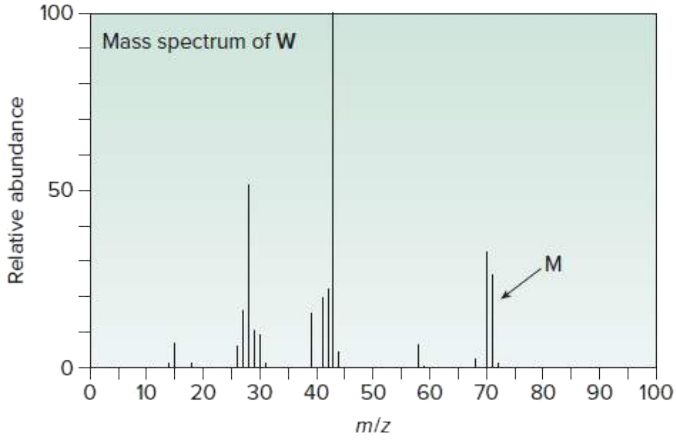
B.35 Reaction of pentanoyl chloride ($CH_3CH_2CH_2CH_2COCl$) with lithium dimethyl cuprate [$LiCu(CH_3)_2$] forms a compound J that has a molecular ion in its mass spectrum at 100, as well as fragments at *m/z* = 85, 57, and 43 (base). The IR spectrum of J has strong peaks at 2962 and 1718 cm^{-1}. Propose a structure for J.

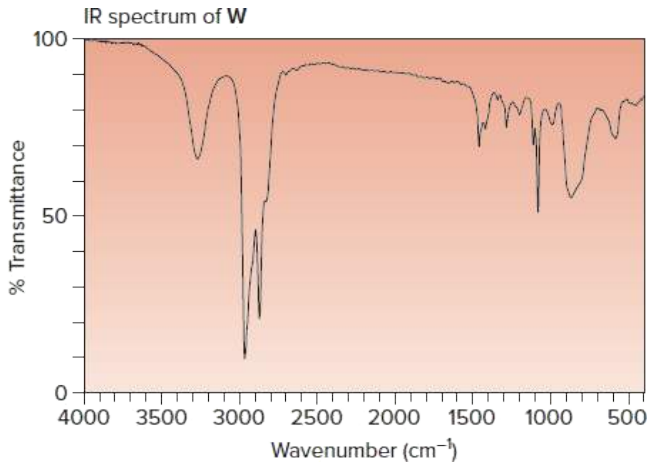
B.36 Benzonitrile (C_6H_5CN) is reduced to two different products depending on the reducing agent used. Treatment with lithium aluminum hydride followed by water forms K, which has a molecular ion in its mass spectrum at 107 and the following IR absorptions: 3373, 3290, 3062, 2920, and 1600 cm^{-1}. Treatment with a milder reducing agent forms L, which has a molecular ion in its mass spectrum at 106 and the following IR

absorptions: 3086, 2820, 2736, 1703, and 1600 cm^{-1}. L shows fragments in its mass spectrum at *m/z* = 105 and 77. Propose structures for K and L, and explain how you arrived at your conclusions.

B.37 Treatment of anisole ($CH_3OC_6H_5$) with Cl_2 and $FeCl_3$ forms P, which has peaks in its mass spectrum at *m/z* = 142 (M), 144 (M + 2), 129, and 127. P has absorptions in its IR spectrum at 3096−2837 (several peaks), 1582, and 1494 cm^{-1}. Propose possible structures for P.

B.38 Reaction of $BrCH_2CH_2CH_2CH_2NH_2$ with NaH forms compound W, which gives the IR and mass spectra shown below. Propose a structure for W and draw a stepwise mechanism that accounts for its formation.

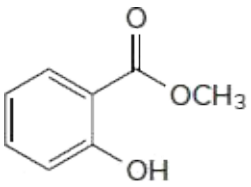




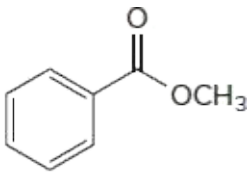
Challenge Problems

B.39 Acid chlorides (RCOCl) constitute another family of compounds that contains a carbonyl group. Would you expect the C=O of an acid chloride to absorb at a higher or lower wavenumber than an ester? Explain your reasoning. We will learn more about acid chlorides in Chapter 20.

B.40 Suggest an explanation for the following observation. The carbonyl group of methyl salicylate absorbs at a significantly lower wavenumber than the carbonyl group of methyl benzoate.



methyl salicylate
$\tilde{\nu}$ = 1680 cm^{-1}

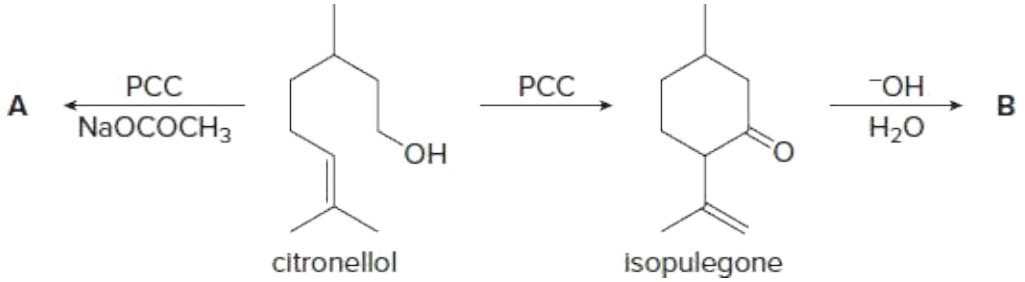


methyl benzoate
$\tilde{\nu}$ = 1728 cm^{-1}

B.41 Explain why a ketone carbonyl typically absorbs at a lower wavenumber than an aldehyde carbonyl (1715 vs. 1730 cm^{-1}).

B.42 Oxidation of citronellol, a constituent of rose and geranium oils, with

PCC in the presence of added NaOCOCH3 forms compound A. A has a molecular ion in its mass spectrum at 154 and a strong peak in its IR spectrum at 1730 cm^{-1}, in addition to C—H stretching absorptions. Without added $NaOCOCH_3$, oxidation of citronellol with PCC yields isopulegone, which is then converted to B with aqueous base. B has a molecular ion at 152 and a peak in its IR spectrum at 1680 cm^{-1}, in addition to C—H stretching absorptions.



a. **Identify the structures of A and B.**

b. **Draw a mechanism for the conversion of citronellol to isopulegone.**

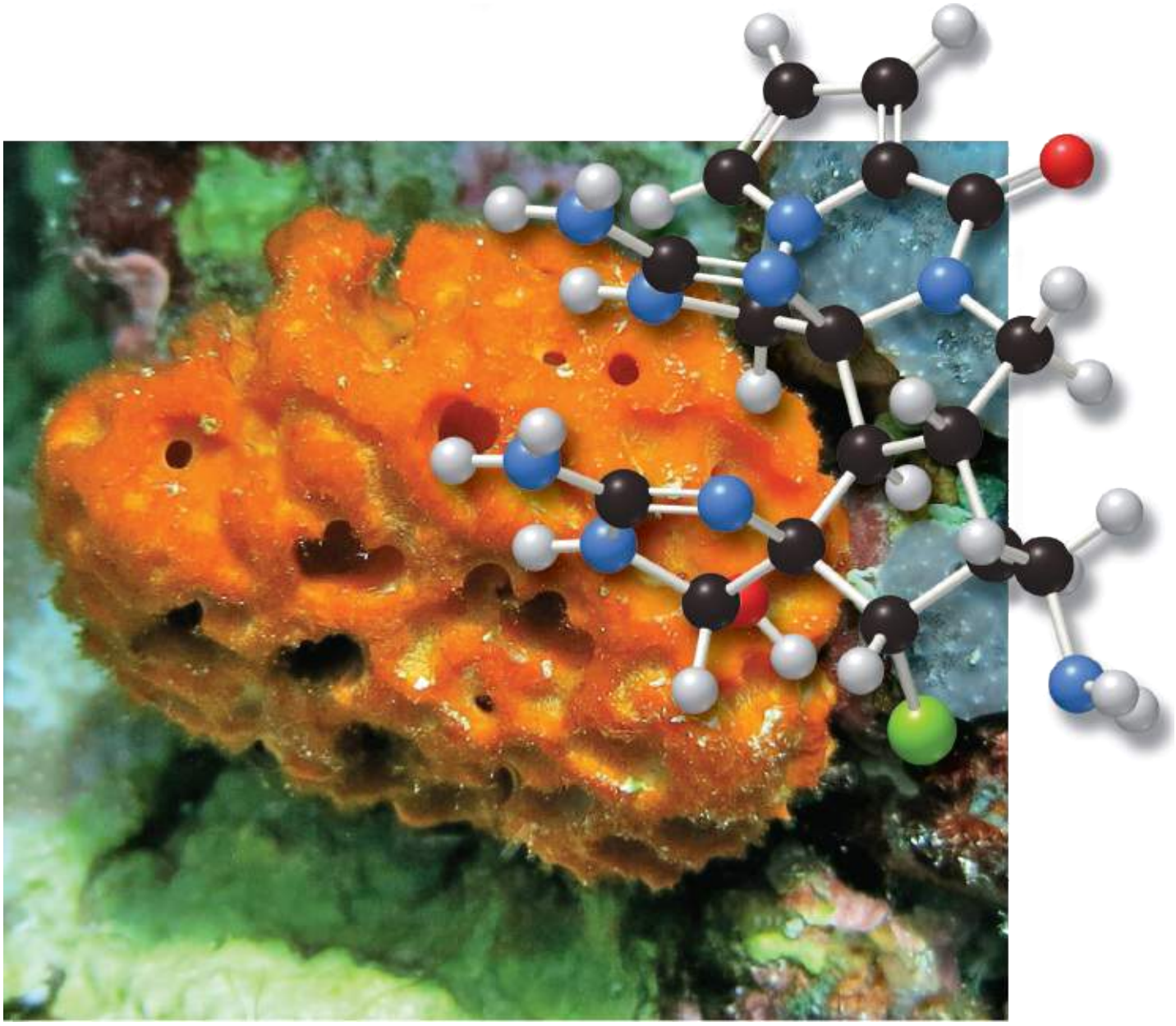
c. **Draw a mechanism for the conversion of isopulegone to B.**

B.43 **The carbonyl absorptions of esters X and Y differ by 25 cm^{-1}. Which compound absorbs at higher wavenumber and why?**

X Y

SPECTROSCOPY

C Nuclear Magnetic Resonance Spectroscopy



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C.1 An introduction to NMR spectroscopy

C.2 ^{1}H NMR: Number of signals

C.3 ^{1}H NMR: Position of signals

C.4 The chemical shift of protons on sp^2 and sp hybridized carbons
C.5 ^{1}H NMR: Intensity of signals
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Palau'amine is a complex natural product isolated from the sea sponge *Hymeniacidon agminata* (formerly *Stylotella agminata*) collected in the Pacific Ocean near the Republic of Palau. The initial structure proposed for palau'amine in 1993 was revised in 2007 using a variety of modern spectroscopic techniques, including nuclear magnetic resonance spectroscopy. The dense array of functional groups in palau'amine and its antitumor and immunosuppressive properties attracted the attention of dozens of organic chemists, leading to its total synthesis in the laboratory in early 2010. In Spectroscopy Part C, we learn how nuclear magnetic resonance spectroscopy plays a key role in structure determination.

Why Study…

Nuclear Magnetic Resonance Spectroscopy?

In Spectroscopy C, we continue our study of organic structure determination by learning about nuclear magnetic resonance (NMR) spectroscopy. NMR spectroscopy is the most powerful tool for characterizing organic molecules, because it can be used to identify the carbon–hydrogen framework in a compound.

C.1 An Introduction to NMR Spectroscopy

Two common types of NMR spectroscopy are used to characterize organic structure:

- ^{1}H NMR (proton NMR) is used to determine the number and type of hydrogen

atoms in a molecule; and

- ^{13}C NMR (carbon NMR) is used to determine the type of carbon atoms in a molecule.

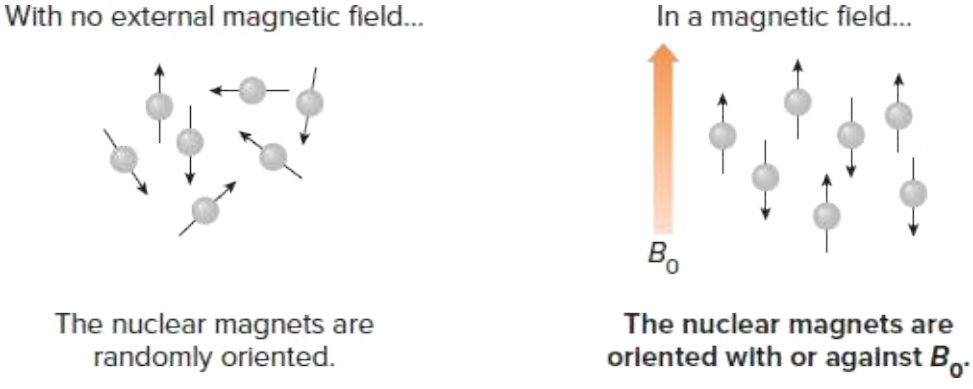
Before you learn how to use NMR spectroscopy to determine the structure of a compound, it is helpful to understand the physics behind it. Keep in mind, though, that NMR stems from the same basic principle as all other forms of spectroscopy: Energy interacts with a molecule, and absorptions occur only when the incident energy matches the energy difference between two states.

C.1A The Basis of NMR Spectroscopy

The source of energy in NMR is radio waves. Radiation in the radiofrequency region of the electromagnetic spectrum (so-called RF radiation) has very long wavelengths, so its corresponding frequency and energy are both low. When these low-energy radio waves interact with a molecule, they can change the nuclear spins of some elements, including ^{1}H and ^{13}C.

A spinning proton creates a magnetic field.

When a charged particle such as a proton spins on its axis, it creates a magnetic field. For the purpose of this discussion, therefore, a nucleus is a tiny bar magnet, symbolized by . Normally these nuclear magnets are randomly oriented in space, but in the presence of an external magnetic field, B_0, they are oriented with or against this applied field. More nuclei are oriented *with* the applied field because this arrangement is lower in energy, but the energy difference between these two states is very small (< 0.4 J/mol).

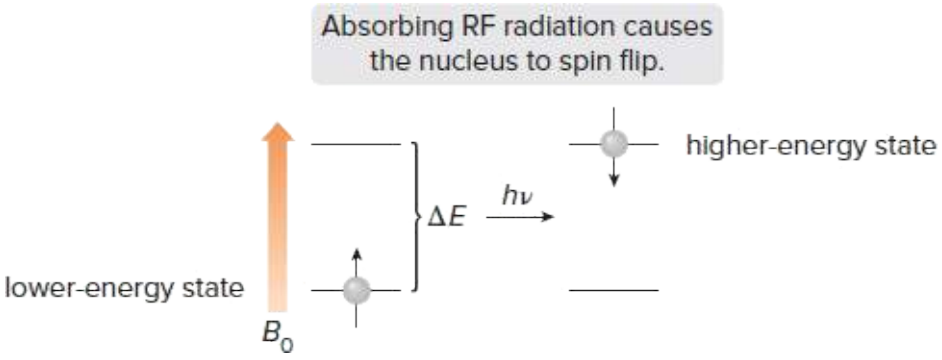


In a magnetic field, there are now two different energy states for a proton:

- In the *lower-energy state* the nucleus is aligned in the *same direction* as B_0.

- In the *higher-energy state* the nucleus is aligned *opposed* to B_0.

When an external energy source ($h\nu$) that matches the energy difference (ΔE) between these two states is applied, energy is absorbed, causing the nucleus to "spin flip" from one orientation to another. The energy difference between these two nuclear spin states corresponds to the low-frequency radiation in the RF region of the electromagnetic spectrum.



- **A nucleus is in *resonance* when it absorbs RF radiation and "spin flips" to a higher-energy state.**

Thus, two variables characterize NMR:

- An applied magnetic field, B_0. Magnetic field strength is measured in tesla (T).
- The frequency ν of radiation used for resonance, measured in hertz (Hz) or megahertz (MHz); (1 MHz = 10^6 Hz).

The frequency needed for resonance and the applied magnetic field strength are proportionally related:

$$\nu \propto B_0$$

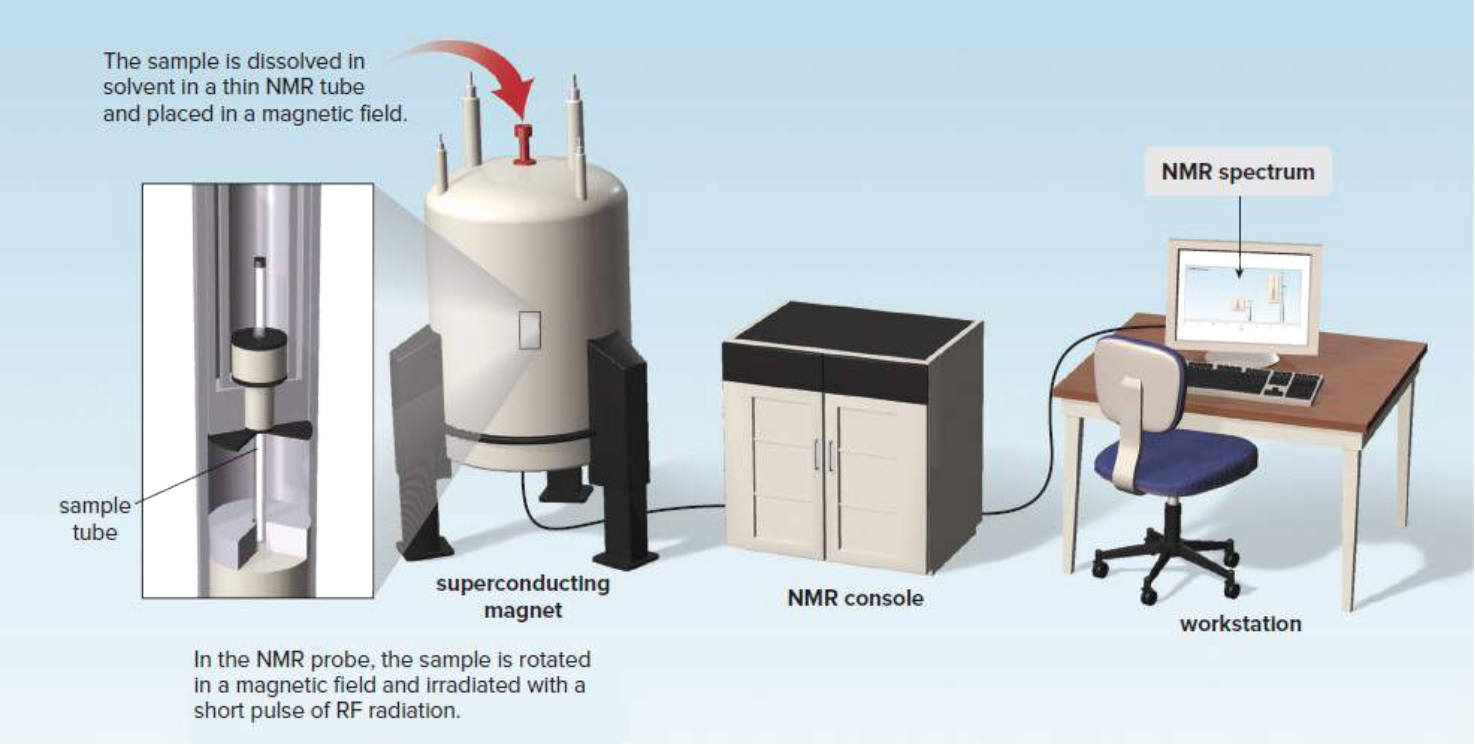
frequency — applied magnetic field strength

- **The stronger the magnetic field, the larger the energy difference between the two nuclear spin states, and the higher the *ν* needed for resonance.**

NMR spectrometers are referred to as 300 MHz instruments, 500 MHz instruments, and so forth, depending on the frequency of RF radiation used for resonance.

Early NMR spectrometers used a magnetic field strength of ~1.4 T, which required RF radiation of 60 MHz for resonance. Modern NMR spectrometers use stronger magnets, thus requiring higher frequencies of RF radiation for resonance. For example, a magnetic field strength of 7.05 T requires a frequency of 300 MHz for a proton to be in resonance. These spectrometers use very powerful magnetic fields to create a small, but measurable energy difference between the two possible spin states. A schematic of an NMR spectrometer is shown in Figure C.1.

If all protons absorbed at the same frequency in a given magnetic field, the spectra of all compounds would consist of a single absorption, rendering NMR useless for structure determination. Fortunately, however, this is not the case.



• **An NMR spectrometer.** The sample is dissolved in a solvent, usually $CDCl_3$ (deuterochloroform), and placed in a magnetic field. A radiofrequency generator then irradiates the sample with a short pulse of radiation, causing resonance. When the nuclei fall back to their lower-energy state, the detector measures the energy released, and a spectrum is recorded. The superconducting magnets in modern NMR spectrometers have coils that are cooled in liquid helium and conduct electricity with essentially no resistance.

Figure C.1 **Schematic of an NMR spectrometer**

- **All protons do *not* absorb at the same frequency. Protons in different environments absorb at slightly different frequencies, so they are distinguishable by NMR.**

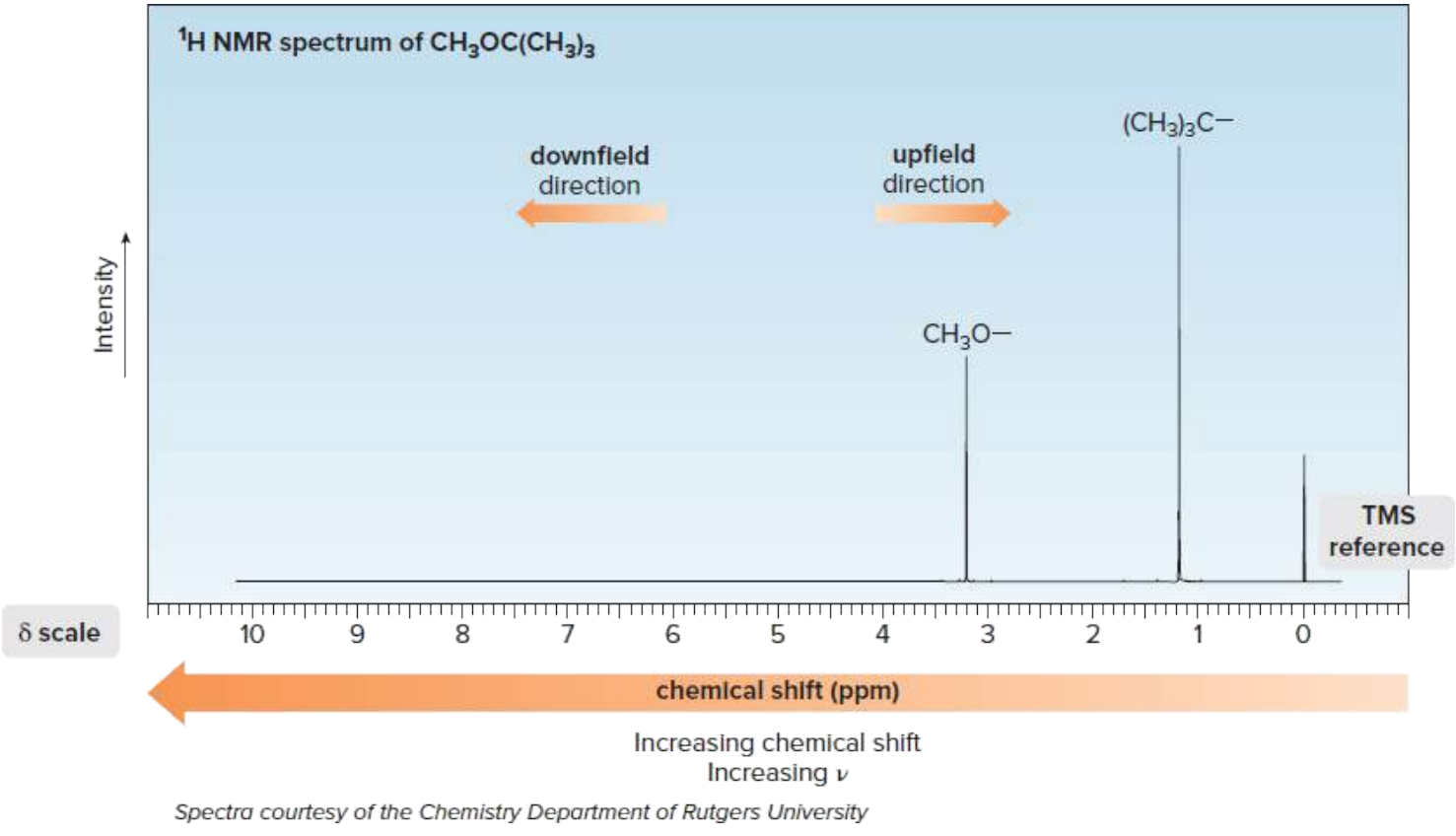
The frequency at which a particular proton absorbs is determined by its electronic environment, as discussed in Section C.3. Because electrons are moving charged

particles, they create a magnetic field opposed to the applied field B_0, and the size of the magnetic field generated by the electrons around a proton determines where it absorbs. Modern NMR spectrometers use a constant magnetic field strength B_0, and then a narrow range of frequencies is applied to achieve the resonance of all protons.

Only nuclei that contain odd mass numbers (such as ^{1}H, ^{13}C, ^{19}F, and ^{31}P) or odd atomic numbers (such as ^{2}H and ^{14}N) give rise to NMR signals. Because both ^{1}H and ^{13}C, the less abundant isotope of carbon, are NMR active, NMR allows us to map the carbon and hydrogen framework of an organic molecule.

C.1B A ^{1}H NMR Spectrum

An NMR spectrum plots the intensity of a signal against its chemical shift measured in parts per million (ppm). The common scale of chemical shifts is called the δ (delta) scale. The proton NMR spectrum of *tert*-butyl methyl ether [$CH_3OC(CH_3)_3$] illustrates several important features:



Spectra courtesy of the Chemistry Department of Rutgers University

***tert*-Butyl methyl ether (MTBE) is the high-octane gasoline additive that has contaminated the water supply in some areas (Section 3.4).**

$(CH_3)_4Si$
tetramethylsilane
TMS

- NMR absorptions generally appear as sharp signals. The ^{1}H NMR spectrum of $CH_3OC(CH_3)_3$ consists of two signals: a tall peak at 1.2 ppm due to the $(CH_3)_3C-$ group, and a smaller peak at 3.2 ppm due to the CH_3O- group.
- Increasing chemical shift is plotted from *right to left*. Most protons absorb somewhere from 0 to 12 ppm.
- The terms upfield and downfield describe the relative location of signals. Upfield means to the *right*. The $(CH_3)_3C-$ peak is upfield from the CH_3O- peak. Downfield means to the *left*. The CH_3O- peak is downfield from the $(CH_3)_3C-$ peak.

NMR absorptions are measured relative to the position of a reference signal at 0 ppm on the δ scale due to tetramethylsilane (TMS). TMS is a volatile and inert compound that gives a single peak upfield from other typical NMR absorptions.

Although chemical shifts are measured relative to the TMS signal at 0 ppm, this reference is often not plotted on a spectrum.

The *positive* direction of the δ scale is *downfield* from TMS. A very small number of absorptions occur upfield from the TMS signal, which is defined as the negative direction of the δ scale. (See Problem C.79.)

The chemical shift on the *x* axis gives the position of an NMR signal, measured in ppm, according to this equation:

$$\text{chemical shift (in ppm on the } \delta \text{ scale)} = \frac{\text{observed chemical shift (in Hz) downfield from TMS}}{\nu \text{ of the NMR spectrometer (in MHz)}}$$

Because the frequency of the radiation required for resonance is proportional to the strength of the applied magnetic field, B_0, reporting NMR absorptions in frequency would be meaningless unless the value of B_0 was also reported. By reporting the absorption as a fraction of the NMR operating frequency, though, we get units—ppm—that are independent of the spectrometer.

Sample Problem C.1 Calculating Chemical Shift

Calculate the chemical shift of an absorption that occurs at 1500 Hz

downfield from TMS using a 300 MHz NMR spectrometer.

Solution

Use the equation that defines the chemical shift in ppm:

$$\text{chemical shift (in ppm on the } \delta \text{ scale)} = \frac{\text{observed chemical shift (in Hz) downfield from TMS}}{\nu \text{ of the NMR spectrometer (in MHz)}}$$

Problem C.1

The ^{1}H NMR spectrum of CH_3OH recorded on a 500 MHz NMR spectrometer consists of two signals, one due to the CH_3 protons at 1715 Hz and one due to the OH proton at 1830 Hz, both measured downfield from TMS. (a) Calculate the chemical shift of each absorption. (b) Do the CH_3 protons absorb upfield or downfield from the OH proton?

More Practice:

Try Problems C.40, C.41.

Problem C.2

The ^{1}H NMR spectrum of 1,2-dimethoxyethane ($CH_3OCH_2CH_2OCH_3$) recorded on a 300 MHz NMR spectrometer consists of signals at 1017 Hz and 1065 Hz downfield from TMS. (a) Calculate the chemical shift of each absorption. (b) At what frequency would each absorption occur if the spectrum were recorded on a 500 MHz NMR spectrometer?

Four different features of a ^{1}H NMR spectrum provide information about a compound's structure:

[1] Number of signals (Section C.2)
[2] Position of signals (Sections C.3 and C.4)
[3] Intensity of signals (Section C.5)
[4] Spin-spin splitting of signals (Sections C.6–C.8)

C.2 ^{1}H NMR: Number of Signals

How many ^{1}H NMR signals does a compound exhibit? The number of NMR signals *equals* the number of different types of protons in a compound.

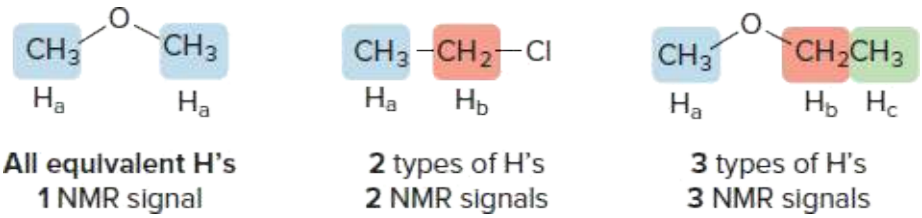
C.2A General Principles

- **Protons in different environments give different NMR signals. Equivalent protons give the same NMR signal.**

In many compounds, deciding whether two protons are in identical or different environments is intuitive.

Any CH_3 group is different from any CH_2 group, which is different from any CH group in a molecule. Two CH_3 groups may be identical (as in CH_3OCH_3) or different (as in $CH_3OCH_2CH_3$), depending on what each CH_3 group is bonded to.

***tert*-Butyl methyl ether [$CH_3OC(CH_3)_3$] (Section C.1) exhibits two NMR signals because it contains two different kinds of protons: one CH_3 group is bonded to $-OC(CH_3)_3$, whereas the other three CH_3 groups are each bonded to the same group, $[-C(CH_3)_2]OCH_3$.**



- CH_3OCH_3: Each CH_3 group is bonded to the same group ($-OCH_3$), making both CH_3 groups equivalent.
- CH_3CH_2Cl: The protons of the CH_3 group are different from those of the CH_2 group.
- $CH_3OCH_2CH_3$: The protons of the CH_2 group are different from those in each CH_3 group. The two CH_3 groups are also different from each other; one CH_3 group is bonded to $-OCH_2CH_3$ and the other is bonded to $-CH_2OCH_3$.

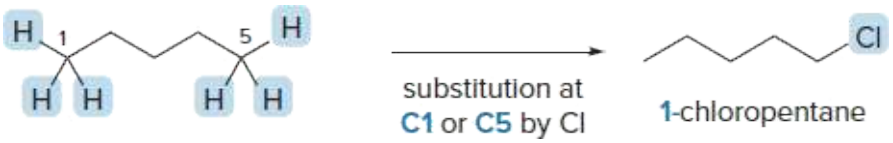
In some cases, it is less obvious by inspection if two protons are equivalent or different. To rigorously determine whether two protons are in identical environments (and therefore give rise to one NMR signal), replace each H atom in question by another atom Z (for example, Z = Cl). If substitution by Z yields the same compound or enantiomers, the two protons are equivalent, as shown in Sample Problem C.2.

Sample Problem C.2 Determining the Different Types of H's in a Molecule

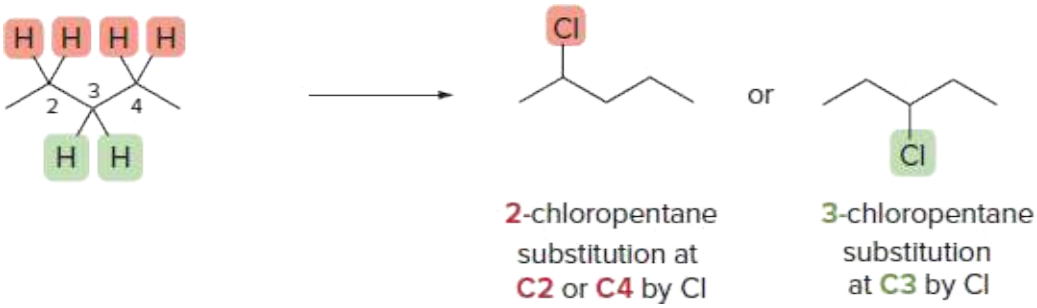
How many different kinds of H atoms does $CH_3CH_2CH_2CH_2CH_3$ contain?

Solution

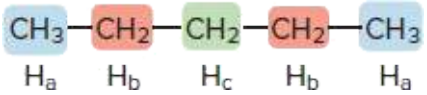
In comparing two H atoms, replace each H by Z (for example, Z = Cl), and examine the substitution products that result. The two CH_3 groups are identical because substitution of one H by Cl on each carbon gives the same product, 1-chloropentane.



There are two different types of CH_2 groups. Substitution of Cl for H on C2 or C4 gives the same product, 2-chloropentane, so these H's are identical. Substitution of Cl for H on C3 gives a different product, 3-chloropentane, so this CH_2 group is different from the other two CH_2 groups.



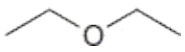
Thus, $CH_3CH_2CH_2CH_2CH_3$ has three different types of protons and gives three different NMR signals.

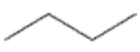


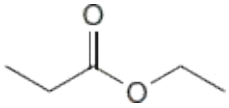
Problem C.3

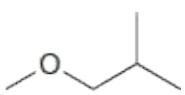
How many ^1H NMR signals does each compound show?

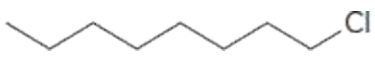
a.

b. 

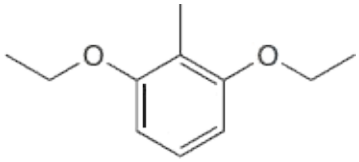
c. 

d. 

e. 

f. 

g.

h. 

More Practice:

Try Problems C.36a, C.37a, C.38, C.39, C.55a, C.56a, C.57d.

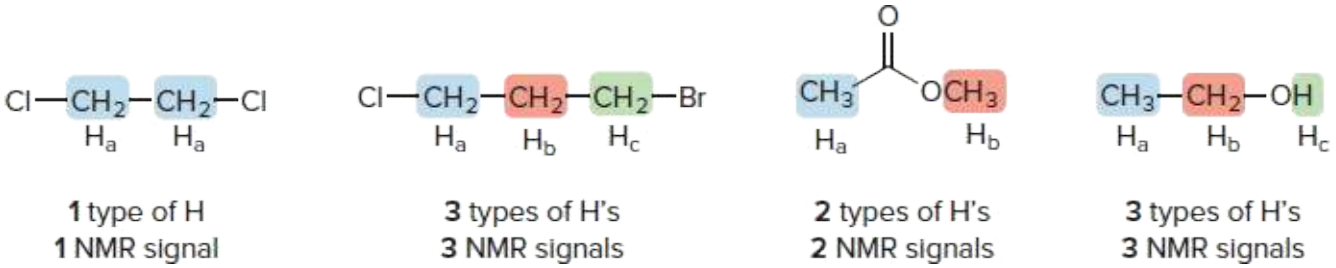


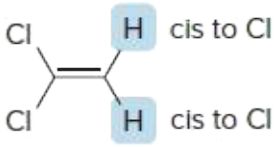
Figure C.2 **The number of ^{1}H NMR signals of some representative organic compounds**

Figure C.2 gives the number of NMR signals exhibited by four additional molecules. All protons—not just protons bonded to carbon atoms—give rise to NMR signals. Ethanol (CH_3CH_2OH), for example, gives three NMR signals, one of which is due to its OH proton.

C.2B Determining Equivalent Protons in Alkenes and Cycloalkanes

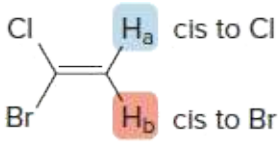
To determine equivalent protons in cycloalkanes and alkenes that have restricted bond rotation, always draw in all bonds to hydrogen.

Then, in comparing two H atoms on a ring or double bond, two protons are equivalent only if they are cis (or trans) to the same groups, as illustrated with 1,1-dichloroethylene, 1-bromo-1-chloroethylene, and chloroethylene.



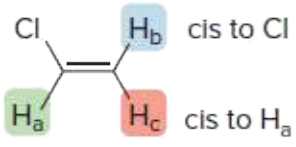
1,1-dichloroethylene

1 type of H
1 NMR signal



1-bromo-1-chloroethylene

2 types of H's
2 NMR signals

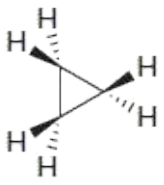


chloroethylene

3 types of H's
3 NMR signals

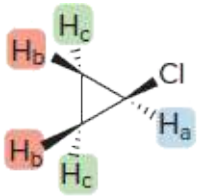
- 1,1-Dichloroethylene: The two H atoms on the C=C are both cis to a Cl atom. Thus, both H atoms are equivalent.
- 1-Bromo-1-chloroethylene: H_a is cis to a Cl atom and H_b is cis to a Br atom. Thus, H_a and H_b are different, giving rise to two NMR signals.
- Chloroethylene: H_a is bonded to the carbon with the Cl atom, making it different from H_b and H_c. Of the remaining two H atoms, H_b is cis to a Cl atom and H_c is cis to a H atom, making them different. All three H atoms in this compound are different.

Proton equivalency in cycloalkanes can be determined similarly.



cyclopropane

All H's are equivalent.
1 NMR signal



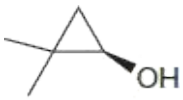
chlorocyclopropane

3 types of H's
3 NMR signals

- Cyclopropane: All H atoms are equivalent, so there is only one NMR signal.
- Chlorocyclopropane: There are now three kinds of H atoms: H_a is bonded to a carbon bonded to a Cl; both H_b protons are cis to the Cl, whereas both H_c protons are cis to another H.

Sample Problem C.3 Determining Proton Equivalency in Cyclic Compounds

How many ^{1}H NMR signals does A exhibit?

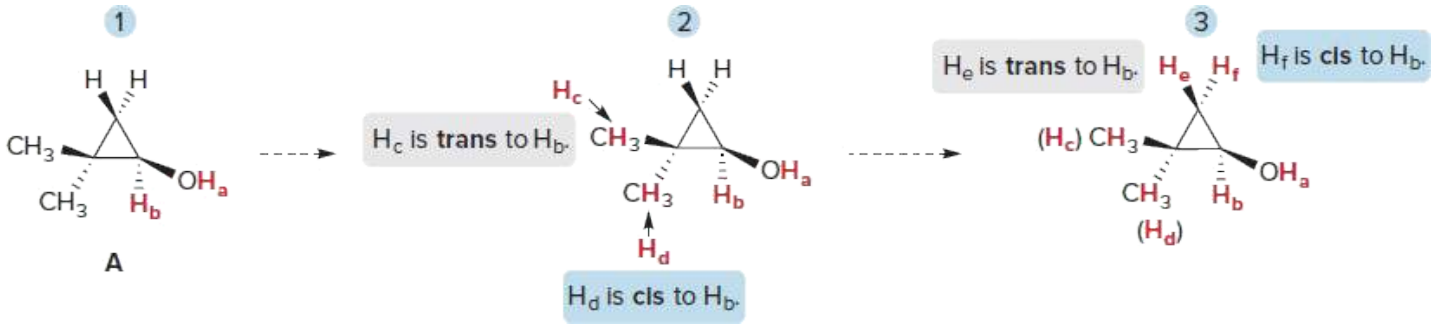


A

Solution

Use wedges and dashed wedges to emphasize the relative location of

groups on a ring. Two protons are equivalent only if they are cis (or trans) to the same groups. Start with the protons that can be assigned most easily. In this example, the OH and the CH on the ring look different from all other protons, so they give two NMR signals. The two CH_3 groups are different from each other because one CH_3 is cis to H_b and one is trans to H_b. Likewise, H_e and H_f are different from each other, because H_e is trans to H_b, whereas H_f is cis to H_b.



Thus, A contains six different types of H's and gives six ^{1}H NMR signals.

Problem C.4

How many ^{1}H NMR signals does each dimethylcyclopropane show?

a.

b.

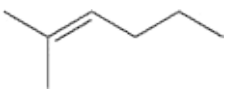
c.

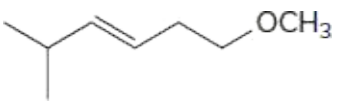
More Practice:

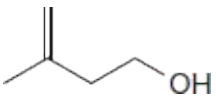
Try Problem C.38h, i, j.

Problem C.5

How many ^{1}H NMR signals does each alkene exhibit?

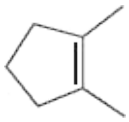
a. 

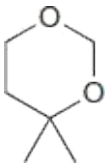
b. 

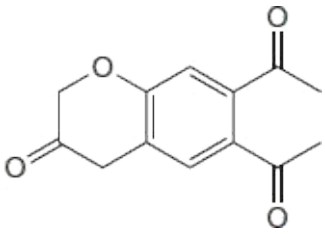
c. 

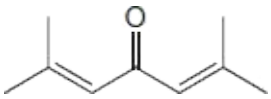
Problem C.6

How many ^{1}H NMR signals does each compound give?

a. 

b. 

c. 

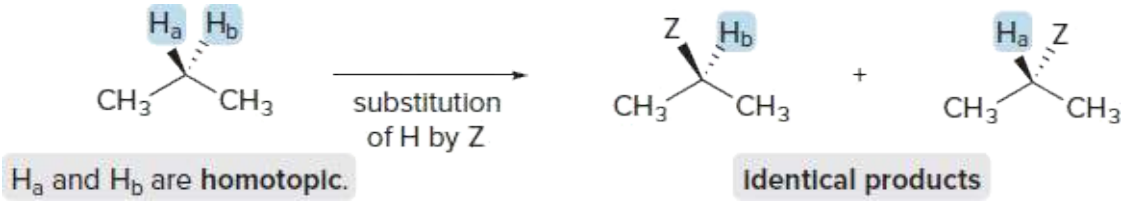
d. 

C.2C Homotopic, Enantiotopic, and Diastereotopic Protons

Let's look more closely at the protons of a single sp^3 hybridized CH_2 group to determine whether these two protons are always equivalent to *each other*. Three examples illustrate different outcomes.

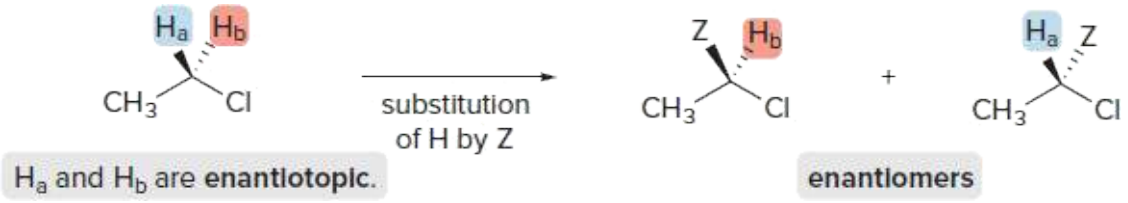
Page 570

$CH_3CH_2CH_3$ has two different types of protons—those of the CH_3 groups and those of the CH_2 group—meaning that the two H atoms of the CH_2 group are *equivalent to each other*. Replacement of each H by Z forms the *same* product, so they give *one* NMR signal.



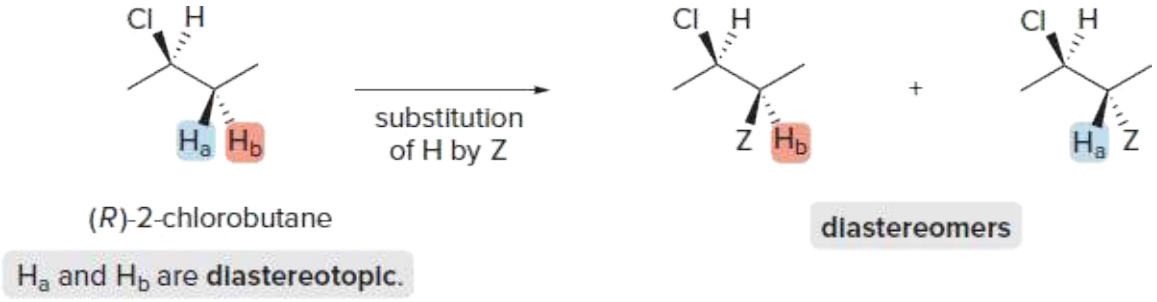
- **When substitution of two H atoms by Z forms the *same* product, these equivalent hydrogens are called *homotopic* protons.**

CH_3CH_2Br has two different types of protons—those of the CH_3 group and those of the CH_2 group—meaning that the two H atoms of the CH_2 group are *equivalent to each other*. Replacement of each H of the CH_2 group by an atom Z creates a new stereogenic center, forming two products that are enantiomers.



- **When substitution of two H atoms by Z forms *enantiomers*, the two H atoms are equivalent and give a single NMR signal. These two H atoms are called *enantiotopic* protons.**

In contrast, the two H atoms of the CH_2 group in (*R*)-2-chlorobutane, which contains one stereogenic center, are *not* equivalent to each other. Substitution of each H by Z forms two diastereomers, and thus, these two H atoms give *different* NMR signals.



- **When substitution of two H atoms by Z forms *diastereomers*, the two H atoms are *not* equivalent, and give two NMR signals. These two H atoms are called *diastereotopic* protons.**

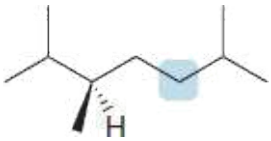
Sample Problem C.4 Classifying Protons as Homotopic, Enantiotopic, or Diastereotopic

Classify the protons in each labeled CH_2 group as homotopic, enantiotopic, or diastereotopic.

a.

b.

c.



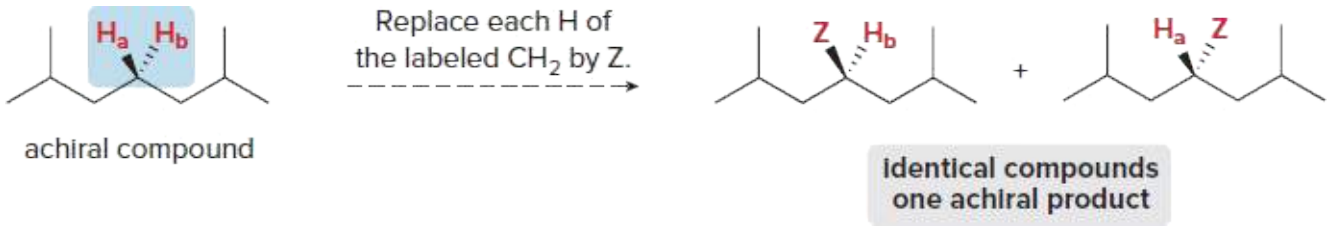
Solution

Page 571

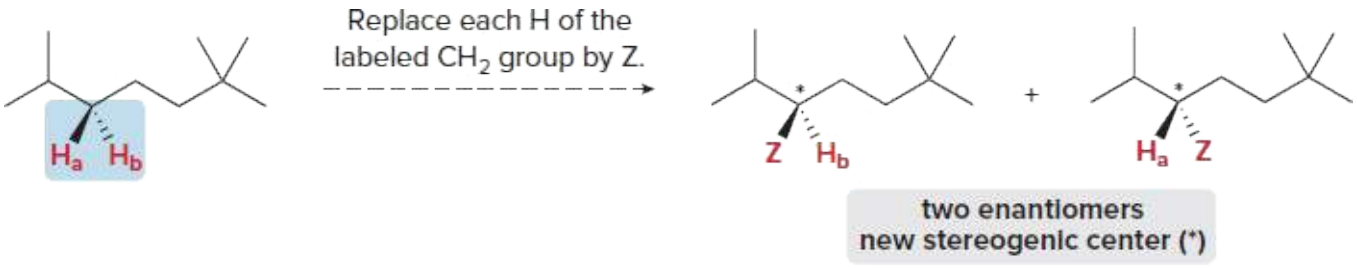
To determine equivalency in these cases, look for whether the compound

has a stereogenic center to begin with and whether a new stereogenic center is formed when H is replaced by Z.

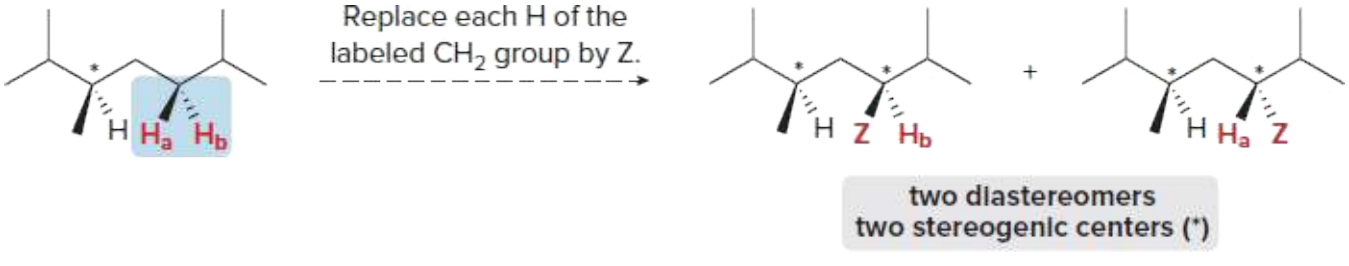
a. The compound is achiral and has no stereogenic center. Replacement of each H on the labeled CH_2 group by Z forms the same product, making them homotopic. The H's within the CH_2 group are *equivalent* to each other and give one NMR signal.



b. The compound is achiral and has no stereogenic center. Because a new stereogenic center is formed on substitution of H by Z, the protons of the CH_2 group are enantiotopic. These H's are *equivalent* to each other and give one NMR signal.



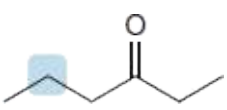
c. The compound has one stereogenic center to begin with. Because a new stereogenic center is formed on substitution of H by Z, the protons are diastereotopic. The H's within the CH_2 group are *different* from each other and give *different* NMR signals.



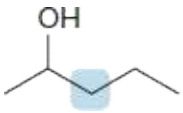
Problem C.7

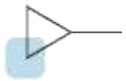
Label the protons in each highlighted CH_2 group as enantiotopic, diastereotopic, or homotopic.

a.



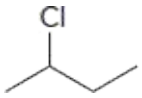
b.

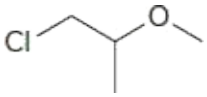
c. 

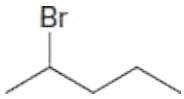
d. 

Problem C.8

How many ^{1}H NMR signals would you expect for each compound?

a. 

b. 

c. 

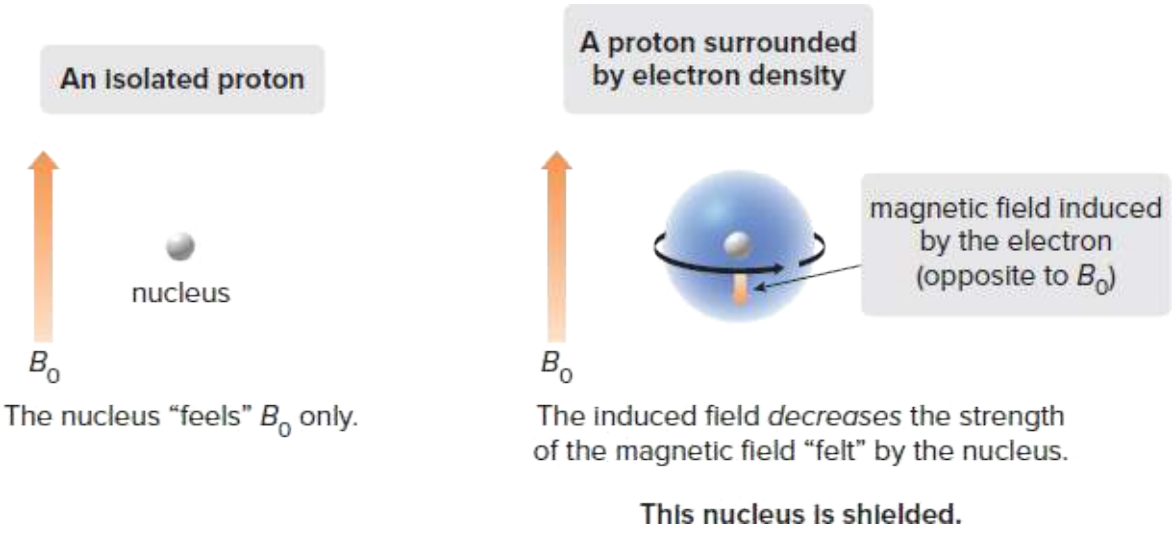
C.3 ^{1}H NMR: Position of Signals

In the NMR spectrum of tert-butyl methyl ether in Section C.1B, why does the CH_3O– group absorb downfield from the $-C(CH_3)_3$ group?

- **Where a particular proton absorbs depends on its electronic environment.**

C.3A Shielding and Deshielding Effects

To understand how the electronic environment around a nucleus affects its chemical shift, recall that in a magnetic field, an electron creates a small magnetic field that opposes the applied magnetic field, B_0. Electrons are said to *shield* the nucleus from B_0.



In the vicinity of the nucleus, therefore, the magnetic field generated by the circulating electron *decreases* the external magnetic field that the proton "feels." Because the proton experiences a lower magnetic field strength, it needs a lower frequency to achieve resonance. Lower frequency is to the right in an NMR spectrum, toward lower chemical shift, so shielding shifts an absorption *upfield*, as shown in Figure C.3a.

What happens if the electron density around a nucleus is *decreased*, instead? For example, how do the chemical shifts of the protons in CH_4 and CH_3Cl compare?

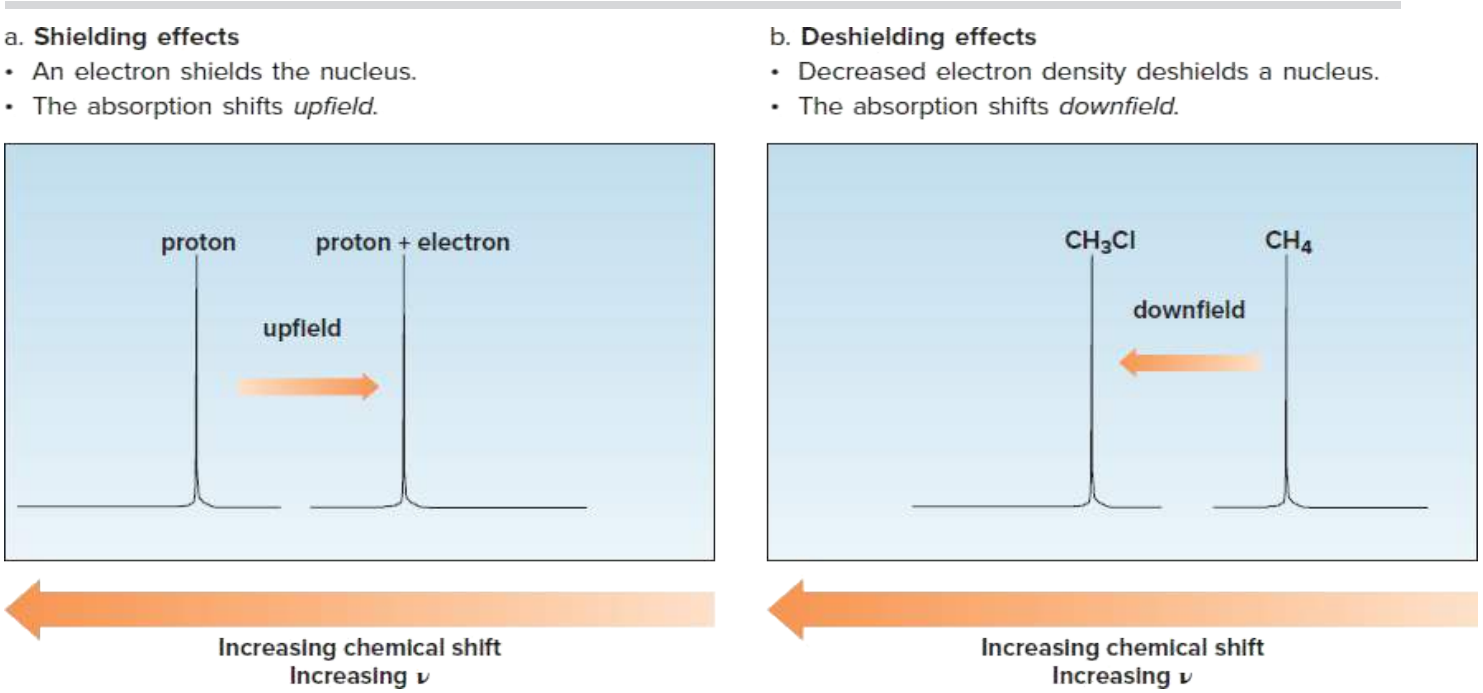


Figure C.3 **How chemical shift is affected by electron density around a nucleus**

The less shielded the nucleus becomes, the more of the applied magnetic field (B_0) it feels. This *deshielded* nucleus experiences a higher magnetic field strength, so it needs a higher frequency to achieve resonance. Higher frequency is to the *left* in an NMR spectrum, toward higher chemical shift, so deshielding shifts an absorption downfield,

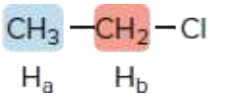
as shown in Figure C.3b for CH_3Cl versus CH_4. The electronegative Cl atom withdraws electron density from the carbon and hydrogen atoms in CH_3Cl, thus deshielding them relative to those in CH_4.

Remember the trend: Decreased electron density deshields a nucleus and an absorption moves downfield.

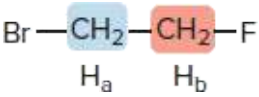
- **Protons near electronegative atoms are deshielded, so they absorb downfield.**

Figure C.4 summarizes the effects of shielding and deshielding.

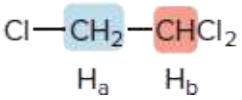
These electron density arguments explain the relative position of NMR signals in many compounds.



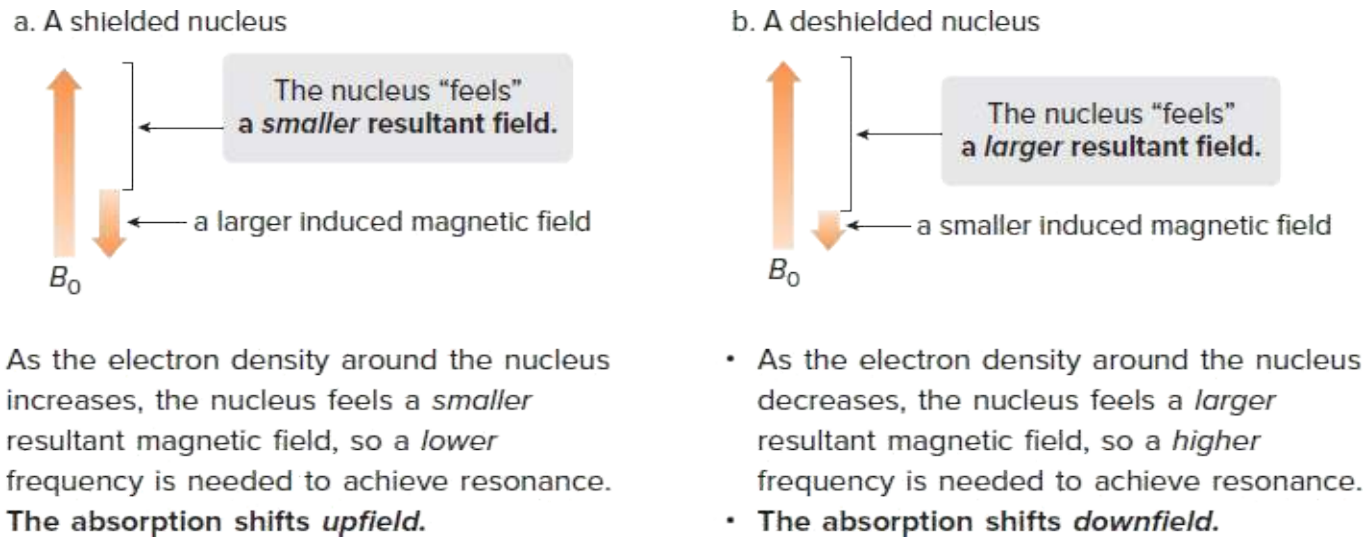
• The H_b protons are deshielded because they are closer to the electronegative Cl atom, so they absorb downfield from H_a.



• Because F is more electronegative than Br, the H_b protons are more deshielded than the H_a protons and absorb farther downfield.



• The larger number of electronegative Cl atoms (two vs. one) deshields H_b more than H_a, so it absorbs downfield from H_a.



- As the electron density around the nucleus increases, the nucleus feels a *smaller* resultant magnetic field, so a *lower* frequency is needed to achieve resonance.
- **The absorption shifts *upfield*.**

- As the electron density around the nucleus decreases, the nucleus feels a *larger* resultant magnetic field, so a *higher* frequency is needed to achieve resonance.
- **The absorption shifts *downfield*.**

Figure C.4 **Shielding and deshielding effects**

Sample Problem C.5 Determining Shielding and Deshielding Effects

Which of the labeled protons in each pair absorbs farther downfield: (a) $CH_3CH_2CH_3$ or CH_3OCH_3; (b) CH_3OCH_3 or CH_3SCH_3?

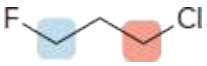
Solution

a. The CH_3 group in CH_3OCH_3 is deshielded by the electronegative O atom. Deshielding shifts the absorption downfield.

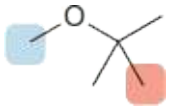
b. Because oxygen is more electronegative than sulfur, the CH_3 group in CH_3OCH_3 is more deshielded and absorbs downfield.

Problem C.9

For each compound, which of the protons on the highlighted carbons absorbs farther downfield?

a. 

b.

c. 

More Practice:

Try Problem C.42.

C.3B Chemical Shift Values

Not only is the *relative* position of NMR absorptions predictable, but it is also possible to predict the approximate chemical shift value for a given type of proton.

- **Protons in a given environment absorb in a predictable region in an NMR spectrum.**

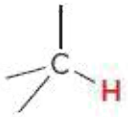
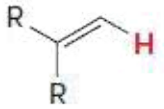
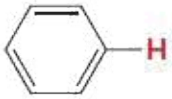
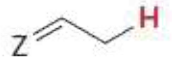
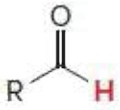
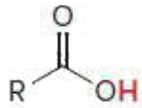
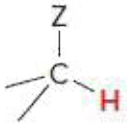
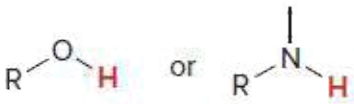
A more detailed list of characteristic chemical shift values is found in Appendix H.

Table C.1 lists the typical chemical shift values for the most common bonds encountered in organic molecules.

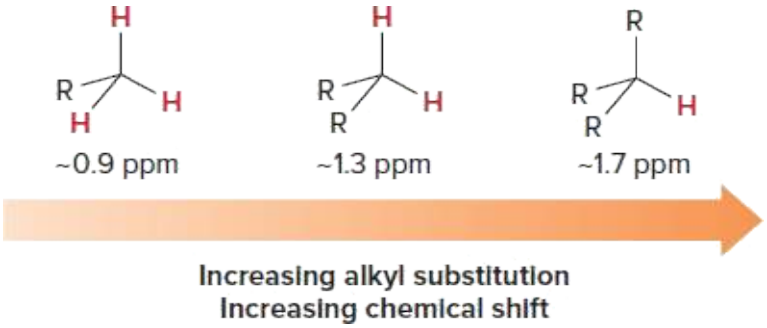
Table C.1 also illustrates that absorptions for a given type of C—H bond occur in a narrow range of chemical shift values, usually 1–2 ppm. For example, all sp^3 hybridized C—H bonds in alkanes and cycloalkanes absorb between 0.9 and 2.0 ppm. By contrast, absorptions due to N—H and O—H protons can occur over a broader range. For example, the OH proton of an alcohol is found anywhere in the 1–5 ppm

range. The position of these absorptions is affected by the extent of hydrogen bonding, making it more variable.

Table C.1 Characteristic Chemical Shifts of Common Types of Protons

Type of proton	Chemical shift (ppm)	Type of proton	Chemical shift (ppm)
	0.9–2		4.5–6
• RCH_3	~0.9		
• R_2CH_2	~1.3		6.5–8
• R_3CH	~1.7		
 Z = C, O, N	1.5–2.5		9–10
	~2.5		10–12
 Z = N, O, X	2.5–4		1–5

The chemical shift of a particular type of C—H bond is also affected by the number of R groups bonded to the carbon atom.

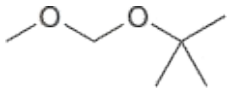


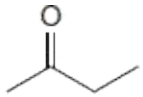
- **The chemical shift of a C—H bond increases with increasing alkyl substitution.**

Problem C.10

For each compound, first label each different type of proton and then rank the protons in order of increasing chemical shift.

a.

b. 

c. 

Problem C.11

Label each statement as True or False.

a. When a nucleus is strongly shielded, the effective field is larger than the applied field and the absorption shifts downfield.

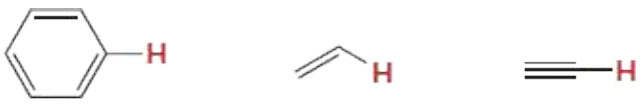
b. When a nucleus is strongly shielded, the effective field is smaller than the applied field and the absorption is shifted upfield.

c. A nucleus that is strongly deshielded requires a lower field strength for resonance.

d. A nucleus that is strongly shielded absorbs at a larger δ value.

C.4 The Chemical Shift of Protons on sp^2 and *sp* Hybridized Carbons

The chemical shift of protons bonded to benzene rings, C—C double bonds, and C—C triple bonds merits additional comment.

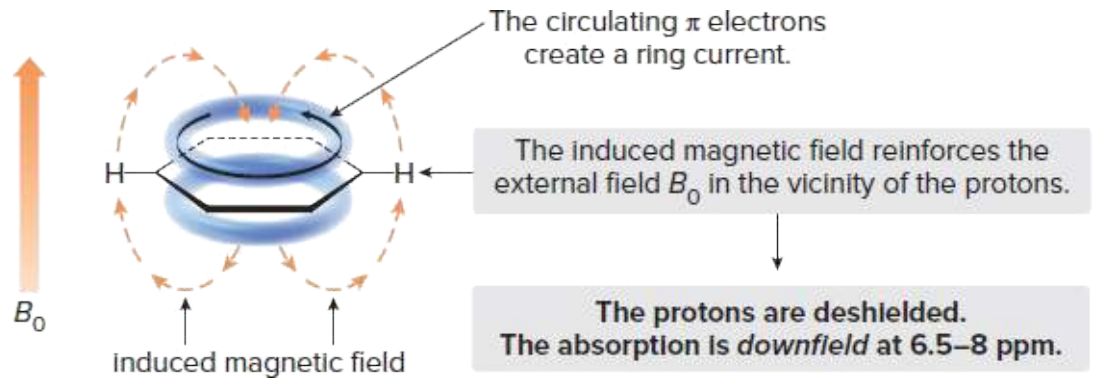


Each of these functional groups contains π bonds with loosely held π electrons. When placed in a magnetic field, these π electrons move in a circular path, inducing a new magnetic field. How this induced magnetic field affects the chemical shift of a proton depends on the direction of the induced field *in the vicinity of the absorbing proton*.

Protons on Benzene Rings

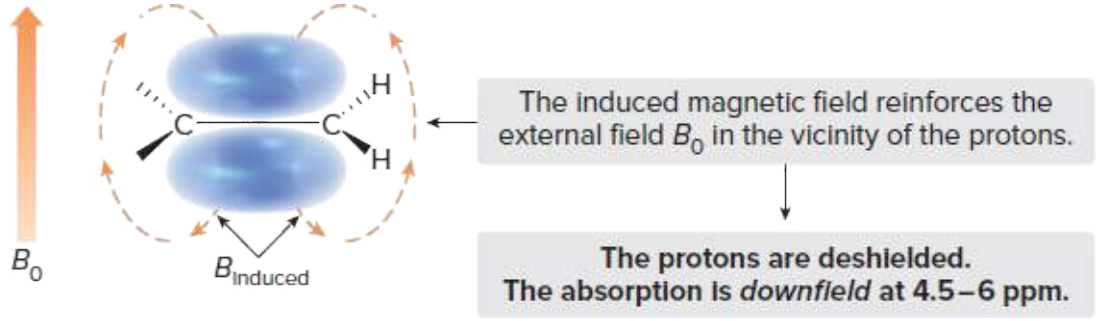
In a magnetic field, the six π electrons in benzene circulate around the ring, creating a ring current. The magnetic field induced by these moving electrons *reinforces* the applied magnetic field in the vicinity of the protons. The protons thus feel a stronger magnetic field and a higher frequency is needed for resonance, so the protons are

deshielded and the absorption is *downfield*.



Protons on Carbon–Carbon Double Bonds

A similar phenomenon occurs with protons on carbon–carbon double bonds. In a magnetic field, the loosely held π electrons create a magnetic field that *reinforces* the applied field in the vicinity of the protons. Because the protons now feel a stronger magnetic field, they require a higher frequency for resonance. The protons are deshielded and the absorption is *downfield*.



Protons on Carbon-Carbon Triple Bonds

Page 576

In a magnetic field, the π electrons of a carbon-carbon triple bond are induced to circulate, but in this case the induced magnetic field *opposes* the applied magnetic field (B_0). The proton thus feels a weaker magnetic field, so a lower frequency is needed for resonance. The nucleus is shielded and the absorption is *upfield*.

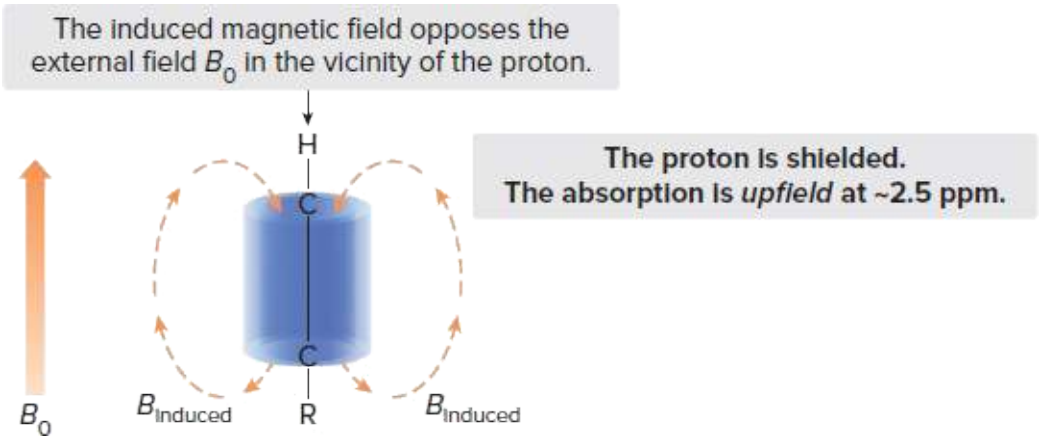
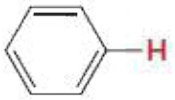
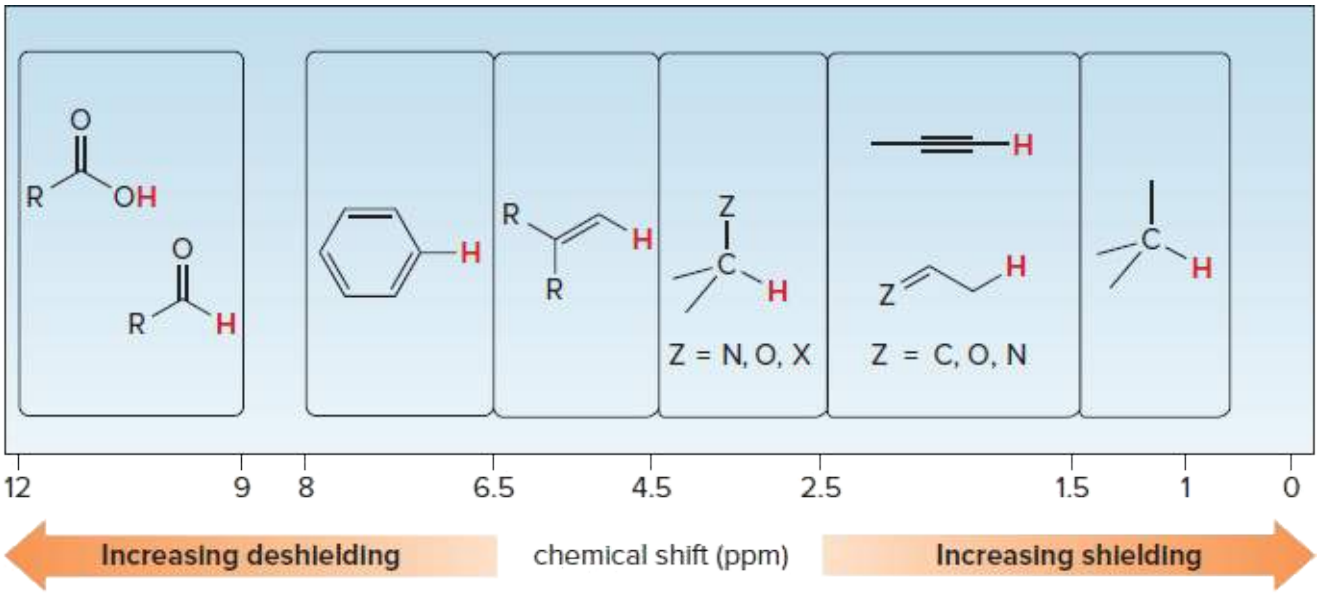


Table C.2 summarizes the shielding and deshielding effects due to circulating π electrons.

Table C.2 Effect of π Electrons on Chemical Shift Values

Proton type	Effect	Chemical shift (ppm)
	highly deshielded	6.5–8
	deshielded	4.5–6
	shielded	~2.5

To remember the chemical shifts of some common bond types, it is helpful to think of a ^{1}H NMR spectrum as being divided into six different regions (Figure C.5).

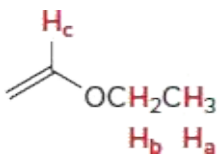


- **Shielded** protons absorb at **lower** chemical shift (to the **right**).
- **Deshielded** protons absorb at **higher** chemical shift (to the **left**).
- Note: The drawn chemical shift scale is not linear.

Figure C.5 Regions in the ^{1}H NMR spectrum

Sample Problem C.6 Predicting the Relative Chemical Shift of Protons

Rank H_a, H_b, and H_c in order of increasing chemical shift.

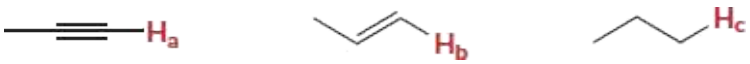


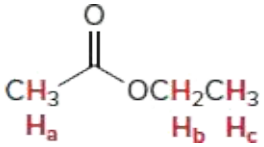
Solution

The H_a protons are bonded to an sp^3 hybridized carbon, so they are shielded and absorb upfield compared to H_b and H_c. Because the H_b protons are deshielded by the electronegative oxygen atom on the C to which they are bonded, they absorb downfield from H_a. The H_c proton is deshielded by two factors. The electronegative O atom withdraws electron density from H_c. Moreover, because H_c is bonded directly to a C=C, the magnetic field induced by the π electrons causes further deshielding. Thus, in order of increasing chemical shift, $H_a < H_b < H_c$.

Problem C.12

Rank each group of protons in order of increasing chemical shift.

a. 

b. 

More Practice:

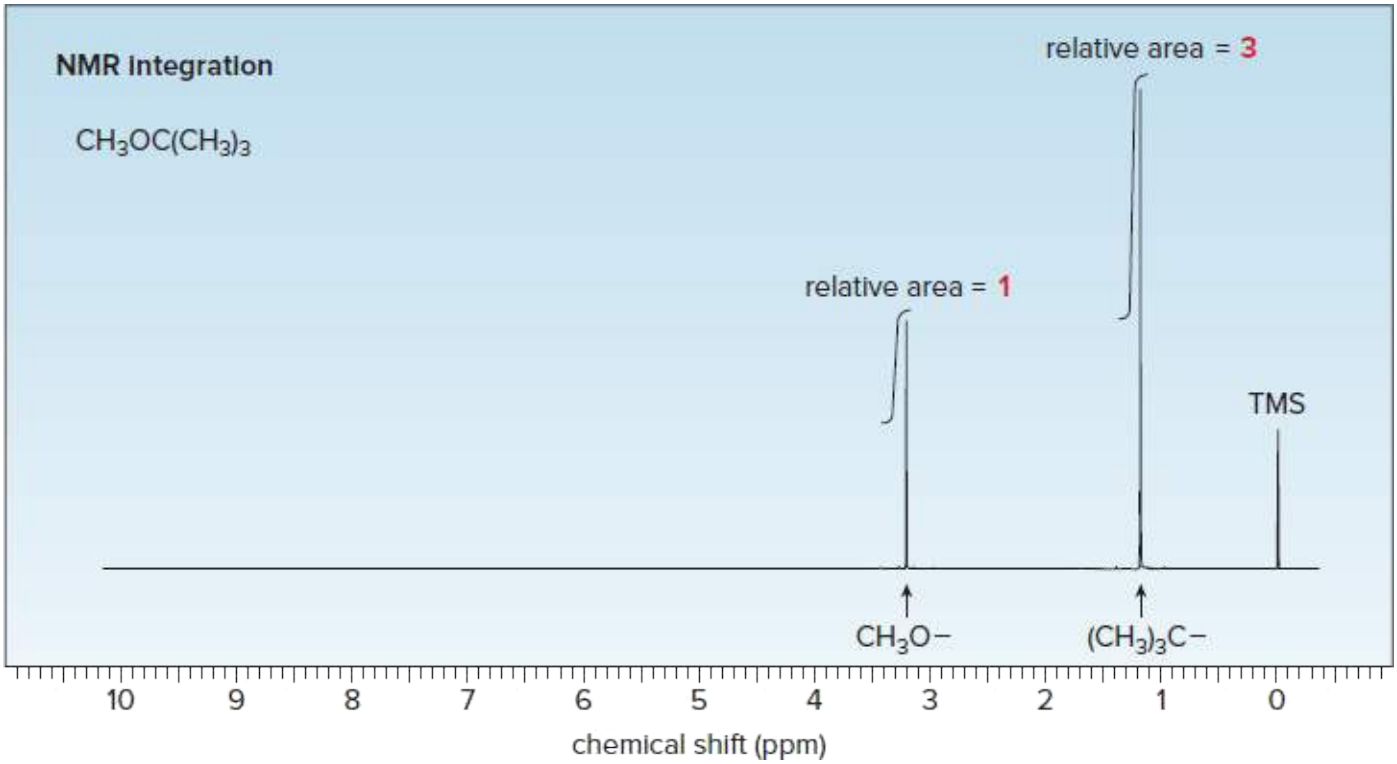
Try Problem C.42.

C.5 ^{1}H NMR: Intensity of Signals

The relative intensity of ^{1}H NMR signals also provides information about a compound's structure.

- **The area under an NMR signal is proportional to the number of absorbing protons.**

For example, in the ^{1}H NMR spectrum of $CH_3OC(CH_3)_3$, the ratio of the area under the downfield peak (due to the CH_3O- group) to the upfield peak [due to the $-C(CH_3)_3$ group] is 1:3. An NMR spectrometer automatically integrates the area under the peaks, and prints out a digital display of the *relative* areas of the NMR signals. Older NMR spectrometers print out a stepped curve (an integral) on the spectrum. The height of each step is proportional to the area under the peak, which is in turn proportional to the number of absorbing protons.



Integrals can be manually measured, but modern NMR spectrometers automatically calculate and plot the value of each integral in arbitrary units. Page 578

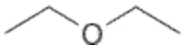
If the heights of two integrals are in a 1:3 ratio, then the ratio of absorbing protons is 1:3, or 2:6, or 3:9, and so forth. This tells the *ratio*, not the absolute number of protons.

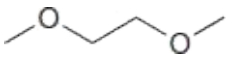
Problem C.13

Which compounds give a ^{1}H NMR spectrum with two signals in a ratio of 2:3?

a.

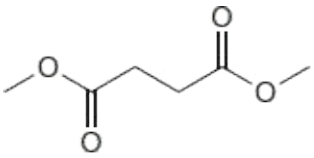
b.

c. 

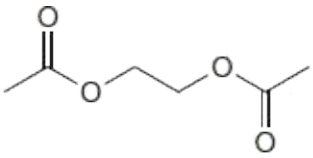
d. 

Problem C.14

Compound A exhibits two signals in its ^{1}H NMR spectrum at 2.64 and 3.69 ppm, and the ratio of the absorbing signals is 2:3. Compound B exhibits two signals in its ^{1}H NMR spectrum at 2.09 and 4.27 ppm, and the ratio of the absorbing signals is 3:2. Which compound corresponds to dimethyl succinate, and which compound corresponds to ethylene diacetate?



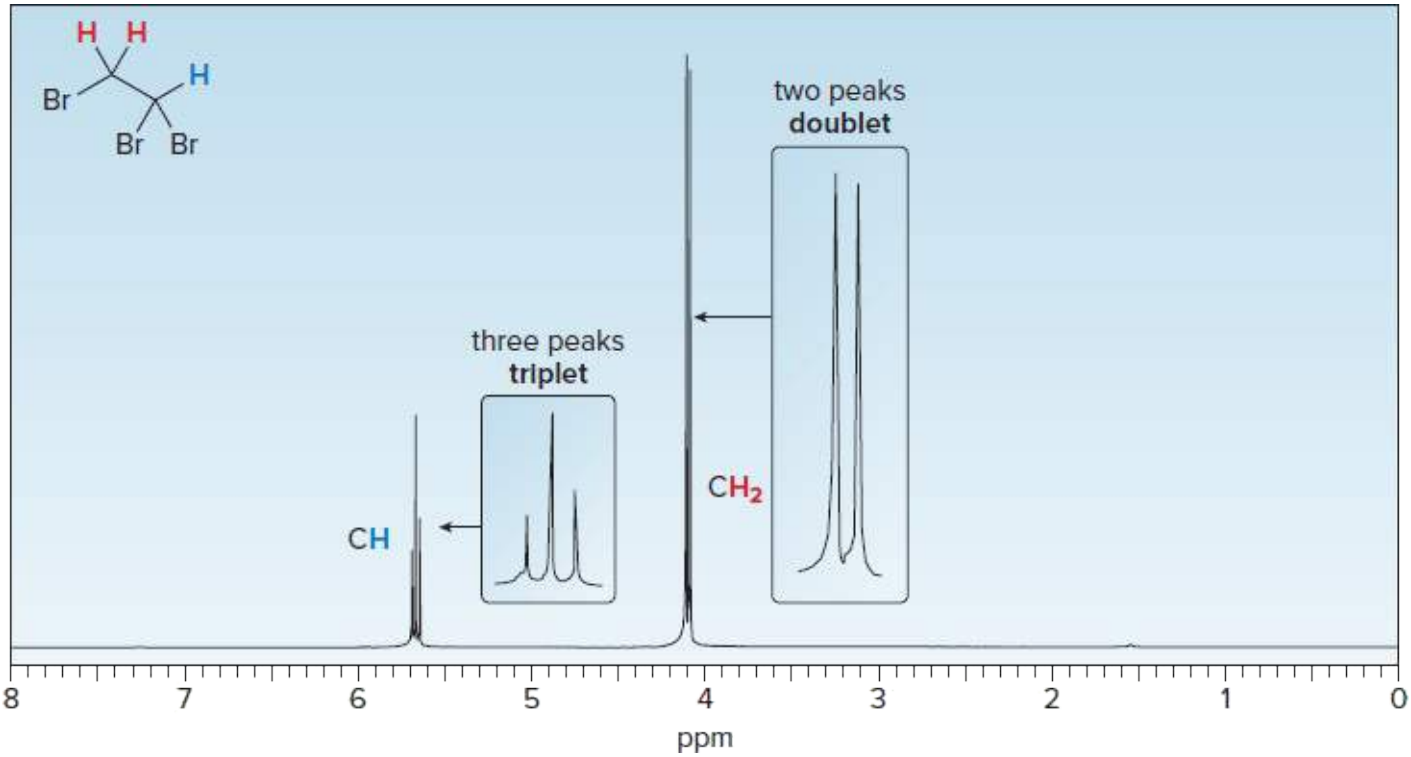
dimethyl succinate



ethylene diacetate

C.6 ^{1}H NMR: Spin-Spin Splitting

The ^{1}H NMR spectra you have seen up to this point have been limited to one or more single absorptions called singlets. In the ^{1}H NMR spectrum of $BrCH_2CHBr_2$, however, the two signals for the two different kinds of protons are each split into more than one peak. The splitting patterns, the result of spin-spin splitting, can be used to determine how many protons reside on the carbon atoms near the absorbing proton.



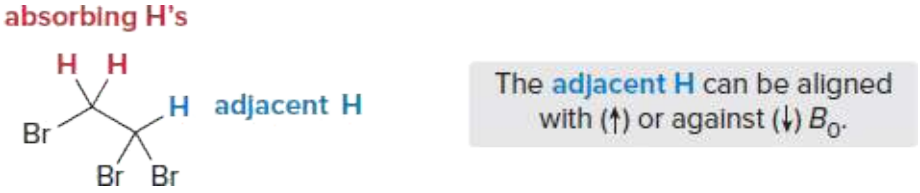
- The CH_2 signal appears as two peaks, called a *doublet*. The relative area under the peaks of a doublet is 1:1.
- The CH signal appears as three peaks, called a *triplet*. The relative area under the peaks of a triplet is 1:2:1.

To understand spin-spin splitting, we must distinguish between the absorbing protons that give rise to an NMR signal, and the adjacent protons that cause the signal to split. The number of adjacent protons determines the observed splitting pattern.

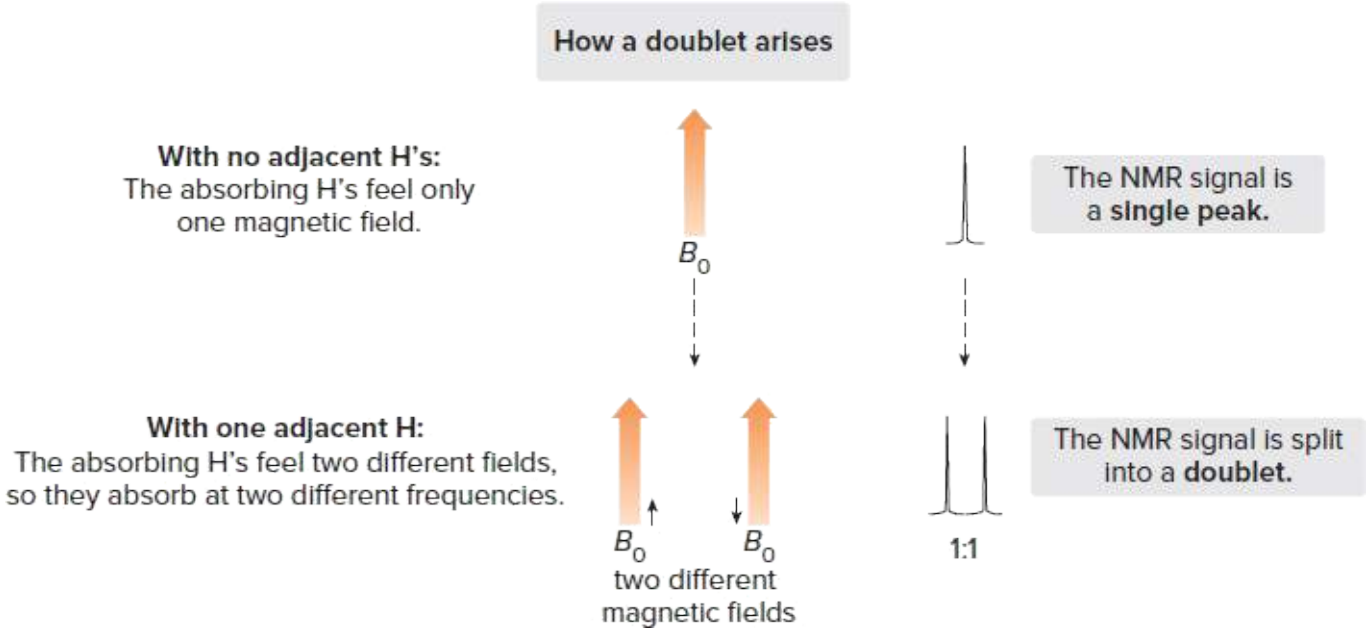
Spin–spin splitting occurs between nonequivalent protons on the same carbon or adjacent carbons. To illustrate how spin-spin splitting arises, we'll examine nonequivalent protons on adjacent carbons, the more common example. Spin-spin splitting arises because protons are little magnets that can be aligned with or against an applied magnetic field, and this affects the magnetic field that a nearby proton feels.

C.6A Splitting: How a Doublet Arises

First, let's examine how the doublet due to the CH2 group in $BrCH_2CHBr_2$ arises. The CH_2 group contains the absorbing protons and the CH group contains the adjacent proton that causes the splitting.

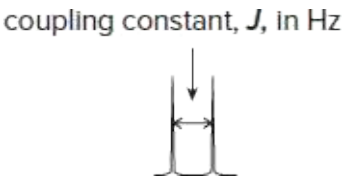


When placed in an applied magnetic field (B_0), the adjacent proton ($CHBr_2$) can be aligned with (↑) or against (↓) B_0. As a result, the absorbing protons (CH_2Br) feel two slightly different magnetic fields—one slightly larger than B_0 and one slightly smaller than B_0. Because the absorbing protons feel two different magnetic fields, they absorb at two different frequencies in the NMR spectrum, thus splitting a single absorption into a doublet.



Keep in mind the difference between an NMR signal and an NMR peak. An NMR signal is the entire absorption due to a particular kind of proton. NMR peaks are contained within a

signal. A doublet constitutes one signal that is split into two peaks.



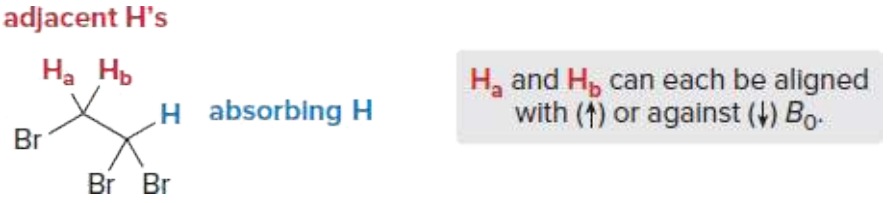
- **One adjacent proton splits an NMR signal into a doublet.**

The two peaks of a doublet are approximately equal in area. The area under both peaks—the entire NMR signal—is due to both protons of the CH_2 group of $BrCH_2CHBr_2$.

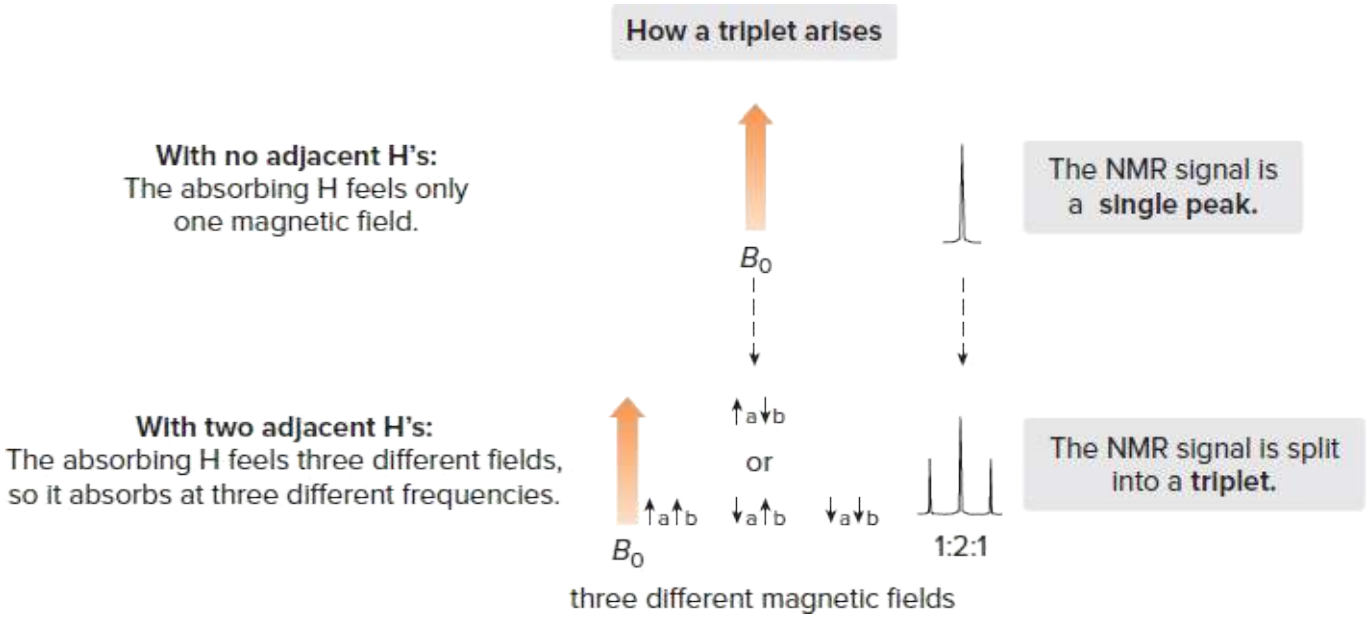
The frequency difference (measured in Hz) between the two peaks of the doublet is called the coupling constant, denoted by *J*. Coupling constants are usually in the range of 0–18 Hz, and are independent of the strength of the applied magnetic field, B_0.

C.6B Splitting: How a Triplet Arises

Now let's examine how the triplet due to the CH group in $BrCH_2CHBr_2$ arises. The CH group contains the absorbing proton and the CH_2 group contains the adjacent protons (H_a and H_b) that cause the splitting.



When placed in an applied magnetic field (B_0), the adjacent protons H_a and H_b can each be aligned with (↑) or against (↓) B_0. As a result, the absorbing proton feels three slightly different magnetic fields—one slightly larger than B_0, one slightly smaller than B_0, and one the same strength as B_0.



Because the absorbing proton feels three different magnetic fields, it absorbs at three different frequencies in the NMR spectrum, thus splitting a single absorption into a triplet. Because there are two different ways to align one proton with B_0 and one proton against B_0—that is, $\uparrow_a\downarrow_b$ and $\downarrow_a\uparrow_b$—the middle peak of the triplet is twice as intense as the two outer peaks, making the ratio of the areas under the three peaks 1:2:1.

- **Two adjacent protons split an NMR signal into a triplet.**

When two protons split each other's NMR signals, they are said to be *coupled*. In $BrCH_2CHBr_2$, the CH proton is coupled to the CH2 protons. The spacing between peaks in a split NMR signal, measured by the *J* value, is *equal* for coupled protons.

C.6C Splitting: The Rules and Examples

Three general rules describe the splitting patterns commonly seen in the ^1H NMR spectra of organic compounds.

Table C.3 Names for a Given Number of Peaks in an NMR Signal

Number of peaks	Name
1	singlet
2	doublet
3	triplet
4	quartet
5	quintet

6	sextet
7	septet
> 7	multiplet

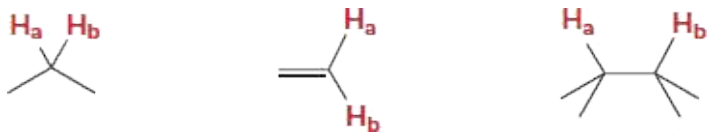
Rule [1] Equivalent protons don't split each other's signals.

Rule [2] A set of *n* nonequivalent protons splits the signal of a nearby proton into *n* + 1 peaks.

- In $BrCH_2CHBr_2$, for example, *one* adjacent CH proton splits an NMR signal into *two* peaks (a doublet), and *two* adjacent CH_2 protons split an NMR signal into *three* peaks (a triplet). Names for split NMR signals containing two to seven peaks are given in Table C.3. An NMR signal having more than seven peaks is called a multiplet.
- The inside peaks of a split NMR signal are always most intense, with the area under the peaks decreasing from the inner to the outer peaks in a given splitting pattern.

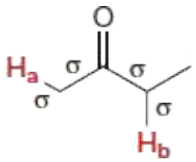
Rule [3] Splitting is observed for nonequivalent protons on the same carbon or adjacent carbons.

If H_a and H_b are not equivalent, splitting is observed in each of the following cases.



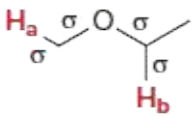
The splitting of an NMR signal reveals the number of nearby nonequivalent protons. It tells nothing about the absorbing proton itself.

Splitting is not generally observed between protons separated by more than three σ bonds. Although H_a and H_b are not equivalent to each other in butan-2-one and ethyl methyl ether, H_a and H_b are separated by four a bonds, so they are too far away to split each other's NMR signals.



butan-2-one
H_a and H_b are separated by **four** σ bonds.

no splitting between H_a and H_b

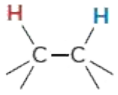
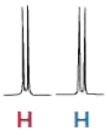
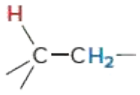
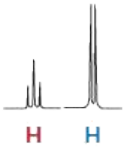
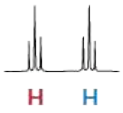
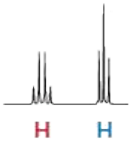
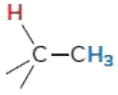
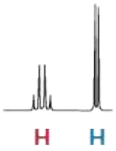


ethyl methyl ether
H_a and H_b are separated by **four** σ bonds.

no splitting between H_a and H_b

Table C.4 illustrates common splitting patterns observed for adjacent nonequivalent protons.

Table C.4 Common Splitting Patterns Observed in ^{1}H NMR

Example	Pattern	Analysis
[1] 		• H: one adjacent H proton ⟶ two peaks ⟶ a **doublet** • H: one adjacent H proton ⟶ two peaks ⟶ a **doublet**
[2] 		• H: two adjacent H protons ⟶ three peaks ⟶ a **triplet** • H: one adjacent H proton ⟶ two peaks ⟶ a **doublet**
[3] $-CH_2CH_2-$		• H: two adjacent H protons ⟶ three peaks ⟶ a **triplet** • H: two adjacent H protons ⟶ three peaks ⟶ a **triplet**
[4] $-CH_2CH_3$		• H: three adjacent H protons ⟶ four peaks ⟶ a **quartet*** • H: two adjacent H protons ⟶ three peaks ⟶ a **triplet**
[5] 		• H: three adjacent H protons ⟶ four peaks ⟶ a **quartet*** • H: one adjacent H proton ⟶ two peaks ⟶ a **doublet**

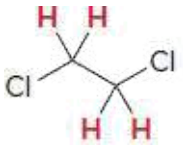
*The relative area under the peaks of a quartet is 1:3:3:1.

Predicting splitting is always a two-step process:

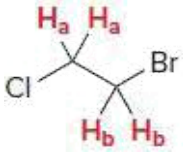
- Determine if two protons are equivalent or different. Only *nonequivalent* protons split each other.
- Determine if two nonequivalent protons are close enough to split each other's signals.

Splitting is observed only for nonequivalent protons on the *same* carbon or *adjacent* carbons.

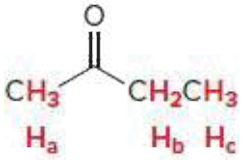
Several examples of spin-spin splitting in specific compounds illustrate the result of this two-step strategy.



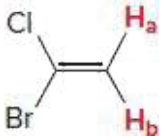
- All protons are equivalent, so there is no splitting and the NMR signal is one singlet.



- There are two NMR signals. H_a and H_b are nonequivalent protons bonded to adjacent C atoms, so they are close enough to split each other's NMR signals. The H_a signal is split into a triplet by the two H_b protons. The H_b signal is split into a triplet by the two H_a protons.



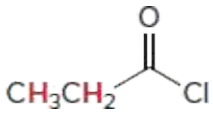
- There are three NMR signals. H_a has no adjacent nonequivalent protons, so its signal is a singlet. The H_b signal is split into a quartet by the three H_c protons. The H_c signal is split into a triplet by the two H_b protons.

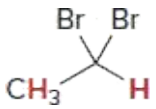


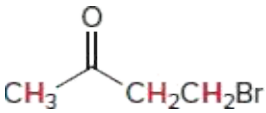
- There are two NMR signals. H_a and H_b are nonequivalent protons on the same carbon, so they are close enough to split each other's NMR signals. The H_a signal is split into a doublet by H_b. The H_b signal is split into a doublet by H_a.

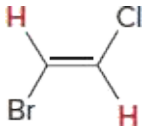
Problem C.15

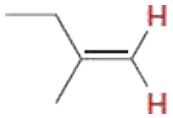
Into how many peaks will each proton shown in red be split?

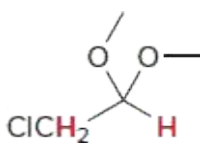
a. 

b. 

c. 

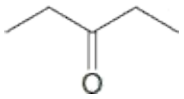
d. 

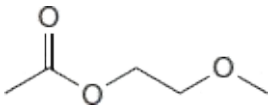
e. 

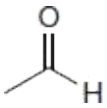
f. 

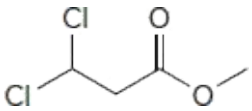
Problem C.16

For each compound, give the number of ^{1}H NMR signals and then determine how many peaks are present for each NMR signal.

a. 

b. 

c. 

d. 

Problem C.17

Sketch the NMR spectrum of CH_3CH_2Cl, giving the approximate location of each NMR signal.

C.7 More-Complex Examples of Splitting

Up to now you have studied examples of spin-spin splitting where the absorbing proton has nearby protons on *one* adjacent carbon only. What happens when the absorbing proton has nonequivalent protons on *two* adjacent carbons? Different outcomes are possible, depending on whether the adjacent nonequivalent protons are *equivalent to* or *different from* each other.

For example, 2-bromopropane [$(CH_3)_2CHBr$] has two types of protons—H_a and H_b—so it exhibits two NMR signals, as shown in Figure C.6.

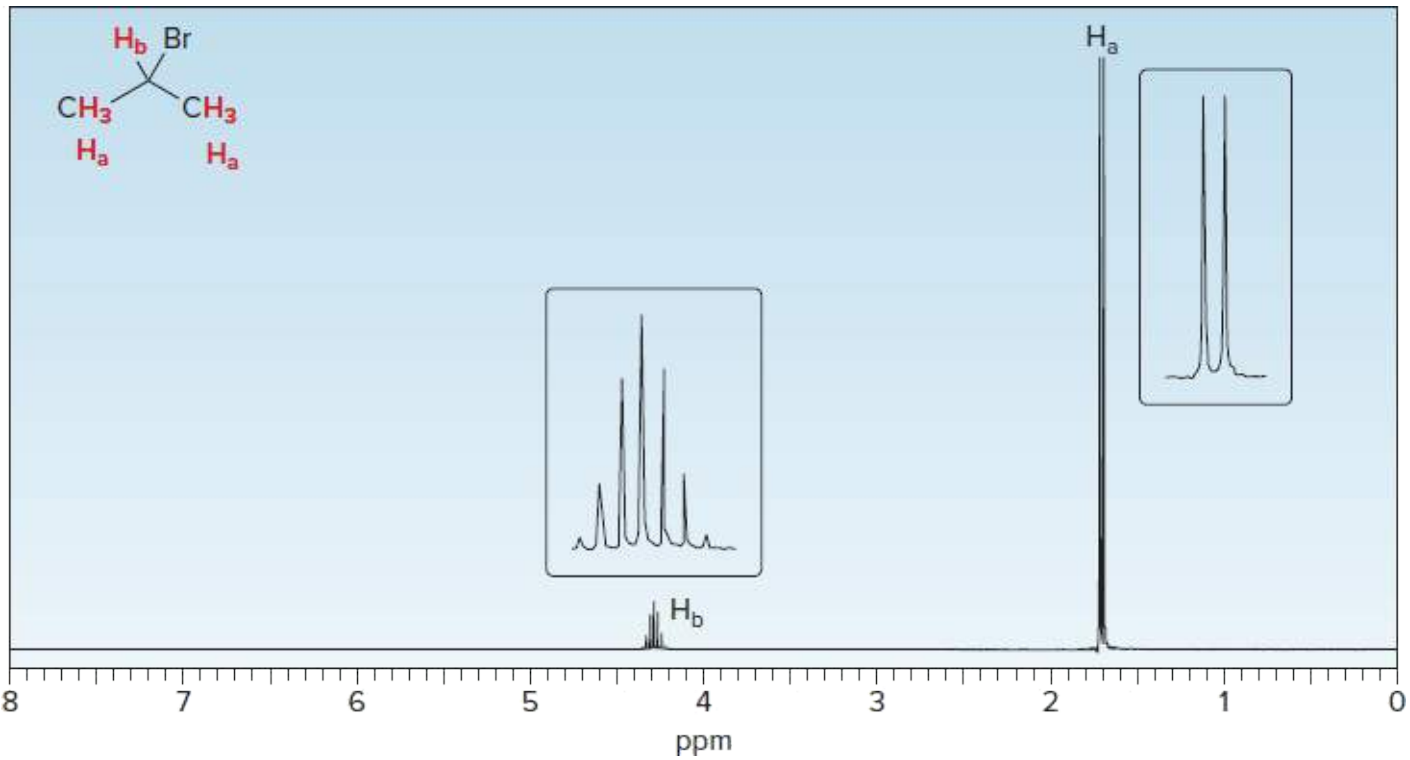


Figure C.6 **The ^{1}H NMR spectrum of 2-bromopropane, $(CH_3)_2CHBr$**

- The H_a protons have only one adjacent nonequivalent proton (H_b), so they are split into two peaks, a doublet.
- H_b has three H_a protons on each side. Because the six H_a protons are *equivalent to each other*, the $n + 1$ rule can be used to determine splitting: $6 + 1 = 7$ peaks, a septet.

This is a specific example of a general rule:

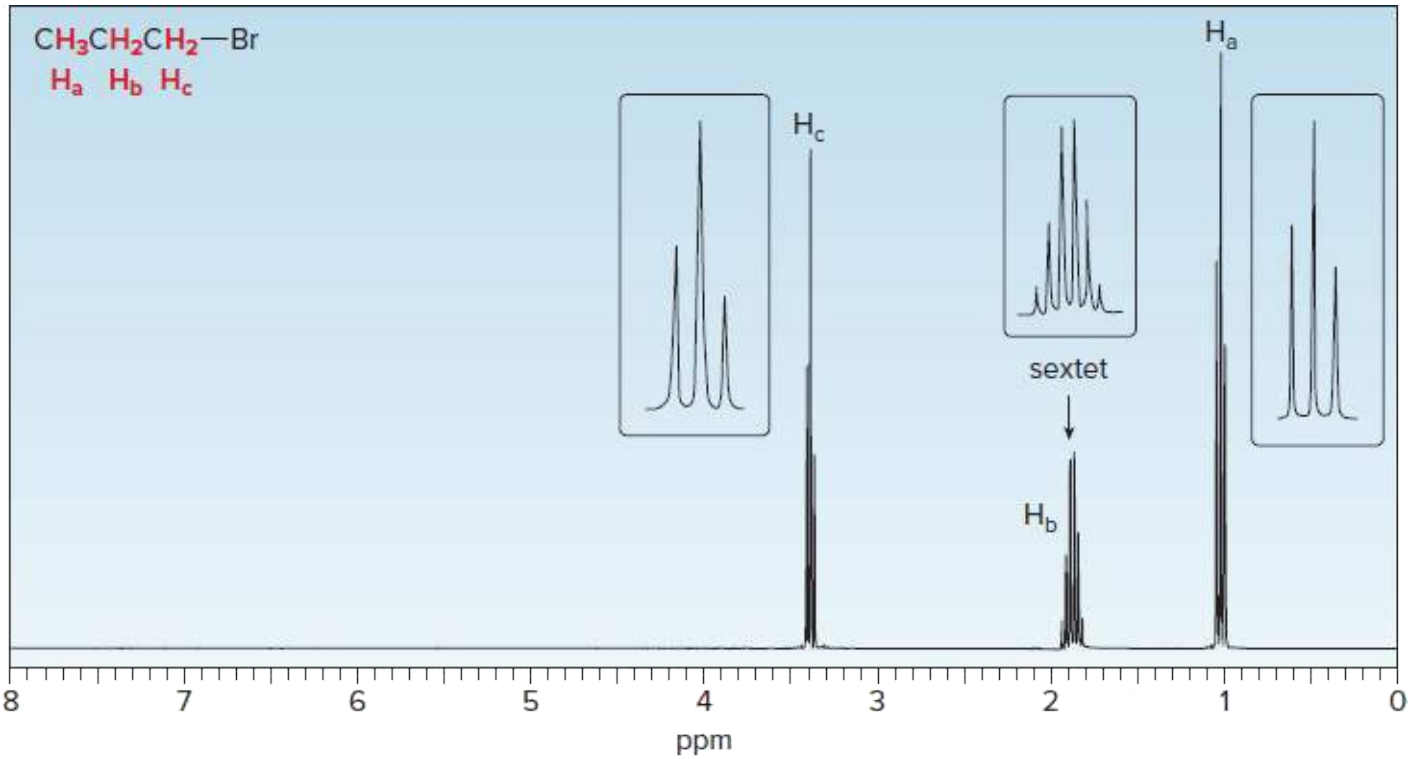
- **Whenever two (or three) sets of adjacent protons are *equivalent to each other*, use the *n* + 1 rule to determine the splitting pattern.**

When an absorbing proton is flanked by two sets of adjacent protons that are *not equivalent to each other*, the outcome depends on the coupling constant (J) between the absorbing proton and its neighboring protons.

Let us begin with the result that occurs in flexible alkyl chains; that is, the absorbing and adjacent protons are *not* bonded to a ring or double bond, as illustrated with 1-bromopropane, $CH_3CH_2CH_2Br$.

$$\underset{H_a\ \ H_b\ \ H_c}{CH_3CH_2CH_2{-}Br}$$

$CH_3CH_2CH_2Br$ has three different types of protons—H_a, H_b, and H_c— so it exhibits three NMR signals. The H_a and H_c signals are both triplets because they are adjacent to two H_b protons, as shown in Figure C.7.



- H_a and H_c are both triplets.
- The signal for H_b appears as a multiplet of six peaks (a sextet), due to peak overlap; the number of peaks = $n + m + 1 = 3 + 2 + 1 = 6$ peaks.

Figure C.7 **The ^{1}H NMR spectrum of 1-bromopropane, $CH_3CH_2CH_2Br$**

What splitting is observed for the H_b protons, which have protons on both adjacent carbons, and H_a and H_c are not equivalent to each other? In acyclic molecules of this sort, which are not constrained by the geometry of a ring or double bond, the coupling constants between the absorbing proton and both sets of adjacent protons are equal (or close to it); that is, $J_{ab} = J_{bc}$. In this case, even though the H_a and H_c protons are not equivalent to each other, we can just add the number of protons on both adjacent carbons together. The 3 H_a protons and the 2 H_c protons split the NMR signal of the H_b protons into 3 + 2 + 1 = 6 peaks, a sextet. This is a specific example of a general phenomenon:

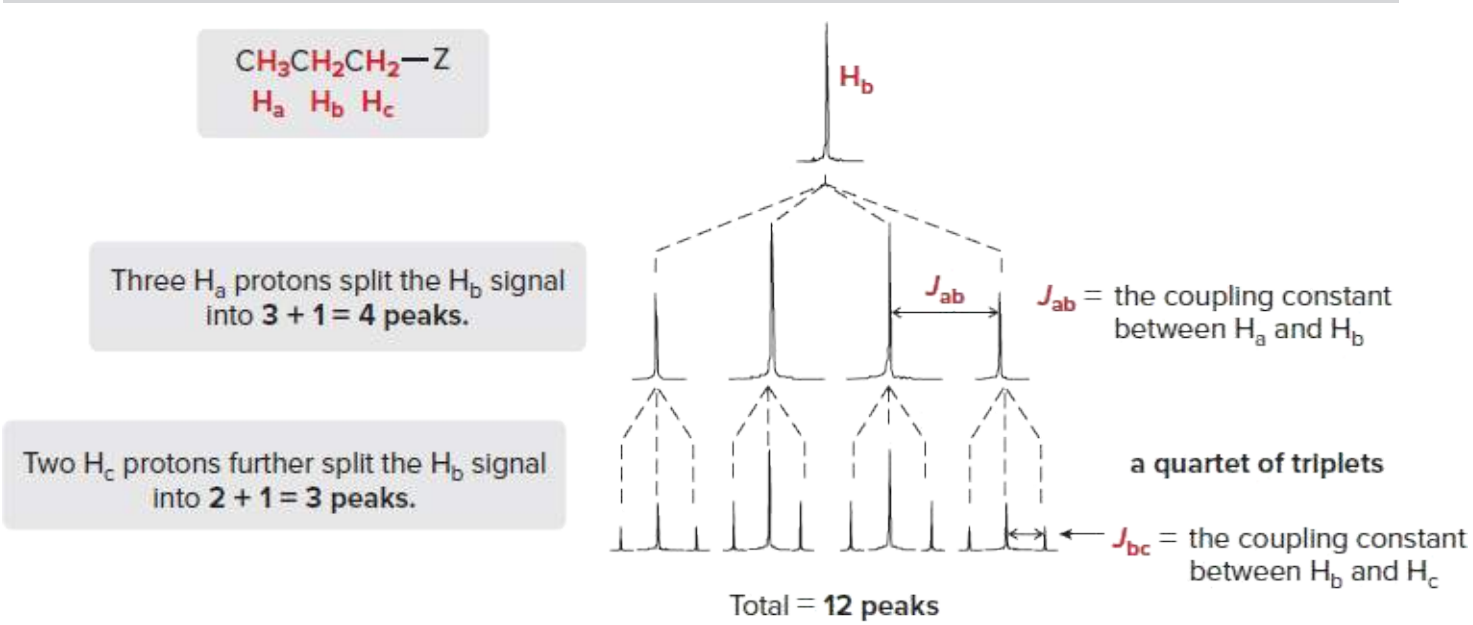
- **In a flexible alkyl chain, the *n* alkyl protons on one adjacent carbon and the *m* protons on the other adjacent carbon split the observed signal into *n* + *m* + 1 peaks.**

Now let's consider the splitting pattern of the H_b protons in the general compound $CH_3CH_2CH_2Z$ when the coupling constants between the absorbing proton H_b and both sets of adjacent protons (H_a and H_c) are different; that is, $J_{ab} \neq J_{bc}$.

$$\underset{H_a\ \ H_b\ \ H_c}{CH_3CH_2CH_2{-}Z}$$

In this case, to determine the splitting of the H_b signal, we must consider the effect of the H_a protons and the H_c protons *separately*. The three H_a protons split the H_b signal into four peaks and the two H_c protons split each of these four peaks into three peaks—that is, the NMR signal due to H_b consists of $4 \times 3 = 12$ peaks. Figure C.8 shows a splitting diagram that illustrates how these 12 peaks arise. This is a specific example of a general phenomenon:

- **When two sets of adjacent protons are *different from each other* (*n* protons on one adjacent carbon and *m* protons on the other), the number of peaks in an NMR signal is (*n* + 1)(*m* + 1).**



- The H_b signal is split into 12 peaks, a quartet of triplets. The number of peaks actually seen for the signal depends on the relative size of the coupling constants, J_{ab} and J_{bc}. When $J_{ab} >> J_{bc}$, as drawn in this diagram, all 12 lines of the pattern are visible. When J_{ab} and J_{bc} are similar in magnitude, peaks overlap and fewer lines are observed.

Figure C.8 **A splitting diagram for the H_b protons in $CH_3CH_2CH_2Z$**

The three possibilities for determining splitting patterns when an absorbing proton has nonequivalent protons on two adjacent carbons are shown with examples in Sample Problem

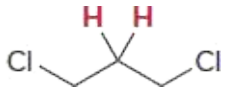
Complex splitting of this sort is seen with protons on carbon-carbon double bonds in Section C.8. Sample Problem C.7 illustrates how to determine splitting in three different compounds.

The $(n + 1)(m + 1)$ rule in splitting always gives the *maximum* number of peaks that is possible when an absorbing proton has n adjacent protons on one side and m protons on the other, and the coupling constants between nearby protons are different. As the difference between J values decreases, peaks overlap and fewer than the maximum number of peaks is observed.

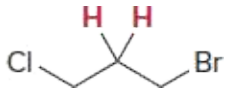
Sample Problem C.7 Determining the Number of Peaks in an NMR Signal

How many peaks are present in the NMR signal of the labeled protons of each compound?

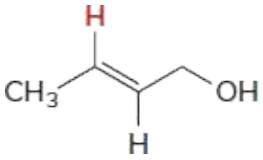
a.



b.



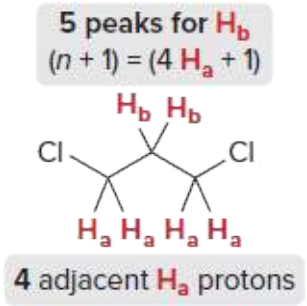
c.



Solution

When an absorbing proton is flanked by two sets of adjacent protons, there are three possibilities for determining the splitting pattern, as seen in parts (a), (b), and (c).

a.



- **H_b has two H_a protons on each adjacent C. Because the four H_a protons are equivalent to each other, the n + 1 rule can be used to determine splitting: 4 + 1 = 5 peaks, a quintet.**
- **Even though H_a and H_c are not equivalent to each other, they are bonded to a flexible alkyl chain. In this case, we can add the**

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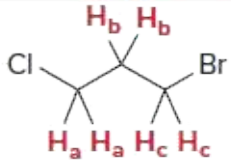
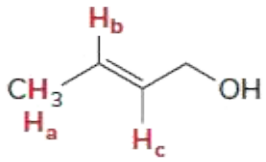
b. 5 peaks for H_b
$(n + m + 1) = (2\ H_a + 2\ H_c + 1)$



2 H_a and 2 H_c protons bonded to an alkyl chain

number of protons on both adjacent carbons together, so the number of peaks for H_b = n + m + 1 = 2 + 2 + 1 = 5 peaks.

c. 8 peaks for H_b
$(n + 1)(m + 1) = (3\ H_a + 1)(1\ H_c + 1)$



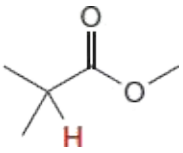
3 H_a protons and 1 H_c proton
H_b is bonded to a C=C.

- H_b has three H_a protons on one adjacent C and one H_c proton on the other. Because H_a and H_c are not equivalent to each other, the number of peaks for H_b = (n + 1) (m + 1) = (3 + 1)(1 + 1) = 8 peaks.

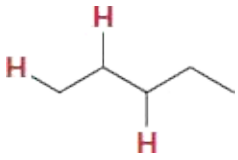
Problem C.18

How many peaks are present in the NMR signal of each labeled proton?

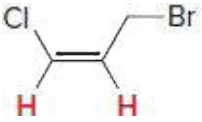
a.



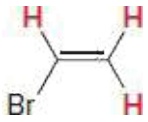
b.



c.



d.



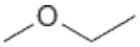
More Practice:

Try Problems C.37b, C.43, C.44, C.55c, C.56b, C.57e.

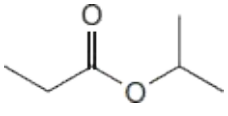
Problem C.19

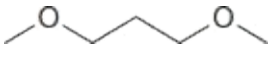
Describe the ^{1}H NMR spectrum of each compound. State how many NMR signals are present, the splitting pattern for each signal, and the approximate chemical shift.

a.



b.

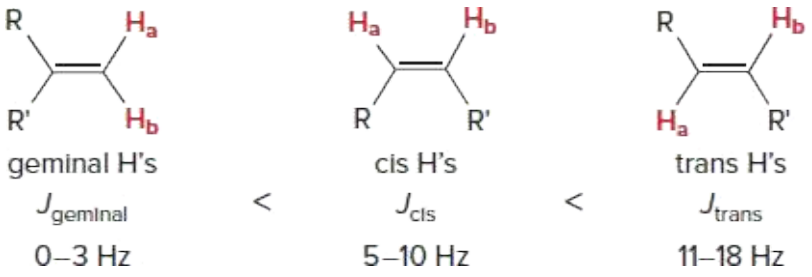


c. 

d.

C.8 Spin–Spin Splitting in Alkenes

Protons on carbon–carbon double bonds often give characteristic splitting patterns. A disubstituted double bond can have two geminal protons (on the same carbon atom), two cis protons, or two trans protons. When these protons are different, each proton splits the NMR signal of the other, so that each proton appears as a doublet. The magnitude of the coupling constant J for these doublets depends on the arrangement of hydrogen atoms.



Thus, the E and Z isomers of 3-chloropropenoic acid both exhibit two doublets for the two alkenyl protons, but the coupling constant is larger when the protons are trans compared to when the protons are cis, as shown in Figure C.9.

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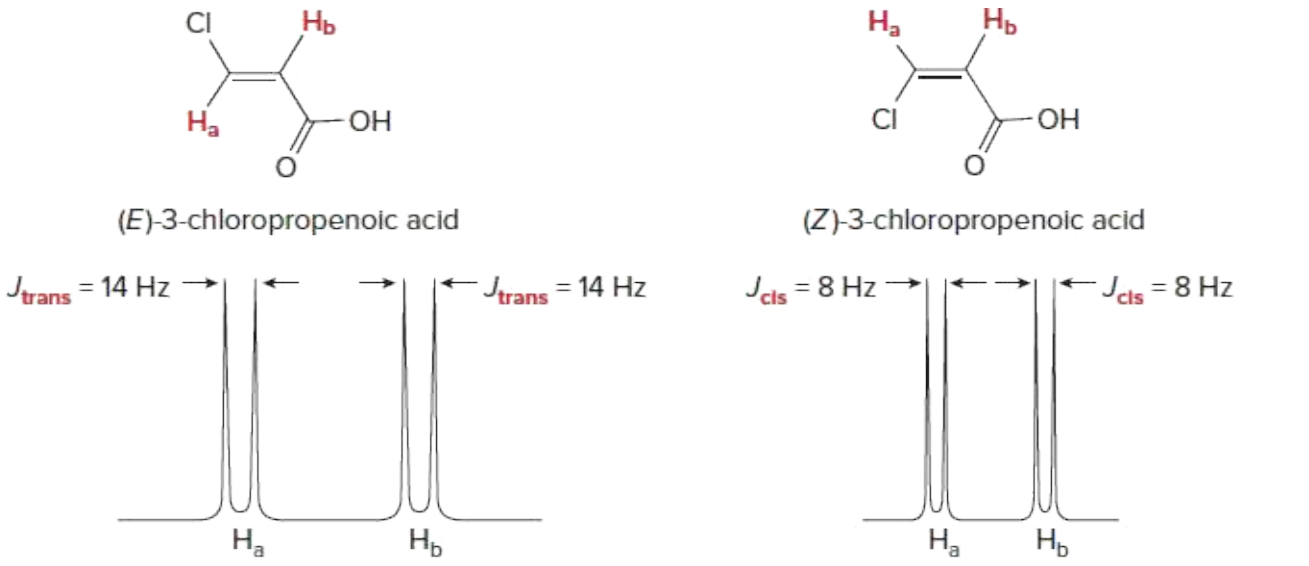


- Although both (*E*)- and (*Z*)-3-chloropropenoic acid show two doublets in their ^{1}H NMR spectra for their alkenyl protons, $J_{trans} > J_{cis}$.

Figure C.9 **^{1}H NMR spectra for the alkenyl protons of (*E*)- and (*Z*)-3-chloropropenoic acid**

When a double bond is monosubstituted, there are three nonequivalent protons, and

the pattern is more complicated because all three protons are coupled to each other. For example, vinyl acetate (CH_2=$CHOCOCH_3$) has four different types of protons, three of which are bonded to the double bond. Besides the singlet for the CH_3 group, each proton on the double bond is coupled to two other different protons on the double bond, giving the spectrum in Figure C.10. Because the protons are bonded to a double bond, we determine the splitting using the $(n + 1)(m + 1)$ rule.

- H_b has two nearby nonequivalent protons that split its signal, the geminal proton H_c and the trans proton H_d. H_d splits the H_b signal into a doublet, and the H_c proton splits the doublet into two doublets. This pattern of four peaks is called a doublet of doublets.
- H_c has two nearby nonequivalent protons that split its signal, the geminal proton H_b and the cis proton H_d. Hd splits the H_c signal into a doublet, and the H_b proton splits the doublet into two doublets, forming another doublet of doublets.
- H_d has two nearby nonequivalent protons that split its signal, the trans proton H_b and the cis proton H_c. H_b splits the H_d signal into a doublet, and the H_c proton splits the doublet into two doublets, forming another doublet of doublets.

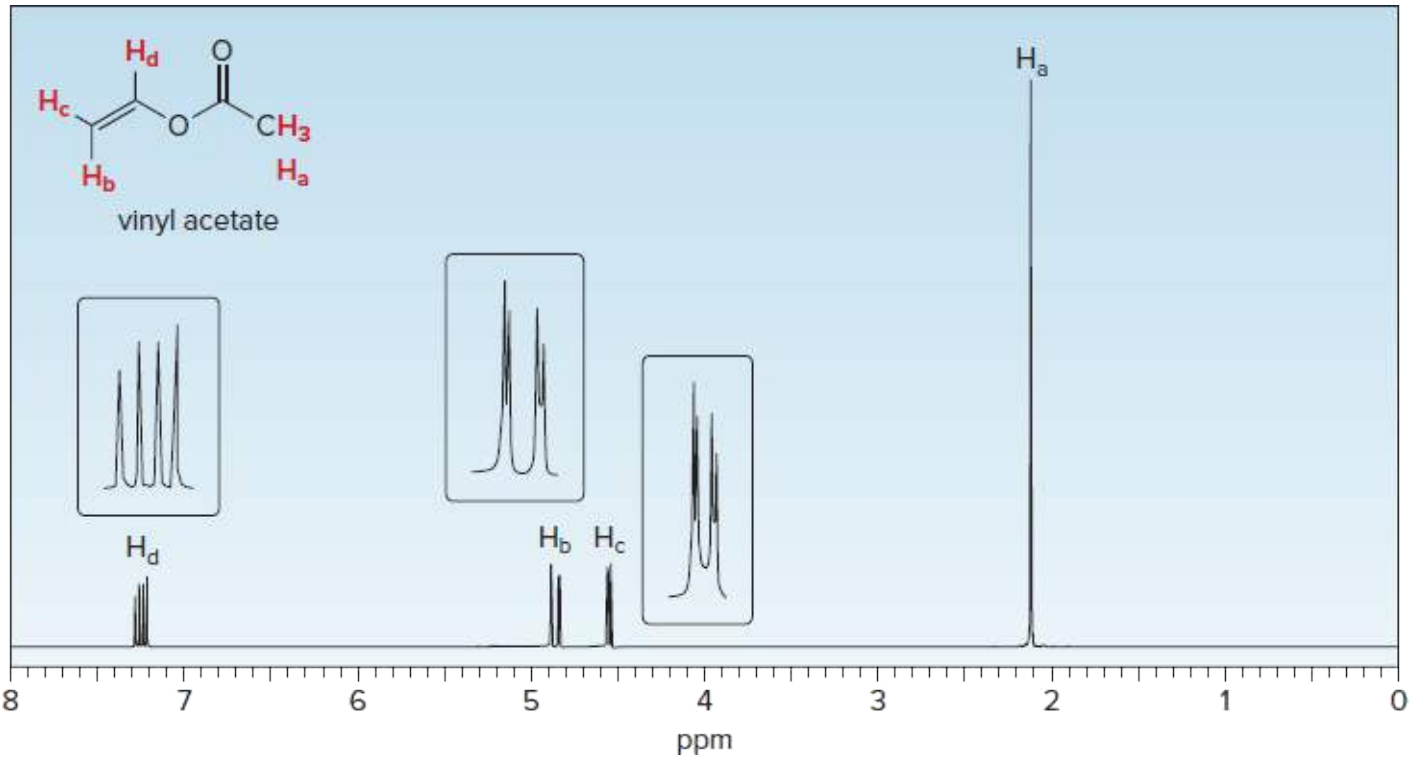


Figure C.10 The ^{1}H NMR spectrum of vinyl acetate (CH_2=$CHOCOCH_3$)

Vinyl acetate is polymerized to poly(vinyl acetate) (Problem 13.25), a polymer used in paints, glues, and adhesives.

Splitting diagrams for the three alkenyl protons in vinyl acetate are drawn in Page 587 Figure C.11. Note that each pattern is different in appearance because the magnitude of the coupling constants forming them is different.

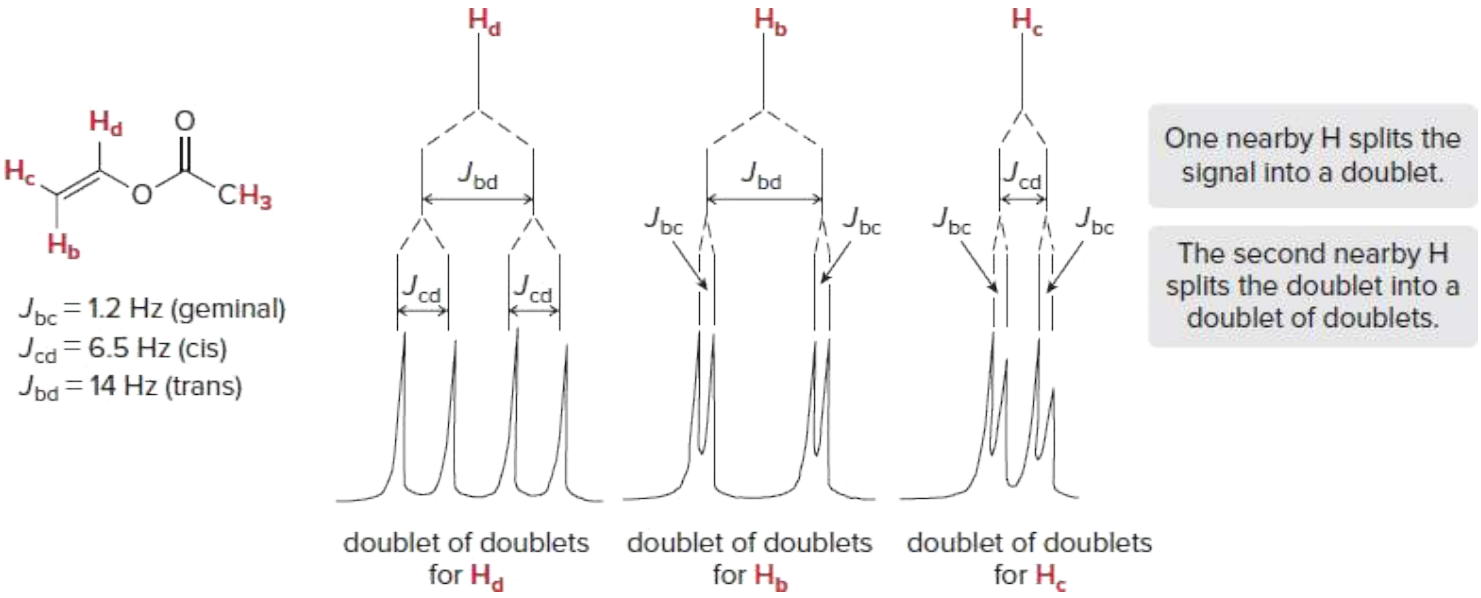
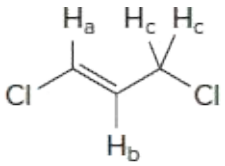


Figure C.11 **Splitting diagram for the alkenyl protons in vinyl acetate (CH_2=CHOCOCH$_3$)**

Problem C.20

Draw a splitting diagram for H_b in *trans*-1,3-dichloropropene, given that J_{ab} = 13.1 Hz and J_{bc} = 7.2 Hz.



trans-1,3-dichloropropene

Problem C.21

Identify A and B, isomers of molecular formula $C_3H_4Cl_2$, from the given ^{1}H NMR data: Compound A exhibits signals at 1.75 (doublet, 3 H, *J* = 6.9 Hz) and 5.89 (quartet, 1 H, *J* = 6.9 Hz) ppm. Compound B exhibits signals at 4.16 (singlet, 2 H), 5.42 (doublet, 1 H, *J* = 1.9 Hz), and 5.59 (doublet, 1 H, *J* = 1.9 Hz) ppm.

C.9 Other Facts About ^{1}H NMR Spectroscopy

C.9A OH Protons

- **Under usual conditions, an OH proton does not split the NMR signal of adjacent protons.**
- **The signal due to an OH proton is not split by adjacent protons.**

Ethanol (CH_3CH_2OH), for example, has three different types of protons, so there are three signals in its ^1H NMR spectrum, as shown in Figure C.12.

- The H_a signal is split by the two H_b protons into three peaks, a triplet.
- The H_b signal is split by only the three H_a protons into four peaks, a quartet. The adjacent OH proton does *not* split the signal due to H_b.
- H_c is a singlet because OH protons are *not* split by adjacent protons.

Why is a proton bonded to an oxygen atom a singlet in a ^1H NMR spectrum? Protons on electronegative elements rapidly exchange between molecules in the presence of trace amounts of acid or base. It is as if the CH_2 group in ethanol never "feels" the presence of the OH proton, because the OH proton is rapidly moving from one molecule to another. We therefore see a peak due to the OH proton, but it is a single peak with no splitting. This phenomenon usually occurs with NH and OH protons.

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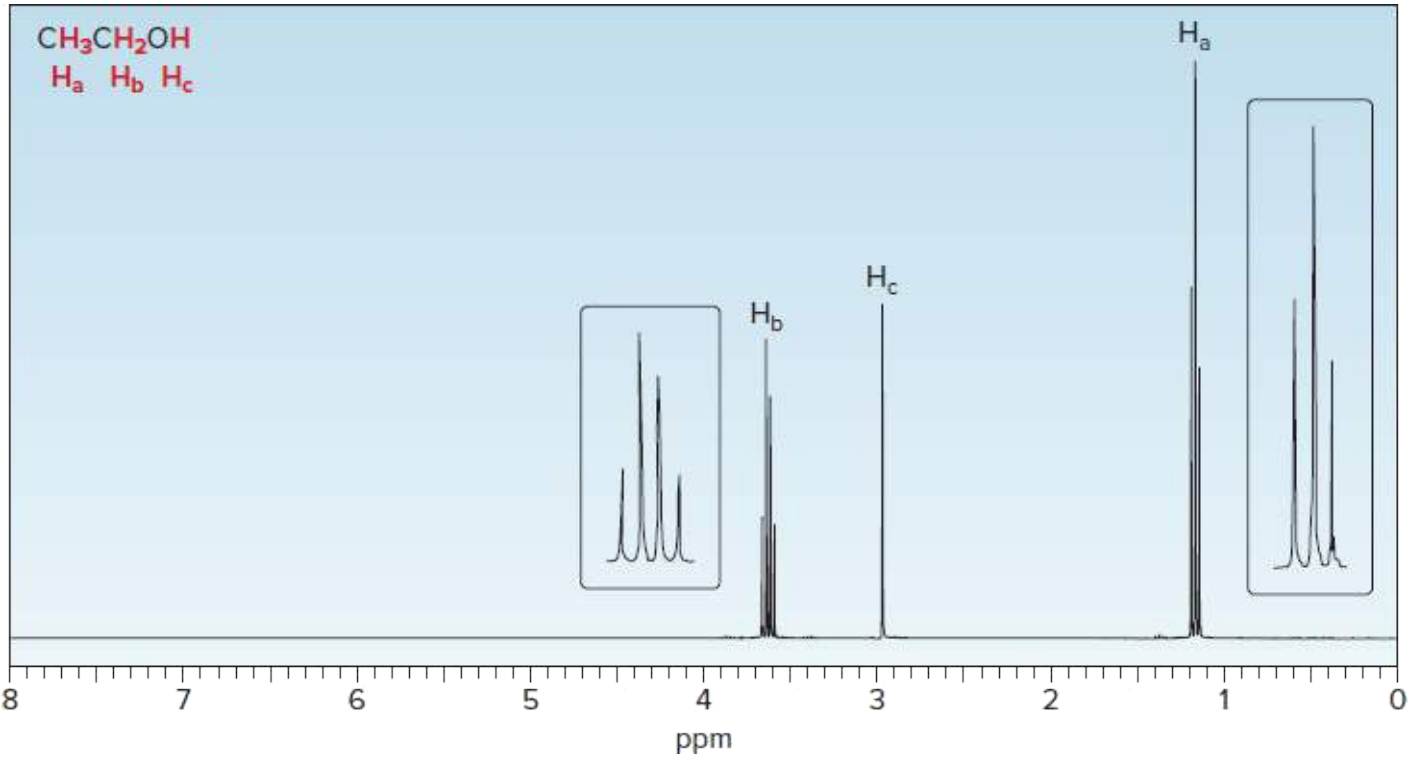
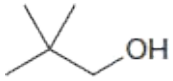


Figure C.12 **The ^1H NMR spectrum of ethanol (CH_3CH_2OH)**

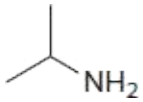
Problem C.22

How many signals are present in the ^1H NMR spectrum for each molecule? What splitting

is observed in each signal?

a. 

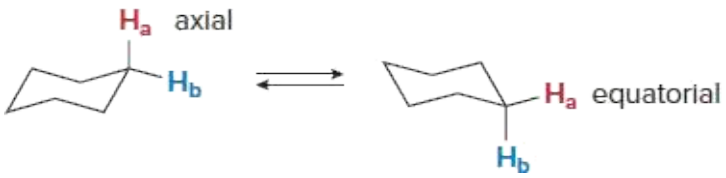
b.

c. 

C.9B Cyclohexane Conformations

How do the rotation around carbon–carbon a bonds and the ring flip of cyclohexane rings affect an NMR spectrum? Because these processes are rapid at room temperature, an NMR spectrum records an average of all conformations that interconvert.

Thus, even though each cyclohexane carbon has two different types of hydrogens—one axial and one equatorial—the two chair forms of cyclohexane rapidly interconvert them, and an NMR spectrum shows a single signal for the average environment that it "sees."

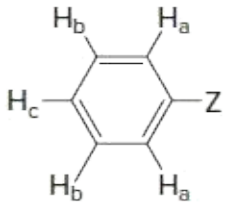


Axial and equatorial H's rapidly interconvert. NMR sees an average environment and shows one signal.

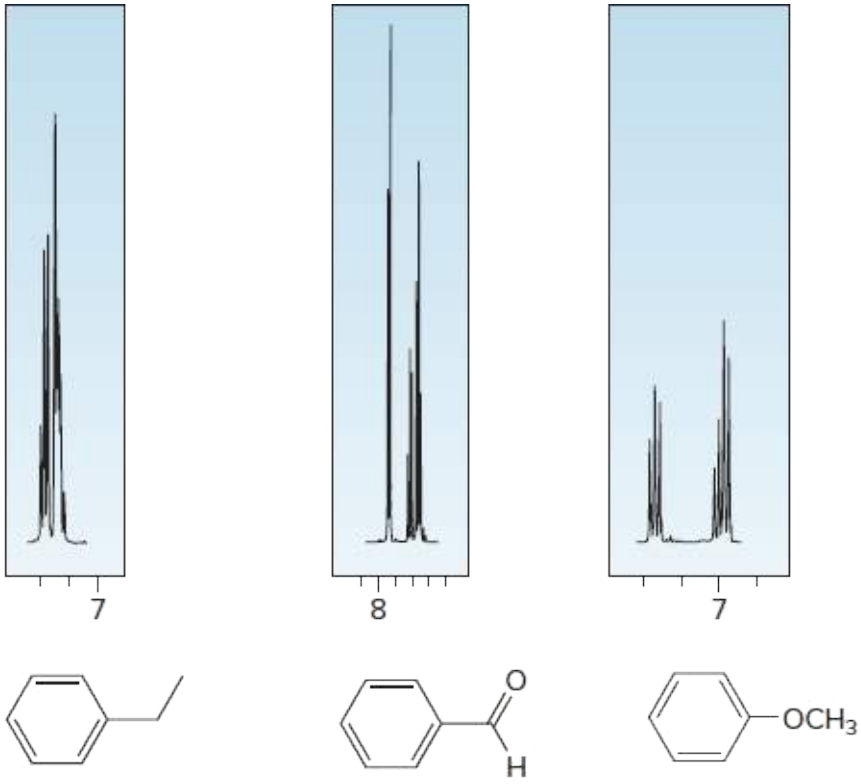
We will learn more about the spectroscopic absorptions of benzene derivatives in Chapter 15.

C.9C Protons on Benzene Rings

Benzene has six equivalent, deshielded protons and exhibits a single peak in its ^{1}H NMR spectrum at 7.27 ppm. Monosubstituted benzene derivatives—that is, benzene rings with one H atom replaced by another substituent Z—contain five deshielded protons that are no longer all equivalent to each other. The identity of Z determines the appearance of this region of a ^{1}H NMR spectrum (6.5–8 ppm), as shown in Figure C.13. We will not analyze the splitting patterns observed for the ring protons of monosubstituted benzenes.



A monosubstituted benzene ring has three different types of H atoms: H_a, H_b, and H_c.

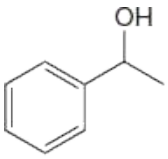


- The appearance of the signals in the 6.5–8 ppm region of the ^{1}H NMR spectrum depends on the identity of Z in C_6H_5Z.

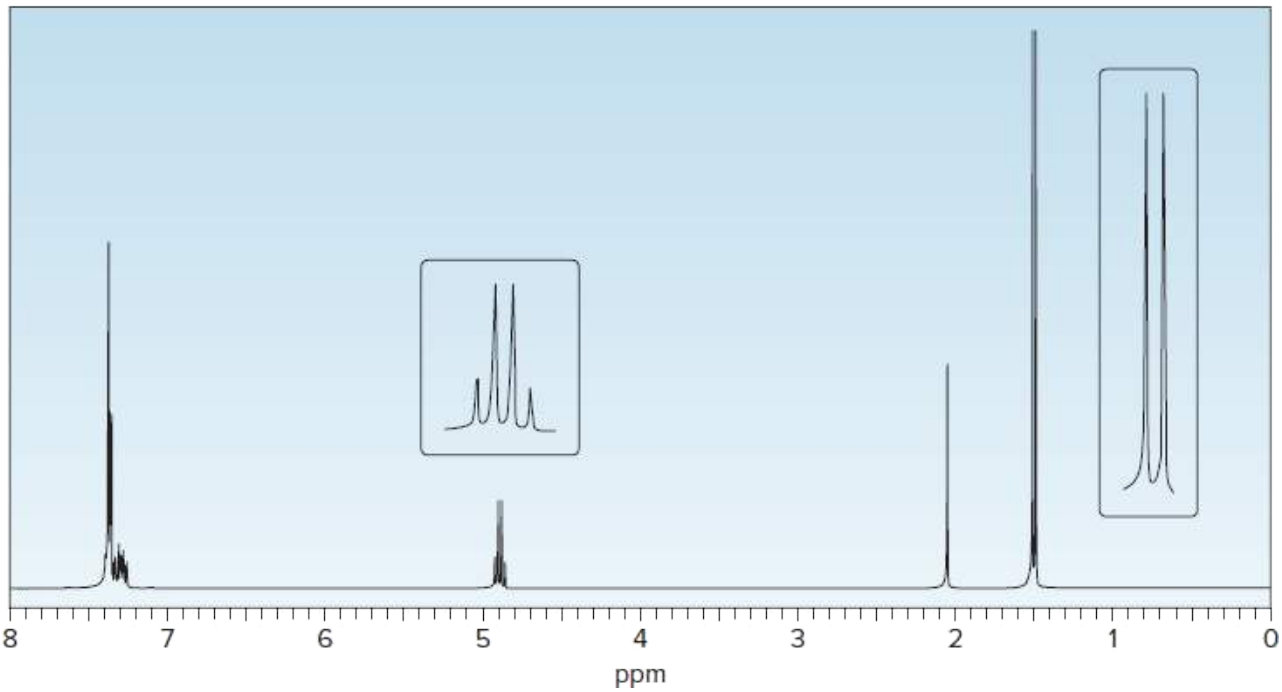
Figure C.13 **The 6.5–8 ppm region of the ^{1}H NMR spectrum of three benzene derivatives**

Problem C.23

What protons in alcohol A give rise to each signal in its ^{1}H NMR spectrum? Explain all splitting patterns observed for absorptions between 0 to 7 ppm.

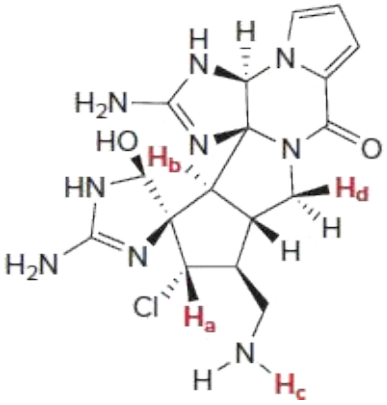


A



Problem C.24

How many peaks are observed in the ^{1}H NMR signal for each proton shown in red in palau'amine, the complex chapter-opening molecule?

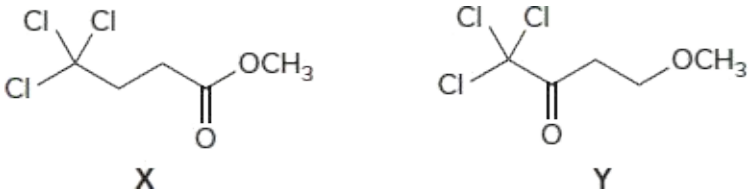


C.10 Using ^{1}H NMR to Identify an Unknown

^{1}H NMR Spectroscopy is a powerful technique that can be used to distinguish between isomers, as shown in Sample Problem C.8.

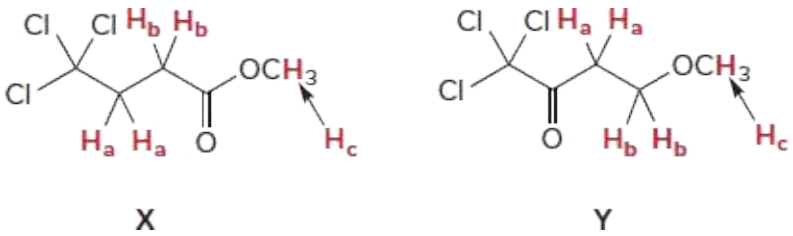
Sample Problem C.8 Using ^{1}H NMR Spectroscopy to Distinguish Between Compounds

How could ^{1}H NMR spectroscopy be used to distinguish between compounds X and Y?



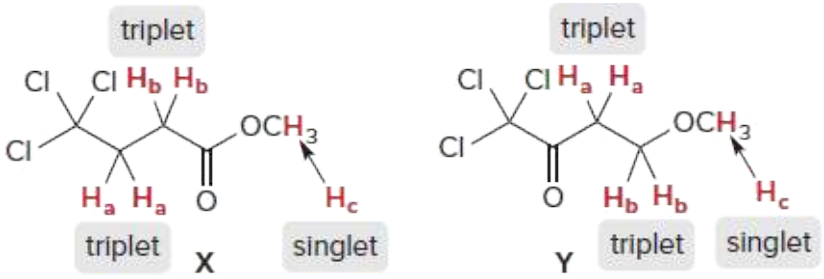
Solution

[1] Determine whether the number of signals expected for each compound differs.



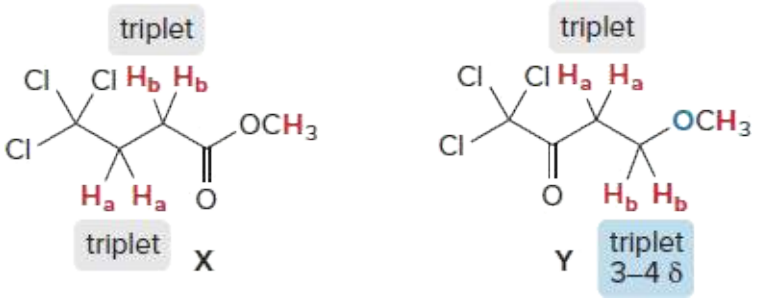
In this example, both X and Y have three types of H's resulting in three signals, so another point of difference must be found.

[2] Determine the splitting pattern for each signal.



The ^{1}H NMR signals for both compounds consist of a singlet and two triplets.

[3] Determine the approximate chemical shift for one or more types of H's.

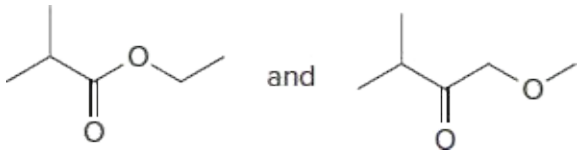


Only one chemical shift difference is needed to distinguish compounds. Y has H_b protons on a carbon bonded to an electronegative O atom, so these protons are deshielded and absorb in the 3–4 δ range. Neither of the triplets in X is located on a carbon that is also bonded to an electronegative atom, so no triplet in X absorbs in this region. Thus approximate chemical shift values can be used to distinguish between these two isomers.

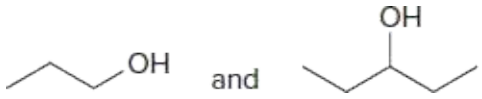
Problem C.25

How could ^{1}H NMR spectroscopy be used to distinguish between each pair of compounds?

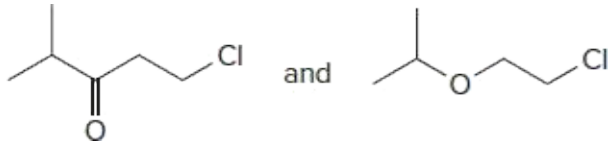
a.



b.



c.



More Practice:

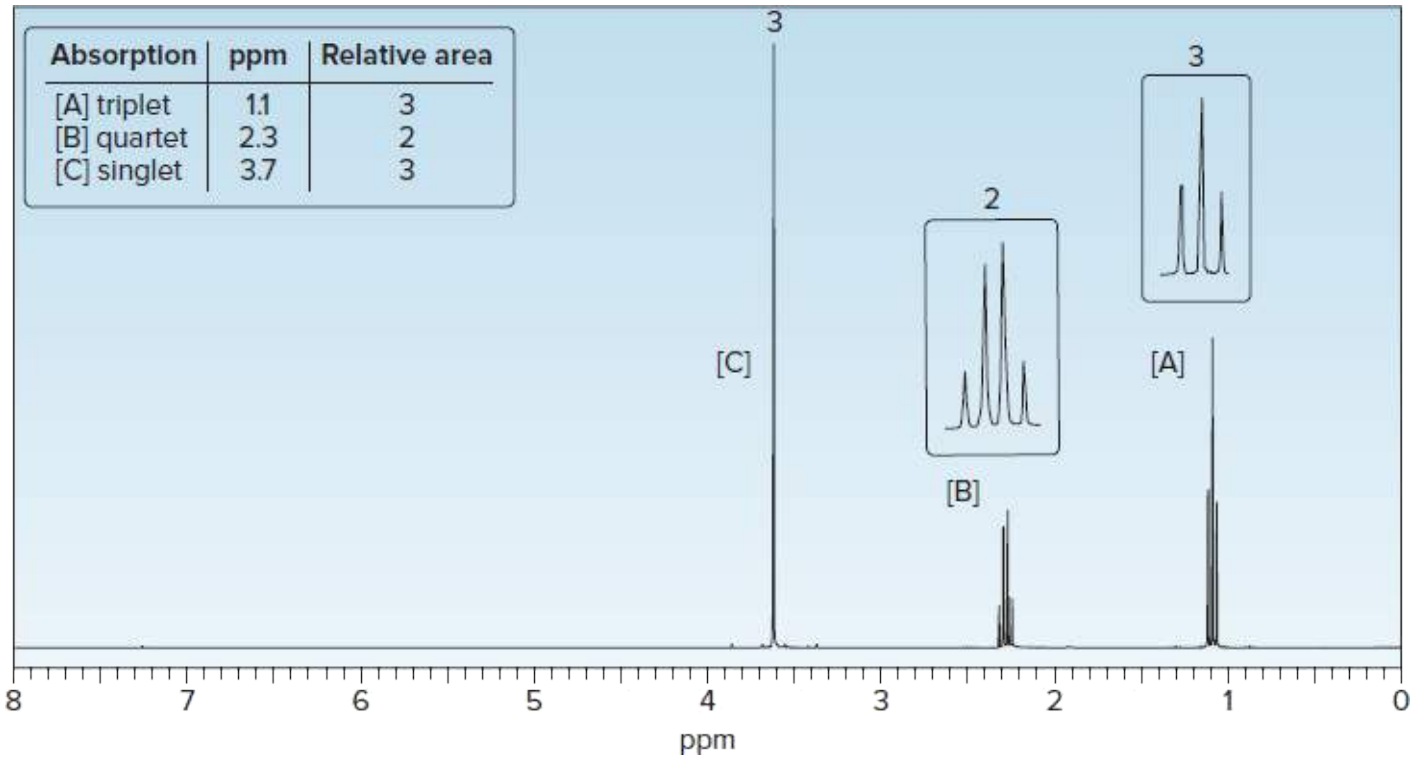
Try Problems C.52, C.54.

Combined with mass spectrometry (which gives a compound's molecular formula) and infrared spectroscopy (which identifies a compound's functional group), we can then use its ^{1}H NMR spectrum to determine the structure of an unknown. A suggested procedure is illustrated for compound X, whose molecular formula ($C_4H_8O_2$) and functional group (C=O) were determined in Section B.5.

How To Use ^{1}H NMR Data to Determine a Structure

Example

Using its ^{1}H NMR spectrum, determine the structure of an unknown compound X that has molecular formula $C_4H_8O_2$ and contains a C=O absorption in its IR spectrum.



Step [1] **Determine the number of different kinds of protons.**

- **The number of NMR signals equals the number of different types of protons.**
- **This molecule has three NMR signals ([A], [B], and [C]) and therefore three types of protons (H_a, H_b, and H_c).**

Step [2] **Use the relative area to determine the number of H atoms giving rise to each signal.**

- **The relative area (printed on top of each signal) gives the *ratio* of absorbing protons responsible for each signal. In this case,**

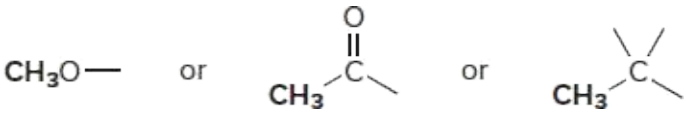
the ratio is 3:2:3 for the signals from left to right.

- **When the sum of the relative areas *equals* the number of H's in the molecular formula, the relative area gives the number of absorbing H's responsible for the NMR signal. In this example, the sum of the relative areas is 3 + 2 + 3 = 8, and the unknown has 8 H's, so the signals are due to 3 H's, 2 H's, and 3 H's from left to right in the spectrum.**

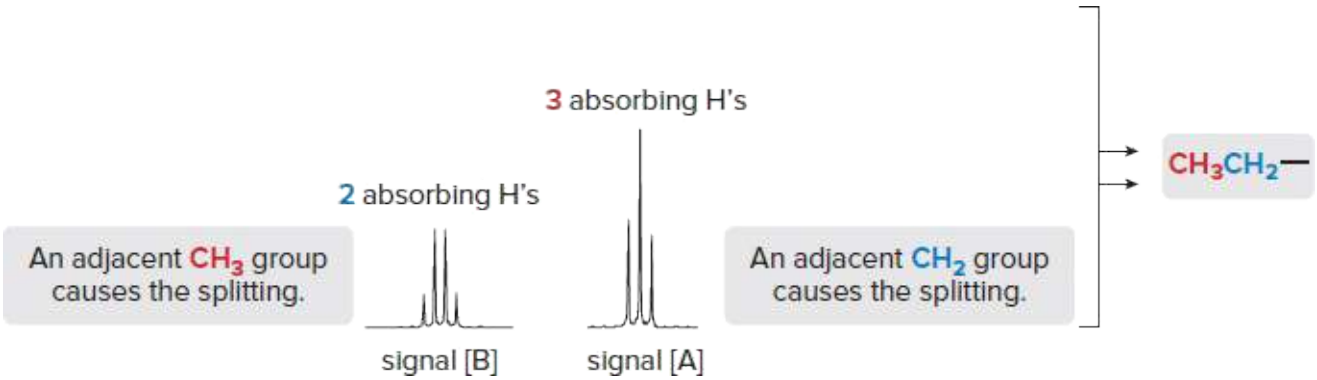
3 H_a protons signal [A]	2 H_b protons signal [B]	3 H_c protons signal [C]
Three equivalent H's usually means a CH_3 group.	Two equivalent H's usually means a CH_2 group.	Three equivalent H's usually means a CH_3 group.

Step [3] Use individual splitting patterns to determine what carbon atoms are bonded to each other.

- **Start with the singlets. Signal [C] is due to a CH_3 group with no adjacent nonequivalent H atoms. Possible structures include:**



- **Because signal [A] is a triplet, there must be 2 H's (CH_2 group) on the adjacent carbon.**
- **Because signal [B] is a quartet, there must be 3 H's (CH3 group) on the adjacent carbon.**
- **This information suggests that X has an ethyl group ⇢ CH_3CH_2–.**

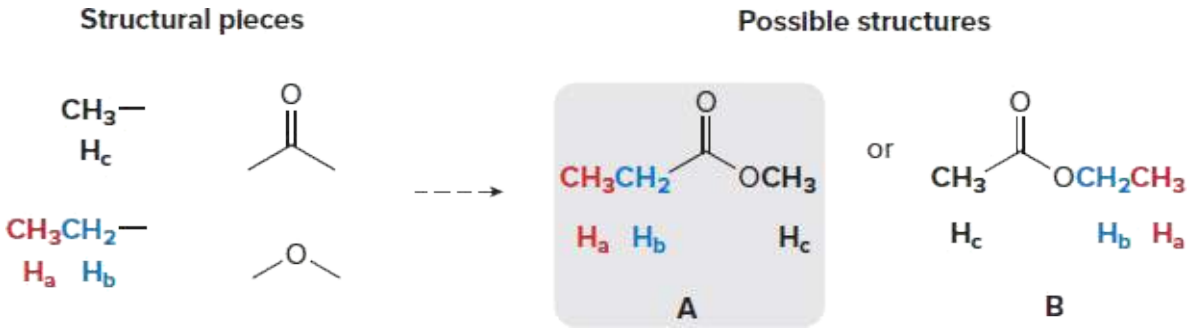


To summarize, X contains CH_3–, CH_3CH_2–, and C=O (from the IR). Comparing these atoms with the molecular formula shows that one O atom is missing. Because O atoms do not absorb in a ^{1}H NMR

spectrum, their presence can be inferred only by examining the chemical shift of protons near them. O atoms are more electronegative than C, thus deshielding nearby protons and shifting their absorption downfield.

Step [4] Use chemical shift data to complete the structure.

- Put the structure together in a manner that preserves the splitting data and is consistent with the reported chemical shifts.
- In this example, two isomeric structures (A and B) are possible for X considering the splitting data only:



- Chemical shift information distinguishes the two possibilities. The electronegative O atom deshields adjacent H's, shifting them downfield between 3 and 4 ppm. If A is the correct structure, the singlet due to the CH_3 group (H_c) should occur downfield, whereas if B is the correct structure, the quartet due to the CH_2 group (H_b) should occur downfield.
- Because the NMR of X has a singlet (not a quartet) at 3.7, A is the correct structure.

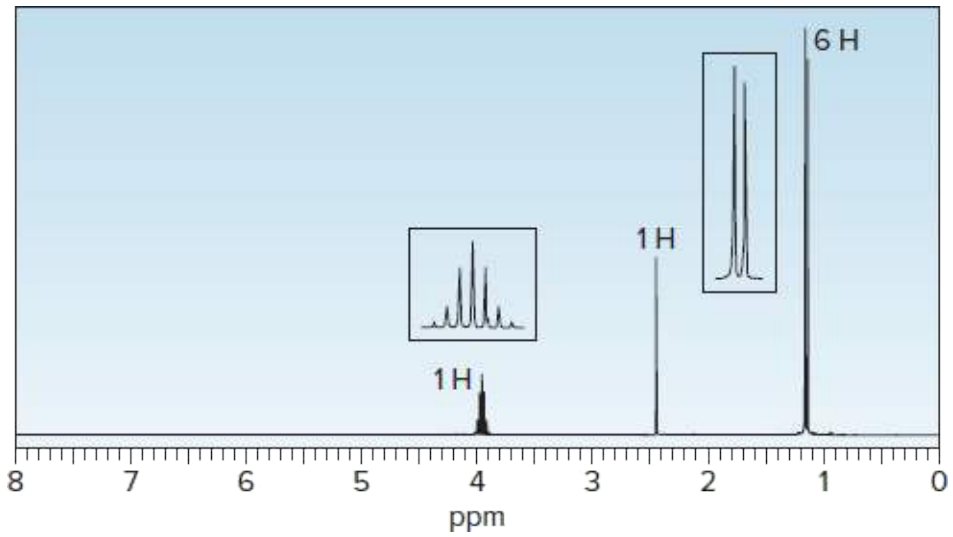
Problem C.26

Propose a structure for a compound of molecular formula $C_7H_{14}O_2$ with an IR absorption at 1740 cm^{-1} and the following ^1H NMR data:

Absorption	ppm	Relative area
singlet	1.2	9
triplet	1.3	3
quartet	4.1	2

Problem C.27

Propose a structure for a compound of molecular formula C_3H_8O with an IR absorption at 3600–3200 cm^{-1} and the following NMR spectrum:



Problem C.28

Identify products A and B from the given ^{1}H NMR data.

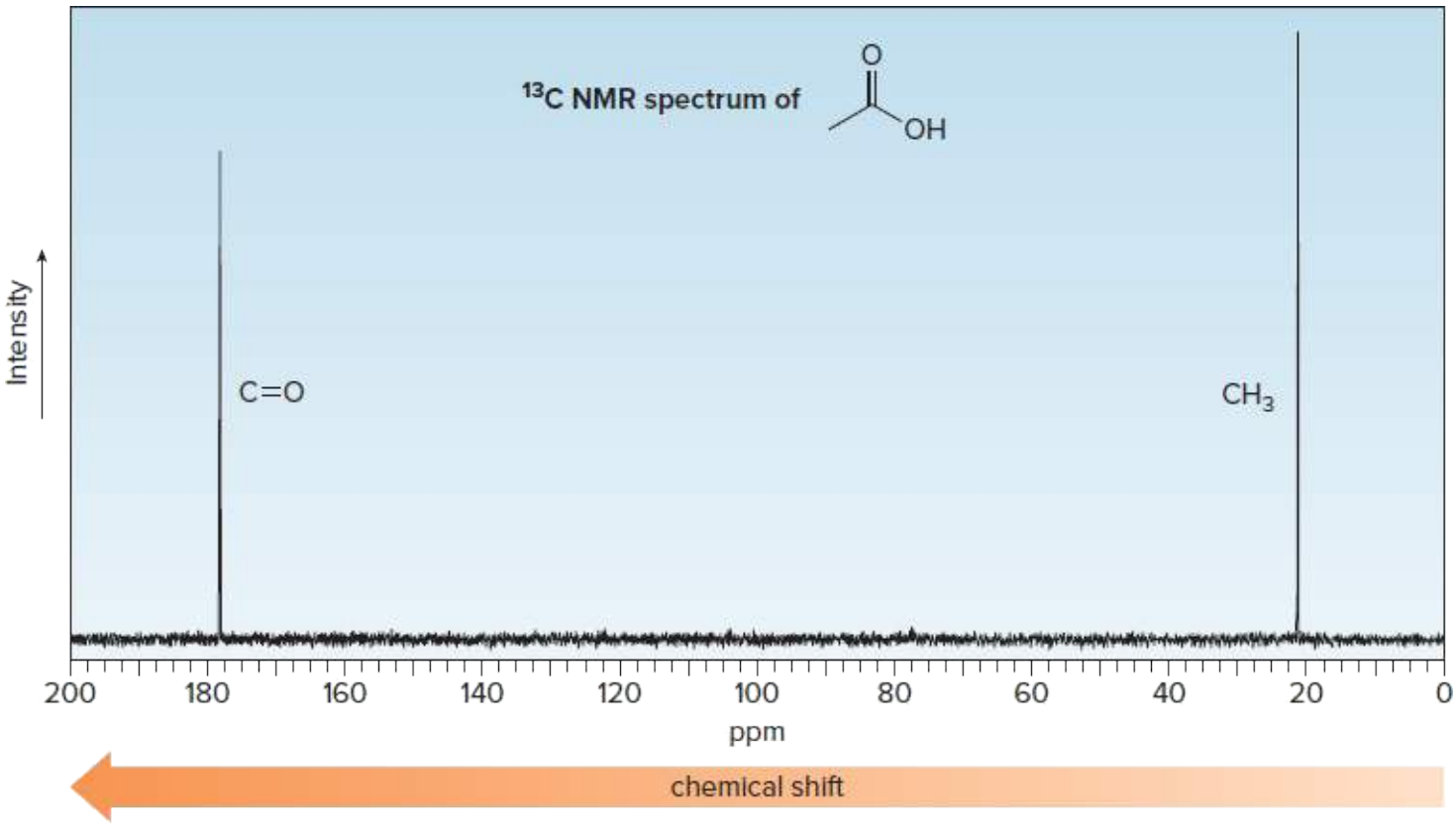
a. Treatment of CH_2=$CHCOCH_3$ with one equivalent of HCl forms compound A. A exhibits the following absorptions in its ^{1}H NMR spectrum: 2.2 (singlet, 3 H), 3.05 (triplet, 2 H), and 3.6 (triplet, 2 H) ppm. What is the structure of A?

b. Treatment of acetone [$(CH_3)_2C$=O] with dilute aqueous base forms B. Compound B exhibits four singlets in its ^{1}H NMR spectrum at 1.3 (6 H), 2.2 (3 H), 2.5 (2 H), and 3.8 (1 H) ppm. What is the structure of B?

C.11 ^{13}C NMR Spectroscopy

^{13}C NMR spectroscopy is also an important tool for organic structure analysis. The physical basis for ^{13}C NMR is the same as for ^{1}H NMR. When placed in a magnetic field, B_0, ^{13}C nuclei can align themselves with or against B_0. More nuclei are aligned with B_0 because this arrangement is lower in energy, but these nuclei can be made to spin flip against the applied field by applying RF radiation of the appropriate frequency.

^{13}C NMR spectra, like ^{1}H NMR spectra, plot peak intensity versus chemical shift, using TMS as the reference signal at 0 ppm. ^{13}C occurs in only 1.1% natural abundance, however, so ^{13}C NMR signals are much weaker than ^{1}H NMR signals. To overcome this limitation, modern spectrometers irradiate samples with many pulses of RF radiation and use mathematical tools to increase signal sensitivity and decrease background noise. The spectrum of acetic acid (CH_3COOH) illustrates the general features of a ^{13}C NMR spectrum.



^{13}C NMR spectra are easier to analyze than ^{1}H spectra because signals are not split. Each type of carbon atom appears as a single peak.

Why aren't ^{13}C signals split by nearby carbon atoms? Recall from Section C.6 that splitting occurs when two NMR active nuclei—like two protons—are close to each other. Because of the low natural abundance of ^{13}C nuclei (1.1%), the chance of two ^{13}C nuclei being bonded to each other is very small (0.01%), so no carbon-carbon splitting is observed.

A ^{13}C NMR signal can also be split by nearby protons. This ^{1}H–^{13}C splitting is usually eliminated from a spectrum, however, by using an instrumental technique that decouples the protoncarbon interactions, so that every signal in a ^{13}C NMR spectrum is a singlet.

Two features of ^{13}C NMR spectra provide the most structural information: the number of signals observed and the chemical shifts of those signals.

C.11A ^{13}C NMR: Number of Signals

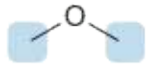
- **The number of signals in a ^{13}C spectrum gives the number of different types of carbon atoms in a molecule.**

Carbon atoms in the same environment give the same NMR signal, whereas carbons in different environments give different NMR signals. The ^{13}C NMR spectrum of

CH_3COOH has two signals because there are two different types of carbon atoms—the C of the CH_3 group and the C of the carbonyl (C=O).

- **Because ^{13}C NMR signals are not split, the number of signals equals the number of lines in the ^{13}C NMR spectrum.**

Thus, the ^{13}C NMR spectra of dimethyl ether, chloroethane, and methyl acetate exhibit one, two, and three lines, respectively, because these compounds contain one, two, and three different types of carbon atoms.

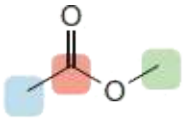


dimethyl ether

1 ^{13}C NMR signal
Both C's are equivalent.

chloroethane

2 ^{13}C NMR signals



methyl acetate

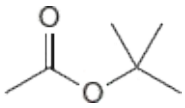
3 ^{13}C NMR signals

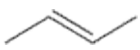
In contrast to what occurs in proton NMR, peak intensity is not proportional to the number of absorbing carbons, so ^{13}C NMR signals are not integrated.

Sample Problem C.9 Determining the Number of Lines in a ^{13}C NMR Spectrum

How many lines are observed in the ^{13}C NMR spectrum of each compound?

a.

b. 

c. 

Solution

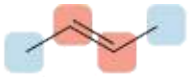
The number of different types of carbons equals the number of lines in a ^{13}C NMR spectrum.

a.

3 types of C's
3 ^{13}C NMR signals

b.

4 types of C's
4 ^{13}C NMR signals

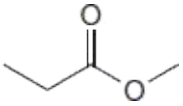
c. 

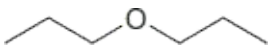
2 types of C's
2 ^{13}C NMR signals

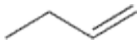
Problem C.29

How many lines are observed in the ^{13}C NMR spectrum of each compound?

a.

b. 

c. 

d. 

More Practice:

Try Problems C.36b, C.47, C.49, C.55b, C.56c, C.57c.

Problem C.30

Draw all constitutional isomers of molecular formula $C_3H_6Cl_2$.

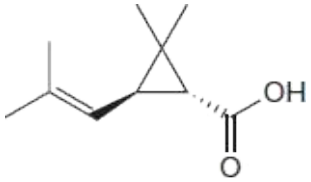
a. How many signals does each isomer exhibit in its ^{1}H NMR spectrum?

b. How many lines does each isomer exhibit in its ^{13}C NMR spectrum?

c. When only the number of signals in both ^{1}H and ^{13}C NMR spectroscopy is considered, is it possible to distinguish all of these constitutional isomers?

Problem C.31

Esters of chrysanthemic acid are naturally occurring insecticides. How many lines are present in the ^{13}C NMR spectrum of chrysanthemic acid?



chrysanthemic acid

Esters of chrysanthemic acid are obtained from the flowers of *Chrysanthemum cinerariifolium.* Because they are biodegradable and active against numerous insect species, these esters are widely used insecticides (see also Section 24.4).

©Gail Whitfield/Alamy Stock Photo

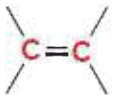
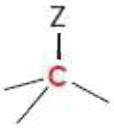
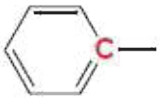
C.11B ^{13}C NMR: Position of Signals

In contrast to the small range of chemical shifts in ^{1}H NMR (0–12 ppm usually), ^{13}C NMR absorptions occur over a much broader range, 0–220 ppm. The chemical shifts of carbon atoms in ^{13}C NMR depend on the same effects as the chemical shifts of protons in ^{1}H NMR:

- **The sp^3 hybridized C atoms of alkyl groups are shielded and absorb upfield.**
- **Electronegative elements like halogen, nitrogen, and oxygen shift absorptions downfield.**
- **The sp^2 hybridized C atoms of alkenes and benzene rings absorb downfield.**
- **Carbonyl carbons are highly deshielded, and absorb farther downfield than other carbon types.**

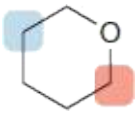
Table C.5 lists common ^{13}C chemical shift values. The ^{13}C NMR spectra of propan-1-ol ($CH_3CH_2CH_2OH$) and methyl acetate ($CH_3CO_2CH_3$) in Figure C.14 illustrate these principles.

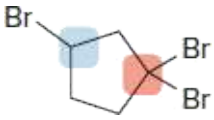
Table C.5 Common ^{13}C Chemical Shift Values

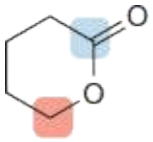
Type of carbon	Chemical shift (ppm)	Type of carbon	Chemical shift (ppm)
	5–45		100–140
 Z = N, O, X	30–80		120–150
	65–100		160–210

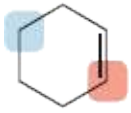
Problem C.32

Which of the highlighted carbon atoms in each molecule absorbs farther downfield?

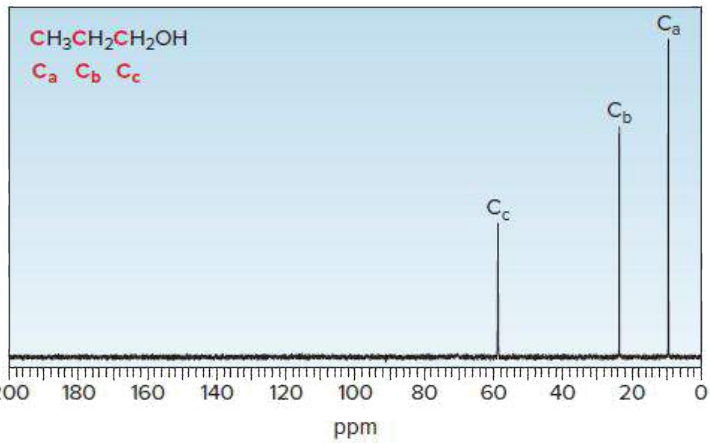
a. 

b. 

c. 

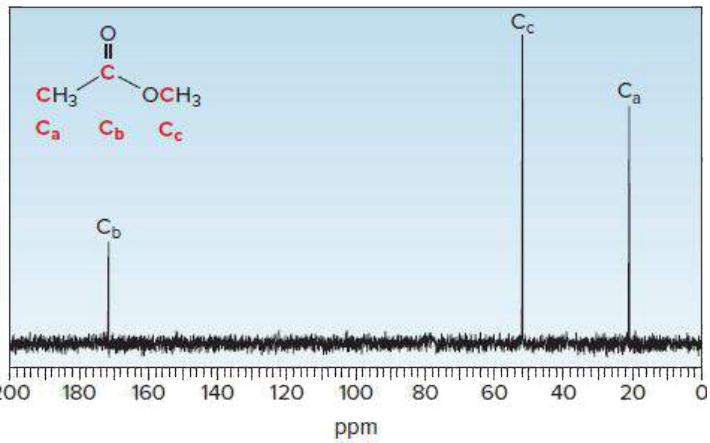
d. 

a. Propan-1-ol



- The three types of C's in propan-1-ol—identified as C_a, C_b, and C_c—give rise to three ^{13}C NMR signals.
- Deshielding increases with increasing proximity to the electronegative O atom, and the absorption shifts downfield; thus, in order of increasing chemical shift: $C_a < C_b < C_c$.

b. Methyl acetate



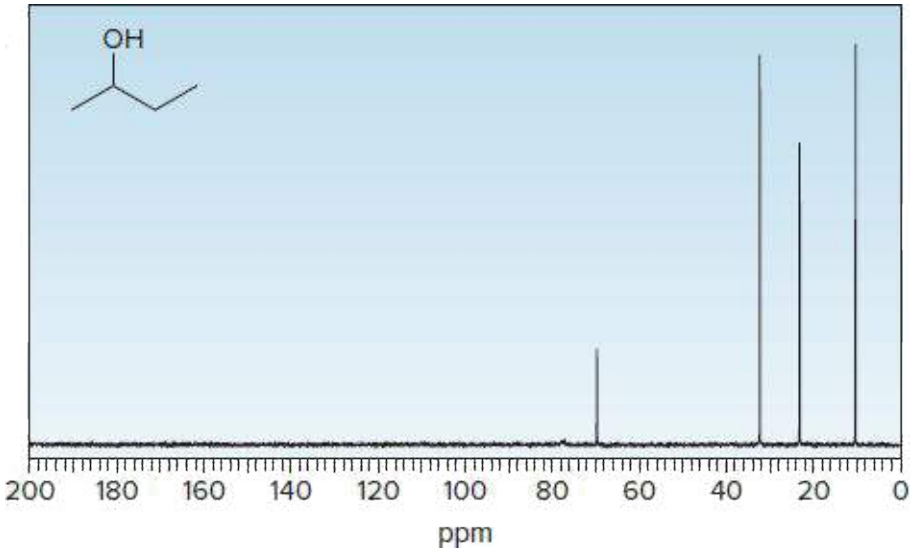
- The three types of C's in methyl acetate—identified as C_a, C_b, and C_c—give rise to three ^{13}C NMR signals.
- **The carbonyl carbon (C_b) is highly deshielded, so it absorbs farthest downfield.**
- C_a, an sp^3 hybridized C that is not bonded to an O atom, is the most shielded, and so it absorbs farthest upfield.
- Thus, in order of increasing chemical shift: $C_a < C_c < C_b$.

Figure C.14 Representative ^{13}C NMR spectra

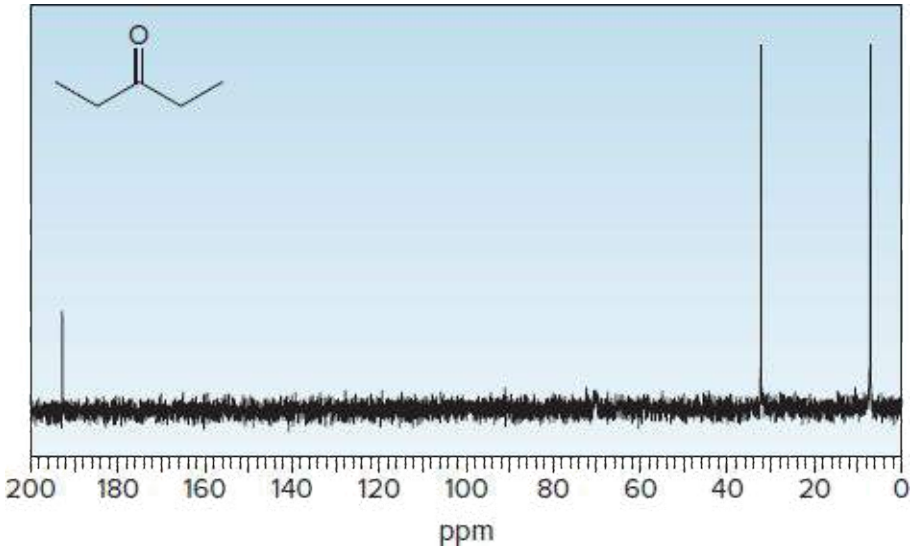
Problem C.33

Identify the carbon atoms that give rise to each NMR signal.

a.



b.



Problem C.34

A compound of molecular formula $C_4H_8O_2$ shows no IR peaks at 3600–3200 or 1700 cm^{-1}. It exhibits one singlet in its ^1H NMR spectrum at 3.69 ppm, and one line in its ^{13}C NMR spectrum at 67 ppm. What is the structure of this unknown?

Problem C.35

Draw the structure of a compound of molecular formula C_4H_8O that has a signal in its ^{13}C NMR spectrum at > 160 ppm. Then draw the structure of an isomer of molecular formula C_4H_8O that has all of its ^{13}C NMR signals at < 160 ppm.

C.12 Magnetic Resonance Imaging (MRI)

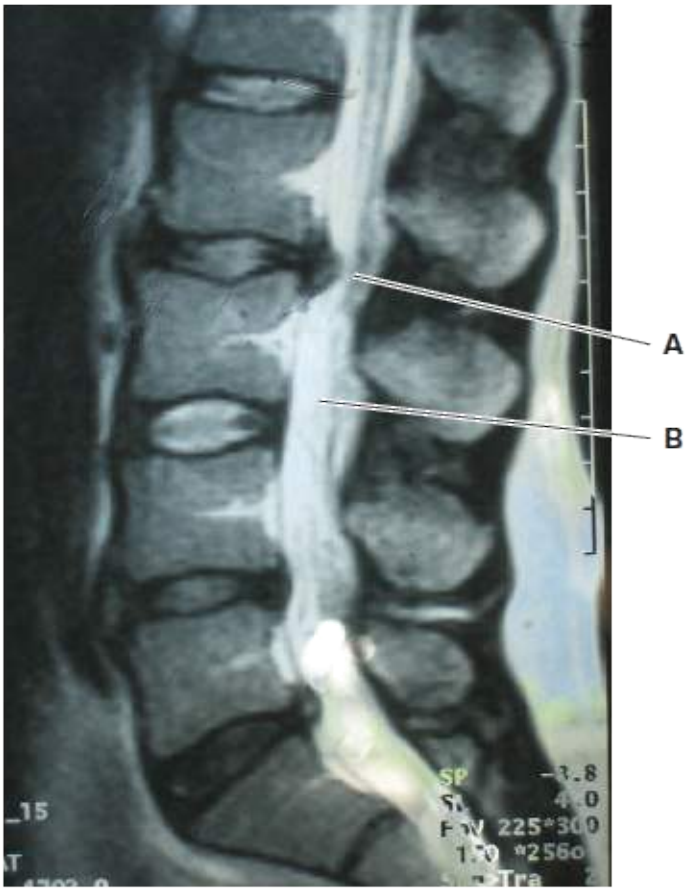
Magnetic resonance imaging (MRI)—NMR spectroscopy in medicine—is a powerful diagnostic technique (Figure C.15a). The "sample" is the patient, who is placed in a large cavity in a magnetic field, and then irradiated with RF energy. Because RF energy has very low frequency and low energy, the method is safer than X-rays or computed tomography (CT) scans that employ high-frequency, high-energy radiation that is known to damage living cells.

Living tissue contains protons (especially the H atoms in H_2O) in different concentrations and environments. When irradiated with RF energy, these protons are excited to a higher-energy spin state, and then fall back to the lower-energy spin state. These data are analyzed by a computer that generates a plot that delineates tissues of different proton density (Figure C.15b). MRIs can be recorded in any plane. Moreover, because the calcium present in bones is not NMR active, an MRI instrument can "see through" bones such as the skull and visualize the soft tissue underneath.

a.

©ERproductions Ltd/Blend Images LLC

b.



With permission, Daniel C. Smith.

a. An MRI instrument: An MRI instrument is especially useful for visualizing soft tissue. The 2003 Nobel Prize in Physiology or Medicine was awarded to chemist Paul C. Lauterbur and physicist Sir Peter Mansfield for their contributions in developing magnetic resonance imaging.
b. An MRI image of the lower back: **A** labels spinal cord compression from a herniated disc. **B** labels the spinal cord, which would not be visualized with conventional X-rays.

Figure C.15 **Magnetic resonance imaging**

Spectroscopy C CHAPTER REVIEW

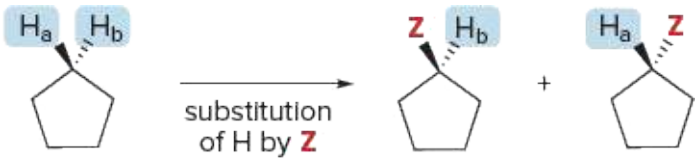
KEY CONCEPTS

Homotopic, enantiotopic, and diastereotopic protons (C.2C)

1 **Two protons are homotopic when replacement of H by Z yields the same compound.**

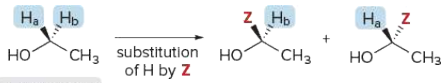
3 **Two protons are diastereotopic when replacement of H by**

yields diastereomers



H_a and H_b are **homotopic.**

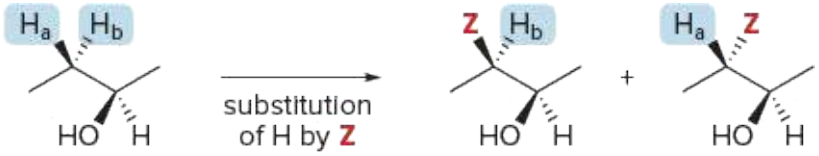
identical products



H_a and H_b are **enantiotopic.**

enantiomers

2 **Two protons are enantiotopic when replacement of H by Z yields enantiomers.**



H_a and H_b are **diastereotopic.**

diastereomers

See Sample Problem C.4. Try Problem C.7.

KEY SKILLS

[1] Calculating the chemical shift of an absorption that occurs at 1000 Hz downfield from TMS using a 400 MHz NMR spectrometer (C.1)

1 **Use the equation that defines chemical shift in ppm.**

2 **Insert th values i the equatio**

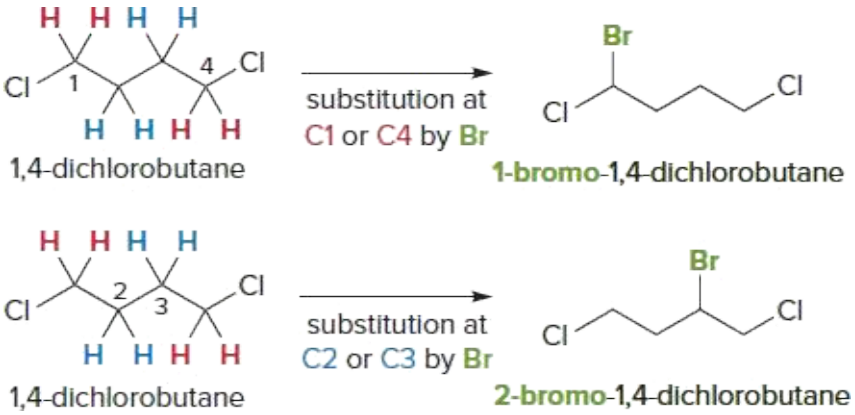
$$\text{chemical shift (in ppm on the } \delta \text{ scale)} = \frac{\text{observed chemical shift (in Hz) downfield from TMS}}{\nu \text{ of the NMR spectrometer (in MHz)}}$$

$$= \frac{1000 \text{ Hz downfield from TMS}}{400 \text{ MHz operating frequency}} = 2.5 \text{ ppm}$$

See Sample Problem C.1. Try Problems C.40, C.41.

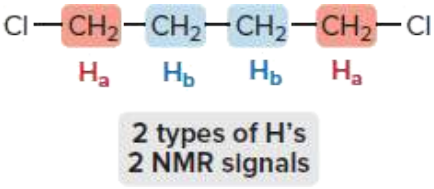
[2] Determining the different types of protons in a compound (C.2A); example: 1,4-dichlorobutane

1 **Replace each H by X (in this example, X = Br), and determine if this yields the same compound or different compounds.**



- **If substitution by X yields the same compound or enantiomers, the two protons are equivalent.**
- **Assigning protons can be done by inspection when obvious.**
- **In determining equivalency, each CH_3 is different from each CH_2, which is different from each CH.**

2 **Identify each differe type of proton.**

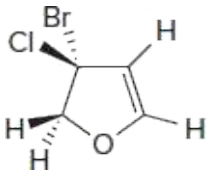


- **Each different type proton has a distir signal in the ^{1}H NM spectrum.**
- **Don't forget about and NH protons.**

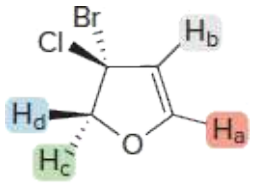
See Sample Problem C.2, Figure C.2. Try Problems C.36a, C.37a, C38, C.39, C.55a, C.56a, C.57d.

[3] Determining equivalency in a cycloalkane (C.2B)

1 **Draw in all bonds to hydrogen using wedges and dashed wedges for tetrahedral carbons.**



2 **Determine if two protons are cis (or trans) to the same groups.**



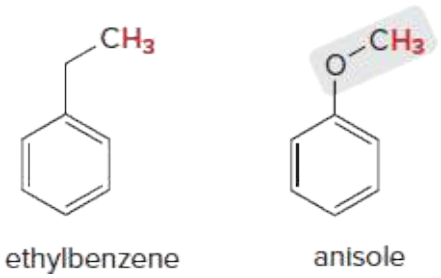
4 types of H's
4 NMR signals

- H_c is cis to Br, and H_d is cis to Cl.

See Sample Problem C.3. Try Problems C.38h, i, j; C.56a.

[4] Determining which protons absorb farther downfield; two factors

1 **Use the presence of nearby electronegative atoms to determine deshielding effects (C.3A).**

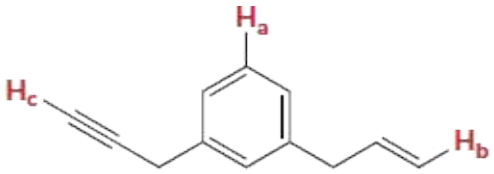


ethylbenzene anisole

- The CH_3 group in anisole is deshielded by the electronegative O atom.
- Electronegative atoms withdraw electron density, deshield a nucleus, and shift an absorption downfield.
- Shielding shifts an absorption upfield.

See Sample Problem C.5.

2 **Determine shielding and deshielding effects when protons are bonded to sp^2 and sp hybridized carbons (C.4).**



- **Hc** is shielded because it is bonded to an sp hybridized carbon.
- **Hb** is deshielded because it is bonded to an sp^2 hybridized carbon.
- **Ha** is highly deshielded because it is bonded to an sp^2 hybridized carbon on a benzene ring.

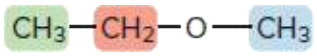
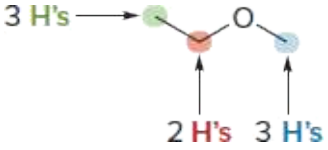
Answer:

In order of increasing chemical shift, $H_c < H_b < H_a$

See Sample Problem C.6.

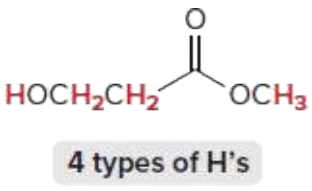
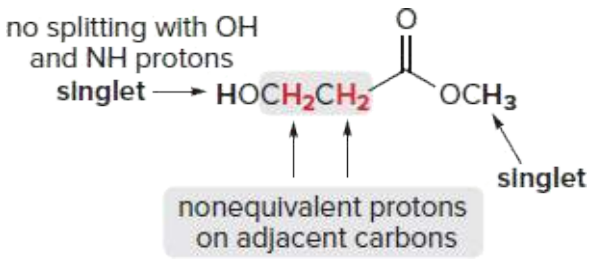
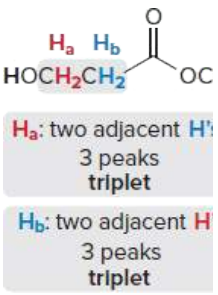
Try Problem C.42.

[5] Determining the ^{1}H NMR integration ratio for a compound (C.5); example: $CH_3CH_2OCH_3$

1 Identify the nonequivalent protons.	2 Count the number of protons in each group.	3 Determine the integration ratio.
 • three types of protons		Answer: 3:2:3 • The area under an NMR signal is proportional to the number of absorbing protons.

Try Problems C.13, C.14.

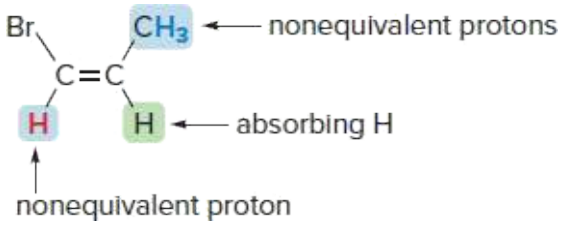
[6] Determining the splitting pattern for a molecule using the *n* + 1 rule (C.6)

1 Identify the nonequivalent protons.	2 Determine if two sets of nonequivalent protons are close enough to split each other's signals.	3 Apply the rule.
	 • Equivalent protons do not split each other's signals.	 • A set of nonequ

		protons the sam carbon adjacen carbons an NMR signal i 1 peaks

See Tables C.3, C.4. Try Problems C.37b, C.43, C.55c, C.56b, C.57e.

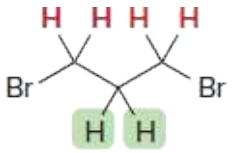
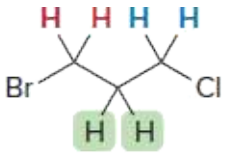
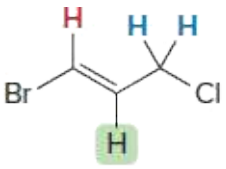
[7] Determining the number of peaks present in the ^{1}H NMR signal of an alkene using the $(n + 1)(m + 1)$ rule (C.7); example: (*Z*)-1-bromoprop-1-ene

1 Determine the number of nonequivalent protons on the same carbon or adjacent carbons.	2 Apply the $(n + 1)(m + 1)$ rule.
	$(n + 1)(m + 1)$ $(1 + 1)(3 + 1) = 8$ peaks

See Figure C.8, Sample Problem C.7. Try Problems C.43i, j; C.44; C.45; C.56b.

[8] Determining splitting patterns when an absorbing proton has nonequivalent protons on two adjacent carbons (C.7–C.8); three possibilities

1 Use *n* + 1 when absorbing H's have nonequivalent H's that are	2 Use *n* + *m* + 1 in a flexible chain when absorbing H's have nonequivalent H's	3 Use (n + 1)(m + 1) when the absorbing H has nonequivalent H's that are

equivalent to each other **on two sides.**	**that are *nonequivalent to each other* on two sides.**	***nonequivalent to each other*** **on *two* sides.**
 Use $n + 1$. $4 + 1 = 5$ peaks **quintet** **See Figure C.6.**	 flexible chain Use $n + m + 1$ because of peak overlap. $2 + 2 + 1 = 5$ peaks • ***J*** **values are identical or very similar with two sets of protons bonded to a flexible chain, so the number of peaks = *n* + *m* + 1.** **See Figures C.7, C.8.**	 Use $(n + 1)(m + 1)$. $(1 + 1)(2 + 1) = 6$ peaks • **The $(n + 1)(m + 1)$ rule is used for protons bonded to C=C's.** **See Figures C.9–C.11.**

See Sample Problem C.7, Tables C.3, C.4. Try Problems C.43d–j, C.44.

[9] Using a molecular formula and ^{1}H NMR data to determine a structure (C.10); example: $C_4H_{10}O$ with the given ^{1}H NMR data

1 Calculate the degrees of unsaturation.	**2 Use the relative area to calculate the number of protons responsible for each absorption.**	**3 Analyze the splitting patte and chemical shifts.**

$C_4H_{10}O$

$2n + 2 = 2(4) + 2 = 10$

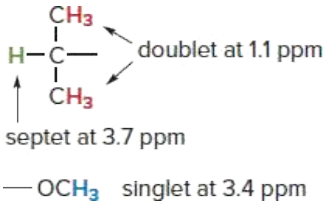
$10 - 10 = 0$ degrees of unsaturation

Absorption	ppm	Relative area
doublet	1.1	6
singlet	3.4	3
septet	3.7	1

three types of protons

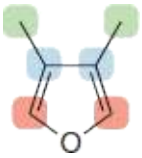
sum of the relative areas = number of absorbing H's
(6 + 3 + 1 = 10)

6 H's, 3 H's, and 1 H



See *How To* (p. 591). Try Problem C.59.

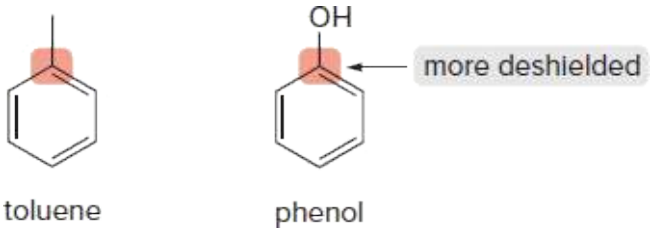
[10] Determining the different types of C atoms in a compound (C.11A)

1 Label each of the different types of carbons.	2 Specify the number of ^{13}C NMR signals.
	3 types of C's 3 NMR signals • All signals are single peaks. • The number of different types of carbon atoms equals the number of lines in the ^{13}C NMR spectrum.

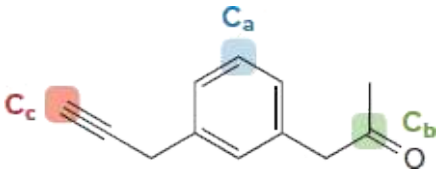
See Sample Problem C.8. Try Problems C.47, C.48.

[11] Determining which C atom absorbs farther downfield (C.11); two factors

1 Use the presence of nearby electronegative atoms to determine deshielding effects.	2 Determine shielding and deshielding effects when carbons are bonded to sp^2 and sp hybridized carbons.



- The C atom in phenol is deshielded by the electronegative O atom.
- The chemical shifts of carbon atoms in ^{13}C NMR depend on the same effects as the chemical shifts of protons in ^{1}H NMR.



- C_c is shielded because it is an *sp* hybridized C.
- C_b is highly deshielded because it is a carbonyl C.
- C_a is deshielded because it is an sp^2 hybridized C on a benzene ring.

Answer:

In order of increasing chemical shift, $C_c < C_a < C_b$

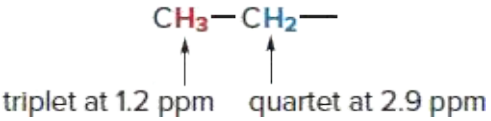
Try Problems C.50, C.51.

[12] Using a molecular formula, IR, ^{1}H NMR, and ^{13}C NMR for structure determination (C.10); example: C3H5ClO

1 Calculate the degrees of unsaturation.	2 Use IR to determine the functional groups and ^{13}C NMR to determine the number of different types of C's.	3 Use ^{1}H NMR to determi the structure of the C— skeleton.
C_3H_5ClO $2n + 2 = 2(3) + 2 = 8$ 8 (maximum H's) − 6 (actual H's + Cl) = 2/2 = 1 1 degree of unsaturation	• IR absorption at 1792 cm^{-1}, due to C=O	

- three ^{13}C NMR signals at 175, 41, and 10 ppm
- three types of carbon, including one at 175 ppm due to a C=O

Absorption	ppm	Relative area
triplet	1.2	3
quartet	2.9	2



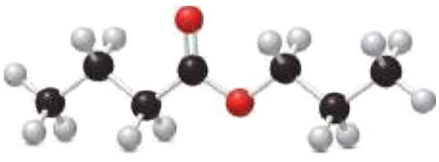
Try Problems C.58, C.60–C.76.

PROBLEMS

Problems Using Three-Dimensional Models

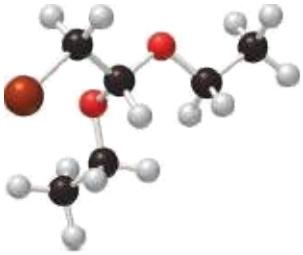
C.36 **(a) How many ^{1}H NMR signals does each of the following compounds exhibit? (b) How many ^{13}C NMR signals does each compound exhibit?**

A

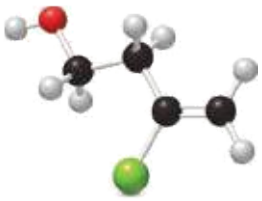


B

C.37 **(a) How many ^{1}H NMR signals does each compound show? (b) Into how many peaks is each signal split?**



C

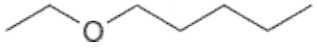


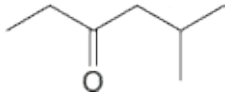
D

^{1}H NMR Spectroscopy—Determining Equivalent Protons

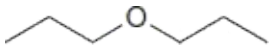
C.38 How many different types of protons are present in each compound?

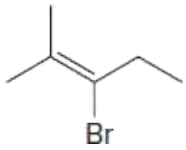
a.

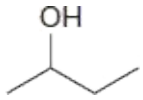
b. 

c. 

d.

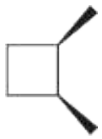
e. 

f. 

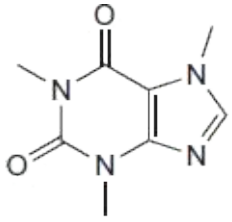
g. 

h.

i.

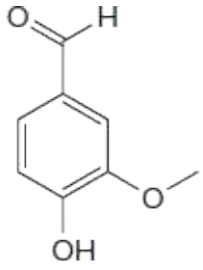
j. 

C.39 How many ^{1}H NMR signals does each natural product exhibit?

a. 

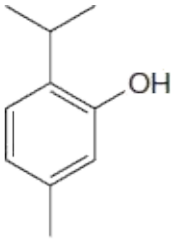
caffeine
(from coffee and
tea leaves)

b.



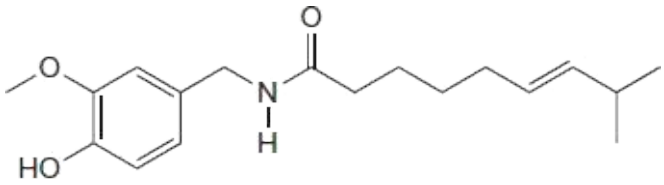
vanillin
(from the vanilla bean)

c.



thymol
(from thyme)

d.



capsaicin
(from hot peppers)

^{1}H NMR—Chemical Shift

C.40 Using a 300 MHz NMR instrument:

a. How many Hz downfield from TMS is a signal at 2.5 ppm?

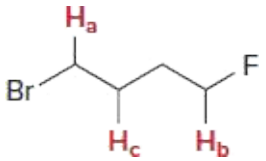
b. If a signal comes at 1200 Hz downfield from TMS, at what ppm does it occur?

c. If two signals are separated by 2 ppm, how many Hz does this correspond to?

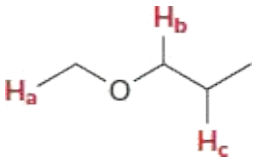
C.41 What effect does increasing the operating frequency of a ^{1}H NMR spectrum have on each value: (a) the chemical shift in 5; (b) the frequency of an absorption in Hz; (c) the magnitude of a coupling constant *J* in Hz?

C.42 Rank the labeled protons in order of increasing chemical shift.

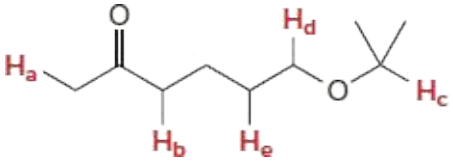
a.



b.



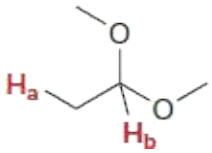
c.



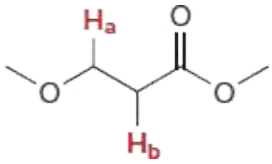
^{1}H NMR—Splitting

C.43 Into how many peaks will the signal for each of the labeled protons be split?

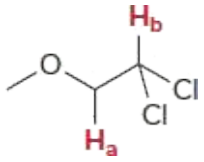
a.



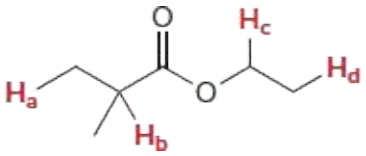
b.



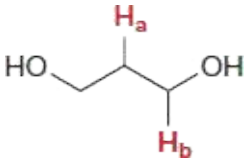
c.



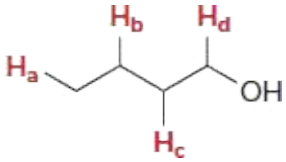
d.



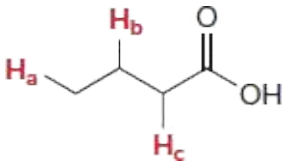
e.



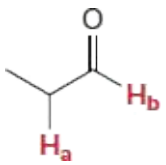
f.



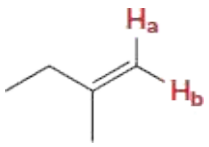
g.



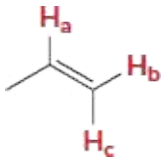
h.



i.

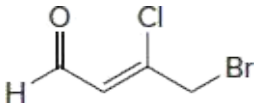


j.

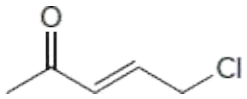


C.44 **What splitting pattern is observed for each proton in the following compounds?**

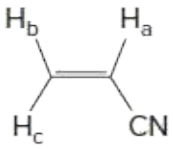
a.



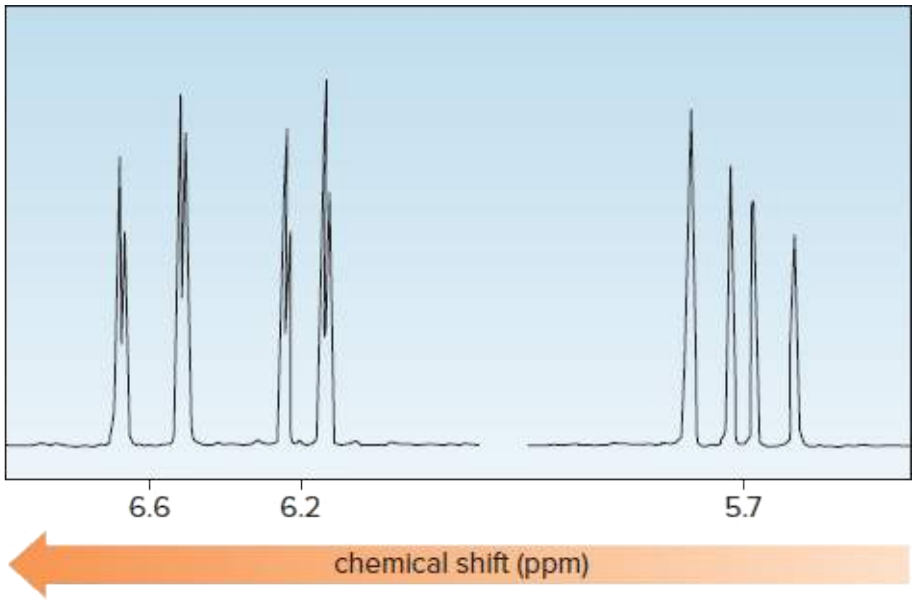
b.



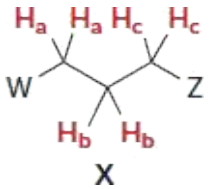
C.45 **Label the signals due to H_a, H_b, and H_c in the ^1H NMR spectrum of acrylonitrile (CH_2=CHCN). Draw a splitting diagram for the absorption due to the H_a proton.**



$J_{ab} = 11.8$ Hz
$J_{bc} = 0.9$ Hz
$J_{ac} = 18$ Hz



C.46 **Draw a splitting diagram for H_b in compound X given the following coupling constants: (a) $J_{ab} >> J_{bc}$; (b) $J_{ab} = J_{bc}$. Clearly indicate how many peaks are visible in the H_b signal in each circumstance.**



X

^{13}C NMR

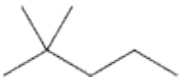
C.47 **Draw the four constitutional isomers having molecular formula C_4H_9Br**

and indicate how many different kinds of carbon atoms each has.

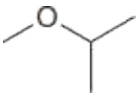
C.48 Explain why the carbonyl carbon of an aldehyde or ketone absorbs farther downfield than the carbonyl carbon of an ester in a ^{13}C NMR spectrum.

C.49 How many ^{13}C NMR signals does each compound exhibit?

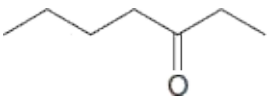
a.



b.



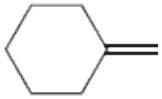
c.



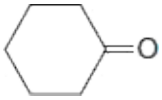
d.

e.

f.



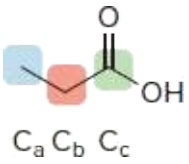
g.



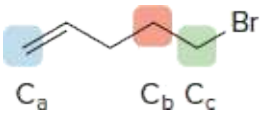
h.

C.50 Rank the highlighted carbon atoms in each compound in order of increasing chemical shift.

a.



b.



C.51 Identify the carbon atoms that give rise to the signals in the ^{13}C NMR spectrum of each compound.

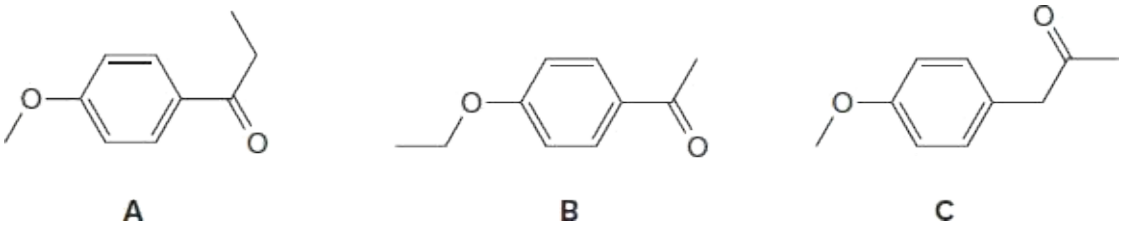
a. $CH_3CH_2CH_2CH_2OH$; ^{13}C NMR: 14, 19, 35, and 62 ppm

b. $(CH_3)_2CHCHO$; ^{13}C NMR: 16, 41, and 205 ppm

c. $CH_2{=}CHCH(OH)CH_3$; ^{13}C NMR: 23, 69, 113, and 143 ppm

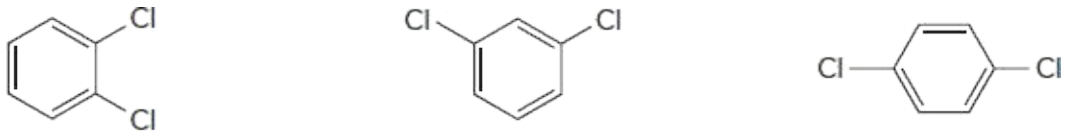
Identifying Isomers Using NMR Spectroscopy

C.52 How could ^{1}H NMR spectroscopy be used to distinguish among isomers A, B, and C?



A B C

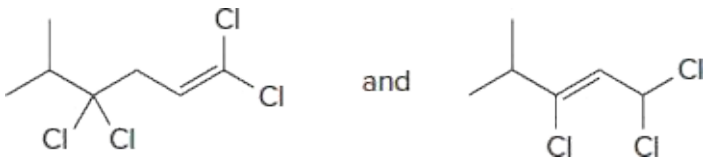
C.53 How could ^{13}C NMR spectroscopy be used to distinguish among isomers X, Y, and Z?



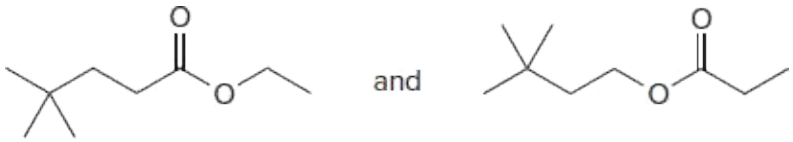
X Y Z

C.54 How could ^{1}H NMR spectroscopy be used to distinguish between each pair of compounds?

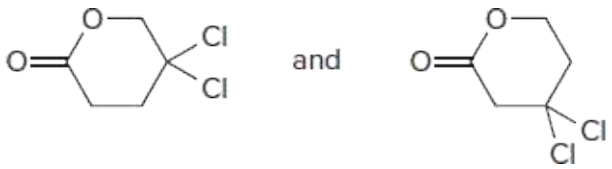
a.



b.



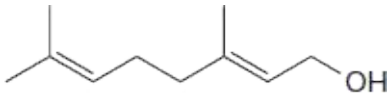
c.



Combined Spectroscopy Problems

Additional spectroscopy problems are located at the end of Chapters 9–12, 13–21, and 23.

C.55 Consider geraniol, the principal constituent of rose oil.



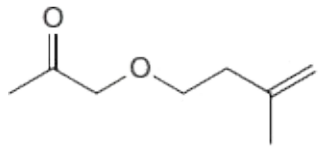
geraniol

a. How many ^{1}H NMR signals does geraniol exhibit?

b. How many ^{13}C NMR signals does geraniol exhibit?

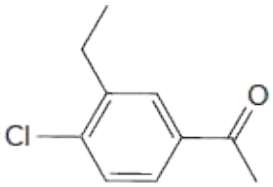
c. Into how many peaks will the protons on each C=C be split?

C.56 Answer the following questions for compounds L, M, and N drawn below.



L

M



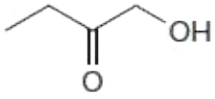
N

a. How many signals are expected in the ^{1}H NMR spectrum?

b. Into how many peaks is each signal in the ^{1}H NMR spectrum split?

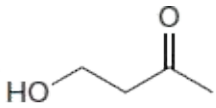
c. How many lines are expected in the ^{13}C NMR spectrum?

C.57 Answer the following questions about each of the hydroxy ketones: 1-hydroxybutan-2-one (A) and 4-hydroxybutan-2-one (B).



1-hydroxybutan-2-one

A



4-hydroxybutan-2-one

B

a. What is the molecular ion in the mass spectrum?

b. What IR absorptions are present in the functional group region?

c. How many lines are observed in the ^{13}C NMR spectrum?

d. How many signals are observed in the ^{1}H NMR spectrum?

e. Give the splitting observed for each type of proton as well as its approximate chemical shift.

C.58 Propose a structure consistent with each set of spectral data:

a. $C_4H_8Br_2$: IR peak at 3000–2850 cm^{-1}; NMR (ppm):

1.87 (singlet, 6 H)

3.86 (singlet, 2 H)

b. $C_3H_6Br_2$: IR peak at 3000–2850 cm^{-1}; NMR (ppm):

2.4 (quintet)

3.5 (triplet)

c. $C_5H_{10}O_2$: IR peak at 1740 cm^{-1}; NMR (ppm):

1.15 (triplet, 3 H) 2.30 (quartet, 2 H)

1.25 (triplet, 3 H) 4.72 (quartet, 2 H)

d. C_3H_6O: IR peak at 1730 cm^{-1}; NMR (ppm):

1.11 (triplet)

2.46 (multiplet)

9.79 (triplet)

C.59 Identify the structures of isomers A and B (molecular formula $C_9H_{10}O$).

Compound A: IR peak at 1742 cm^{-1}; ^1H NMR data (ppm) at 2.15 (singlet, 3 H), 3.70 (singlet, 2 H), and 7.20 (broad singlet, 5 H).

Compound B: IR peak at 1688 cm^{-1}; ^1H NMR data (ppm) at 1.22 (triplet, 3 H), 2.98 (quartet, 2 H), and 7.28–7.95 (multiplet, 5 H).

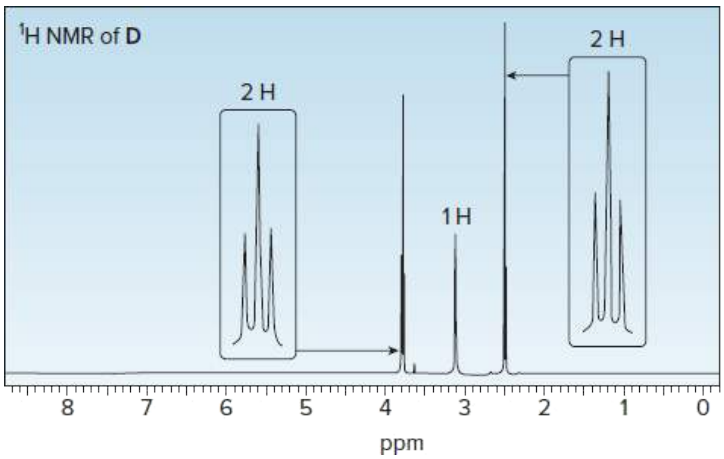
C.60 Reaction of $C_6H_5CH_2CH_2OH$ with CH_3COCl affords compound W, which has molecular formula $C_{10}H_{12}O_2$. W shows prominent IR absorptions at 3088–2897, 1740, and 1606 cm^{-1}. W exhibits the following signals in its ^1H NMR spectrum: 2.02 (singlet), 2.91 (triplet), 4.25 (triplet), and 7.20–7.35 (multiplet) ppm. What is the structure of W? We will learn about this reaction in Chapter 20.

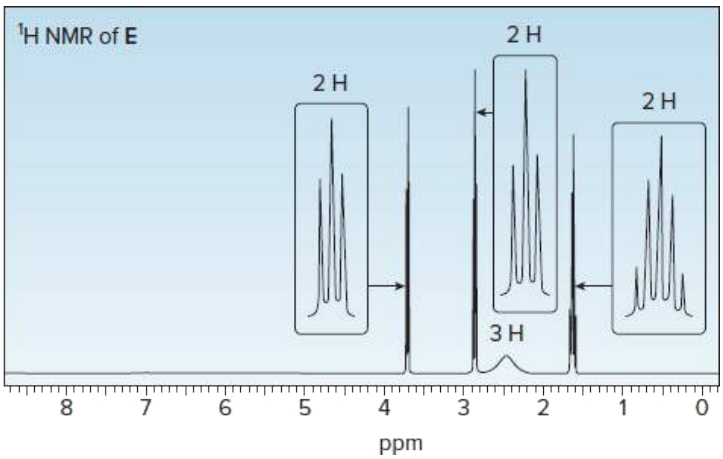
C.61 Treatment of 2-methylpropanenitrile $[(CH_3)_2CHCN]$ with $CH_3CH_2CH_2MgBr$, followed by aqueous acid, affords compound V, which has molecular formula $C_7H_{14}O$. V has a strong absorption in its IR spectrum at 1713 cm^{-1}, and gives the following ^1H NMR data: 0.91 (triplet, 3 H), 1.09 (doublet, 6 H), 1.6 (multiplet, 2 H), 2.43 (triplet, 2 H), and 2.60 (septet, 1 H) ppm. What is the structure of V? We will learn about this reaction in Chapter 20.

C.62 Compound C has a molecular ion in its mass spectrum at 146 and a prominent absorption in its IR spectrum at 1762 cm^{-1}. C shows the following ^1H NMR spectral data: 1.47 (doublet, 3 H), 2.07 (singlet, 6 H), and 6.84 (quartet, 1 H) ppm. What is the structure of C?

C.63 Treatment of compound D with $LiAlH_4$ followed by H_2O forms compound E. D shows a molecular ion in its mass spectrum at *m/z* = 71 and IR

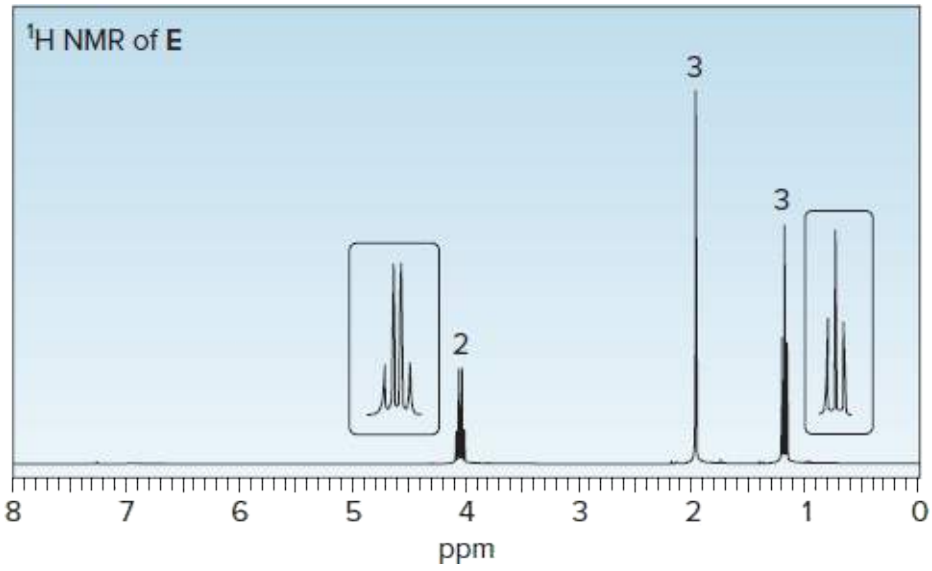
absorptions at 3600–3200 and 2263 cm^{-1}. E shows a molecular ion in its mass spectrum at *m/z* = 75 and IR absorptions at 3636 and 3600–3200 cm^{-1}. Propose structures for D and E from these data and the given ^1H NMR spectra.



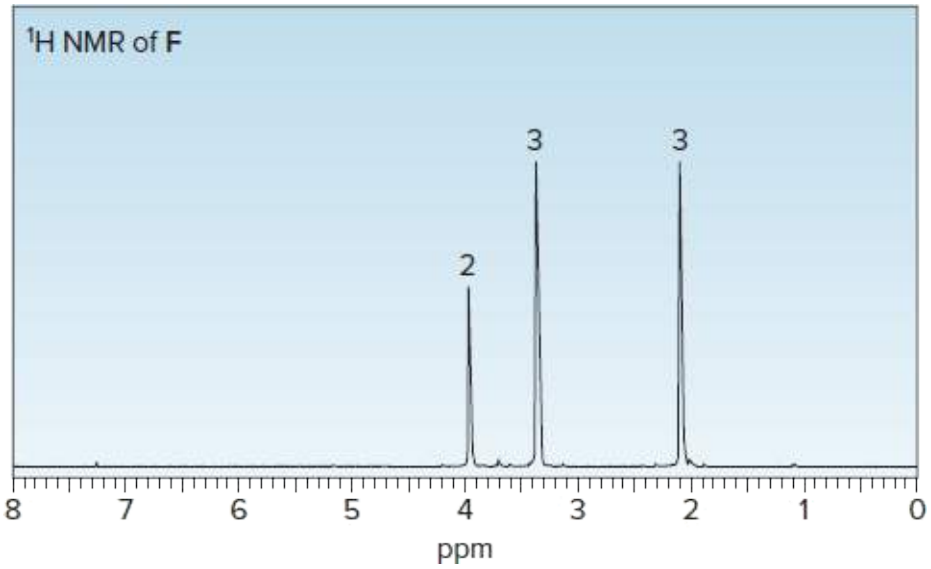


C.64 Identify the structures of isomers E and F (molecular formula $C_4H_8O_2$). Relative areas are given above each signal.

a. Compound E: IR absorption at 1743 cm^{-1}

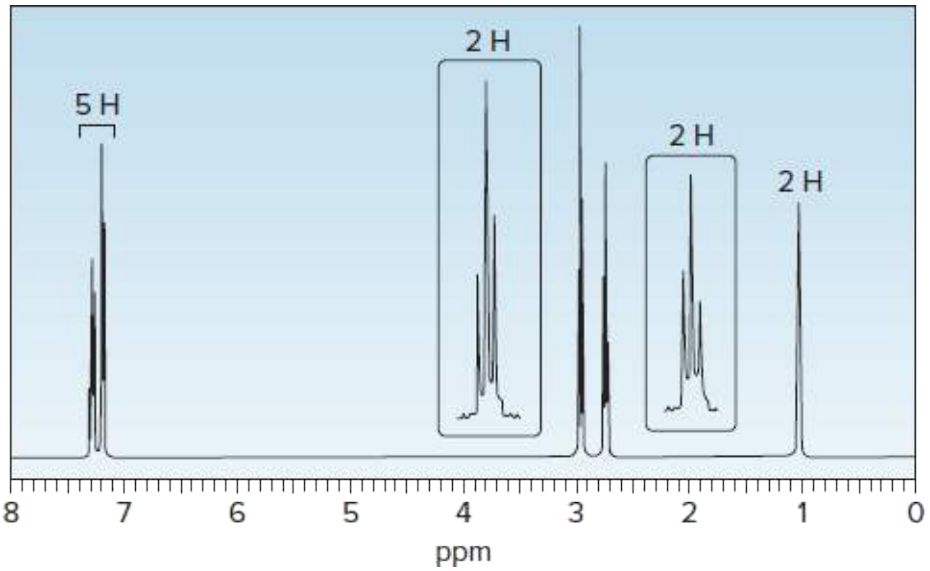


b. Compound F: IR absorption at 1730 cm^{-1}

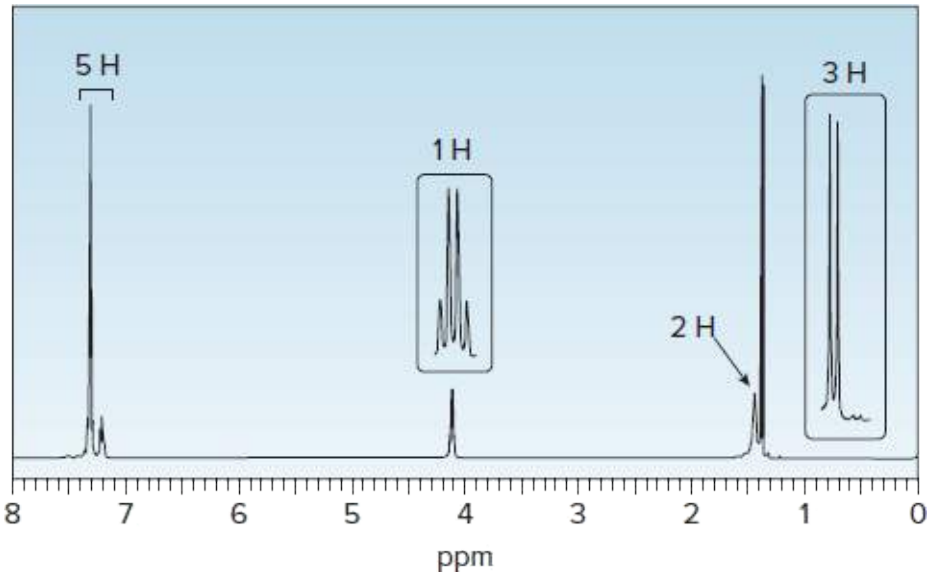


C.65 Identify the structures of isomers H and I (molecular formula $C_8H_{11}N$).

a. Compound H: IR absorptions at 3365, 3284, 3026, 2932, 1603, and 1497 cm^{-1}

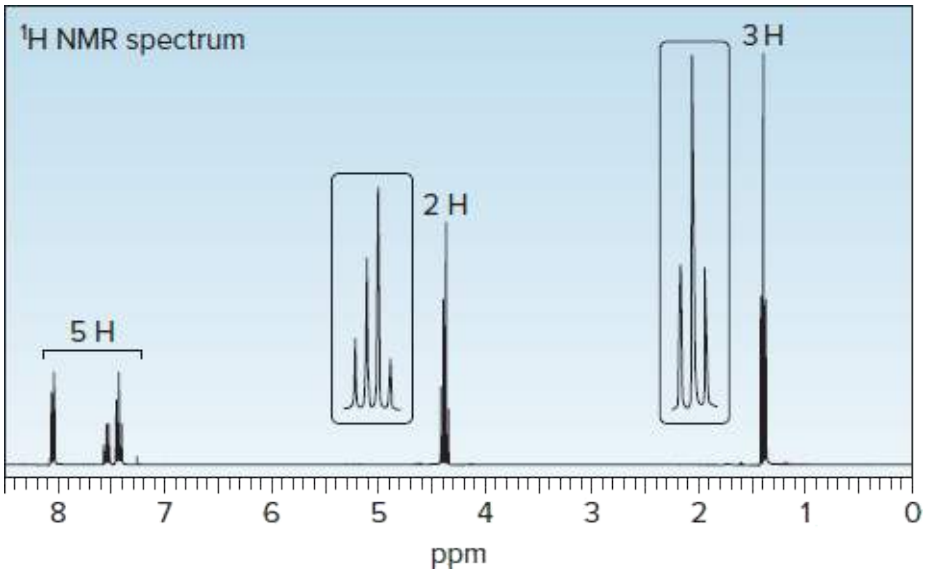


b. Compound I: IR absorptions at 3367, 3286, 3027, 2962, 1604, and 1492 cm^{-1}

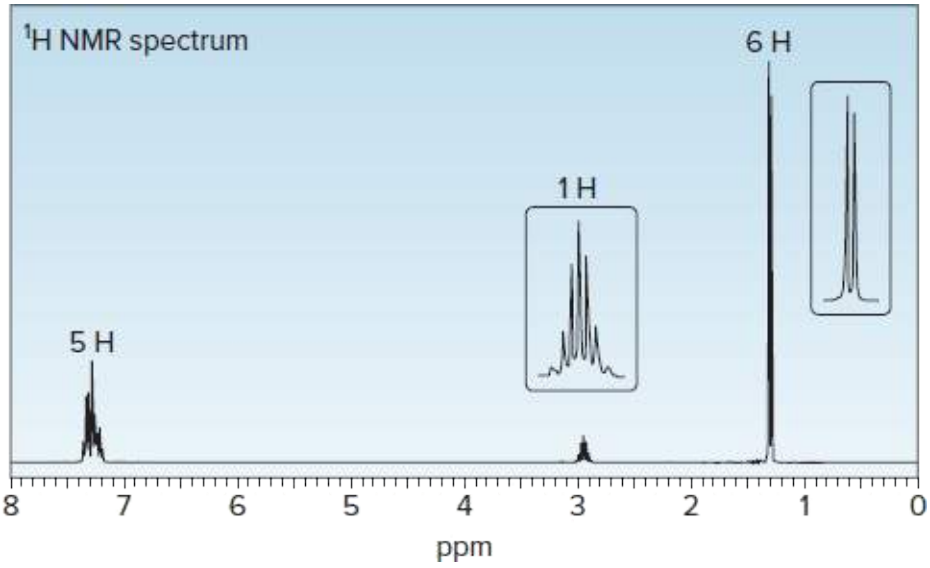


C.66 Propose a structure consistent with each set of data.

a. $C_9H_{10}O_2$: IR absorption at 1718 cm^{-1}

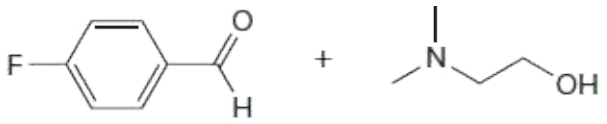


b. C_9H_{12}: IR absorption at 2850–3150 cm^{-1}



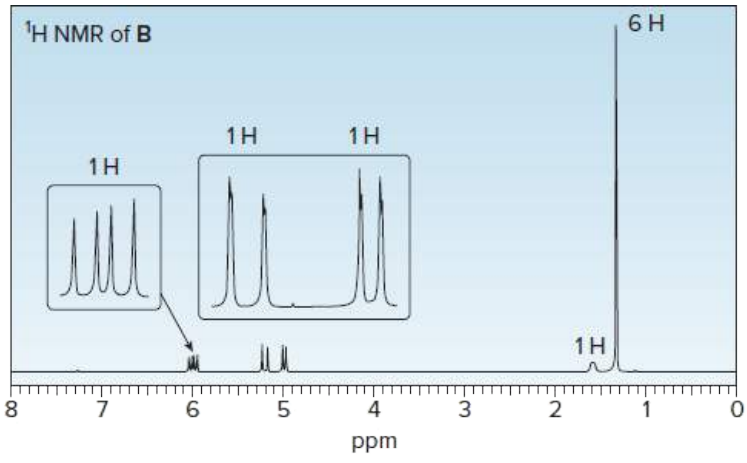
C.67 Reaction of $(CH_3)_3CCHO$ with $(C_6H_5)_3P{=}C(CH_3)OCH_3$, followed by treatment with aqueous acid, affords R ($C_7H_{14}O$). R has a strong absorption in its IR spectrum at 1717 cm^{-1} and three singlets in its ^1H NMR spectrum at 1.02 (9 H), 2.13 (3 H), and 2.33 (2 H) ppm. What is the structure of R? We will learn about this reaction in Chapter 18.

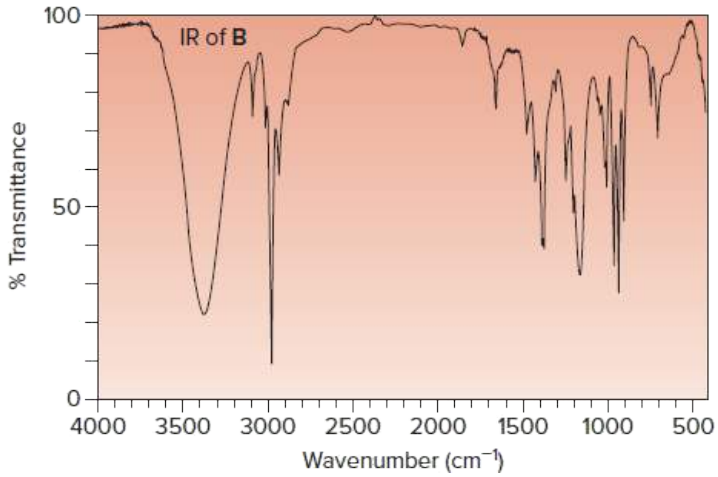
C.68 Reaction of aldehyde D with amino alcohol E in the presence of NaH forms F (molecular formula $C_{11}H_{15}NO_2$). F absorbs at 1730 cm^{-1} in its IR spectrum. F also shows eight lines in its ^{13}C NMR spectrum, and gives the following ^1H NMR spectrum: 2.32 (singlet, 6 H), 3.05 (triplet, 2 H), 4.20 (triplet, 2 H), 6.97 (doublet, 2 H), 7.82 (doublet, 2 H), and 9.97 (singlet, 1 H) ppm. Propose a structure for F. We will learn about this reaction in Chapter 16.



D E

C.69 The treatment of $(CH_3)_2C{=}CHCH_2Br$ with H_2O forms B (molecular formula $C_5H_{10}O$) as one of the products. Determine the structure of B from its ^1H NMR and IR spectra.



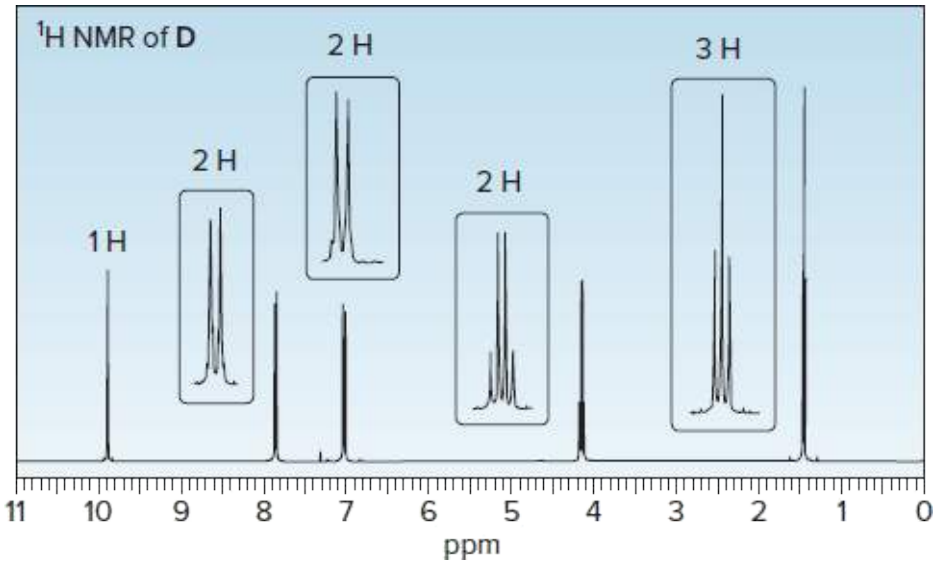


C.70 Propose a structure consistent with each set of data.

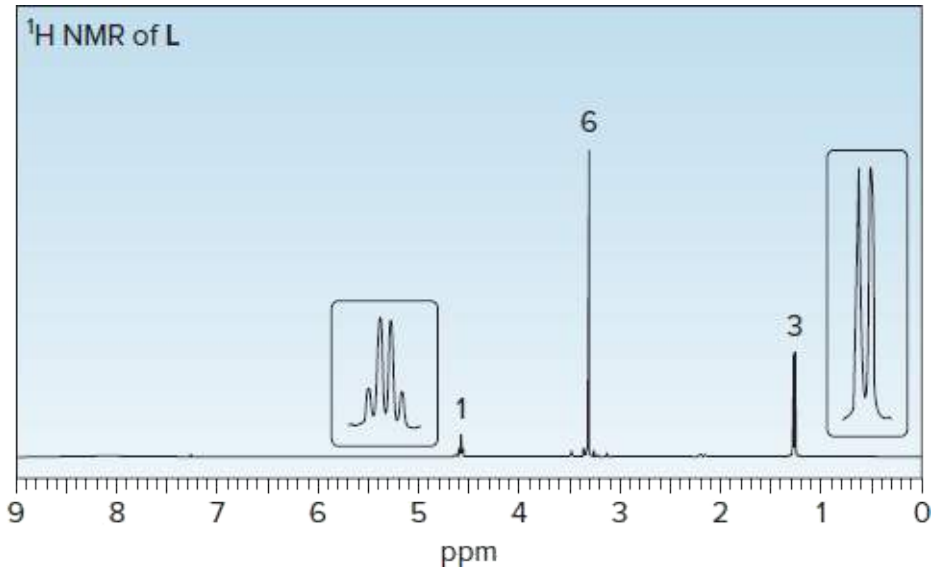
a. Compound J: molecular ion at 72; IR peak at 1710 cm^{-1}; ^1H NMR data (ppm) at 1.0 (triplet, 3 H), 2.1 (singlet, 3 H), and 2.4 (quartet, 2 H)

b. Compound K: molecular ion at 88; IR peak at 3600-3200 cm^{-1}; ^1H NMR data (ppm) at 0.9 (triplet, 3 H), 1.2 (singlet, 6 H), 1.5 (quartet, 2 H), and 1.6 (singlet, 1 H)

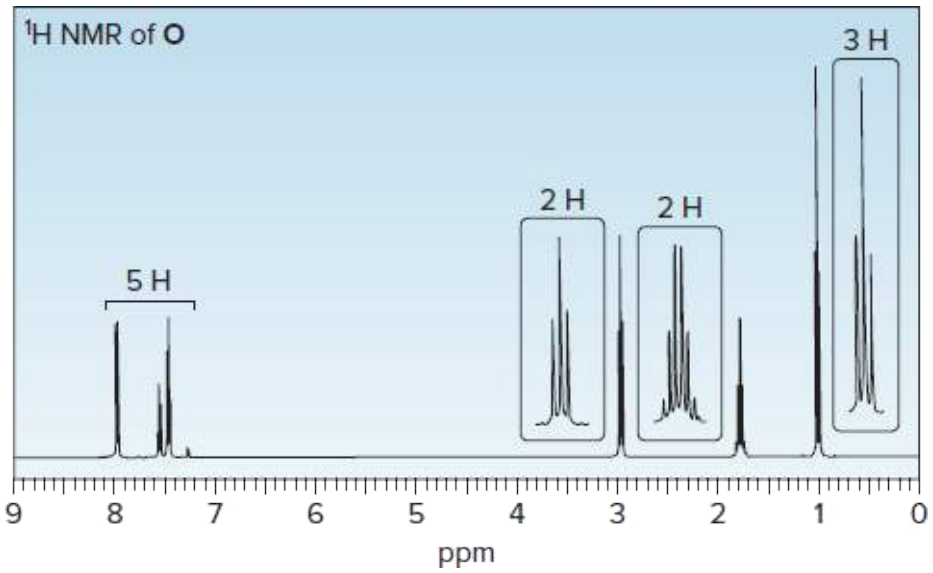
C.71 **An unknown compound D exhibits a strong absorption in its IR spectrum at 1692 cm^{-1}. The mass spectrum of D shows a molecular ion at *m/z* = 150 and a base peak at 121. The ^1H NMR spectrum of D is shown below. What is the structure of D?**



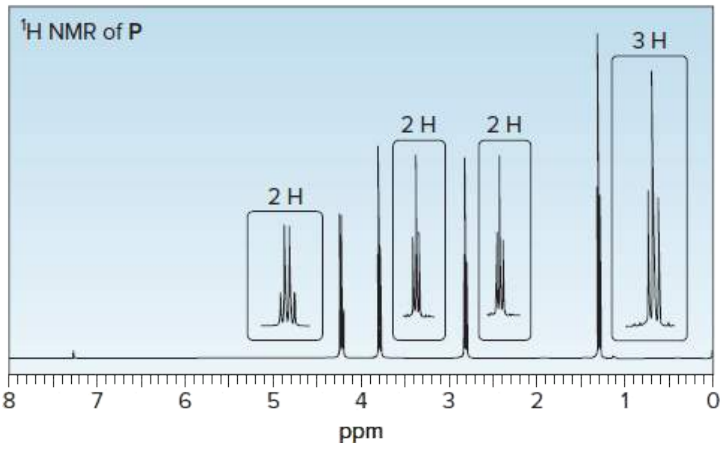
C.72 **In the presence of a small amount of acid, a solution of acetaldehyde (CH_3CHO) in methanol (CH_3OH) was allowed to stand and a new compound L was formed. L has a molecular ion in its mass spectrum at 90 and IR absorptions at 2992 and 2941 cm^{-1}. L shows three signals in its ^{13}C NMR at 19, 52, and 101 ppm. The ^1H NMR spectrum of L is given below. What is the structure of L?**

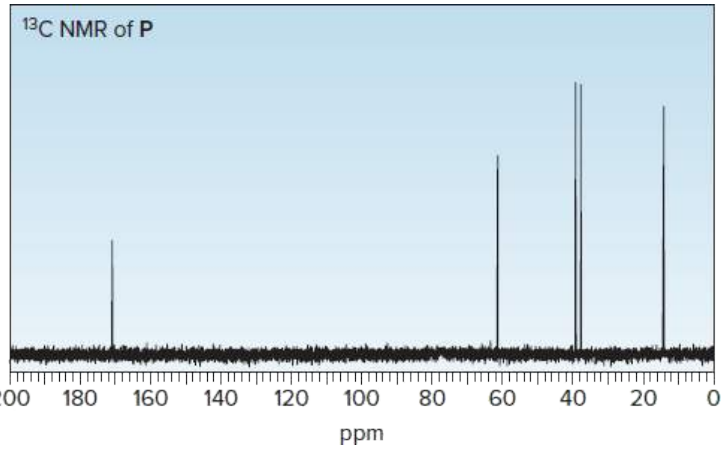


C.73 **Compound O has molecular formula $C_{10}H_{12}O$ and shows an IR absorption at 1687 cm^{-1}. The ^1H NMR spectrum of O is given below. What is the structure of O?**

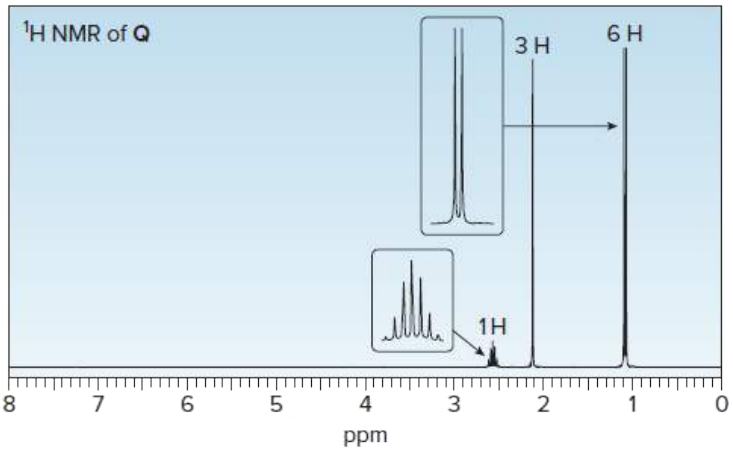


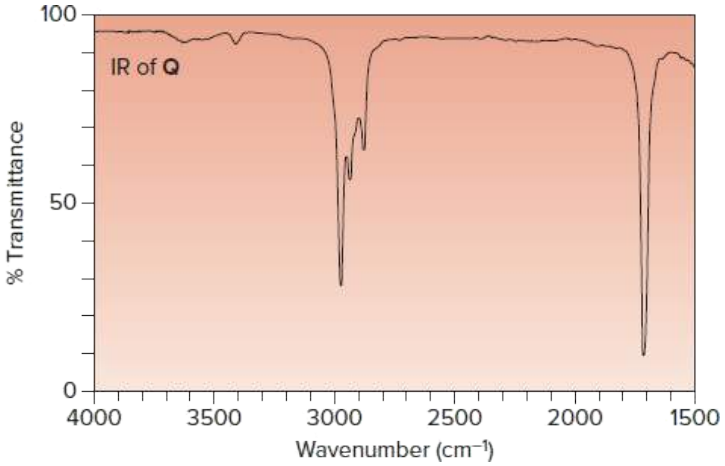
C.74 Compound P has molecular formula $C_5H_9ClO_2$. Deduce the structure of P from its ^1H and ^{13}C NMR spectra.





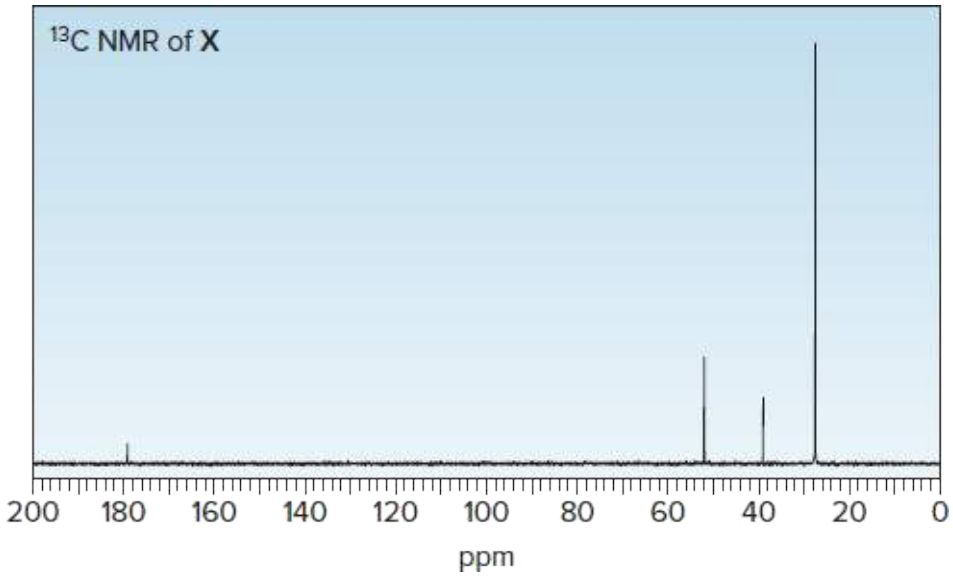
C.75 Treatment of butan-2-one ($CH_3COCH_2CH_3$) with strong base followed by CH_3I forms a compound Q, which gives a molecular ion in its mass spectrum at 86. The IR (> 1500 cm^{-1} only) and ^1H NMR spectra of Q are given below. What is the structure of Q?





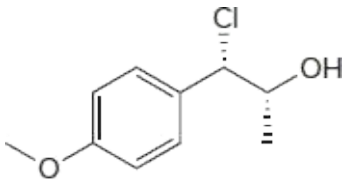
C.76 Propose a structure for compound X (molecular formula $C_6H_{12}O_2$), which

gives a strong peak in its IR spectrum at 1740 cm^{-1}. The ^1H NMR spectrum of X shows only two singlets, including one at 3.5 ppm. The ^{13}C NMR spectrum is given below. Propose a structure for X.



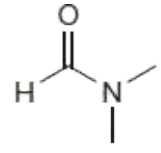
Challenge Problems

C.77 Reaction of unknown A with HCl forms chlorohydrin B as the major product. A shows no absorptions in its IR spectrum at 1700 cm^{-1} or 3600-3200 cm^{-1}, and gives the following ^1H NMR data: 1.4 (doublet, 3 H), 3.0 (quartet of doublets, 1 H), 3.5 (doublet, 1 H), 3.8 (singlet, 3 H), 6.9 (doublet, 2 H), and 7.2 (doublet, 2 H) ppm. (a) Propose a structure for A, including stereochemistry. (b) Explain why B is the major product in this reaction.



B

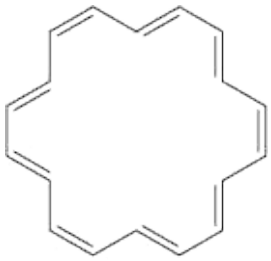
C.78 The ^1H NMR spectrum of *N,N*-dimethylformamide shows three singlets at 2.9, 3.0, and 8.0 ppm. Explain why the two CH3 groups are not equivalent to each other, thus giving rise to two NMR signals.



N,N-dimethylformamide

C.79 18-Annulene shows two signals in its ^1H NMR spectrum, one at 8.9 (12 H)

and one at −1.8 (6 H) ppm. Using a similar argument to that offered for the chemical shift of benzene protons, explain why both shielded and deshielded values are observed for 18-annulene.

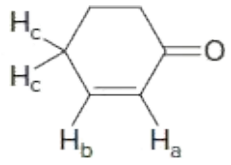


18-annulene

C.80 **Explain why the ^{13}C NMR spectrum of 3-methylbutan-2-ol shows five signals.**

C.81 **Because ^{31}P has an odd mass number, ^{31}P nuclei absorb in the NMR and, in many ways, these nuclei behave similarly to protons in NMR spectroscopy. With this in mind, explain why the ^{1}H NMR spectrum of methyl dimethylphosphonate, $CH_3PO(OCH_3)_2$, consists of two doublets at 1.5 and 3.7 ppm.**

C.82 **Cyclohex-2-enone has two protons on its carbon-carbon double bond (labeled H_a and H_b) and two protons on the carbon adjacent to the double bond (labeled H_c). (a) If J_{ab} = 11 Hz and J_{bc} = 4 Hz, sketch the splitting pattern observed for each proton on the sp^2 hybridized carbons. (b) Despite the fact that H_a is located adjacent to an electron-withdrawing C=O, its absorption occurs upfield from the signal due to H_b (6.0 vs. 7.0 ppm). Offer an explanation.**



cyclohex-2-enone

Radical Reactions

13

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13.1 Introduction

13.2 General features of radical reactions

13.3 Halogenation of alkanes

13.4 The mechanism of halogenation

13.5 Chlorination of other alkanes

13.6 Chlorination versus bromination

13.7 Halogenation as a tool in organic synthesis
13.8 The stereochemistry of halogenation reactions
13.9 Application: The ozone layer and CFCs
13.10 Radical halogenation at an allylic carbon
13.11 Application: Oxidation of unsaturated lipids
13.12 Application: Antioxidants
13.13 Radical addition reactions to double bonds
13.14 Polymers and polymerization

Poly(vinyl chloride) (PVC), a synthetic polymer prepared from the monomer vinyl chloride, is used in a wide variety of medical, industrial, and home products. Rigid PVC is found in pipes and bottles, whereas flexible PVC is used in blood bags, tubing, and materials needed for hemodialysis and heart bypass. Because PVC is water insoluble, garden hoses, drainpipes, and rain gear are made of PVC. PVC is lightweight, tear resistant, and easily sterilized, and it can be recycled many times before it is no longer usable. In Chapter 13, we learn how polymers like poly(vinyl chloride) are prepared.

Why Study…

Radical Reactions?

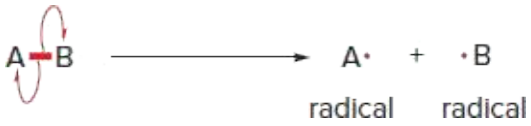
A small but significant group of reactions involves the homolysis of nonpolar bonds to form highly reactive radical intermediates. Although they are unlike other organic reactions, radical transformations are important in many biological and industrial processes. The gases O_2 and NO (nitric oxide) are both radicals. Many oxidation reactions with O_2 involve radical intermediates, and biological processes mediated by NO such as blood clotting and neurotransmission may involve radicals. Many useful industrial products such as Styrofoam and polyethylene are prepared by radical processes.

In Chapter 13 we examine the cleavage of nonpolar bonds by radical reactions.

13.1 Introduction

Radicals were first discussed in Section 6.3.

- **A *radical* is a reactive intermediate with a single unpaired electron, formed by homolysis of a covalent bond.**

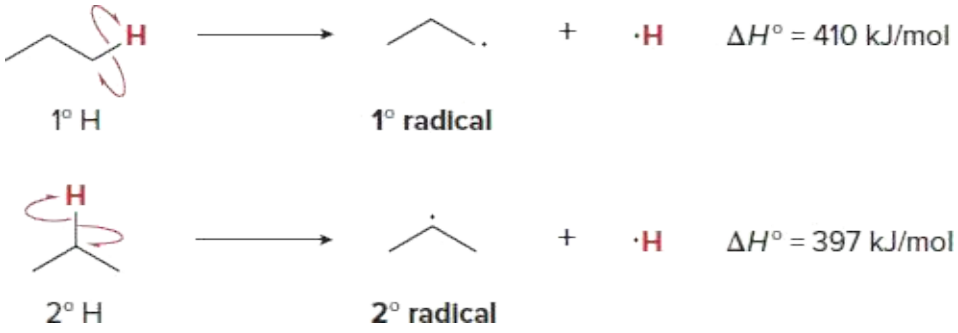


Use half-headed curved arrows in radical reactions.

A radical contains an atom that does not have an octet of electrons, making it reactive and unstable. Radical processes involve single electrons, so half-headed arrows are used to show the movement of electrons. One half-headed arrow is used for each electron.

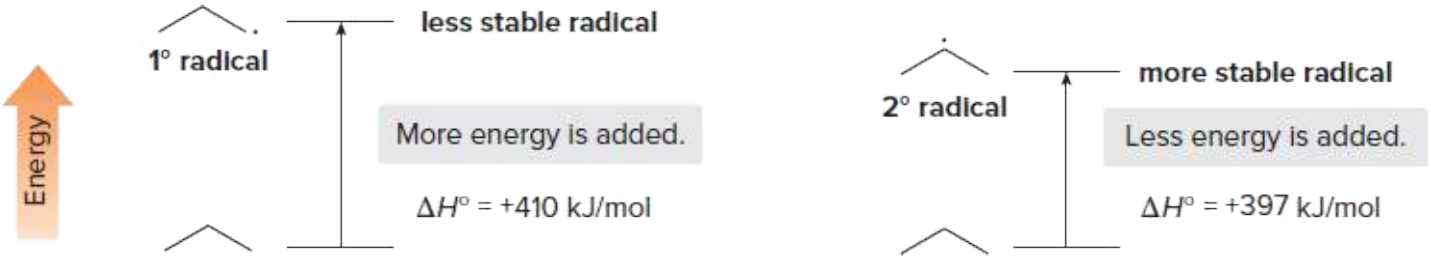
Carbon radicals are classified as primary (1°), secondary (2°), or tertiary (3°) by the number of R groups bonded to the carbon with the unpaired electron. A carbon radical is sp^2 hybridized and trigonal planar, like sp^2 hybridized carbocations. The unhybridized *p* orbital contains the unpaired electron and extends above and below the trigonal planar carbon.

Bond dissociation energies for the cleavage of C–H bonds are used as a measure of radical stability. For example, two different radicals can be formed by cleavage of the C–H bonds in $CH_3CH_1CH_3$.

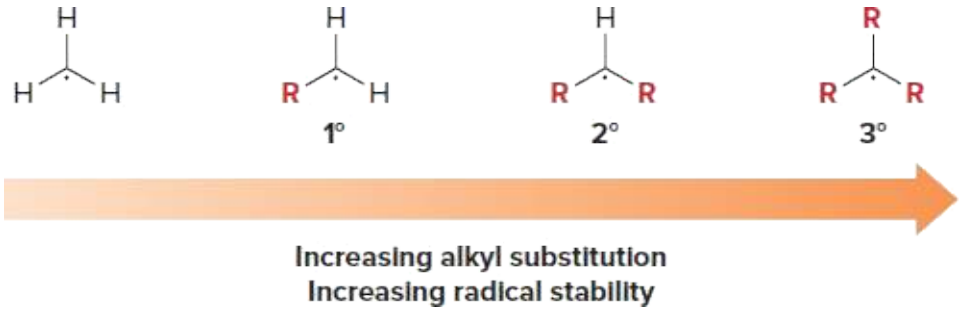


Cleavage of the stronger 1° C–H bond to form the 1° radical ($CH_3CH_1CH_1$•) requires *more* energy than cleavage of the weaker 2° C–H bond to form the 1° radical [$(CH_3)_2CH$•]—410 versus 397 kJ/mol. This makes the 1° radical more stable, because less energy is required for its formation, as illustrated in Figure 13.1. Thus, cleavage of the weaker bond forms the more stable radical, a specific example of a general trend.

Figure 13.1 **The relative stability of 1° and 2° carbon radicals**



- **The stability of a radical increases as the number of alkyl groups bonded to the radical carbon increases.**



The lower the bond dissociation energy for a C–H bond, the more stable the resulting carbon radical.

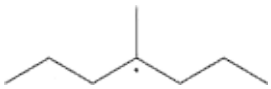
Thus, a 3° radical is more stable than a 2° radical, and a 2° radical is more stable than a 1° radical. Increasing alkyl substitution increases radical stability in the same way it increases carbocation stability. Alkyl groups are more polarizable than hydrogen atoms, so they can more easily donate electron density to the electron-deficient carbon radical, thus increasing stability.

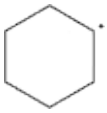
Unlike carbocations, however, less stable radicals generally do *not* rearrange to more stable radicals. This difference can be used to distinguish between reactions involving radical intermediates and those involving carbocations.

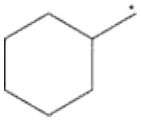
Problem 13.1

Classify each radical as 1°, 2°, or 3°.

a.

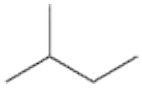
b. 

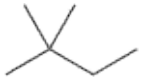
c. 

d. 

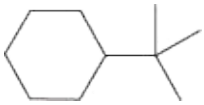
Problem 13.2

Draw the most stable radical that can result from cleavage of a C–H bond in each molecule.

a. 

b. 

c.

d. 

13.2 General Features of Radical Reactions

Radicals are formed from covalent bonds by adding energy in the form of heat (Δ) or light (*hν*). Some radical reactions are carried out in the presence of a radical initiator, a compound that contains an especially weak bond that serves as a source of radicals. Peroxides, compounds with the general structure RO–OR, are the most commonly used radical initiators. Heating a peroxide readily causes homolysis of the weak O–O bond, forming two RO• radicals.

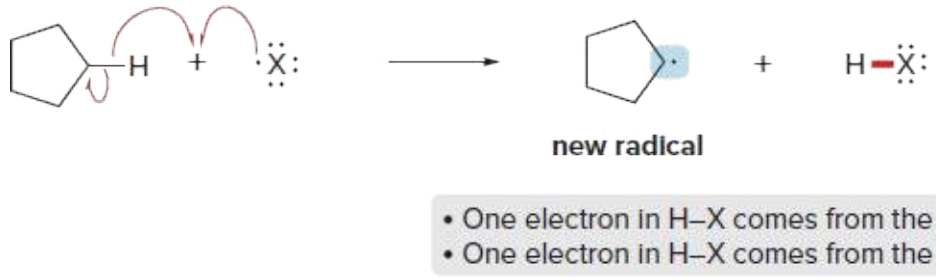
13.2A Two Common Reactions of Radicals

Radicals undergo two main types of reactions: they react with σ bonds, and they add to π bonds, in both cases achieving an octet of electrons.

[1] Reaction of a Radical X• with a C–H Bond

A radical X• abstracts a hydrogen atom from a C–H σ bond to form H–X and a carbon radical. One electron from the C–H bond is used to form the new H–X bond, and the other electron in the C–H bond remains on carbon. The result is that the original

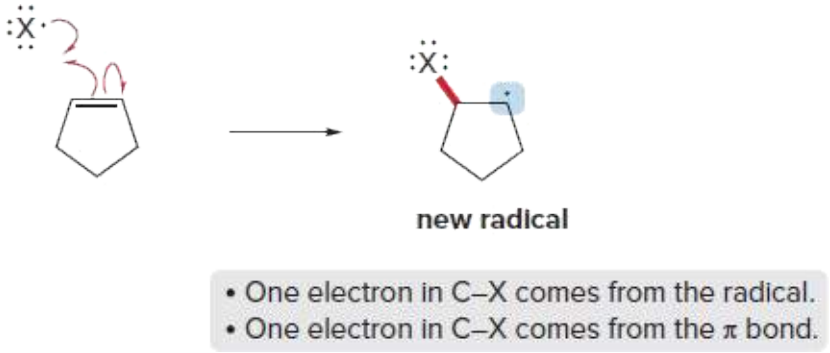
radical X• is now surrounded by an octet of electrons, and a new radical is formed.



This radical reaction is typically seen with the nonpolar C–H bonds of alkanes, which cannot react with polar or ionic electrophiles and nucleophiles.

[2] Reaction of a Radical X• with a C=C

A radical X• also adds to the π bond of a carbon–carbon double bond. One electron from the double bond is used to form a new C–X bond, and the other electron remains on the other carbon originally part of the double bond.

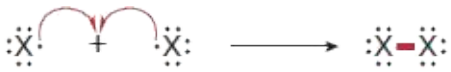


Whenever a radical reacts with a stable single or double bond, a new radical is formed in the products.

Although the electron-rich double bond of an alkene reacts with electrophiles by ionic addition mechanisms, it also reacts with radicals because these reactive intermediates are also electron deficient.

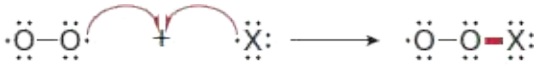
13.2B Two Radicals Reacting with Each Other

A radical, once formed, rapidly reacts with whatever is available. Usually that means a stable a or π bond. Occasionally, however, two radicals come into contact with each other, and they react to form a a bond.



• One electron in X–X comes from each radical.

The reaction of a radical with oxygen, a diradical in its ground state electronic configuration, is another example of two radicals reacting with each other. In this case, the reaction of O_2 with X• forms a new radical, thus preventing X• from reacting with an organic substrate.

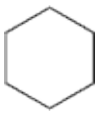


a diradical

Compounds that prevent radical reactions from occurring are called *radical inhibitors* or *radical scavengers*. Besides O_2, vitamin E and related compounds, discussed in Section 13.12, are radical scavengers, too. The fact that these compounds inhibit a reaction often suggests that the reaction occurs via radical intermediates.

Problem 13.3

Draw the products formed when a chlorine atom (Cl •) reacts with each species.

a. 

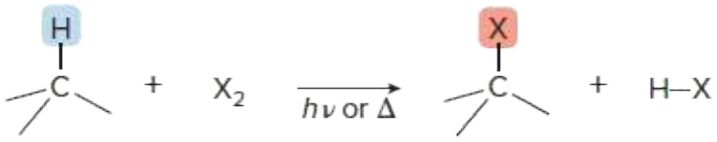
b. $CH_2{=}CH_2$

c. $CH_2{=}CH_2$

d. O_2

13.3 Halogenation of Alkanes

In the presence of light or heat, alkanes react with halogens to form alkyl halides. Halogenation is a radical substitution reaction, because a halogen atom X replaces a hydrogen via a mechanism that involves radical intermediates.

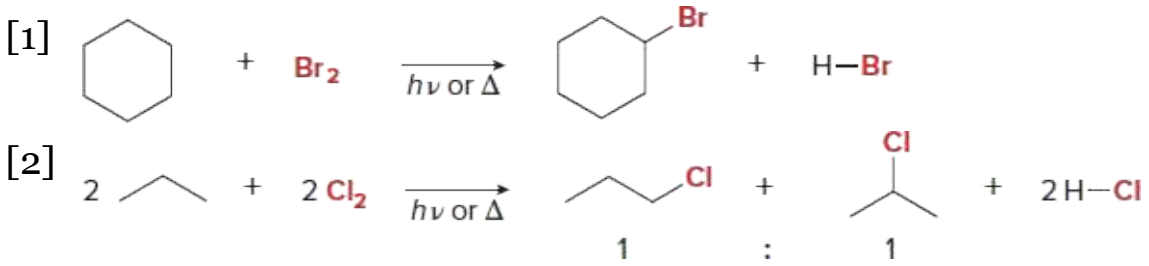


X = Cl or Br **alkyl halide**

Halogenation of alkanes is useful only with Cl_2 and Br_2. Reaction with F_2 is too violent and reaction with I_2 is too slow to be useful. With an alkane that has more than one

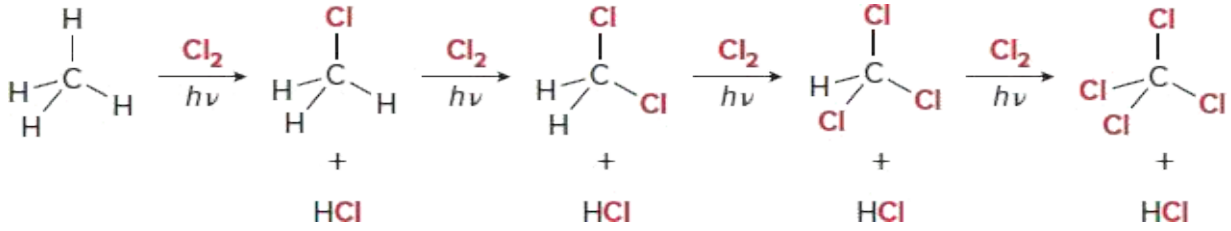
type of hydrogen atom, a mixture of alkyl halides may result (Reaction [2]).

When asked to draw the products of halogenation of an alkane, draw the products of monohalogenation only, unless specifically directed to do otherwise.



In these examples of halogenation, a halogen has replaced a single hydrogen atom on the alkane. Can the other hydrogen atoms be replaced, too? Figure 13.2 shows that when CH_4 is treated with excess Cl_2, all four hydrogen atoms can be successively replaced by Cl to form CCl_4. Monohalogenation—the substitution of a single H by X—can be achieved experimentally by adding halogen X_2 to an excess of alkane.

Figure 13.2 **Complete halogenation of CH_4 using excess Cl_2**

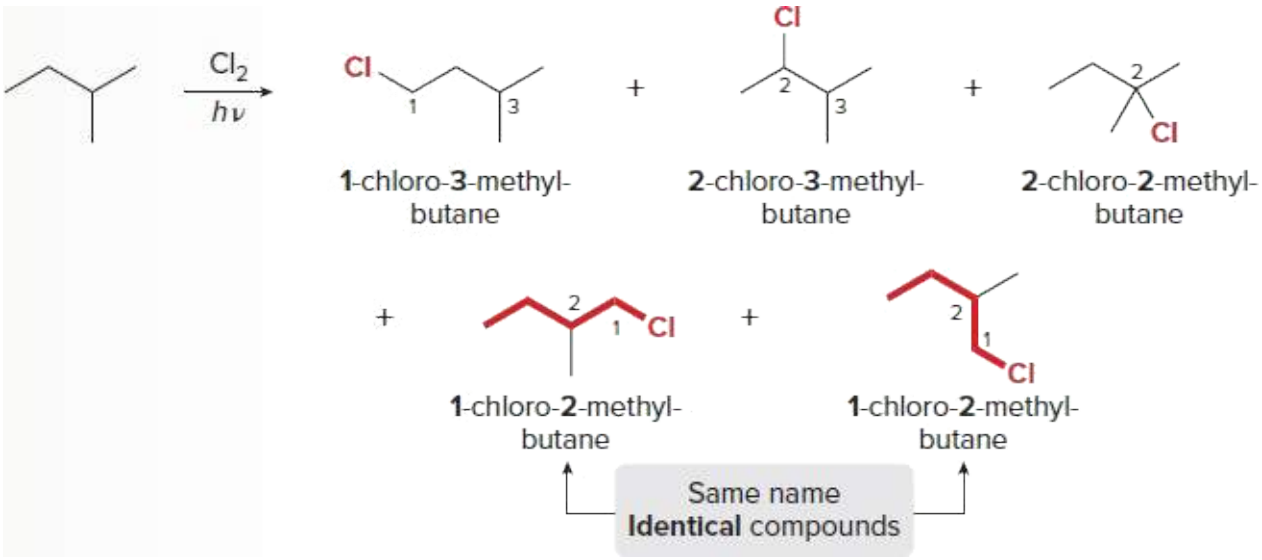


Sample Problem 13.1 Drawing the Products of the Chlorination of an Alkane

Draw all the constitutional isomers formed by monohalogenation of $(CH_3)_2CHCH_2CH_3$ with Cl_2 and hv.

Solution

Substitute Cl for H on every carbon, and then check to see if any products are identical. The starting material has five C's, but replacement of one H atom on two C's gives the same product. Thus, $(CH_3)_2CHCH_2CH_3$ affords four monochloro substitution products.



Problem 13.4

Draw all constitutional isomers formed by monochlorination of each alkane.

a.

b.

c.

More Practice:

Try Problems 13.27a, 13.32, 13.44a.

Problem 13.5

Compounds A and B are isomers having molecular formula C_5H_{12}. Heating A with Cl_2 gives a single product of monohalogenation, whereas heating B under the same conditions forms three constitutional isomers. What are the structures of A and B?

13.4 The Mechanism of Halogenation

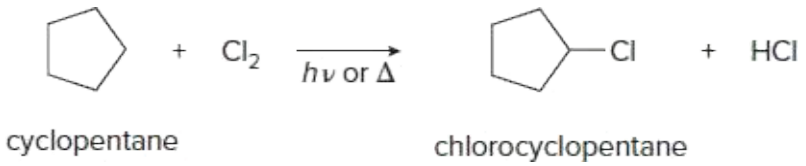
Unlike nucleophilic substitution, which proceeds by two different mechanisms depending on the starting material and reagent, all halogenation reactions of alkanes—regardless of the halogen and alkane used—proceed by the *same* mechanism. Three facts about halogenation suggest that the mechanism involves radical, not ionic, intermediates.

Fact	Explanation
[1] Light, heat, or added peroxide is necessary for the reaction.	• Light or heat provides the energy needed for homolytic bond cleavage

	to form radicals. Breaking the weak O–O bond of peroxides initiates radical reactions as well.
[2] O_2 inhibits the reaction.	• The diradical O_2 removes radicals from a reaction mixture, thus preventing reaction.
[3] No rearrangements are observed.	• Radicals do *not* rearrange.

13.4A The Steps of Radical Halogenation

The chlorination of cyclopentane illustrates the three distinct parts of radical halogenation (Mechanism 13.1):



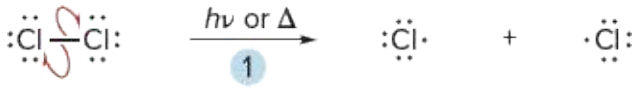
- ***Initiation*: Two radicals are formed by homolysis of a σ bond and this begins the reaction.**
- ***Propagation*: A radical reacts with another reactant to form a new σ bond and another radical.**
- ***Termination*: Two radicals combine to form a stable bond. Removing radicals from the reaction mixture without generating any new radicals stops the reaction.**

Although initiation generates the Cl• radicals needed to begin the reaction, the propagation steps ([2] and [3]) form the two reaction products—chlorocyclopentane and HCl. Once the process has begun, propagation occurs over and over without the need for Step [1] to occur. A mechanism such as radical halogenation that involves two or more repeating steps is called a *chain mechanism*. Each propagation step involves a reactive radical abstracting an atom from a stable bond to form a new bond and another radical that continues the chain.

Usually a radical reacts with a stable bond to propagate the chain, but occasionally two radicals combine, and this reaction terminates the chain. Depending on the reaction and the reaction conditions, some radical chain mechanisms can repeat thousands of times before termination occurs.

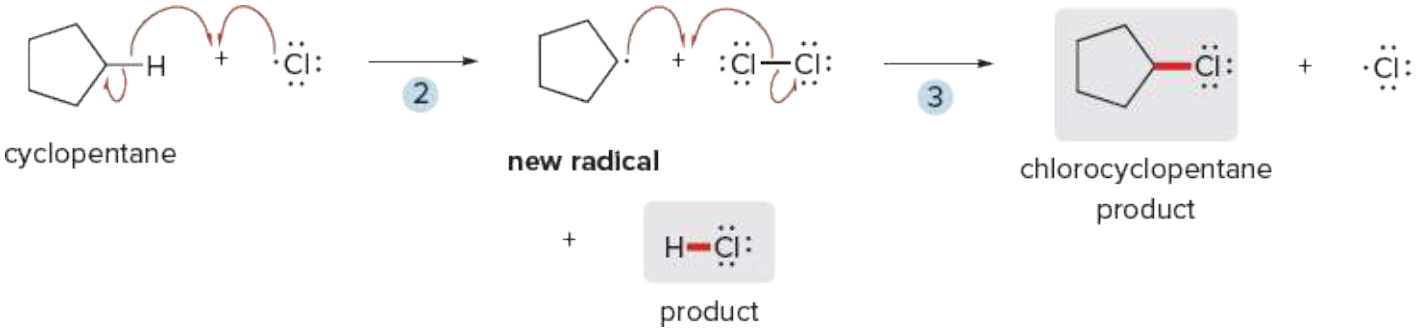
Mechanism 13.1 Radical Halogenation of Alkanes

Part [1] Initiation



1 **Bond cleavage forms two radicals. Homolysis of the weakest bond (Cl–Cl) requires light or heat and forms two chlorine radicals.**

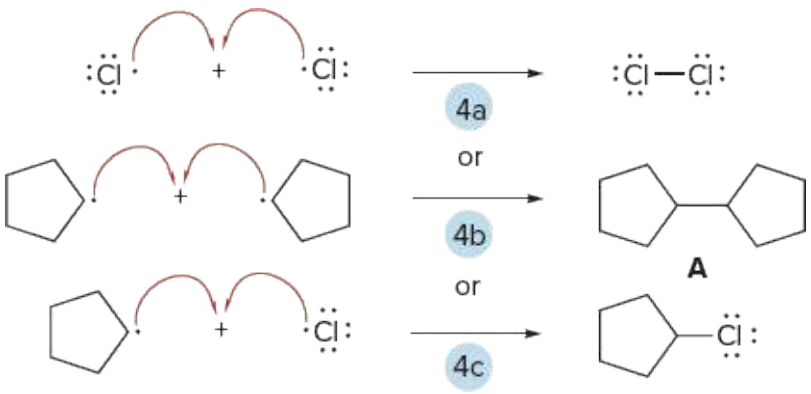
Part [2] Propagation



2 **The Cl• radical abstracts a hydrogen from cyclopentane to form HCl (a reaction product) and a new carbon radical.**

3 **The carbon radical abstracts a chlorine atom from Cl_2 to form chlorocyclopentane (a reaction product) and Cl•. Because Cl• is a reactant in Step [2], Steps [2] and [3] can occur repeatedly without additional initiation (Step [1]).**

Part [3] Termination



4 **Termination of the chain occurs when any two radicals combine to form a bond.**

Termination Step [4a] forms Cl_2, a reactant, whereas Step [4c] forms chlorocyclopentane, one of the reaction products. Termination Step [4b] forms A, which is neither a reactant nor a desired product. The formation of a small quantity of A, however, is evidence that radicals are formed in the reaction.

The most important steps of radical halogenation are those that lead to product formation—the propagation steps—so subsequent discussion of this reaction concentrates on these steps only.

Problem 13.6

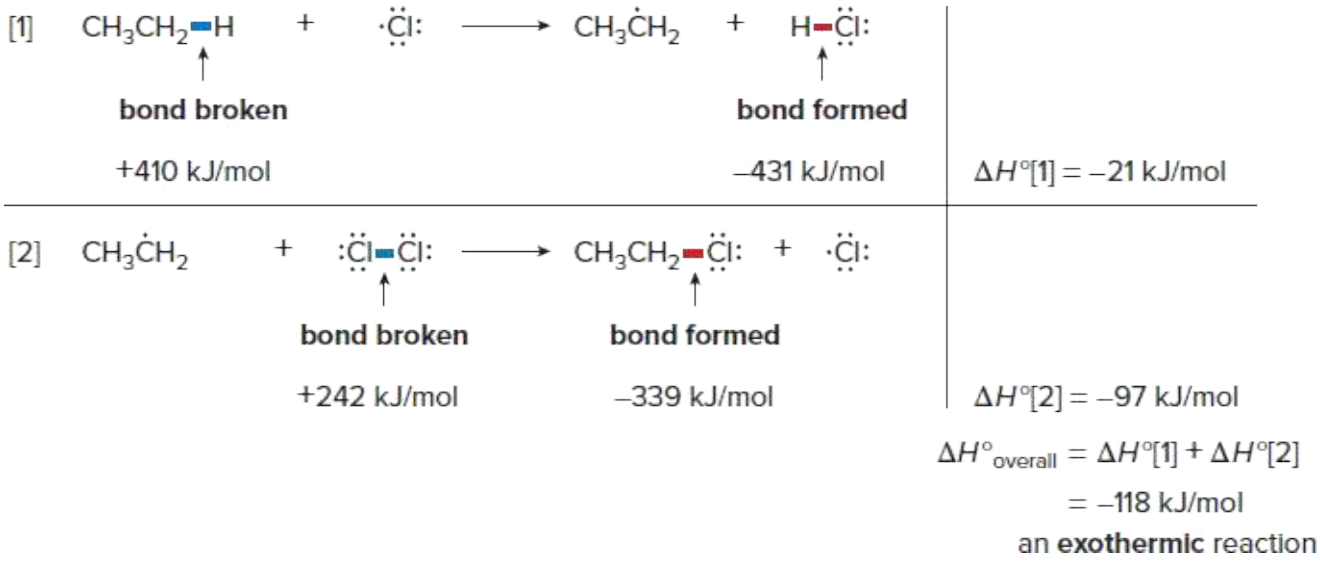
Using Mechanism 13.1 as a guide, write the mechanism for the reaction of CH_4 with Br_2 to form CH_3Br and HBr. Classify each step as initiation, propagation, or termination.

13.4B Energy Changes During the Chlorination of Ethane

The chlorination of ethane illustrates how bond dissociation energies (Section 6.4) can be used to calculate ΔH^0 in chain propagation.

$$CH_3CH_3 + Cl_2 \xrightarrow{h\nu \text{ or } \Delta} CH_3CH_2Cl + HCl$$

Figure 13.3 **Energy changes in the propagation steps during the chlorination of ethane**



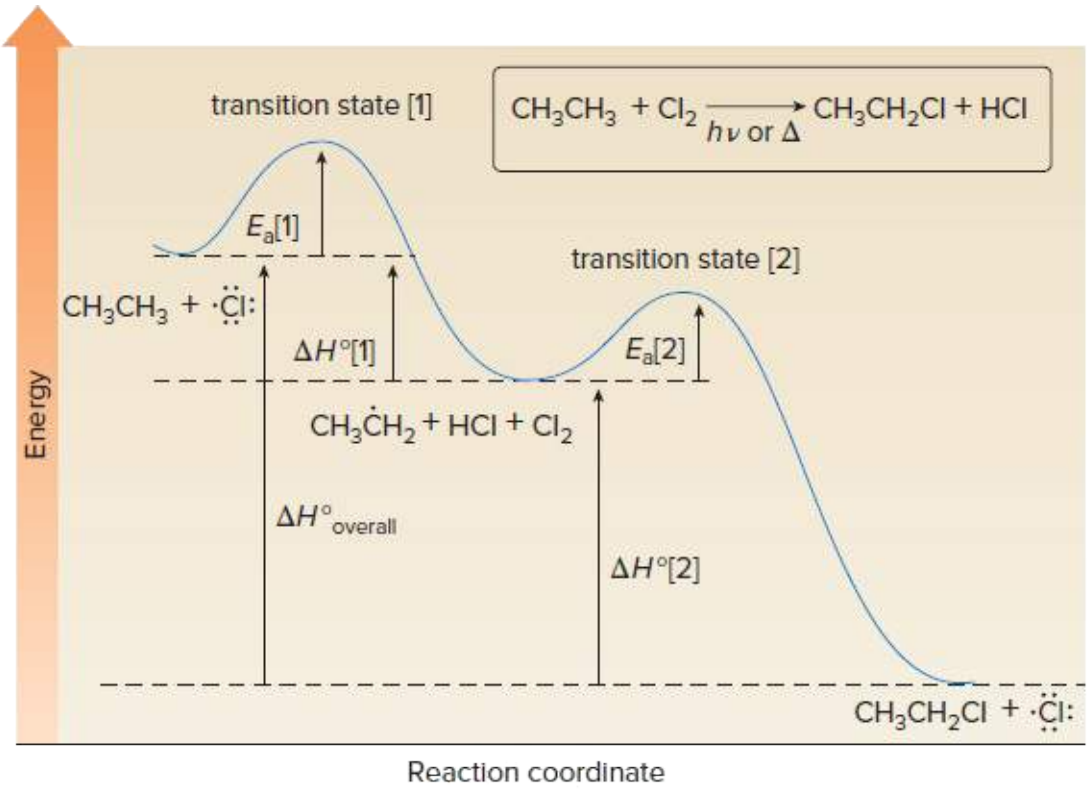
As shown in Figure 13.3, chain propagation consists of the same two steps drawn in Mechanism 13.1: abstraction of a hydrogen atom to form CH_3CH_2• and HCl, followed by abstraction of a chlorine atom by CH_3CH_2• to form CH_3CH_2Cl and a chlorine radical (Cl•). The AH° for each step is negative, making the overall AH° negative and the reaction exothermic. Because the transition state for the first propagation step is

higher in energy than the transition state for the second propagation step, the first step is rate-determining. Both of these facts are illustrated in the energy diagram in Figure 13.4.

Problem 13.7

Calculate $\Delta H°$ for the rate-determining step of the reaction of CH_4 with I_2. Explain why this result illustrates that this reaction is extremely slow.

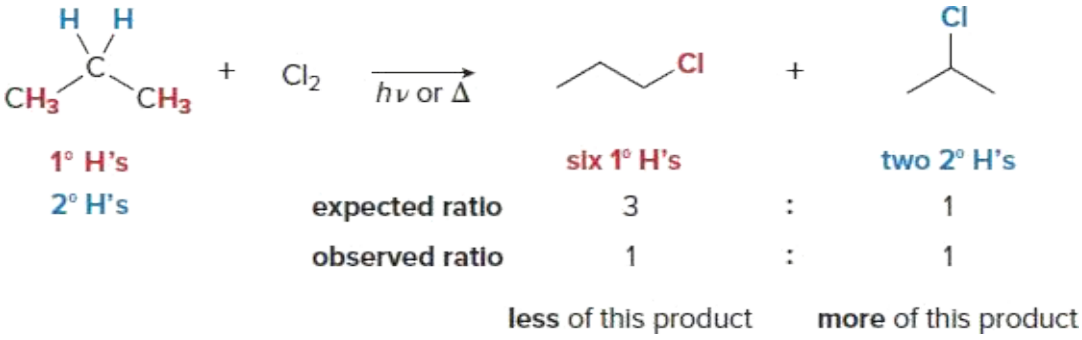
Figure 13.4 **Energy diagram for the propagation steps in the chlorination of ethane**



- Because radical halogenation consists of two propagation steps, the energy diagram has two energy barriers.
- The **first step is rate-determining** because its transition state is at higher energy.
- The **reaction is exothermic** because $\Delta H°_{overall}$ is negative.

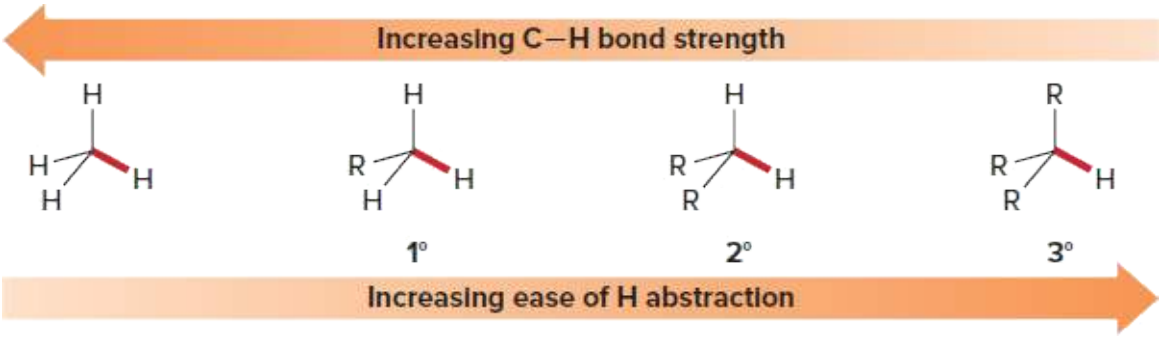
13.5 Chlorination of Other Alkanes

Recall from Section 13.3 that the chlorination of $CH_3CH_2CH_3$ affords a 1:1 mixture of $CH_3CH_2CH_2Cl$ (formed by removal of a 1° hydrogen) and (CH3)2CHCl (formed by removal of a 2° hydrogen).



$CH_3CH_2CH_3$ has six 1° hydrogen atoms and only two 2° hydrogens, so the expected product ratio of $CH_3CH_2CH_2Cl$ to $(CH_3)_2CHCl$ (assuming all hydrogens are *equally* reactive) is 3:1. Because the observed ratio is 1:1, however, the 2° C–H bonds must be *more* reactive; that is, it must be easier to homolytically cleave a 2° C–H bond than a 1° C–H bond. Recall from Section 13.2 that 2° C–H bonds are *weaker* than 1° C–H bonds. Thus,

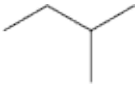
- **The *weaker* the C–H bond, the *more readily* the hydrogen atom is removed in radical halogenation.**



When alkanes react with Cl_2, a mixture of products results, with more product formed by cleavage of the weaker C–H bond than you would expect on statistical grounds.

Problem 13.8

Which C–H bond in each compound is most readily broken during radical halogenation?

a. 

b.

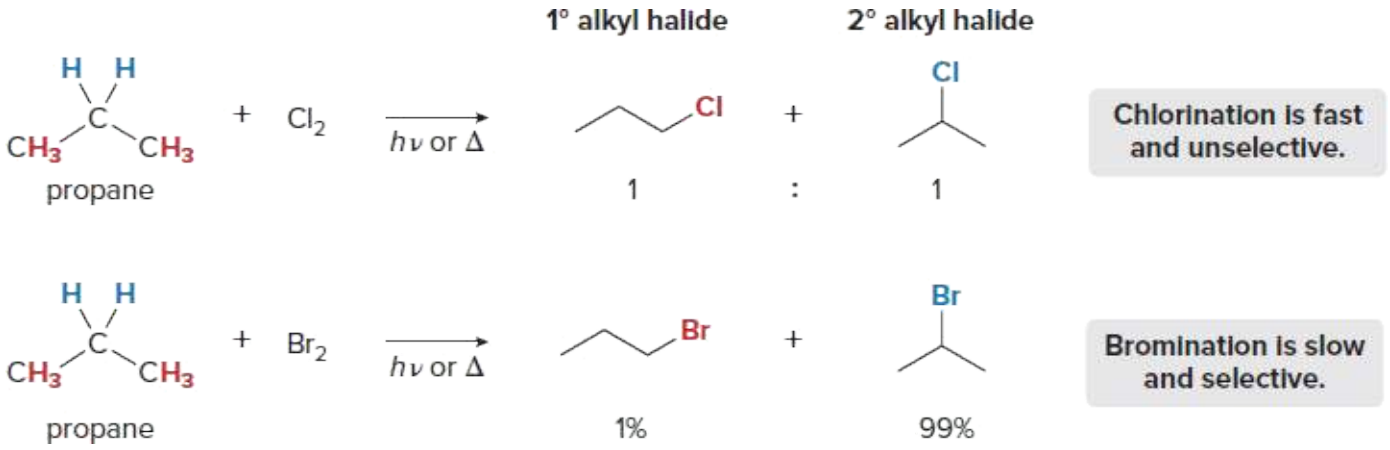
c.

13.6 Chlorination Versus Bromination

Although alkanes undergo radical substitution reactions with both Cl_2 and Br_2, chlorination and bromination exhibit two important differences:

- **Chlorination is *faster* than bromination.**
- **Although chlorination is *unselective*, yielding a mixture of products, bromination is often *selective*, yielding one major product.**

For example, propane reacts rapidly with Cl_2 to form a 1:1 mixture of 1° and 2° alkyl chlorides. On the other hand, propane reacts with Br_2 much more slowly and forms 99% $(CH_3)_2CHBr$. Page 620



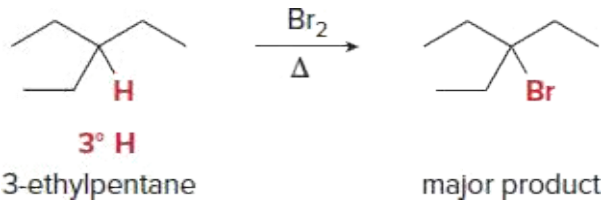
- **In bromination, the major (and sometimes exclusive) product results from cleavage of the *weakest* C–H bond.**

Sample Problem 13.2 Drawing the Product of Bromination of an Alkane

Draw the major product formed when 3-ethylpentane is heated with Br_2.

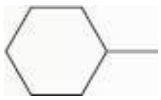
Solution

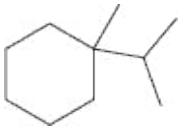
Keep in mind: the *more substituted* the carbon atom, the *weaker* the C–H bond. The major bromination product in 3-ethylpentane is formed by cleavage of the sole 3° C–H bond, its weakest C–H bond.

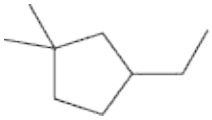


Problem 13.9

Draw the major product formed when each cycloalkane is heated with Br_2.

a. 

b. 

c. 

d.

More Practice:

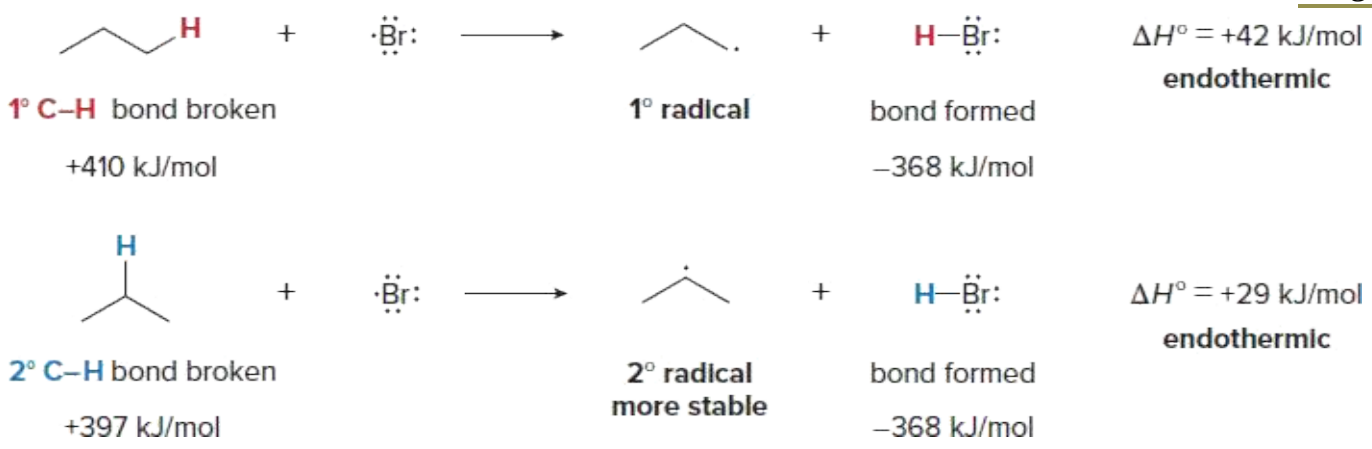
Try Problems 13.27b, 13.33, 13.44b.

To explain the difference between chlorination and bromination, we return to the Hammond postulate (Section 7.14). The rate-determining step in halogenation is the abstraction of a hydrogen atom by the halogen radical, so we must compare these steps for bromination and chlorination. Keep in mind:

- **Transition states in endothermic reactions resemble the *products.* The more stable product is formed faster.**
- **Transition states in exothermic reactions resemble the *starting materials.* The relative stability of the products does not greatly affect the relative energy of the transition states, so a mixture of products often results.**

Bromination: $CH_3CH_2CH_3 + Br_2$

A bromine radical can abstract either a 1° or a 2° hydrogen from propane, generating either a 1° radical or a 2° radical. Calculating $\Delta H°$ using bond dissociation energies reveals that both reactions are *endothermic*, but it takes *less energy* to form the *more stable* 2° radical.

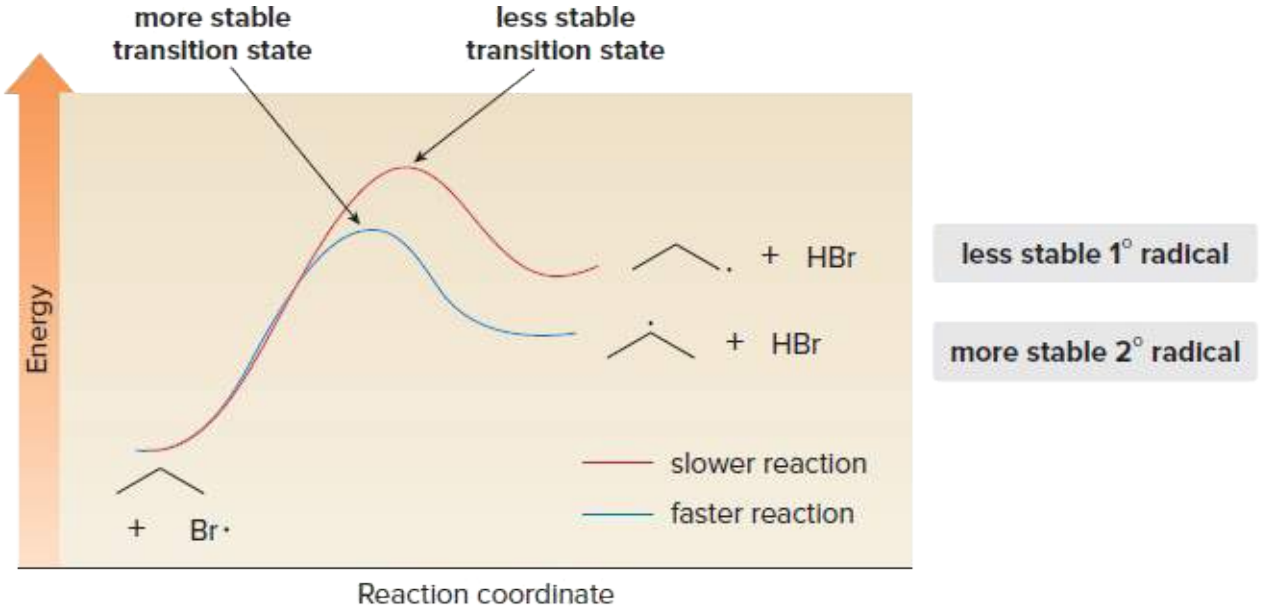


According to the Hammond postulate, the transition state of an endothermic reaction

resembles the *products*, so the energy of activation to form the more stable 2° radical is lower and it is formed faster, as shown in the energy diagram in Figure 13.5. Because the 2° radical [$(CH_3)_2CH•$] is converted to 2-bromopropane [(CH3)2CHBr] in the second propagation step, this 2° alkyl halide is the major product of bromination.

- **Conclusion: Because the rate-determining step in bromination is *endothermic*, the *more stable* radical is formed faster, and often a single radical halogenation product predominates.**

Figure 13.5 **Energy diagram for a selective endothermic reaction**



- The transition state to form the less stable 1° radical ($CH_3CH_2CH_2•$) is higher in energy than the transition state to form the more stable 2° radical [$(CH_3)_2CH•$]. Thus, **the 2° radical is formed faster.**

Chlorination: $CH_3CH_2CH_3 + Cl_2$

A chlorine radical can also abstract either a 1° or a 2° hydrogen from propane, generating either a 1° radical or a 2° radical. Calculating $\Delta H°$ using bond dissociation energies reveals that both reactions are exothermic.

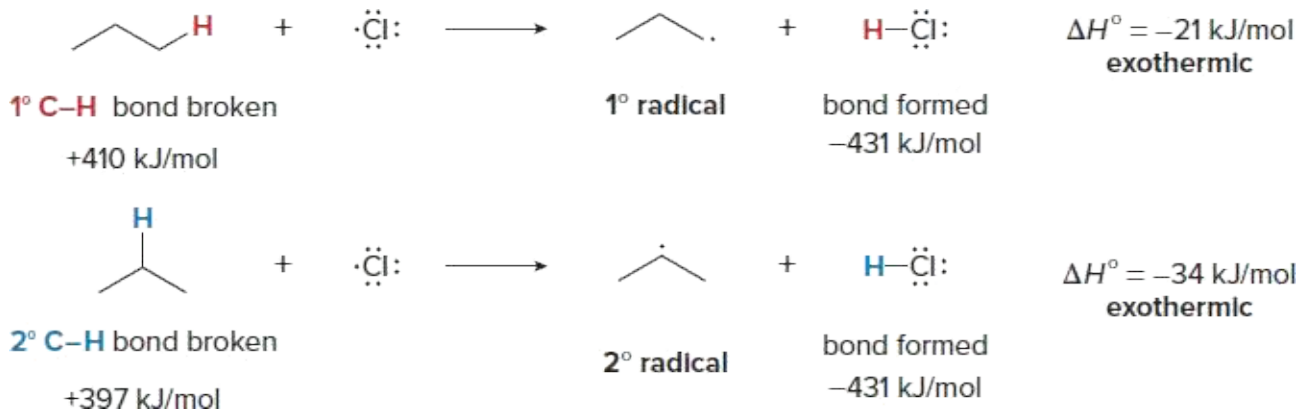
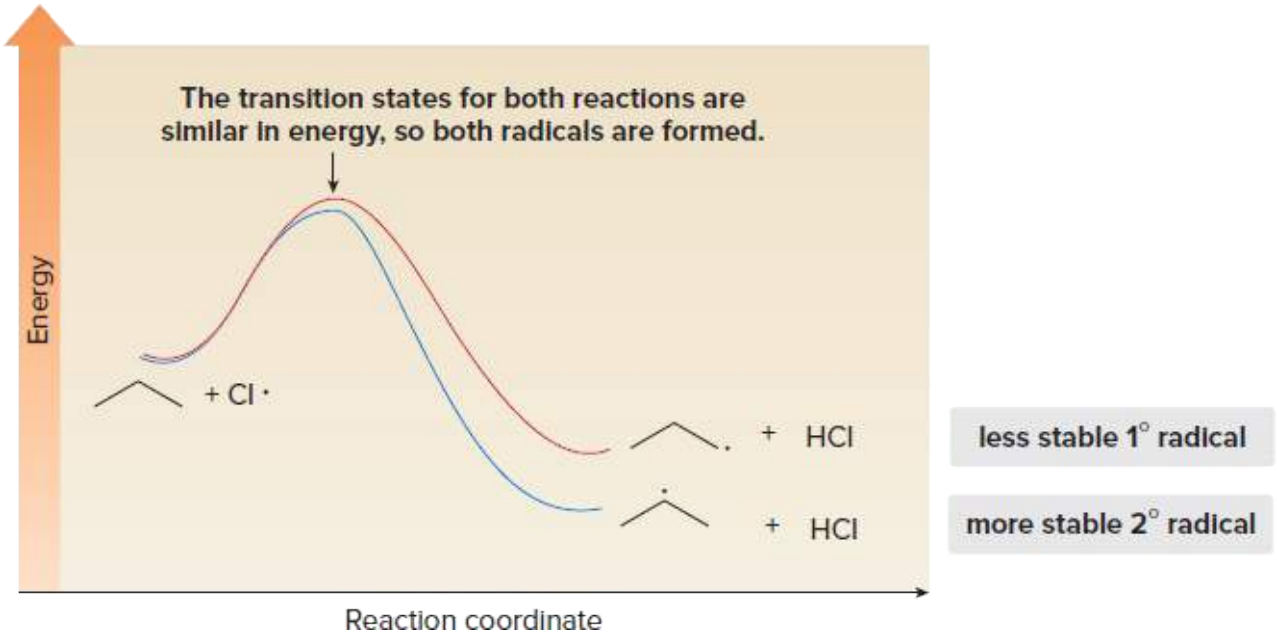


Figure 13.6 **Energy diagram for a nonselective exothermic reaction**



Because chlorination has an *exothermic* rate-determining step, the transition state to form both radicals resembles the same starting material, $CH_3CH_2CH_3$. As a result, the relative stability of the two radicals is much less important and both radicals are formed. An energy diagram for these processes is drawn in Figure 13.6. Because the 1° and 2° radicals are converted to 1-chloropropane ($CH_3CH_2CH_2Cl$) and 2-chloropropane [$(CH_3)_2CHCl$], respectively, in the second propagation step, both alkyl halides are formed in chlorination.

- **Conclusion: Because the rate-determining step in chlorination is *exothermic*, the transition state resembles the starting material, both radicals are formed, and a *mixture* of products results.**

Problem 13.10

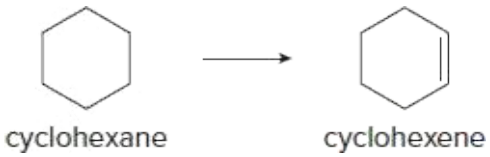
Reaction of $(CH_3)_3CH$ with Cl_2 forms two products: $(CH_3)_2CHCH_2Cl$ (63%) and $(CH_3)_3CCl$ (37%). Why is the major product formed by cleavage of the stronger 1° C–H bond?

13.7 Halogenation as a Tool in Organic Synthesis

Halogenation is a useful tool because it adds a functional group to a previously unfunctionalized molecule, making an alkyl halide. These alkyl halides can then be converted to alkenes by elimination, and to alcohols and ethers by nucleophilic substitution.

Sample Problem 13.3 Using Halogenation in Synthesis

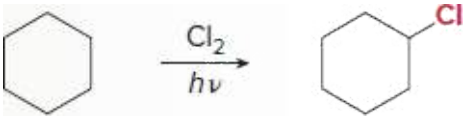
Show how cyclohexane can be converted to cyclohexene by a stepwise sequence.



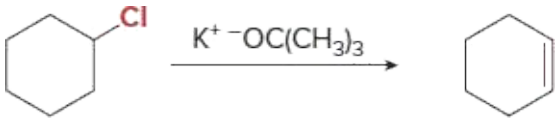
Solution

There is no one-step method to convert an alkane to an alkene. A two-step method is needed:

[1] Radical halogenation produces an alkyl halide.

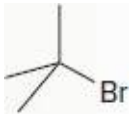


[2] Elimination of HCl with a strong base produces cyclohexene.

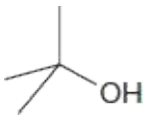


Problem 13.11

Synthesize each compound from $(CH_3)_3CH$.

a. 

b.

c. 

More Practice:

Try Problems 13.58a, b, d; 13.59; 13.61–13.63.

Problem 13.12

Show all steps and reagents needed to convert cyclohexane into each compound: (a) the two enantiomers of trans-1,2-dibromocyclohexane; and (b) 1,2-epoxycyclohexane.

13.8 The Stereochemistry of Halogenation Reactions

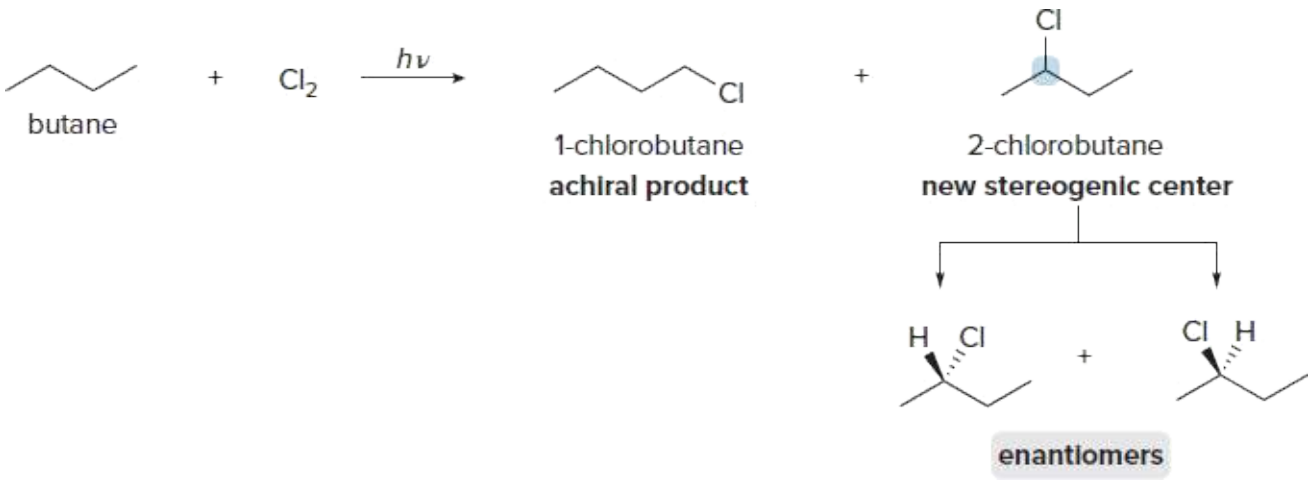
The stereochemistry of a reaction product depends on whether the reaction occurs at a stereogenic center or at another atom, and whether a new stereogenic center is formed. The rules predicting the stereochemistry of reaction products are summarized in Table 13.1.

Table 13.1 Rules for Predicting the Stereochemistry of Reaction Products

Starting material	Result
Achiral	• An achiral starting material always gives either an achiral or a racemic product.
Chiral	• If a reaction does not occur at a stereogenic center, the configuration at a stereogenic center is *retained* in the product. • I f a reaction occurs at a stereogenic center, we must know the *mechanism* to predict the stereochemistry of the product.

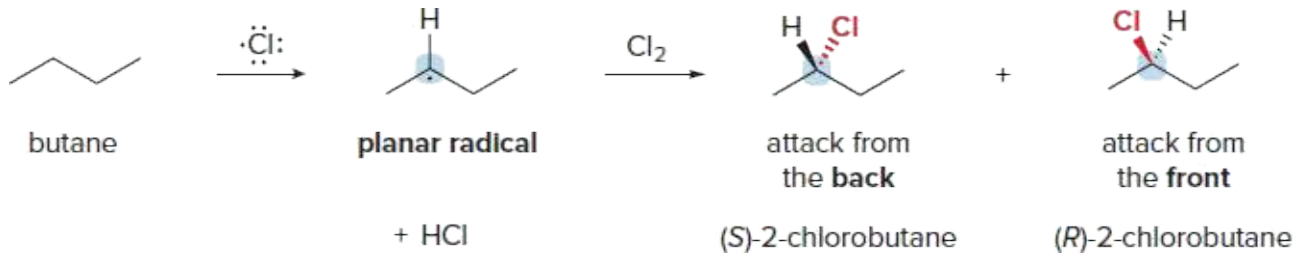
13.8A Halogenation of an Achiral Starting Material

Halogenation of the achiral starting material $CH_3CH_2CH_2CH_3$ forms two constitutional isomers by replacement of either a 1° or 2° hydrogen.



- 1-Chlorobutane ($CH_3CH_2CH_2CH_2Cl$) has no stereogenic center, so it is an achiral compound.
- 2-Chlorobutane [$CH_3CH(Cl)CH_2CH_3$] has a new stereogenic center, so an equal amount of two enantiomers must form—a racemic mixture.

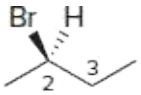
A racemic mixture results when a new stereogenic center is formed because the first propagation step generates a planar, sp^2 hybridized radical. Cl_2 then reacts with the planar radical from either the front or back side to form an equal amount of two enantiomers.



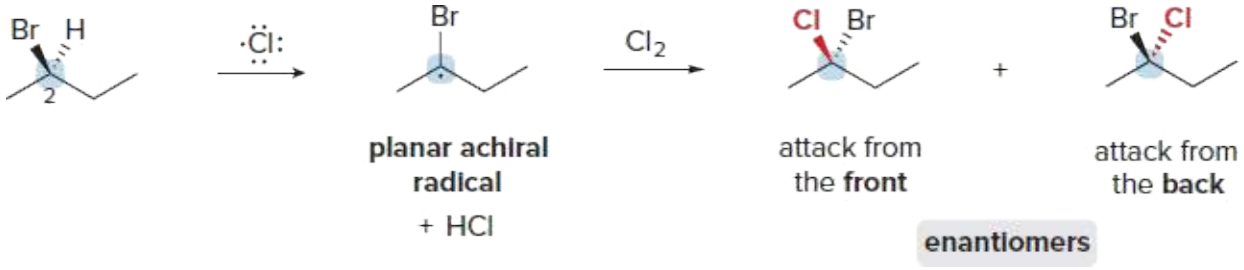
Thus, the achiral starting material butane forms an achiral product (1-chlorobutane) and a racemic mixture of two enantiomers [(*R*)- and (*S*)-2-chlorobutane].

13.8B Halogenation of a Chiral Starting Material

Let's now examine chlorination of the chiral starting material (*R*)-2-bromobutane at C2 and C3.



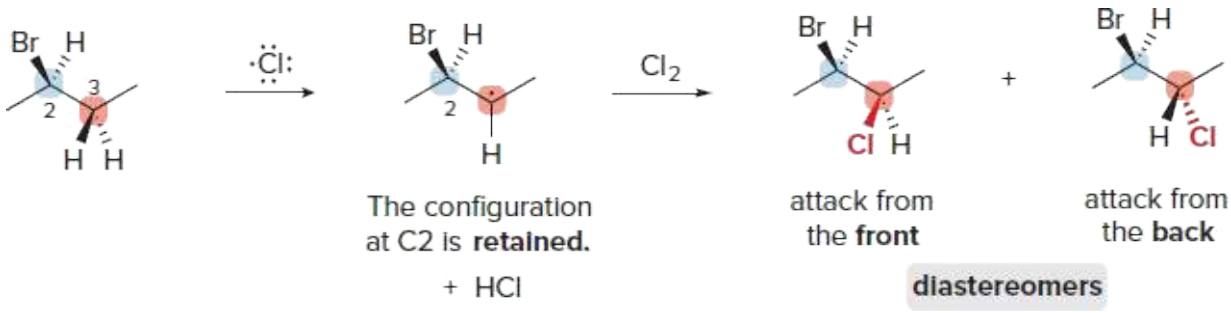
Chlorination at C2 occurs at the stereogenic center. Abstraction of a hydrogen atom at C2 forms a trigonal planar sp^2 hybridized radical that is now achiral. This achiral radical then reacts with Cl_2 from either side to form a new stereogenic center, resulting in an equal amount of two enantiomers—a racemic mixture.



- **Radical halogenation reactions occur with *racemization* at a stereogenic center.**

Chlorination at C3 does *not* occur at the stereogenic center, but it forms a new stereogenic center. Because no bond is broken to the stereogenic center at C2, its configuration is *retained* during the reaction. Abstraction of a hydrogen atom at C3 forms a trigonal planar sp^2 hybridized radical that still contains this stereogenic

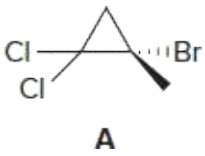
center. Reaction of the radical with Cl_2 from either side forms a new stereogenic center, so the products have two stereogenic centers: the configuration at C2 is the *same* in both compounds, but the configuration at C3 is *different*, making them diastereomers.



Thus, four isomers are formed by chlorination of (*R*)-2-bromobutane at C2 and C3. Attack at the stereogenic center (C2) gives a product with one stereogenic center, resulting in a mixture of enantiomers. Attack at C3 forms a new stereogenic center, giving a mixture of diastereomers.

Sample Problem 13.4 Drawing All Stereoisomers Formed by Monochlorination

Draw all stereoisomers formed by monochlorination of A.



A

Solution

Look at each C bonded to H's *separately*, and consider whether the reaction occurs *at* a stereogenic center or if it *forms* a stereogenic center. The reactant A contains one stereogenic center, making it chiral.

The CH_3 in blue is *not* a stereogenic center, and substitution of a H atom by Cl does *not* form a new stereogenic center. One stereoisomer B is formed, and the configuration of the stereogenic center is retained.

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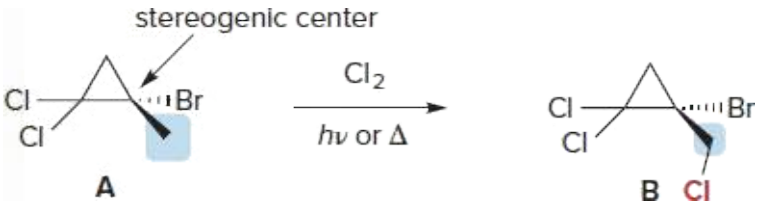
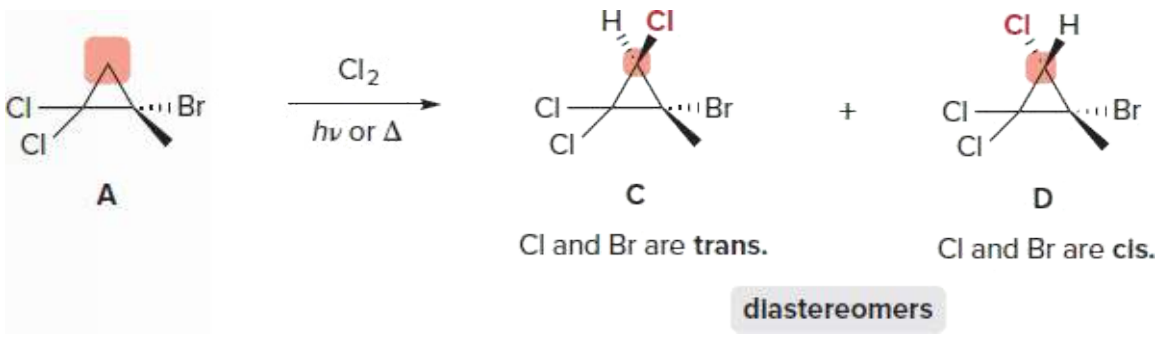


The CH_2 in red is *not* a stereogenic center, but substitution of a H atom by Cl forms a *new* stereogenic center, and the new bond to Cl can form from either

above or below the planar radical intermediate. Two products, C and D, are diastereomers.



Thus, chlorination of A forms three products, B, C, and D.

Problem 13.13

What products are formed from monochlorination of (*R*)-2-bromobutane at C1 and C4? Assign *R* and S designations to each stereogenic center.

More Practice:

Try Problems 13.47–13.51.

Problem 13.14

Draw the monochlorination products formed when each compound is heated with Cl_2. Include the stereochemistry at any stereogenic center.

a.

b.

c.

d.

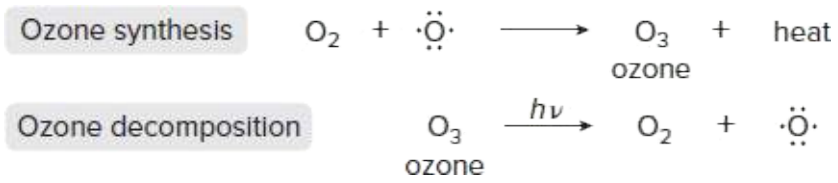
H Cl

(Consider attack at C2 and C3 only.)

The 1995 Nobel Prize in Chemistry was awarded to Mario Molina, Paul Crutzen, and F. Sherwood Rowland for their work in elucidating the interaction of ozone with CFCs.

13.9 Application: The Ozone Layer and CFCs

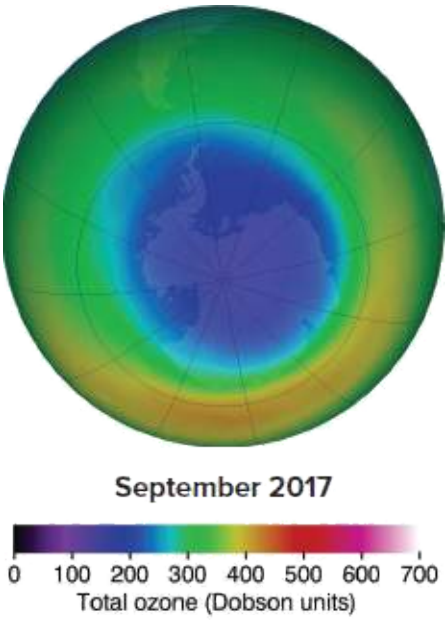
Ozone is formed in the upper atmosphere by reaction of oxygen molecules with oxygen atoms. Ozone is also decomposed with sunlight back to these same two species. The overall result of these reactions is to convert high-energy ultraviolet light into heat.



Ozone is vital to life; it acts like a shield, protecting the earth's surface from destructive ultraviolet radiation. A decrease in ozone concentration in this protective layer would have some immediate consequences, including an increase in the incidence of skin cancer and eye cataracts. Other long-term effects include a reduced immune response, interference with photosynthesis in plants, and harmful effects on the growth of plankton, the mainstay of the ocean food chain.

Propane and butane are now used as propellants in spray cans in place of CFCs.

©McGraw-Hill Education/Jill Braaten, photographer



O_3 destruction is most severe in the region of the South Pole, where a large ozone hole is visible with satellite imaging.
Source: NASA Ozone Watch

Current research suggests that chlorofluorocarbons (CFCs) are responsible for destroying ozone in the upper atmosphere. CFCs are simple halogen-containing organic compounds manufactured under the trade name Freons.

$CFCl_3$

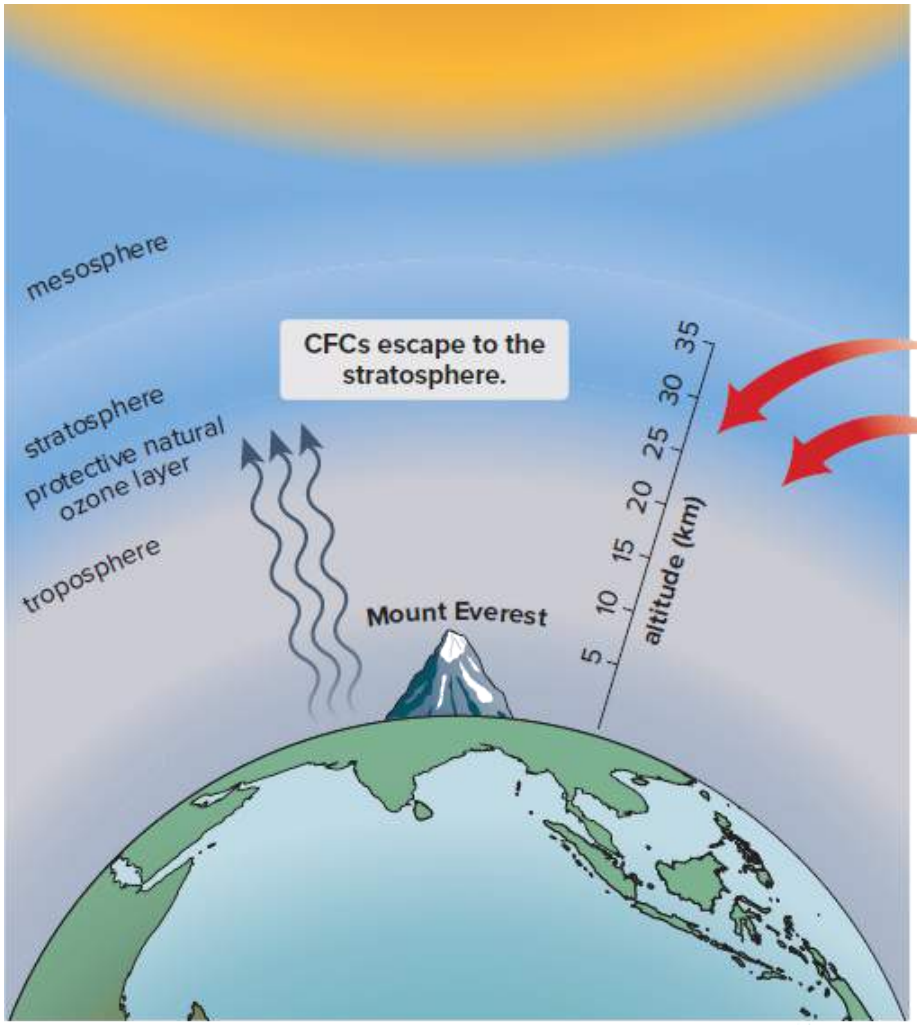
trichlorofluoromethane
CFC 11
Freon 11

CF_2Cl_2

dichlorodifluoromethane
CFC 12
Freon 12

CFCs are inert, odorless, and nontoxic, and they have been used as refrigerants, solvents, and aerosol propellants. Because CFCs are volatile and water insoluble, they readily escape into the upper atmosphere, where they are decomposed by high-energy sunlight to form radicals that destroy ozone by the radical chain mechanism shown in Figure 13.7.

Figure 13.7 **CFCs and the destruction of the ozone layer**



Initiation: CFCs are decomposed by sunlight to form chlorine radicals.

$$CFCl_3 \xrightarrow{h\nu} \cdot CFCl_2 + \cdot\ddot{Cl}:$$

Propagation: Ozone is destroyed by a chain reaction with radical intermediates.

$$\cdot\ddot{Cl}: + O_3 \longrightarrow :\ddot{Cl}-\ddot{O}\cdot + O_2$$

$$:\ddot{Cl}-\ddot{O}\cdot + \cdot\ddot{O}\cdot \longrightarrow \cdot\ddot{Cl}: + O_2$$

- The chain reaction is initiated by homolysis of a C—Cl bond in $CFCl_3$.
- Propagation consists of two steps. Reaction of Cl· with O_3 forms chlorine monoxide (ClO·), which reacts with oxygen atoms to form O_2 and Cl·.

The overall result is that O_3 is consumed as a reactant and O_2 molecules are formed. In this way, a small amount of CFC can destroy a large amount of O_3. These findings led to a ban on the use of CFCs in aerosol propellants in the United States in 1978 and to the phasing out of their use in refrigeration systems.

Newer alternatives to CFCs are hydrofluorocarbons (HFCs) such as CH_2FCF_3 and hydrofluoroolefins (HFOs) such as $CH_2{=}CFCF_3$. These compounds have many properties in common with CFCs, but they are largely decomposed before they reach the stratosphere and therefore have little impact on the ozone layer. HFOs are especially attractive because, unlike CFCs, they also have little global warming potential.

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CH_2FCF_3
HFC-134a

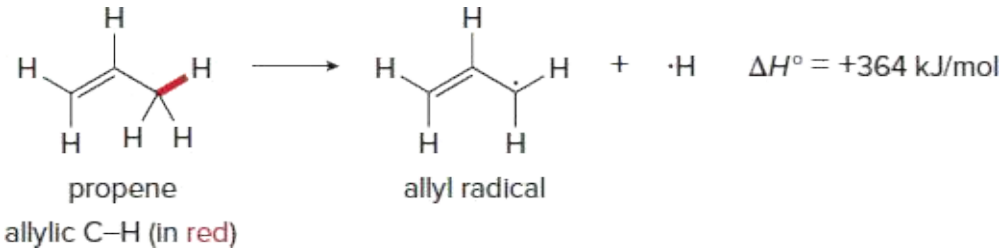
2,3,3,3-tetrafluoropropene
HFO-1234yf

Problem 13.15

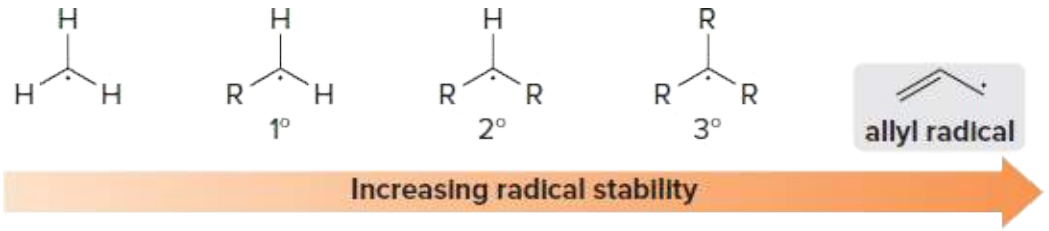
CH_2FCF_3 is decomposed before it reaches the stratosphere by abstraction of a hydrogen atom by the hydroxy radical (•OH). Draw the products of this reaction.

13.10 Radical Halogenation at an Allylic Carbon

Now let's examine radical halogenation at an *allylic carbon*—the carbon adjacent to a double bond. Homolysis of the allylic C–H bond of propene generates the allyl radical, which has an unpaired electron on the carbon adjacent to the double bond.

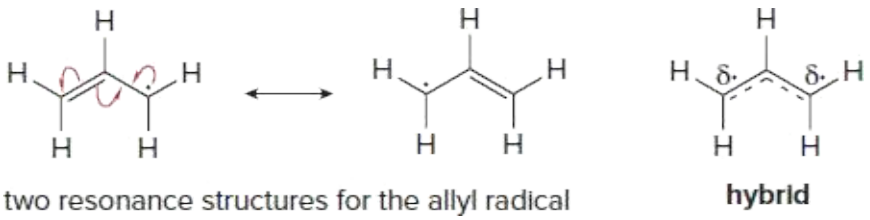


The bond dissociation energy for this process (364 kJ/mol) is even less than that for a 3° C–H bond (381 kJ/mol). Because the weaker the C–H bond, the more stable the resulting radical, an allyl radical is more stable than a 3° radical, and the following order of radical stability results:



The position of the atoms and the σ bonds stays the same in drawing resonance structures. Resonance structures differ in the location of only % bonds and nonbonded electrons.

The allyl radical is more stable than other radicals because two resonance structures can be drawn for it.



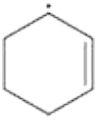
- **The "true" structure of the allyl radical is a hybrid of the two resonance structures. In the hybrid, the % bond and the unpaired electron are delocalized.**

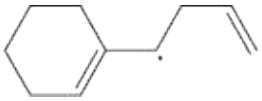
- **Delocalizing electron density lowers the energy of the hybrid, thus stabilizing the allyl radical.**

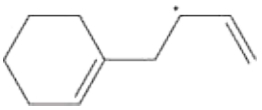
Problem 13.16

Draw a second resonance structure for each radical. Then draw the hybrid.

a.

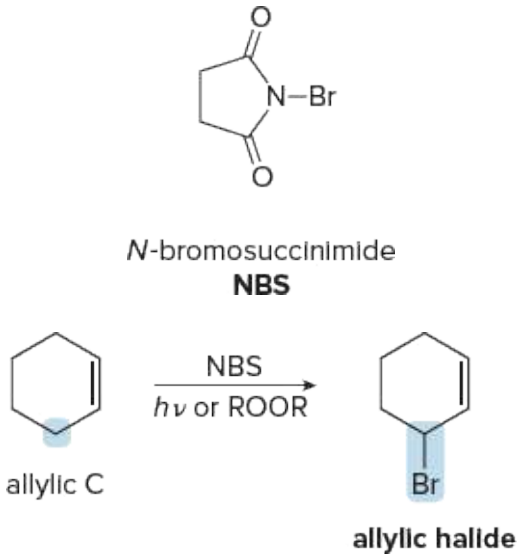
b. 

c. 

d. 

13.10A Selective Bromination at Allylic C–H Bonds

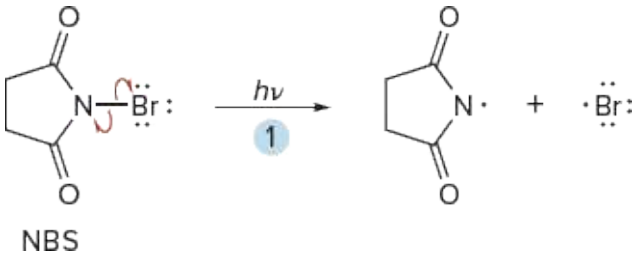
Because allylic C–H bonds are *weaker* than other sp^3 hybridized C–H bonds, the allylic carbon can be selectively halogenated by using *N*-bromosuccinimide (NBS, Section 10.15) in the presence of light or peroxides. Under these conditions only the allylic C–H bond in cyclohexene reacts to form an allylic halide.



NBS contains a weak N–Br bond that is homolytically cleaved with light to generate a bromine radical, initiating an allylic halogenation reaction. Propagation then consists of the usual two steps of radical halogenation as shown in Mechanism 13.2.

Mechanism 13.2 Allylic Bromination with NBS

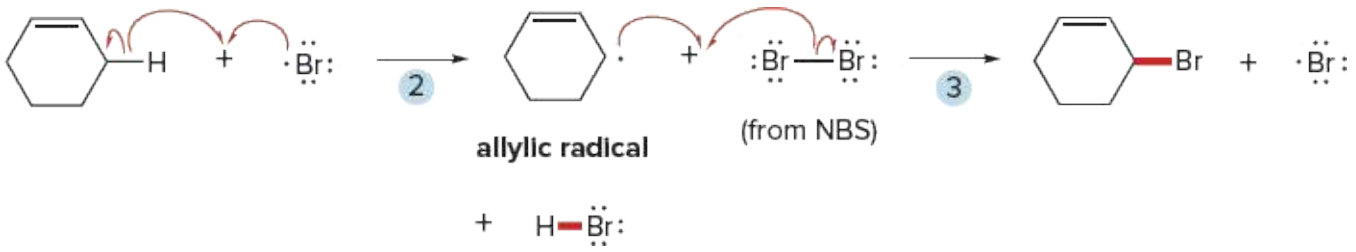
Part [1] Initiation



NBS

1 Homolysis of the weak N–Br bond with light energy forms a Br• radical that initiates radical halogenation.

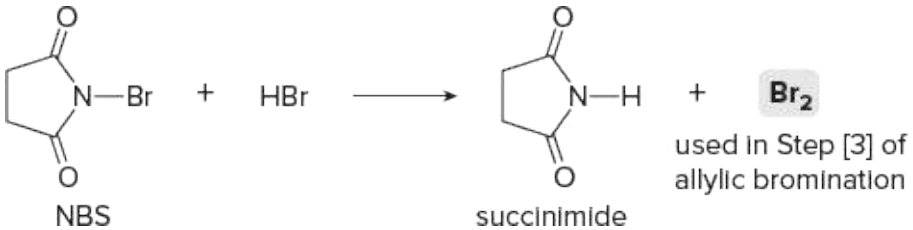
Part [2] Propagation



2 The Br• radical abstracts an allylic H to afford an allylic radical. (Only one resonance structure is drawn.)

3 The allylic radical reacts with Br_2 to form the allylic halide. The radical Br• formed in Step [3] can now react in Step [2], so Steps [2] and [3] can repeatedly occur without additional initiation.

Besides acting as a source of Br• to initiate the reaction, NBS generates a low concentration of Br_2 needed in the second chain propagation step (Step [3] of the mechanism). The HBr formed in Step [2] reacts with NBS to form Br_2, which is then used for halogenation in Step [3] of the mechanism.

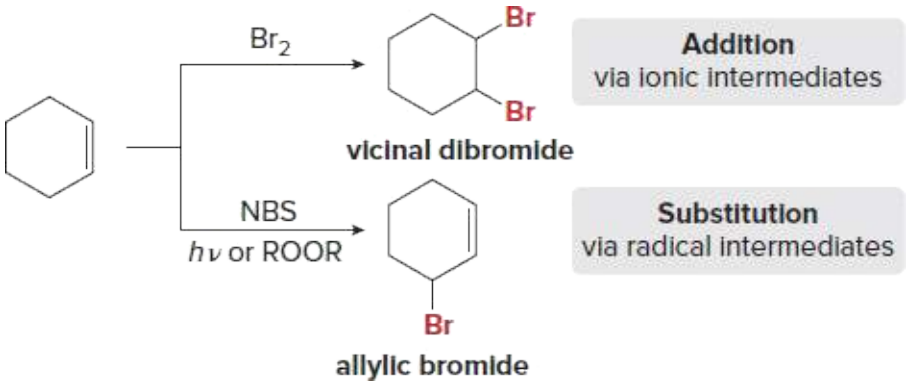


NBS succinimide

A low concentration of Br_2 (from NBS) favors allylic substitution (over addition) in part because bromine is needed for only *one* step of the mechanism. When Br_2 adds to a double bond, a low Br_2 concentration would first form a low

concentration of bridged bromonium ion (Section 10.13), which must then react with more bromine (in the form of Br^-) in a second step to form a dibromide. If concentrations of both intermediates–bromonium ion and Br^-–are low, the overall rate of addition is very slow.

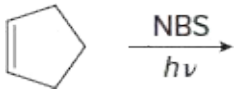
Thus, an alkene with allylic C–H bonds undergoes two different reactions depending on the reaction conditions.

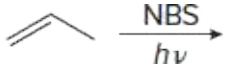


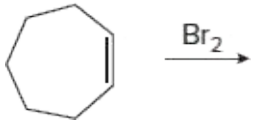
- Treatment of cyclohexene with Br2 (in an organic solvent like CCl_4) leads to addition via ionic intermediates (Section 10.13).
- Treatment of cyclohexene with NBS (+ *hν* or ROOR) leads to allylic substitution, via radical intermediates.

Problem 13.17

Draw the products of each reaction.

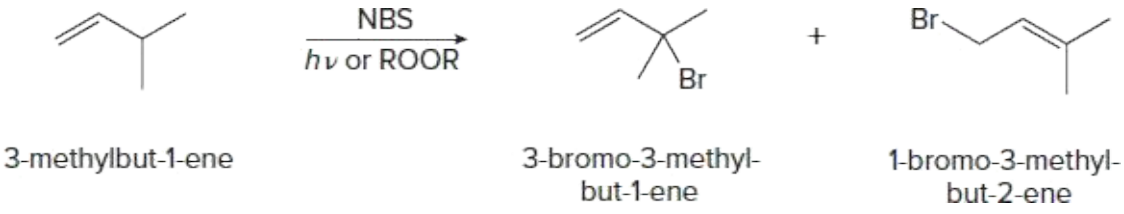
a. 

b. 

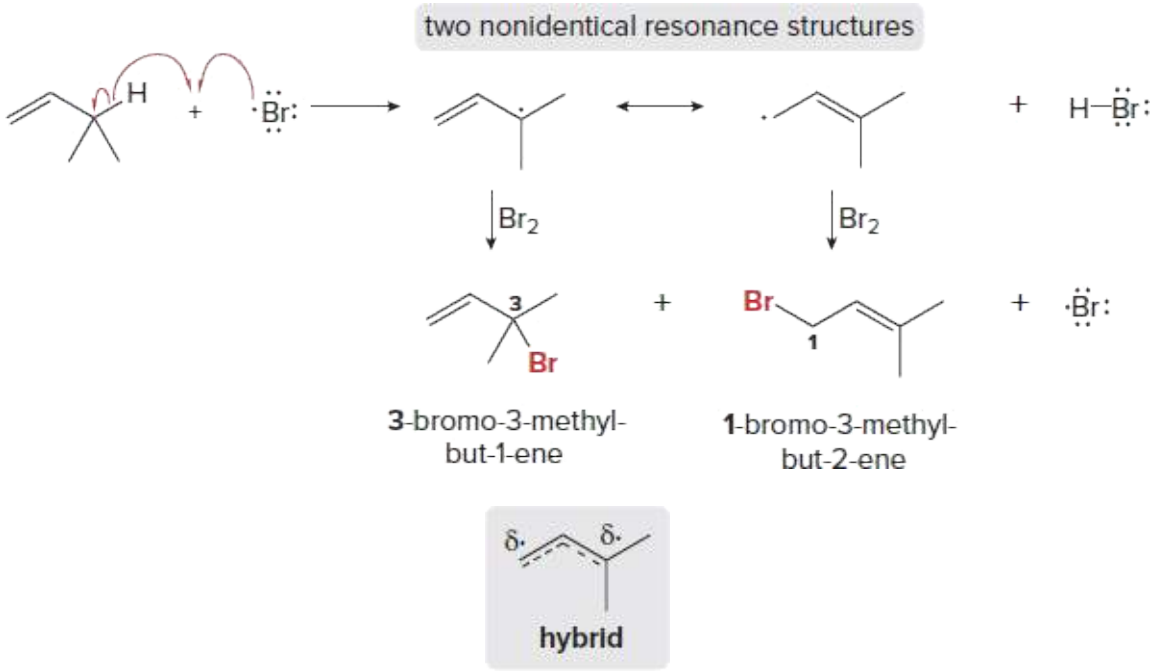
c. 

13.10B Product Mixtures in Allylic Halogenation

Halogenation at an allylic carbon often results in a mixture of products. For example, bromination of 3-methylbut-1-ene under radical conditions forms a mixture of 3-bromo-3-methylbut-1-ene and 1-bromo-3-methylbut-2-ene.



A mixture is obtained because the reaction proceeds by way of a resonance-stabilized radical. Abstraction of an allylic hydrogen from the alkene with a Br• radical (from NBS) forms an allylic radical for which two different Lewis structures can be drawn.

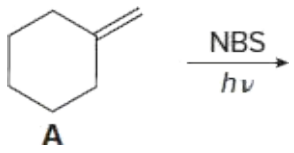


As a result, two different C atoms have partial radical character (indicated by δ•), so that Br_2 reacts at two different sites and two allylic halides are formed.

- **Whenever two different resonance structures can be drawn for an allylic radical, two *different* allylic halides are formed by radical substitution.**

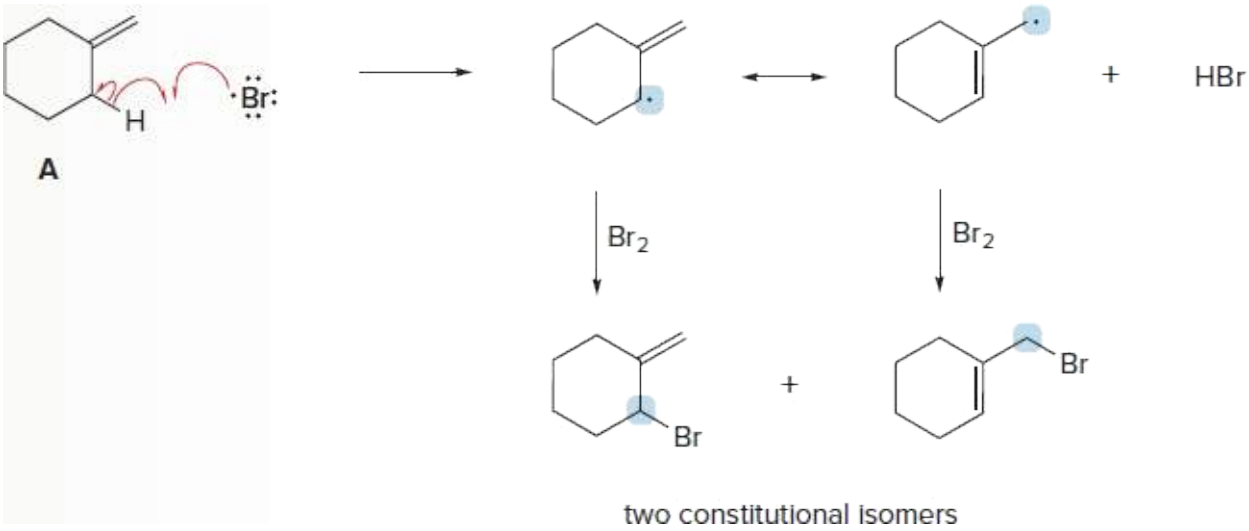
Sample Problem 13.5 Drawing the Products of Allylic Halogenation

Draw the products formed when A is treated with NBS + *hν*.



Solution

Hydrogen abstraction at the allylic C forms a resonance-stabilized radical (with two different resonance structures) that reacts with Br_2 to form two constitutional isomers as products.



Problem 13.18

Draw all constitutional isomers formed when each alkene is treated with NBS + *hv*.

a.

b.

c.

More Practice:

Try Problems 13.41, 13.42, 13.44f.

Problem 13.19

Draw the structure of the four allylic halides formed when 3-methylcyclohexene undergoes allylic halogenation with NBS + *hv*.

13.11 Application: Oxidation of Unsaturated Lipids

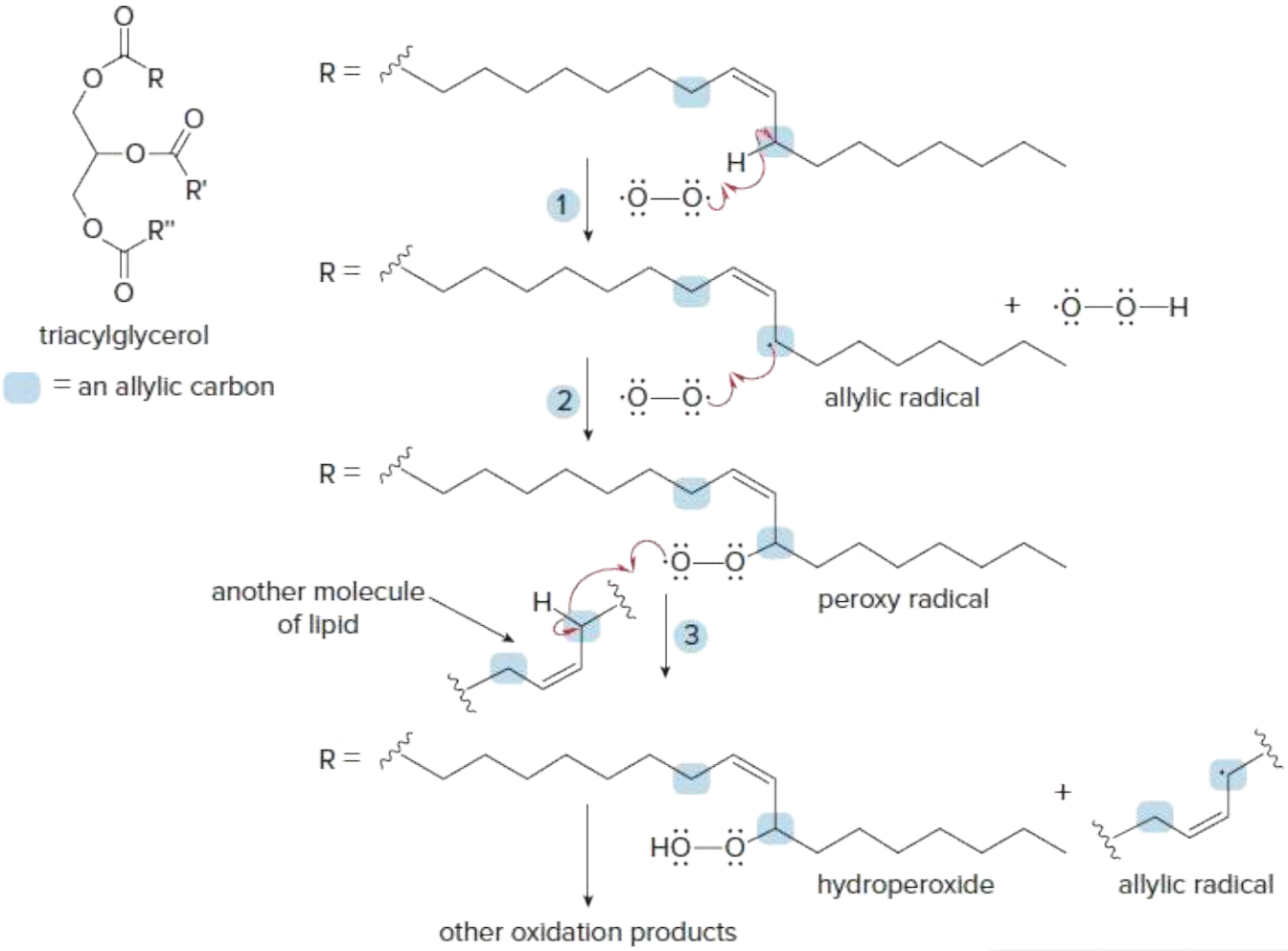
Oils—triacylglycerols having one or more sites of unsaturation in their long carbon chains—are susceptible to oxidation at their allylic carbon atoms. Oxidation occurs by way of a radical chain mechanism, as shown in Figure 13.8.

- Step [1] Oxygen in the air abstracts an allylic hydrogen atom to form an allylic radical because the allylic C–H bond is weaker than the other C–H bonds.
- Step [2] The allylic radical reacts with another molecule of O_2 to form a peroxy radical.
- Step [3] The peroxy radical abstracts an allylic hydrogen from another lipid molecule to form a hydroperoxide and another allylic radical that continues the

chain. Steps [2] and [3] can repeat again and again until some other radical terminates the chain.

The hydroperoxides formed by this process are unstable and decompose to other oxidation products, many of which have a disagreeable odor and taste. This process turns an oil rancid. Unsaturated lipids are more easily oxidized than saturated ones because they contain weak allylic C–H bonds that are readily cleaved in Step [1] of this reaction, forming resonance-stabilized allylic radicals. Because saturated fats have no double bonds and thus no weak allylic C–H bonds, they are much less susceptible to air oxidation, resulting in increased shelf life of products containing them.

Figure 13.8 **The oxidation of unsaturated lipids with O_2**

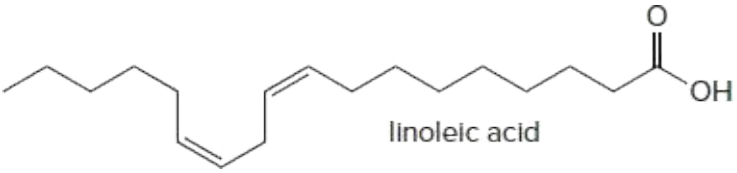


- Oxidation is shown at one allylic carbon only. Reaction at the other labeled allylic carbon is also possible.

Problem 13.20

Which C–H bond is most readily cleaved in linoleic acid? Draw all possible resonance structures for the resulting radical. Draw all the hydroperoxides formed by reaction of

this resonance-stabilized radical with O_2.



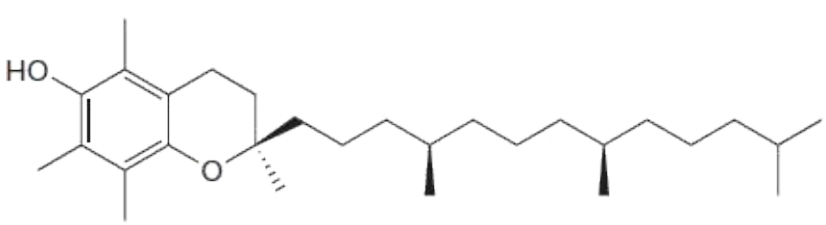
linoleic acid

The purported health benefits of antioxidants have made them a popular component in anti-aging formulations.
©McGraw-Hill Education/Elite Images

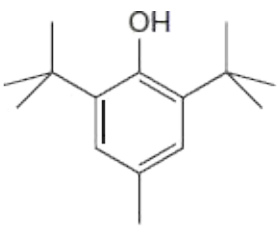
13.12 Application: Antioxidants

An *antioxidant* is a compound that stops an oxidation reaction from occurring.

- Naturally occurring antioxidants such as vitamin E prevent radical reactions that can cause cell damage.
- Synthetic antioxidants such as BHT—butylated hydroxy toluene—are added to packaged and prepared foods to prevent oxidation and spoilage.



vitamin E

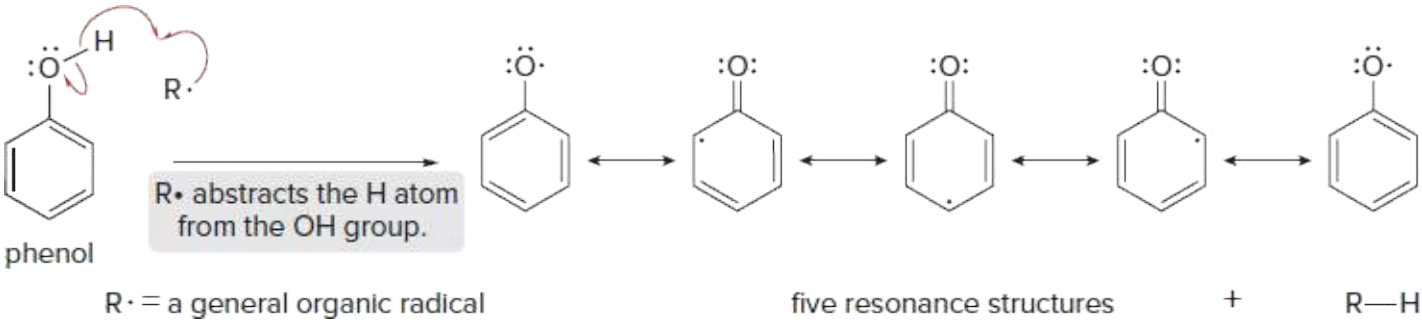


BHT
(butylated hydroxy toluene)

Hazelnuts, almonds, and many other types of nuts are an excellent source of the natural antioxidant vitamin E.
©Stockbyte/Corbis

Vitamin E and BHT are radical inhibitors, so they terminate radical chain mechanisms by reacting with radicals. How do they trap radicals? Both vitamin E and BHT use a hydroxy group bonded to a benzene ring—a general structure called a phenol.

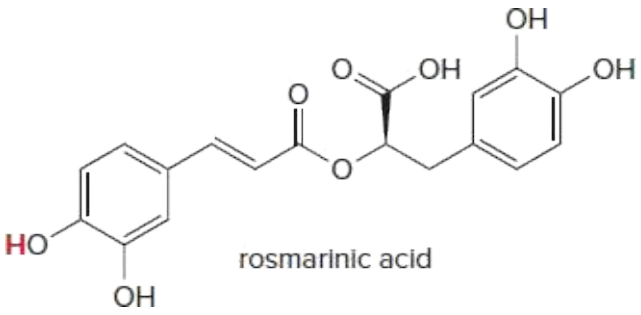
Radicals (R•) abstract a hydrogen atom from the OH group of an antioxidant, forming a new resonance-stabilized radical. This new radical does not participate in chain propagation, but rather terminates the chain and halts the oxidation process. All phenols (including vitamin E and BHT) inhibit oxidation by this radical process.



The many nonpolar C–C and C–H bonds of vitamin E make it fat soluble, and thus it dissolves in the nonpolar interior of the cell membrane, where it is thought to inhibit the oxidation of the unsaturated fatty acid residues in the phospholipids. Oxidative damage to lipids in cells via radical mechanisms is thought to play an important role in the aging process. For this reason, many anti-aging formulas with antioxidants like vitamin E are now popular consumer products.

Problem 13.21

Rosmarinic acid is an antioxidant isolated from rosemary. Draw resonance structures for the radical that results from removal of the labeled H atom in rosmarinic acid.



rosmarinic acid

Rosemary extracts contain rosmarinic acid (Problem 13.21), an antioxidant that helps prevent the oxidation of unsaturated vegetable oils.

©Pixtal/SuperStock

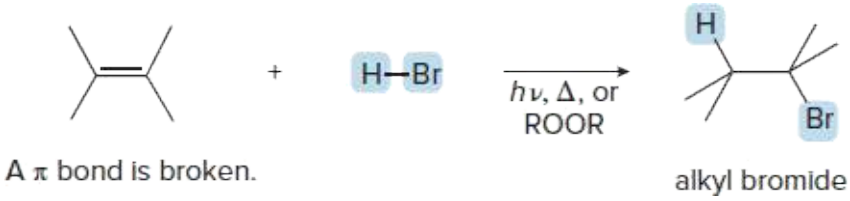
13.13 Radical Addition Reactions to Double Bonds

We now turn our attention to the second common reaction of radicals, addition to double bonds. Because an alkene contains an electron-rich, easily broken π bond, it reacts with an electron-deficient radical.

Radicals react with alkenes via a radical chain mechanism that consists of initiation, propagation, and termination steps analogous to those discussed previously for radical substitution.

13.13A Addition of HBr

HBr adds to alkenes to form alkyl bromides in the presence of light, heat, or peroxides.



The regioselectivity of addition to an unsymmetrical alkene is *different* from the addition of HBr without added light, heat, or peroxides.

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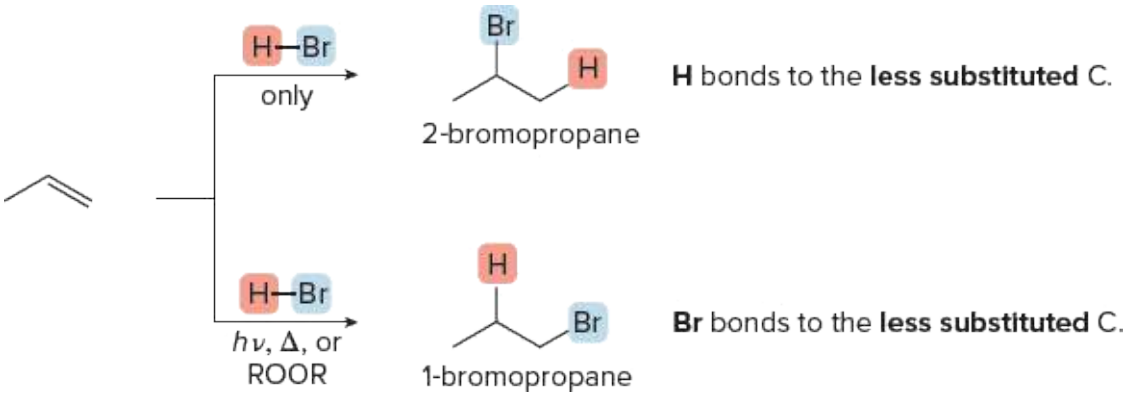
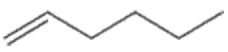
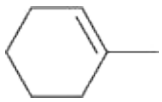


- HBr addition to propene *without* added light, heat, or peroxides gives 2-bromopropane: the H atom is added to the less substituted carbon. This reaction occurs via carbocation intermediates (Section 10.10).
- HBr addition to propene *with* added light, heat, or peroxides gives 1-bromopropane: the Br atom is added to the less substituted carbon. This reaction occurs via radical intermediates.

Problem 13.22

Draw the product(s) formed when each alkene is treated with either [1] HBr alone; or [2] HBr in the presence of peroxides.

a. 

b. 

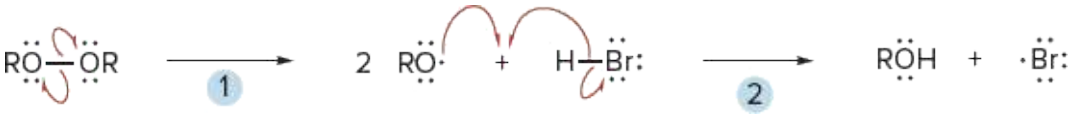
c.

13.13B The Mechanism of the Radical Addition of HBr to an Alkene

In the presence of added light, heat, or peroxides, HBr addition to an alkene forms radical intermediates and, like other radical reactions, proceeds by a mechanism with three distinct parts: initiation, propagation, and termination. Mechanism 13.3 is written for the reaction of $CH_3CH{=}CH_2$ with HBr and ROOR to form $CH_3CH_2CH_2Br$.

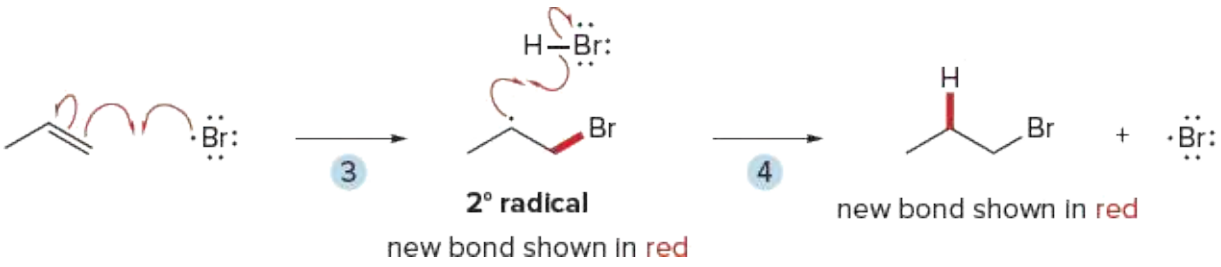
Mechanism 13.3 Radical Addition of HBr to an Alkene

Part [1] Initiation



1 – 2 Initiation with ROOR occurs in two steps–homolysis of the weak O–O bond and abstraction of H to form a bromine radical.

Part [2] Propagation



3 Addition of Br to the terminal carbon forms a 2° radical.

4 Abstraction of H from HBr forms a new C–H bond and a bromine radical, so Steps [3] and [4] can occur repeatedly.

Part [3] Termination

5 **Termination of the chain occurs when any two radicals combine to form a bond.**

The first propagation step (Step [3] of the mechanism, the addition of Br• to the double bond) is worthy of note. With propene there are two possible paths for this step, depending on which carbon atom of the double bond forms the new bond to bromine. Path [A] forms a less stable 1° radical, whereas Path [B] forms a more stable 2° radical. The more stable 2° radical forms faster, so Path [B] is preferred.

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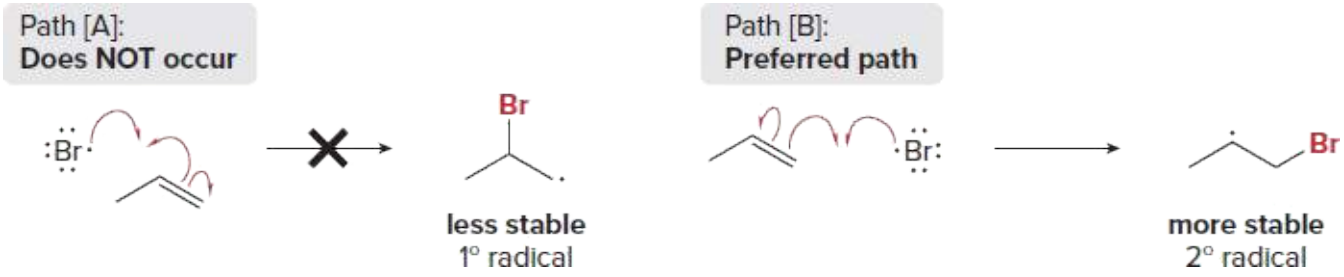
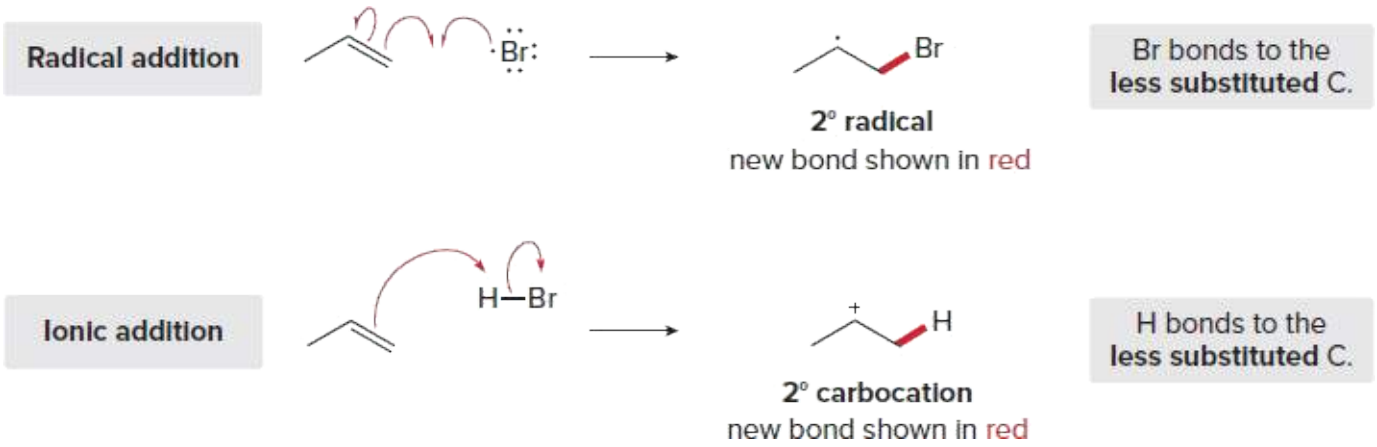


The mechanism also illustrates why the regioselectivity of HBr addition is different depending on the reaction conditions. In both reactions, H and Br add to the double bond, but the *order* of addition depends on the mechanism.



- **In radical addition (HBr with added light, heat, or ROOR), *Br• adds first* to generate the more stable radical.**
- **In ionic addition (HBr alone), *H^+ adds first* to generate the more stable carbocation.**

Problem 13.23

When HBr adds to $(CH_3)_2C{=}CH_2$ under radical conditions, two radicals are possible products in the first step of chain propagation. Draw the structure of both radicals and indicate which one is formed. Then draw the preferred product from HBr addition under radical conditions.

Problem 13.24

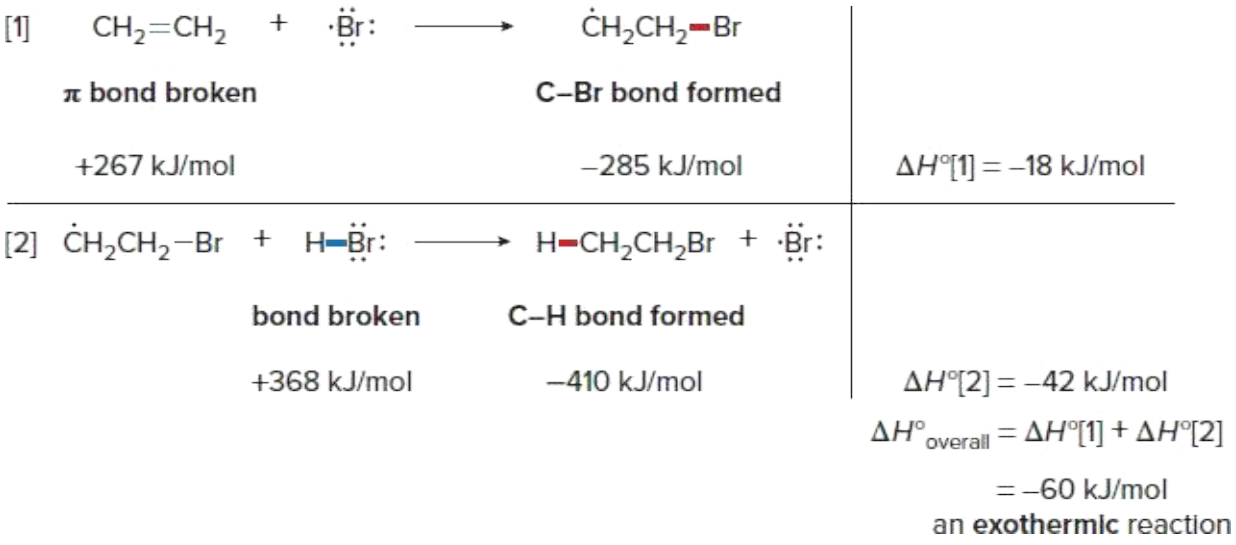
What reagents are needed to convert 1-ethylcyclohexene into (a) 1-bromo-2-ethylcyclohexane; (b) 1-bromo-1-ethylcyclohexane; (c) 1,2-dibromo-1-ethylcyclohexane?

13.13C Energy Changes in the Radical Addition of HBr

The energy changes during propagation in the radical addition of HBr to CH_2=CH_2 can be calculated from bond dissociation energies, as shown in Figure 13.9.

Both propagation steps for the addition of HBr are exothermic, so propagation is exothermic (energetically favorable) overall. For the addition of HCl or HI, however, one of the chain-propagating steps is quite endothermic and thus too difficult to be part of a repeating chain mechanism. Thus, HBr adds to alkenes under radical conditions, but HCl and HI do not.

Figure 13.9 **Energy changes during the propagation steps: CH_2=CH_2 + HBr → CH_3CH_2Br**



13.14 Polymers and Polymerization

HDPE (high-density polyethylene) and LDPE (low-density polyethylene) are two common types of polyethylene prepared under different reaction conditions and having different physical properties. HDPE is opaque and rigid, and is used in milk containers and water jugs. LDPE is less opaque and more flexible, and is used in plastic bags and electrical insulation. Products containing HDPE and LDPE (and other plastics) are often labeled with a symbol indicating recycling ease: the lower the number, the easier to recycle.

©McGraw-Hill Education/Jill Braaten, photographer

Polymers—large molecules made up of repeating units of smaller molecules called *monomers*—include such biologically important compounds as proteins and carbohydrates. They also include such industrially important plastics as polyethylene, poly(vinyl chloride) (PVC, mentioned in the chapter opener), and polystyrene.

13.14A Synthetic Polymers

Many synthetic polymers—that is, those synthesized in the lab—are among the most widely used organic compounds in modern society. Although some synthetic polymers resemble natural substances, many have different and unusual properties that make them more useful than naturally occurring materials. Soft drink bottles, plastic bags, food wrap, compact discs, Teflon, and Styrofoam are all made of synthetic polymers. In this section we examine polymers derived from alkene monomers. Chapter 28 is devoted to a detailed discussion of the synthesis and properties of several different types of synthetic polymers.

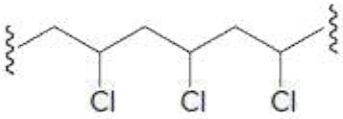
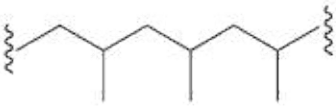
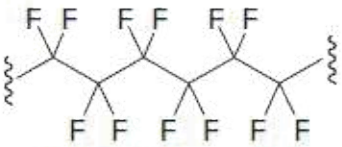
- ***Polymerization*** **is the joining together of monomers to make polymers.**

For example, joining ethylene monomers together forms the polymer polyethylene, a plastic used in milk containers and sandwich bags.

Many ethylene derivatives having the general structure CH_2=CHZ are also used as monomers for polymerization. The identity of Z affects the physical properties of the resulting polymer, making some polymers more suitable for one consumer product

(e.g., plastic bags or food wrap) than another (e.g., soft drink bottles or compact discs). Polymerization of $CH_2{=}CHZ$ usually affords polymers with the Z groups on every other carbon atom in the chain. Table 13.2 lists some common monomers and polymers used in medicine and dentistry.

Table 13.2 Common Monomers and Polymers Used in Medicine and Dentistry

Monomer	→	Polymer	Consumer product
vinyl chloride	→	 poly(vinyl chloride) PVC	PVC blood bags and tubing ©Image Source/Getty Images
propene	→	 polypropylene	polypropylene syringes ©Image Source Trading Ltd/Shutterstock
tetrafluoroethylene	→	 polytetrafluoroethylene Teflon	dental floss ©Jill Braaten

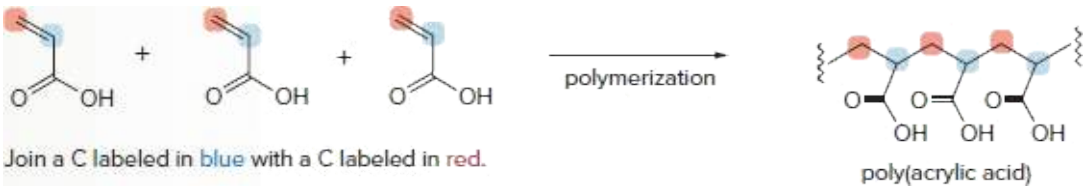
Poly(acrylic acid) (Sample Problem 13.6) is used in disposable diapers because it absorbs 30 times its weight in water.
©Image Source

Sample Problem 13.6 Drawing the Structure of a Polymer Formed from a Monomer

What polymer is formed when CH_2=$CHCO_2H$ (acrylic acid) is polymerized to form poly(acrylic acid)?

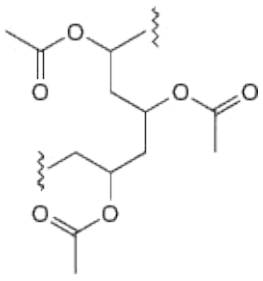
Solution

Draw three or more alkene monomers, break one bond of each double bond, and join the alkenes together with single bonds. With unsymmetrical alkenes, substituents are bonded to every other carbon.



Problem 13.25

(a) Draw the structure of polystyrene, which is formed by polymerizing the monomer styrene, C_6H_5CH=CH_2. (b) What monomer is used to form poly(vinyl acetate), a polymer used in paints and adhesives?



More Practice:

Try Problems 13.69, 13.72a.

The polystyrene foam (Problem 13.25a) used in packaging materials and drinking cups for hot beverages is called Styrofoam. Recycled polystyrene can be molded into trays and trash cans.

©Jamie Grill/Getty Images

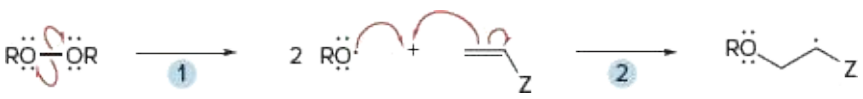
13.14B Radical Polymerization

The polymers described in Section 13.14A are prepared by polymerization of alkene monomers by adding a radical to a π bond. The mechanism resembles the radical addition of HBr to an alkene, except that a carbon radical rather than a bromine atom is added to the double bond. Mechanism 13.4 is written with the general monomer CH_2=CHZ, and again has three parts: initiation, propagation, and termination.

The alkene monomers used in polymerization are prepared from petroleum.

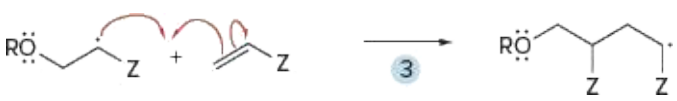
Mechanism 13.4 Radical Polymerization of CH_2=CHZ

Part [1] Initiation



1 – 2 Initiation with ROOR occurs in two steps—homolysis of the weak O–O bond and addition of RO• to the alkene to form a carbon radical.

Part [2] Propagation

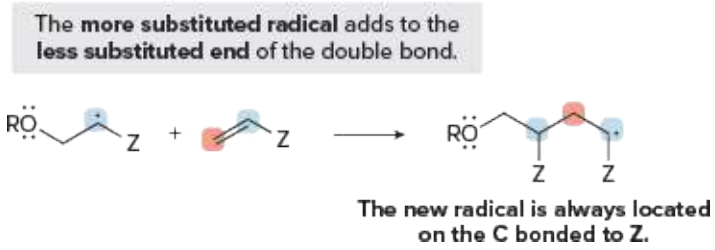


3 **Chain propagation consists of a single step. The carbon radical adds to another alkene to form a new C–C bond and another carbon radical. Addition forms the radical with the unpaired electron on the atom with the Z substituent.**

Part [3] Termination

4 **Termination of the chain occurs when any two radicals combine to form a bond.**

In radical polymerization, the more substituted radical always adds to the Page 638 less substituted end of the monomer, a process called head-to-tail polymerization.



Problem 13.26

Draw the steps of the mechanism that converts vinyl chloride (CH_2=CHCl) to poly(vinyl chloride).

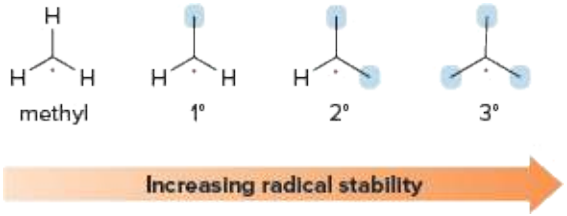
Chapter 13 REVIEW

KEY CONCEPTS

Radical stability (13.1)

- **A radical is a reactive intermediate with a single unpaired electron.**
- **The stability of a radical increases as the number of electron-donating**

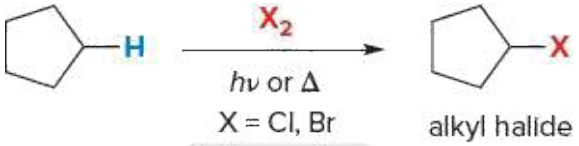
groups, such as alkyl groups, bonded to the radical carbon increases.

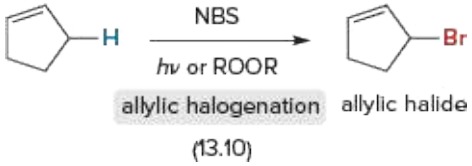


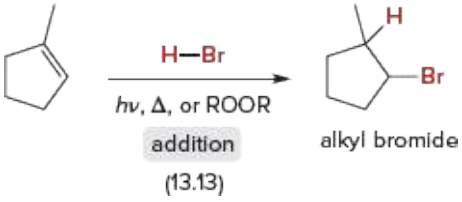
Try Problems 13.29c, 13.30.

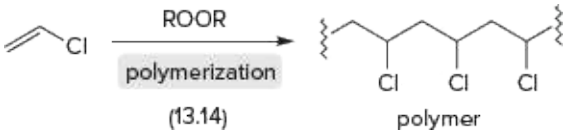
KEY REACTIONS

Radical Reactions

1 

2 

3 

4 

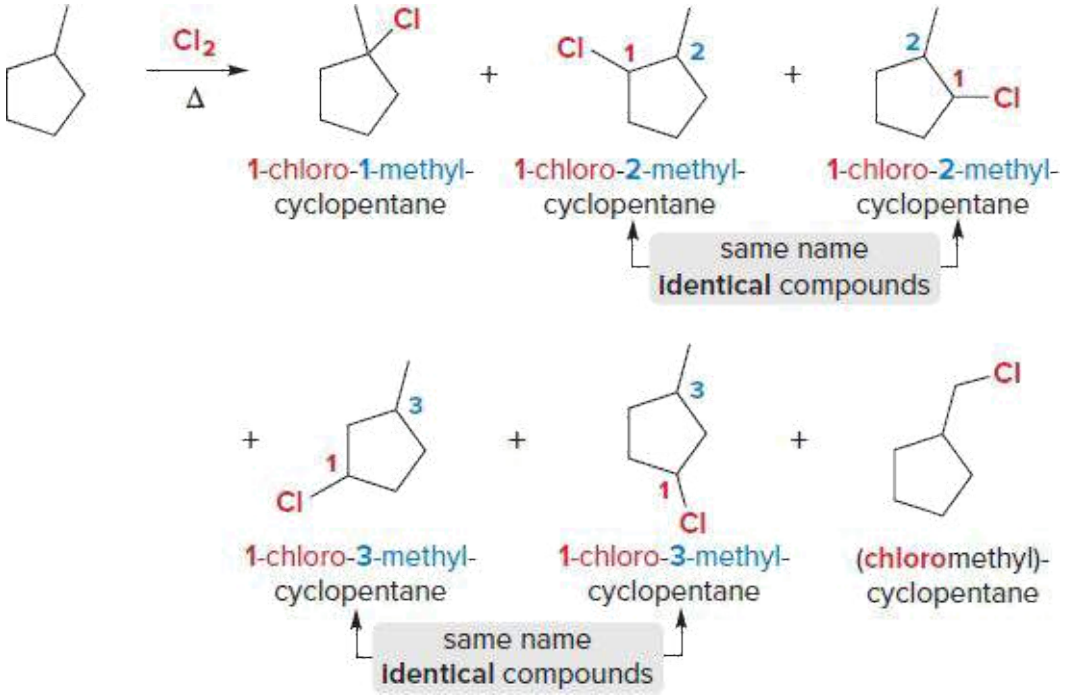
Try Problems 13.27, 13.32, 13.33, 13.41, 13.42, 13.44, 13.69, 13.72a.

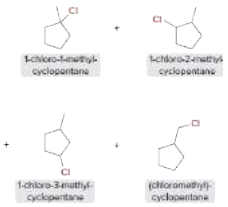
KEY SKILLS

[1] Drawing all the constitutional isomers formed by monochlorination of methylcyclopentane with Cl_2 and heat (13.3)

1 Substitute Cl for H on every carbon, and name each product.

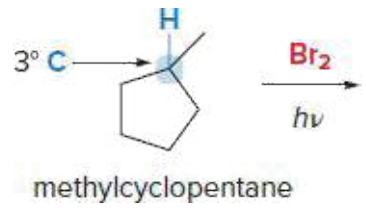
2 Ignore identica compou to draw product





See Sample Problem 13.1. Try Problems 13.27a, 13.32, 13.44a.

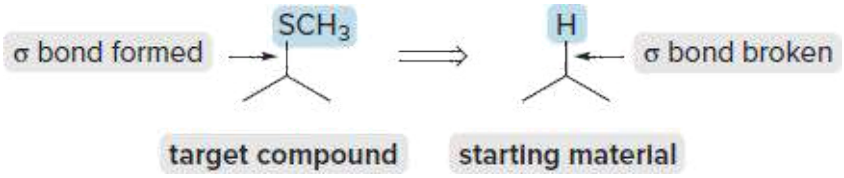
[2] Drawing the major product formed by bromination of methylcyclopentane with Br_2 and *hv* (13.6)

1 Find the most reactive C–H bond in the starting materials.	**2** Replace the H on the most substituted C atom with a Br atom.
 methylcyclopentane	major product
• The most reactive C–H bond is on the most substituted carbon.	• Bromination is slower and more selective than chlorination.

See Sample Problem 13.2. Try Problems 13.27b, 13.33, 13.44b.

[3] Devising a synthesis (13.7); example: $CH_3CH(SCH_3)CH_3$ from $CH_3CH_2CH_3$

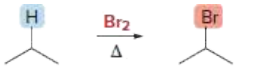
1 **Compare the carbon skeletons and functional groups.**



2 **Work backwards.**

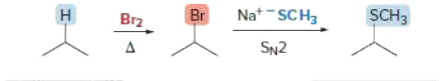
A **sulfide** is made from an **alkyl bromide** via an S_N2 **reaction.**

3 **Work forwards.**



An **alkane** is converted to an **alkyl bromide** using radical halogenation.

4 **Complete the synthesis.**



See Sample Problem 13.3. Try Problems 13.58–13.63.

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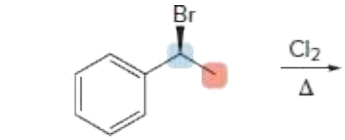
[4] Drawing the stereoisomers formed by the monochlorination of a chiral starting material with Cl_2 and heat (13.8)

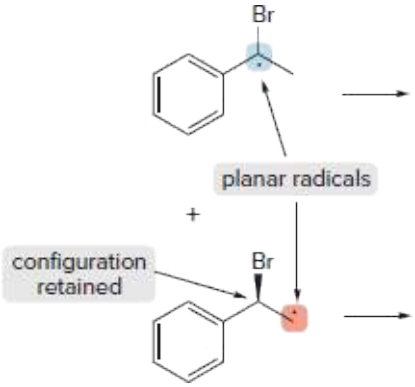
1 **Identify the C atoms that will be chlorinated.**



(*S*)-(1-bromoethyl)benzene

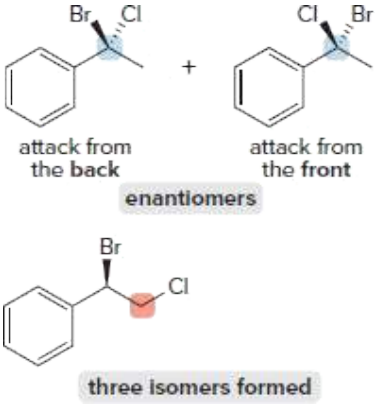
- **Only the sp^3 hybridized C–H bonds are**

2 **Use the mechanism to determine the stereochemistry.**



- **Hydrogen abstraction results in a planar, sp^2**

3 **Draw the product(s).**

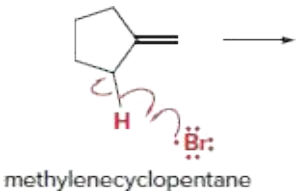
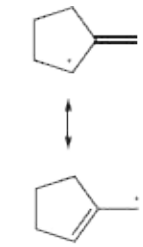
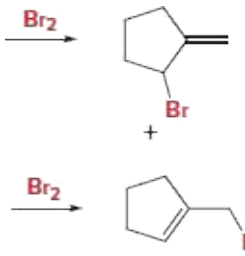


- **Radical substitution at stereogenic ce**

broken. • Chlorination is fast and unselective.	hybridized radical on two different carbon atoms.	results in racemization to form two enantiomers.

See Sample Problem 13.4. Try Problems 13.47a, d; 13.48; 13.49; 13.51.

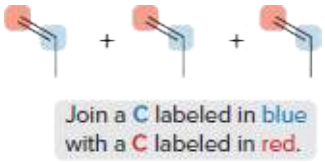
[5] Drawing the products formed when methylenecyclopentane is treated with NBS + ROOR (13.10)

1 Abstract an H atom at the allylic carbon.	2 Draw the resonance-stabilized allylic radical.	3 Draw the products.
 methylenecyclopentane	 allylic radical	 allylic bromides constitutional isomers
• A bromine radical abstracts an allylic hydrogen.	• Allylic radicals are stabilized by resonance, making them more stable than 3° radicals.	

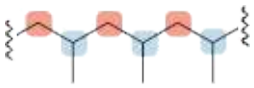
See Sample Problem 13.5. Try Problems 13.41, 13.42, 13.44f.

[6] Drawing the product of a polymerization reaction (13.14); example: polymerization of CH_2=$CHCH_3$

1 Draw three (or more) alkene monomers.	2 Break one bond of each double bond, and join the alkenes together with single bonds.



- **Break the π bonds, and join a carbon labeled in blue with a carbon labeled in red.**



polypropylene

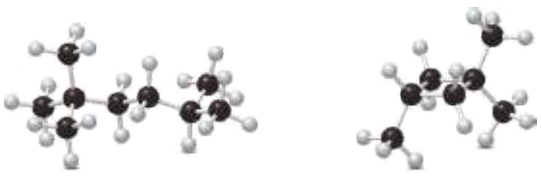
- **With unsymmetrical alkenes, substituents are bonded to every other carbon.**

See Sample Problem 13.6. Try Problems 13.69, 13.72a.

PROBLEMS

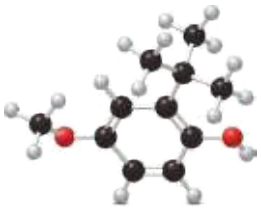
Problems Using Three-Dimensional Models

13.27 **(a) Draw all constitutional isomers formed by monochlorination of each alkane with Cl_2 and hv. (b) Draw the major monobromination product formed by heating each alkane with Br_2.**



A B

13.28 **Draw all resonance structures of the radical that results from abstraction of a hydrogen atom from the antioxidant BHA (butylated hydroxy anisole).**



BHA

Radicals and Bond Strength

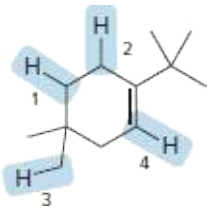
13.29 **With reference to the indicated C–H bonds in the following compound:**

a. Rank the C–H bonds in order of increasing bond strength.

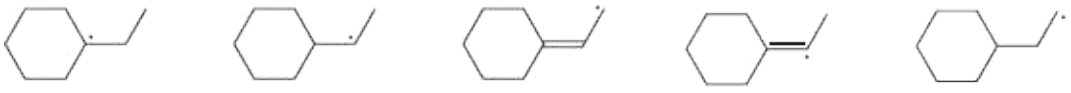
b. Draw the radical resulting from cleavage of each C–H bond, and classify it as 1°, 2°, or 3°.

c. Rank the radicals in order of increasing stability.

d. Rank the C–H bonds in order of increasing ease of H abstraction in a radical halogenation reaction.

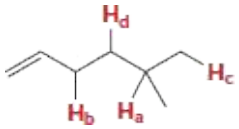


13.30 Rank the following radicals in order of increasing stability.

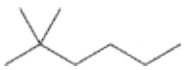


Halogenation of Alkanes

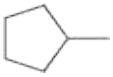
13.31 Rank the indicated hydrogen atoms in order of increasing ease of abstraction in a radical halogenation reaction.



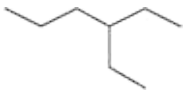
13.32 Draw all constitutional isomers formed by monochlorination of each alkane with Cl_2 and *hv*.

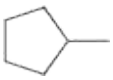
a. 

b.

c 

13.33 What is the major monobromination product formed by heating each alkane with Br_2?

a. 

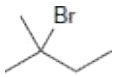
b. 

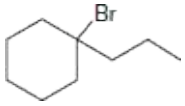
c.

13.34 Five isomeric alkanes (A–E) having the molecular formula C_6H_{14} are

each treated with Cl_2 + *hv* to give alkyl halides having molecular formula $C_6H_{13}Cl$. A yields five constitutional isomers. B yields four constitutional isomers. C yields two constitutional isomers. D yields three constitutional isomers, two of which possess stereogenic centers. E yields three constitutional isomers, only one of which possesses a stereogenic center. Identify the structures of A–E.

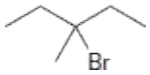
13.35 What alkane is needed to make each alkyl halide by radical halogenation?

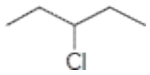
a. 

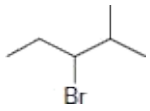
b. 

c.

13.36 Which alkyl halides can be prepared in good yield by radical halogenation of an alkane?

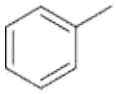
a. 

b. 

c. 

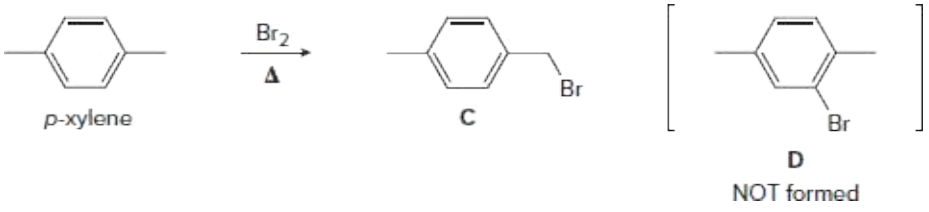
13.37 Draw the products of radical chlorination and bromination of each compound. For which compounds is a single constitutional isomer formed for both reactions? What must be true about the structure of a reactant for both reactions to form a single product?

a.

b. 

c.

13.38 Explain why radical bromination of *p*-xylene forms C rather than D.

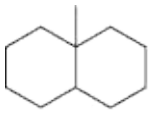


p-xylene C D
NOT formed

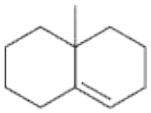
13.39 a. What product(s) (excluding stereoisomers) are formed when Y is heated with Cl_2?

b. What product(s) (excluding stereoisomers) are formed when Y is heated with Br_2?

c. What steps are needed to convert Y to the alkene Z?



Y

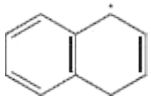


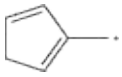
Z

Resonance

13.40 Draw resonance structures for each radical.

a.

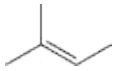
b. 

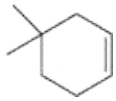
c. 

Allylic Halogenation

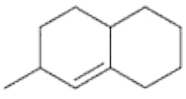
13.41 Draw the products formed when each alkene is treated with NBS + *hv*.

a.

b. 

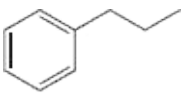
c. 

13.42 Draw all constitutional isomers formed when X is treated with NBS + *hv*.



X

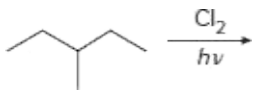
13.43 Treatment of propylbenzene with NBS + *hv* affords a single constitutional isomer. Suggest a structure for the product and a reason for its formation.

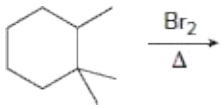


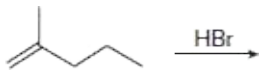
propylbenzene

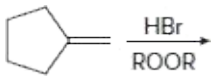
Reactions

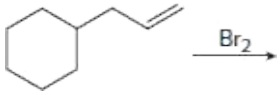
13.44 Draw the organic products formed in each reaction.

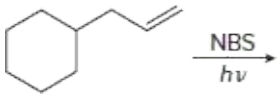
a. 

b. 

c. 

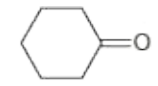
d. 

e. 

f. 

13.45 What reagents are needed to convert cyclopentene to (a) bromocyclopentane; (b) *trans*-1,2-dibromocyclopentane; (c) 3-bromocyclopentene?

13.46 Treatment of a hydrocarbon A (molecular formula C_9H_{18}) with Br_2 in the presence of light forms alkyl halides B and C, both having molecular formula $C_9H_{17}Br$. Reaction of either B or C with $KOC(CH_3)_3$ forms compound D (C_9H_{16}) as the major product. Ozonolysis of D forms cyclohexanone and acetone. Identify the structures of A–D.

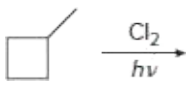


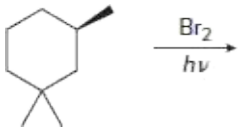
cyclohexanone

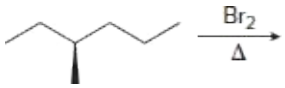
acetone

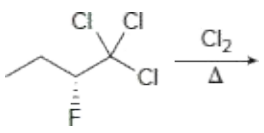
Stereochemistry and Reactions

13.47 Draw the products formed in each reaction and include the stereochemistry around any stereogenic centers.

a. 

b. 

c. 

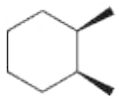
d. 

13.48 (a) Draw the products of molecular formula $C_3H_4Cl_2$, including stereoisomers, formed when chlorocyclopropane is heated with Cl_2. (b)

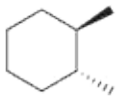
Assuming that compounds that have different physical properties are separable, how many fractions would be present if the mixture of products were distilled using an efficient fractional distillation? (c) How many fractions would be optically active?

13.49 **(a) Draw all stereoisomers of molecular formula $C_5H_{10}Cl_2$ formed when (*R*)-2-chloropentane is heated with Cl_2. (b) Assuming that products having different physical properties can be separated into fractions by some physical method (such as fractional distillation), how many different fractions would be obtained? (c) Which of these fractions would be optically active?**

13.50 **(a) Draw all stereoisomers formed by monobromination of the cis and trans isomers of 1,2-dimethylcyclohexane drawn below. (b) How do the products formed from each reactant compare—identical compounds, stereoisomers, or constitutional isomers?**



cis-1,2-dimethylcyclohexane



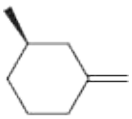
trans-(1*R*,2*S*)-dimethylcyclohexane

13.51 **(a) Draw all stereoisomers formed by monochlorination of the cis and trans isomers of 1,2-dimethylcyclobutane drawn below. (b) How many constitutional isomers are formed in each reaction? (c) Label any pairs of enantiomers formed.**

cis-1,2-dimethylcyclobutane

trans-(1*R*,2*S*)-dimethylcyclobutane

13.52 **Draw the six products (including stereoisomers) formed when A is treated with NBS + *hv*.**



A

13.53 **(a) Draw the products (including stereoisomers) formed when 2-methylhex-2-ene is treated with HBr in the presence of peroxides. (b) Draw the products (including stereoisomers) formed when (*S*)-2,4-dimethylhex-2-ene is treated with HBr and peroxides under similar conditions.**

Mechanisms

13.54 **Consider the following bromination:** $(CH_3)_3CH + Br_2 \xrightarrow{\Delta} (CH_3)_3CBr + HBr.$

a. Calculate $\Delta H°$ for this reaction by using the bond dissociation energies in Table 6.2.

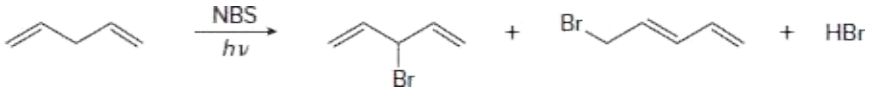
b. Draw out a stepwise mechanism for the reaction, including the initiation, propagation, and termination steps.

c. Calculate $\Delta H°$ for each propagation step.

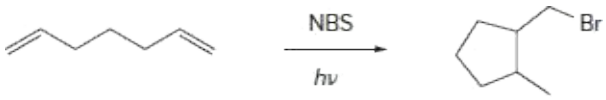
d. Draw an energy diagram for the propagation steps.

e. Draw the structure of the transition state of each propagation step.

13.55 Draw a stepwise mechanism for the following reaction.



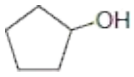
13.56 Like carbocations, radicals formed from compounds that contain another functional group can undergo intramolecular reactions. Draw a stepwise mechanism for the chain-propagating steps of the following intramolecular reaction.

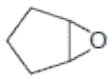


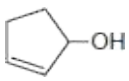
13.57 When 3,3-dimethylbut-1-ene is treated with HBr alone, the major product is 2-bromo-2,3-dimethylbutane. When the same alkene is treated with HBr and peroxide, the sole product is 1-bromo-3,3-dimethylbutane. Explain these results by referring to the mechanisms.

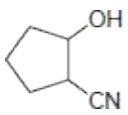
Synthesis

13.58 Devise a synthesis of each compound from cyclopentane and any other required organic or inorganic reagents.

a. 

b. 

c. 

d. 

13.59 Devise a synthesis of 1-methylcyclohexene oxide from methylcyclohexane. You may use any other required organic or inorganic reagents.

13.60 Devise a synthesis of $CH_3CH_2CH_2CH_2Br$ from HC=CH. You may use any

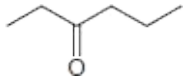
other required organic compounds or inorganic reagents.

13.61 Devise a synthesis of each compound using CH_3CH_3 as the only source of carbon atoms. You may use any other required organic or inorganic reagents.

a. HC≡CH

b.

c.

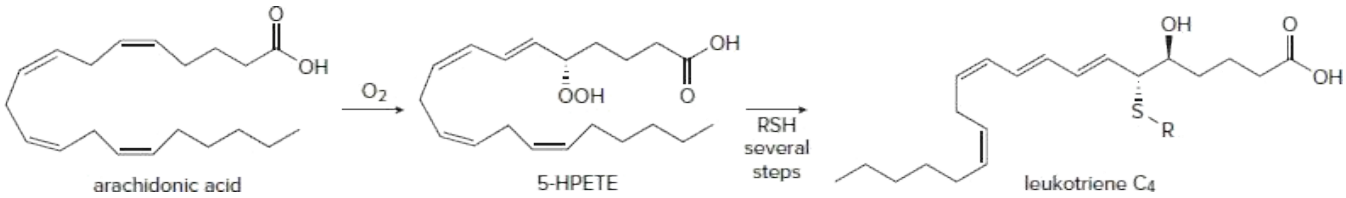
d. 

13.62 Devise a synthesis of $OHC(CH_2)_4CHO$ from cyclohexane using any required organic or inorganic reagents.

13.63 Devise a synthesis of hexane-2,3-diol from propane as the only source of carbon atoms. You may use any other required organic or inorganic reagents.

Radical Oxidation Reactions

13.64 As described in Section 9.17, the leukotrienes, important components in the asthmatic response, are synthesized from arachidonic acid via the hydroperoxide 5-HPETE. Write a stepwise mechanism for the conversion of arachidonic acid to 5-HPETE with O_2.

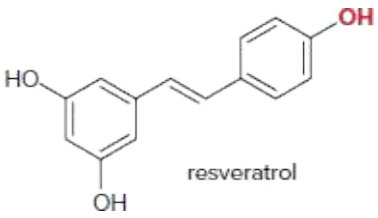


13.65 Ethers are oxidized with O_2 to form hydroperoxides that decompose violently when heated. Draw a stepwise mechanism for this reaction.

unstable hydroperoxide

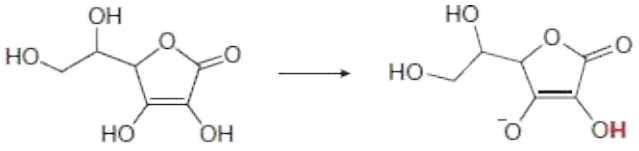
Antioxidants

13.66 Resveratrol is an antioxidant found in the skin of red grapes. Its anticancer, anti-inflammatory, and various cardiovascular effects are under active investigation. (a) Draw all resonance structures for the radical that results from homolysis of the OH bond shown in red. (b) Explain why homolysis of this OH bond is preferred to homolysis of either OH bond in the other benzene ring.



resveratrol

13.67 **In cells, vitamin C exists largely as its conjugate base X. X is an antioxidant because radicals formed in oxidation processes abstract the labeled H atom, forming a new radical that halts oxidation. Draw the structure of the radical formed by H abstraction, and explain why this H atom is most easily removed.**

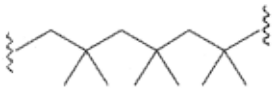


vitamin C X

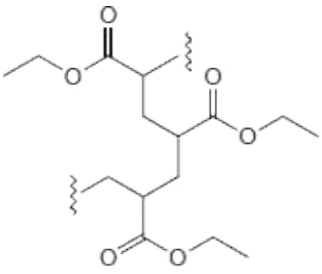
Polymers and Polymerization

13.68 **What monomer is needed to form each polymer?**

a.


polyisobutylene
(used to make basketballs)

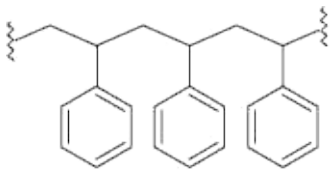
b.



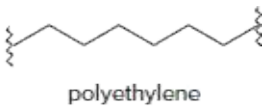
poly(ethyl acrylate)
(used in latex paints)

13.69 **(a) Hard contact lenses, which first became popular in the 1960s, were made by polymerizing methyl methacrylate [CH2=C(CH_3)CO_2CH3] to form poly(methyl methacrylate) (PMMA). Draw the structure of PMMA. (b) More-comfortable softer contact lenses introduced in the 1970s were made by polymerizing hydroxyethyl methacrylate [CH_2=C(CH_3)$CO_2CH_2CH_2$OH] to form poly(hydroxyethyl methacrylate) (poly-HEMA). Draw the structure of poly-HEMA. Because neither polymer allows oxygen from the air to pass through to the retina, newer contact lenses that are both comfortable and oxygen-permeable have now been developed.**

13.70 **Explain why polystyrene is much more readily oxidized by O_2 in the air than polyethylene is. Which H's in polystyrene are most easily abstracted and why?**

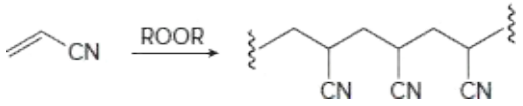


polystyrene



polyethylene

13.71 **Draw a stepwise mechanism for the following polymerization reaction.**



13.72 **As we will learn in Chapter 28, styrene derivatives such as A can be polymerized by way of cationic rather than radical intermediates. Cationic polymerization is an example of electrophilic addition to an alkene involving carbocations.**

A

a. **Draw a short segment of the polymer formed by the polymerization of A.**

b. **Why does A react faster than styrene ($C_6H_5CH{=}CH_2$) in a cationic polymerization?**

13.73 **When two monomers (X and Y) are polymerized together, a copolymer results. An alternating copolymer is formed when the two monomers X and Y alternate regularly in the polymer chain. Draw the structure of the alternating copolymer formed when the two monomers, $CH_2{=}CCl_2$ and $CH_2{=}CHC_6H_5$, are polymerized together.**

Spectroscopy

13.74 **A and B, isomers of molecular formula $C_3H_5Cl_3$, are formed by the radical chlorination of a dihalide C of molecular formula $C_3H_6Cl_2$.**

a. **Identify the structures of A and B from the following ^1H NMR data:**

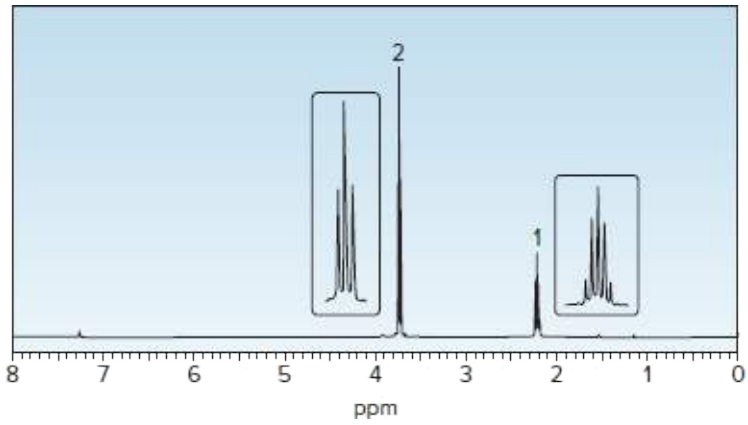
Compound A: singlet at 2.23 and singlet at 4.04 ppm

Compound B: doublet at 1.69, multiplet at 4.34, and doublet at 5.85 ppm

b. **What is the structure of C?**

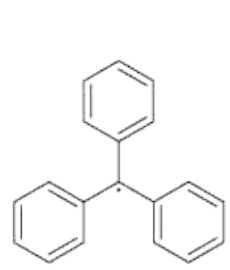
13.75 **Identify the structure of a minor product formed from the radical chlorination of propane, which has molecular formula $C_3H_6Cl_2$ and**

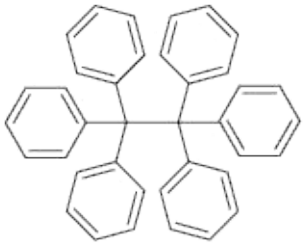
exhibits the given ^{1}H NMR spectrum.

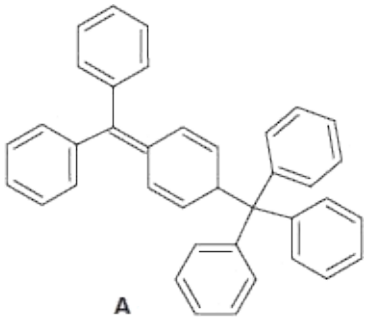


Challenge Problems

13.76 The triphenylmethyl radical is an unusual persistent radical present in solution in equilibrium with its dimer. For 70 years the dimer was thought to be hexaphenylethane, but in 1970, NMR data showed it to be A.


triphenylmethyl radical


hexaphenylethane


A

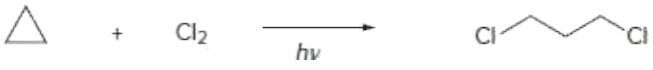
a. Why is the triphenylmethyl radical more stable than most other radicals?

b. Use curved arrow notation to show how two triphenylmethyl radicals dimerize to form A.

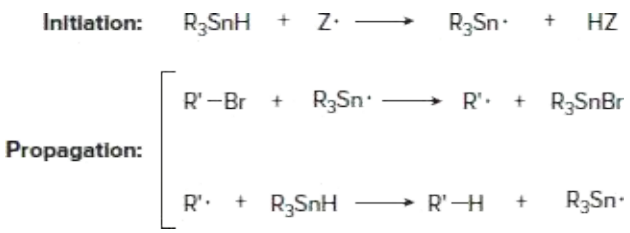
c. Propose a reason for the formation of A rather than hexaphenylethane.

d. How could ^{1}H and ^{13}C NMR spectroscopy be used to distinguish between hexaphenylethane and A?

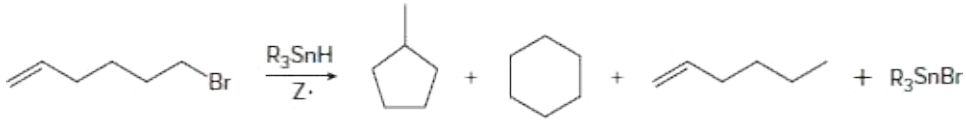
13.77 Draw a stepwise mechanism for the chain-propagating steps of the following ring-opening reaction.



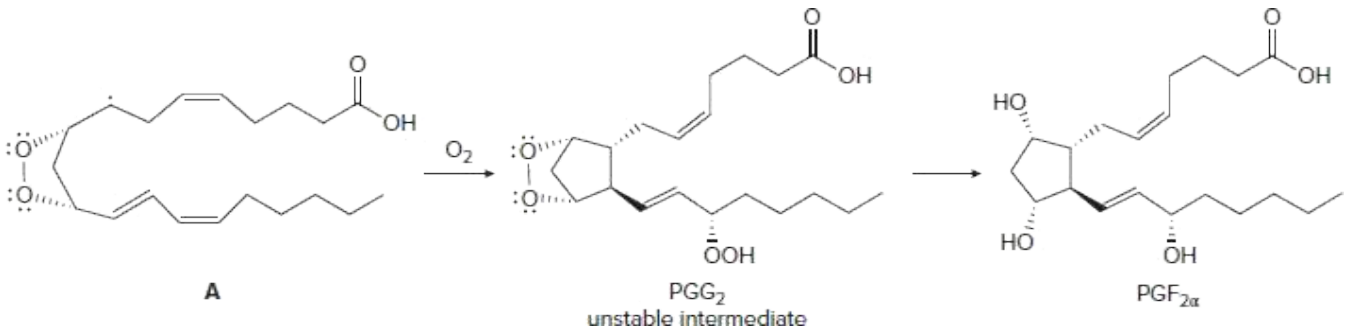
13.78 In the presence of a radical initiator (Z•), tributyltin hydride (R_3SnH, R = $CH_3CH_2CH_2CH_2$) reduces alkyl halides to alkanes: $R'X + R_3SnH \rightarrow R'H + R_3SnX$. The mechanism consists of a radical chain process with an intermediate tin radical:



This reaction has been employed in many radical cyclization reactions. Draw a stepwise mechanism for the following reaction.

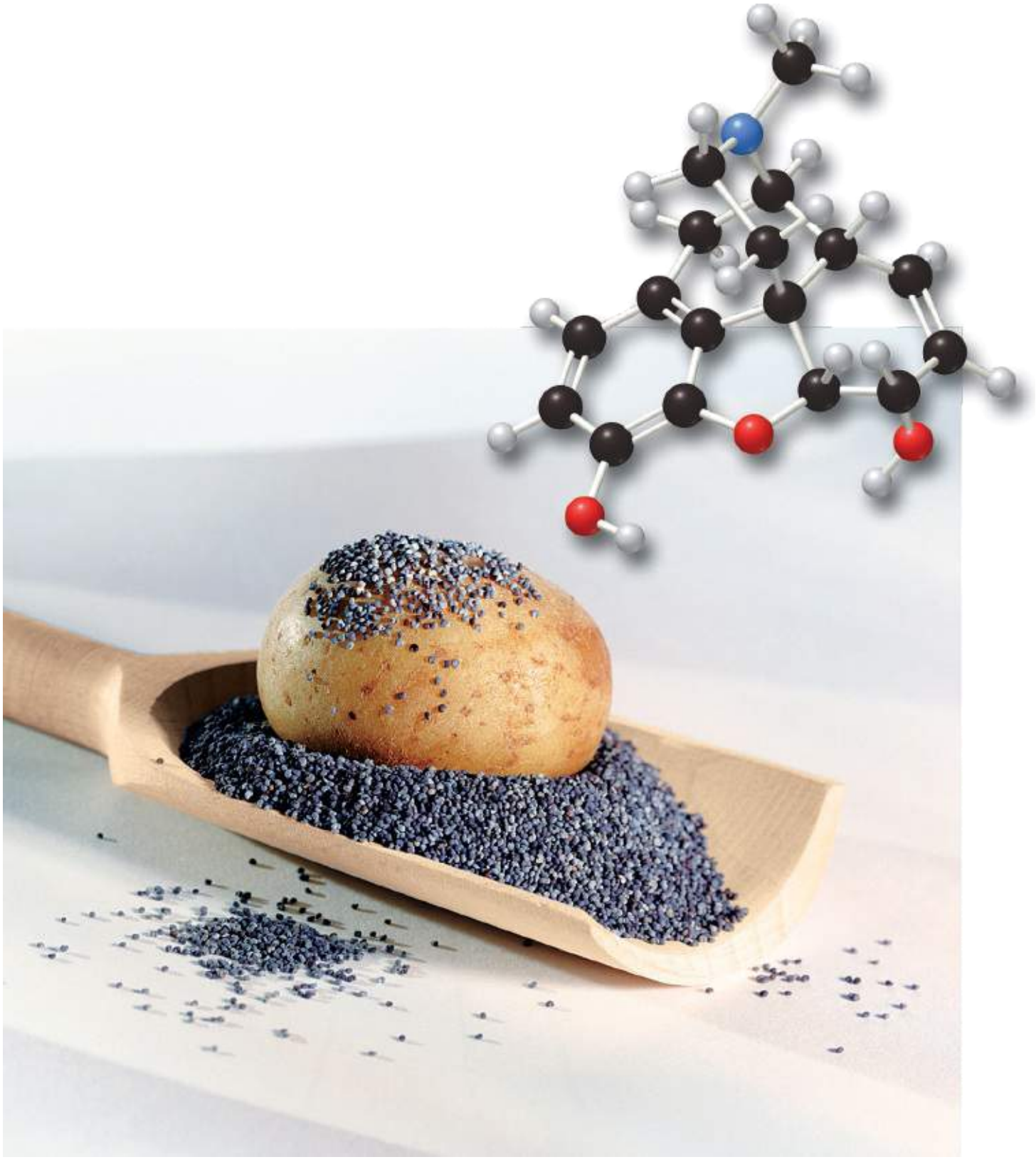


13.79 $PGF_{2\alpha}$ (Section 4.15) is synthesized in cells from arachidonic acid ($C_{20}H_{32}O_2$) using a cyclooxygenase enzyme that catalyzes a multistep radical pathway. Part of this process involves the conversion of radical A to PGG_2, an unstable intermediate, which is then transformed to $PGF_{2\alpha}$ and other prostaglandins. Draw a stepwise mechanism for the conversion of A to PGG_2. (Hint: The mechanism begins with radical addition to a carbon–carbon double bond to form a resonance-stabilized radical.)



14

Conjugation, Resonance, and Dienes



©John Foxx/Getty Images

14.1 Conjugation

14.2 Resonance and allylic carbocations

14.3 Common examples of resonance

14.4 The resonance hybrid

14.5 Electron delocalization, hybridization, and geometry

14.6 Conjugated dienes

14.7 Interesting dienes and polyenes

14.8 The carbon–carbon σ bond length in buta-1,3-diene

14.9 Stability of conjugated dienes

14.10 Electrophilic addition: 1,2- versus 1,4-addition

14.11 Kinetic versus thermodynamic products

14.12 The Diels–Alder reaction

14.13 Specific rules governing the Diels–Alder reaction

14.14 Other facts about the Diels–Alder reaction

14.15 Conjugated dienes and ultraviolet light

Morphine is an analgesic and narcotic isolated from the opium poppy *Papaver somniferum*. Opium has been widely used as a recreational drug and painkilling remedy for centuries, and poppy seed tea, which contains morphine, was used as a folk remedy in parts of England until World War II. A key step in a laboratory synthesis of morphine involves the Diels–Alder reaction, a powerful reaction of conjugated dienes discussed in Chapter 14.

Why Study…

Conjugated Systems?

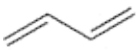
Chapter 14 is the first of three chapters that discuss the chemistry of conjugated

molecules—molecules with overlapping *p* orbitals on three or more adjacent atoms. Chapter 14 focuses mainly on acyclic conjugated compounds, whereas Chapters 15 and 16 discuss the chemistry of benzene and related compounds that have a *p* orbital on every atom in a ring.

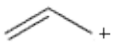
Much of Chapter 14 is devoted to the properties and reactions of 1,3-dienes, most notably the Diels–Alder reaction, which is widely used in the synthesis of naturally occurring compounds. To understand 1,3-dienes, however, we must first learn about the consequences of having *p* orbitals on three or more adjacent atoms. Because the ability to draw resonance structures is also central to mastering this material, the key aspects of resonance theory are presented in detail.

14.1 Conjugation

Conjugation occurs whenever *p* orbitals can overlap on three or more adjacent atoms. Two common conjugated systems are 1,3-dienes and allylic carbocations.



1,3-diene



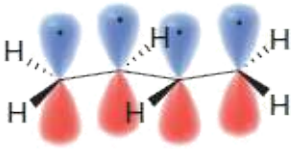
allylic carbocation

14.1A 1,3-Dienes

1,3-Dienes such as buta-1,3-diene contain two carbon–carbon double bonds joined by a single σ bond. Each carbon atom of a 1,3-diene is bonded to three other atoms and has no nonbonded electron pairs, so each carbon atom is sp^2 hybridized and has one *p* orbital containing an electron. The four *p* orbitals on adjacent atoms make a 1,3-diene a conjugated system.

buta-1,3-diene

one σ bond between the double bonds

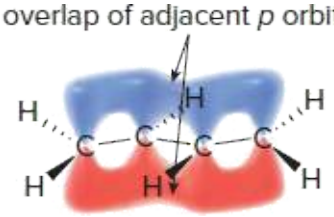


four adjacent *p* orbitals

Each C is sp^2 hybridized and has a *p* orbital containing one electron.

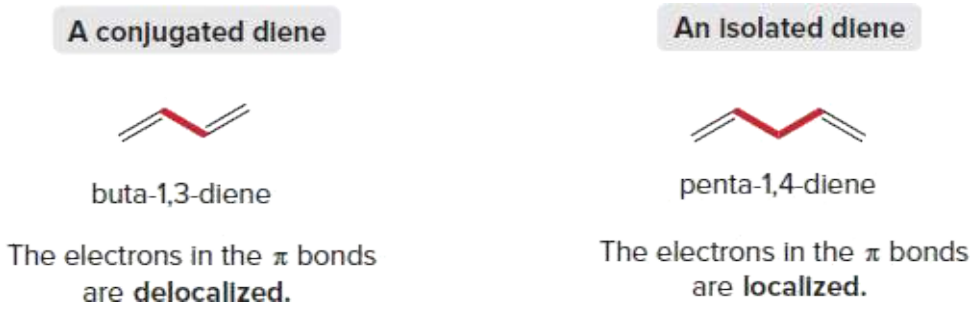
What is special about conjugation? Having three or more *p* orbitals on adjacent atoms allows *p* orbitals to overlap and electrons to delocalize.

The electron density in the two π bonds is **delocalized.**



- **When *p* orbitals overlap, the electron density in each of the π bonds is spread out over a larger volume, thus lowering the energy of the molecule and making it more stable.**

Conjugation makes buta-1,3-diene inherently different from penta-1,4-diene, a compound having two double bonds separated by more than one σ bond. The π bonds in penta-1,4-diene are too far apart to be conjugated.



Penta-1,4-diene is an isolated diene. The electron density in each π bond of Page 650 an isolated diene is *localized* between two carbon atoms. In buta-1,3-diene, however, the electron density of both π bonds is *delocalized* over the four atoms of the diene. Electrostatic potential maps in Figure 14.1 clearly indicate the difference between these localized and delocalized π bonds.

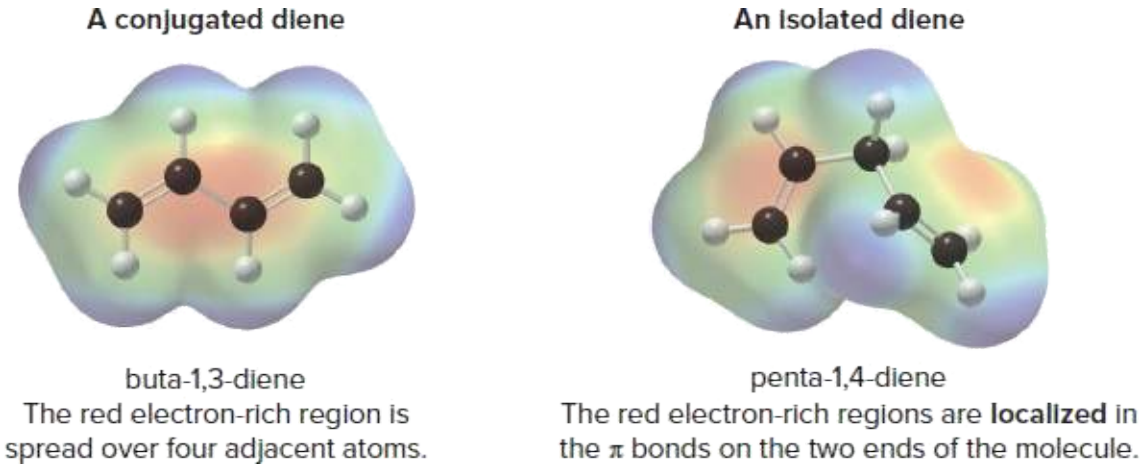
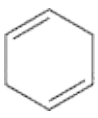


Figure 14.1 **Electrostatic potential plots for a conjugated and an isolated diene**

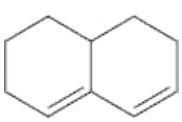
Problem 14.1

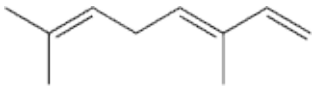
Classify each carbon–carbon double bond as isolated or conjugated.

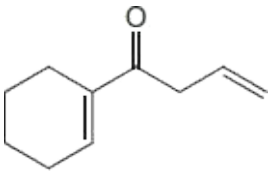
a.

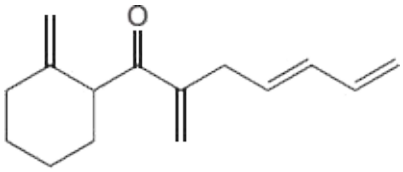


b.



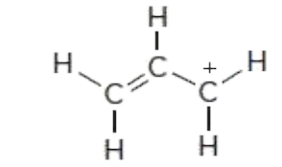
c. 

d. 

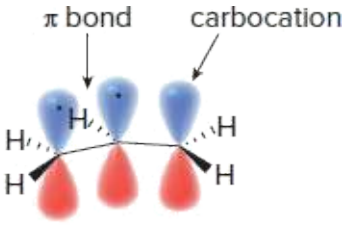
e. 

14.1B Allylic Carbocations

The allyl carbocation is another example of a conjugated system. The three carbon atoms of the allyl carbocation—the positively charged carbon atom and the two that form the double bond—are sp^2 hybridized and have an unhybridized p orbital. The p orbitals for the double bond carbons each contain an electron, whereas the p orbital for the carbocation is empty.



allyl carbocation
Each C is sp^2 hybridized and has a p orbital.



three adjacent p orbitals

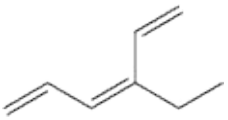
- **Three p orbitals on three adjacent atoms, even if one of the p orbitals is empty, make the allyl carbocation conjugated.**

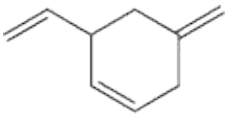
Conjugation stabilizes the allyl carbocation because overlap of three adjacent p orbitals delocalizes the electron density of the π bond over three atoms.

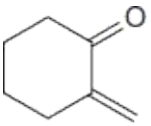
overlap of adjacent p orbitals

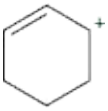
Problem 14.2

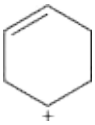
Which of the following species are conjugated?

a. 

b. 

c. 

d. 

e. 

14.2 Resonance and Allylic Carbocations

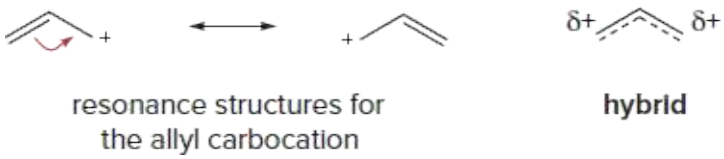
Recall from Section 1.6 that resonance structures are two or more different Lewis structures for the same arrangement of atoms. Being able to draw correct resonance structures is crucial to understanding conjugation and the reactions of conjugated dienes.

The word *resonance* is used in two different contexts. In NMR spectroscopy, a nucleus is *in resonance* when it absorbs energy, promoting it to a higher-energy state. In drawing molecules, there is *resonance* when two different Lewis structures can be drawn for the same arrangement of atoms.

- **Two resonance structures differ in the placement of π bonds and nonbonded electrons. The placement of atoms and σ bonds stays the same.**

14.2A The Stability of Allylic Carbocations

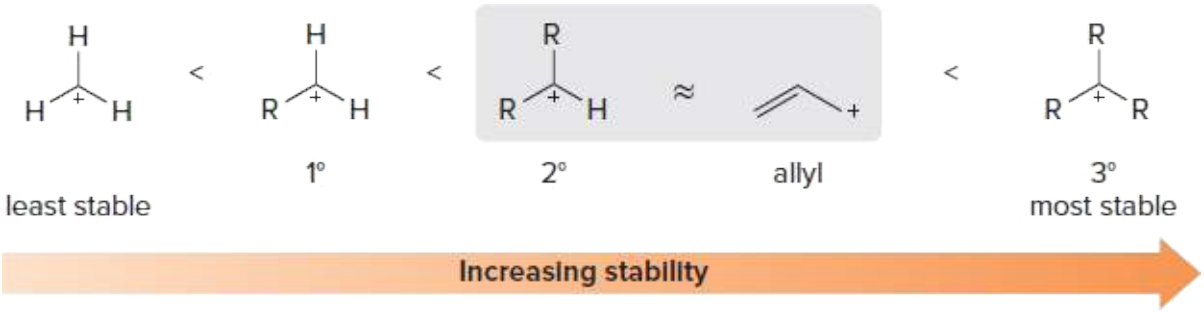
We have already drawn resonance structures for the acetate anion (Section 2.5C) and the allyl radical (Section 13.10). The conjugated allyl carbocation is another example of a species for which two resonance structures can be drawn. Drawing resonance structures for the allyl carbocation is a way to use Lewis structures to illustrate how conjugation delocalizes electrons.



resonance structures for the allyl carbocation

hybrid

The true structure of the allyl carbocation is a hybrid of the two resonance structures. In the hybrid, the π bond is delocalized over all three atoms. As a result, the positive charge is also delocalized over the two terminal carbons. Delocalizing electron density lowers the energy of the hybrid, thus stabilizing the allyl carbocation and making it more stable than a normal 1° carbocation. Experimental data show that its stability is comparable to a more substituted 2° carbocation.



The electrostatic potential maps in Figure 14.2 compare the resonance-stabilized allyl carbocation with $CH_3CH_2CH_2^+$, a localized 1° carbocation. The electron-deficient region—the site of the positive charge—is concentrated on a single carbon atom in the 1° carbocation $CH_3CH_2CH_2^+$. In the allyl carbocation, however, the electron-poor region is spread out on both terminal carbons.

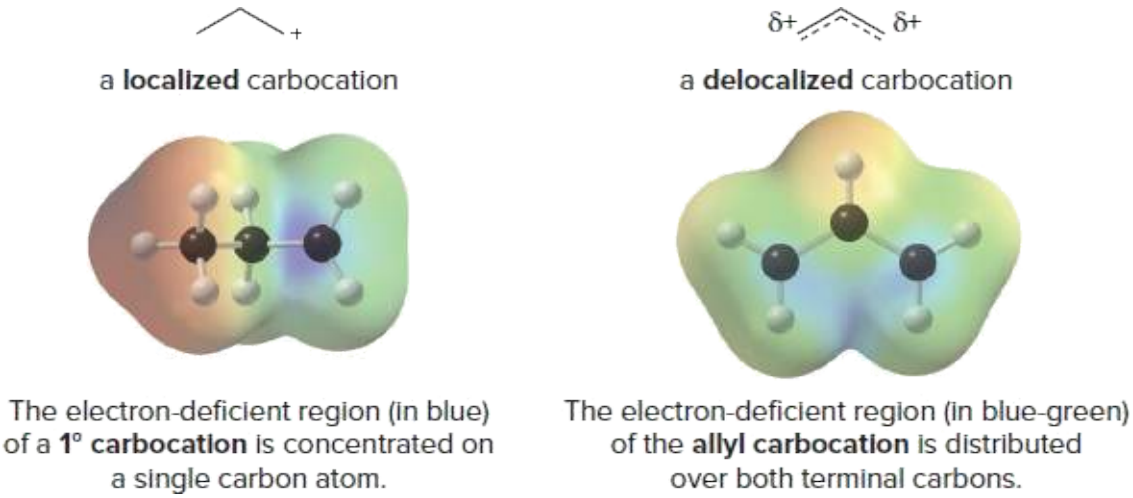
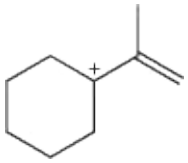


Figure 14.2 **Electrostatic potential maps for a localized and a delocalized carbocation**

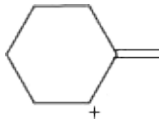
Problem 14.3

Draw a second resonance structure for each carbocation. Then draw the hybrid.

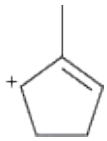
a.



b.



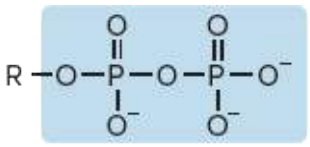
c.



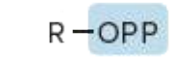
Problem 14.4

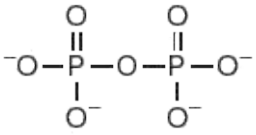
Use resonance theory and the Hammond postulate to explain why 3-chloroprop-1-ene (CH_2=$CHCH_2Cl$) is more reactive than 1-chloropropane ($CH_3CH_2CH_2Cl$) in S_N1 reactions.

14.2B Allylic Carbocations in Biological Reactions



organic diphosphate





diphosphate leaving group

PP_i

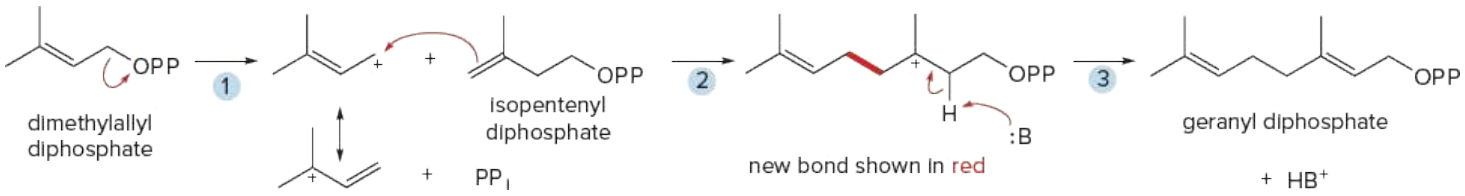
Allylic carbocations formed from diphosphates (Section 7.16) are key intermediates in a variety of biological reactions, including the synthesis of geranyl diphosphate from two five-carbon substrates—dimethylallyl diphosphate and isopentenyl diphosphate. Geranyl diphosphate is the precursor of many lipids that occur in plants and animals.

dimethylallyl diphosphate + isopentenyl diphosphate → geranyl diphosphate

This biological process results in the formation of a new carbon–carbon bond and involves two key steps—loss of a good leaving group (diphosphate, $P_2O_7^{4-}$, abbreviated as PP_i) to form an allylic carbocation, followed by nucleophilic attack with

an electron-rich double bond. The steps of the mechanism are shown in Mechanism 14.1.

Mechanism 14.1 Biological Formation of Geranyl Diphosphate

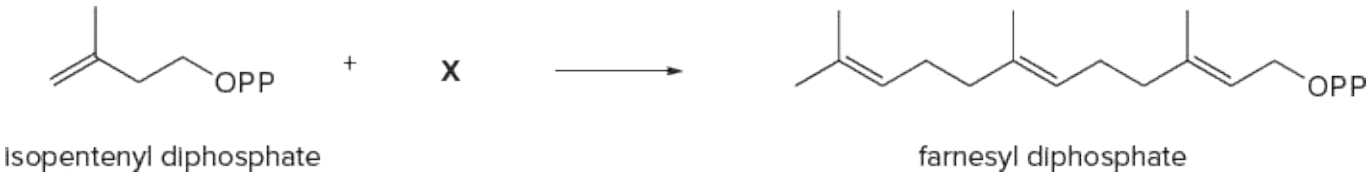


1. **Loss of the diphosphate leaving group forms an allylic carbocation.**
2. **Nucleophilic attack of isopentenyl diphosphate on the allylic carbocation forms the new C–C σ bond.**
3. **Loss of a proton (shown with the general base, B:) forms geranyl diphosphate.**

We will learn more about biological reactions involving allylic carbocations derived from diphosphates in Chapter 29.

Problem 14.5

Farnesyl diphosphate is synthesized from isopentenyl diphosphate and X by a pathway similar to Mechanism 14.1. Draw the structure of X.



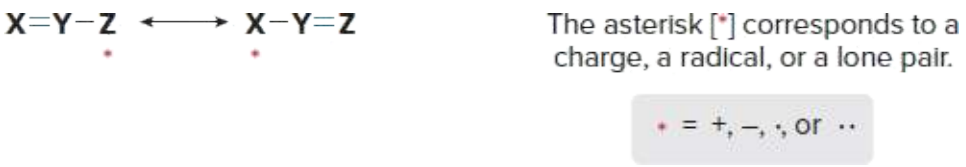
14.3 Common Examples of Resonance

When are resonance structures drawn for a molecule or reactive intermediate? Because resonance involves delocalizing π bonds and nonbonded electrons, one or both of these structural features must be present to draw additional resonance forms. There are four common bonding patterns for which more than one Lewis structure can be drawn.

Type [1] The Three Atom "Allyl" System, X=Y–Z*

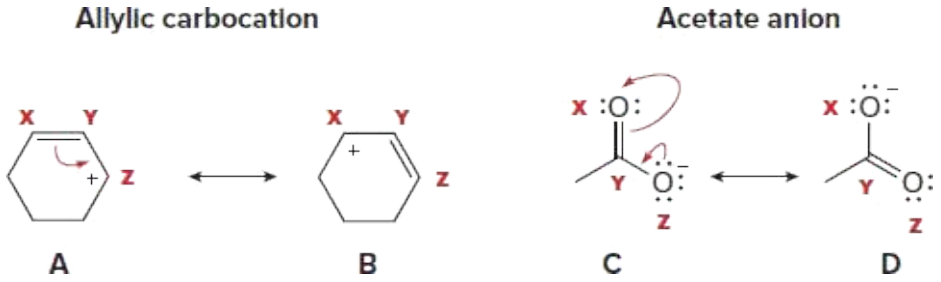
- **For any group of three atoms having a double bond X=Y and an atom Z**

that contains a *p* orbital with zero, one, or two electrons, two resonance structures are possible:



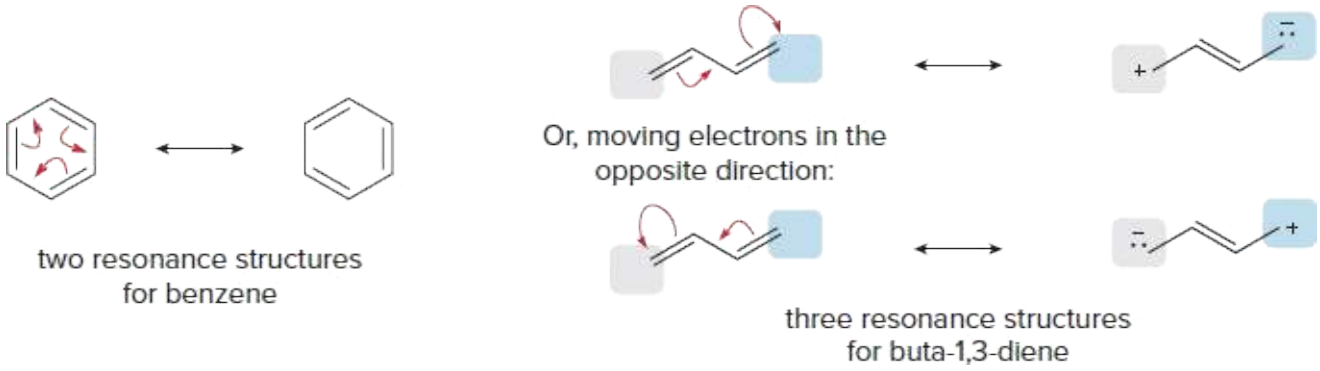
This is called allyl type resonance because it can be drawn for allylic carbocations, allylic carbanions, and allylic radicals.

X, Y, and Z may all be carbon atoms, as in the case of an allylic carbocation (resonance structures A and B), or they may be heteroatoms, as in the case of the acetate anion (resonance structures C and D). The atom Z bonded to the multiple bond can be charged (a net positive or negative charge) or neutral (having zero, one, or two nonbonded electrons). The two resonance structures differ in the location of the double bond, and in the charge, or the radical, or the lone pair, generalized by [*].



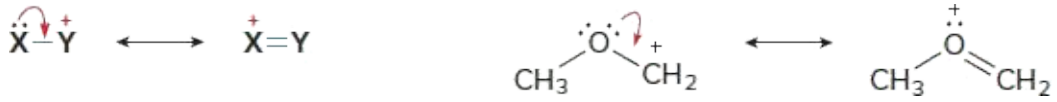
Type [2] Conjugated Double Bonds

Cyclic, completely conjugated rings like benzene have two resonance structures, drawn by moving the electrons in a cyclic manner around the ring. Three resonance structures can be drawn for conjugated dienes, two of which involve charge separation.



Type [3] Cations Having a Positive Charge Adjacent to a Lone Pair

- **When a lone pair and a positive charge are located on adjacent atoms, two resonance structures can be drawn.**



The overall charge is the same in both resonance structures. Based on formal charge, a neutral X in one structure must bear a (+) charge in the other.

Type [4] Double Bonds Having One Atom More Electronegative Than the Other

- **For a double bond X=Y in which the electronegativity of Y > X, a second resonance structure can be drawn by moving the π electrons onto Y.**

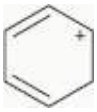
Electronegativity of **Y** > **X**.

Sample Problem 14.1 illustrates how to apply these different types of resonance to actual molecules.

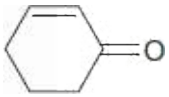
Sample Problem 14.1 Drawing Resonance Structures

Draw two more resonance structures for each species.

a.



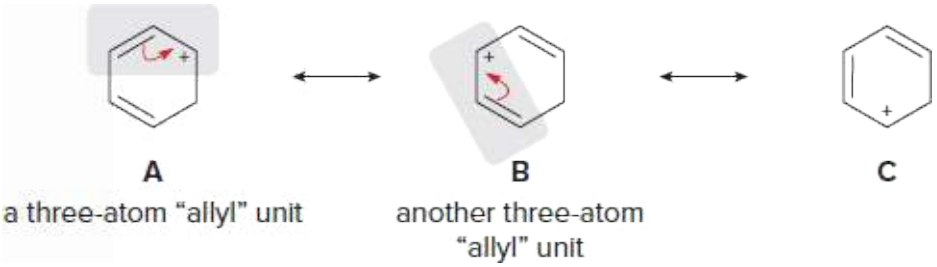
b.



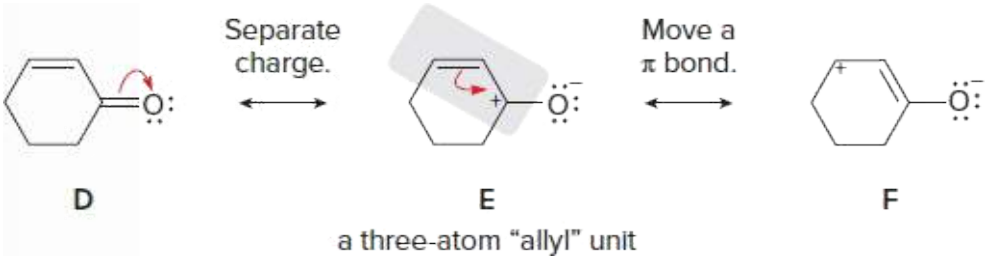
Solution

Mentally breaking a molecule into two- or three-atom units can make it easier to draw additional resonance structures.

a. Think of the top three atoms of the six-membered ring in A as an "allyl" unit. Moving the π bond forms a new "allyl" unit in B, and moving the π bond in B generates a third resonance structure C. No new valid resonance structures are generated by moving electrons in C.



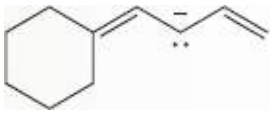
b. Compound D contains a carbonyl group, so moving the electron pair in the double bond to the more electronegative oxygen atom separates the charge and generates structure E. E now has a three-atom "allyl" unit, so the remaining π bond can be moved to form structure F.



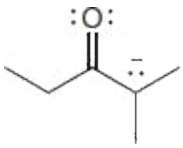
Problem 14.6

Draw additional resonance structures for each ion.

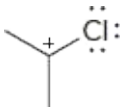
a.



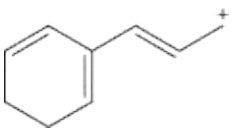
b.



c.



d.



More Practice:

Try Problems 14.34, 14.36.

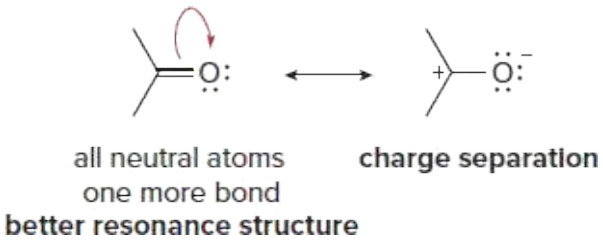
14.4 The Resonance Hybrid

The lower its energy, the more a resonance structure contributes to the overall structure of the hybird.

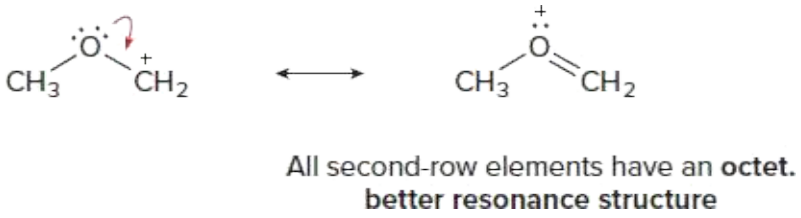
Although the resonance hybrid is some combination of all of its valid resonance structures, the hybrid more closely resembles the best resonance structure. Recall from Section 1.6C that the best resonance structure is called the major contributor to the hybrid, and other resonance structures are called the minor contributors. Two identical resonance structures are equal contributors to the hybrid.

Use three rules to evaluate the relative energies of two or more valid resonance structures.

Rule [1] **Resonance structures with more bonds and fewer charges are better.**

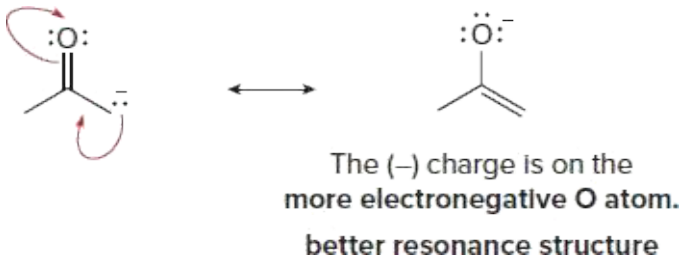


Rule [2] **Resonance structures in which every atom has an octet are better.**



In this example, the resonance structure in which all atoms have octets is better, even though it places a (+) charge on a more electronegative O atom.

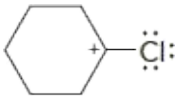
Rule [3] **Resonance structures that place a negative charge on a *more* electronegative atom are better.**



Sample Problem 14.2 illustrates how to determine the relative energy of contributing resonance structures and the hybrid.

Sample Problem 14.2 Determining the Relative Energy of Resonance Structures and the Hybrid

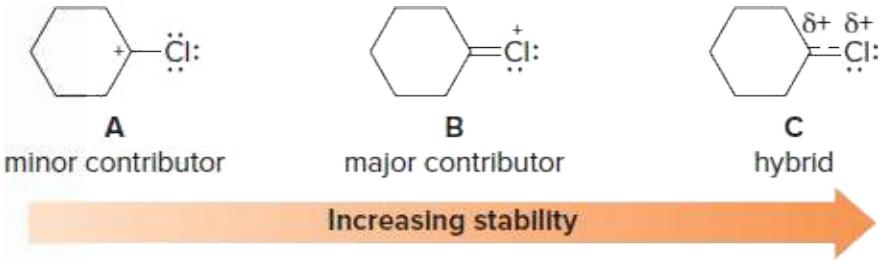
Draw a second resonance structure for carbocation A, as well as the hybrid of both resonance structures. Then use Rules [1]–[3] to rank the relative stability of both resonance structures and the hybrid.



A

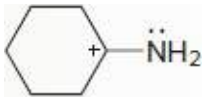
Solution

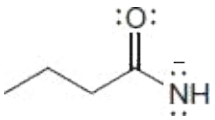
Because A contains a positive charge and a lone pair on adjacent atoms, a second resonance structure B can be drawn. Because B has more bonds and all second-row atoms have octets, B is a better resonance structure than A, making it the major contributor to the hybrid C. Because the hybrid is more stable than either resonance contributor, the order of stability is:

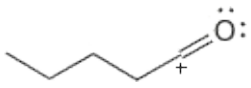


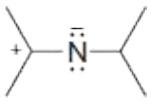
Problem 14.7

Draw a second resonance structure and the hybrid for each species, and then rank the two resonance structures and the hybrid in order of increasing stability.

a. 

b. 

c. 

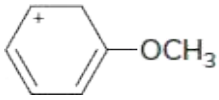
d. 

More Practice:

Try Problem 14.35.

Problem 14.8

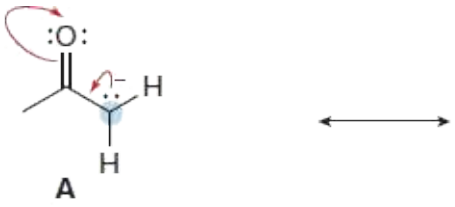
Draw all possible resonance structures for the following cation, and indicate which structure makes the largest contribution to the resonance hybrid.



14.5 Electron Delocalization, Hybridization, and Geometry

To delocalize nonbonded electrons or electrons in π bonds, there must be *p* orbitals that can overlap. This may mean that the hybridization of an atom is *different* than would have been predicted using the rules first outlined in Chapter 1.

For example, there are two Lewis structures (A and B) for the resonance-stabilized anion $(CH_3COCH_2)^-$.

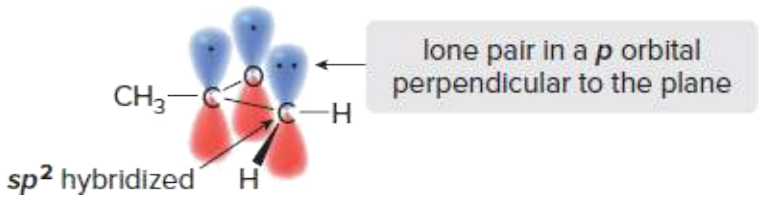


The labeled C is surrounded by four groups—three atoms and one nonbonded electron pair. **Is it sp^3 hybridized?**

The labeled C is surrounded by three groups—three atoms and no nonbonded electron pairs. **Is it sp^2 hybridized?**

Based on structure A, the labeled carbon is sp^3 hybridized, with the lone pair of electrons in an sp^3 hybrid orbital. Based on structure B, though, it is sp^2 hybridized with the unhybridized *p* orbital forming the π portion of the double bond.

Delocalizing electrons stabilizes a molecule. The electron pair on the carbon atom adjacent to the C=O can only be delocalized, though, if it has a *p* orbital that can overlap with two other *p* orbitals on two adjacent atoms. Thus, the terminal carbon atom is sp^2 hybridized with trigonal planar geometry. Three adjacent *p* orbitals make the anion conjugated.



- **In a system X=Y–Z:, Z is generally sp^2 hybridized, and the nonbonded electron pair occupies a *p* orbital to make the system conjugated.**

Sample Problem 14.3 **Determining Hybridization in a Conjugated System**

Determine the hybridization around the labeled carbon atom in the following anion.

Solution

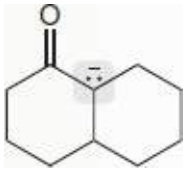
Because this is an example of an allyl-type system (X=Y–Z*), a second resonance structure can be drawn that "moves" the lone pair and the π bond. To delocalize the lone pair and make the system conjugated, the labeled carbon atom must be sp^2 hybridized with the lone pair occupying a *p* orbital.

The labeled C atom must be sp^2 hybridized, with the lone pair in a *p* orbital.

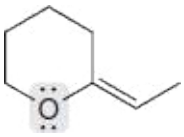
Problem 14.9

Determine the hybridization of the labeled atom in each species.

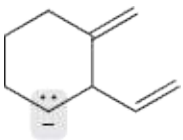
a.



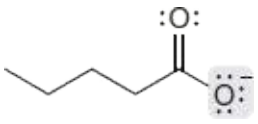
b.



c.



d.



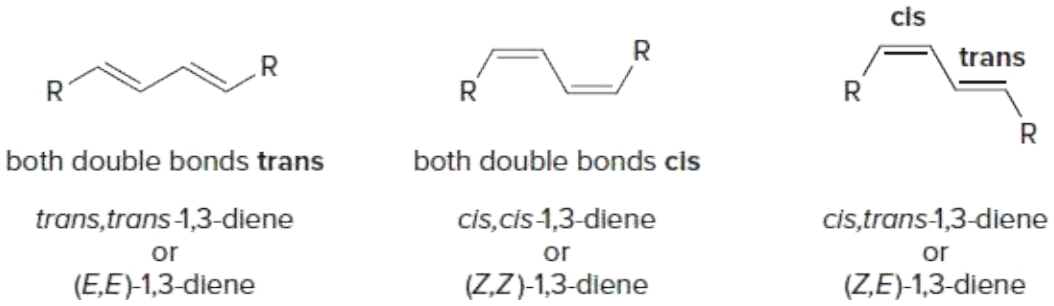
14.6 Conjugated Dienes

In the remainder of Chapter 14 we examine conjugated dienes, compounds having two

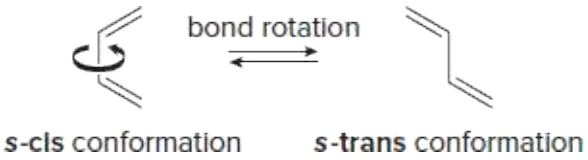
double bonds joined by one σ bond. Conjugated dienes are also called 1,3-dienes. Buta-1,3-diene (CH_2=CH–CH=CH_2) is the simplest conjugated diene.

Compounds with many π bonds are called polyenes.

Three stereoisomers are possible for 1,3-dienes with alkyl groups bonded to each end carbon of the diene (RCH=CH-CH=CHR).



Two possible conformations result from rotation about the C–C bond that joins the two double bonds.



- **The s-cis conformation has two double bonds on the *same* side of the single bond.**
- **The s-trans conformation has two double bonds on *opposite* sides of the single bond.**

Keep in mind that stereoisomers are discrete molecules, whereas conformations interconvert. Three structures drawn for hexa-2,4-diene illustrate the differences between stereoisomers and conformations in a 1,3-diene:

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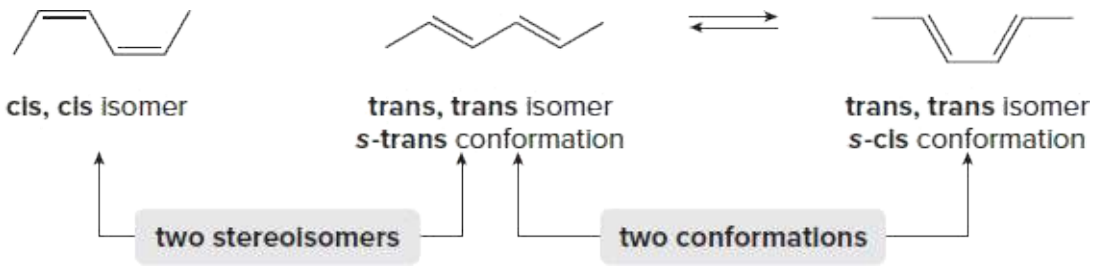
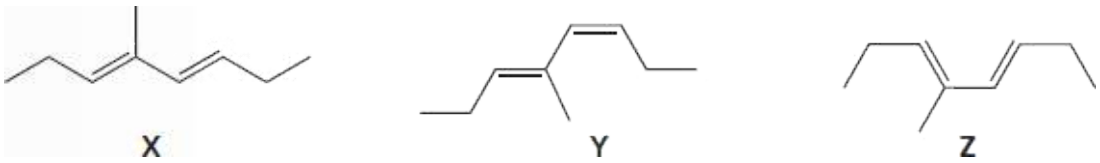


Sample Problem 14.4 Classifying Compounds as Stereoisomers or Different Conformations

Classify each pair of compounds as stereoisomers or conformations: (a) X

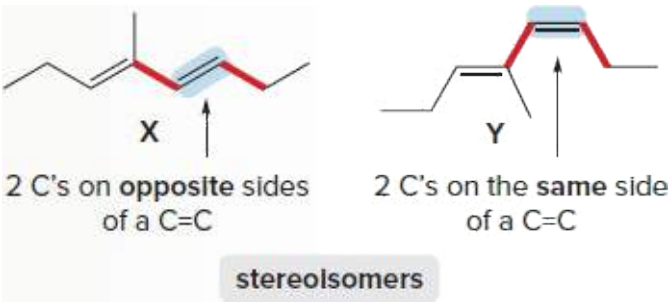
and Y; (b) X and Z.



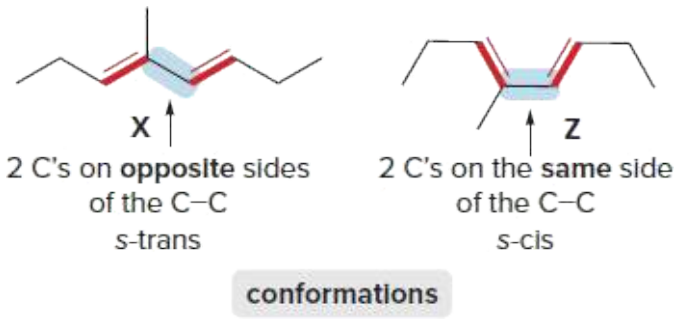
Solution

- **Stereoisomers are *different* compounds. Groups on each end of a carbon–carbon double bond are arranged differently.**
- **Two conformations are the *same* compound, which interconvert by bond rotation.**

a. X and Y are stereoisomers because the groups around the C=C in blue are arranged differently; in X two groups are trans, and in Y two groups are cis.

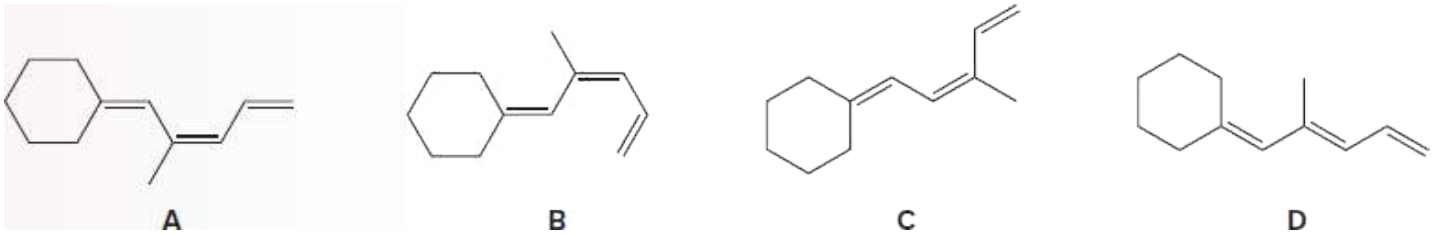


b. Each C=C in X and Z is bonded to the same groups and has the E configuration. X has the two double bonds on opposite sides of the C–C in blue, whereas Z has two double bonds on the same side of the single bond that joins them together. X and Z are different conformations.



Problem 14.10

Label compounds B–D as stereoisomers, conformations, or constitutional isomers of A.



More Practice:

Try Problem 14.41.

Problem 14.11

Draw the structure consistent with each description.

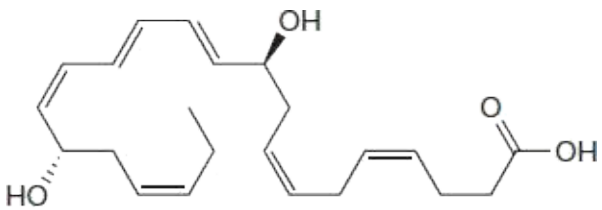
a. (2*E*,4*E*)-octa-2,4-diene in the *s*-trans conformation

b. (3*E*,5*Z*)-nona-3,5-diene in the *s*-cis conformation

c. (3*Z*,5*Z*)-4,5-dimethyldeca-3,5-diene. Draw both the *s*-cis and *s*-trans conformations.

Problem 14.12

Neuroprotectin D1 (NPD1) is synthesized in the body from highly unsaturated essential fatty acids. NPD1 is a potent natural anti-inflammatory agent.



NPD1

a. Label each carbon–carbon double bond as conjugated or isolated.

b. Label each double bond as *E* or *Z*.

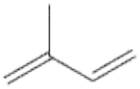
c. For each conjugated system, label the given conformation as *s*-cis or *s*-trans.

14.7 Interesting Dienes and Polyenes

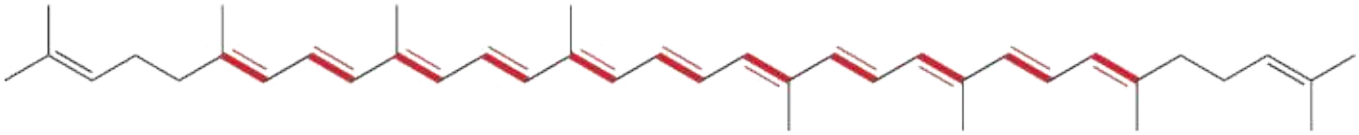
Isoprene and lycopene are two naturally occurring compounds with conjugated double bonds.

Isoprene is a component of the blue haze seen above forested hillsides, such as Virginia's Blue Ridge Mountains.

©daveallenphoto/123RF



isoprene
(2-methylbuta-1,3-diene)



11 conjugated double bonds shown in red

lycopene

Isoprene, the common name for 2-methylbuta-1,3-diene, is given off by plants as the temperature rises, a process thought to increase a plant's tolerance for heat stress.

Lycopene, a naturally occurring molecule responsible for the red color of tomatoes and other fruits, is an antioxidant like vitamin E. The 11 conjugated double bonds of lycopene cause its red color, a phenomenon discussed in Section 14.15A.

Simvastatin and calcitriol are two drugs that contain conjugated double bonds in addition to other functional groups (Figure 14.3). Simvastatin is the generic name of the widely used cholesterol-lowering medicine Zocor. Calcitriol, a biologically active hormone formed from vitamin D_3 obtained in the diet, is responsible for regulating calcium and phosphorus metabolism. Sold under the trade name of Rocaltrol, calcitriol is used to treat patients who are unable to convert vitamin D3 to the active hormone. Because calcitriol promotes the absorption of calcium ions, it is also used to treat hypocalcemia, the presence of low calcium levels in the blood.

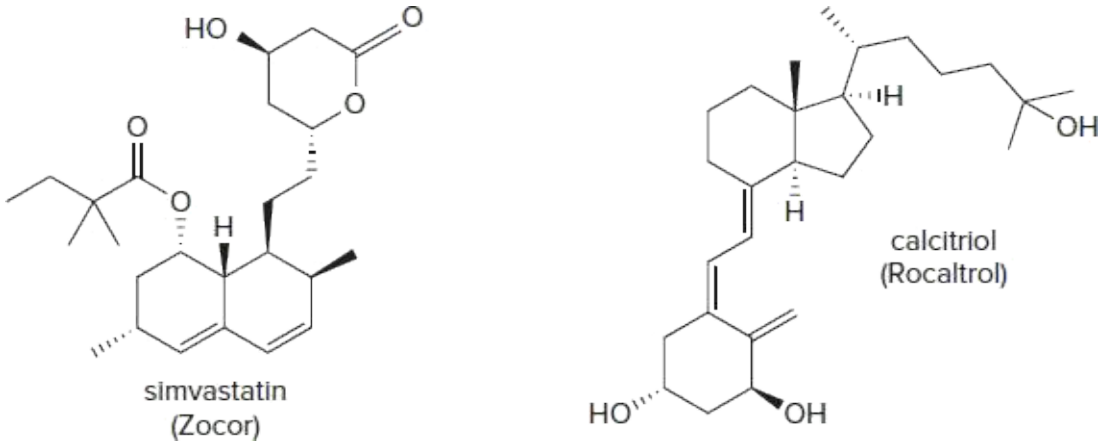


Figure 14.3 **Biologically active organic compounds that contain conjugated double bonds**

14.8 The Carbon-Carbon σ Bond Length in Buta-1,3-diene

Four features distinguish conjugated dienes from isolated dienes:

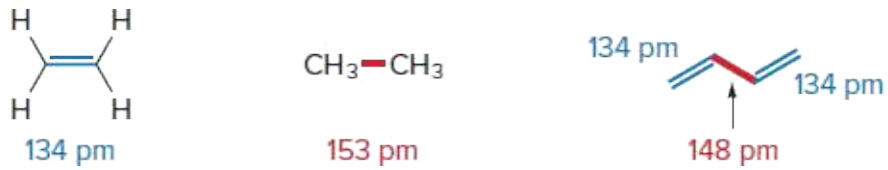
[1] The C–C single bond joining the two double bonds is unusually short.

[2] Conjugated dienes are more stable than similar isolated dienes.

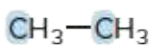
[3] Some reactions of conjugated dienes are different than reactions of isolated double bonds.

[4] Conjugated dienes absorb longer wavelengths of ultraviolet light.

Hybridization can explain why the central carbon–carbon single bond is shorter than the C–C bond in ethane (148 pm vs. 153 pm).



Each carbon atom in buta-1,3-diene is sp^2 hybridized, so the central C–C single bond is formed by the overlap of two sp^2 hybridized orbitals, rather than the sp^3 hybridized orbitals used to form the C–C bond in CH_3CH_3.



sp^3 C's

25% *s*-character

lower percent *s*-character
longer bond

sp^2 C's

33% *s*-character

higher percent *s*-character
shorter bond

Recall from Section 1.11B that increasing percent *s*-character decreases bond length.

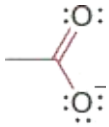
- **Based on hybridization, a $C_{sp}2–C_{sp}2$ bond should be shorter than a $C_{sp}3–C_{sp}3$ bond because it is formed from orbitals having a *higher* percent *s*-character.**

Problem 14.13

Using hybridization, predict how the bond length of the C–C σ bond in HC≡C–C≡CH should compare with the C–C σ bonds in CH_3CH_3 and CH_2=CH–CH=CH_2.

Problem 14.14

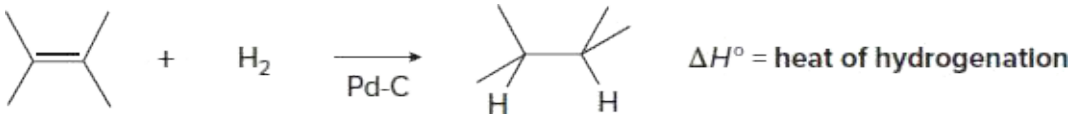
Use resonance theory to explain why the labeled C–O bond lengths are equal in the acetate anion.



acetate

14.9 Stability of Conjugated Dienes

In Section 12.3, we learned that hydrogen adds to alkenes to form alkanes and that the heat released in this reaction, the heat of hydrogenation, can be used as a measure of alkene stability.

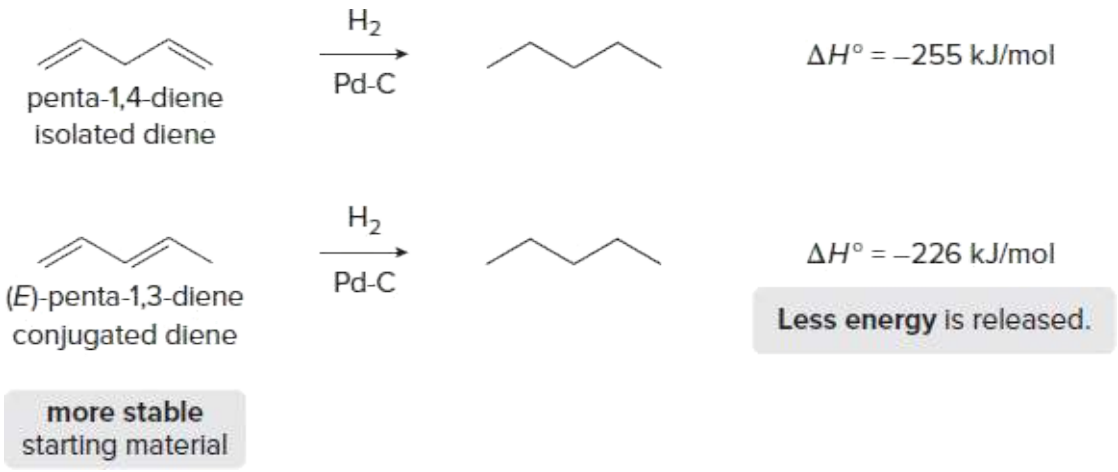


The relative stability of conjugated and isolated dienes can also be determined by comparing their heats of hydrogenation.

- **When hydrogenation gives the same alkane from two dienes, the more**

stable diene has the *smaller* heat of hydrogenation.

For example, both penta-1,4-diene (an isolated diene) and (*E*)-penta-1,3-diene (a conjugated diene) are hydrogenated to pentane with two equivalents of H_2. Because *less* energy is released in converting the conjugated diene to pentane, it must be *lower in energy* (more stable) to begin with. The relative energies of these isomeric pentadienes are illustrated in Figure 14.4.



- **A conjugated diene has a smaller heat of hydrogenation and is more stable than a similar isolated diene.**

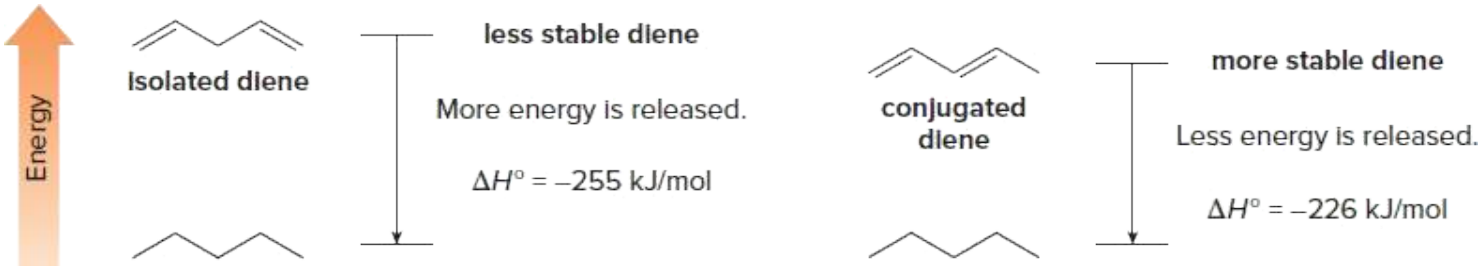
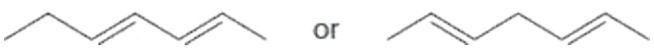


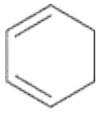
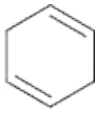
Figure 14.4 **Relative energies of an isolated and conjugated diene**

In Section 14.1, we learned why a conjugated diene is more stable than an isolated diene. A conjugated diene has overlapping *p* orbitals on four adjacent atoms, so its π electrons are delocalized over four atoms, thus stabilizing the diene. This delocalization cannot occur in an isolated diene, so an isolated diene is less stable than a conjugated diene.

Problem 14.15

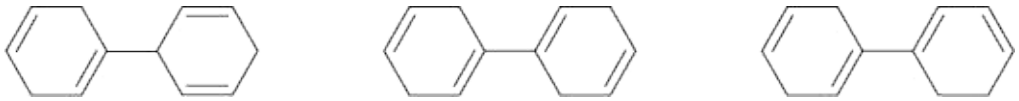
Which diene in each pair has the larger heat of hydrogenation?

a.  or

b.  or 

Problem 14.16

Rank the following compounds in order of increasing stability.

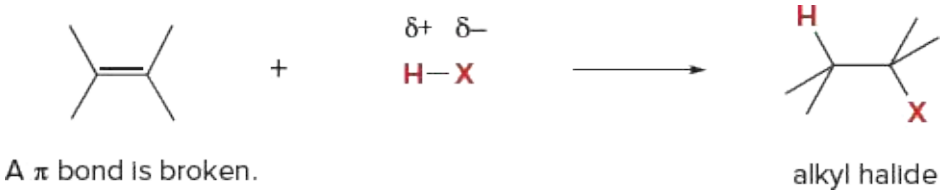


14.10 Electrophilic Addition: 1,2- Versus 1,4-Addition

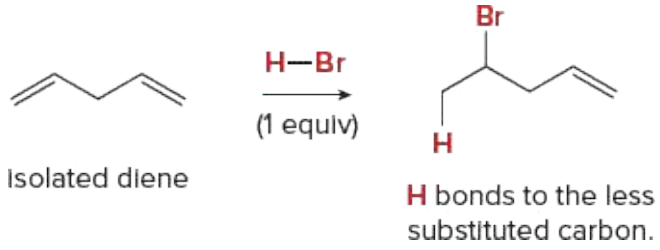
Recall from Chapters 10 and 11 that the characteristic reaction of compounds with π bonds is addition. The π bonds in conjugated dienes undergo addition reactions, too, but they differ in two ways from the addition reactions to isolated double bonds.

- **Electrophilic addition in conjugated dienes gives a mixture of products.**
- **Conjugated dienes undergo a unique addition reaction not seen in alkenes or isolated dienes.**

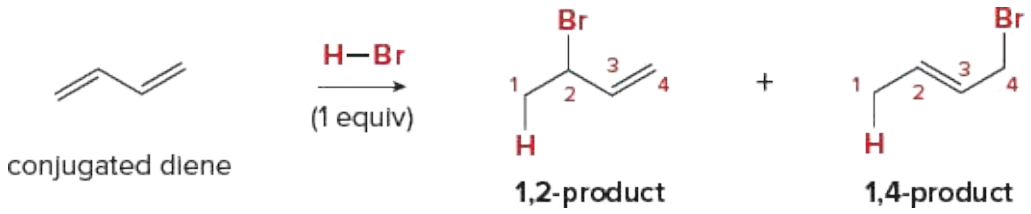
We learned in Chapter 10 that HX adds to the π bond of alkenes to form alkyl halides. Page 662



With an isolated diene, electrophilic addition of one equivalent of HBr yields *one* product and Markovnikov's rule is followed. The H atom bonds to the less substituted carbon—that is, the carbon atom of the double bond that had more H atoms to begin with.



With a conjugated diene, electrophilic addition of one equivalent of HBr affords *two* products.

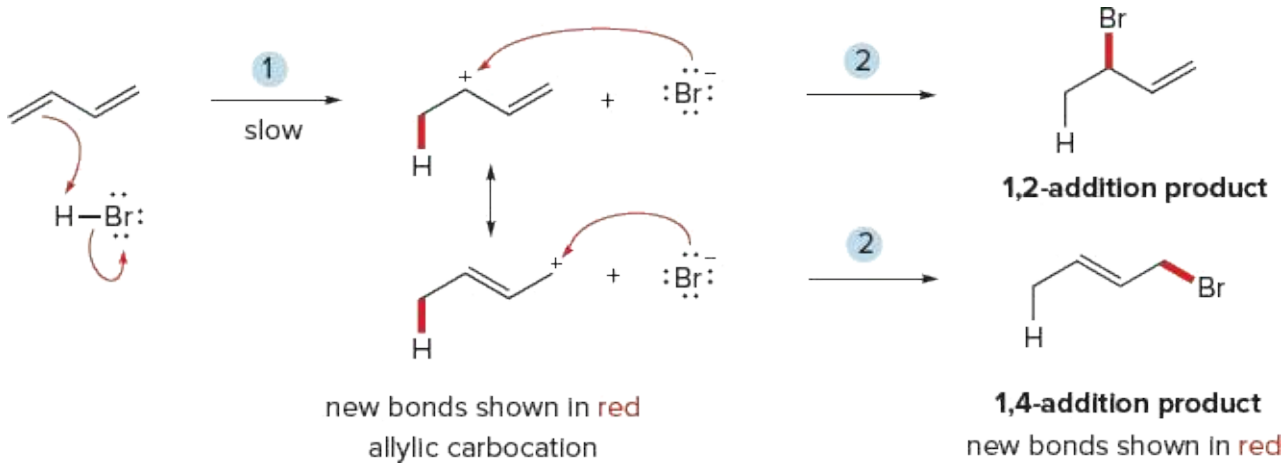


The ends of the 1,3-diene are called C1 and C4 arbitrarily, without regard to IUPAC numbering.

- The 1,2-addition product results from Markovnikov addition of HBr across two adjacent carbon atoms (C1 and C2) of the diene.
- The 1,4-addition product results from addition of HBr to the two end carbons (C1 and C4) of the diene. 1,4-Addition is also called conjugate addition.

The mechanism of electrophilic addition of HX involves two steps: addition of H^+ (from HX) to form a resonance-stabilized carbocation, followed by nucleophilic attack of X^- at either electrophilic end of the carbocation to form two products. Mechanism 14.2 illustrates the reaction of buta-1,3-diene with HBr.

Mechanism 14.2 Electrophilic Addition of HBr to a 1,3-Diene—1,2- and 1,4-Addition



1 **H^+ of HBr adds to a terminal carbon of the 1,3-diene to form a resonance-stabilized allylic carbocation.**

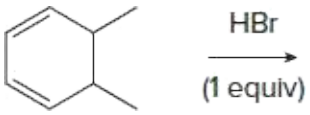
2 **Nucleophilic attack of Br^- occurs at either site of the resonance-stabilized carbocation that bears a (+) charge, forming the 1,2- and 1,4-addition products.**

Like the electrophilic addition of HX to an alkene, the addition of HBr to a conjugated diene forms the more stable carbocation in Step [1], the rate-determining step. In this case, however, the carbocation is both 2° and allylic, and thus two Lewis structures can be drawn for it. In the second step, nucleophilic attack of Br^- can then occur at two different electrophilic sites, forming two different products.

- **Addition of HX to a conjugated diene forms 1,2- and 1,4-products because of the resonance-stabilized allylic carbocation intermediate.**

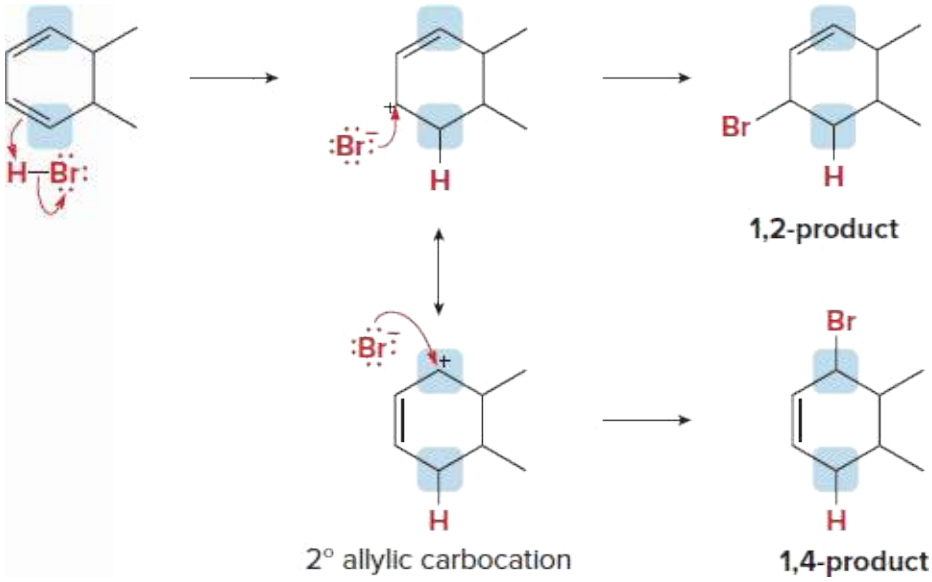
Sample Problem 14.5 Drawing the Products of 1,2- and 1,4-Addition

Draw the products of the following reaction.



Solution

Write the steps of the mechanism to determine the structure of the products. Addition of H^+ forms the more stable 2° allylic carbocation, for which two resonance structures can be drawn. H^+ always bonds to a terminal carbon of the 1,3-diene, labeled in blue. Nucleophilic attack of Br^- at either end of the allylic carbocation gives two constitutional isomers, formed by 1,2-addition and 1,4-addition to the diene.

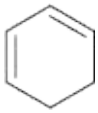


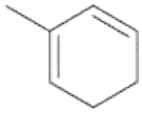
Problem 14.17

Draw the products formed when each diene is treated with one equivalent of HCl.

a.

b.

c. 

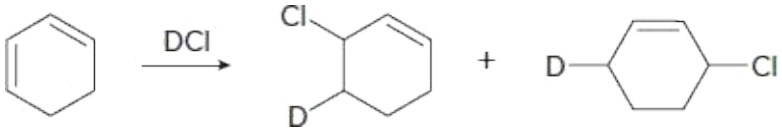
d. 

More Practice:

Try Problems 14.43; 14.61a, d.

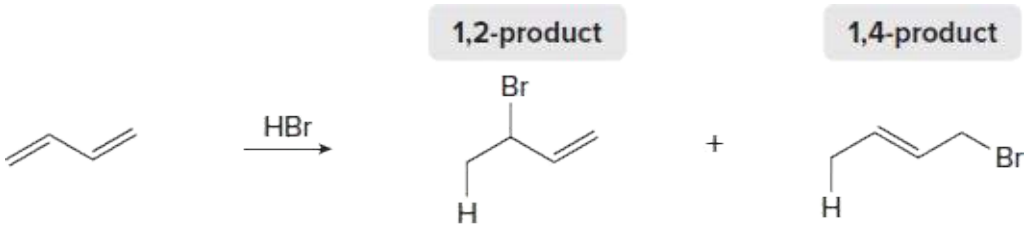
Problem 14.18

Draw a stepwise mechanism for the following reaction.



14.11 Kinetic Versus Thermodynamic Products

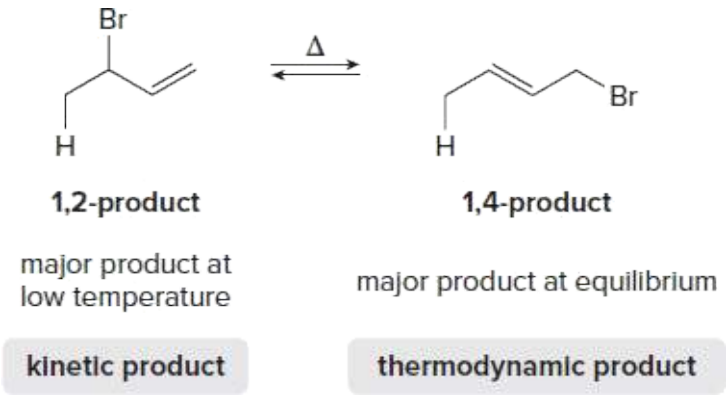
The amount of 1,2- and 1,4-addition products formed in the electrophilic addition reactions of buta-1,3-diene, a conjugated diene, depends greatly on the reaction conditions.



	1,2-product	1,4-product
low temperature (–80 °C)	80%	20%
high temperature (40 °C)	20%	80%

- At low temperature the major product is formed by 1,2-addition.
- At higher temperature the major product is formed by 1,4-addition.

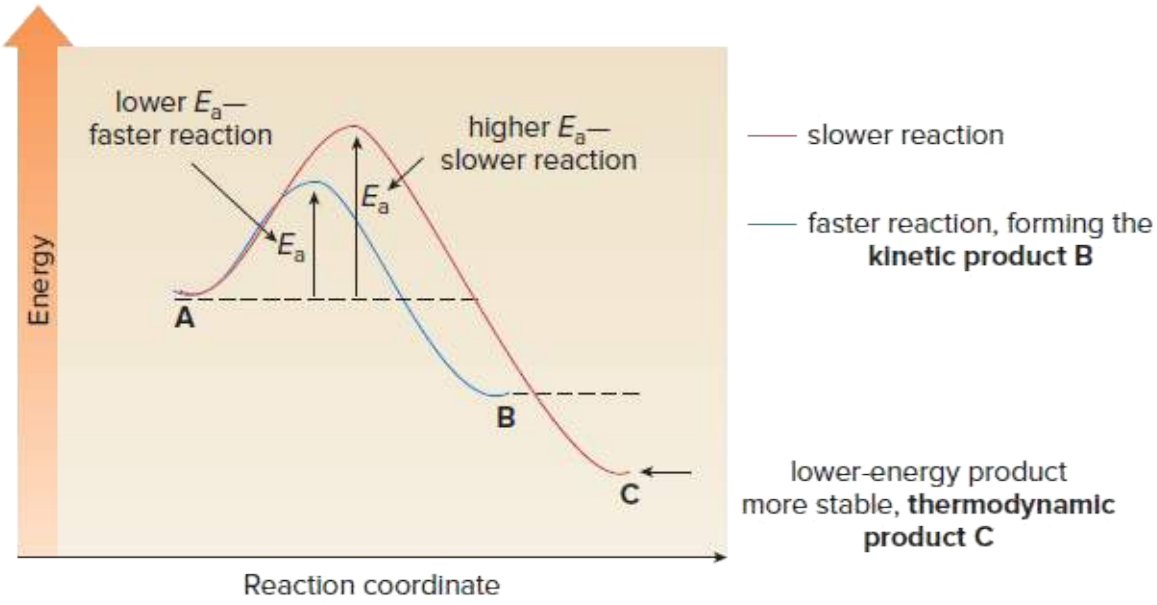
Moreover, when a mixture containing predominately the 1,2-product is heated, the 1,4-addition product becomes the major product at equilibrium.



- **The 1,2-product is formed *faster* because it predominates at low temperature. The product that is formed faster is called the *kinetic product*.**
- **The 1,4-product must be *more stable* because it predominates at equilibrium. The product that predominates at equilibrium is called the *thermodynamic product*.**

In many of the reactions we have learned thus far, the more stable product is formed faster—that is, the kinetic and thermodynamic products are the same. The electrophilic addition of HBr to buta-1,3-diene is different, in that the more stable product is formed more slowly—that is, the kinetic and thermodynamic products are *different*. Why is the more stable product formed more slowly?

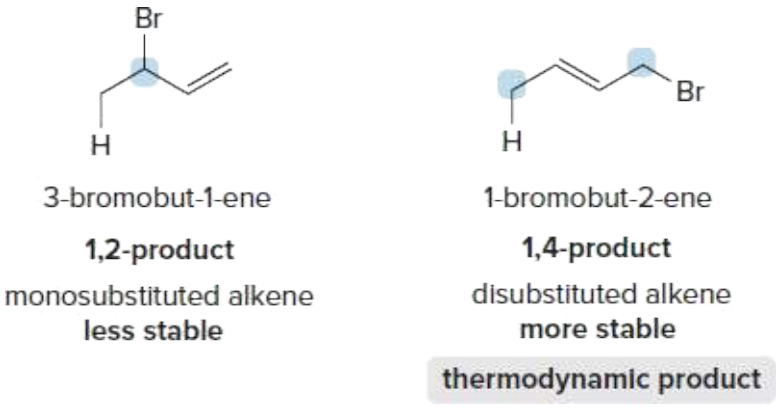
To answer this question, recall that the rate of a reaction is determined by its energy of activation (E_a), whereas the amount of product present at equilibrium is determined by its stability (Figure 14.5). When a single starting material A forms two different products (B and C) by two exothermic pathways, the relative height of the energy barriers determines how fast B and C are formed, whereas the relative energies of B and C determine the amount of each at equilibrium. In an exothermic reaction, the relative energies of B and C do not determine the relative energies of activation to form B and C.



- The conversion of **A** → **B** is a faster reaction because the energy of activation leading to **B** is *lower*. **B** is the **kinetic product.**
- Because **C** is *lower* in energy, **C** is the **thermodynamic product.**

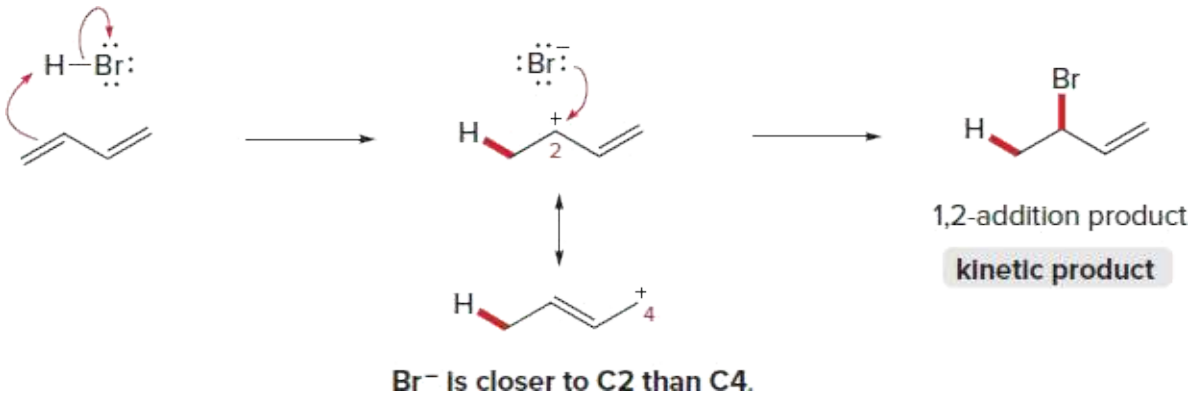
Figure 14.5 **How kinetic and thermodynamic products form in a reaction: A → B + C**

Why, in the addition of HBr to buta-1,3-diene, is the 1,4-product the more stable thermodynamic product? The 1,4-product (1-bromobut-2-ene) is more stable because it has two alkyl groups bonded to the carbon–carbon double bond, whereas the 1,2-product (3-bromobut-1-ene) has only one. Page 665



- **The more substituted alkene—1-bromobut-2-ene in this case—is the thermodynamic product.**

The 1,2-product is the kinetic product because of a proximity effect. When H^+ (from HBr) adds to the double bond, Br^- is *closer* to the adjacent carbon (C2) than it is to C4. Even though the resonance-stabilized carbocation bears a partial positive charge on both C2 and C4, attack at C2 is faster simply because Br^- is closer to this carbon.



A proximity effect occurs because one species is close to another.

- **The 1,2-product forms faster because of the proximity of Br^- to C2.**

The overall two-step mechanism for addition of HBr to buta-1,3-diene, forming a 1,2-addition product and 1,4-addition product, is illustrated with the energy diagram in Figure 14.6.

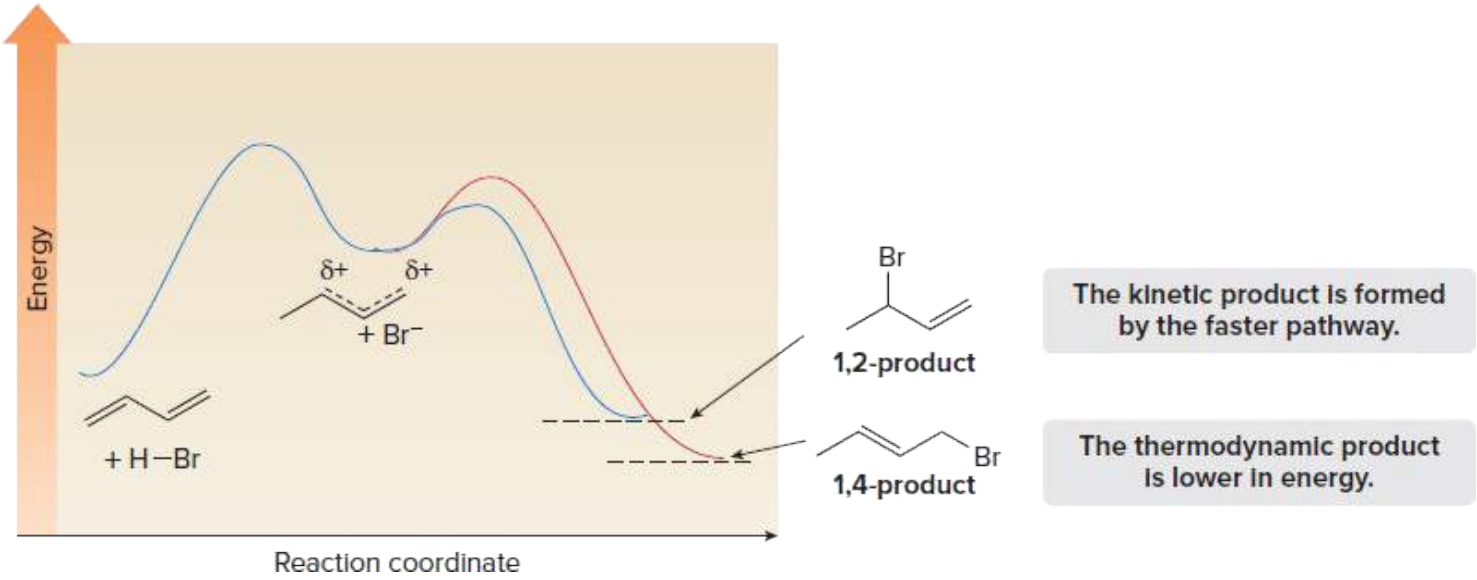


Figure 14.6 **Energy diagram for the two-step addition of HBr to CH_2=CH–CH=CH_2**

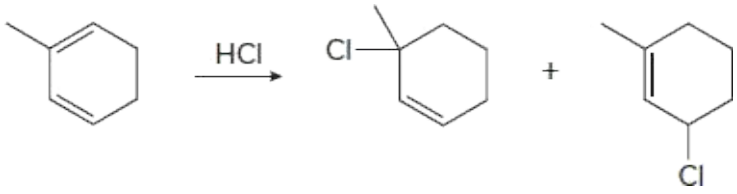
Why is the ratio of products temperature dependent?

- At low temperature, the energy of activation is the more important factor. Because most molecules do not have enough kinetic energy to overcome the higher energy barrier at lower temperature, they react by the faster pathway, forming the kinetic product.
- At higher temperature, most molecules have enough kinetic energy to reach

either transition state. The two products are in equilibrium with each other, and the more stable compound—which is lower in energy—becomes the major product.

Problem 14.19

Label each product in the following reaction as a 1,2-product or a 1,4-product, and decide which is the kinetic product and which is the thermodynamic product.

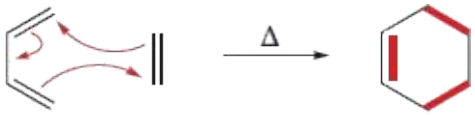


14.12 The Diels–Alder Reaction

The Diels–Alder reaction, named for German chemists Otto Diels and Kurt Alder, is an addition reaction between a 1,3-diene and an alkene called a dienophile, to form a new six-membered ring.

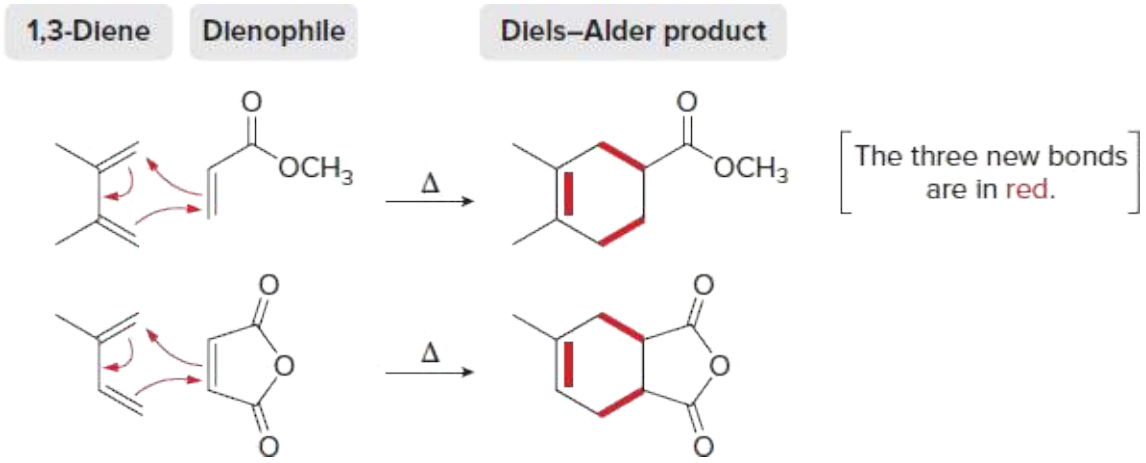
Diels and Alder shared the 1950 Nobel Prize in Chemistry for unraveling the intricate details of this remarkable reaction.

The arrows may be drawn in a clockwise or counterclockwise direction to show the flow of electrons in a Diels–Alder reaction.



1,3-diene dienophile

Three curved arrows are needed to show the cyclic movement of electron pairs because three π bonds break and two σ bonds and one π bond form. Because each new σ bond is ~100 kJ/mol stronger than a π bond that is broken, a typical Diels–Alder reaction releases ~200 kJ/mol of energy. The following equations illustrate two examples of the Diels–Alder reaction.



All Diels–Alder reactions have these features in common:

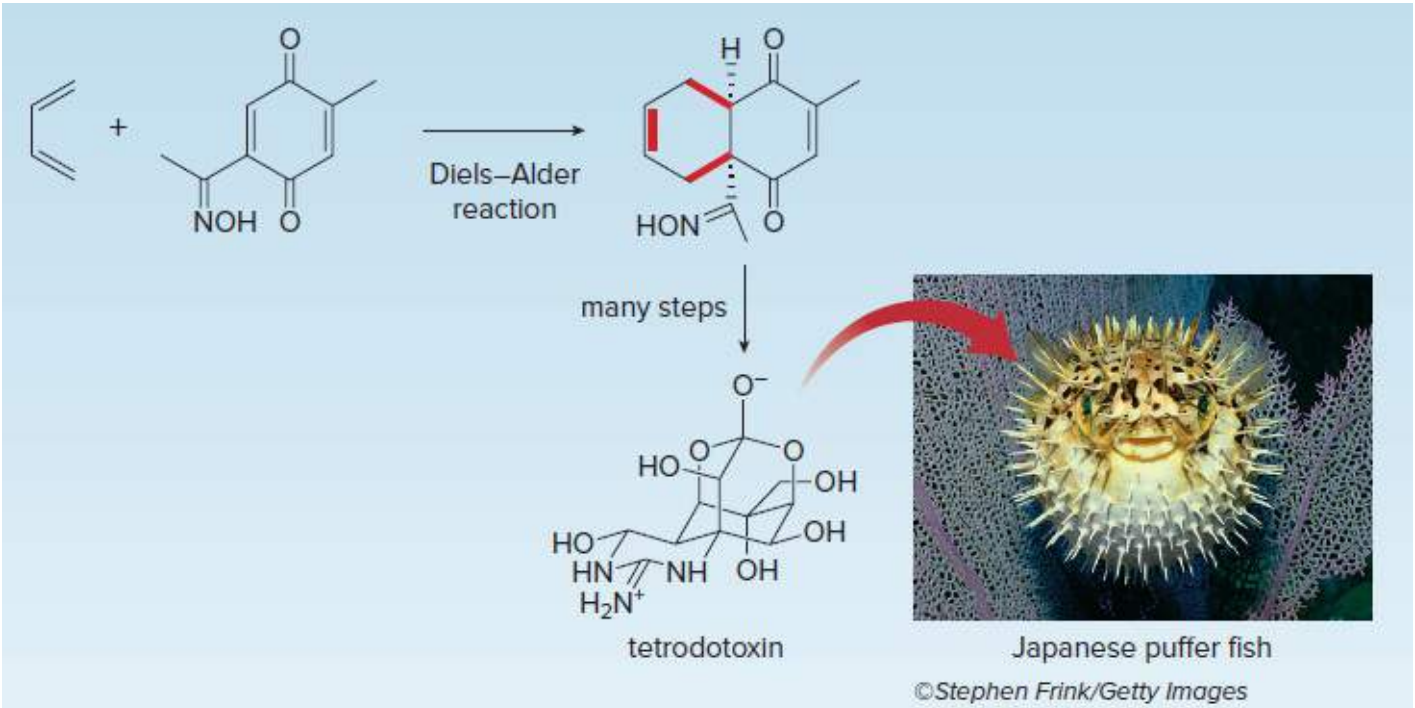
[1] They are initiated by heat; that is, the Diels–Alder reaction is a *thermal* reaction.

[2] They form new six-membered rings.

[3] Three π bonds break, and two new C–C σ bonds and one new C–C π bond form.

[4] They are concerted; that is, all bonds are broken and formed in a single step.

The Diels–Alder reaction forms new carbon–carbon bonds, so it can be used to synthesize larger, more complex molecules from smaller ones. For example, Figure 14.7 illustrates a Diels–Alder reaction used in the synthesis of tetrodotoxin, a toxin isolated from many different types of puffer fish.



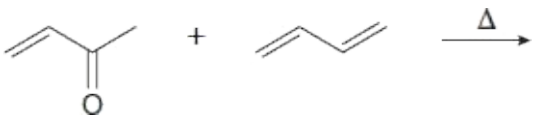
- Tetrodotoxin, a complex natural product containing several six-membered rings joined together, is a poison isolated from the ovaries and liver of the puffer fish, so named because the fish inflates itself into a ball when alarmed. One step in the synthesis of tetrodotoxin involves forming a six-membered ring by a Diels–Alder reaction.

Figure 14.7 **Synthesis of a natural product using the Diels–Alder reaction**

Diels–Alder reactions may seem complicated at first, but they are really less complicated than many of the reactions you have already learned, especially those with multistep mechanisms and carbocation intermediates. The key is to learn how to arrange the starting materials to more easily visualize the structure of the product.

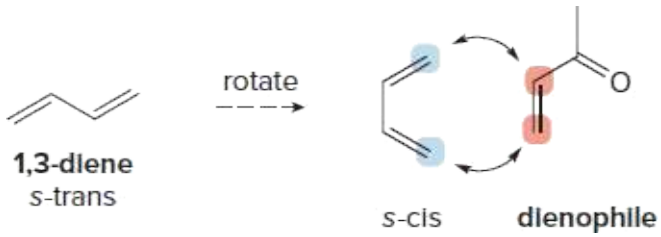
How To Draw the Product of a Diels–Alder Reaction

Example Draw the product of the following Diels–Alder reaction:

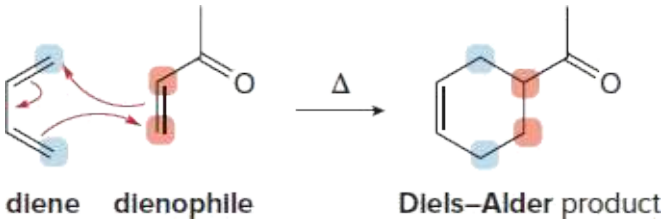


Step [1] **Arrange the 1,3-diene and the dienophile next to each other, with the diene drawn in the *s*-cis conformation.**

- **This step is key: Rotate the diene so that it is drawn in the *s*-cis conformation, and place the end C's of the diene close to the double bond of the dienophile.**



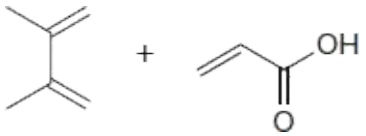
Step [2] **Cleave the three π bonds and use arrows to show where the new bonds will be formed.**



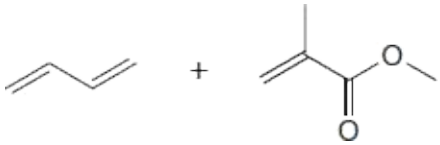
Problem 14.20

Draw the product formed when each diene and dienophile react in a Diels–Alder reaction.

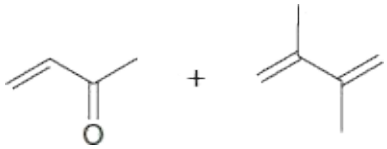
a.



b.



c.



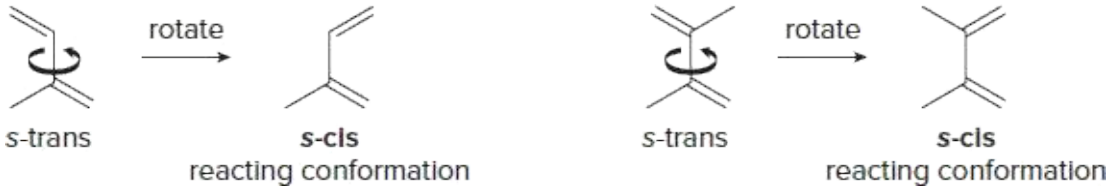
14.13 Specific Rules Governing the Diels–Alder Reaction

Several rules govern the course of the Diels–Alder reaction.

14.13A Diene Reactivity

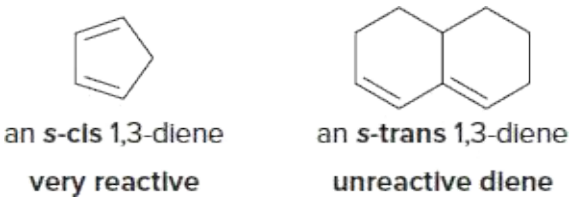
Rule [1] **The diene can react only when it adopts the *s*-cis conformation.**

Both ends of the conjugated diene must be close to the π bond of the dienophile for reaction to occur. Thus, an acyclic diene in the *s*-trans conformation must rotate about the central C–C σ bond to form the *s*-cis conformation before reaction can take place.



This rotation is prevented in cyclic dienes. As a result:

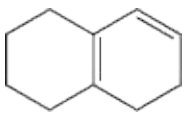
- **When the two double bonds are constrained in the *s*-cis conformation, the diene is unusually *reactive.***
- **When the two double bonds are constrained in the *s*-trans conformation, the diene is *unreactive.***



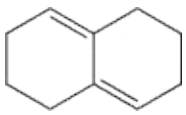
Problem 14.21

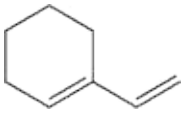
Label each diene as reactive or unreactive in a Diels–Alder reaction.

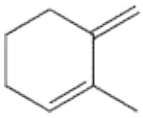
a.

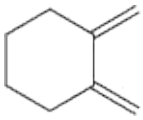


b.



c. 

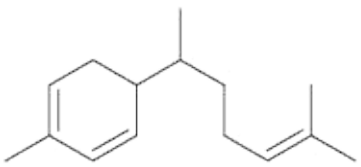
d. 

e. 

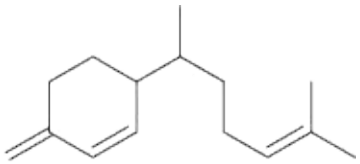
Zingiberene and β-sesquiphellandrene (Problem 14.22) are trienes obtained from ginger root. Ginger is used as a spice in Indian and Chinese cooking. Ginger candy is sometimes used to treat nausea resulting from seasickness. ©*Alvis Upitis/Getty Images*

Problem 14.22

Zingiberene and β-sesquiphellandrene, natural products obtained from ginger root, contain conjugated diene units. Which diene reacts faster in the Diels–Alder reaction and why?



zingiberene

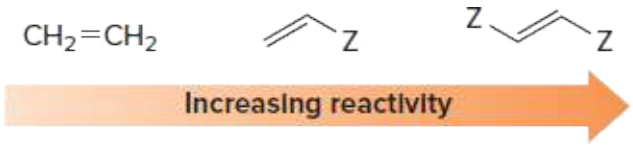


β-sesquiphellandrene

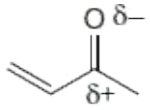
14.13B Dienophile Reactivity

Rule [2] **Electron-withdrawing substituents in the dienophile increase the reaction rate.**

In a Diels–Alder reaction, the conjugated diene acts as a nucleophile and the dienophile acts as an electrophile. As a result, electron-withdrawing groups make the dienophile more electrophilic (and, thus, more reactive) by withdrawing electron density from the carbon–carbon double bond. If Z is an electron-withdrawing group, then the reactivity of the dienophile increases as follows:



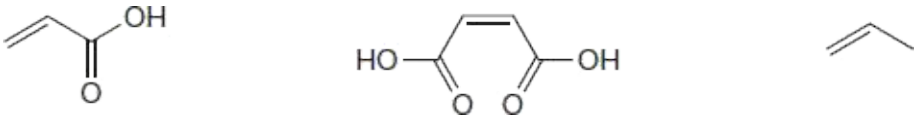
A carbonyl group is an effective electron-withdrawing group because the carbonyl carbon bears a partial positive charge (δ+), which withdraws electron density from the carbon–carbon double bond of the dienophile. Common dienophiles that contain a carbonyl group are shown in Figure 14.8.

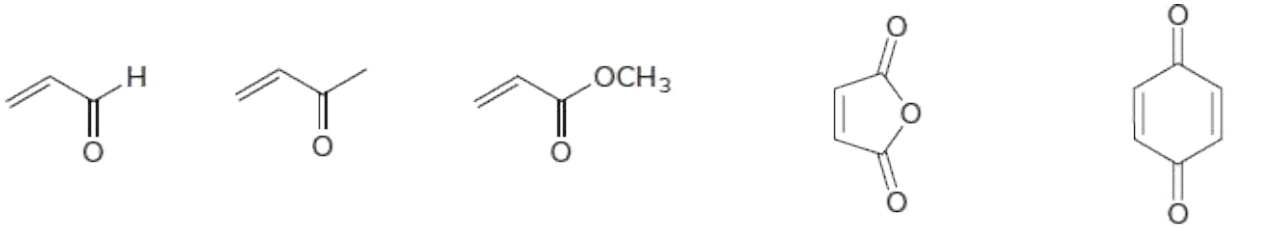


electron-deficient carbonyl carbon

Problem 14.23

Rank the following dienophiles in order of increasing reactivity.





acrolein | methyl vinyl ketone | methyl acrylate | maleic anhydride | benzoquinone

Figure 14.8 **Common dienophiles in the Diels–Alder reaction**

14.13C Stereospecificity

Rule [3] **The stereochemistry of the dienophile is retained in the product.**

- **A cis dienophile forms a cis-substituted cyclohexene.**
- **A trans dienophile forms a trans-substituted cyclohexene.**

The two cis CO_2H groups of maleic acid become two cis substituents in a Diels–Alder adduct. The CO_2H groups can be drawn both above or both below the plane to afford a single achiral meso compound. The trans dienophile fumaric acid yields two enantiomers with trans CO_2H groups.

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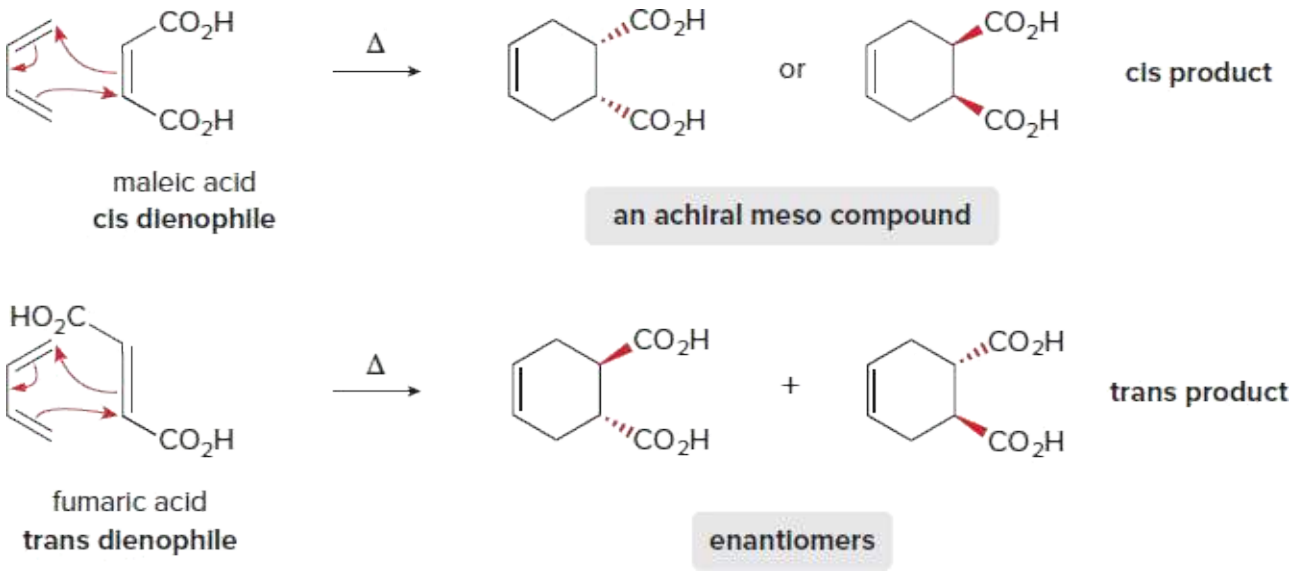
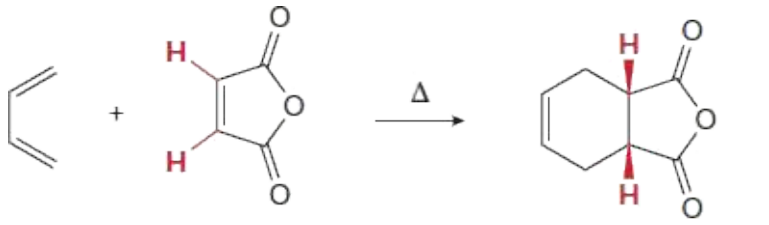


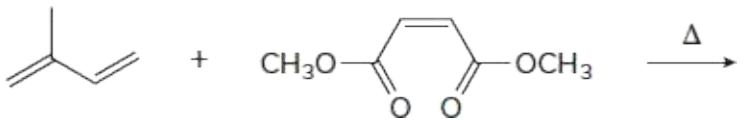
A cyclic dienophile forms a bicyclic product. A bicyclic system in which the two rings share a common C–C bond is called a fused ring system. The two H atoms at the ring fusion must be cis, because they were cis in the starting dienophile. A bicyclic system of this sort is said to be cis-fused.



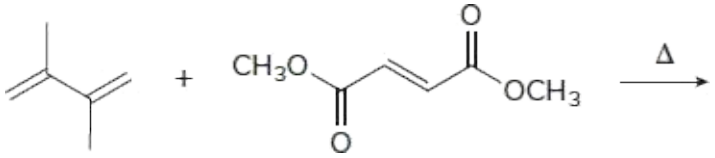
Problem 14.24

Draw the products of each Diels–Alder reaction, and indicate the stereochemistry.

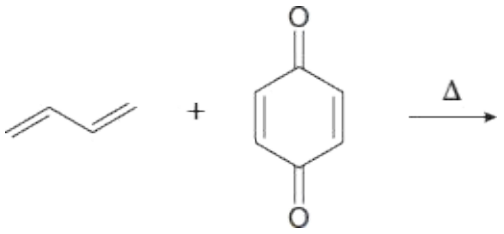
a.



b.



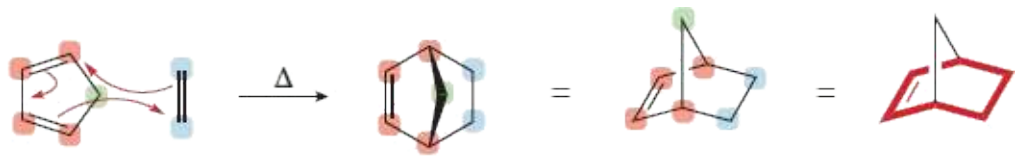
c.



14.13D The Rule of Endo Addition

Rule [4] **When endo and exo products are possible, the endo product is preferred.**

To understand the rule of endo addition, we must first examine Diels–Alder products that result from cyclic 1,3-dienes. When cyclopentadiene reacts with a dienophile such as ethylene, a new six-membered ring forms, and above the ring there is a one atom "bridge," labeled in green. This carbon atom originated as the sp^3 hybridized carbon of the diene that was not involved in the reaction.



cyclic 1,3-diene — **a bridged bicyclic ring system**

The product of the Diels–Alder reaction of a cyclic 1,3-diene is bicyclic, but Page 671 the carbon atoms shared by both rings are *non-adjacent*. Thus, this bicyclic product differs from the fused ring system obtained when the dienophile is cyclic.

- **A bicyclic ring system in which the two rings share non-adjacent carbon atoms is called a *bridged* ring system.**

Fused and bridged bicyclic ring systems are compared in Figure 14.9.

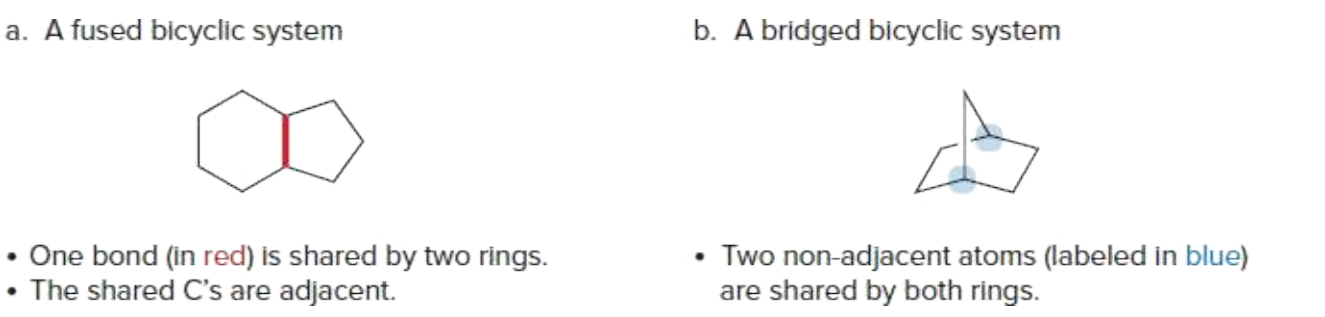
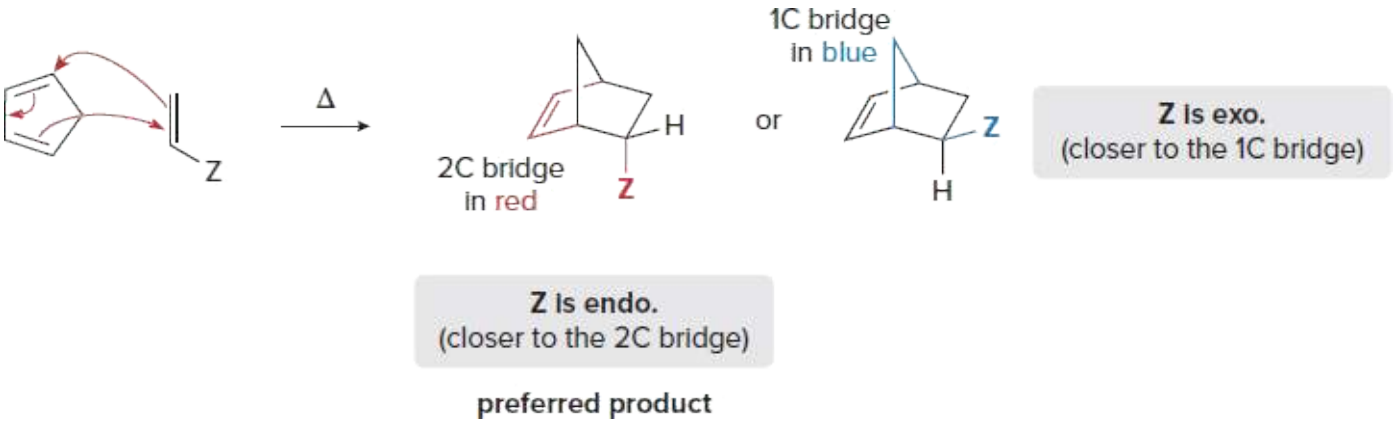


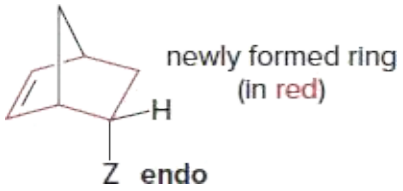
Figure 14.9 **Fused and bridged bicyclic ring systems compared**

When cyclopentadiene reacts with a substituted alkene as the dienophile (CH_2=CHZ), the substituent Z can be oriented in one of two ways in the product. The terms endo and exo are used to indicate the position of Z.

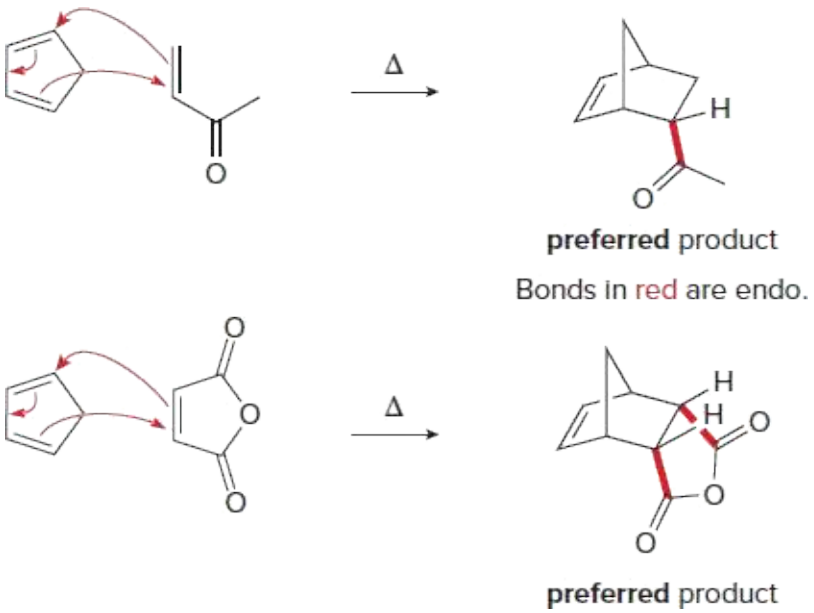


- **A substituent on one bridge is *endo* if it is closer to the *longer* bridge that joins the two carbons common to both rings.**
- **A substituent is *exo* if it is closer to the *shorter* bridge that joins the carbons together.**

To help you distinguish endo and exo, remember that *endo* is *under* the newly formed six-membered ring.



In a Diels–Alder reaction, the endo product is preferred, as shown in two examples.



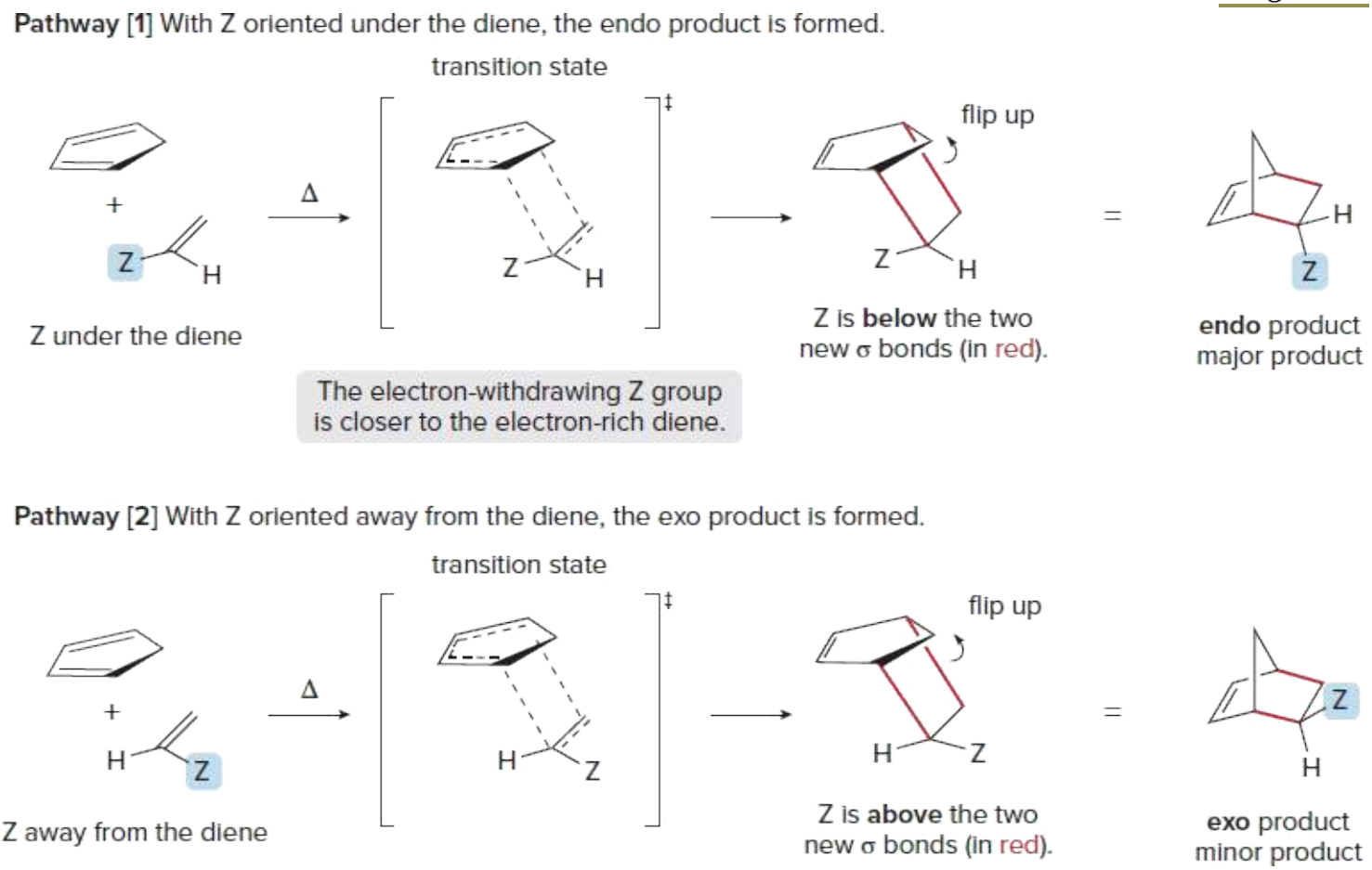


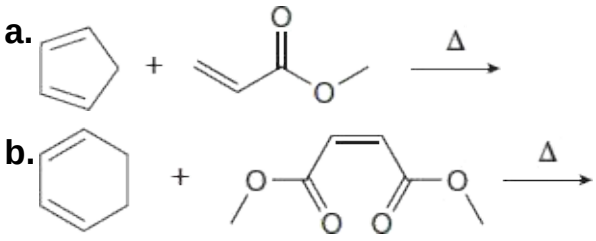
Figure 14.10 **How endo and exo products are formed in the Diels–Alder reaction**

The Diels–Alder reaction is concerted, and the reaction occurs with the diene and the dienophile arranged one above the other, as shown in Figure 14.10, not side-by-side. In theory, the substituent Z can be oriented either directly *under* the diene to form the endo product (Pathway [1] in Figure 14.10) or *away* from the diene to form the exo product (Pathway [2] in Figure 14.10). In practice, though, the endo product is the major product. The transition state leading to the endo product allows more interaction between the electron-rich diene and the electron-withdrawing substituent Z on the dienophile, an energetically favorable arrangement.

More details on the Diels–Alder reaction are given in Section 25.4.

Problem 14.25

Draw the product of each Diels–Alder reaction.



14.14 Other Facts About the Diels–Alder Reaction

14.14A Retrosynthetic Analysis of a Diels–Alder Product

The Diels–Alder reaction is used widely in organic synthesis, so you must be able to look at a compound and determine what conjugated diene and what dienophile were used to make it. To draw the starting materials from a given Diels–Alder adduct:

- **Locate the six-membered ring that contains the C=C.**
- **Draw three arrows around the cyclohexene ring, beginning with the π bond. Each arrow moves two electrons to the adjacent bond, cleaving one π bond and two σ bonds, and forming three π bonds.**
- **Retain the stereochemistry of substituents on the C=C of the dienophile. Cis substituents on the six-membered ring give a cis dienophile.**

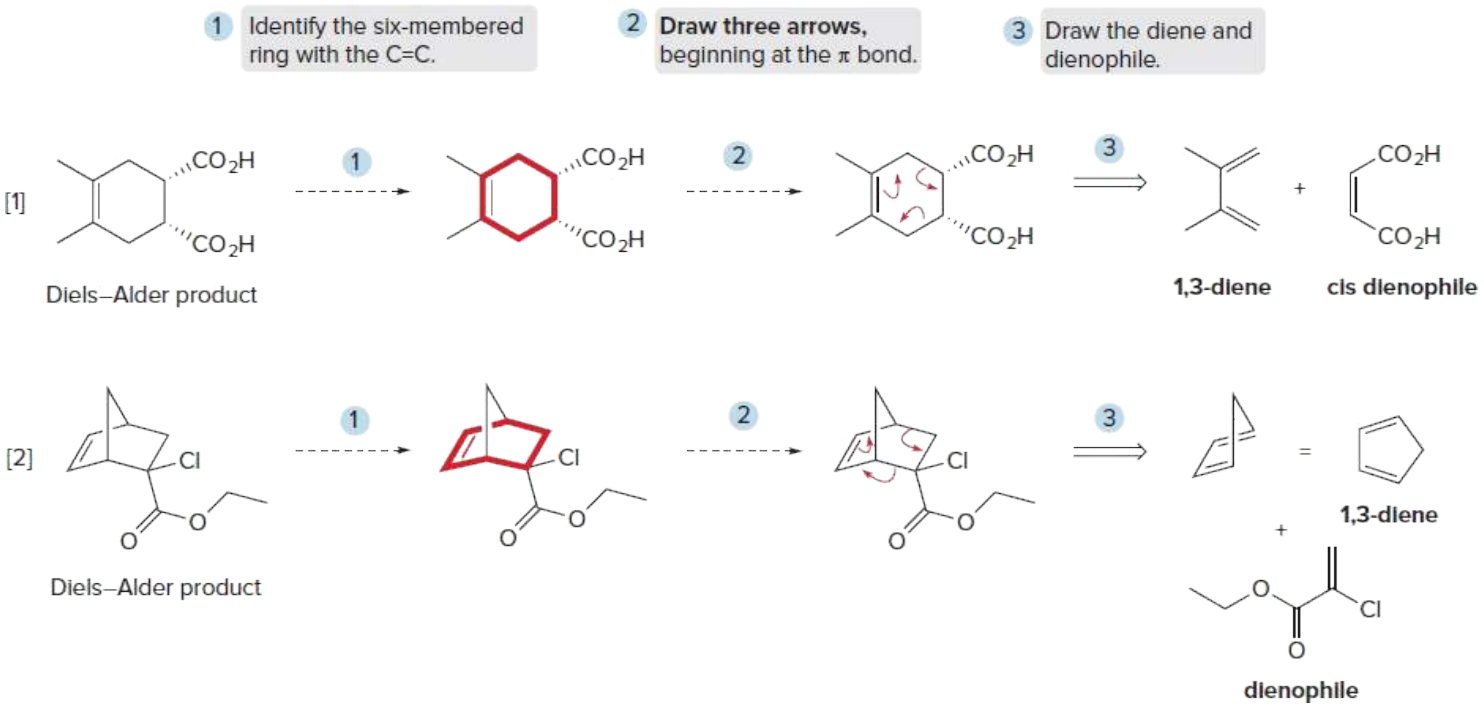


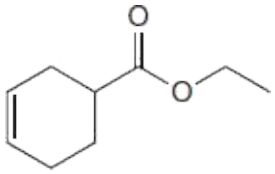
Figure 14.11 **Finding the diene and dienophile needed for a Diels–Alder reaction**

This stepwise retrosynthetic analysis gives the 1,3-diene and dienophile needed for any Diels–Alder reaction, as shown in the two examples in Figure 14.11.

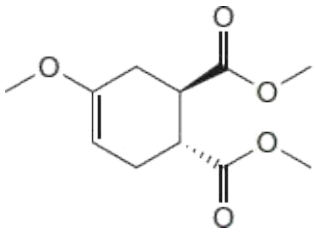
Problem 14.26

What diene and dienophile are needed to prepare each product?

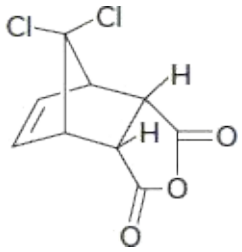
a.



b.

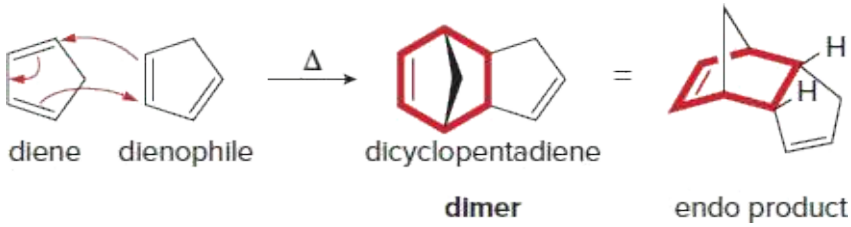


c.



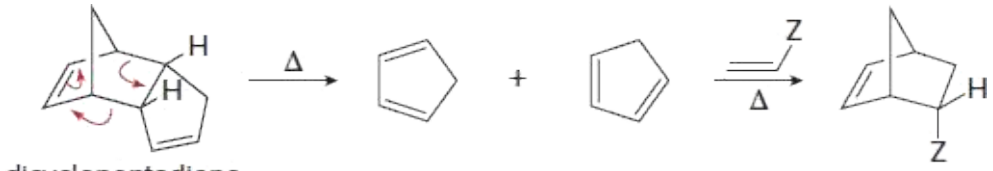
14.14B Retro Diels–Alder Reaction

A reactive diene like cyclopenta-1,3-diene readily undergoes a Diels–Alder reaction with *itself;* that is, cyclopenta-1,3-diene dimerizes because one molecule acts as the diene and another acts as the dienophile.



The formation of dicyclopentadiene is so rapid that it takes only a few hours at room temperature for cyclopentadiene to completely dimerize. How, then, can cyclopentadiene be used in a Diels–Alder reaction if it really exists as a dimer?

When heated, dicyclopentadiene undergoes a retro Diels–Alder reaction, and two molecules of cyclopentadiene are re-formed. If cyclopentadiene is immediately treated with a different dienophile, it reacts to form a new Diels–Alder adduct with this dienophile.



dicyclopentadiene

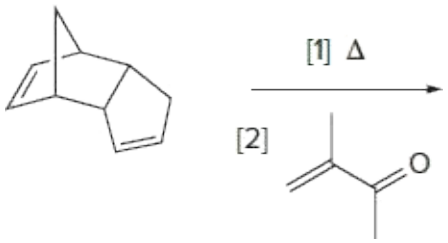
two molecules of cyclopentadiene

This diene can now be used with a different dienophile.

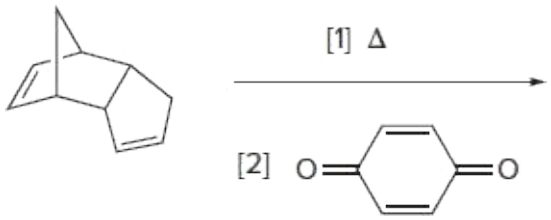
Problem 14.27

Draw the products of each reaction sequence.

a.



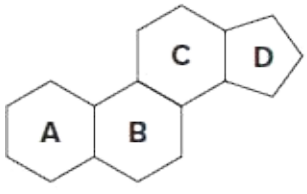
b.



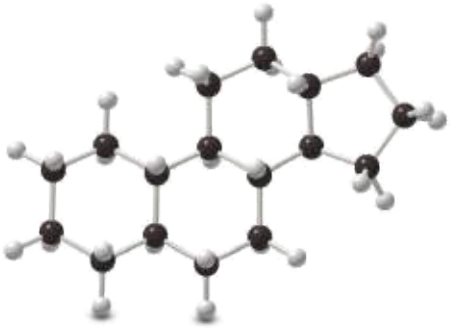
14.14C Application: Diels–Alder Reaction in the Synthesis of Steroids

Steroids are tetracyclic lipids containing three six-membered rings and one five-membered ring. The four rings are designated as A, B, C, and D.

Recall from Section 4.15 that lipids are water-insoluble biomolecules that have diverse structures.



steroid skeleton

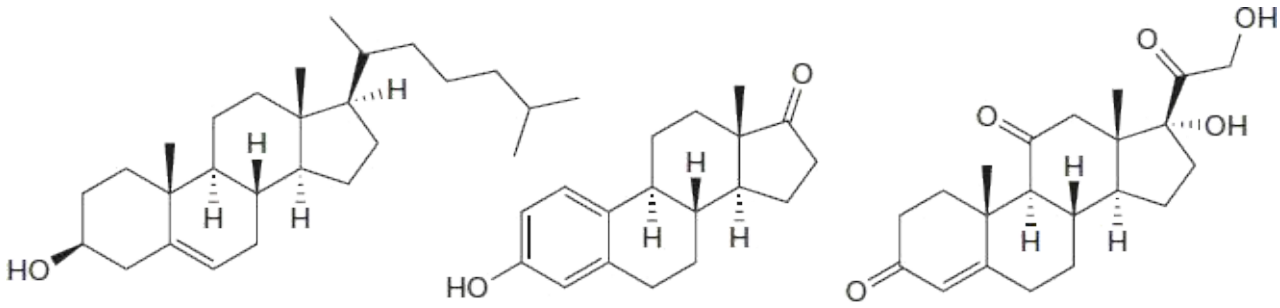


three-dimensional view from above

carbon skeleton viewed from the side

Steroids exhibit a wide range of biological properties, depending on the substitution pattern of functional groups on the rings. They include cholesterol (a component of cell membranes that is implicated in cardiovascular disease), estrone (a female sex

hormone responsible for the regulation of the menstrual cycle), and cortisone (a hormone responsible for the control of inflammation and the regulation of carbohydrate metabolism).



Diels–Alder reactions have been used widely in the laboratory syntheses of steroids. The key Diels–Alder reactions used to prepare the C ring of estrone and the B ring of cortisone are drawn.

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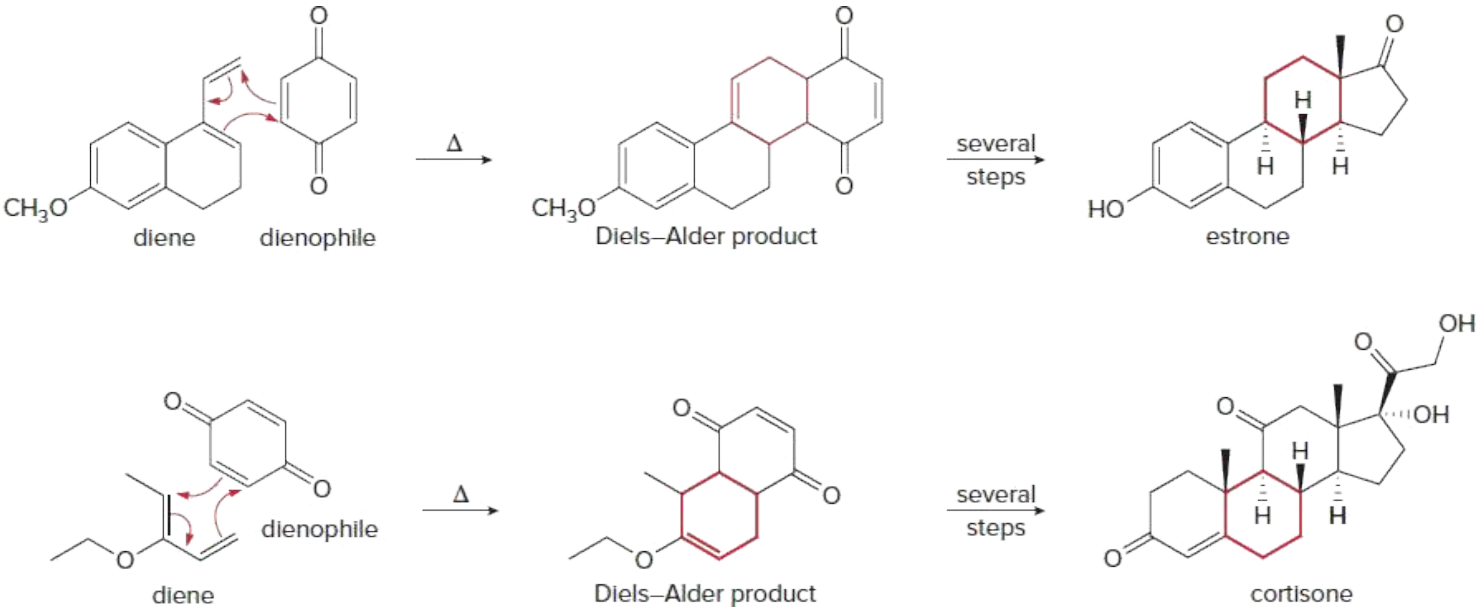
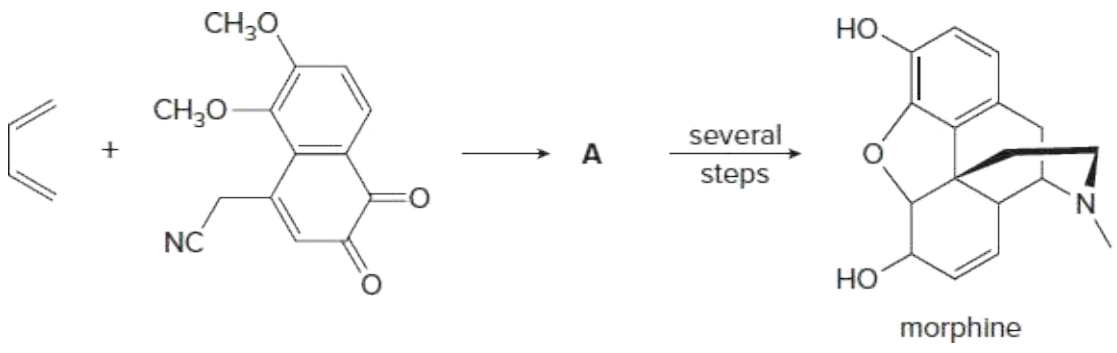


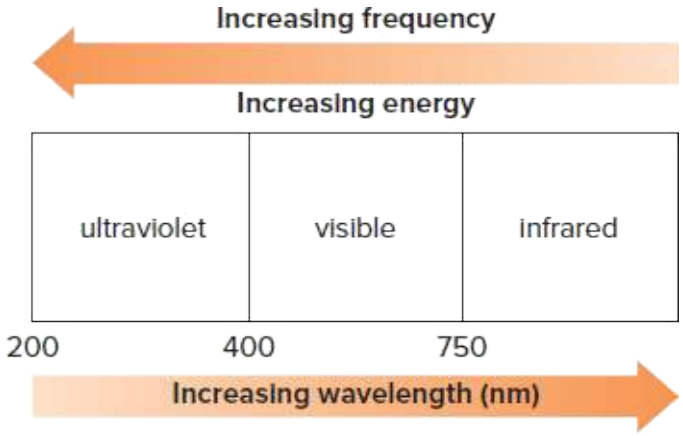
Problem 14.28

Draw the product (A) of the following Diels–Alder reaction. A was a key intermediate in the synthesis of the addicting pain reliever morphine, the chapter-opening molecule.



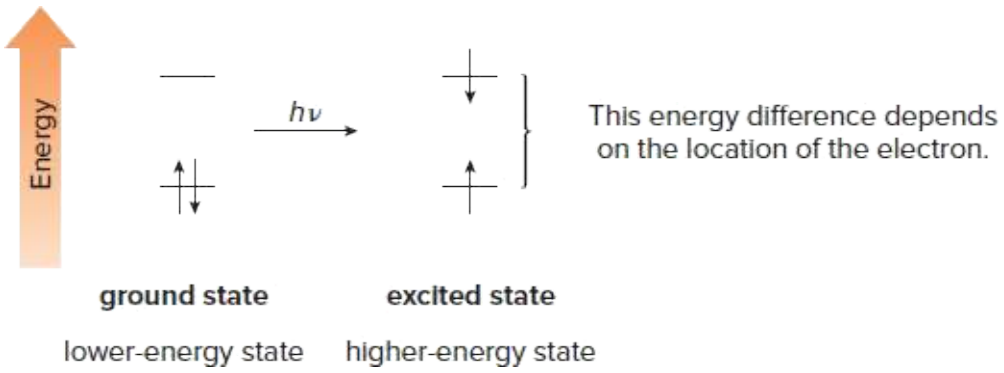
14.15 Conjugated Dienes and Ultraviolet Light

Recall from Spectroscopy Part B that the absorption of infrared light can promote a molecule from a lower vibrational state to a higher one. In a similar fashion, the absorption of ultraviolet (UV) light can promote an electron from a lower electronic state to a higher one. Ultraviolet light has a slightly shorter wavelength (and, thus, higher frequency) than visible light. The most useful region of UV light for this purpose is 200–400 nm.



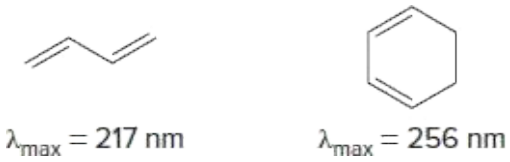
14.15A General Principles

When electrons in a lower-energy state (the ground state) absorb light having the appropriate energy, an electron is promoted to a higher electronic state (the excited state).



The energy difference between the two states depends on the location of the electron. The promotion of electrons in σ bonds and unconjugated π bonds requires light having a wavelength of < 200 nm; that is, it has a shorter wavelength and higher energy than light in the UV region of the electromagnetic spectrum. With conjugated dienes, however, the energy difference between the ground and excited states decreases, so longer wavelengths of light can be used to promote electrons. The wavelength of UV light absorbed by a compound is often referred to as its λ_{max}. Buta-1,3-diene, for

example, absorbs UV light at λ_{max} = 217 nm and cyclohexa-1,3-diene has a λ_{max} of 256 nm.



- **Conjugated dienes and polyenes absorb light in the UV region of the electromagnetic spectrum (200–400 nm).**

A UV spectrum is a plot of the absorbance of UV light versus wavelength. A spectrum consists of very broad bands, and the maximum absorbance corresponds to the λ_{max}, as shown in the UV spectrum of isoprene in Figure 14.12.

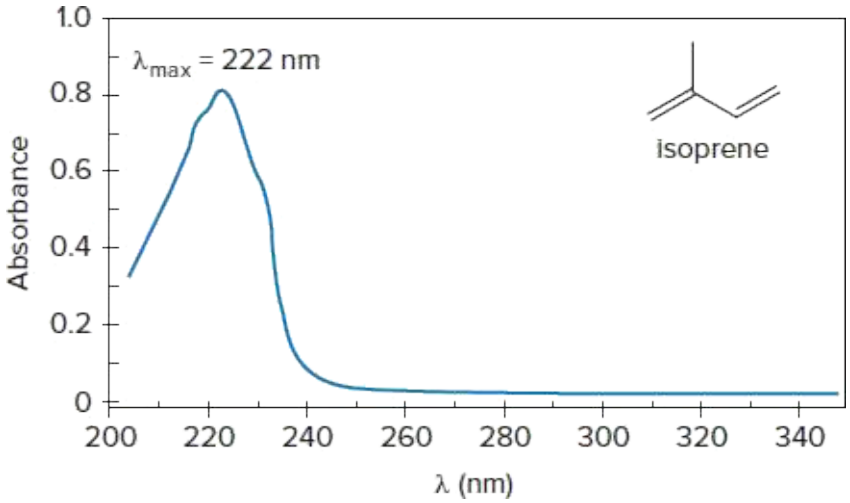
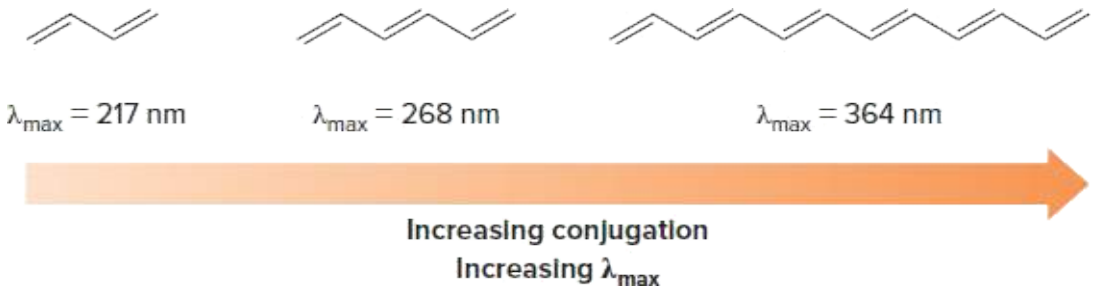


Figure 14.12 **UV spectrum of isoprene**

As the number of conjugated π bonds *increases*, the energy difference between the ground and excited state *decreases*, shifting the absorption to *longer* wavelengths.



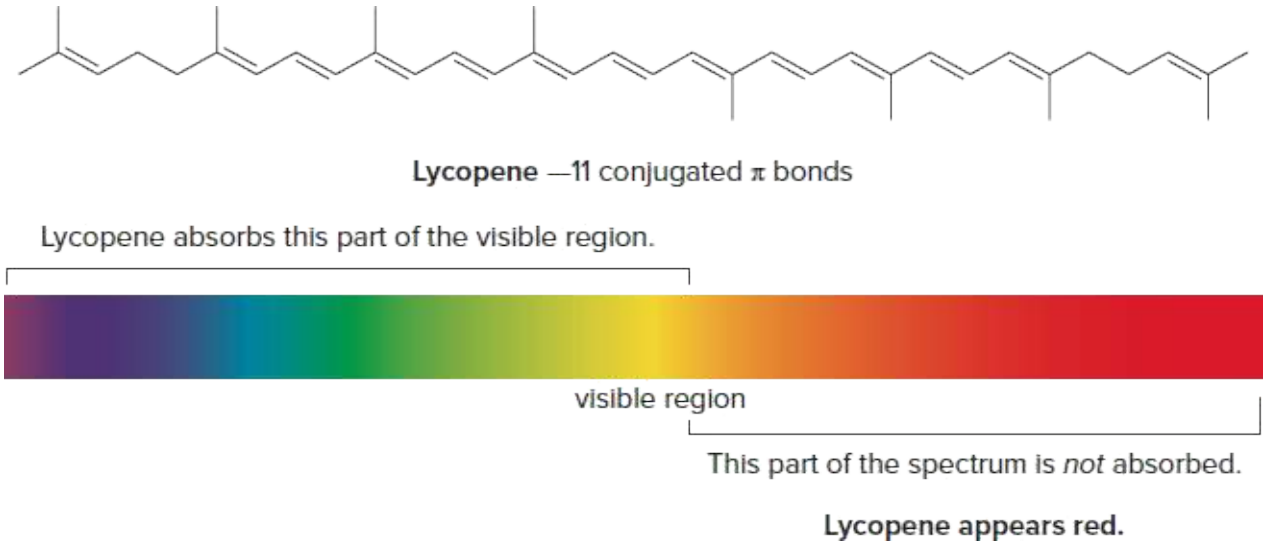


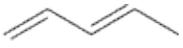
Figure 14.13 **Why lycopene appears red**

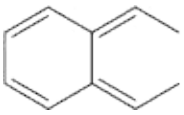
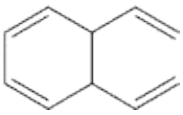
With molecules having eight or more conjugated π bonds, the absorption shifts from the UV to the visible region and the compound takes on the color of those wavelengths of visible light it does *not* absorb. For example, lycopene absorbs visible light at λ_{max} = 470 nm, in the blue-green region of the visible spectrum. Because it does not absorb light in the red region, lycopene appears bright red (Figure 14.13).

Lycopene is the red pigment found in tomatoes, watermelon, papaya, guava, and pink grapefruit. Lycopene is not destroyed when fruits and vegetables are processed, so tomato juice and ketchup are high in lycopene. ©C *Squared Studios/Getty Images*

Problem 14.29

Which compound in each pair absorbs UV light at longer wavelength?

a.  or

b.  or 

14.15B Sunscreens

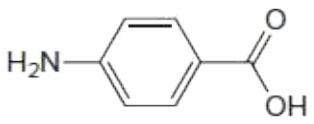
Ultraviolet radiation from the sun is high enough in energy to cleave bonds, forming radicals that can prematurely age skin and cause skin cancers. The ultraviolet region is often subdivided, based on the wavelength of UV light: UV-A (320–400 nm), UV-B (290–320 nm), and UV-C (< 290 nm). Fortunately, much of the highest-energy UV light (UV-C) is filtered out by the ozone layer, so that only UV light having wavelengths > 290 nm reaches the skin's surface. Much of this UV light is absorbed by melanin, the highly conjugated colored pigment in the skin that serves as the body's natural protection against the harmful effects of UV radiation.

Commercial sunscreens are given an SPF rating (sun protection factor), according to the amount of sunscreen present. The higher the number, the greater the protection.

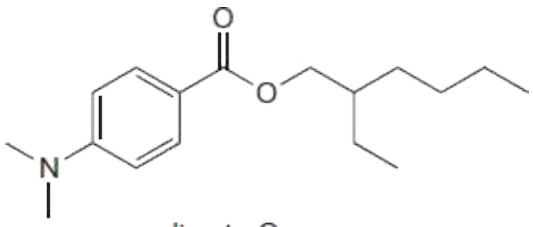
©McGraw-Hill Education/Jill Braaten, photographer

Prolonged exposure to the sun can allow more UV radiation to reach your skin than melanin can absorb. A commercial sunscreen can offer added protection, however,

because it contains conjugated compounds that absorb UV light, thus shielding your skin (for a time) from the harmful effects of UV radiation. Two sunscreens that have been used for this purpose are *para*-aminobenzoic acid (PABA) and padimate O.



para-aminobenzoic acid (PABA)



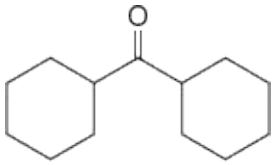
padimate O

Many sunscreens contain more than one component to filter out different regions of the UV spectrum. Conjugated compounds generally shield the skin from UV-B radiation, but often have little effect on longer-wavelength UV-A radiation, which does not burn the skin, but can still cause long-term damage to skin cells.

Problem 14.30

Which of the following compounds might be an ingredient in a commercial sunscreen? Explain why or why not.

a.



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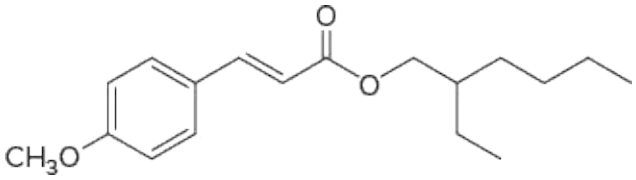
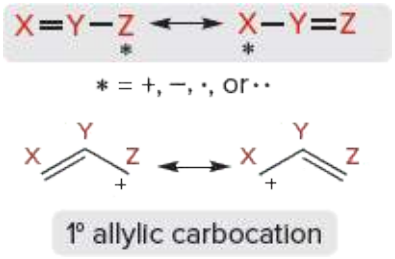
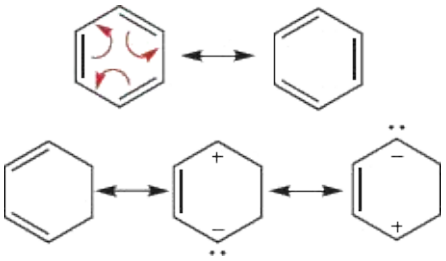
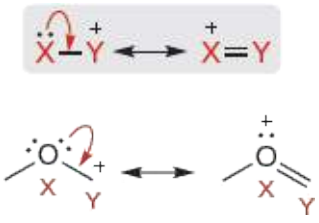


Chapter 14 REVIEW

KEY CONCEPTS

[1] Four common examples of resonance (14.3)

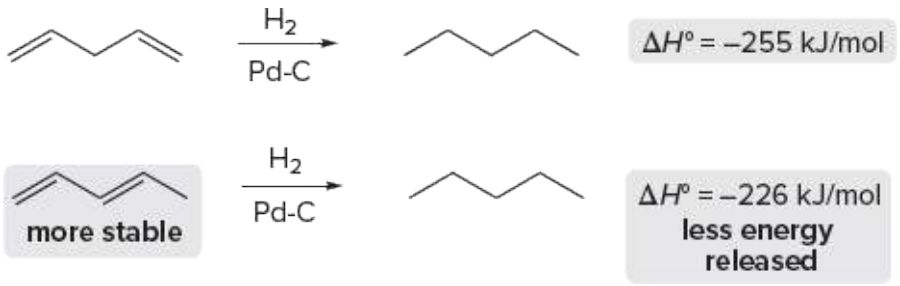
1 The three-atom "allyl" system	**2** Conjugated double bonds	**3** Cations having a positive	**4**

		charge adjacent to a lone pair
		

See Sample Problem 14.1. Try Problems 14.34, 14.36.

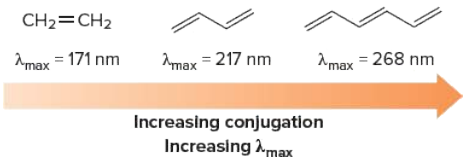
[2] The unusual properties of conjugated dienes

1 **Conjugated dienes are more stable than the corresponding isolated dienes. (14.9)**



- **$\Delta H°$ of hydrogenation is *smaller* for a conjugated diene than for an isolated diene converted to the same product.**

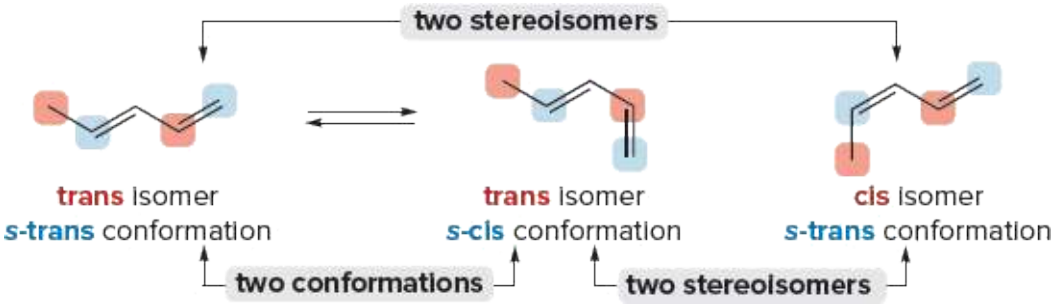
2 **Conjugated dienes absorb UV light in the 200–400 nm region. (14.15)**



- **As the number of conjugated π bonds increases, the absorption shifts to longer wavelength.**

See Figure 14.4. Try Problems 14.42; 14.59a, d; 14.67.

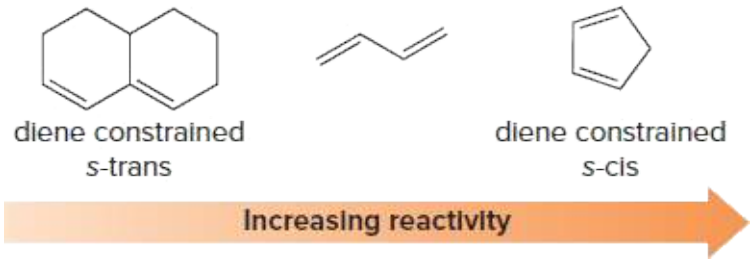
[3] The difference between two conformations and two stereoisomers in 1,3-dienes (14.6)



See Sample Problem 14.4. Try Problem 14.41.

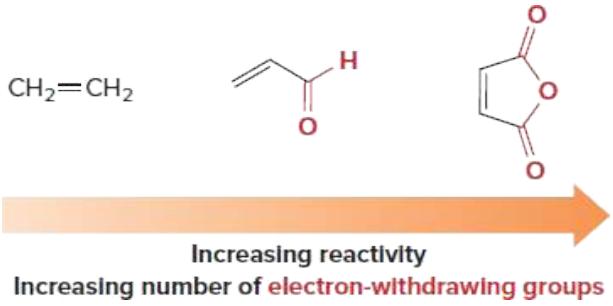
[4] Relative reactivity in the Diels–Alder reaction

1 Diene reactivity (14.13A)



- **When the two double bonds are constrained in the *s*-cis conformation, the diene is unusally reactive.**
- **When the two double bonds are constrained in the *s*-trans conformation, the diene is unreactive.**

2 Dienophile reactivity (14.13B)



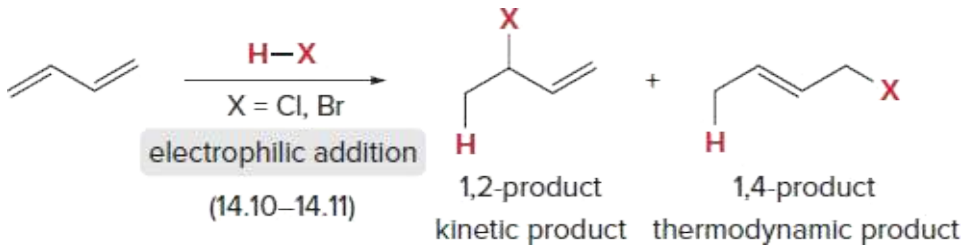
- **Electron-withdrawing substituents in the dienophile increase the reaction rate.**

Try Problems 14.50; 14.59b, c.

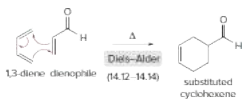
KEY REACTIONS

Reactions of conjugated dienes

1



2



Try Problems 14.43b, c; 14.51; 14.61.

KEY SKILLS

[1] Drawing resonance structures for a conjugated compound (14.3, 14.4)

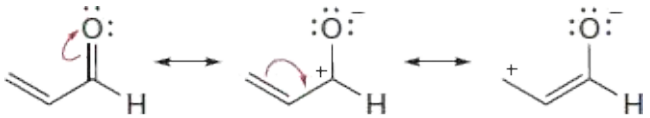
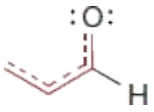
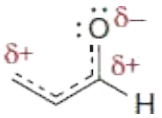
1 Identify a three-atom unit, and

2 Identify a different three-atom

move a lone pair and π bond or move two π bonds.	unit, and move a lone pair and π bond or move two π bonds.
	 Better resonance structures contain • more bonds and fewer charges, • all atoms with octets, and • negative charges on more electronegative atoms.

See Sample Problem 14.1. Try Problems 14.34, 14.36.

[2] Drawing a resonance hybrid from three resonance structures (14.4); example: acrolein

1 Draw the three resonance structures.	2 Draw the bonds and partial bonds in the resonance hybrid.	3 Draw the partial charges.
 acrolein	 • Use a dashed line between atoms that have a π bond in one resonance	 • Use a δ symbol for atoms with a charge or radical

	structure and not another.	in one structure but not another.

See Sample Problem 14.2. Try Problem 14.35.

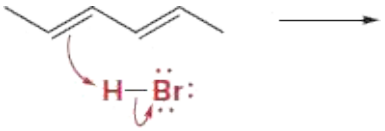
[3] Using two resonance structures to determine the hybridization around a given carbon atom (14.5)

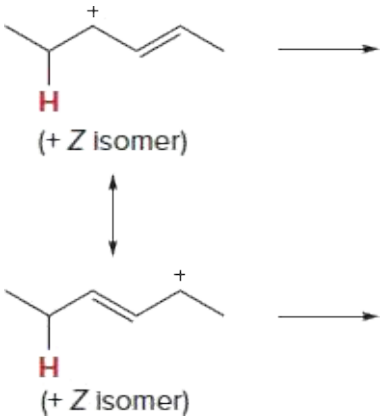
1 Draw the two resonance structures.	2 Determine the hybridization based on orbitals used in both resonance structures.
	• The labeled C atom must be sp^2 hybridized with the lone pair occupying a *p* orbital. • In a system X=Y–Z:, Z is generally sp^2 hybridized to allow the lone pair to occupy a *p* orbital, making the system conjugated.

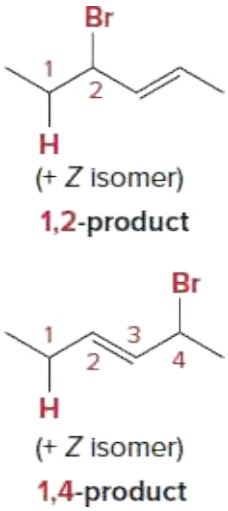
See Sample Problem 14.3.

[4] Drawing the products from HX addition to a diene (14.10)

1 Add H^+ to form an allylic carbocation.	2 Draw both resonance structures for the carbocation.	3 Draw the products resulting from nucleophilic attack at the positive charge of both resonance structures.



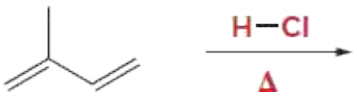
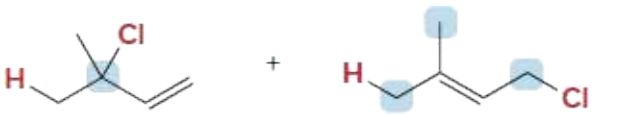




- **A 2° allylic carbocation is more stable than a 2° carbocation because of *p* orbital overlap (14.2).**

See Sample Problem 14.5. Try Problems 14.43b, c; 14.61a, d.

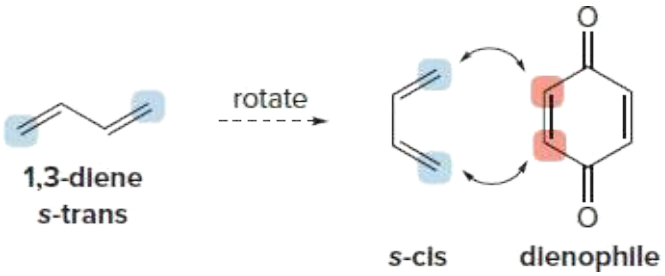
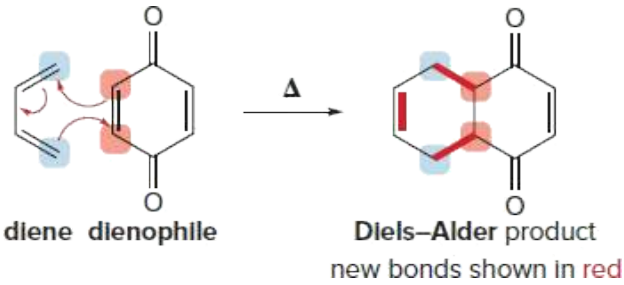
[5] Determining whether the major product is the kinetic or thermodynamic product (14.11)

1 Identify the reaction conditions, including the temperature.	2 Draw both products, and identify the kinetic product and the thermodynamic product.	3 I
 • **High temperature is used in this reaction.** • **At higher temperature, the major product is the thermodynamic**	 1,2-product monosubstituted alkene kinetic product 1,4-product trisubstituted alkene thermodynamic product • **The 1,2-product is the kinetic product by the proximity effect.** • **In this example, the 1,4-product is the thermodynamic product because it has the more substituted**	•

product.	double bond.	

Try Problems 14.47, 14.48.

[6] Drawing the product of a Diels–Alder reaction (14.12)

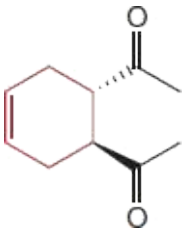
1 Rotate the diene to the *s*-cis conformation.	2 Cleave the three π bonds, and use arrows to show where the new bonds will be formed.
	

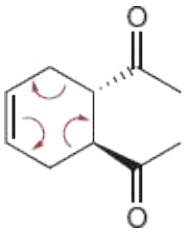
- The mechanism is concerted. All bonds are broken and formed in a single step.

See *How To*, p. 667. Try Problem 14.51.

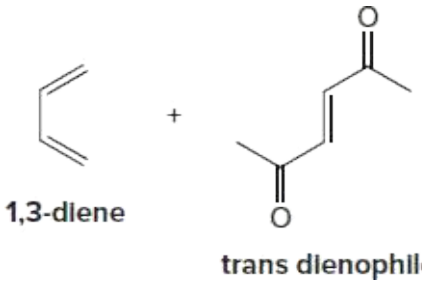
[7] Finding the diene and dienophile needed for a Diels–Alder reaction (14.14)

1 Identify the six-membered ring with the C=C.	2 Draw three arrows, beginning at the π bond.	3 Draw the diene and the dienophile.





- The two substituents on the six-membered ring are trans.



See Figure 14.11. Try Problems 14.32, 14.52, 14.53.

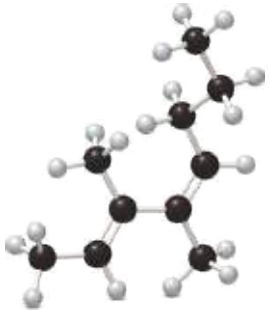
PROBLEMS

Problems Using Three-Dimensional Models

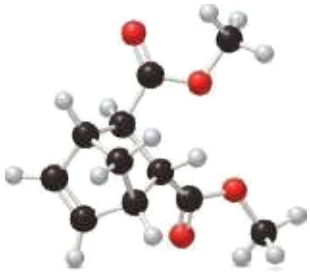
14.31 Name each diene and state whether the ball-and-stick model shows the diene in the *s*-cis or *s*-trans conformation.

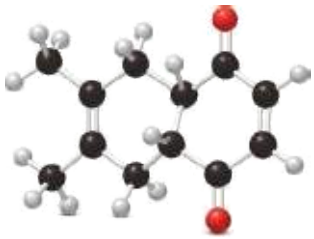
a.

b.



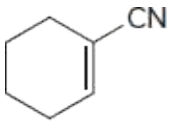
14.32 What diene and dienophile are needed to prepare each compound by a Diels–Alder reaction?

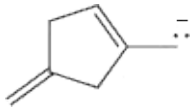
a. 

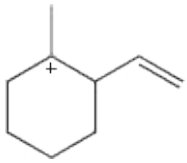
b. 

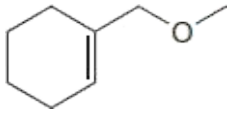
Conjugation

14.33 Which of the following systems are conjugated?

a. 

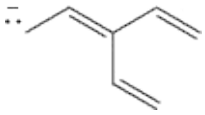
b. 

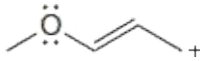
c. 

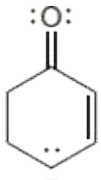
d. 

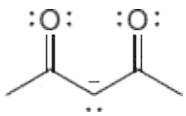
Resonance and Hybridization

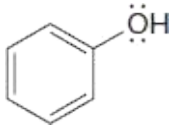
14.34 Draw all reasonable resonance structures for each species.

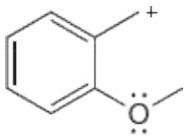
a. 

b. 

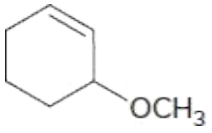
c. 

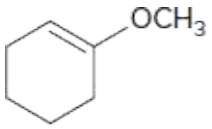
d. 

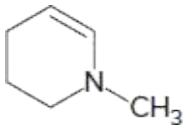
e. 

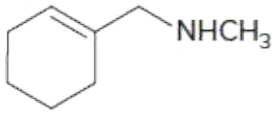
f. 

14.35 For which compounds can a second resonance structure be drawn? Draw an additional resonance structure and the hybrid for each resonance-stabilized compound.

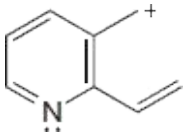
a. 

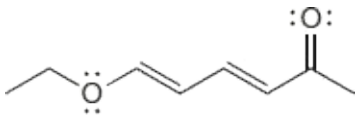
b. 

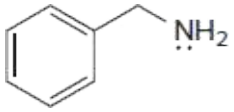
c. 

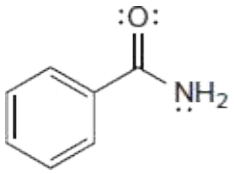
d. 

14.36 Draw all reasonable resonance structures for each compound.

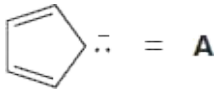
a. 

b. 

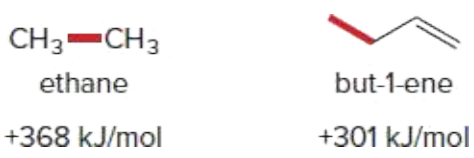
c. 

d. 

14.37 Explain why the cyclopentadienide anion A gives only one signal in its ^{13}C NMR spectrum.



14.38 Why is the bond dissociation energy for the C–C bond in ethane much higher than the bond dissociation energy for the labeled C–C bond in but-1-ene?



14.39 Draw the structure of each compound.

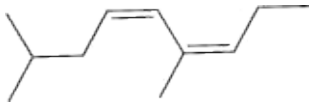
a. (*Z*)-penta-1,3-diene in the *s*-trans conformation

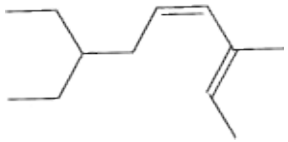
b. (2*E*,4*Z*)-1-bromo-3-methylhexa-2,4-diene

c. (2*E*,4*E*,6*E*)-octa-2,4,6-triene

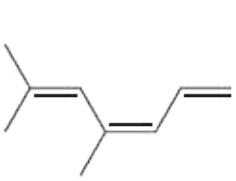
d. (2*E*,4*E*)-3-methylhexa-2,4-diene in the *s*-cis conformation

14.40 Name each compound and indicate the conformation around the σ bond that joins the two double bonds.

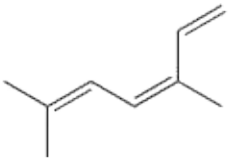
a. 

b. 

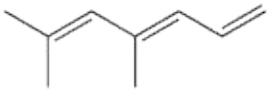
14.41 Label each pair of compounds as stereoisomers, conformations, or constitutional isomers: (a) A and B; (b) A and C; (c) A and D; (d) C and D.



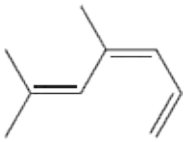
A



B

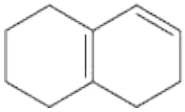


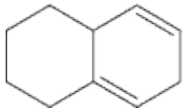
C

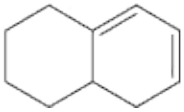


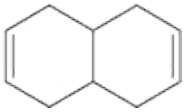
D

14.42 Rank the following dienes in order of increasing heat of hydrogenation.



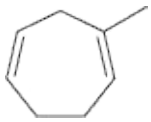


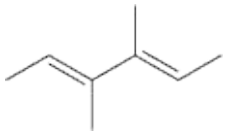


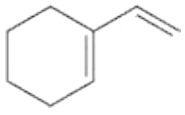


Electrophilic Addition

14.43 Draw the products formed when each compound is treated with one equivalent of HBr.

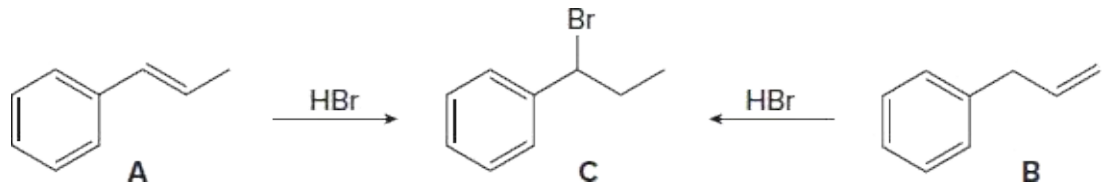
a. 

b. 

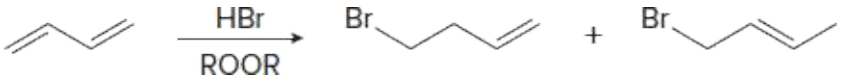
c. 

14.44 Ignoring stereoisomers, draw all products that form by addition of HBr to (*E*)-hexa-1,3,5-triene.

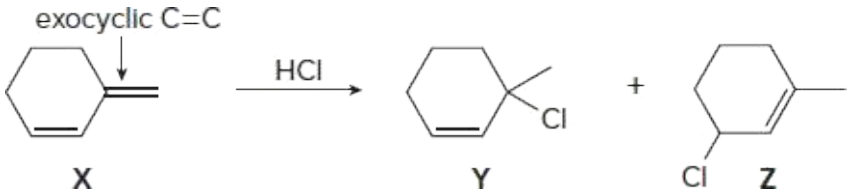
14.45 Treatment of alkenes A and B with HBr gives the same alkyl halide C. Draw a mechanism for each reaction, including all reasonable resonance structures for any intermediate.



14.46 Draw a stepwise mechanism for the following reaction.



14.47 Addition of HCl to alkene X forms two alkyl halides Y and Z.



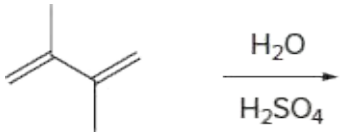
a. Label Y and Z as a 1,2-addition product or a 1,4-addition product.

b. Label Y and Z as the kinetic or thermodynamic product and explain why.

c. Explain why addition of HCl occurs at the indicated C=C (called an exocyclic double bond), rather than the other C=C (called an endocyclic double bond).

14.48 The major product formed by addition of HBr to $(CH_3)_2C{=}CH{-}CH{=}C(CH_3)_2$ is the same at low and high temperature. Draw the structure of the major product, and explain why the kinetic and thermodynamic products are the same in this reaction.

14.49 From what you have learned about the reaction of conjugated dienes in Section 14.10, predict the products of each of the following electrophilic additions.

a. 

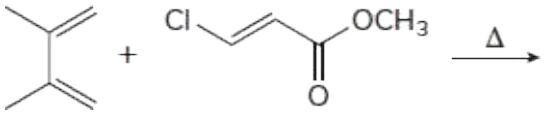
b.

Diels–Alder Reaction

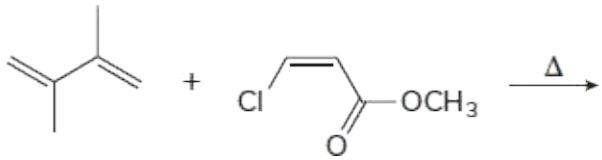
14.50 **Explain why methyl vinyl ether (CH_2=$CHOCH_3$) is not a reactive dienophile in the Diels–Alder reaction.**

14.51 **Draw the products of the following Diels–Alder reactions. Indicate stereochemistry where appropriate.**

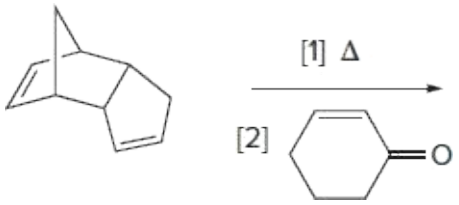
a.



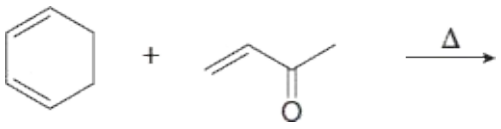
b.



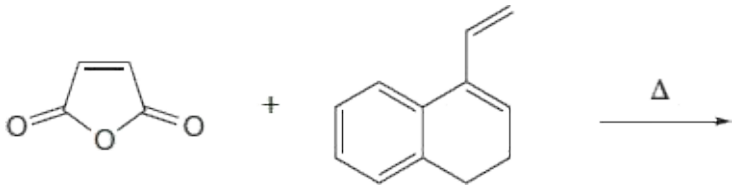
c.



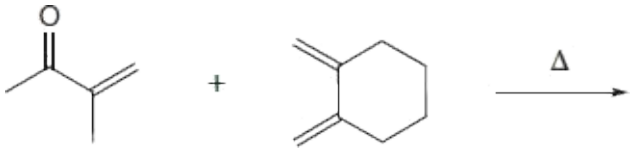
d.



e.

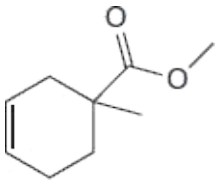


f.

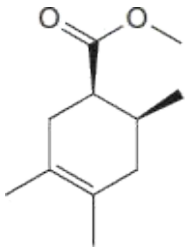


14.52 **What diene and dienophile are needed to prepare each Diels–Alder product?**

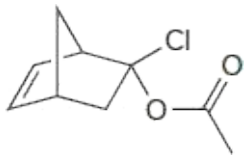
a.



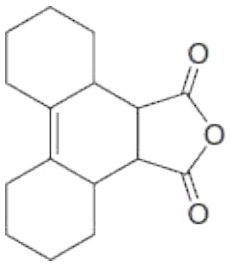
b.



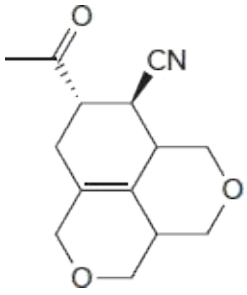
c.



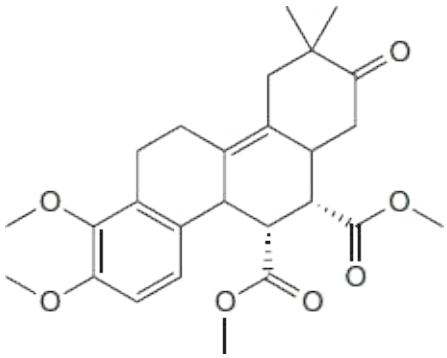
d.



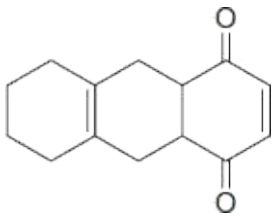
e.



f.

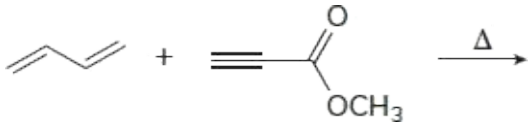


14.53 Give two different ways to prepare the following compound by the Diels–Alder reaction. Explain which method is preferred.

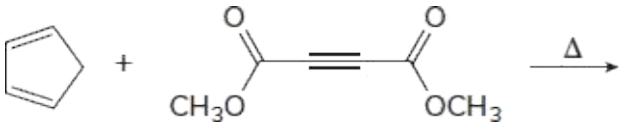


14.54 Compounds containing triple bonds are also Diels–Alder dienophiles. With this in mind, draw the products of each reaction.

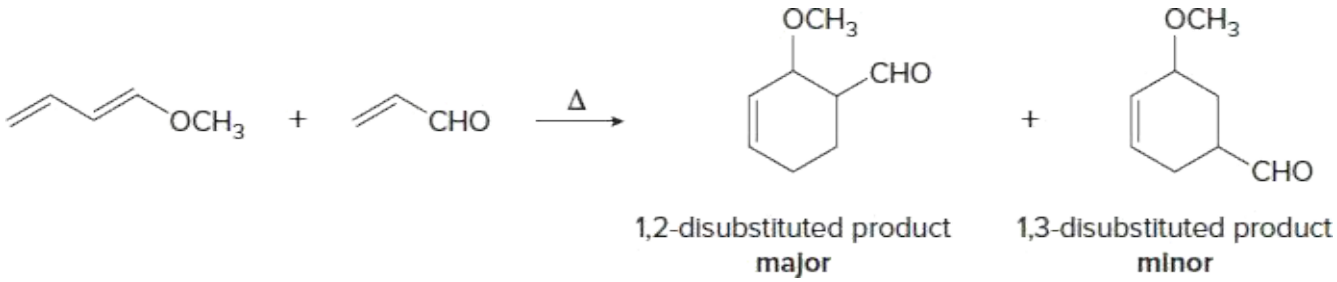
a.



b.



14.55 Diels–Alder reaction of a monosubstituted diene (such as CH_2=CH–CH=$CHOCH_3$) with a monosubstituted dienophile (such as CH_2=CHCHO) gives a mixture of products, but the 1,2-disubstituted product often predominates. Draw the resonance hybrid for each reactant, and use the charge distribution of the hybrids to explain why the 1,2-disubstituted product is the major product.

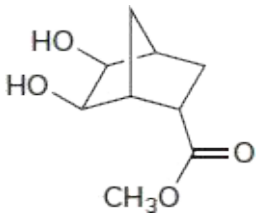


1,2-disubstituted product
major

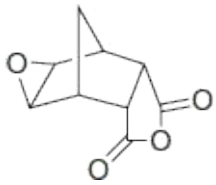
1,3-disubstituted product
minor

14.56 Devise a stepwise synthesis of each compound from dicyclopentadiene using a Diels–Alder reaction as one step. You may also use organic compounds having ≤ 4 C's, and any required organic or inorganic reagents.

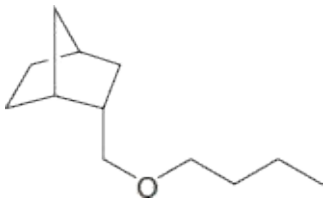
a.



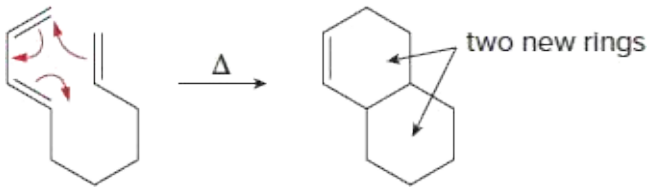
b.



c.

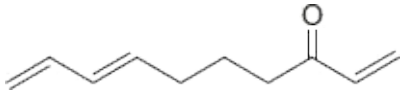


14.57 Intramolecular Diels–Alder reactions are possible when a substrate contains both a 1,3-diene and a dienophile, as shown in the following general reaction.

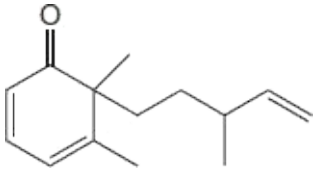


With this in mind, draw the product when each compound undergoes an intramolecular Diels–Alder reaction.

a.

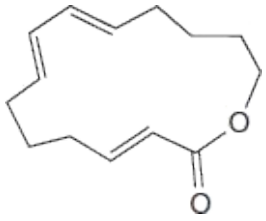


b.



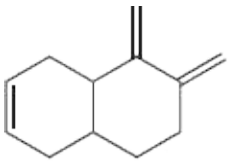
14.58 A transannular Diels–Alder reaction is an intramolecular reaction that occurs when the diene and dienophile are contained in one ring, resulting in the formation of a tricyclic ring system. Draw the product

formed when the following triene undergoes a transannular Diels–Alder reaction.

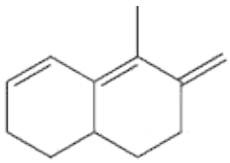


General Problems

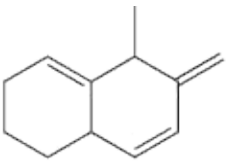
14.59 Consider the four trienes E–H.



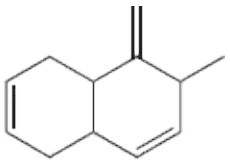
E



F



G



H

a. Rank compounds E–H in order of increasing heat of hydrogenation.

b. Which compound is most reactive in the Diels–Alder reaction?

c. Which compound(s) are unreactive in the Diels–Alder reaction?

d. Which compound absorbs the longest wavelength of ultraviolet light?

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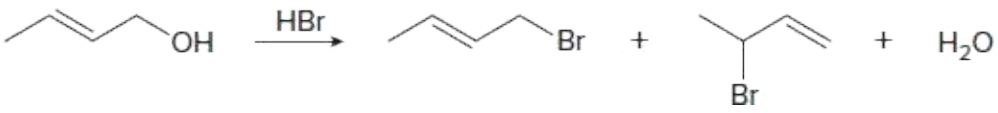
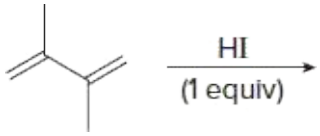
14.60 Draw a stepwise mechanism for the following reaction.

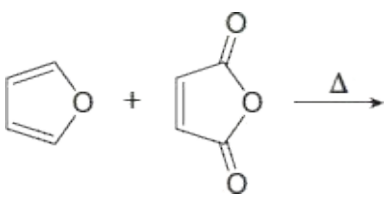


14.61 Draw the products of each reaction. Indicate the stereochemistry of Diels–Alder products.

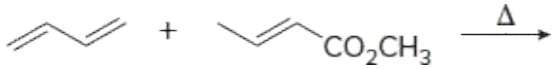
a.



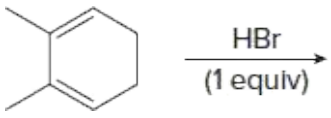
b.



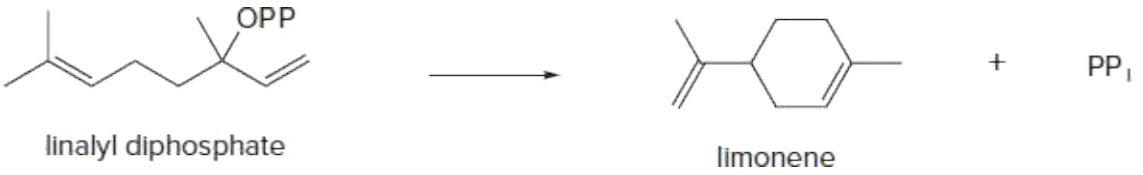
c.



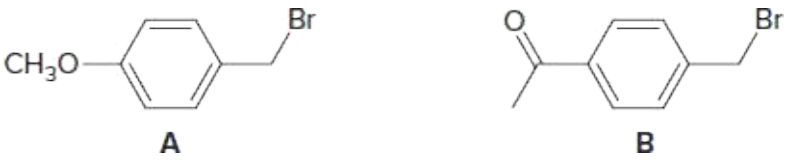
d.



14.62 **Draw a stepwise mechanism for the biological conversion of linalyl diphosphate to limonene.**



14.63 **Which benzylic halide reacts faster in an S_N1 reaction? Explain.**

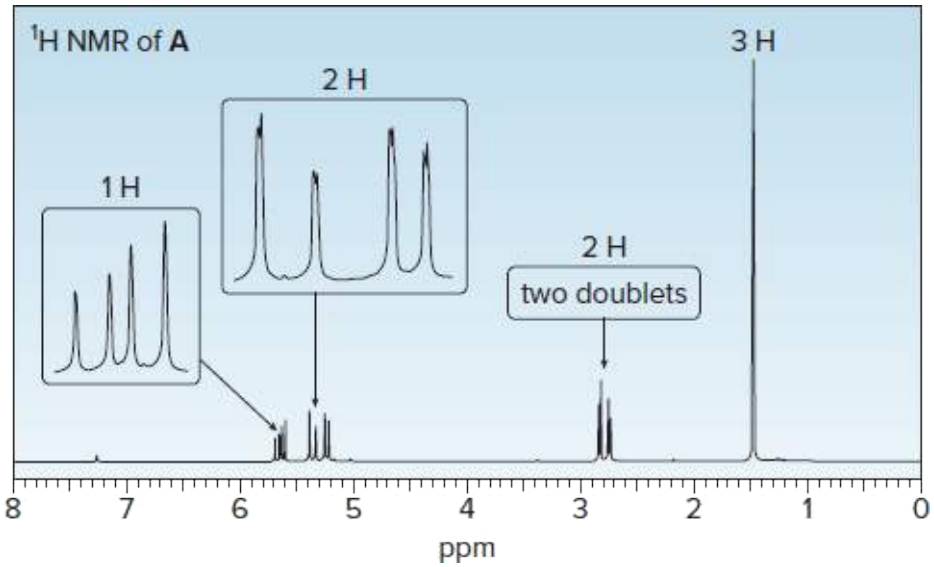


14.64 **Like alkenes, conjugated dienes can be prepared by elimination reactions. Draw a stepwise mechanism for the acid-catalyzed dehydration of 3-methylbut-2-en-1-ol [$(CH_3)_2C{=}CHCH_2OH$] to isoprene [$CH_2{=}C(CH_3)CH{=}CH_2$].**

14.65 **(a) Draw the two isomeric dienes formed when $CH_2{=}CHCH_2CH(Cl)CH(CH_3)_2$ is treated with an alkoxide base. (b) Explain why the major product formed in this reaction does not contain the more highly substituted alkene.**

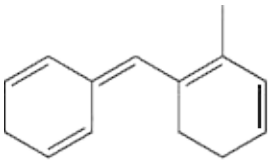
Spectroscopy

14.66 **The treatment of isoprene [$CH_2{=}C(CH_3)CH{=}CH_2$] with one equivalent of mCPBA forms A as the major product. A gives a molecular ion at 84 in its mass spectrum, and peaks at 2850–3150 cm^{-1} in its IR spectrum. The ^1H NMR spectrum of A is given below. What is the structure of A?**

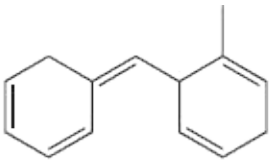


UV Absorption

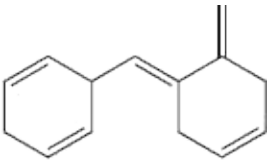
14.67 **Rank the following compounds in order of increasing wavelength of ultraviolet light absorbed.**



A

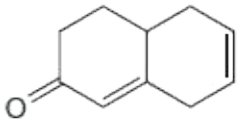


B

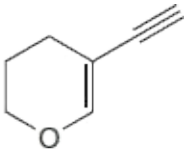


C

14.68 **Explain why both C and D absorb light in the UV region of the electromagnetic spectrum, despite the fact that they are not 1,3-dienes.**

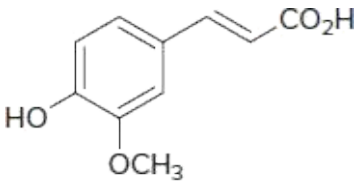


C



D

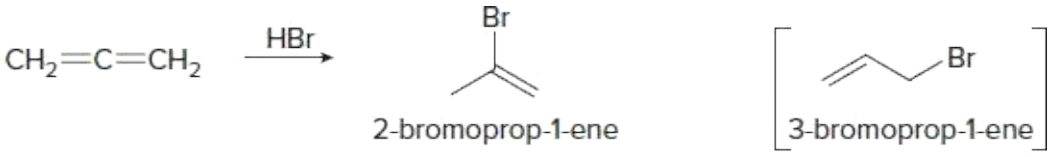
14.69 **Explain why ferulic acid, a natural product found in rice, oats, and other plants, is both an antioxidant and a sunscreen.**



ferulic acid

Challenge Problems

14.70 **Addition of HBr to allene (CH_2=C=CH_2) forms 2-bromoprop-1-ene rather than 3-bromoprop-1-ene, even though 3-bromoprop-1-ene is formed from an allylic carbocation. Considering the arrangement of orbitals in the allene reactant, explain this result.**



2-bromoprop-1-ene

3-bromoprop-1-ene

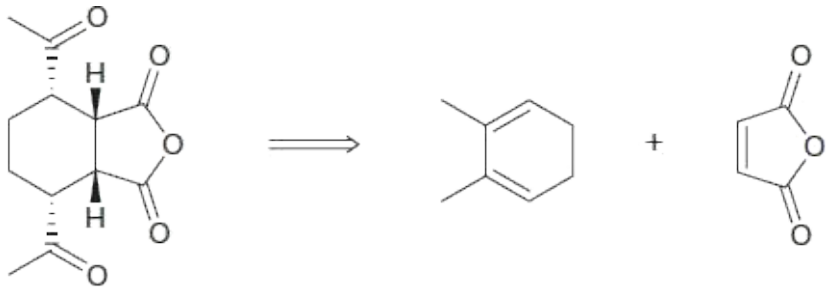
NOT formed

14.71 **Determine the hybridization around the N atom in each amine, and explain why cyclohexanamine is 10^6 times more basic than aniline.**

cyclohexanamine

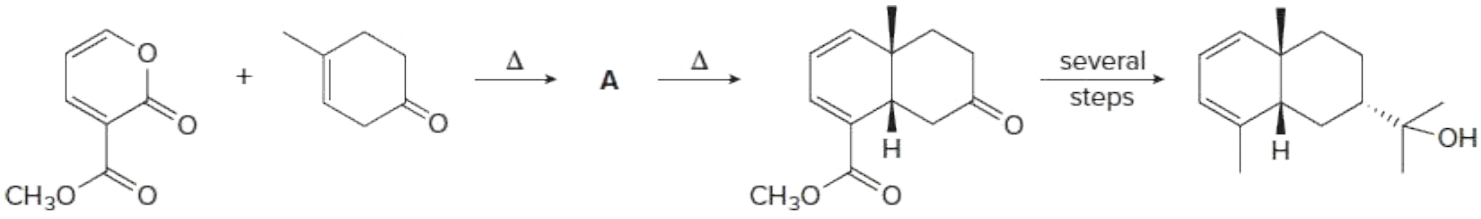
aniline

14.72 **Devise a synthesis of X from the given starting materials. You may use any organic or inorganic reagents. Account for the stereochemistry observed in X.**

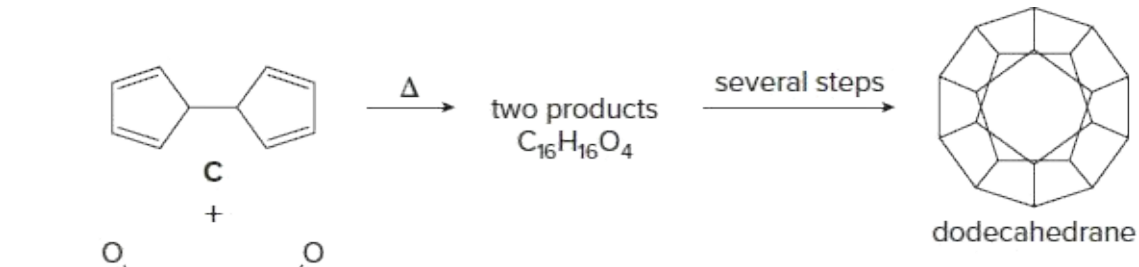


X

14.73 **One step in the synthesis of occidentalol, a natural product isolated from the eastern white cedar tree, involves the following reaction. Identify the structure of A and show how A is converted to B.**



14.74 **One step in the synthesis of dodecahedrane (Section 4.11) involves reaction of the tetraene C with dimethylacetylene dicarboxylate (D) to afford two compounds having molecular formula $C_{16}H_{16}O_4$. This reaction has been called a domino Diels–Alder reaction. Identify the two products formed.**



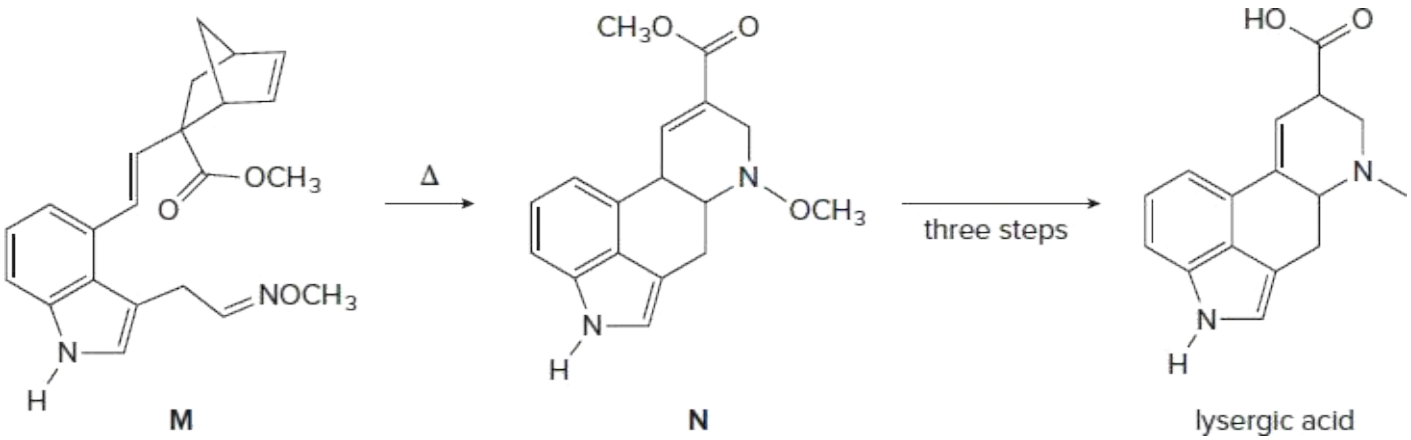
C

+

dimethylacetylene dicarboxylate

D

14.75 **Devise a stepwise mechanism for the conversion of M to N. N has been converted in several steps to lysergic acid, a naturally occurring precursor of the hallucinogen LSD (Figure 16.4).**



M **N** lysergic acid

Benzene and Aromatic Compounds

15

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15.1 Background

15.2 The structure of benzene

15.3 Nomenclature of benzene derivatives

15.4 Spectroscopic properties

15.5 Interesting aromatic compounds

15.6 Benzene's unusual stability
15.7 The criteria for aromaticity—Hückel's rule
15.8 Examples of aromatic compounds
15.9 What is the basis of Hückel's rule?
15.10 The inscribed polygon method for predicting aromaticity
15.11 Buckminsterfullerene—Is it aromatic?

Scombroid fish poisoning, associated with facial flushing, hives, and general itching, is caused by the ingestion of inadequately refrigerated fish, typically tuna or mahimahi. This clinical syndrome results when bacteria convert the amino acid histidine in the tissues of the fish to the neurotransmitter histamine, an aromatic heterocycle that causes blood vessels to dilate and produces the common symptoms of an allergic reaction. In Chapter 15, we learn about the characteristics of aromatic compounds, and why an amine like histamine is considered aromatic.

Why Study…

Aromatic Compounds?

The hydrocarbons we have examined thus far—including the alkanes, alkenes, and alkynes, as well as the conjugated dienes and polyenes of Chapter 14—have been aliphatic hydrocarbons. In Chapter 15, we continue our study of conjugated systems with aromatic hydrocarbons.

We begin with benzene and then examine other cyclic, planar, and conjugated ring systems to learn the modern definition of what it means to be aromatic. Then, in Chapter 16, we will learn about the reactions of aromatic compounds, highly unsaturated hydrocarbons that do not undergo addition reactions like other unsaturated compounds. An explanation of this behavior relies on an understanding of the structure of aromatic compounds presented in Chapter 15. Many naturally occurring compounds contain aromatic rings, and many useful drugs are aromatic.

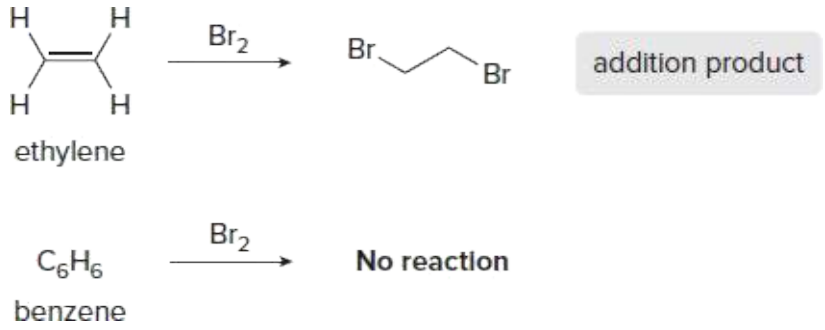
15.1 Background

Benzene (C_6H_6) is the simplest aromatic hydrocarbon (or arene). Since its isolation by

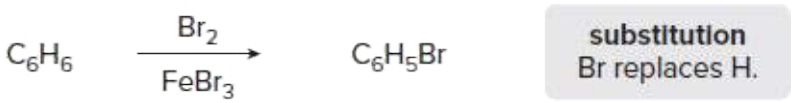
Michael Faraday from the oily residue remaining in the illuminating gas lines in London in 1825, it has been recognized as an unusual compound. Based on the calculation introduced in Section 10.2, benzene has four degrees of unsaturation, making it a highly unsaturated hydrocarbon. But, whereas unsaturated hydrocarbons such as alkenes, alkynes, and dienes readily undergo addition reactions, *benzene does not*. For example, bromine adds to ethylene to form a dibromide, but benzene is inert under similar conditions.

For 6 C's, the maximum number of H's = 2*n* + 2 = 2(6) + 2 = 14.

Because benzene contains only 6 H's, it has 14 − 6 = 8 H's fewer than the maximum number. This corresponds to 8 H's/2 H's for each degree of unsaturation = four degrees of unsaturation in benzene.

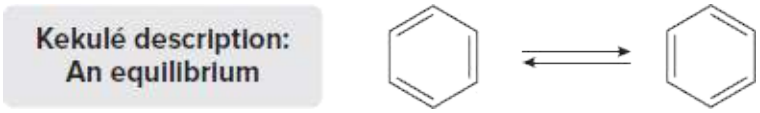


Benzene *does* react with bromine, but only in the presence of $FeBr_3$ (a Lewis acid), and the reaction is a substitution, *not* an addition.



Thus, any structure proposed for benzene must account for its high degree of unsaturation and its lack of reactivity toward electrophilic addition.

In the last half of the nineteenth century August Kekulé proposed structures that were close to the modern description of benzene. In the Kekulé model, benzene was thought to be a rapidly equilibrating mixture of two compounds, each containing a six-membered ring with three alternating π bonds. These structures are now called Kekulé structures. In the Kekulé description, the bond between any two carbon atoms is sometimes a single bond and sometimes a double bond.



Although benzene is still drawn as a six-membered ring with three alternating π bonds, in reality there is no equilibrium between two different kinds of benzene molecules. Instead, current descriptions of benzene are based on resonance and electron delocalization due to orbital overlap, as detailed in Section 15.2.

In the nineteenth century, many other compounds having properties similar to those of benzene were isolated from natural sources. Because these compounds possessed strong and characteristic odors, they were called *aromatic* compounds. It is their chemical properties, though, not their odor that make these compounds special.

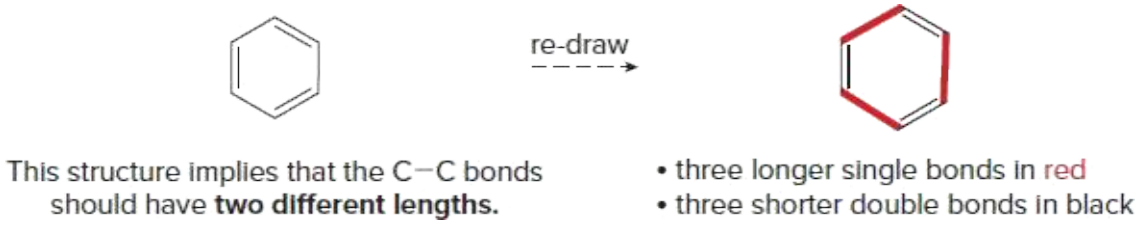
- **Aromatic compounds resemble benzene—they are unsaturated compounds that do not undergo the addition reactions characteristic of alkenes.**

15.2 The Structure of Benzene

Any structure for benzene must account for the following:

- **Benzene contains a six-membered ring and three additional degrees of unsaturation.**
- **Benzene is planar.**
- **All C—C bond lengths are equal.**

Although the Kekulé structures satisfy the first two criteria, they break down with the third, because having three alternating π bonds would mean that benzene should have three short double bonds alternating with three longer single bonds.

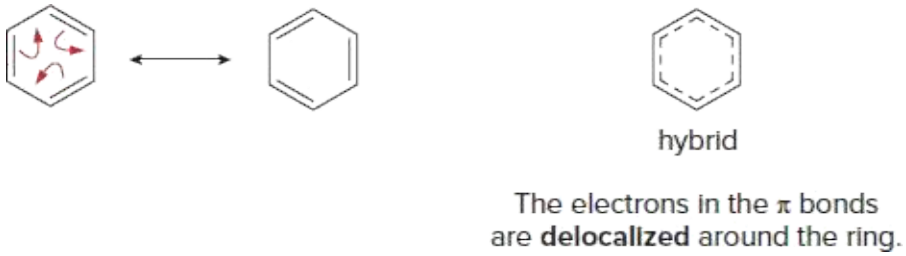


Resonance

Benzene is conjugated, so we must use resonance and orbitals to describe its structure. The resonance description of benzene consists of two equivalent Lewis structures, each with three double bonds that alternate with three single bonds.

Some texts draw benzene as a hexagon with an inner circle:

The circle represents the six π electrons, distributed over the six atoms of the ring.

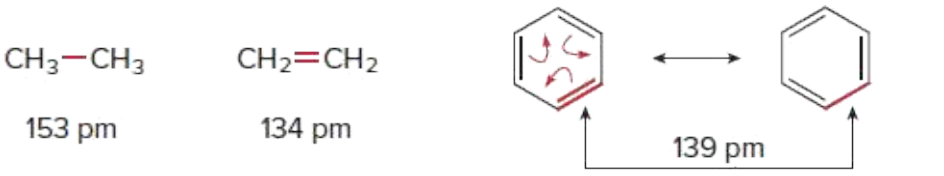


The resonance description of benzene matches the Kekulé description with one important exception: The two Kekulé representations are *not* in equilibrium with each other. Instead, the true structure of benzene is a resonance hybrid of the two Lewis structures, with the dashed lines of the hybrid indicating the position of the π bonds.

We will use one of the two Lewis structures and not the hybrid in drawing benzene, because it is easier to keep track of the electron pairs in the π bonds (the π electrons).

- **Because each π bond has two electrons, benzene has six π electrons.**

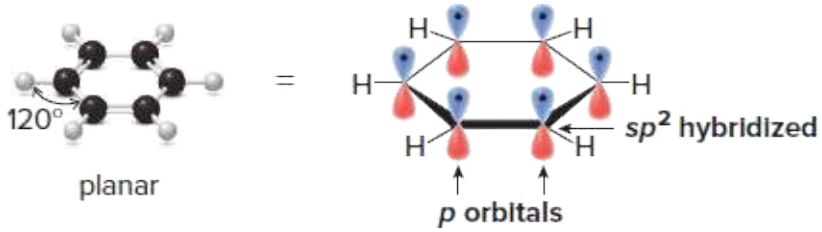
The resonance hybrid of benzene explains why all C—C bond lengths are the same. Each C—C bond is single in one resonance structure and double in the other, so the actual bond length (139 pm) is *intermediate* between a carbon–carbon single bond (153 pm) and a carbon–carbon double bond (134 pm).



The C–C bonds in benzene are equal and intermediate in length.

Hybridization and Orbitals

Each carbon atom in a benzene ring is surrounded by three atoms and no lone pairs of electrons, making it sp^2 hybridized and trigonal planar with all bond angles 120°. Each carbon also has a *p* orbital with one electron that extends above and below the plane of the molecule.



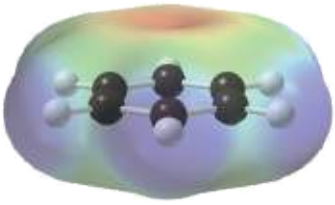
The six adjacent *p* orbitals overlap, delocalizing the six electrons over the six atoms of the ring and making benzene a conjugated molecule. Because each *p* orbital has two lobes, one above and one below the plane of the benzene ring, the overlap of the *p* orbitals creates two "doughnuts" of electron density, as shown in Figure 15.1a. The electrostatic potential plot in Figure 15.1b also shows that the electron-rich region is concentrated above and below the plane of the molecule, where the six π electrons are located.

- **Benzene's six π electrons make it electron rich, so it reacts with electrophiles.**

a. View of the *p* orbital overlap

- Overlap of six adjacent *p* orbitals creates two rings of electron density, one above and one below the plane of the benzene ring.

b. Electrostatic potential plot

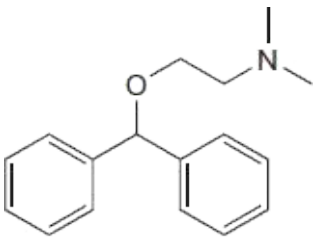


- The electron-rich region (in red) is concentrated above and below the ring carbons, where the six π electrons are located. (The electron-rich region below the plane is hidden from view.)

Figure 15.1 **Two views of the electron density in a benzene ring**

Problem 15.1

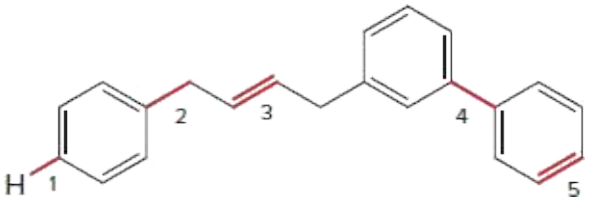
Draw all possible resonance structures for the antihistamine diphenhydramine, the active ingredient in Benadryl.



diphenhydramine

Problem 15.2

What orbitals are used to form the labeled bonds in the following molecule? Of the labeled C—C bonds, which is the shortest?

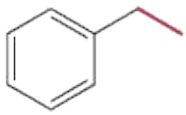


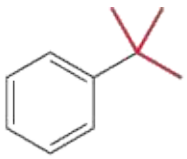
15.3 Nomenclature of Benzene Derivatives

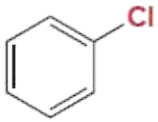
Many organic molecules contain a benzene ring with one or more substituents, so we must learn how to name them. Many common names are recognized by the IUPAC system, however, so this complicates the nomenclature of benzene derivatives somewhat.

15.3A Monosubstituted Benzenes

To name a benzene ring with one substituent, name the substituent and add the word *benzene*. Carbon substituents are named as alkyl groups.

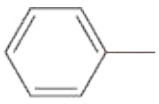

ethylbenzene

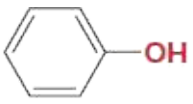

tert-butylbenzene



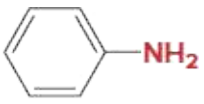
chlorobenzene

Many monosubstituted benzenes, such as those with methyl (CH_3–), hydroxy (–OH), and amino (–NH_2) groups, have common names that you must learn, too.


toluene
(methylbenzene)



phenol
(hydroxybenzene)

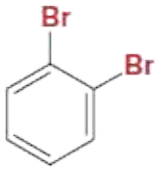


aniline
(aminobenzene)

15.3B Disubstituted Benzenes

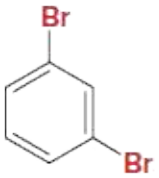
There are three different ways that two groups can be attached to a benzene ring, so a prefix—ortho, meta, or para—can be used to designate the relative position of the two substituents. Ortho, meta, and para are also abbreviated as *o*, *m*, and *p*, respectively.

1,2-Disubstituted benzene
ortho isomer



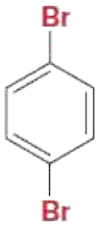
o-dibromobenzene
or
1,2-dibromobenzene

1,3-Disubstituted benzene
meta isomer



m-dibromobenzene
or
1,3-dibromobenzene

1,4-Disubstituted benzene
para isomer



p-dibromobenzene
or
1,4-dibromobenzene

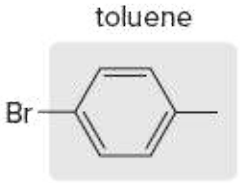
If the two groups on the benzene ring are different, alphabetize the names of the substituents preceding the word *benzene*. If one of the substituents is part of a common root, name the molecule as a derivative of that monosubstituted benzene.

Alphabetize two different substituent names:

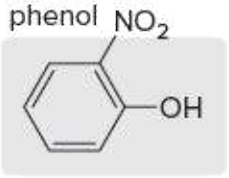
o-bromochloro-
benzene

m-fluoronitro-
benzene

Use a common root name:



p-bromo**toluene**



o-nitro**phenol**

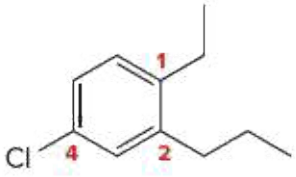
15.3C Polysubstituted Benzenes

For three or more substituents on a benzene ring:

[1] Number to give the lowest possible set of numbers around the ring.

[2] Alphabetize the substituent names.

[3] When substituents are part of common roots, name the molecule as a derivative of that monosubstituted benzene. The substituent that comprises the common root is located at C1.



- Assign the lowest possible set of numbers.
- Alphabetize the names of all the substituents.

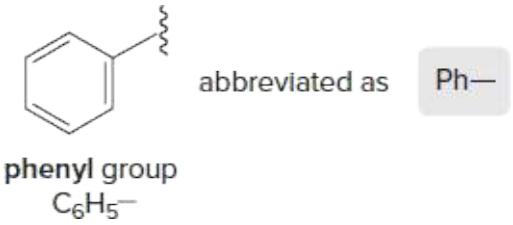
4-chloro-1-ethyl-2-propylbenzene

- Name the molecule as a derivative of the common root **aniline.**
- Designate the position of the NH_2 group as "1," and then assign the lowest possible set of numbers to the other substituents.

2,5-dichloroaniline

15.3D Naming Aromatic Rings as Substituents

A benzene substituent (C_6H_5–) is called a phenyl group, and it can be abbreviated in a structure as Ph–.



- **A phenyl group (C_6H_5–) is formed by removing one hydrogen from benzene (C_6H_6).**

Benzene, therefore, can be represented as PhH, and phenol would be PhOH.

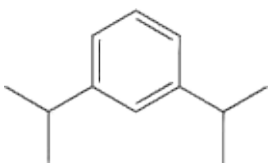
The benzyl group contains a benzene ring bonded to a CH_2 group. Thus, a benzyl group and a phenyl group differ by the presence of a CH_2 group.

Finally, substituents derived from benzene, as well as all other substituted aromatic rings, are collectively called aryl groups, abbreviated as Ar–.

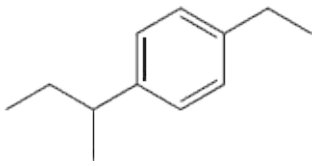
Problem 15.3

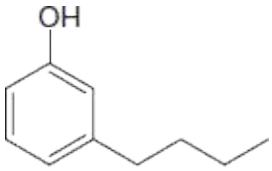
Give the IUPAC name for each compound.

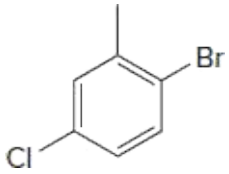
a.



b.



c. 

d. 

Problem 15.4

Draw the structure corresponding to each name:

a. isobutylbenzene

b. *o*-dichlorobenzene

c. *cis*-1,2-diphenylcyclohexane

d. *m*-bromoaniline

e. 4-chloro-1,2-diethylbenzene

f. 3-*tert*-butyl-2-ethyltoluene

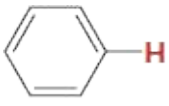
Problem 15.5

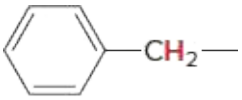
What is the structure of propofol, which has the IUPAC name 2,6-diisopropylphenol? Propofol is an intravenous medication used to induce and maintain anesthesia.

15.4 Spectroscopic Properties

The IR spectroscopy of aromatic compounds was discussed in Section B.4A; the NMR spectroscopy of aromatics was presented in Sections C.4 and C.9C. The important IR and NMR absorptions of aromatic compounds are summarized in Table 15.1.

Table 15.1 Characteristic Spectroscopic Absorptions of Benzene Derivatives

Type of spectroscopy	Type of C, H	Absorption
IR absorptions	C_{sp^2}–H C=C (arene)	**3150–3000 cm^{-1}** **1600, 1500 cm^{-1}**
^{1}H NMR absorptions	 (aryl H)	**6.5–8 ppm (highly deshielded protons)**

	 (benzylic H)	**1.5–2.5 ppm (somewhat deshielded C_{sp^3}—H)**
^{13}C NMR absorption	C_{sp^2} of arenes	**120–150 ppm**

^{13}C NMR spectroscopy is used to determine the substitution patterns in disubstituted benzenes, because each line in a spectrum corresponds to a different kind of carbon atom. For example, *o*-, *m*-, and *p*-dibromobenzene each exhibit a different number of lines in its ^{13}C NMR spectrum, as shown in Figure 15.2.

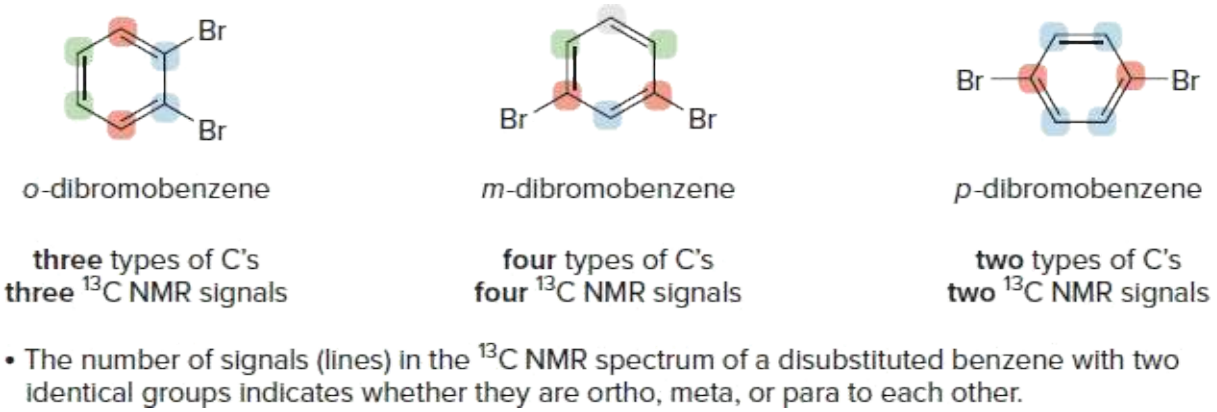
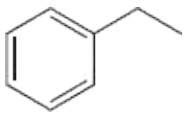
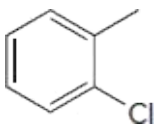


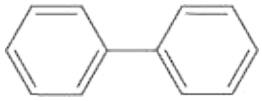
Figure 15.2 **^{13}C NMR absorptions of the three isomeric dibromobenzenes**

Problem 15.6

How many ^{13}C NMR signals does each compound exhibit?

a. 

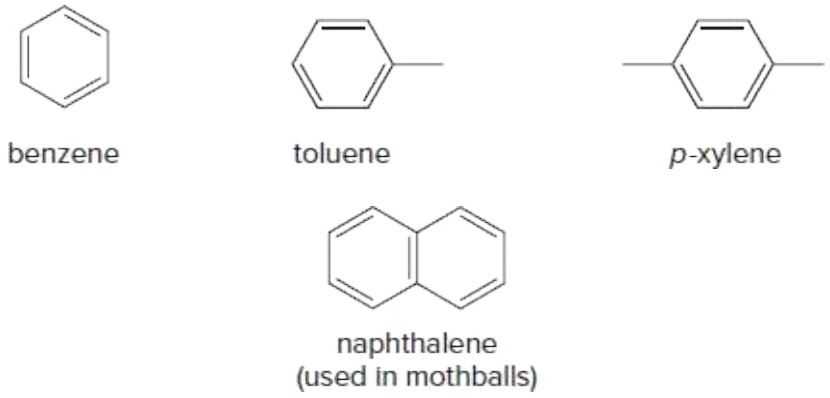
b. 

c. 

15.5 Interesting Aromatic Compounds

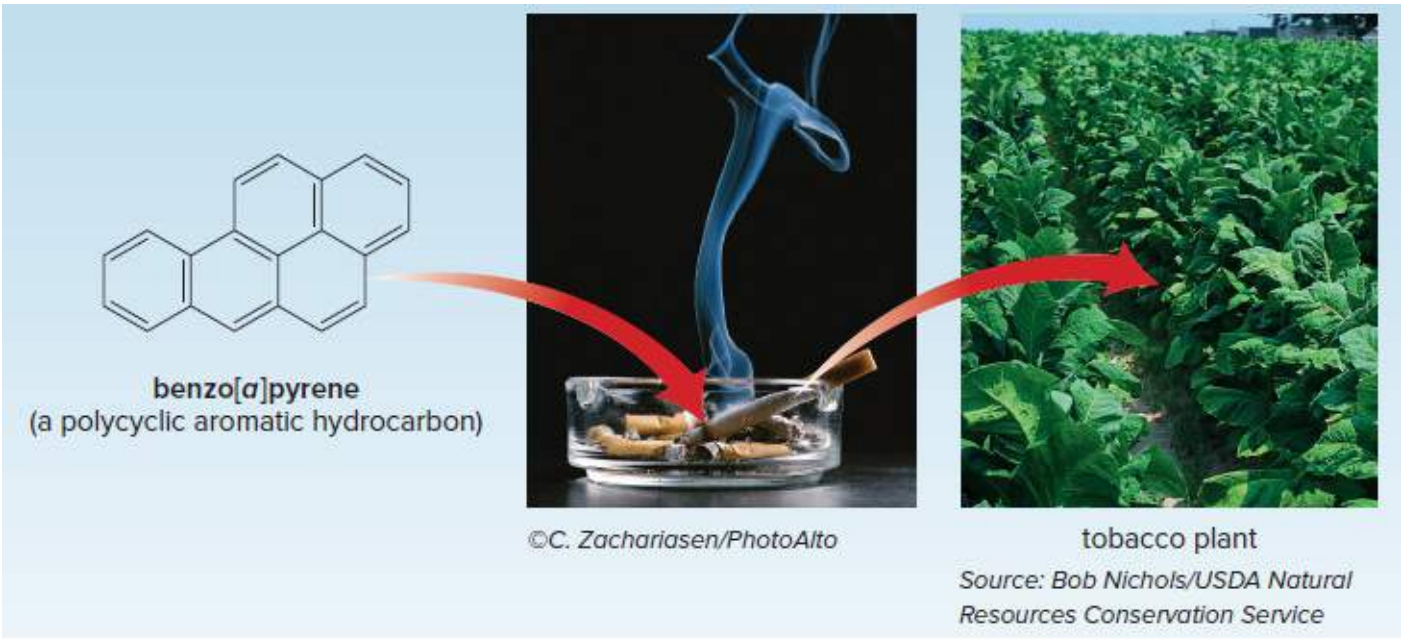
Benzene and toluene, the simplest aromatic hydrocarbons obtained from petroleum refining, are useful starting materials for synthetic polymers. They are two components of the BTX mixture added to gasoline to boost octane ratings.

BTX contains benzene, toluene, and xylene (the common name for dimethylbenzene).



Compounds containing two or more benzene rings that share carbon–carbon bonds are called polycyclic aromatic hydrocarbons (PAHs). Naphthalene, the simplest PAH, is present in mothballs.

Benzo[*a*]pyrene, a more complicated PAH shown in Figure 15.3, is formed by the incomplete combustion of organic materials. It is found in cigarette smoke, automobile exhaust, and the fumes from charcoal grills. When ingested or inhaled, benzo[*a*]pyrene and other similar PAHs are oxidized to carcinogenic products, as discussed in Section 9.18.



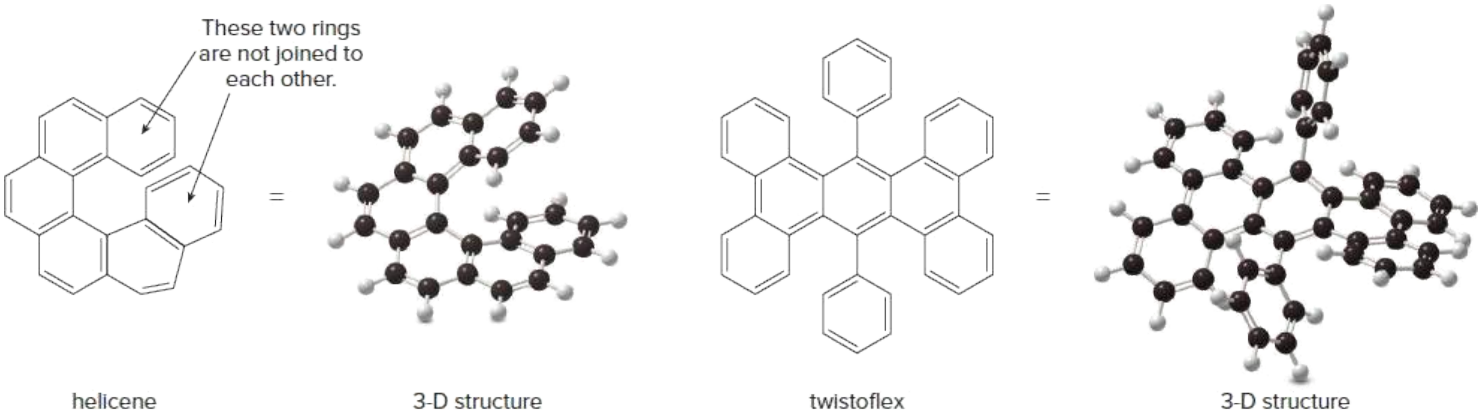
- Benzo[*a*]pyrene, produced by the incomplete oxidation of organic compounds in tobacco, is found in cigarette smoke.

Figure 15.3 **Benzo[*a*]pyrene, a common PAH**

Helicene and twistoflex are two synthetic PAHs whose unusual shapes are shown in

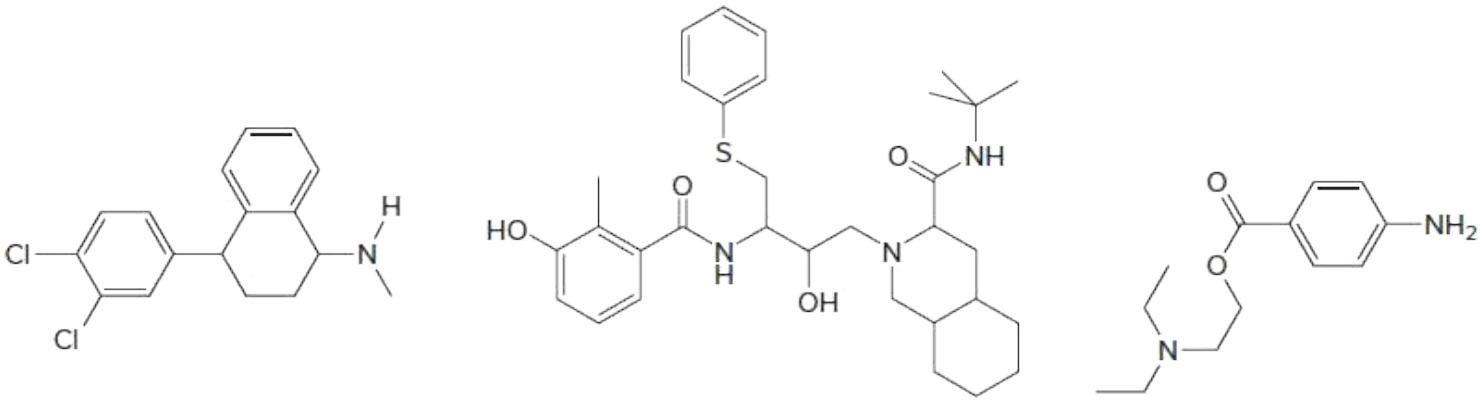
Figure 15.4. Both helicene and twistoflex are chiral molecules—that is, they are not superimposable on their mirror images, even though neither of them contains a stereogenic center. It's their shape that makes them chiral, not the presence of carbon atoms bonded to four different groups. Each ring system is twisted into a shape that lacks a mirror plane, and each structure is rigid, thus creating the chirality.

Many widely used drugs contain a benzene ring. Three examples are shown in Figure 15.5.



- Helicene consists of six benzene rings. Because the rings at both ends are not bonded to each other, all of the rings twist slightly, creating a rigid helical shape that prevents the hydrogen atoms on both ends from crashing into each other. Similarly, to reduce steric hindrance between the hydrogen atoms on nearby benzene rings, twistoflex is also nonplanar.

Figure 15.4 **Helicene and twistoflex—Two synthetic polycyclic aromatic hydrocarbons**



- Trade name **Zoloft**
- Generic name **sertraline**
- Use: a psychotherapeutic drug for depression and panic disorders

- Trade name **Viracept**
- Generic name **nelfinavir**
- Use: an antiviral drug used to treat HIV

- Trade name **Novocain**
- Generic name **procaine**
- Use: a local anesthetic

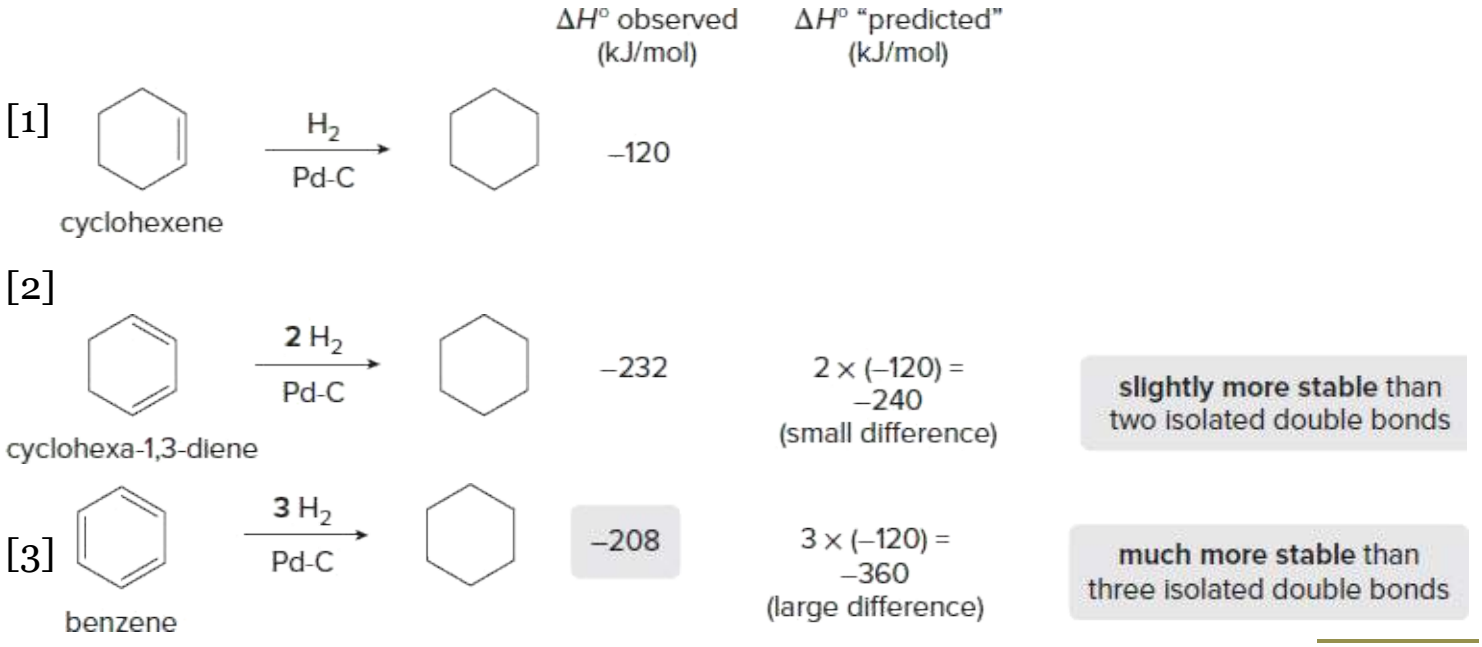
Figure 15.5 **Selected drugs that contain a benzene ring**

15.6 Benzene's Unusual Stability

Considering benzene as the hybrid of two resonance structures adequately explains its

equal C—C bond lengths, but does not account for its unusual stability and lack of reactivity toward addition.

Heats of hydrogenation, which were used in Section 14.9 to show that conjugated dienes are more stable than isolated dienes, can also be used to estimate the stability of benzene. Equations [1]–[3] compare the heats of hydrogenation of cyclohexene, cyclohexa-1,3-diene, and benzene, all of which give cyclohexane when treated with excess hydrogen in the presence of a metal catalyst.



The relative stability of conjugated dienes versus isolated dienes was first discussed in Section 14.9.

The addition of one mole of H_2 to cyclohexene releases –120 kJ/mol of energy (Equation [1]). If each double bond is worth –120 kJ/mol of energy, then the addition of two moles of H_2 to cyclohexa-1,3-diene (Equation [2]) should release 2 × (–120 kJ/mol) = –240 kJ/mol of energy. The observed value, however, is –232 kJ/mol. This is *slightly smaller* than expected because cyclohexa-1,3-diene is a conjugated diene, and conjugated dienes are more stable than two isolated carbon–carbon double bonds.

The hydrogenations of cyclohexene and cyclohexa-1,3-diene occur readily at room temperature, but benzene can be hydrogenated only under forcing conditions, and even then the reaction is extremely slow. If each double bond is worth –120 kJ/mol of energy, then the addition of three moles of H2 to benzene should release 3 × (–120 kJ/mol) = –360 kJ/mol of energy. In fact, the observed heat of hydrogenation is only –208 kJ/mol, which is 152 kJ/mol less than predicted and even *lower* than the observed value for cyclohexa-1,3-diene.

Figure 15.6 compares the hypothetical and observed heats of hydrogenation for benzene.

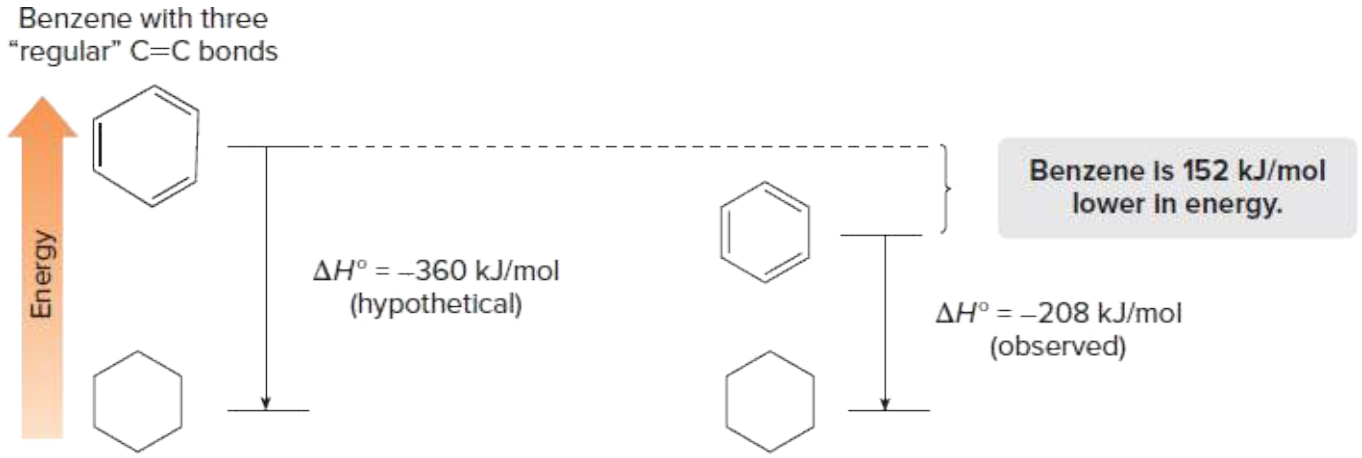
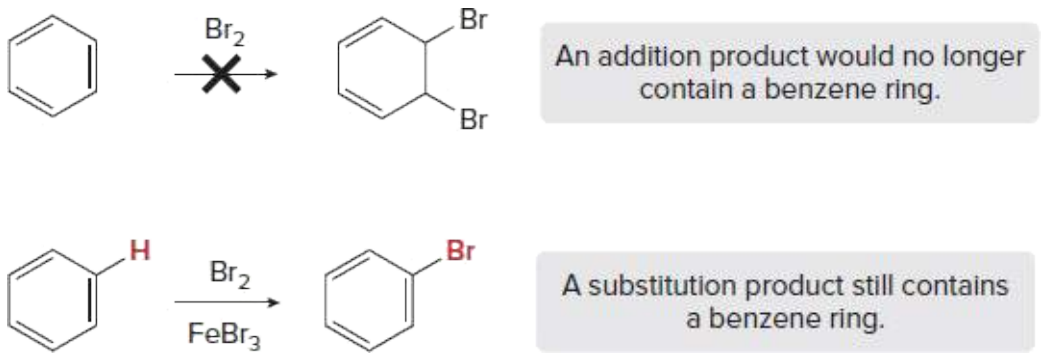


Figure 15.6 **A comparison between the observed and hypothetical heats of hydrogenation for benzene**

The huge difference between the hypothetical and observed heats of hydrogenation for benzene cannot be explained solely on the basis of resonance and conjugation.

- **The low heat of hydrogenation of benzene means that benzene is *especially stable*, even more so than the conjugated compounds introduced in Chapter 14. This unusual stability is characteristic of aromatic compounds.**

Benzene's unusual behavior in chemical reactions is not limited to hydrogenation. As mentioned in Section 15.1, benzene does *not* undergo addition reactions typical of other highly unsaturated compounds, including conjugated dienes. Benzene does not react with Br2 to yield an addition product. Instead, in the presence of a Lewis acid, bromine *substitutes* for a hydrogen atom, thus yielding a product that retains the benzene ring.

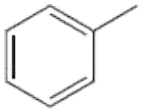


This behavior is characteristic of aromatic compounds. The structural features that

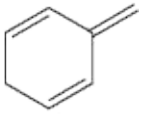
distinguish aromatic compounds from the rest are discussed in Section 15.7.

Problem 15.7

Compounds A and B are both hydrogenated to methylcyclohexane. Which compound has the larger heat of hydrogenation? Which compound is more stable?



A



B

15.7 The Criteria for Aromaticity—Hückel's Rule

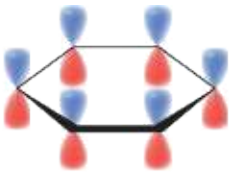
Four structural criteria must be satisfied for a compound to be aromatic:

- **A molecule must be cyclic, planar, completely conjugated, and contain a particular number of π electrons.**

[1] A molecule must be cyclic.

- **To be aromatic, each *p* orbital must overlap with *p* orbitals on two adjacent atoms.**

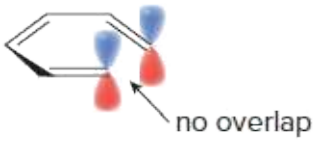
The *p* orbitals on all six carbons of benzene continuously overlap, so benzene is aromatic. Hexa-1,3,5-triene has six *p* orbitals, too, but the two on the terminal carbons cannot overlap with each other, so hexa-1,3,5-triene is *not* aromatic.



benzene

Every *p* orbital overlaps with two neighboring *p* orbitals.

aromatic



hexa-1,3,5-triene

There can be no overlap between the *p* orbitals on the two terminal C's.

not aromatic

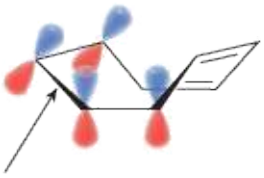
[2] A molecule must be planar.

- **All adjacent *p* orbitals must be aligned so that the π electron density**

can be delocalized.

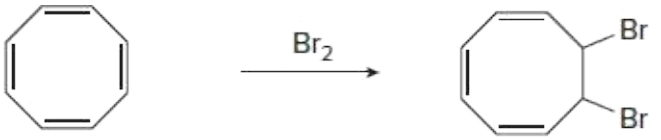
cyclooctatetraene
not aromatic

a tub-shaped,
eight-membered ring



Adjacent *p* orbitals cannot overlap.
Electrons cannot delocalize.

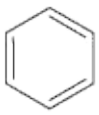
Cyclooctatetraene resembles benzene in that it is a cyclic molecule with alternating double and single bonds. Cyclooctatetraene is tub shaped, however, not planar, so overlap between adjacent π bonds is impossible. Cyclooctatetraene, therefore, is *not* aromatic, so it undergoes addition reactions like those of other alkenes.



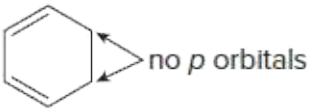
cyclooctatetraene **addition** product

[3] A molecule must be completely conjugated.

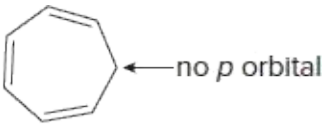
- **Aromatic compounds must have a *p* orbital on every atom in the ring.**



benzene
a *p* orbital on **every** C
aromatic



cyclohexa-1,3-diene
not aromatic



cyclohepta-1,3,5-triene
not aromatic

Both cyclohexa-1,3-diene and cyclohepta-1,3,5-triene contain at least one carbon atom that does not have a *p* orbital, so they are not completely conjugated and therefore *not* aromatic.

[4] A molecule must satisfy Hückel's rule, and contain a particular number of π electrons.

Some compounds satisfy the first three criteria for aromaticity, but still they show none of the stability typical of aromatic compounds. For example, cyclobutadiene is so highly reactive that it can be prepared only at extremely low temperatures.

cyclobutadiene

a planar, cyclic, completely conjugated molecule that is *not* aromatic

Hückel's rule refers to the number of π electrons, *not* the number of atoms in a particular ring.

It turns out that in addition to being cyclic, planar, and completely conjugated, a compound needs a particular number of π electrons to be aromatic. Erich Hückel first recognized in 1931 that the following criterion, expressed in two parts and now known as Hückel's rule, had to be satisfied, as well:

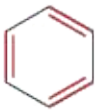
- **An aromatic compound must contain $4n + 2$ π electrons ($n = 0, 1, 2$, and so forth).**
- **Cyclic, planar, and completely conjugated compounds that contain $4n$ π electrons are especially unstable, and are said to be *antiaromatic*.**

Thus, compounds that contain 2, 6, 10, 14, 18, and so forth π electrons are aromatic, as shown in Table 15.2. Benzene is aromatic and especially stable because it contains 6 π electrons. Cyclobutadiene is antiaromatic and especially unstable because it contains 4 π electrons.

Table 15.2

The Number of π Electrons That Satisfy Hückel's Rule

n	4*n* + 2
0	2
1	6
2	10
3	14
4, etc.	18

Benzene An aromatic compound	Cyclobutadiene An antiaromatic compound
	
$4n + 2 = 4(1) + 2 =$ 6 π electrons aromatic	$4n = 4(1) =$ 4 π electrons antiaromatic

Considering aromaticity, all compounds can be classified in one of three ways:

[1] Aromatic

- **A cyclic, planar, completely conjugated compound with $4n + 2$ π electrons**

[2] Antiaromatic

- **A cyclic, planar, completely conjugated compound with $4n$ π electrons**

[3] Not aromatic or nonaromatic

- **A compound that lacks one (or more) of the four requirements to be aromatic or antiaromatic**

Many compounds in addition to benzene are aromatic. Several examples are presented in Section 15.8. Page 701

15.8 Examples of Aromatic Compounds

In Section 15.8, we look at many different types of aromatic compounds.

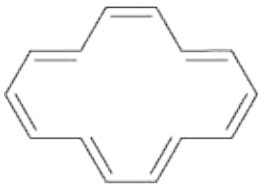
15.8A Aromatic Compounds with a Single Ring

Benzene is the most common aromatic compound having a single ring. Completely conjugated rings larger than benzene are also aromatic if they are planar and have $4n + 2$ π electrons.

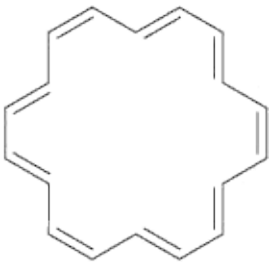
- **Hydrocarbons containing a single ring with alternating double and single bonds are called *annulenes*.**

To name an annulene, indicate the number of atoms in the ring in brackets and add

the word *annulene*. Thus, benzene is [6]-annulene. Both [14]-annulene and [18]-annulene are cyclic, planar, completely conjugated molecules that follow Hückel's rule, so they are aromatic.

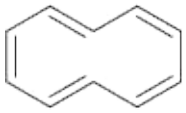


[14]-annulene
$4n + 2 = 4(3) + 2 =$
14 π electrons
aromatic



[18]-annulene
$4n + 2 = 4(4) + 2 =$
18 π electrons
aromatic

[10]-Annulene has 10 π electrons, which satisfies Hückel's rule, but a planar molecule would place the two H atoms inside the ring too close to each other, so the ring puckers to relieve this strain. Because [10]-annulene is not planar, the 10 π electrons can't delocalize over the entire ring and it is not aromatic.



[10]-annulene
10 π electrons
not planar
not aromatic

=

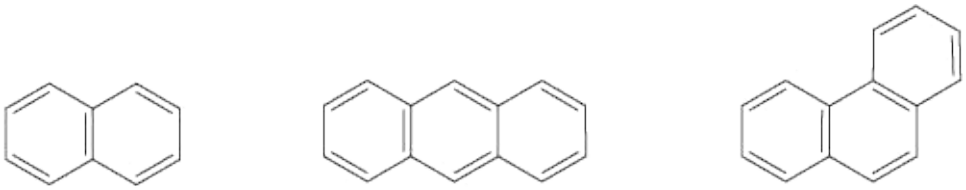
The molecule puckers to keep these H's farther away from each other.

Problem 15.8

Would [16]-, [20]-, or [22]-annulene be aromatic if each ring is planar?

15.8B Aromatic Compounds with More Than One Ring

Hückel's rule for determining aromaticity can be applied only to monocyclic systems, but many aromatic compounds containing several benzene rings joined together are also known. Two or more six-membered rings with alternating double and single bonds can be fused together to form polycyclic aromatic hydrocarbons (PAHs). Joining two benzene rings together forms naphthalene. There are two different ways to join three rings together, forming anthracene and phenanthrene, and many more complex hydrocarbons are known.

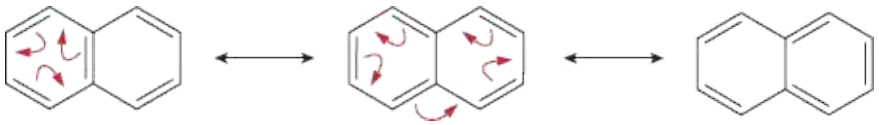


naphthalene
10 π electrons

anthracene
14 π electrons

phenanthrene
14 π electrons

As the number of fused benzene rings increases, the number of resonance structures increases as well. Although two resonance structures can be drawn for benzene, naphthalene is a hybrid of three resonance structures.



Problem 15.9

Draw the four resonance structures for anthracene.

15.8C Aromatic Heterocycles

Heterocycles containing oxygen, nitrogen, or sulfur—atoms that also have at least one lone pair of electrons—can also be aromatic. With heteroatoms, we must always determine whether the lone pair is localized on the heteroatom or part of the delocalized π system. Two examples, pyridine and pyrrole, illustrate these different possibilities.

Recall from Section 9.3 that a heterocycle is a ring that contains at least one heteroatom.

Pyridine

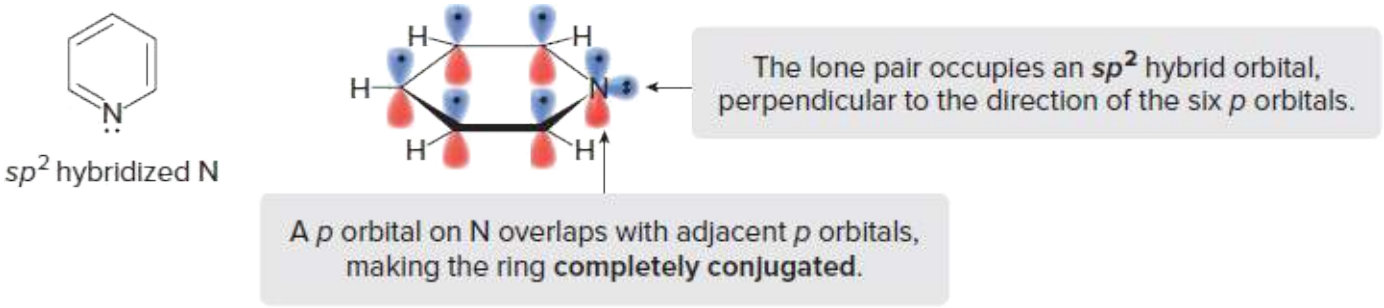
Pyridine is a heterocycle containing a six-membered ring with three π bonds and one nitrogen atom. Similar to benzene, two resonance structures (with all neutral atoms) can be drawn.

two resonance structures for pyridine
6 π electrons

Pyridine is cyclic, planar, and completely conjugated, because the three single and three double bonds alternate around the ring. Pyridine has six π electrons, two from

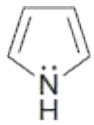
each π bond, thus satisfying Hückel's rule and making pyridine aromatic. The nitrogen atom of pyridine also has a nonbonded electron pair, which is *localized* on the N atom, so it is *not* part of the delocalized π electron system of the aromatic ring.

How is the nitrogen atom of the pyridine ring hybridized? The N atom is surrounded by three groups (two atoms and a lone electron pair), making it sp^2 hybridized, and leaving one unhybridized *p* orbital with one electron that overlaps with adjacent *p* orbitals. The lone pair on N resides in an sp^2 hybrid orbital that is perpendicular to the delocalized π electrons.



Pyrrole

Pyrrole contains a five-membered ring with two π bonds and one nitrogen atom. The N atom also has a lone pair of electrons.



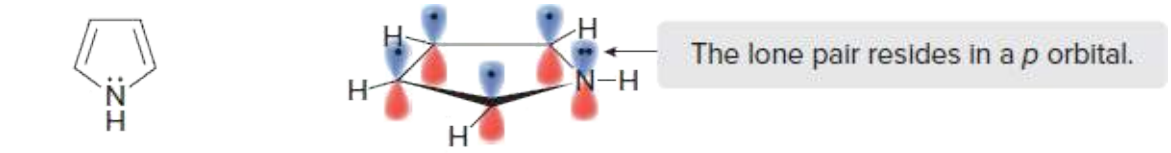
pyrrole

Pyrrole is cyclic and planar, with a total of four π electrons from the two π bonds. Is the nonbonded electron pair localized on N or part of a delocalized π electron system? The lone pair on N is *adjacent* to a double bond. Recall the following general rule from Section 14.5:

- **In a system X=Y−Z:, Z is generally sp^2 hybridized and the lone pair occupies a *p* orbital to make the system conjugated.**

If the lone pair on the N atom occupies a *p* orbital:

- Pyrrole has a *p* orbital on every adjacent atom, so it is completely conjugated.
- Pyrrole has six π electrons—four from the π bonds and two from the lone pair.

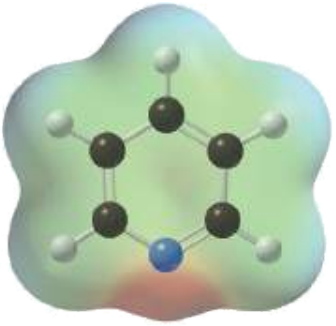


sp^2 hybridized N

The ring is completely conjugated with **6 π electrons.**

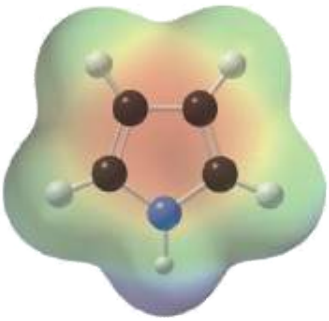
Because pyrrole is cyclic, planar, completely conjugated, and has $4n + 2$ π electrons, pyrrole is aromatic. The number of electrons—not the size of the ring—determines whether a compound is aromatic.

Electrostatic potential maps, shown in Figure 15.7 for pyridine and pyrrole, illustrate that the lone pair in pyridine is localized on N, whereas the lone pair in pyrrole is part of the delocalized π system. Thus, a fundamental difference exists between the N atoms in pyridine and pyrrole.



pyridine

- In pyridine, the nonbonded electron pair is localized on the N atom in an sp^2 hybridized orbital, as shown by the region of high electron density (in red) on N.



pyrrole

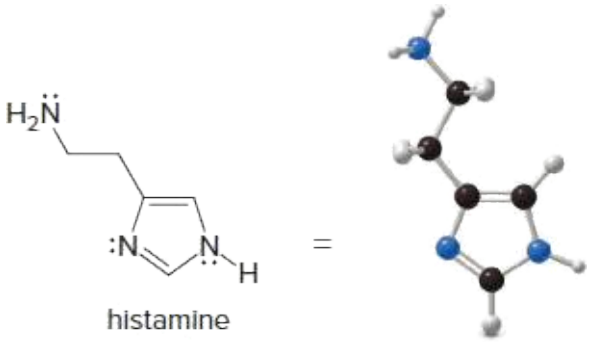
- In pyrrole, the nonbonded electron pair is in a *p* orbital and is delocalized over the ring, so the entire ring is electron rich (red).

Figure 15.7 **Electrostatic potential maps of pyridine and pyrrole**

- **When a heteroatom is already part of a double bond (as in the N of pyridine), its lone pair *cannot* occupy a *p* orbital, so it *cannot* be delocalized over the ring.**
- **When a heteroatom is *not* part of a double bond (as in the N of pyrrole), its lone pair can be located in a *p* orbital and *delocalized* over a ring to make it aromatic.**

Histamine

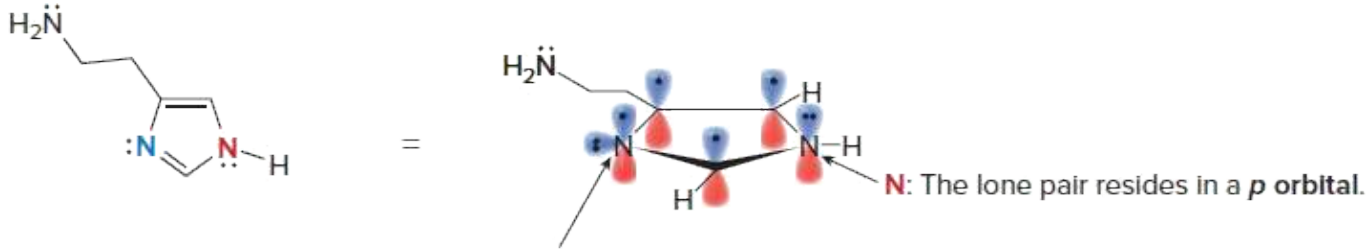
Histamine, the chapter-opening biologically active amine formed in many tissues, has an aromatic heterocycle with two N atoms, one of which is similar to the N atom of pyridine and one of which is similar to the N atom of pyrrole.



Antihistamines that block the action of histamine on the H1 histamine receptor are used to treat the runny nose and watery eyes of an allergic reaction.

©Bob *London/Alamy Stock Photo*

Histamine has a five-membered ring with two π bonds and two nitrogen atoms, each of which contains a lone pair of electrons. The heterocycle has four π electrons from the two double bonds. The lone pair on the N in red also occupies a *p* orbital, making the heterocycle completely conjugated and giving it a total of six π electrons. The lone pair on this N atom is thus delocalized over the five-membered ring and the heterocycle is aromatic. The lone pair on the N in blue occupies an sp^2 hybrid orbital perpendicular to the delocalized π electrons.



- N (in red) resembles the N atom of pyrrole.
- N (in blue) resembles the N atom of pyridine.

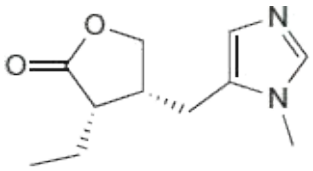
Histamine produces a wide range of physiological effects in the body. Excess histamine is responsible for the runny nose and watery eyes symptomatic of hay fever. It also stimulates the overproduction of stomach acid and contributes to the formation of hives. These effects result from the interaction of histamine with two different cellular

receptors. We will learn more about antihistamines and antiulcer drugs, compounds that block the effects of histamine, in Section 23.5.

Sample Problem 15.1 Determining the Hybridization of a Heteroatom in an Aromatic Heterocycle

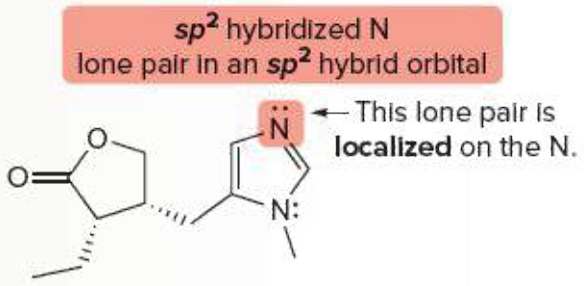
Pilocarpine (Sample Problem 15.1) is a naturally occurring glaucoma medication isolated from the plant *Pilocarpus microphyllus*, commonly called jaborandi, grown in Brazil. ©*Schafer & Hill/Photolibrary/Getty Images*

How is each N atom in pilocarpine hybridized, and in what type of orbital does the lone pair on each N reside?

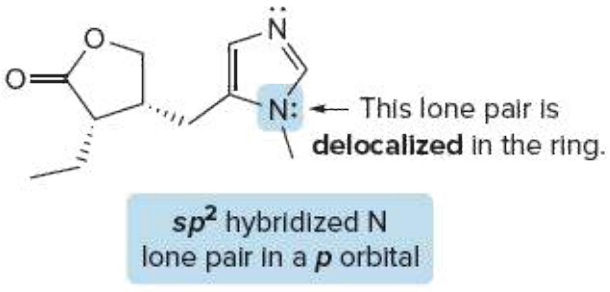


pilocarpine

Solution



The N atom labeled in red is already part of a double bond, so it is sp^2 **hybridized** and its unhybridized *p* orbital is used to form the π bond. As a result, the **lone pair on N occupies one of the sp^2 hybrid orbitals.**



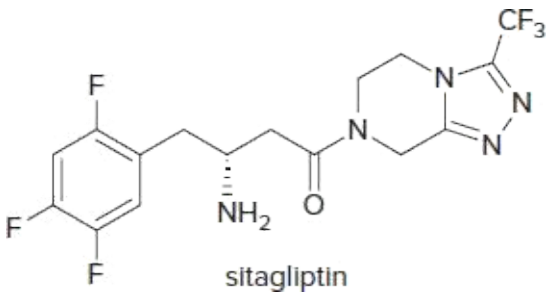
The N atom labeled in blue is sp^2 **hybridized,** so its **lone pair can occupy a *p* orbital** and delocalize in the five-membered ring. Delocalization gives the ring six π electrons and makes the ring aromatic.

Problem 15.10

Januvia, the trade name for sitagliptin, was introduced in 2006 for the treatment of type 2 diabetes. (a) Explain why the five-membered ring in sitagliptin is aromatic. (b) Determine the hybridization of each N atom. (c) In what type of orbital does the lone pair on each N atom reside?

Januvia (Problem 15.10) increases the body's ability to lower blood sugar levels, so it is used alone or in combination with other drugs to treat type 2 diabetes.

©Bloomberg/Getty Images



sitagliptin

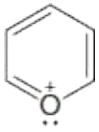
More Practice:

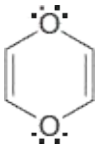
Try Problems 15.32a, b; 15.33; 15.34; 15.57b, c; 15.58a; 15.60b.

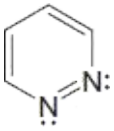
Problem 15.11

Which heterocycles are aromatic?

a.

b. 

c. 

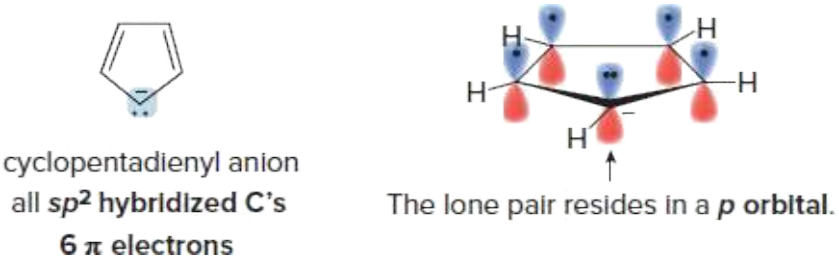
d. 

15.8D Charged Aromatic Compounds

Both negatively and positively charged ions can also be aromatic if they satisfy all the necessary criteria.

Cyclopentadienyl Anion

The cyclopentadienyl anion is a cyclic and planar anion with two double bonds and a nonbonded electron pair. In this way it resembles pyrrole. The two π bonds contribute four electrons and the lone pair contributes two more, for a total of six. By Hückel's rule, having six π electrons confers aromaticity. Like the N atom in pyrrole, the negatively charged carbon atom must be sp^2 hybridized, and the nonbonded electron pair must occupy a *p* orbital for the ring to be completely conjugated.



- **The cyclopentadienyl anion is aromatic because it is cyclic, planar, completely conjugated, and has six π electrons.**

We can draw five equivalent resonance structures for the cyclopentadienyl anion, delocalizing the negative charge over every carbon atom of the ring.

Although five resonance structures can also be drawn for both the cyclopentadienyl cation and radical, only the cyclopentadienyl anion has six π electrons, a number that satisfies Hückel's rule. The cyclopentadienyl cation has four π electrons, making it antiaromatic and especially unstable. The cyclopentadienyl radical has five π electrons, so it is neither aromatic nor antiaromatic. Having the "right" number of electrons is necessary for a species to be unusually stable by virtue of aromaticity.

cyclopentadienyl anion
- **6** π electrons
- contains **4*n* + 2** π **electrons**

aromatic

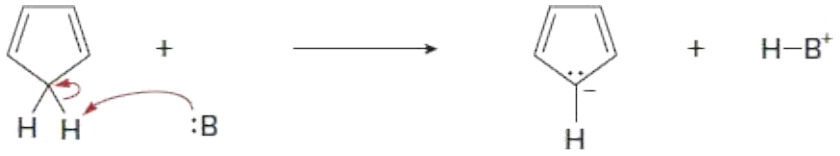
cyclopentadienyl cation
- **4** π electrons
- contains **4*n*** π **electrons**

antiaromatic

cyclopentadienyl radical
- **5** π electrons
- does *not* contain either 4*n* or 4*n* + 2 π electrons

nonaromatic

The cyclopentadienyl anion is readily formed from cyclopentadiene by a Brønsted–Lowry acid–base reaction.



cyclopentadiene
not aromatic
$pK_a = 15$

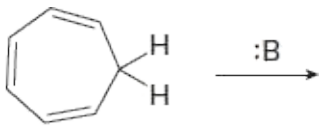
cyclopentadienyl anion
aromatic
a stabilized conjugate base

Cyclopentadiene itself is not aromatic because it is not fully conjugated. The cyclopentadienyl anion, however, is aromatic, so it is a very stable base. As such, it makes cyclopentadiene more acidic than other hydrocarbons. In fact, the pK_a of cyclopentadiene is 15, much *lower* (more acidic) than the pK_a of any C—H bond discussed thus far.

- **Cyclopentadiene is more acidic than many hydrocarbons because its conjugate base is aromatic.**

Problem 15.12

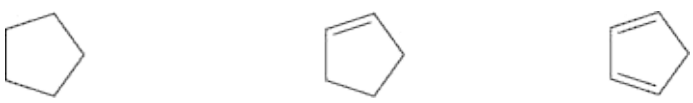
Draw the product formed when cyclohepta-1,3,5-triene (pK_a = 39) is treated with a strong base. Why is its pK_a so much higher than the pK_a of cyclopentadiene?



cyclohepta-1,3,5-triene
$pK_a = 39$

Problem 15.13

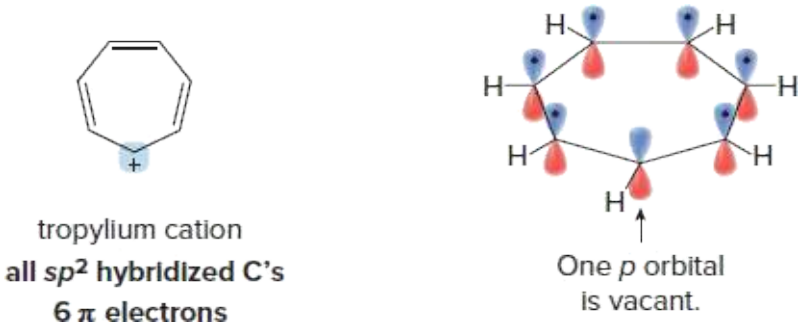
Rank the following compounds in order of increasing acidity.



Tropylium Cation

The tropylium cation is a planar carbocation with three double bonds and a positive charge contained in a seven-membered ring. This carbocation is completely conjugated, because the positively charged carbon is sp^2 hybridized and has a vacant *p* orbital that overlaps with the six *p* orbitals from the carbons of the three double bonds. Because the tropylium cation has three π bonds and no other nonbonded electron pairs, it contains six π electrons, thereby satisfying Hückel's rule.

The cyclopentadienyl anion and the tropylium cation both illustrate an important principle: The number of π electrons determines aromaticity, not the number of atoms in a ring or the number of *p* orbitals that overlap. The cyclopentadienyl anion and tropylium cation are aromatic because they each have six π electrons.



tropylium cation
all sp^2 hybridized C's
6 π electrons

One *p* orbital
is vacant.

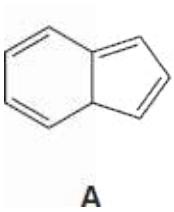
- **The tropylium cation is aromatic because it is cyclic, planar, completely conjugated, and has six π electrons delocalized over the seven atoms of the ring.**

Problem 15.14

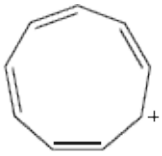
Draw the seven resonance structures for the tropylium cation.

Sample Problem 15.2 Characterizing a Compound as Aromatic, Antiaromatic, or Not Aromatic

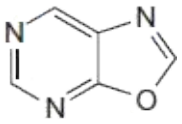
Label each compound as aromatic, antiaromatic, or not aromatic. Assume all completely conjugated rings are planar.



A



B

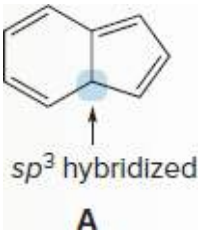


C

Solution

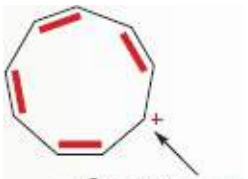
Each compound is cyclic, and from the problem statement, we assume that completely conjugated rings are planar, so we must answer just two questions to decide on aromaticity:

- **Is the compound completely conjugated? If a compound is not completely conjugated, it is *not* aromatic.**
- **How many π electrons does the compound contain? A compound with $4n + 2$ π electrons is *aromatic;* a compound with $4n$ π electrons is *antiaromatic*. A compound with an odd number of π electrons satisfies neither equation and is *not* aromatic.**



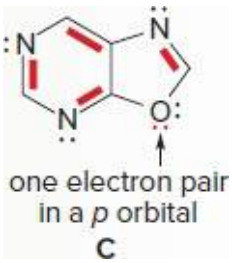
A

- **The C labeled in blue is sp^3 hybridized, so there is orbital for overlap and the system is not compl conjugated. A is not aromatic.**



B

- **The ring is completely conjugated because each C o C=C's and the positively charged C are sp^2 hybridize each C has an unhybridized *p* orbital. The ring has electrons from the four C=C's, so it has $4n$ π electror is antiaromatic.**



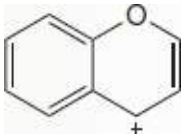
C

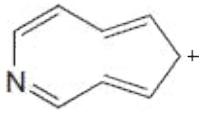
- **For the ring to be completely conjugated, the O a must be sp^2 hybridized and one electron pair on O r occupy a *p* orbital. The ring has 10 π electrons from four C=C's and the O atom, so it has $4n + 2$ π electror is aromatic.**

Problem 15.15

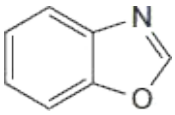
Label each compound as aromatic, antiaromatic or not aromatic. Assume all

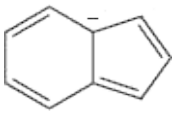
completely conjugated rings are planar.

a. 

b. 

c.

d. 

e. 

More Practice:

Try Problems 15.21, 15.27–15.29.

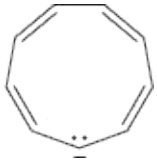
Problem 15.16

Assuming the rings are planar, label each ion as aromatic, antiaromatic, or not aromatic.

a.

b.

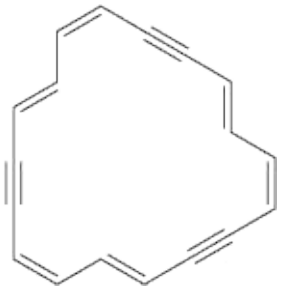
c.

d. 

Problem 15.17

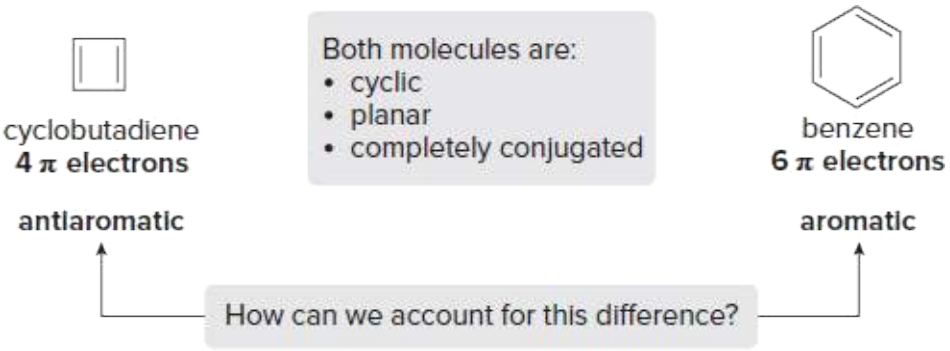
Compound A exhibits a peak in its ^{1}H NMR spectrum at 7.6 ppm, indicating that it is aromatic. (a) How are the carbon atoms of the triple bonds hybridized? (b) In what type of orbitals are the π electrons of the triple bonds contained? (c) How many π electrons are delocalized around the ring in A?

A =



15.9 What Is the Basis of Hückel's Rule?

Why does the number of π electrons determine whether a compound is aromatic? Cyclobutadiene is cyclic, planar, and completely conjugated, just like benzene, but why is benzene aromatic and cyclobutadiene antiaromatic?



A complete explanation is beyond the scope of an introductory organic chemistry text, but nevertheless, you can better understand the basis of aromaticity by learning more about orbitals and bonding.

15.9A Bonding and Antibonding Orbitals

So far we have used these basic concepts to describe how bonds are formed:

- **Hydrogen uses its 1s orbital to form σ bonds with other elements.**
- **Second-row elements use hybrid orbitals (*sp*, sp^2, or sp^3) to form σ bonds.**
- **Second-row elements use *p* orbitals to form π bonds.**

This description of bonding is called valence bond theory. In valence bond theory, a covalent bond is formed by the overlap of two atomic orbitals, and the electron pair in the resulting bond is shared by both atoms. Thus, a carbon–carbon double bond consists of a σ bond, formed by overlap of two sp^2 hybrid orbitals, each containing one electron, and a π bond, formed by overlap of two *p* orbitals, each containing one electron.

This description of bonding works well for most of the organic molecules we have encountered thus far. Unfortunately, it is inadequate for describing systems with many adjacent *p* orbitals that overlap, as there are in aromatic compounds. To more fully explain the bonding in these systems, we must utilize molecular orbital (MO) theory.

MO theory describes bonds as the mathematical combination of atomic orbitals that form a new set of orbitals called molecular orbitals (MOs). A molecular orbital occupies a region of space *in a molecule* where electrons are likely to be found. When forming molecular orbitals from atomic orbitals, keep in mind:

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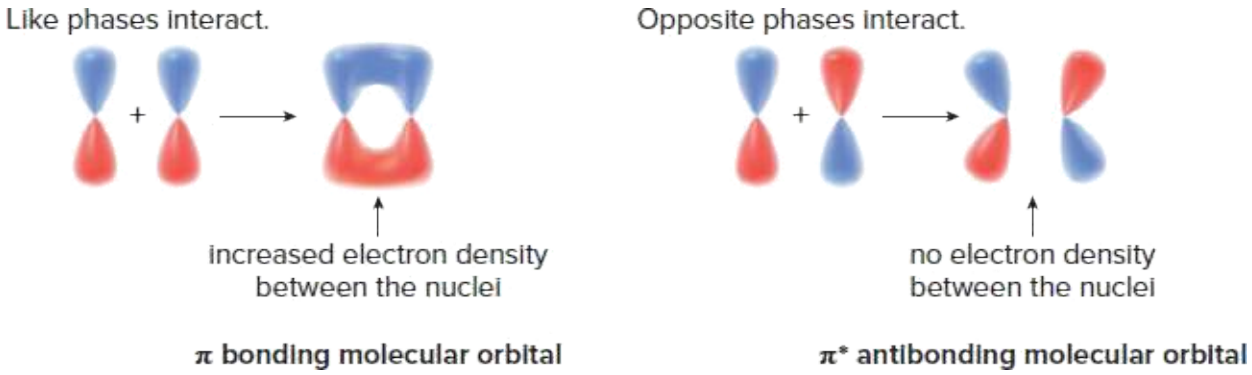
- **A set of *n* atomic orbitals forms *n* molecular orbitals.**

If *two* atomic orbitals combine, *two* molecular orbitals are formed. This is fundamentally different than valence bond theory. Because aromaticity is based on *p* orbital overlap, what does MO theory predict will happen when two *p* (atomic) orbitals combine?

The two lobes of each *p* orbital are opposite in phase, with a node of electron density at the nucleus. When two *p* orbitals combine, two molecular orbitals should form. The two *p* orbitals can add together constructively—that is, with like phases interacting—or destructively—that is, with opposite phases interacting.

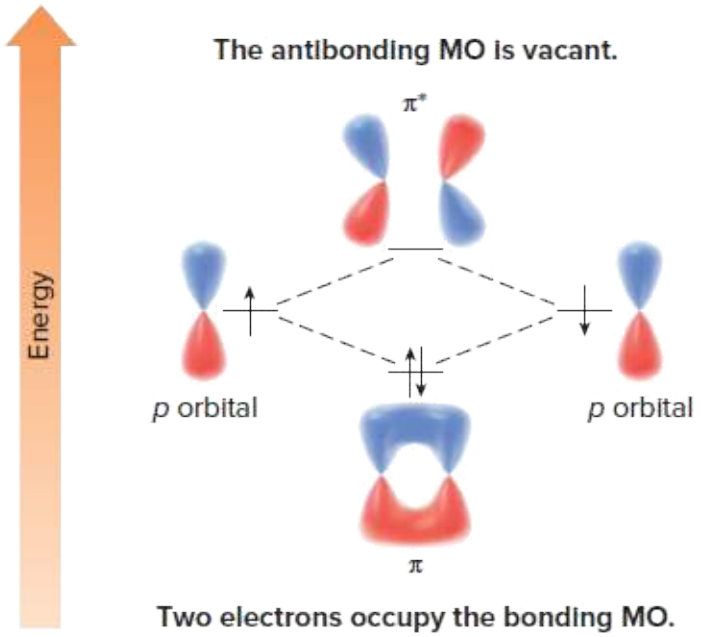


- **When two *p* orbitals of similar phase overlap side-by-side, a π bonding molecular orbital results.**
- **When two *p* orbitals of opposite phase overlap side-by-side, a π* antibonding molecular orbital results.**

A π bonding MO is lower in energy than the two atomic *p* orbitals from which it is formed because a stable bonding interaction results when orbitals of similar phase combine. A bonding interaction holds nuclei together. Similarly, a π* antibonding MO is higher in energy because a destabilizing node results when orbitals of opposite phase

combine. A destabilizing interaction pushes nuclei apart.

If two atomic *p* orbitals each have one electron and then combine to form MOs, the two electrons will occupy the lower-energy π bonding MO, as shown in Figure 15.8.

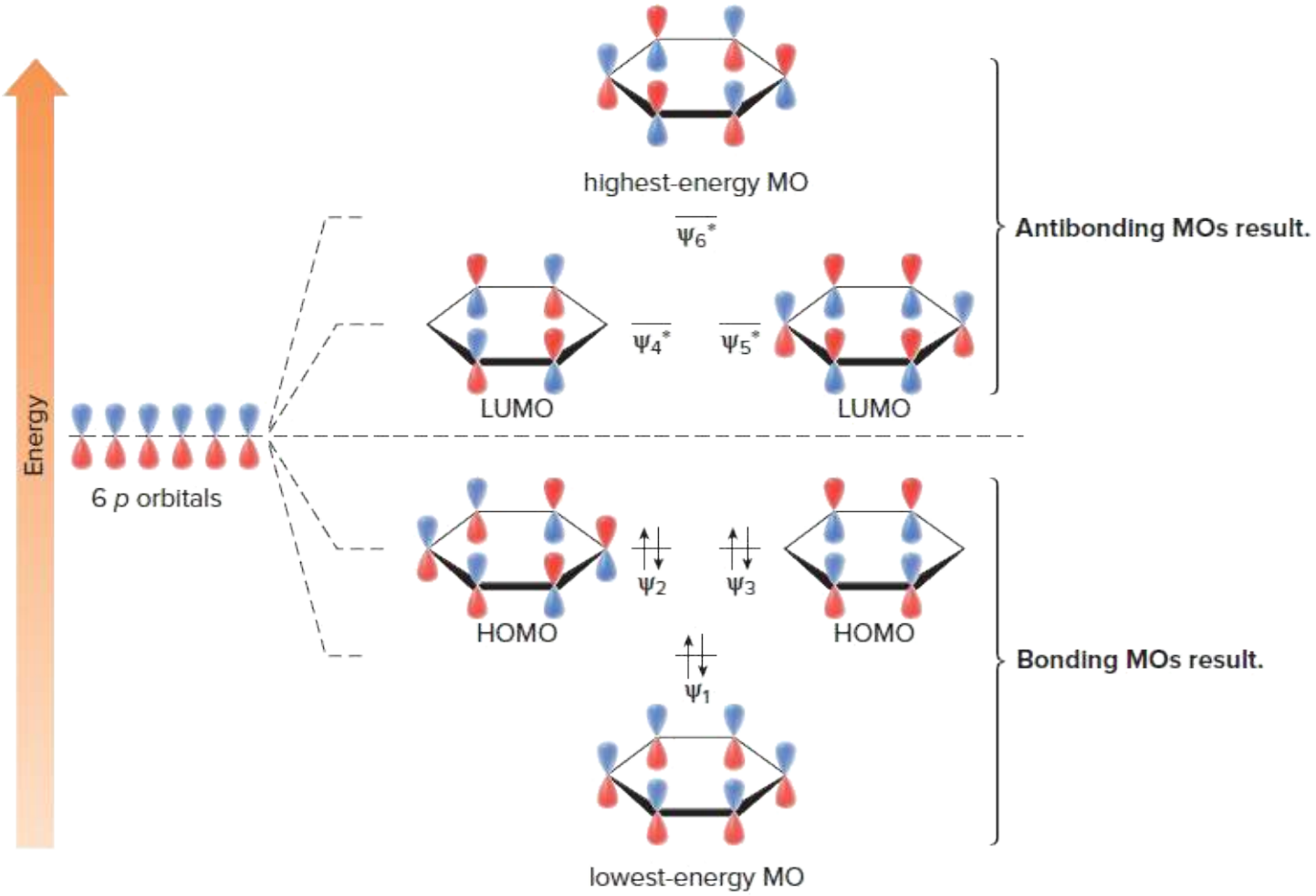


- Two atomic *p* orbitals combine to form two molecular orbitals. The bonding π MO is lower in energy than the two *p* orbitals from which it was formed, and the antibonding π* MO is higher in energy than the two *p* orbitals from which it was formed.
- Two electrons fill the lower-energy bonding MO first.

Figure 15.8 **Combination of two *p* orbitals to form π and π* molecular orbitals**

15.9B Molecular Orbitals Formed When More Than Two *p* Orbitals Combine

The molecular orbital description of benzene is much more complex than the two MOs formed in Figure 15.8. Because each of the six carbon atoms of benzene has a *p* orbital, six atomic *p* orbitals combine to form six π molecular orbitals, as shown in Figure 15.9. A description of the exact appearance and energies of these six MOs requires more sophisticated mathematics and understanding of MO theory than is presented in this text. Nevertheless, note that the six MOs are labeled ψ_1–ψ_6, with ψ_1 being the lowest in energy and ψ_6 the highest.



- Depicted in this diagram are the interactions of the six atomic *p* orbitals of benzene, which form six molecular orbitals. When orbitals of like phase combine, a bonding interaction results. When orbitals of opposite phase combine, a destabilizing node results.

Figure 15.9 **How the six *p* orbitals of benzene overlap to form six molecular orbitals**

The most important features of the six benzene MOs are as follows:

- The larger the number of bonding interactions, the lower in energy the MO.The lowest-energy molecular orbital (ψ_1) has all bonding interactions between the *p* orbitals.
- The larger the number of nodes, the higher in energy the MO. The highest-energy MO (ψ_6^*) has all nodes between the *p* orbitals.
- Three MOs are lower in energy than the starting *p* orbitals, making them bonding MOs (ψ_1, ψ_2, and ψ_3), whereas three MOs are higher in energy than the starting *p* orbitals, making them antibonding MOs (ψ_4^*, ψ_5^*, and ψ_6^*).
- The two pairs of MOs (ψ_2 and ψ_3; ψ_4^* and ψ_5^*) with the same energy are called degenerate orbitals.
- The highest-energy orbital that contains electrons is called the *highest occupied molecular orbital* (HOMO). For benzene, the degenerate orbitals ψ_2 and ψ_3 are

the HOMOs.

- The lowest-energy orbital that does *not* contain electrons is called the *lowest unoccupied molecular orbital* (LUMO). For benzene, the degenerate orbitals ψ_4^* and ψ_5^* are the LUMOs.

To fill the MOs, the six electrons are added, two to an orbital, beginning with the lowest-energy orbital. As a result, the six electrons completely fill the bonding MOs, leaving the antibonding MOs empty. This is what gives benzene and other aromatic compounds their special stability, and this is why six π electrons satisfies Hückel's $4n + 2$ rule.

- **All bonding MOs (and HOMOs) are completely filled in aromatic compounds. No π electrons occupy antibonding MOs.**

15.10 The Inscribed Polygon Method for Predicting Aromaticity

An inscribed polygon is also called a Frost circle.

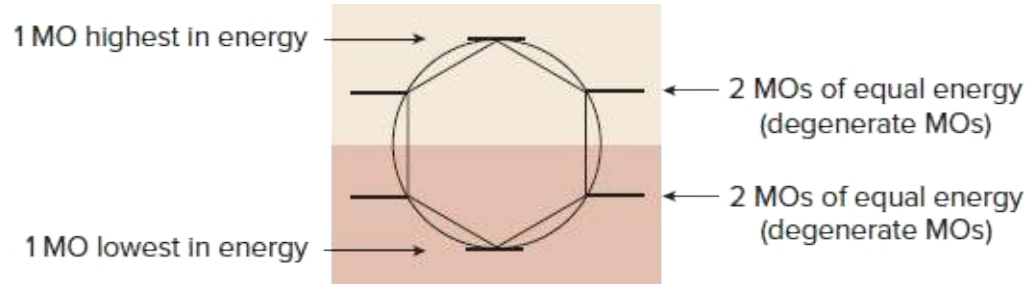
To predict whether a compound has π electrons completely filling bonding MOs, we must know how many bonding molecular orbitals and how many π electrons it has. It is possible to predict the relative energies of cyclic, completely conjugated compounds, without sophisticated math (or knowing what the resulting MOs look like) by using the inscribed polygon method.

How To Use the Inscribed Polygon Method to Determine the Relative Energies of MOs for Cyclic, Completely Conjugated Compounds

Example Plot the relative energies of the MOs of benzene.

Step [1] Draw the polygon in question inside a circle with its vertices touching the circle and one of the vertices pointing down. Mark the points at which the polygon intersects the circle.

- Inscribe a hexagon inside a circle for benzene. The six vertices of the hexagon form six points of intersection, corresponding to the six MOs of benzene. The pattern—a single MO having the lowest energy, two degenerate pairs of MOs, and a single highest-energy MO—matches that found in Figure 15.9.

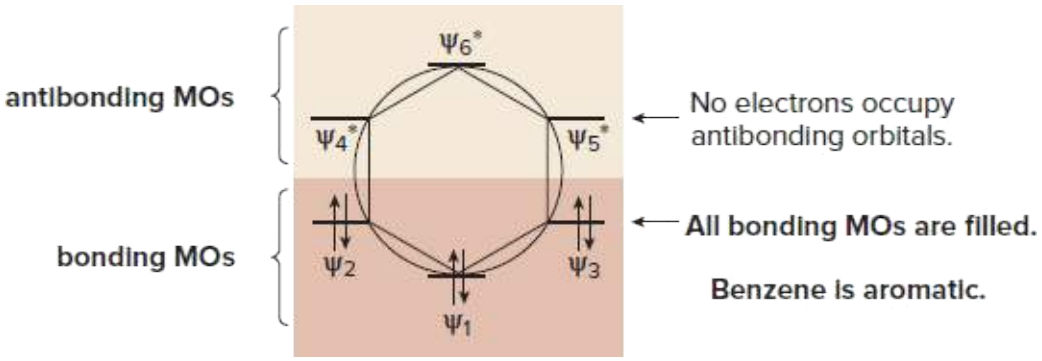


Step [2] **Draw a line horizontally through the center of the circle and label MOs as bonding, nonbonding, or antibonding.**

- **MOs below this line are bonding, and lower in energy than the *p* orbitals from which they were formed. Benzene has three bonding MOs.**
- **MOs at this line are nonbonding, and equal in energy to the *p* orbitals from which they were formed. Benzene has no nonbonding MOs.**
- **MOs above this line are antibonding, and higher in energy than the *p* orbitals from which they were formed. Benzene has three antibonding MOs.**

Step [3] **Add the electrons, beginning with the lowest-energy MO.**

- **All the bonding MOs (and the HOMOs) are completely filled in aromatic compounds. No π electrons occupy antibonding MOs.**
- **Benzene is aromatic because it has six π electrons that completely fill the bonding MOs.**



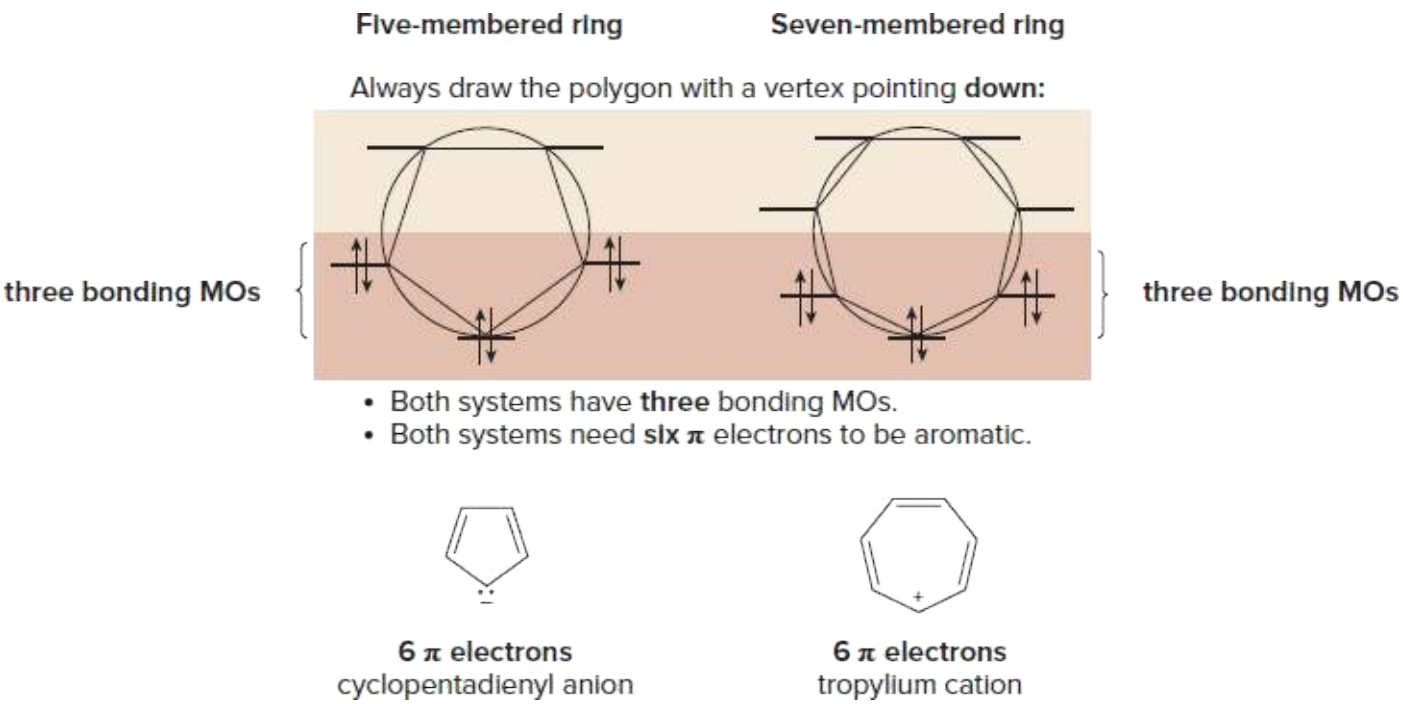


Figure 15.10 **Using the inscribed polygon method for five- and seven-membered rings**

This method works for all monocyclic, completely conjugated hydrocarbons regardless of ring size. Figure 15.10 illustrates MOs for completely conjugated five- and seven-membered rings using this method. The total number of MOs always equals the number of vertices of the polygon. Because both systems have three bonding MOs, each needs six π electrons to fully occupy them, making the cyclopentadienyl anion and the tropylium cation aromatic, as we learned in Section 15.8D.

The inscribed polygon method is consistent with Hückel's $4n + 2$ rule; that is, there is always one lowest-energy bonding MO that can hold two π electrons and the other bonding MOs come in degenerate pairs that can hold a total of four π electrons. For the compound to be aromatic, these MOs must be completely filled with electrons, so the "magic numbers" for aromaticity fit Hückel's $4n + 2$ rule (Figure 15.11).

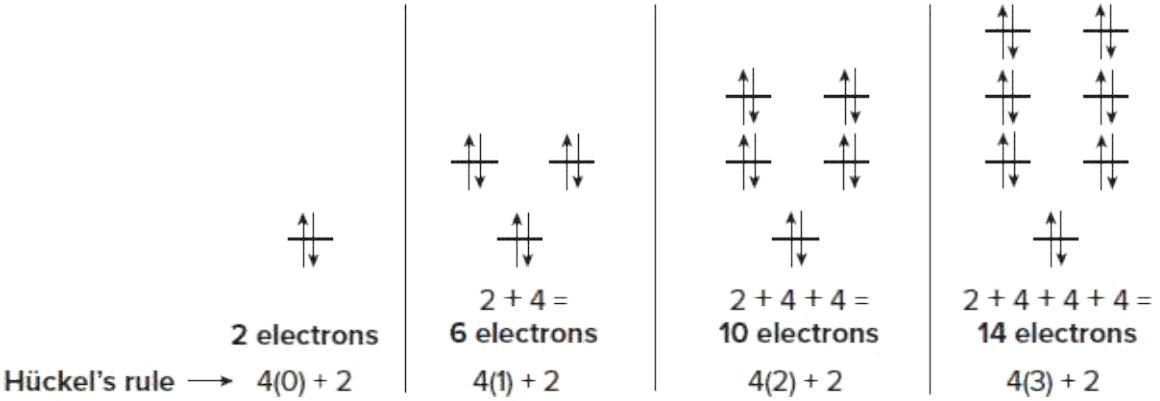


Figure 15.11 **MO patterns for cyclic, completely conjugated systems**

Sample Problem 15.3 Using the Inscribed Polygon Method in Determining Aromaticity

Use the inscribed polygon method to show why cyclobutadiene is not aromatic.

cyclobutadiene
4 π electrons

Solution

Cyclobutadiene has four MOs (formed from its four *p* orbitals), to which its four π electrons must be added.

Step [1] Inscribe a square with a vertex down and mark its four points of intersection with the circle.

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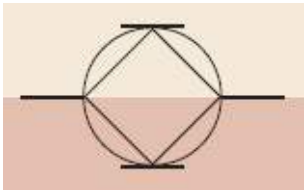
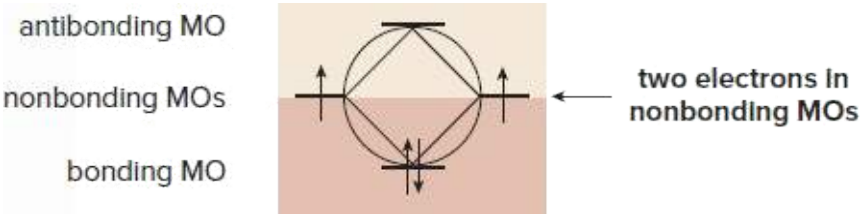


- **The four points of intersection correspond to the four MOs of cyclobutadiene.**

Steps [2] and [3] Draw a line through the center of the circle, label the MOs, and add the electrons.



- **Cyclobutadiene has four MOs—one bonding, two nonbonding, and one antibonding.**
- **Adding cyclobutadiene's four π electrons to these orbitals places two in the lowest-energy bonding MO and one each in the two nonbonding MOs.**
- **Separating electrons in two degenerate MOs keeps like charges farther away from each other.**

Conclusion: Cyclobutadiene is not aromatic because its HOMOs, two

degenerate nonbonding MOs, are not completely filled.

Problem 15.18

Use the inscribed polygon method to show why the following cation is aromatic.

More Practice:

Try Problems 15.48, 15.49.

Problem 15.19

Use the inscribed polygon method to show why the cyclopentadienyl cation and radical are not aromatic.

The procedure followed in Sample Problem 15.3 also illustrates why cyclobutadiene is antiaromatic. Having the two unpaired electrons in nonbonding MOs suggests that cyclobutadiene should be a highly unstable diradical. In fact, antiaromatic compounds resemble cyclobutadiene because their HOMOs contain two unpaired electrons, making them especially unstable.

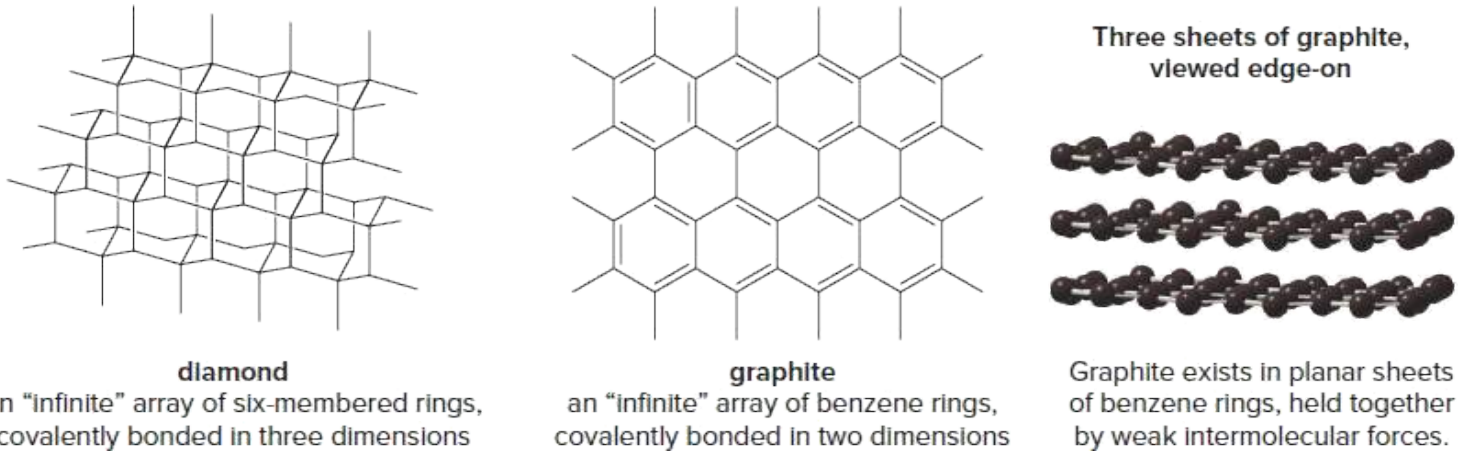
15.11 Buckminsterfullerene—Is It Aromatic?

The two most common elemental forms of carbon are diamond and graphite. Diamond, one of the hardest substances known, is used for industrial cutting tools, whereas graphite, a slippery black substance, is used as a lubricant. Their physical characteristics are so different because their molecular structures are very different.

The structure of diamond consists of a continuous tetrahedral network of sp^3 hybridized carbon atoms, thus creating an infinite array of chair cyclohexane rings. The structure of graphite, on the other hand, consists of parallel sheets of sp^2 hybridized carbon atoms, thus creating an infinite array of benzene rings. The parallel sheets are then held together by weak intermolecular interactions.

Diamond and graphite are two elemental forms of carbon.

(Top): ©merial/Getty Images; (bottom): ©Siim Sepp/Alamy Stock Photo



diamond
an "infinite" array of six-membered rings, covalently bonded in three dimensions

graphite
an "infinite" array of benzene rings, covalently bonded in two dimensions

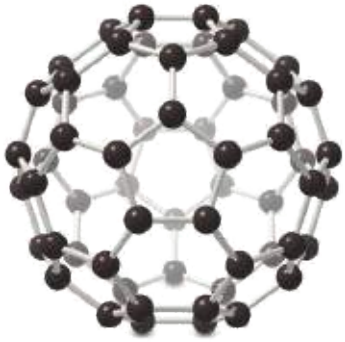
Graphite exists in planar sheets of benzene rings, held together by weak intermolecular forces.

Buckminsterfullerene (C_{60}) is a third elemental form of carbon. Its structure consists of 20 hexagons and 12 pentagons of sp^2 hybridized carbon atoms joined in a spherical arrangement. It is completely conjugated because each carbon atom has a *p* orbital with an electron in it.

Buckminsterfullerene (or buckyball) was discovered by

Smalley, Curl, and Kroto, who shared the 1996 Nobel Prize in Chemistry for their work. Its unusual name stems from its shape, which resembles the geodesic dome invented by R. Buckminster Fuller. The pattern of five- and six-membered rings also resembles the pattern of rings on a soccer ball.

©Atomic Imagery/Getty Images



buckminsterfullerene, C_{60}

20 hexagons + 12 pentagons
of carbon atoms joined together

The 60 C's of buckminsterfullerene are drawn. Each C also contains a *p* orbital with one electron, which is not drawn.

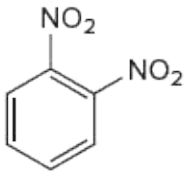
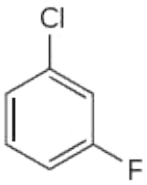
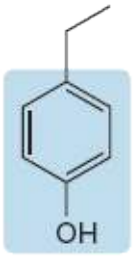
Is C_{60} aromatic? Although it is completely conjugated, it is not planar. Because of its curvature, it is not as stable as benzene. In fact, it undergoes addition reactions with electrophiles in much the same way as ordinary alkenes. Benzene, on the other hand, undergoes substitution reactions with electrophiles, which preserves the unusually stable benzene ring intact. These reactions are the subject of Chapter 16.

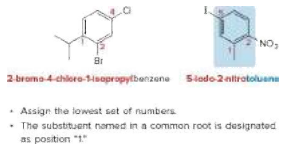
Chapter 15 REVIEW

KEY CONCEPTS

[1] Nomenclature of disubstituted and trisubstituted benzenes (15.3)

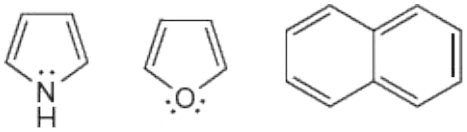
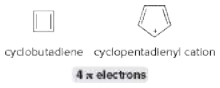
1 **Naming disubstituted benzenes**	2 **Naming trisubstitut benzenes**

1,2-disubstituted benzene **ortho** isomer	1,3-disubstituted benzene **meta** isomer	1,4-disubstituted benzene **para** isomer
		
o-dinitrobenzene **1,2**-dinitrobenzene	*m*-chlorofluorobenzene **1**-chloro-**3**-fluorobenzene	*p*-ethylphenol **4**-ethylphenol
	Alphabetize substituent names.	**using a common name**



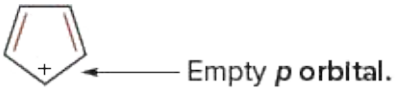
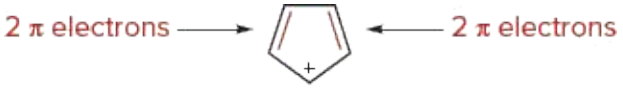
Try Problems 15.20, 15.23, 15.25b.

[2] Examples of aromatic, nonaromatic, and antiaromatic compounds (15.7, 15.8)

1 Aromatic compounds	**2** Nonaromatic compounds	**3** Antiaro compo
		
pyrrole furan naphthalene	**not cyclic** **not completely conjugated** **not planar**	cyclobutadiene cyclopentadienyl cation
6 π electrons **10 π electrons**		**4 π electrons**

KEY SKILLS

[1] Determining if a cyclic, planar compound is aromatic, antiaromatic, or not aromatic (15.7, 15.8); example: cyclopentadienyl cation

1 Determine if the molecule is completely conjugated.	**2** Check if the molecule satisfies Hückel's rule.
	
Empty *p* orbital.	2 π electrons 2 π electrons
cyclopentadienyl cation	$4n$ π electrons, where $n = 1$.
The electrons in bonds shown in red reside in *p* orbitals.	**4 π electrons**
The cyclopentadienyl cation is **completely conjugated.**	

- **Aromatic and antiaromatic compounds must have a *p* orbital on every atom in the ring.**

- **Antiaromatic compounds must contain $4n$ π electrons (n = 0, 1, 2, and so forth).**

Answer: antiaromatic

See Sample Problem 15.2. Try Problems 15.21, 15.27–15.29.

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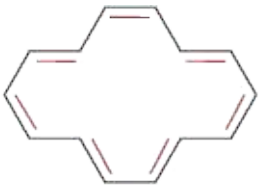
[2] Determining if a planar compound is aromatic, antiaromatic, or not aromatic (15.7, 15.8); example: [14]-annulene

1 Determine if the molecule is completely conjugated.



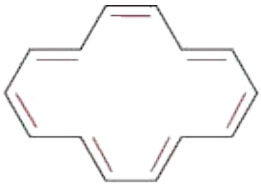
[14]-annulene

The electrons in bonds shown in red reside in *p* orbitals.

[14]-Annulene is **completely conjugated.**

- **Aromatic and antiaromatic compounds must have a *p* orbital on every atom in the ring.**

2 Check if the molecule satisfies Hückel's rule.



$4n + 2$ π electrons, where $n = 3$.

14 π electrons

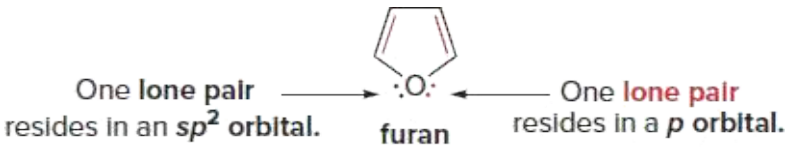
- **Aromatic compounds must contain $4n + 2$ π electrons (n = 0, 1, 2, and so forth).**

Answer: aromatic

See Sample Problem 15.2, Table 15.2. Try Problems 15.21, 15.27–15.29.

[3] Determining if a planar heterocyclic compound is aromatic, antiaromatic, or not aromatic (15.7, 15.8); example: furan

1 Determine if the molecule is completely conjugated.

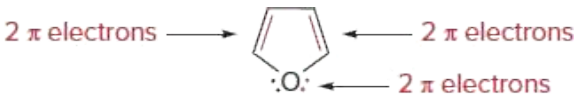


The electrons in bonds shown in red reside in *p* orbitals.

Furan is **completely conjugated.**

- **Count a nonbonded electron pair if it makes the ring aromatic in**

2 Check if the molecule satisfies Hückel's rule.



$4n + 2$ π electrons, where $n = 1$.

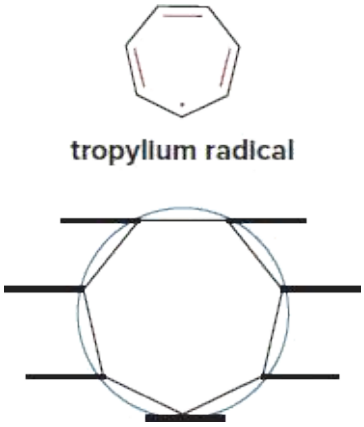
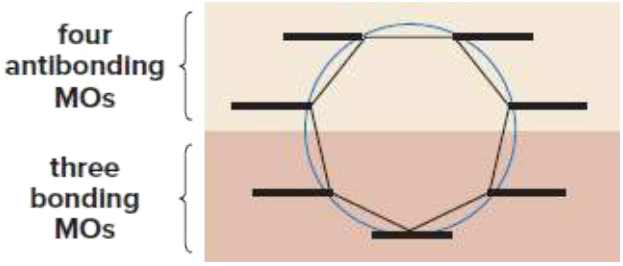
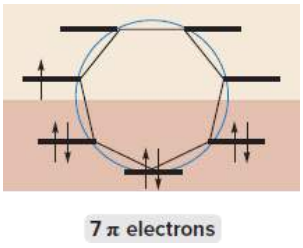
6 π electrons

- **Aromatic compounds must contain $4n + 2$ π**

calculating $4n + 2$.	electrons (n = 0, 1, 2, and so forth). **Answer: aromatic**

See Sample Problems 15.1, 15.2. Try Problems 15.21b, c; 15.28; 15.29f; 15.32d; 15.57a; 15.58b; 15.60a.

[4] Using the inscribed polygon method to determine if a compound is aromatic (15.10); example: the tropylium radical

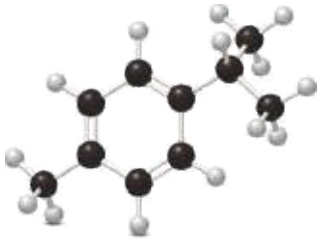
1 Draw the inscribed polygon with the vertex pointing down.	2 Label the molecular orbitals.	3 Add the electrons.
		
• Mark the points at which the polygon intersects the circle.	• Draw a line horizontally through the center of the circle, and label MOs as bonding, nonbonding, or antibonding.	• The bonding MOs are completely filled, and a single π electron occupies an antibonding MO. **Answer: not aromatic**

PROBLEMS

Problems Using Three-Dimensional Models

15.20 Name each compound and state how many lines are observed in its ^{13}C NMR spectrum.

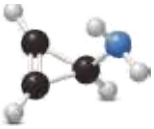
a.



b.

15.21 Classify each compound as aromatic, antiaromatic, or not aromatic.

a.



b.

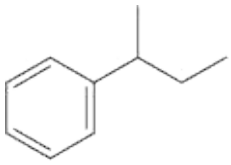
c.

Benzene Structure and Nomenclature

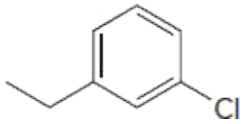
15.22 Draw all aromatic hydrocarbons that have molecular formula C_8H_{10}. For each compound, determine how many isomers of molecular formula C_8H_9Br would be formed if one H atom on the benzene ring were replaced by a Br atom.

15.23 Give the IUPAC name for each compound.

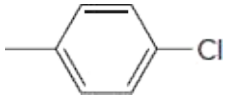
a.



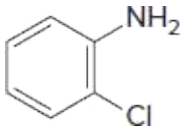
b.



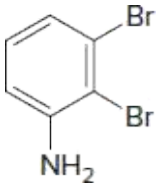
c.



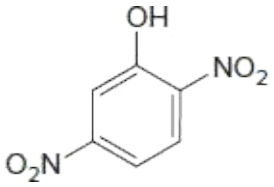
d.



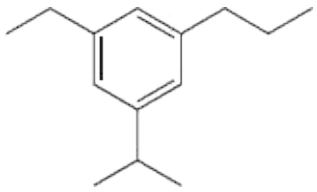
e.



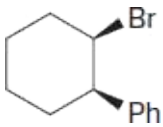
f.



g.



h.



15.24 Draw a structure corresponding to each name.

a. *p*-dichlorobenzene

b. *p*-iodoaniline

c. *o*-bromonitrobenzene

d. 2,6-dimethoxytoluene

e. 2-phenylprop-2-en-1-ol

f. *trans*-1-benzyl-3-phenylcyclopentane

15.25 a. Draw the 14 constitutional isomers of molecular formula C_8H_9Cl that contain a benzene ring.

b. Name all compounds that contain a trisubstituted benzene ring.

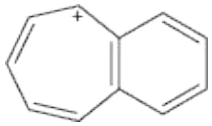
c. For which compound(s) are stereoisomers possible? Draw all possible stereoisomers.

Aromaticity

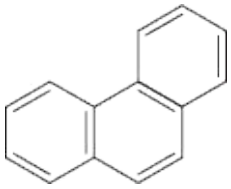
15.26 How many π electrons are contained in each molecule?

a.

b.

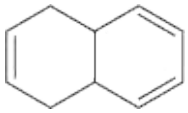


c.



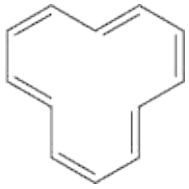
15.27 Which compounds are aromatic? For any compound that is not aromatic, state why this is so.

a.

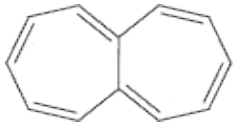


b.

c.

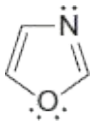


d.

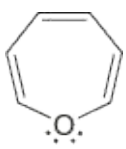


15.28 Label each heterocycle as aromatic, antiaromatic, or not aromatic.

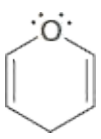
a.



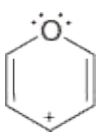
b.



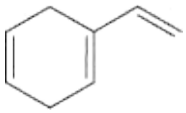
c.

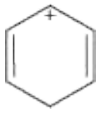


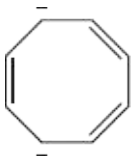
d.

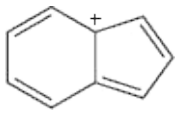


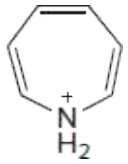
15.29 Label each compound as aromatic, antiaromatic, or not aromatic. Assume all completely conjugated rings are planar.

a. 

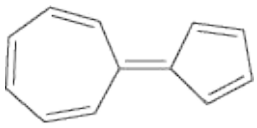
b. 

c. 

d. 

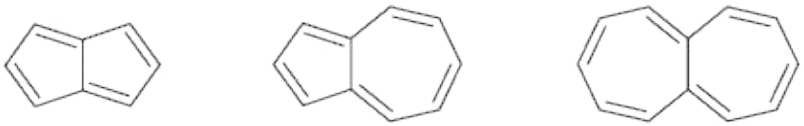
e. 

15.30 Hydrocarbon A possesses a significant dipole, even though it is composed of only C—C and C—H bonds. Explain why the dipole arises and use resonance structures to illustrate the direction of the dipole. Which ring is more electron rich?



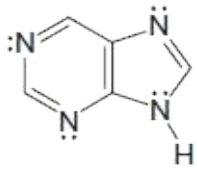
A

15.31 Pentalene, azulene, and heptalene are conjugated hydrocarbons that do not contain a benzene ring. Which hydrocarbons are especially stable or unstable based on the number of π electrons they contain? Explain your choices.



pentalene azulene heptalene

15.32 The purine heterocycle occurs commonly in the structure of DNA.



purine

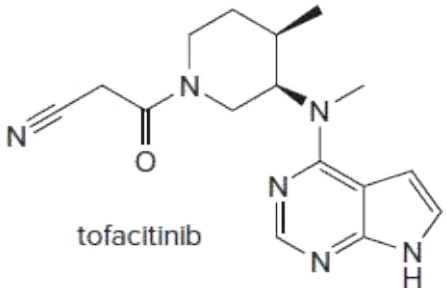
a. How is each N atom hybridized?

b. In what type of orbital does each lone pair on a N atom reside?

c. How many π electrons does purine contain?

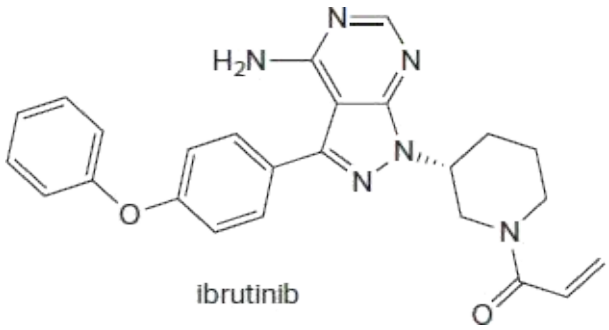
d. Why is purine aromatic?

15.33 **(a) Determine the hybridization of each N atom in tofacitinib, a drug used to treat rheumatoid arthritis. (b) In what type of orbital does the lone pair on each N atom reside?**



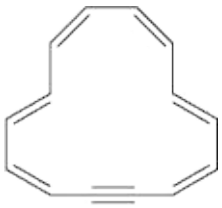
tofacitinib

15.34 **(a) Determine the hybridization of each N atom in ibrutinib, a drug used to treat mantle cell lymphoma and chronic lymphocytic leukemia. (b) In what type of orbital does the lone pair on each N atom reside? (c) How many sp^2 hybridized atoms does ibrutinib contain?**



ibrutinib

15.35



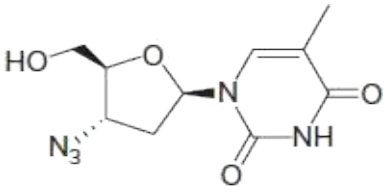
C

a. How many π electrons does C contain?

b. How many π electrons are delocalized in the ring?

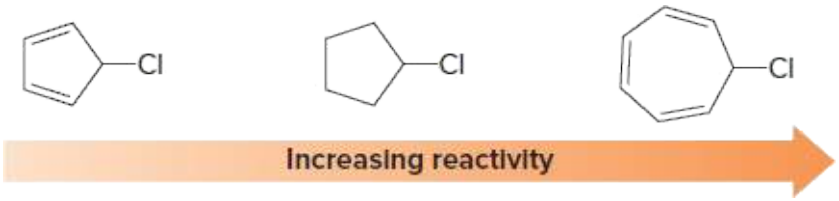
c. Explain why C is aromatic.

15.36 **AZT was the first drug approved to treat HIV, the virus that causes AIDS. Explain why the six-membered ring of AZT is aromatic.**

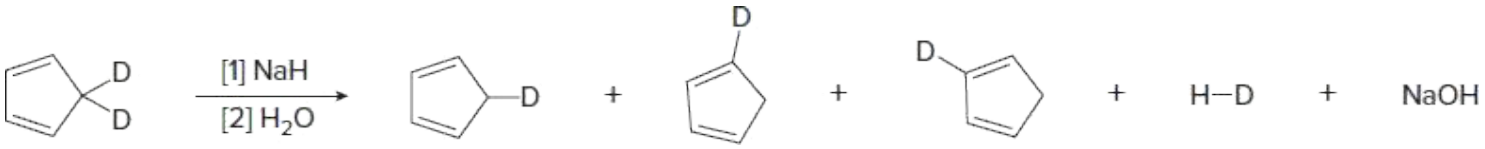


AZT

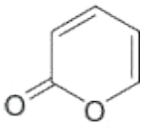
15.37 Explain the observed rate of reactivity of the following 2° alkyl halides in an S_N1 reaction.



15.38 Draw a stepwise mechanism for the following reaction.



15.39 Explain why α-pyrone reacts with Br_2 to yield a substitution product (like benzene does), rather than an addition product to one of its C=C bonds.



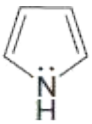
α-pyrone

Resonance

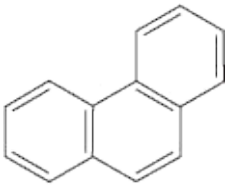
15.40 Draw additional resonance structures for each species.

a.

cyclopropenyl radical

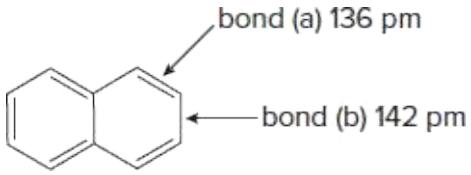
b. 

pyrrole

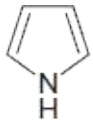
c. 

phenanthrene

15.41 **The carbon–carbon bond lengths in naphthalene are not equal. Use a resonance argument to explain why bond (a) is shorter than bond (b).**



15.42



pyrrole

furan

a. Draw all reasonable resonance structures for pyrrole, and explain why pyrrole is less resonance stabilized than benzene.

b. Draw all reasonable resonance structures for furan, and explain why furan is less resonance stabilized than pyrrole.

Acidity

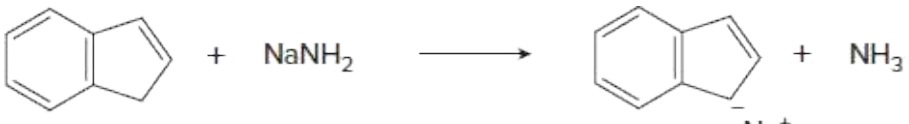
15.43 **Rank the following compounds in order of increasing acidity.**

A

B

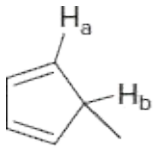
C

15.44 **Treatment of indene with $NaNH_2$ forms its conjugate base in a Brønsted–Lowry acid–base reaction. Draw all reasonable resonance structures for indene's conjugate base, and explain why the pK_a of indene is lower than the pK_a of most hydrocarbons.**

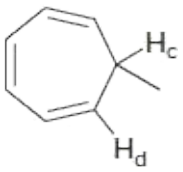


Indene
$pK_a = 20$

15.45 **Considering both 5-methylcyclopenta-1,3-diene (A) and 7-methylcyclohepta-1,3,5-triene (B), which labeled H atom is most acidic? Which labeled H atom is least acidic? Explain your choices.**



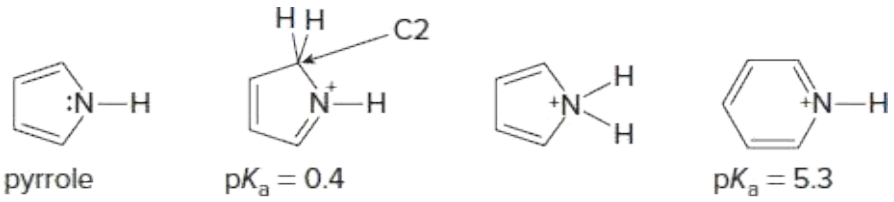
A



B

15.46 **Draw the conjugate bases of pyrrole and cyclopentadiene. Explain why the sp^3 hybridized C—H bond of cyclopentadiene is more acidic than the N —H bond of pyrrole.**

15.47 **a. Explain why protonation of pyrrole occurs at C2 to form A, rather than on the N atom to form B. b. Explain why A is more acidic than C, the conjugate acid of pyridine.**

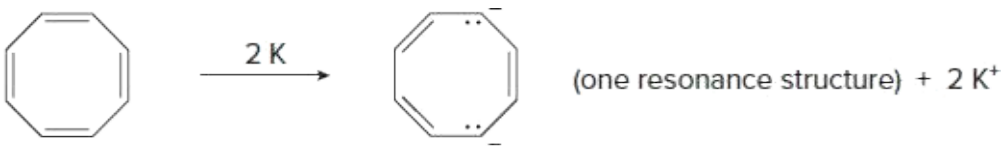


pyrrole $pK_a = 0.4$ $pK_a = 5.3$

A B C

Inscribed Polygon Method

15.48 **Use the inscribed polygon method to show the pattern of molecular orbitals in cyclooctatetraene.**



cyclooctatetraene dianion of cyclooctatetraene

a. Label the MOs as bonding, antibonding, or nonbonding.

b. Indicate the arrangement of electrons in these orbitals for cyclooctatetraene, and explain why cyclooctatetraene is not aromatic.

c. Treatment of cyclooctatetraene with potassium forms a dianion. How many π electrons does this dianion contain?

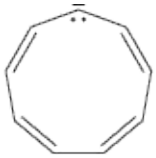
d. How are the π electrons in this dianion arranged in the molecular orbitals?

e. Classify the dianion of cyclooctatetraene as aromatic, antiaromatic, or not aromatic, and explain why this is so.

15.49 **Use the inscribed polygon method to show the pattern of molecular orbitals in cyclonona-1,3,5,7-tetraene, and use it to label its cation, radical, and anion as aromatic, antiaromatic, or not aromatic.**

cyclononatetraenyl cation

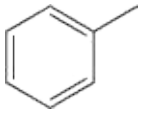
cyclononatetraenyl radical

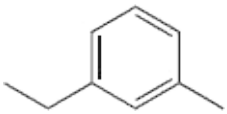


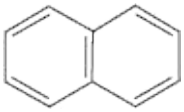
cyclononatetraenyl anion

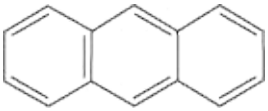
Spectroscopy

15.50 **How many ^{13}C NMR signals does each compound exhibit?**

a. 

b. 

c. 

d. 

15.51 **Which of the diethylbenzene isomers (ortho, meta, or para) corresponds to each set of ^{13}C NMR spectral data?**

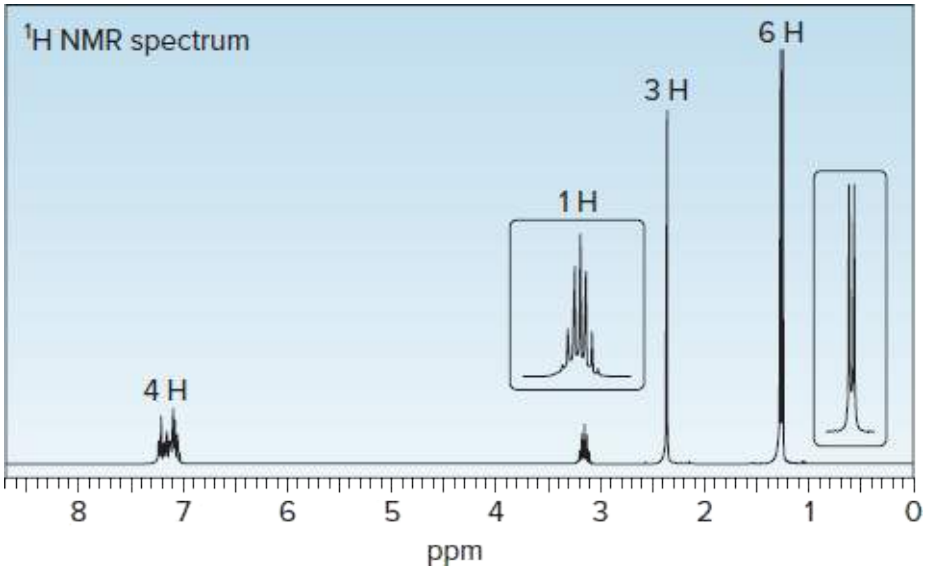
[A] ^{13}C NMR signals: 16, 29, 125, 127.5, 128.4, and 144 ppm

[B] ^{13}C NMR signals: 15, 26, 126, 128, and 142 ppm

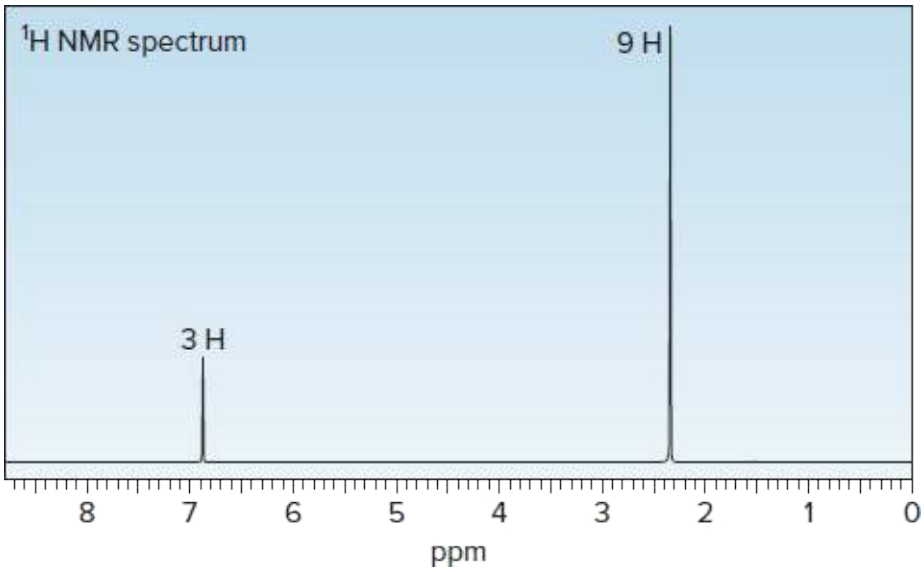
[C] ^{13}C NMR signals: 16, 29, 128, and 141 ppm

15.52 **Propose a structure consistent with each set of data.**

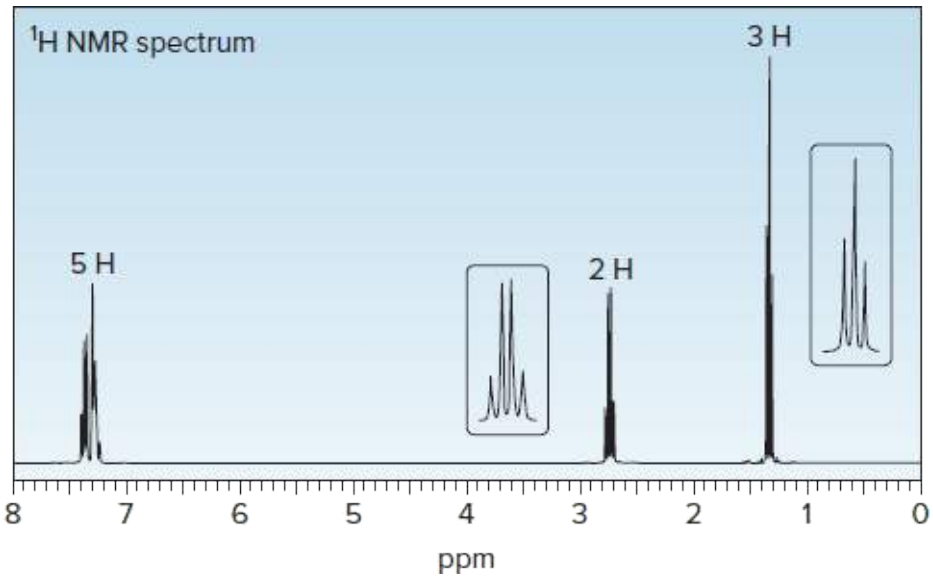
a. **$C_{10}H_{14}$: IR absorptions at 3150–2850, 1600, and 1500 cm^{-1}**



b. C_9H_{12}: ^{13}C NMR signals at 21, 127, and 138 ppm



c. C_8H_{10}: IR absorptions at 3108–2875, 1606, and 1496 cm^{-1}



15.53 Propose a structure consistent with each set of data.

a. Compound A:

Molecular formula: $C_8H_{10}O$

IR absorption at 3150−2850 cm^{-1}

^1H NMR data: 1.4 (triplet, 3 H), 3.95 (quartet, 2 H), and 6.8–7.3 (multiplet, 5 H) ppm

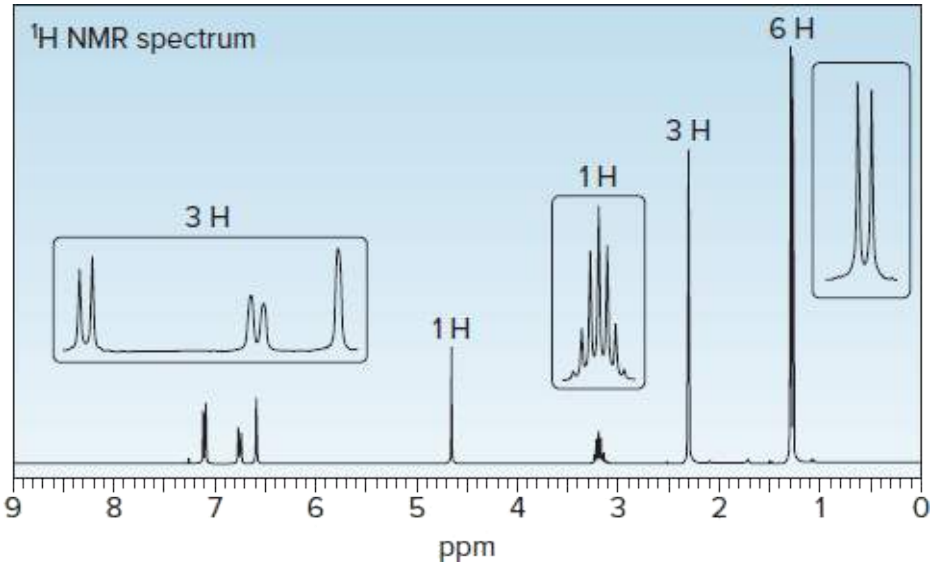
b. Compound B:

Molecular formula: $C_9H_{10}O_2$

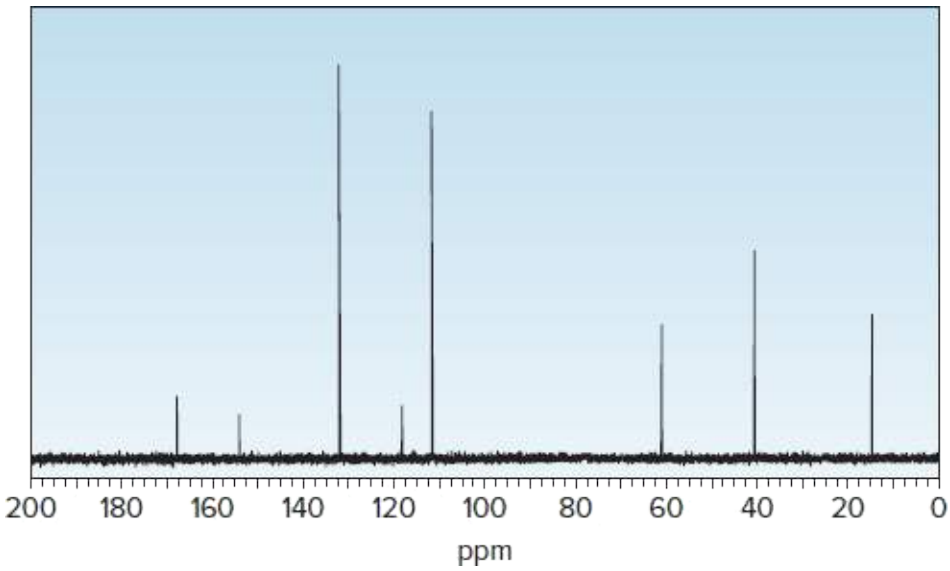
IR absorption at 1669 cm^{-1}

^1H NMR data: 2.5 (singlet, 3 H), 3.8 (singlet, 3 H), 6.9 (doublet, 2 H), and 7.9 (doublet, 2 H) ppm

15.54 **Thymol (molecular formula $C_{10}H_{14}O$) is the major component of the oil of thyme. Thymol shows IR absorptions at 3500–3200, 3150–2850, 1621, and 1585 cm^{-1}. The ^1H NMR spectrum of thymol is given below. Propose a possible structure for thymol.**



15.55 **You have a sample of a compound of molecular formula $C_{11}H_{15}NO_2$, which has a benzene ring substituted by two groups, $(CH_3)_2N-$ and $-CO_2CH_2CH_3$, and exhibits the given ^{13}C NMR. What disubstituted benzene isomer corresponds to these ^{13}C data?**



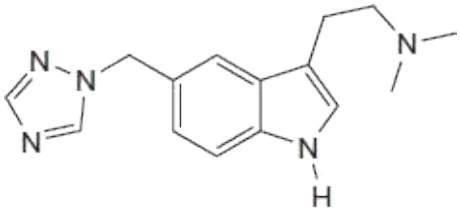
General Problems

15.56 **Explain why tetrahydrofuran has a higher boiling point and is much more water soluble than furan, even though both compounds are cyclic ethers containing four carbons.**

tetrahydrofuran

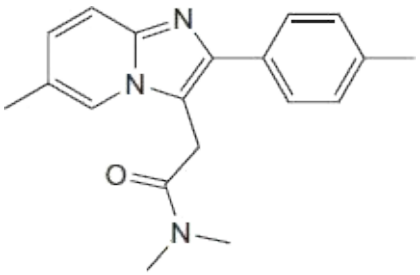
furan

15.57 **Rizatriptan (trade name Maxalt) is a prescription drug used for the treatment of migraines. (a) How many aromatic rings does rizatriptan contain? (b) Determine the hybridization of each N atom. (c) In what type of orbital does the lone pair on each N reside? (d) Draw all the resonance structures for rizatriptan that contain only neutral atoms. (e) Draw all reasonable resonance structures for the five-membered ring that contains three N atoms.**



rizatriptan

15.58 **Zolpidem (trade name Ambien) promotes the rapid onset of sleep, making it a widely prescribed drug for treating insomnia.**



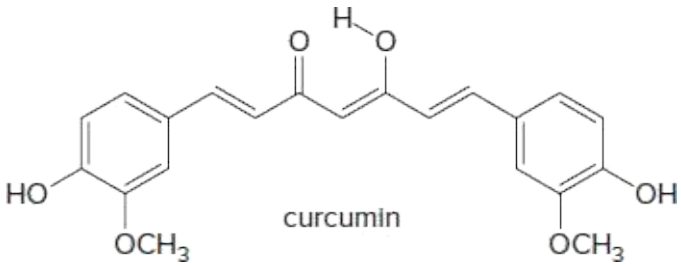
zolpidem

a. **In what type of orbital does the lone pair on each N atom in the heterocycle reside?**

b. **Explain why the bicyclic ring system that contains both N atoms is aromatic.**

c. **Draw all reasonable resonance structures for the bicyclic ring system.**

15.59 Answer the following questions about curcumin, a yellow pigment isolated from turmeric, a tropical perennial in the ginger family and a principal ingredient in curry powder.



curcumin

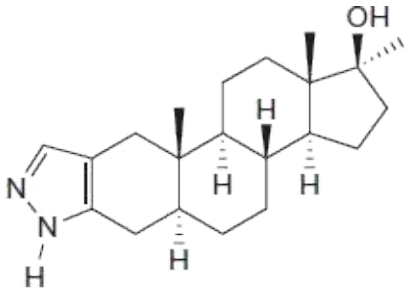
a. **In Chapter 11, we learned that most enols, compounds that contain a hydroxy group bonded to a C=C, are unstable and tautomerize to carbonyl groups. Draw the keto form of the enol of curcumin, and explain why the enol is more stable than many other enols.**

b. **Explain why the enol O—H proton is more acidic than an alcohol O—H proton.**

c. **Why is curcumin colored?**

d. **Explain why curcumin is an antioxidant.**

15.60 Stanozolol is an anabolic steroid that promotes muscle growth. Although stanozolol has been used by athletes and body builders, many physical and psychological problems result from prolonged use and it is banned in competitive sports.



stanozolol

a. **Explain why the nitrogen heterocycle—a pyrazole ring—is aromatic.**

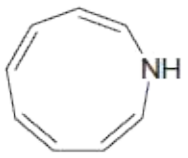
b. **In what type of orbital is the lone pair on each N atom contained?**

c. **Draw all reasonable resonance structures for stanozolol.**

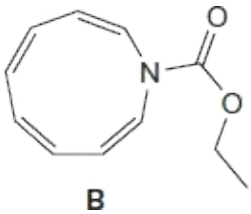
d. **Explain why the pK_a of the N—H bond in the pyrazole ring is comparable to the pK_a of the O—H bond, making it considerably more acidic than amines such as CH_3NH_2 (pK_a = 40).**

Challenge Problems

15.61 **Explain why A is aromatic but B is not aromatic.**



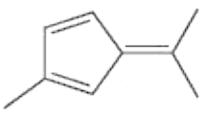
A



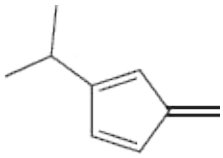
B

Page 724

15.62 **(a) Which proton in A is most acidic? (b) Decide whether A is more or less acidic than B, and explain your choice.**

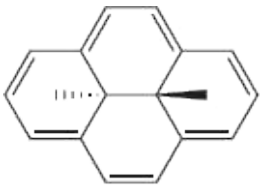


A



B

15.63 **Use the observed ^{1}H NMR data to decide whether C and its dianion are aromatic, antiaromatic, or not aromatic. C shows NMR signals at −4.25 (6 H) and 8.14–8.67 (10 H) ppm. The dianion of C shows NMR signals at −3 (10 H) and 21 (6 H) ppm. Why are the signals shifted upfield (or downfield) to such a large extent?**

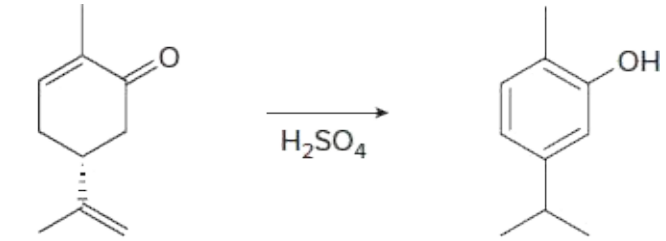


C

15.64 Explain why compound A is much more stable than compound B.

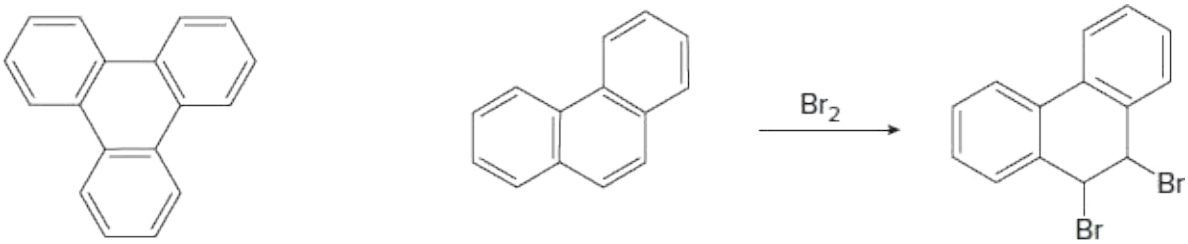
A B

15.65 (*R*)-Carvone, the major component of the oil of spearmint, undergoes acid-catalyzed isomerization to carvacrol, a major component of the oil of thyme. Draw a stepwise mechanism and explain why this isomerization occurs.



(*R*)-carvone carvacrol

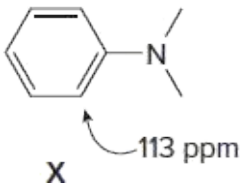
15.66 Explain why triphenylene resembles benzene in that it does not undergo addition reactions with Br_2, but phenanthrene reacts with Br2 to yield the addition product drawn. (Hint: Draw resonance structures for both triphenylene and phenanthrene, and use them to determine how delocalized each π bond is.)



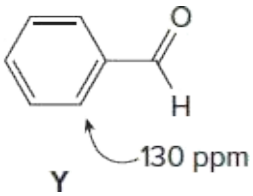
triphenylene phenanthrene

15.67 Although benzene itself absorbs at 128 ppm in its ^{13}C NMR spectrum, the carbons of substituted benzenes absorb either upfield or downfield from this value depending on the substituent. Explain the observed values for the carbon ortho to the given substituent in the

monosubstituted benzene derivatives X and Y.

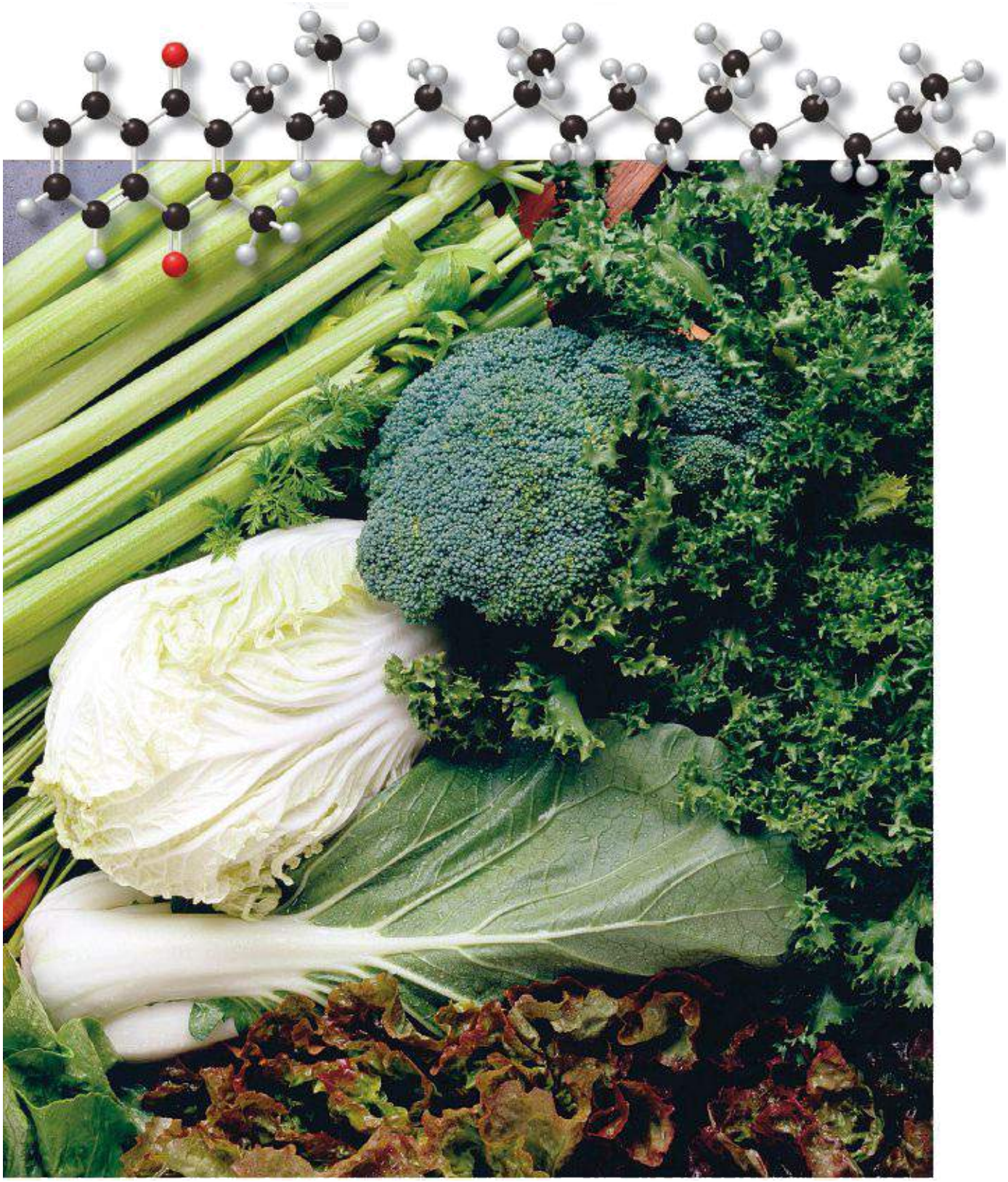


X



Y

16 Reactions of Aromatic Compounds



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16.1 Electrophilic aromatic substitution

16.2 The general mechanism

16.3 Halogenation

16.4 Nitration and sulfonation

16.5 Friedel–Crafts alkylation and Friedel–Crafts acylation

16.6 Substituted benzenes

16.7 Electrophilic aromatic substitution of substituted benzenes

16.8 Why substituents activate or deactivate a benzene ring

16.9 Orientation effects in substituted benzenes

16.10 Limitations on electrophilic substitution reactions with substituted benzenes

16.11 Disubstituted benzenes

16.12 Synthesis of benzene derivatives

16.13 Nucleophilic aromatic substitution

16.14 Halogenation of alkyl benzenes

16.15 Oxidation and reduction of substituted benzenes

16.16 Multistep synthesis

Vitamin K_1, phylloquinone, is a fat-soluble vitamin that regulates the synthesis of proteins needed for blood to clot. Dietary sources of vitamin K_1 include cauliflower, broccoli, soybeans, leafy greens, and green tea. A severe deficiency of vitamin K_1 leads to excessive and sometimes fatal bleeding because of inadequate blood clotting. Vitamin K_1 is synthesized by a biological Friedel–Crafts reaction, one of the many examples of electrophilic aromatic substitution, a key reaction of aromatic compounds presented in Chapter 16.

Why Study…

Reactions of Aromatic Compounds?

Chapter 16 discusses the chemical reactions of benzene and other aromatic compounds. Although aromatic rings are unusually stable, making benzene unreactive in most of the reactions discussed so far, benzene acts as a nucleophile with certain electrophiles, yielding substitution products with an intact aromatic ring.

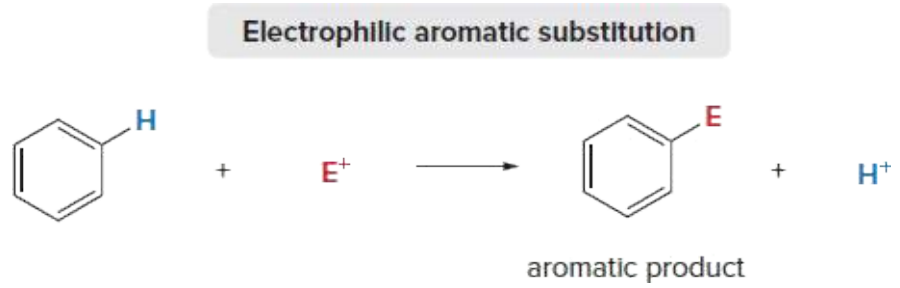
We begin with the basic features and mechanism of electrophilic aromatic substitution (Sections 16.1–16.5), the most prevalent reaction of benzene. Next, we discuss the electrophilic aromatic substitution of substituted benzenes (Sections 16.6–16.12), and conclude with nucleophilic aromatic substitution and other useful reactions of benzene derivatives (Sections 16.13–16.15). These reactions have been used to prepare antidepressants, antipsychotics, and drugs to treat diabetes.

16.1 Electrophilic Aromatic Substitution

Based on its structure and properties, what kinds of reactions should benzene undergo? Are any of its bonds particularly weak? Does it have electron-rich or electron-deficient atoms?

- **Benzene has six π electrons delocalized in six *p* orbitals that overlap above and below the plane of the ring. These loosely held π electrons make the benzene ring electron rich, so it reacts with *electrophiles*.**
- **Because benzene's six π electrons satisfy Hückel's rule, benzene is especially stable. Reactions that keep the aromatic ring *intact* are therefore favored.**

As a result, the characteristic reaction of benzene is *electrophilic aromatic substitution*—a hydrogen atom is replaced by an electrophile.



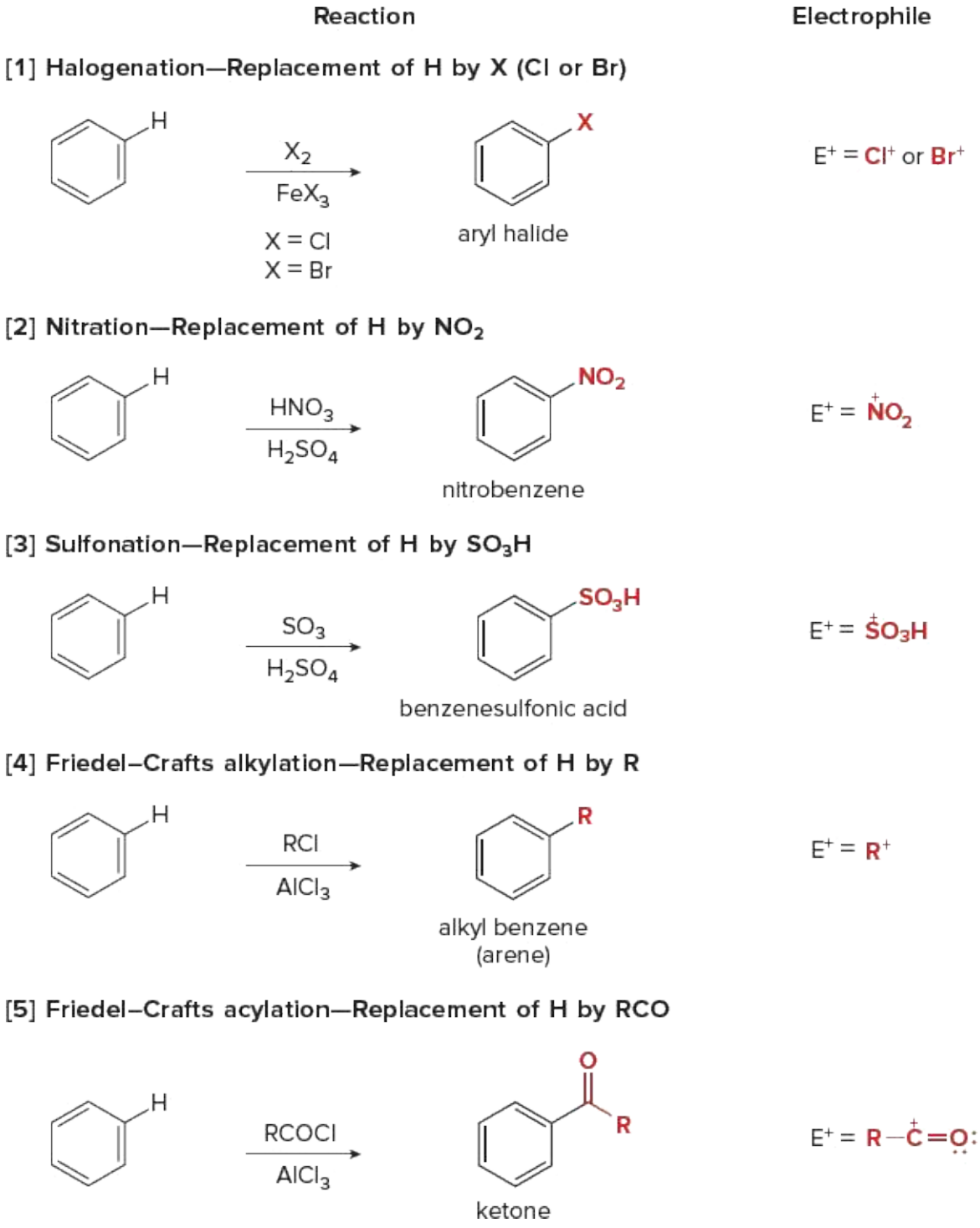
As we learned in Section 15.6, benzene does *not* undergo addition reactions like other unsaturated hydrocarbons, because addition would yield a product that is not aromatic. Substitution of a hydrogen, on the other hand, keeps the aromatic ring intact.

Five specific examples of electrophilic aromatic substitution are shown in Figure 16.1. The basic mechanism, discussed in Section 16.2, is the same in all five cases. The reactions differ only in the identity of the electrophile, E^+.

Problem 16.1

Why is benzene less reactive toward electrophiles than an alkene, even though it has more π electrons than an alkene (six versus two)?

Figure 16.1 Five examples of electrophilic aromatic substitution

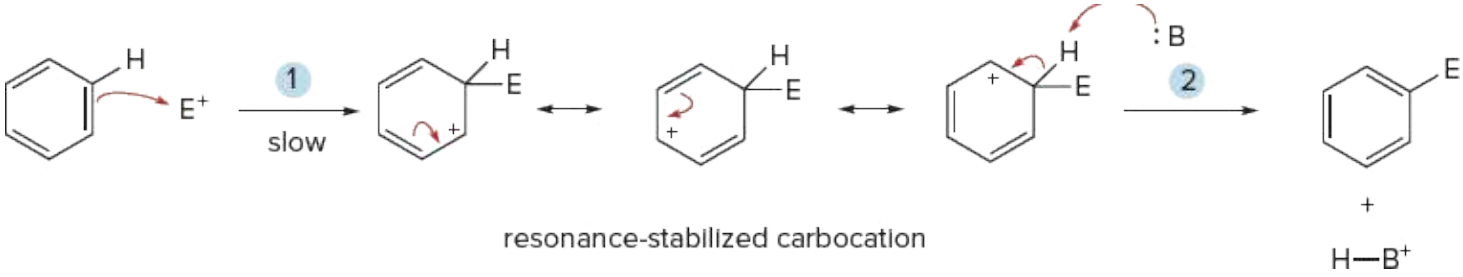


Friedel–Crafts alkylation and acylation, named for Charles Friedel and James Crafts, who discovered the reactions in the nineteenth century, form new carbon–carbon bonds.

16.2 The General Mechanism

No matter what electrophile is used, all electrophilic aromatic substitution reactions occur via a two-step mechanism: addition of the electrophile E^+ to form a resonance-stabilized carbocation, followed by deprotonation with base, as shown in Mechanism 16.1.

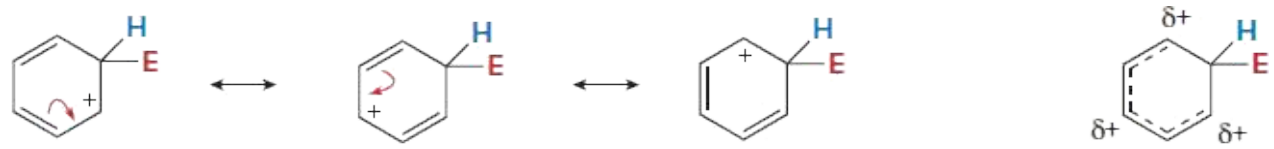
Mechanism 16.1 General Mechanism—Electrophilic Aromatic Substitution



1. **Addition of the electrophile E^+ forms a new C–E bond and a resonance-stabilized carbocation. This step is rate-determining because the aromaticity of the benzene ring is lost.**
2. **A base removes the proton *on the carbon bonded to the electrophile*, re-forming the aromatic ring. Any resonance structure can be used to draw the product.**

The first step in electrophilic aromatic substitution forms a carbocation, for Page 728 which three resonance structures can be drawn. To help keep track of the location of the positive charge:

- **Always draw in the H atom on the carbon bonded to E. This serves as a reminder that it is the only sp^3 hybridized carbon in the carbocation intermediate.**
- **Notice that the positive charge in a given resonance structure is always located ortho or para to the new C–E bond. In the hybrid, therefore, the charge is delocalized over three atoms of the ring.**



(+) ortho to E (+) para to E (+) ortho to E hybrid

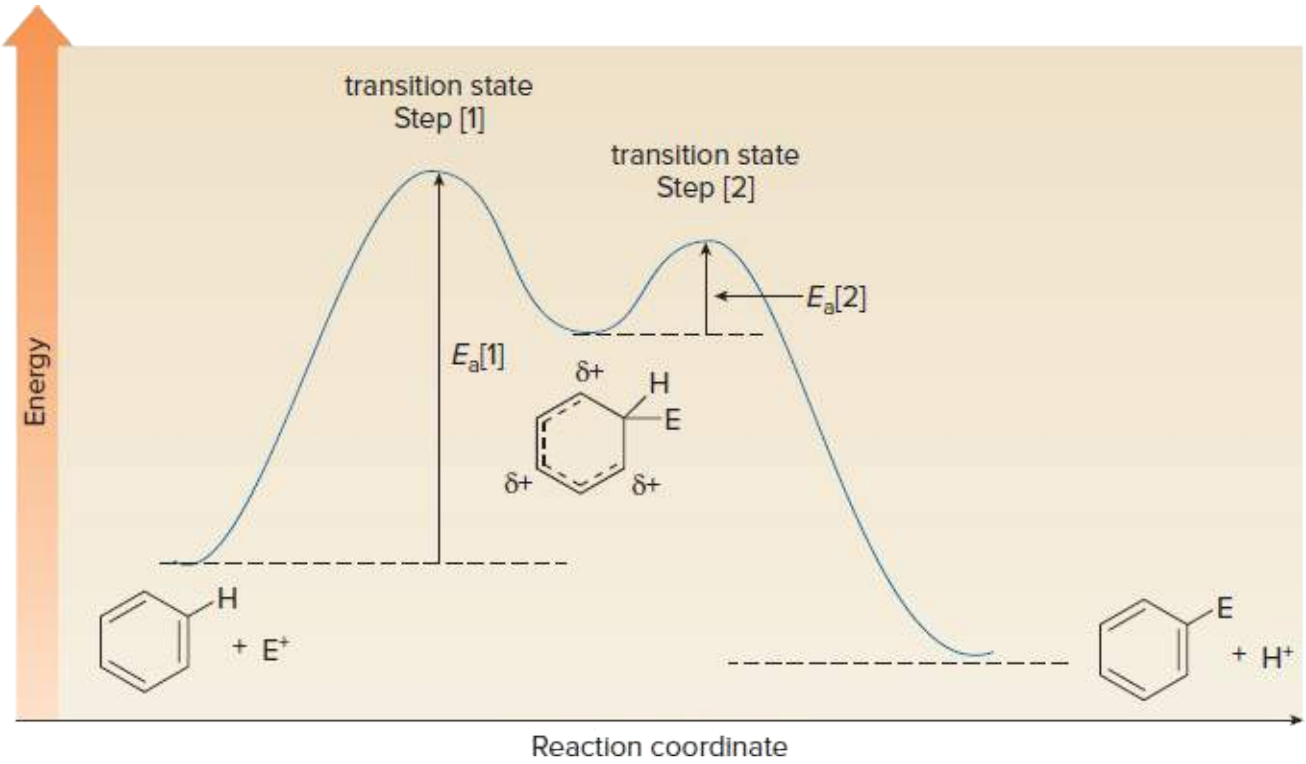
This two-step mechanism for electrophilic aromatic substitution applies to all of the electrophiles in Figure 16.1. The net result of addition of an electrophile (E^+) followed by elimination of a proton (H^+) is substitution of E for H.

The energy changes in electrophilic aromatic substitution are shown in Figure 16.2. Because the transition state of the first step is higher in energy, it is rate-determining.

Problem 16.2

In Step [2] of Mechanism 16.1, loss of a proton to form the substitution product was drawn using only one resonance structure. Use curved arrows to show how the other two resonance structures can be converted to the substitution product (PhE) by removal of a proton with :B.

Figure 16.2 **Energy diagram for electrophilic aromatic substitution: PhH + E^+ → PhE + H^+**



- The mechanism has two steps, so there are two energy barriers.
- **Step [1] is rate-determining;** its transition state is at higher energy.

16.3 Halogenation

The general mechanism outlined in Mechanism 16.1 can now be applied to each of the five specific examples of electrophilic aromatic substitution shown in Figure 16.1. For each mechanism we must learn how to generate a specific electrophile. This step is *different* with each electrophile. Then, the electrophile reacts with benzene by the two-step process of Mechanism 16.1. These two steps are the *same* for all five reactions.

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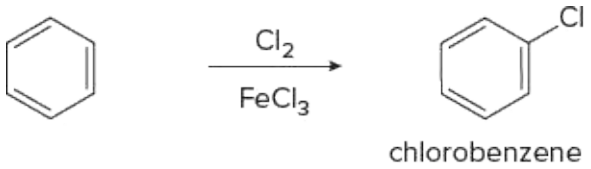
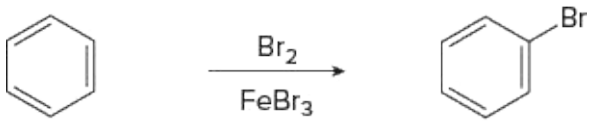
In halogenation, benzene reacts with Cl_2 or Br_2 in the presence of a Lewis acid catalyst, such as $FeCl_3$ or $FeBr_3$, to give the aryl halides chlorobenzene or bromobenzene, respectively. Analogous reactions with I_2 and F_2 are not synthetically useful because I_2 is too unreactive and F_2 reacts too violently.



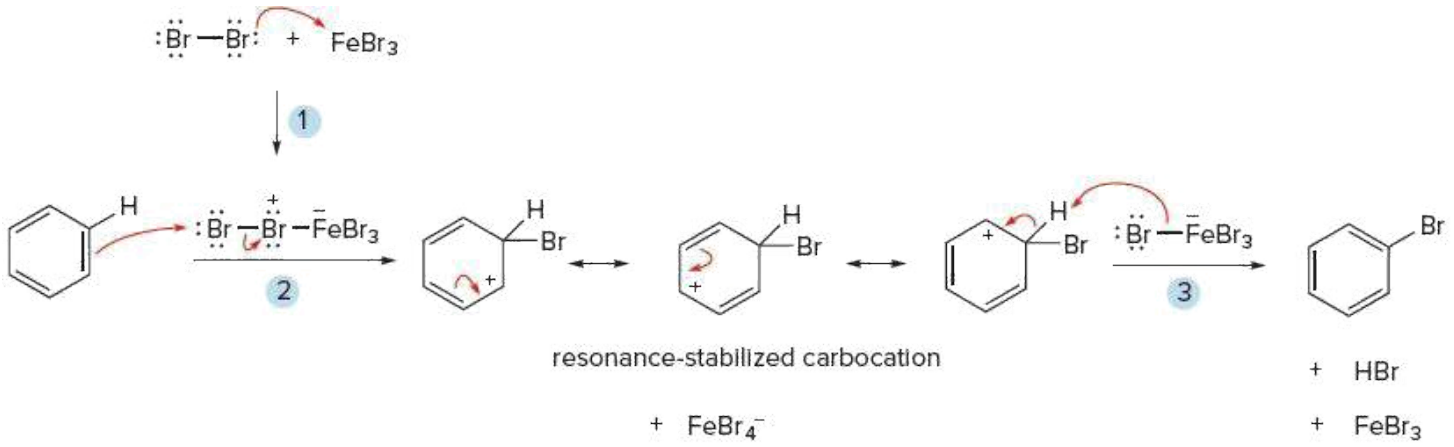
chlorobenzene



bromobenzene

In bromination (Mechanism 16.2), the Lewis acid $FeBr_3$ reacts with Br_2 to form a Lewis acid–base complex that weakens and polarizes the Br–Br bond, making it more electrophilic. This reaction is Step [1] of the mechanism for the bromination of benzene. The remaining two steps follow directly from the general mechanism for electrophilic aromatic substitution: addition of the electrophile (Br^+ in this case) forms a resonance-stabilized carbocation, and loss of a proton regenerates the aromatic ring.

Mechanism 16.2 Bromination of Benzene



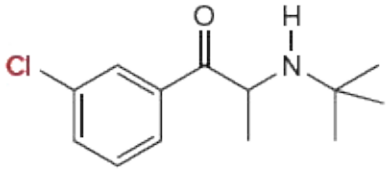
1. **Lewis acid–base reaction of Br_2 with $FeBr_3$ forms a species with a weakened Br–Br bond that serves as source of Br^+.**
2. **Addition of the electrophile forms a new C–Br bond and a resonance-stabilized carbocation.**
3. **$FeBr_4^-$ removes the proton *on the carbon bonded to the electrophile*, re-forming the aromatic ring. The Lewis acid catalyst $FeBr_3$ is regenerated for another reaction cycle.**

Chlorination proceeds by a similar mechanism. Reactions that introduce a halogen substituent on a benzene ring are widely used, and many halogenated aromatic compounds with a range of biological activity have been synthesized, as shown in Figure 16.3.

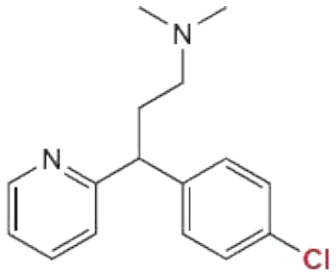
Problem 16.3

Draw a detailed mechanism for the chlorination of benzene using Cl_2 and $FeCl_3$.

Figure 16.3 Examples of biologically active aryl chlorides

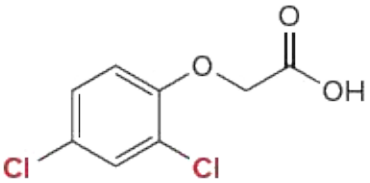


Generic name **bupropion**
Trade names **Wellbutrin, Zyban**
antidepressant,
also used to reduce nicotine cravings

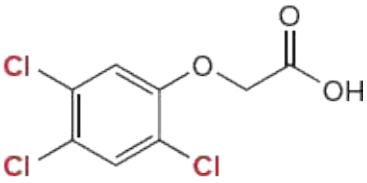


chlorpheniramine
antihistamine

Source: National Archives and Records Administration [NWDNS-111-C-CC59950]



2,4-D
2,4-dichlorophenoxy-
acetic acid
herbicide



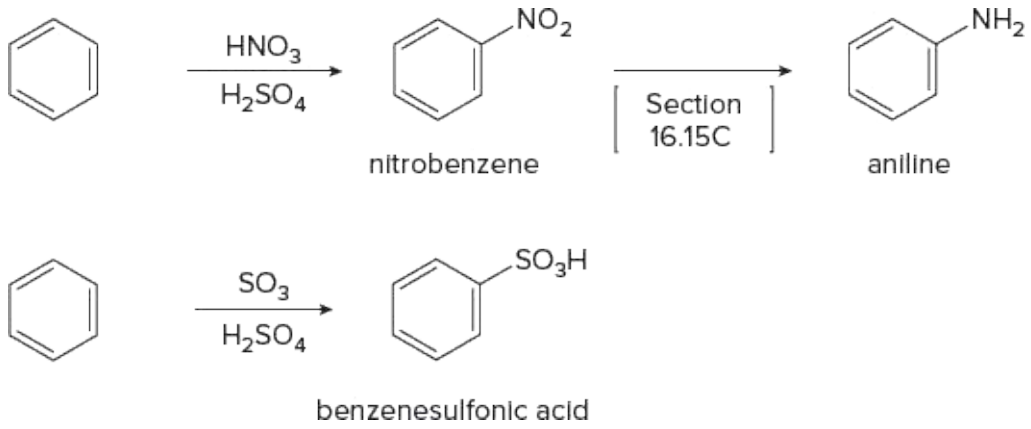
2,4,5-T
2,4,5-trichlorophenoxy-
acetic acid
herbicide

the active components in **Agent Orange**,
a defoliant used in the Vietnam War

Herbicides were used extensively during the Vietnam War to defoliate dense jungle areas. The concentration of certain herbicide by-products in the soil remains high today.

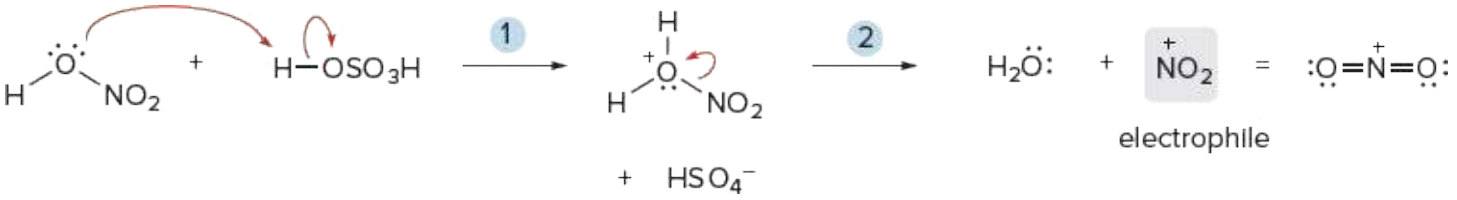
16.4 Nitration and Sulfonation

Nitration and sulfonation of benzene introduce two different functional groups on an aromatic ring. Nitration is an especially useful reaction because a nitro group can then be reduced to an NH_2 group, a common benzene substituent, in a reaction discussed in Section 16.15.



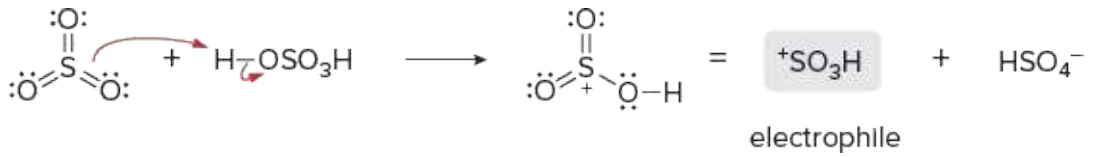
Generation of the electrophile in both nitration and sulfonation requires strong acid. In nitration, the electrophile is $^{+}NO_2$ (the nitronium ion), formed by protonation of HNO_3 followed by loss of water (Mechanism 16.3).

Mechanism 16.3 Formation of the Nitronium Ion ($^{+}NO_2$) for Nitration



In sulfonation, protonation of sulfur trioxide, SO_3, forms a positively charged sulfur species ($^{+}SO_3H$) that acts as an electrophile (Mechanism 16.4).

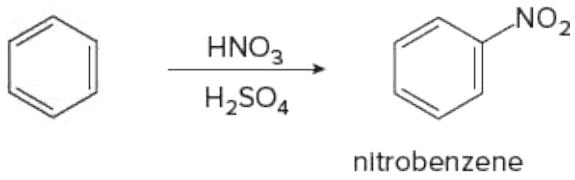
Mechanism 16.4 Formation of the Electrophile $^{+}SO_3H$ for Sulfonation



These steps illustrate how to generate the electrophile E^+ for nitration and sulfonation, the process that begins any mechanism for electrophilic aromatic substitution. To complete either of these mechanisms, you must replace the electrophile E^+ by either $^+NO_2$ or $^+SO_3H$ in the general mechanism (Mechanism 16.1). Thus, the two-step sequence that replaces H by E is the same regardless of E^+. This is shown in Sample Problem 16.1 using the reaction of benzene with the nitronium ion.

Sample Problem 16.1 Drawing the Mechanism for Nitration of Benzene

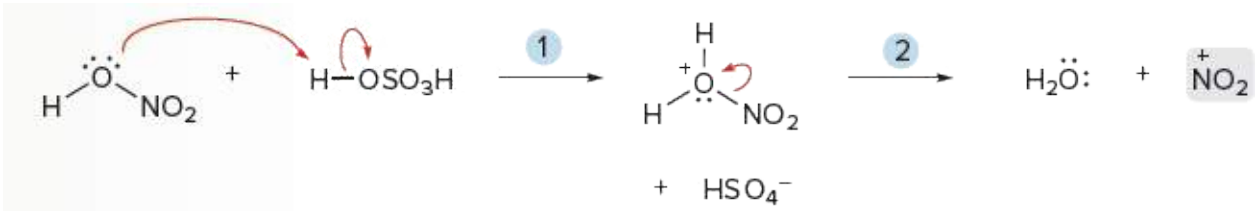
Draw a stepwise mechanism for the nitration of a benzene ring.



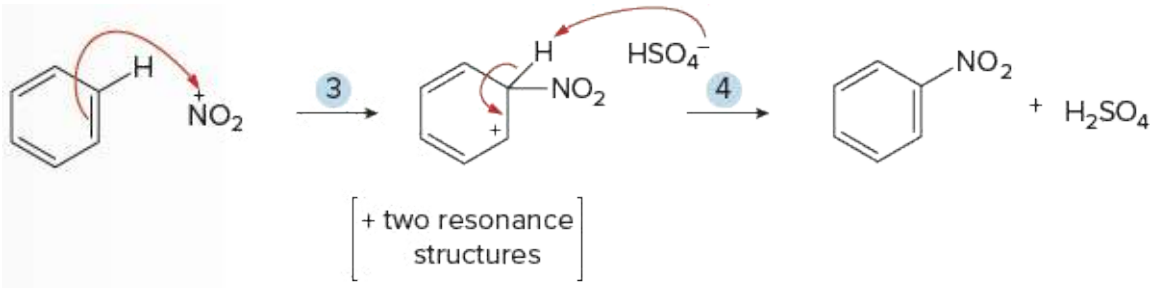
Solution

We must first generate the electrophile and then write the two-step mechanism for electrophilic aromatic substitution using it.

Part [1] Generation of the electrophile $^+NO_2$



Part [2] Two-step mechanism for electrophilic aromatic substitution

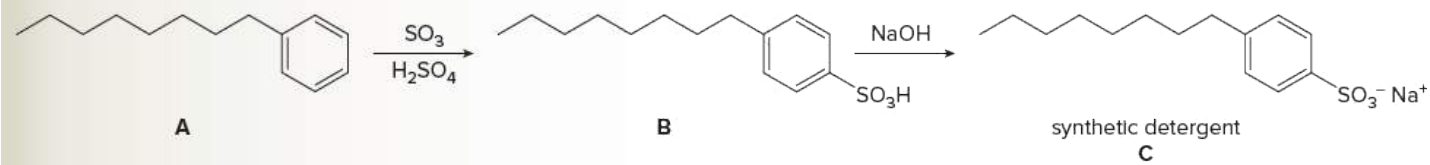


Any species with a lone pair of electrons can be used to remove the proton

in the last step. In this case, the mechanism is drawn with HSO_4^-, formed when $^+NO_2$ is generated as the electrophile.

Problem 16.4

Draw a stepwise mechanism for the sulfonation of an alkyl benzene such as A to form a substituted benzenesulfonic acid B. Treatment of B with base forms a sodium salt C that can be used as a synthetic detergent to clean away dirt (see Problem 3.24).



More Practice:

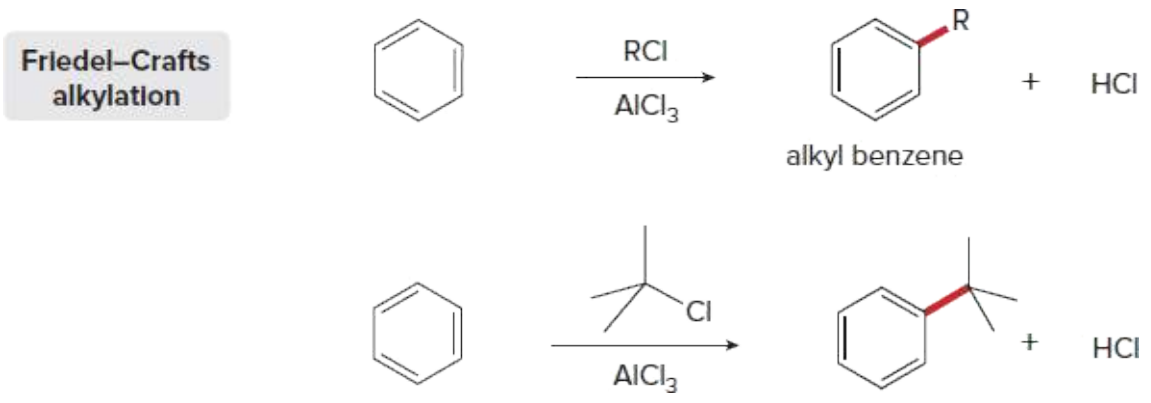
Try Problem 16.62.

16.5 Friedel–Crafts Alkylation and Friedel–Crafts Acylation

Friedel–Crafts alkylation and Friedel–Crafts acylation form new carbon–carbon bonds.

16.5A General Features

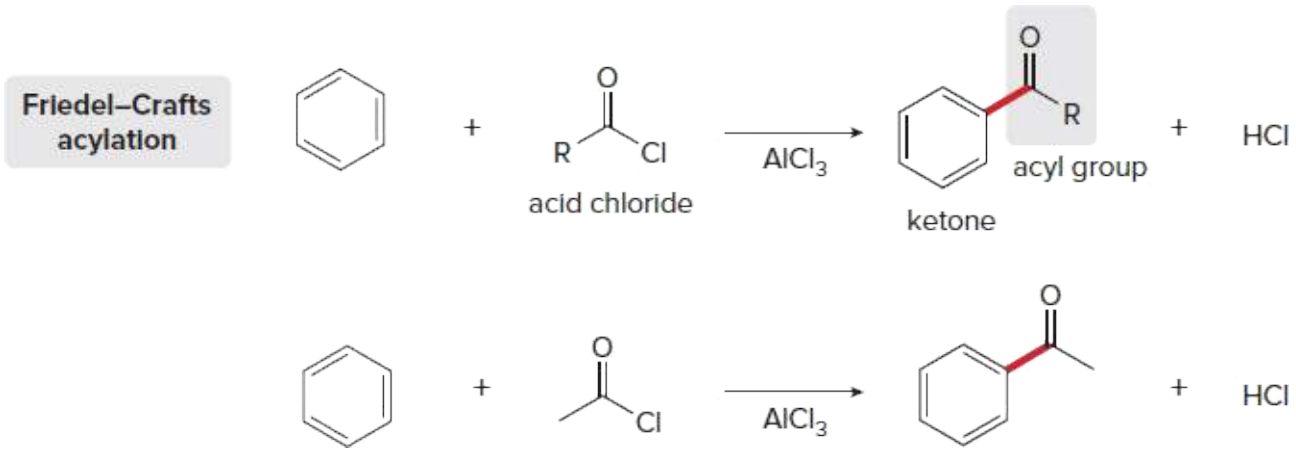
In Friedel–Crafts alkylation, treatment of benzene with an alkyl halide and a Lewis acid ($AlCl_3$) forms an alkyl benzene. This reaction is an alkylation because it results in transfer of an alkyl group from one atom to another (from Cl to benzene).



In Friedel–Crafts acylation, a benzene ring is treated with an acid chloride (RCOCl) and $AlCl_3$ to form a ketone. Because the new group bonded to the benzene ring is called an acyl group, the transfer of an acyl group from one atom to another is an

acylation.

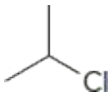
Acid chlorides are also called acyl chlorides.



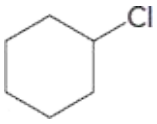
Problem 16.5

What product is formed when benzene is treated with each organic halide in the presence of $AlCl_3$?

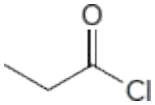
a.



b.



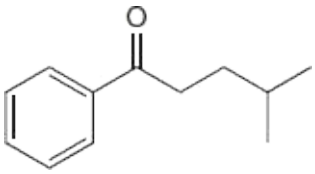
c.



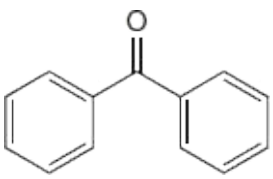
Problem 16.6

What acid chloride would be needed to prepare each of the following ketones from benzene using a Friedel–Crafts acylation?

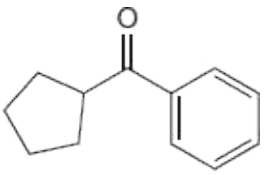
a.



b.



c.



16.5B Mechanism

The mechanisms of alkylation and acylation proceed in a manner analogous to those for halogenation, nitration, and sulfonation. The unique feature in each reaction is how the electrophile is generated.

In Friedel–Crafts alkylation, the Lewis acid $AlCl_3$ reacts with the alkyl chloride to form a Lewis acid–base complex, illustrated with CH_3CH_2Cl and $(CH_3)_3CCl$ as alkyl chlorides.

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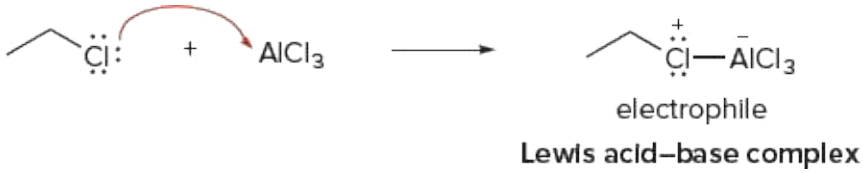
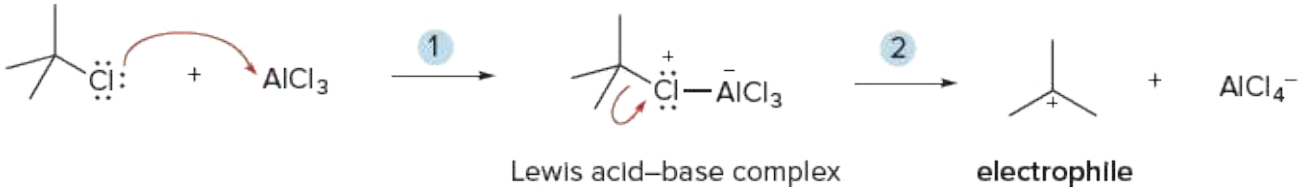
The identity of the alkyl chloride determines the exact course of the reaction as shown in Mechanism 16.5.

Mechanism 16.5 Formation of the Electrophile in Friedel–Crafts Alkylation—Two Possibilities

Possibility [1] For CH_3Cl and 1° RCl



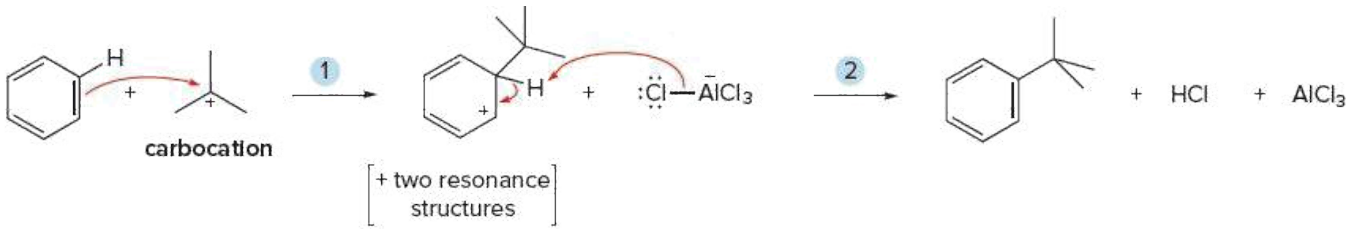
Possibility [2] For 2° and 3° RCl



- **For CH_3Cl and 1° RCl, the Lewis acid–base complex itself serves as the electrophile for electrophilic aromatic substitution.**
- **With 2° and 3° RCl, the Lewis acid–base complex reacts further to give a 2° or 3° carbocation, which serves as the electrophile. Carbocation formation occurs only with 2° and 3° alkyl chlorides, because they afford more stable carbocations.**

In either case, the electrophile goes on to react with benzene in the two-step mechanism characteristic of electrophilic aromatic substitution, illustrated in Mechanism 16.6 using the 3° carbocation, $(CH_3)_3C^+$.

Mechanism 16.6 Friedel–Crafts Alkylation Using a 3° Carbocation

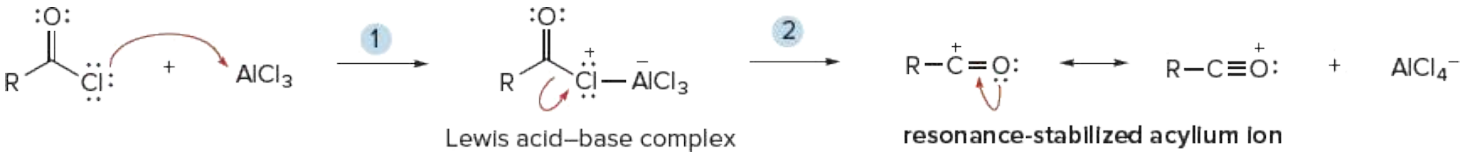


1 **Addition of the carbocation electrophile forms a new carbon–carbon bond.**

2 **$AlCl_4^-$ removes a proton on the carbon bearing the new substituent to re-form the aromatic ring.**

In Friedel–Crafts acylation, the Lewis acid $AlCl_3$ ionizes the carbon–halogen bond of the acid chloride, thus forming a positively charged carbon electrophile called an acylium ion, which is resonance stabilized (Mechanism 16.7). The positively charged carbon atom of the acylium ion then goes on to react with benzene in the two-step mechanism of electrophilic aromatic substitution.

Mechanism 16.7 Formation of the Electrophile in Friedel–Crafts Acylation



To complete the mechanism for acylation, insert the electrophile into the general mechanism and draw the last two steps, as illustrated in Sample Problem 16.2.

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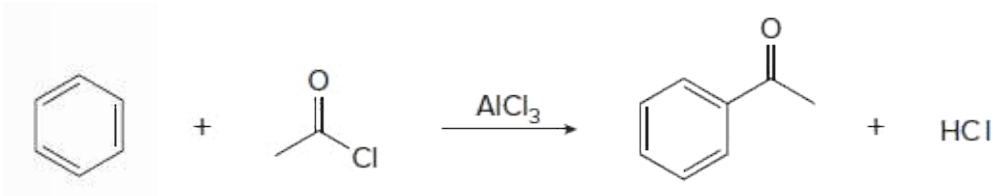
Sample Problem 16.2 Drawing a Mechanism for a Friedel–Crafts Reaction

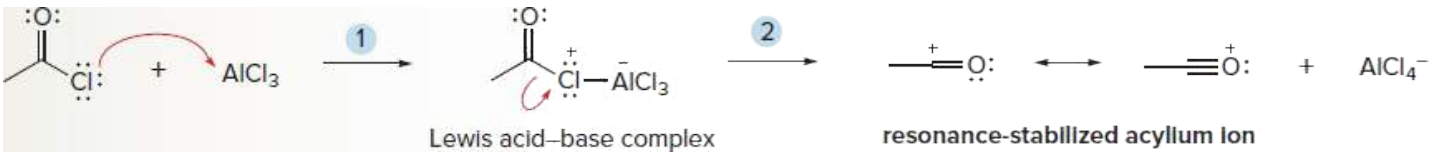
Draw a stepwise mechanism for the following Friedel–Crafts acylation.



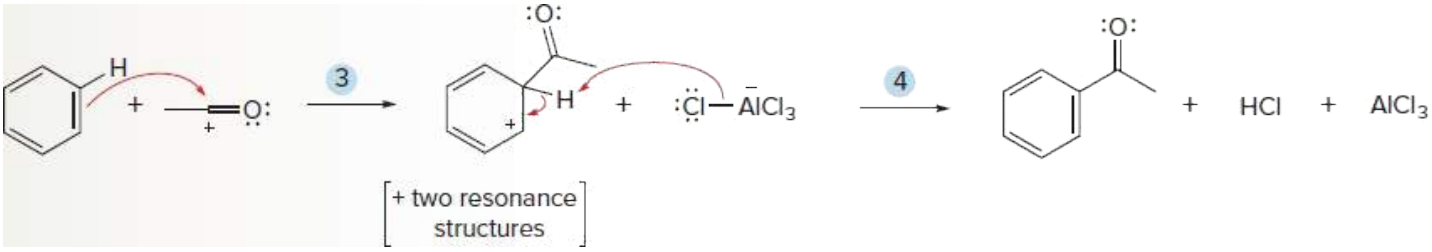
Solution

First generate the acylium ion, and then write the two-step mechanism for electrophilic aromatic substitution using it for the electrophile.

Part [1] Generation of the electrophile $(CH_3CO)^+$



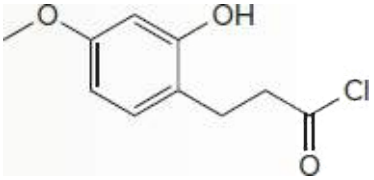
Part [2] Two-step mechanism for electrophilic aromatic substitution



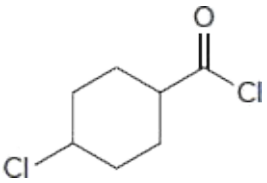
Problem 16.7

What acylium ion is formed from each acid chloride?

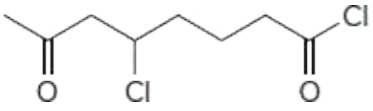
a.



b.



c.



More Practice:

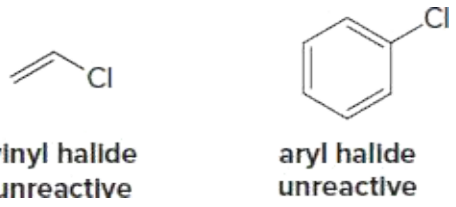
Try Problems 16.11, 16.38.

16.5C Other Facts About Friedel–Crafts Alkylation

Three additional facts about Friedel–Crafts alkylations must be kept in mind.

[1] **Vinyl halides and aryl halides do *not* react in Friedel–Crafts alkylation.**

Most Friedel–Crafts reactions involve carbocation electrophiles. Because the carbocations derived from vinyl halides and aryl halides are highly unstable and do not readily form, these organic halides do *not* undergo Friedel–Crafts alkylation.

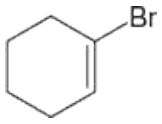


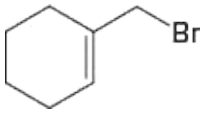
vinyl halide
unreactive

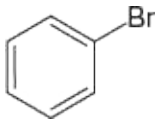
aryl halide
unreactive

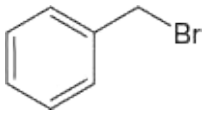
Problem 16.8

Which halides are unreactive in a Friedel–Crafts alkylation reaction?

a. 

b. 

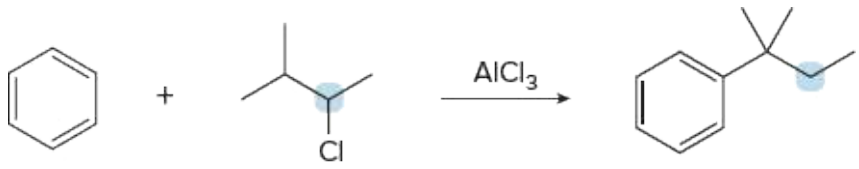
c. 

d. 

[2] Rearrangements can occur.

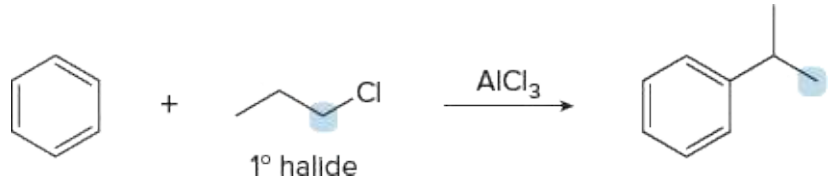
The Friedel–Crafts reaction can yield products having rearranged carbon skeletons when 1° and 2° alkyl halides are used as starting materials, as shown in Equations [1] and [2]. In both reactions, the carbon atom bonded to the halogen in the starting material (labeled in blue) is not bonded to the benzene ring in the product, thus indicating that a rearrangement has occurred.

Recall from Section 9.9 that a 1,2-shift converts a less stable carbocation to a more stable carbocation by shift of a hydrogen atom or an alkyl group.

[1] 

2° halide

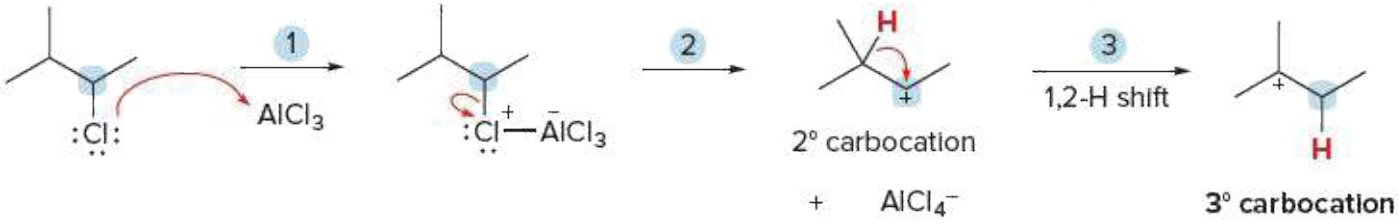
[2]



The result in Equation [1] is explained by a carbocation rearrangement involving a 1,2-hydride shift: the less stable 2° carbocation (formed from the 2° halide) rearranges to a more stable 3° carbocation, as illustrated in Mechanism 16.8.

Mechanism 16.8 Friedel–Crafts Alkylation Involving Carbocation Rearrangement

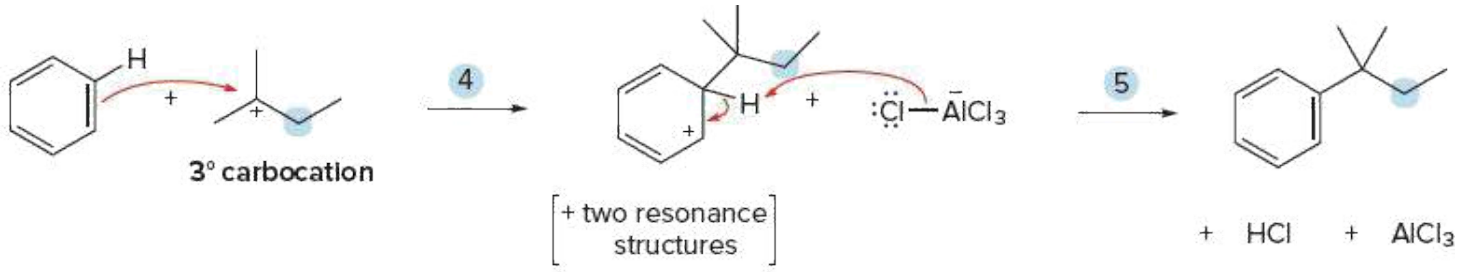
Part [1] Formation of a 2° carbocation and rearrangement



1 – 2 Lewis acid–base reaction of the alkyl chloride with $AlCl_3$ and cleavage of the C–Cl bond form a 2° carbocation.

3 1,2-Hydride shift converts a 2° carbocation to a more stable 3° carbocation.

Part [2] Two-step mechanism for electrophilic aromatic substitution



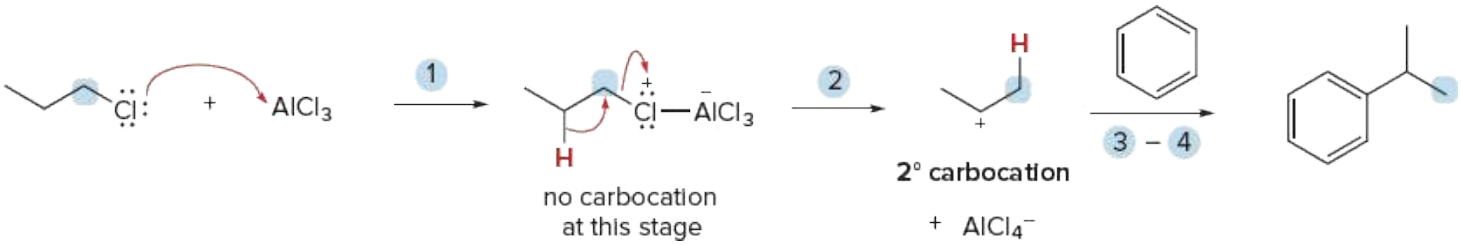
4 Addition of the 3° carbocation forms a new carbon–carbon bond and a resonance-stabilized carbocation.

5 $AlCl_4^-$ removes a proton on the carbon bearing the new substituent to re-form the aromatic ring.

Rearrangements can occur even when no free carbocation is formed initially. Page 736 For example, the 1° alkyl chloride in Equation [2] forms a complex with $AlCl_3$, which does *not* decompose to an unstable 1° carbocation, as shown in

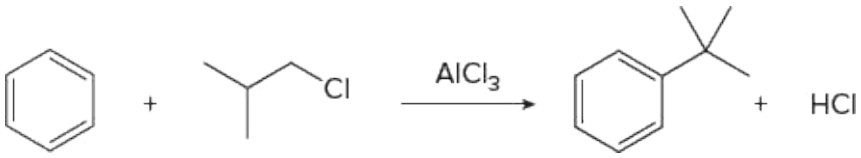
Mechanism 16.9. Instead, a 1,2-hydride shift forms a 2° carbocation, which then serves as the electrophile in the two-step mechanism for electrophilic aromatic substitution.

Mechanism 16.9 A Rearrangement Reaction Beginning with a 1° Alkyl Chloride



Problem 16.9

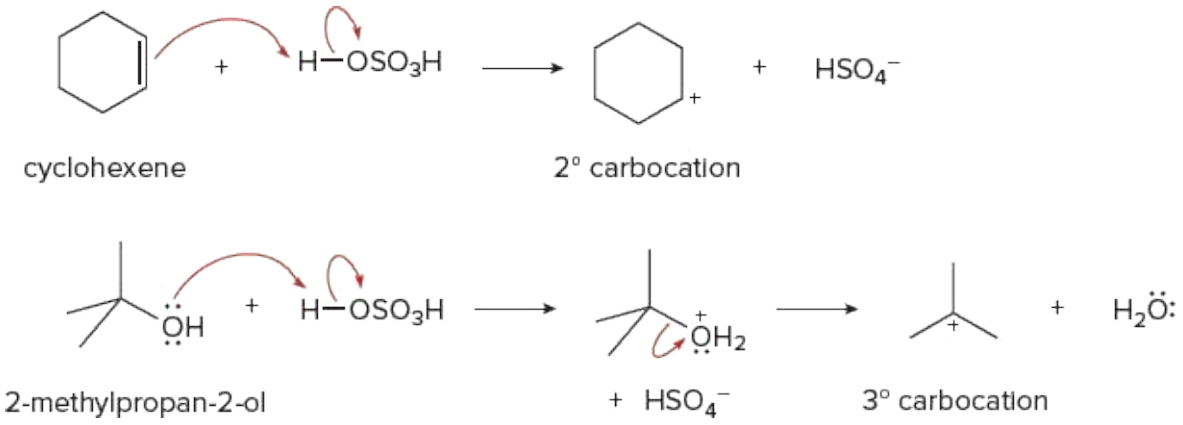
Draw a stepwise mechanism for the following reaction.



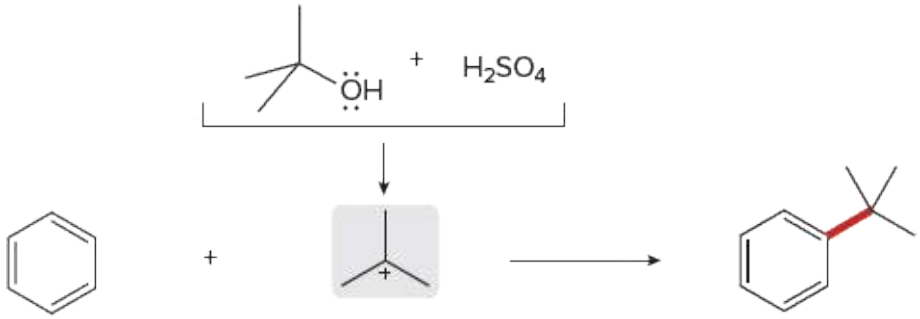
[3] Other functional groups that form carbocations can also be used as starting materials.

Although Friedel–Crafts alkylation works well with alkyl halides, any compound that readily forms a carbocation can be used instead. The two most common alternatives are alkenes and alcohols, both of which afford carbocations in the presence of strong acid.

- **Protonation of an alkene forms a carbocation, which can then serve as an electrophile in a Friedel–Crafts alkylation.**
- **Protonation of an alcohol, followed by loss of water, likewise forms a carbocation.**



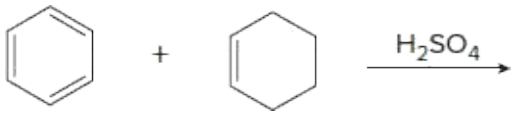
Each carbocation can then go on to react with benzene to form a product of electrophilic aromatic substitution. For example:



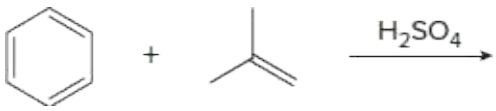
Problem 16.10

Draw the product of each reaction.

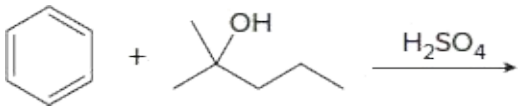
a.



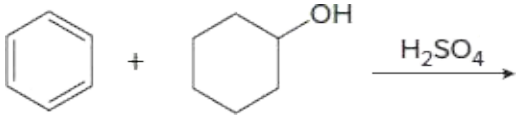
b.



c.

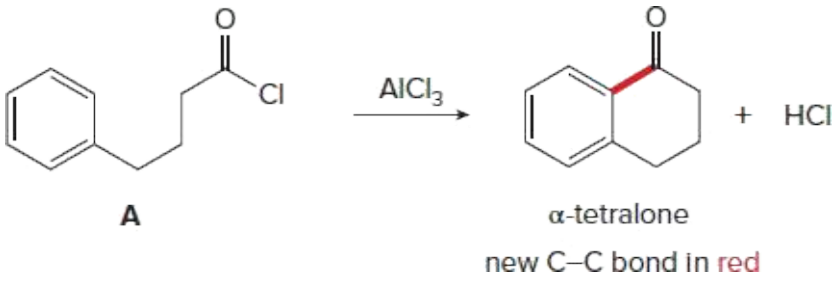


d.



16.5D Intramolecular Friedel–Crafts Reactions

All of the Friedel–Crafts reactions discussed thus far have resulted from intermolecular reaction of a benzene ring with an electrophile. Starting materials that contain both units are capable of intramolecular reaction, and this forms a new ring. Treatment of compound A, which contains both a benzene ring and an acid chloride, with $AlCl_3$, forms α-tetralone by an intramolecular Friedel–Crafts acylation reaction.



Such an intramolecular Friedel–Crafts acylation was a key step in the synthesis of the hallucinogen LSD, as shown in Figure 16.4.

Ergot-infected grain, the source of lysergic acid. ©Rene *Dulhoste/Science Source*

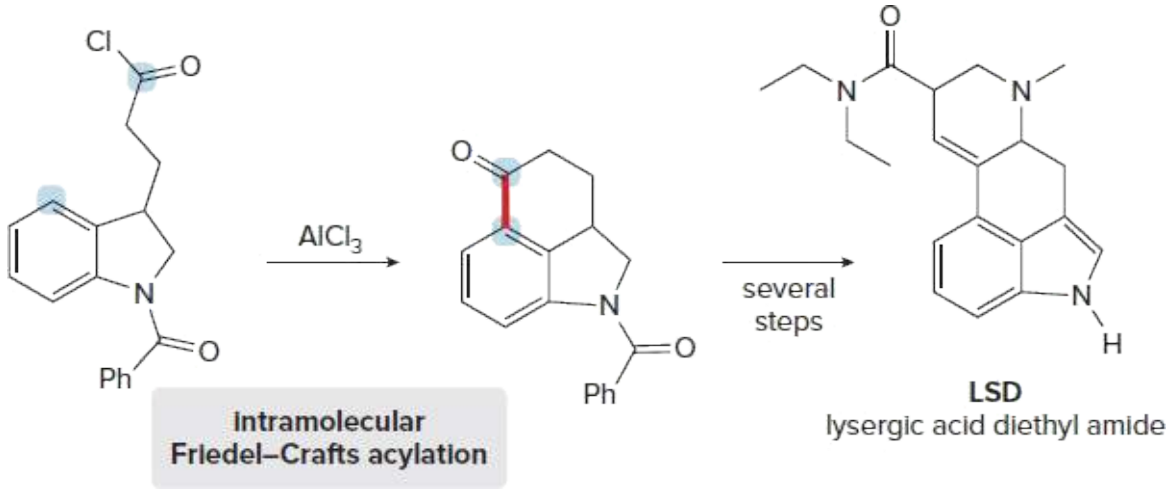


Figure 16.4 **Intramolecular Friedel–Crafts acylation in the synthesis of LSD**

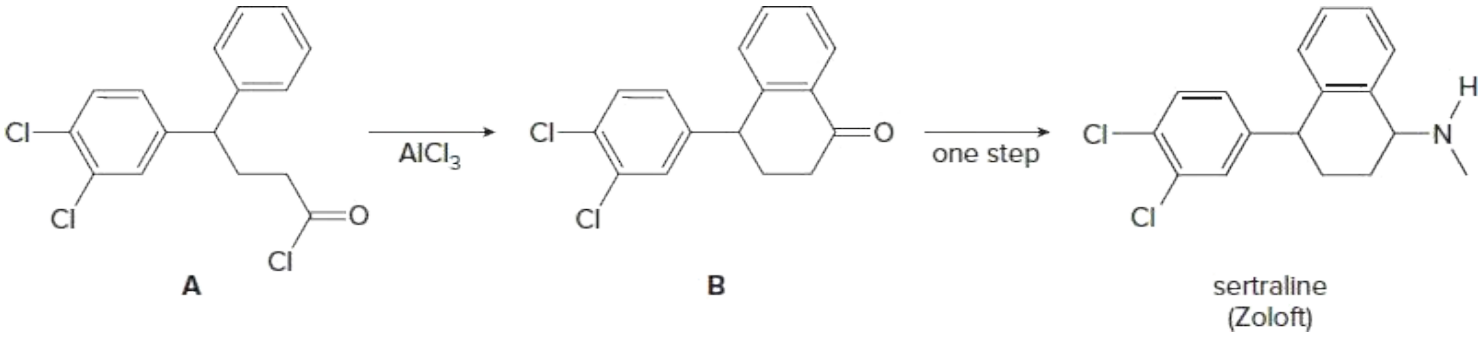
- **Intramolecular Friedel–Crafts acylation at the labeled carbons formed a product containing a new six-membered ring, which was converted to**

LSD in several steps.

- LSD was first prepared by Swiss chemist Albert Hofmann in 1938 from a related organic compound isolated from the ergot fungus that attacks rye and other grains. Ergot has a long history as a dreaded poison, affecting individuals who become ill from eating ergot-contaminated bread. The hallucinogenic effects of LSD were first discovered when Hofmann accidentally absorbed a small amount of the drug through his fingertips.

Problem 16.11

Draw a stepwise mechanism for the intramolecular Friedel–Crafts acylation of compound A to form B. B can be converted in one step to the antidepressant sertraline.



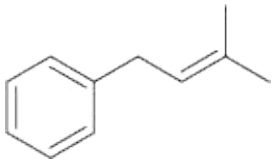
A B sertraline (Zoloft)

Sertraline (trade name Zoloft, Problem 16.11) is an effective antidepressant because it increases the concentration of the neurotransmitter serotonin in the brain. ***©Omeletzz/Shutterstock***

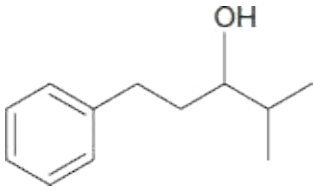
Problem 16.12

Intramolecular reactions are also observed in Friedel–Crafts alkylation. Draw the intramolecular alkylation product formed from each of the following reactants. (Watch out for rearrangements!)

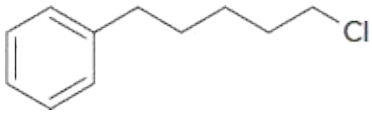
a.



b.



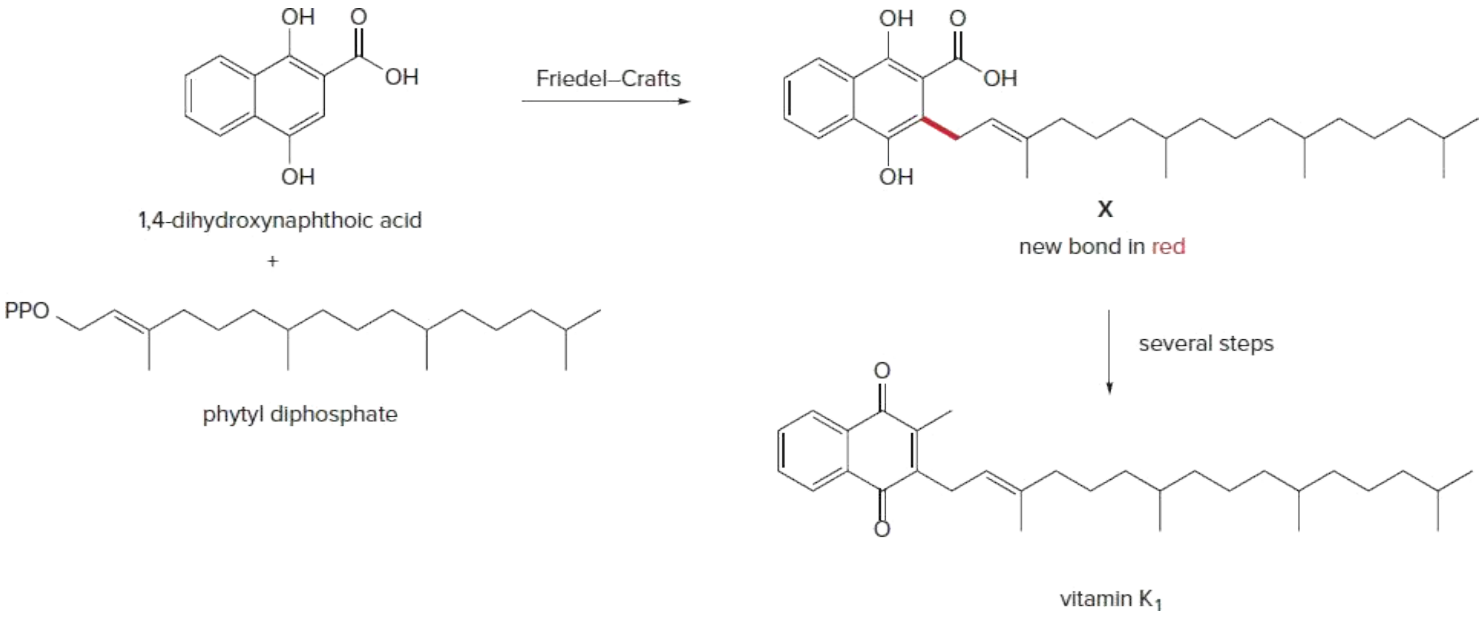
c.



16.5E Biological Friedel–Crafts Reactions

Biological Friedel–Crafts reactions occur as well. As we learned in Section 14.2, allylic diphosphates contain a good leaving group, so they can serve as a source of allylic carbocations. A key step in the biological synthesis of vitamin K_1, the chapter-opening molecule, involves Friedel–Crafts reaction of 1,4-dihydroxynaphthoic acid with phytyl diphosphate to form X, which is converted to vitamin K_1 in several steps, as shown in Figure 16.5.

Figure 16.5 **Friedel–Crafts reaction in the synthesis of vitamin K_1**



Problem 16.13

(a) Draw resonance structures for the carbocation formed after loss of a leaving group from phytyl diphosphate. (b) Draw the two-step mechanism for Friedel–Crafts alkylation of 1,2-dihydroxynaphthoic acid with this carbocation to form X.

16.6 Substituted Benzenes

Many substituted benzene rings undergo electrophilic aromatic substitution. Common substituents include halogens, OH, NH_2, alkyl, and many functional groups that contain a carbonyl. Each substituent either increases or decreases the electron density in the benzene ring, and this affects the course of electrophilic aromatic substitution, as we will learn in Section 16.7.

What makes a substituent on a benzene ring electron donating or electron withdrawing? The answer is inductive effects and resonance effects, both of which can add or remove electron density.

Inductive Effects

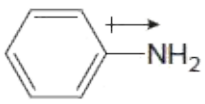
Inductive effects stem from the electronegativity of the atoms in the substituent and the polarizability of the substituent group.

Inductive and resonance effects were first discussed in Sections 2.5B and 2.5C, respectively.

- **Atoms more electronegative than carbon—including N, O, and X—pull electron density away from carbon and thus exhibit an electron-*withdrawing* inductive effect.**
- **Polarizable alkyl groups donate electron density, and thus exhibit an electron-*donating* inductive effect.**

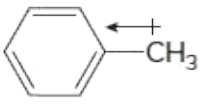
Considering inductive effects *only*, an NH_2 group withdraws electron density and CH_3 donates electron density.

Electron-withdrawing inductive effect



- N is *more* **electronegative** than C.
- N inductively **withdraws** electron density.

Electron-donating inductive effect



- Alkyl groups are **polarizable**, making them electron-**donating** groups.

Problem 16.14

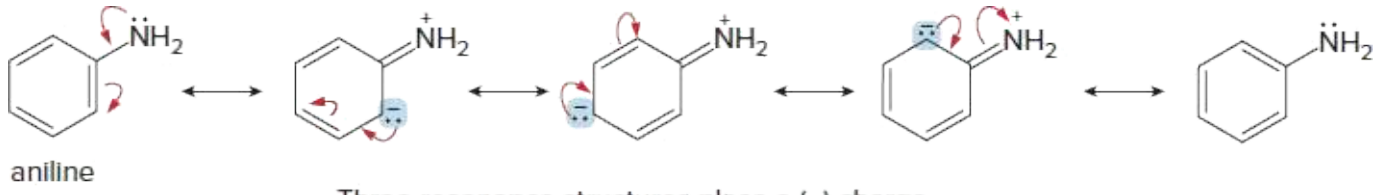
Which substituents have an electron-withdrawing and which have an electron-donating inductive effect: (a) $CH_3CH_2CH_2CH_2-$; (b) $Br-$; (c) CH_3CH_2O-?

Resonance Effects

Resonance effects can either donate or withdraw electron density, depending on whether they place a positive or negative charge on the benzene ring.

- **A resonance effect is electron *donating* when resonance structures place a *negative* charge on carbons of the benzene ring.**
- **A resonance effect is electron *withdrawing* when resonance structures place a *positive* charge on carbons of the benzene ring.**

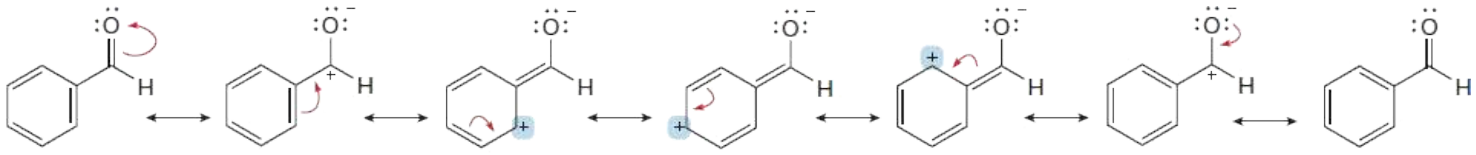
An electron-donating resonance effect is observed whenever an atom Z having a lone pair of electrons is bonded directly to a benzene ring (general structure—C_6H_5–Z:). Common examples of Z include N, O, and halogen. For example, five resonance structures can be drawn for aniline ($C_6H_5NH_2$). Because three of them place a *negative* charge on a carbon atom of the benzene ring, an NH_2 group *donates* electron density to a benzene ring by a resonance effect.



aniline

Three resonance structures place a (–) charge on atoms in the ring.

In contrast, an electron-withdrawing resonance effect is observed in Page 740 substituted benzenes having the general structure C_6H_5–Y=Z, where Z is more electronegative than Y. For example, seven resonance structures can be drawn for benzaldehyde (C_6H_5CHO). Because three of them place a *positive* charge on a carbon atom of the benzene ring, a CHO group *withdraws* electron density from a benzene ring by a resonance effect.

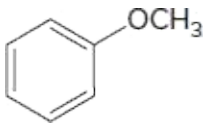


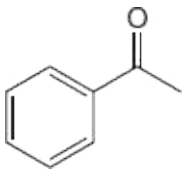
benzaldehyde

Three resonance structures place a (+) charge on atoms in the ring.

Problem 16.15

Draw all resonance structures for each compound, and use the resonance structures to determine if the substituent has an electron-donating or electron-withdrawing resonance effect.

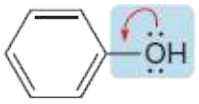
a. 

b. 

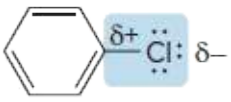
Considering Both Inductive and Resonance Effects

To predict whether a substituted benzene is more or less electron rich than benzene itself, we must consider the net balance of *both* the inductive and the resonance effects. Alkyl groups, for instance, donate electrons by an inductive effect, but they have no resonance effect because they lack nonbonded electron pairs or π bonds. As a result,

- **An alkyl group is an electron-*donating* group and an alkyl benzene is more electron rich than benzene.**



OH is electron donating.
The resonance effect predominates.



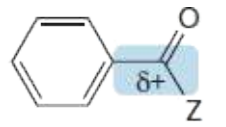
Cl is electron withdrawing.
The inductive effect predominates.

When electronegative atoms, such as N, O, or halogen, are bonded to the benzene ring, they inductively *withdraw* electron density from the ring. All of these groups also have a nonbonded pair of electrons, so they *donate* electron density to the ring by resonance. The *identity of the element* determines the net balance of these opposing effects.

Z = N, O, X

Induction and resonance have opposite effects.
- Z inductively *withdraws* electron density.
- Z *donates* electron density by resonance.

- **When a neutral O or N atom is bonded directly to a benzene ring, the resonance effect dominates and the net effect is *electron donation*.**
- **When a halogen X is bonded to a benzene ring, the inductive effect dominates and the net effect is *electron withdrawal*.**

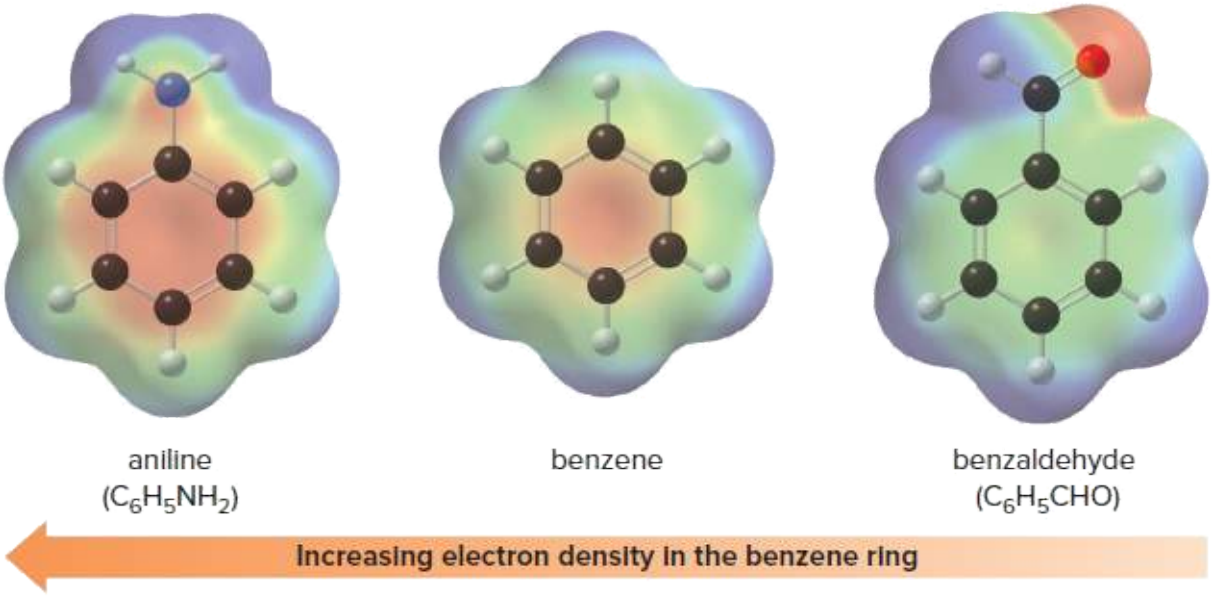


C=O is electron withdrawing.

Thus, NH_2 and OH are electron-*donating* groups because the resonance effect predominates, whereas Cl and Br are electron-*withdrawing* groups because the inductive effect predominates.

Finally, the inductive and resonance effects in compounds having the general structure C_6H_5–Y=Z (with Z more electronegative than Y) are both electron withdrawing; in other words, the two effects *reinforce* each other. This is true for benzaldehyde (C_6H_5CHO) and all other compounds that contain a carbonyl group bonded directly to the benzene ring.

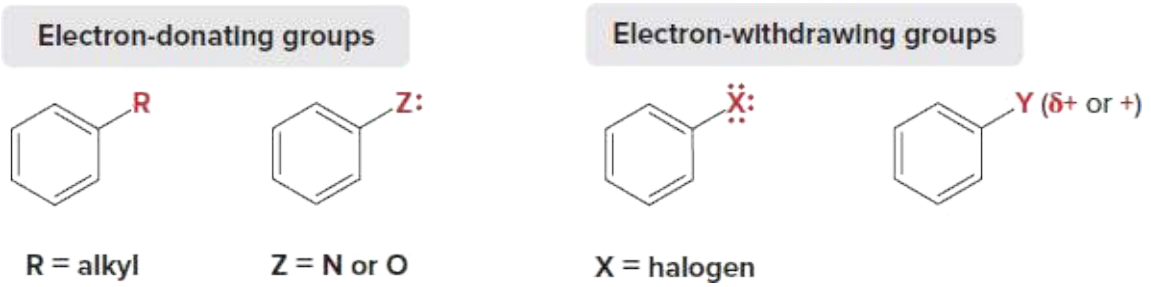
Figure 16.6 **The effect of substituents on the electron density in substituted benzenes**



- The NH_2 group donates electron density, making the benzene ring more electron rich (redder), whereas the CHO group withdraws electron density, making the benzene ring less electron rich (greener).

Thus, on balance, an NH_2 group is electron *donating*, so the benzene ring of aniline ($C_6H_5NH_2$) has more electron density than benzene. An aldehyde group (CHO), on the

other hand, is electron *withdrawing*, so the benzene ring of benzaldehyde (C_6H_5CHO) has less electron density than benzene. These effects are illustrated in the electrostatic potential maps in Figure 16.6. These compounds represent examples of the general structural features in electron-donating and electron-withdrawing substituents:

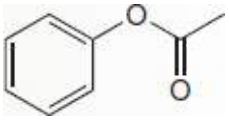


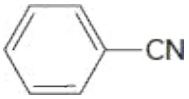
- **Common electron-donating groups are alkyl groups or groups with an N or O atom (with a lone pair) bonded to the benzene ring.**
- **Common electron-withdrawing groups are halogens or groups with an atom Y bearing a full or partial positive charge (+ or δ+) bonded to the benzene ring.**

The net effect of electron donation and withdrawal on the reactions of substituted aromatics is discussed in Sections 16.7–16.9.

Sample Problem 16.3 Classifying a Substituent as Electron Donating or Electron Withdrawing

Classify each substituent as electron donating or electron withdrawing.

a. 

b. 

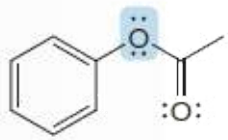
Solution

If necessary, draw out the atoms and bonds of the substituent to clearly see lone pairs and multiple bonds. Always look at the atom bonded directly to the benzene ring to determine electron-donating or electron-withdrawing effects.

- **An O or N atom with a lone pair of electrons makes a substituent electron donating.**
- **A halogen or an atom with a partial positive charge makes a**

substituent electron withdrawing.

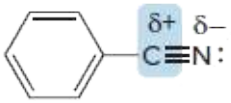
a.



- An O atom with a lone pair is bonded directly to the benzene ring.

an electron-donating group

b.



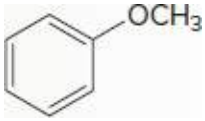
- An atom with a partial (+) charge is bonded directly to the benzene ring.

an electron-withdrawing group

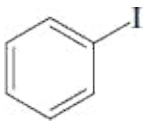
Problem 16.16

Classify each substituent as electron donating or electron withdrawing.

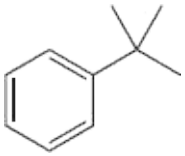
a.



b.



c.



More Practice:

Try Problem 16.50.

16.7 Electrophilic Aromatic Substitution of Substituted Benzenes

Electrophilic aromatic substitution is a general reaction of *all* aromatic compounds, including polycyclic aromatic hydrocarbons, heterocycles, and substituted benzene derivatives. A substituent affects two aspects of electrophilic aromatic substitution:

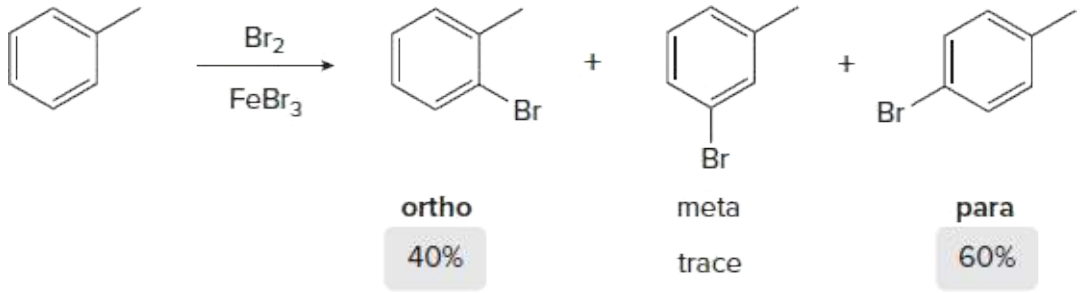
- The rate of reaction: A substituted benzene reacts faster or slower than benzene itself.
- The orientation: The new group is located either ortho, meta, or para to the

existing substituent. The identity of the first substituent determines the position of the second substituent.

Toluene ($C_6H_5CH_3$) and nitrobenzene ($C_6H_5NO_2$) illustrate two possible outcomes.

[1] Toluene

Toluene reacts faster than benzene in all substitution reactions. Thus, its electron-donating CH_3 group *activates* the benzene ring to electrophilic attack. Although three products are possible, compounds with the new group ortho or para to the CH_3 group predominate. The CH_3 group is therefore called an ortho, para director.



[2] Nitrobenzene

Nitrobenzene reacts more slowly than benzene in all substitution reactions. Thus, its electron-withdrawing NO_2 group *deactivates* the benzene ring to electrophilic attack. Although three products are possible, the compound with the new group meta to the NO_2 group predominates. The NO_2 group is called a meta director.

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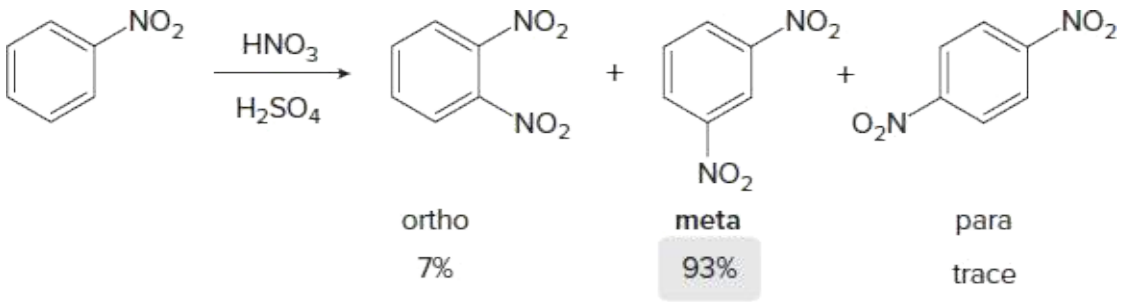
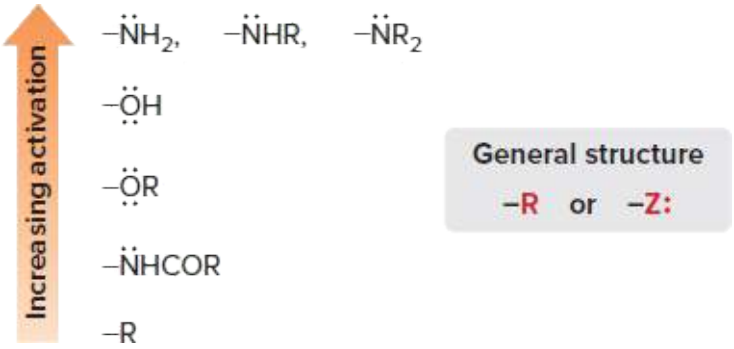


Substituents either activate or deactivate a benzene ring toward electrophiles, and direct selective substitution at specific sites on the ring. All substituents can be divided into three general types.

[1] Ortho, para directors and activators

- Substituents that *activate* a benzene ring and direct substitution ortho and para.

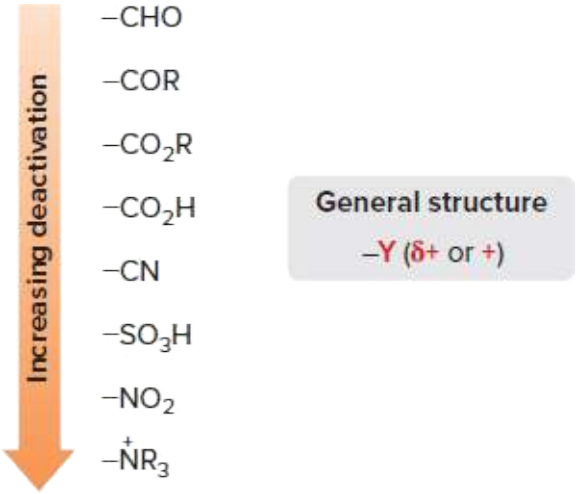


[2] Ortho, para deactivators

- Substituents that *deactivate* a benzene ring and direct substitution ortho and para.

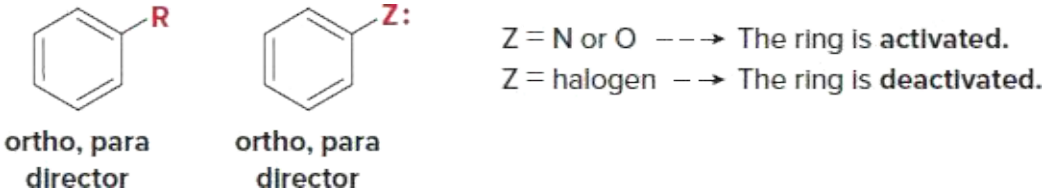
[3] Meta directors

- Substituents that direct substitution meta.
- All meta directors *deactivate* the ring.

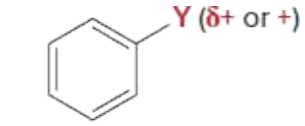


To learn these lists: Keep in mind that the halogens are in a class by themselves. Then learn the general structures for each type of substituent.

- **All ortho, para directors are R groups or have a nonbonded electron pair on the atom bonded to the benzene ring.**



- **All meta directors have a full or partial positive charge on the atom bonded to the benzene ring.**



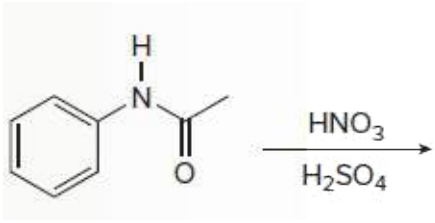
meta director

Sample Problem 16.4 shows how this information can be used to predict the products of electrophilic aromatic substitution reactions.

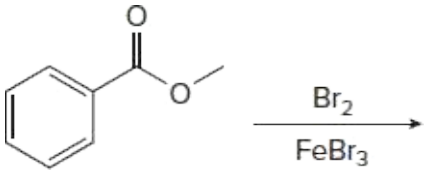
Sample Problem 16.4 Drawing the Electrophilic Substitution Products of a Substituted Benzene

Draw the products of each reaction, and state whether the reaction is faster or slower than a similar reaction with benzene.

a.



b.

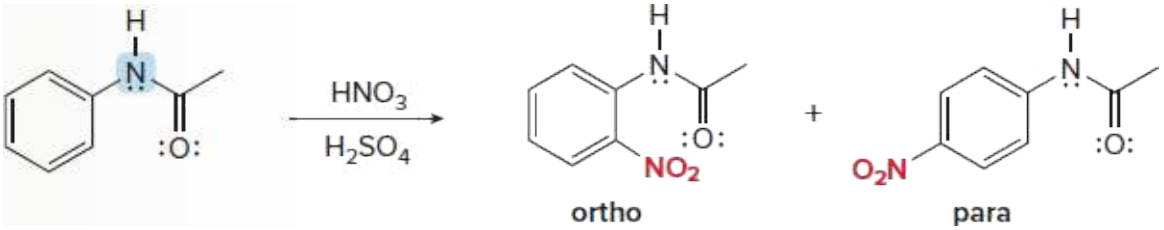


Solution

To draw the products:

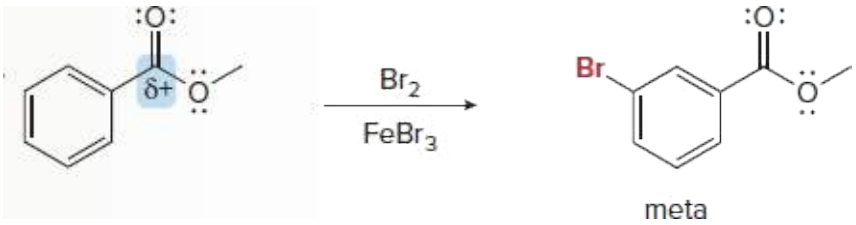
- **Draw the Lewis structure for the substituent to see if it has a lone pair or partial positive charge on the atom bonded to the benzene ring.**
- **Classify the substituent—ortho, para activating; ortho, para deactivating; or meta deactivating—and draw the products.**

a.



ortho para

The lone pair on N makes this group an ortho, para activator. This compound reacts *faster* than benzene.

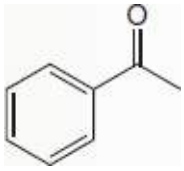
b. 

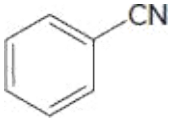
meta

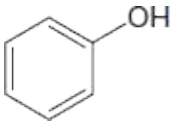
The δ+ on the C bonded to the benzene ring makes the group a meta deactivator. This compound reacts *more slowly* than benzene.

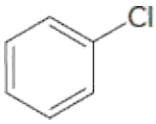
Problem 16.17

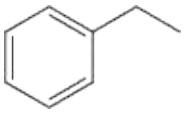
Draw the products formed when each compound is treated with HNO_3 and H_2SO_4. State whether the reaction occurs faster or slower than a similar reaction with benzene.

a. 

b. 

c. 

d. 

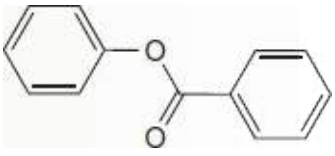
e. 

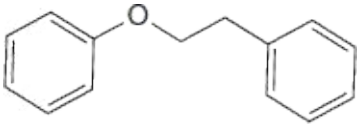
More Practice:

Try Problems 16.39, 16.53.

Sample Problem 16.5 Determining Which Ring in a Polycyclic Compound Is More Reactive in Electrophilic Aromatic Substitution

Which ring in each compound is more reactive toward electrophiles?

a. 

b. 

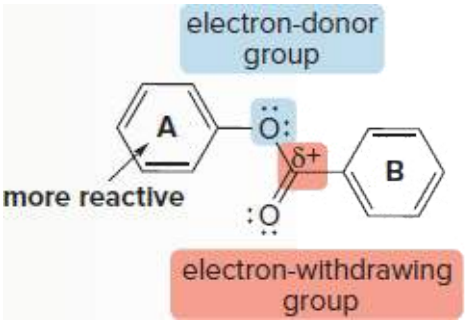
Solution

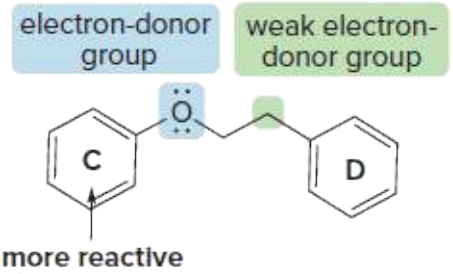
Look at the atom bonded *directly* to the aromatic ring to decide on reactivity in electrophilic aromatic substitution.

- **An N or O atom with a lone pair makes a ring *more* reactive.**
- **An alkyl group makes a ring *somewhat more* reactive.**
- **An atom with a full or partial positive charge makes a ring *less* reactive.**

a. Ring A is bonded to an O atom with a lone pair, whereas ring B is bonded to a C that bears a δ+. Ring A is more electron rich and more reactive.

b. Ring C is bonded to an O atom with a lone pair, whereas ring D is bonded to an alkyl carbon. Ring C is more electron rich and more reactive.

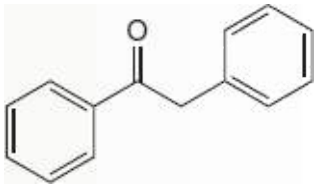




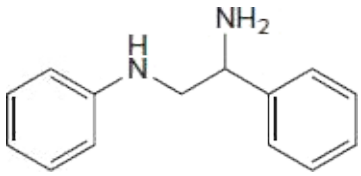
Problem 16.18

Determine which ring in each compound is more reactive toward electrophiles, and explain your choice.

a.



b.

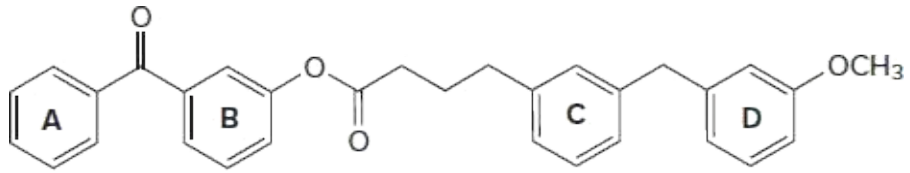


More Practice:

Try Problems 16.51–16.53.

Problem 16.19

Consider the tetracyclic compound with rings labeled A–D. (a) Which ring is the *most* reactive in electrophilic aromatic substitution? (b) Which ring is the *least* reactive in electrophilic aromatic substitution?

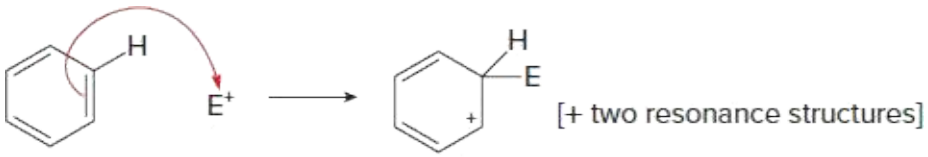


16.8 Why Substituents Activate or Deactivate a Benzene Ring

- Why do substituents activate or deactivate a benzene ring?
- Why are particular orientation effects observed? Why are some groups ortho, para directors and some groups meta directors?

To understand why some substituents make a benzene ring react *faster* than benzene itself (activators), whereas others make it react *slower* (deactivators), we must evaluate the rate-determining step (the first step) of the mechanism. Recall from Section 16.2 that the first step in electrophilic aromatic substitution is the addition of an electrophile (E^+) to form a resonance-stabilized carbocation. The Hammond postulate (Section 7.14) makes it possible to predict the relative rate of the reaction by looking at the stability of the carbocation intermediate.

- **The more stable the carbocation, the lower in energy the transition state that forms it, and the faster the reaction.**



Stabilizing the carbocation makes the reaction faster.

The principles of inductive effects and resonance effects, first introduced in Section 16.6, can now be used to predict carbocation stability.

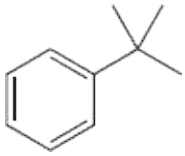
- **Electron-donating groups stabilize the carbocation and *activate* a benzene ring toward electrophilic attack. All activators are R groups, or they have an N or O atom with a lone pair bonded directly to the benzene ring.**
- **Electron-withdrawing groups destabilize the carbocation and *deactivate* a benzene ring toward electrophilic attack. All deactivators are halogens, or they have an atom with a full or partial positive charge bonded directly to the benzene ring.**

The energy diagrams in Figure 16.7 illustrate the effect of electron-donating and electron-withdrawing groups on the energy of the transition state of the rate-determining step in electrophilic aromatic substitution.

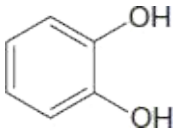
Problem 16.20

Label each compound as more or less reactive than benzene in electrophilic aromatic substitution.

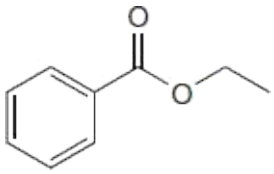
a.



b.



c.



d.

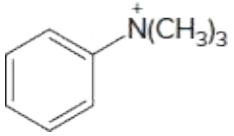
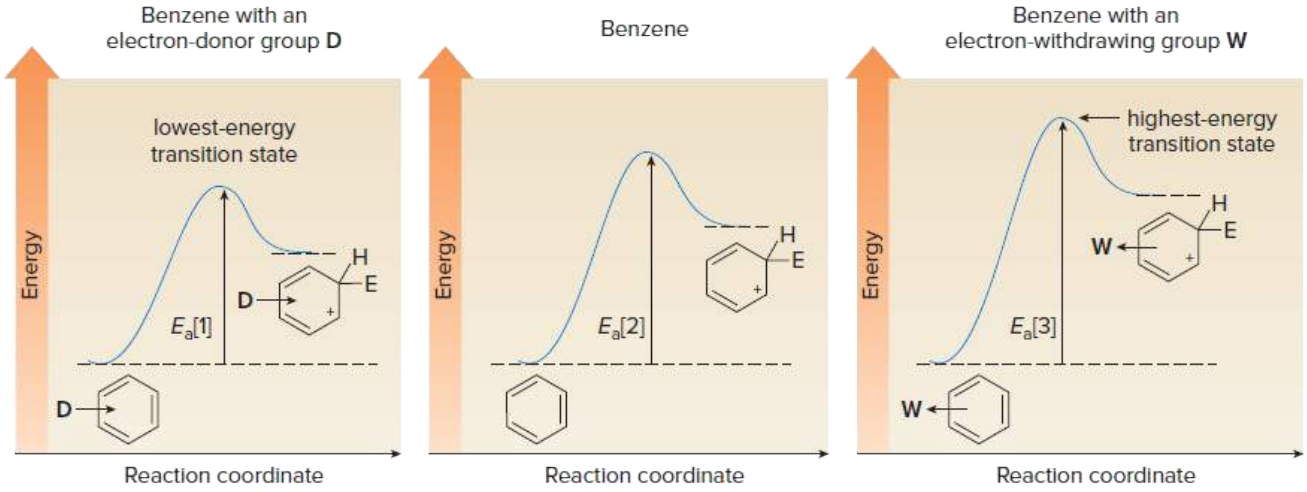


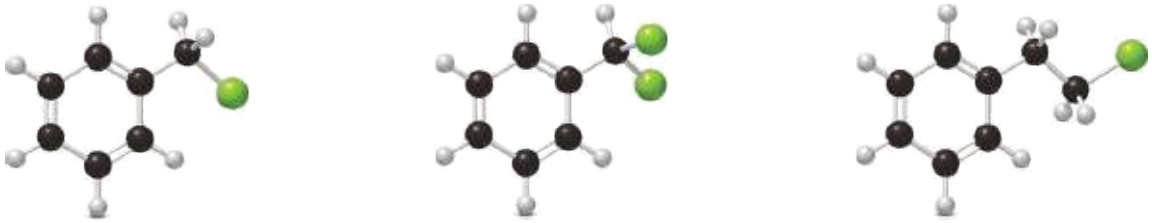
Figure 16.7 **Energy diagrams comparing the rate of electrophilic aromatic substitution of substituted benzenes**



- Electron-donor groups **D** *stabilize* the carbocation intermediate, lower the energy of the transition state, and *increase* the rate of reaction.
- Electron-withdrawing groups **W** *destabilize* the carbocation intermediate, raise the energy of the transition state, and *decrease* the rate of reaction.

Problem 16.21

Rank the following compounds in order of increasing reactivity in electrophilic aromatic substitution.



16.9 Orientation Effects in Substituted Benzenes

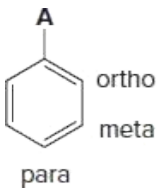
To understand why particular orientation effects arise, you must keep in mind the general structures for ortho, para directors and for meta directors already given in Section 16.7. There are two general types of ortho, para directors and one general type of meta director:

- **All ortho, para directors are R groups or have a nonbonded electron pair on the atom bonded to the benzene ring.**
- **All meta directors have a full or partial positive charge on the atom bonded to the benzene ring.**

To evaluate the directing effects of a given substituent, we can follow a stepwise procedure.

How To Determine the Directing Effects of a Particular Substituent

Step [1] **Draw all resonance structures for the carbocation formed from attack of an electrophile E^+ at the ortho, meta, and para positions of a substituted benzene (C_6H_5–A).**



- There are at least three resonance structures for each site of reaction.
- Each resonance structure places a positive charge **ortho** or **para** to the new C–E bond.

Step [2] **Evaluate the stability of the intermediate resonance structures. The electrophile attacks at those positions that give the *most stable* carbocation.**

Sections 16.9A–C show how this two-step procedure can be used to evaluate the directing effects of the CH_3 group in toluene, the NH_2 group in aniline, and the NO_2 group in nitrobenzene, respectively.

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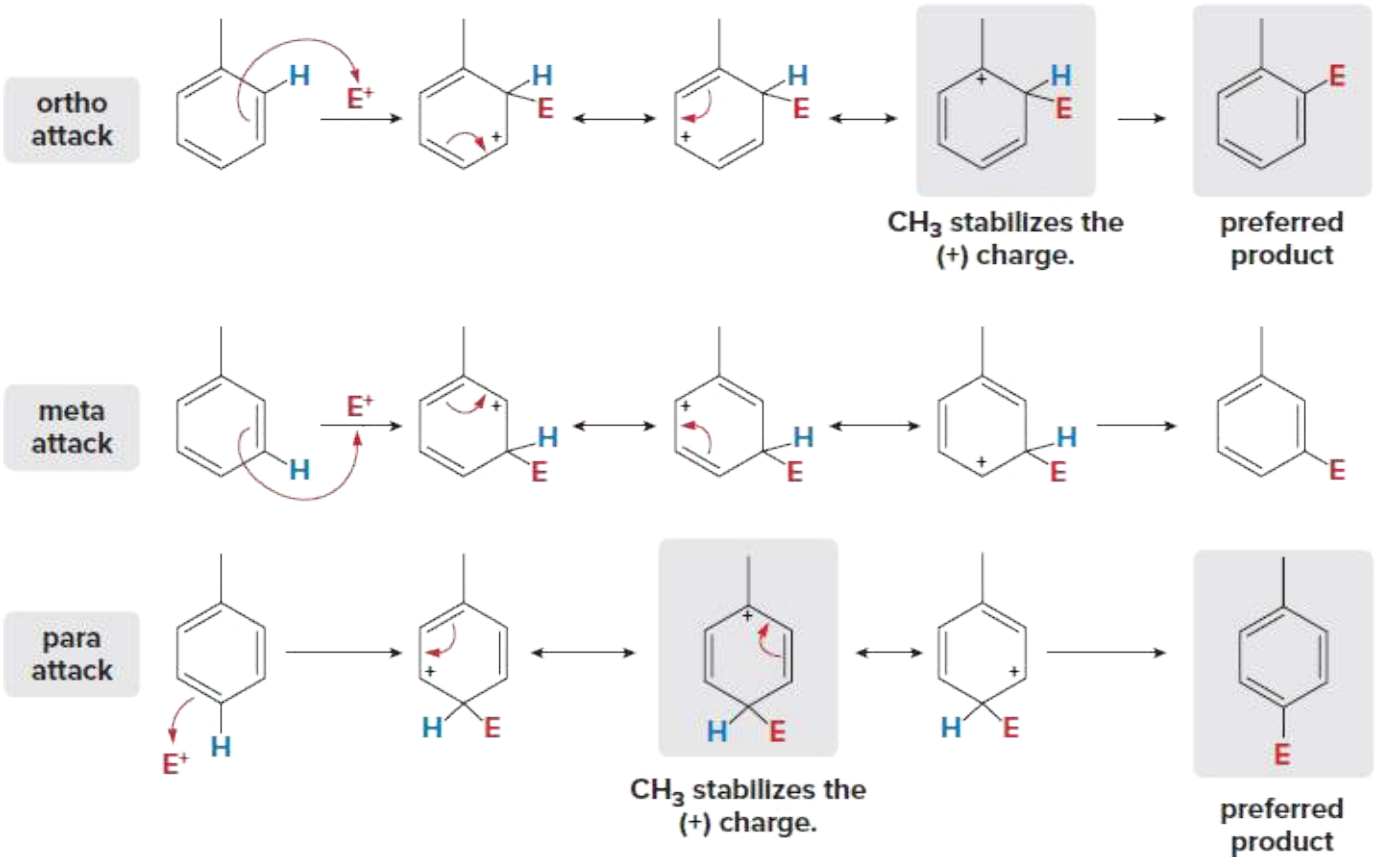
16.9A The CH_3 Group—An ortho, para Director

To understand why a CH_3 group directs electrophilic aromatic substitution to the ortho and para positions, first draw all resonance structures that result from electrophilic attack at the ortho, meta, and para positions to the CH_3 group.

Always draw in the H atom at the site of electrophilic attack. This will help you keep track of where the charges go.



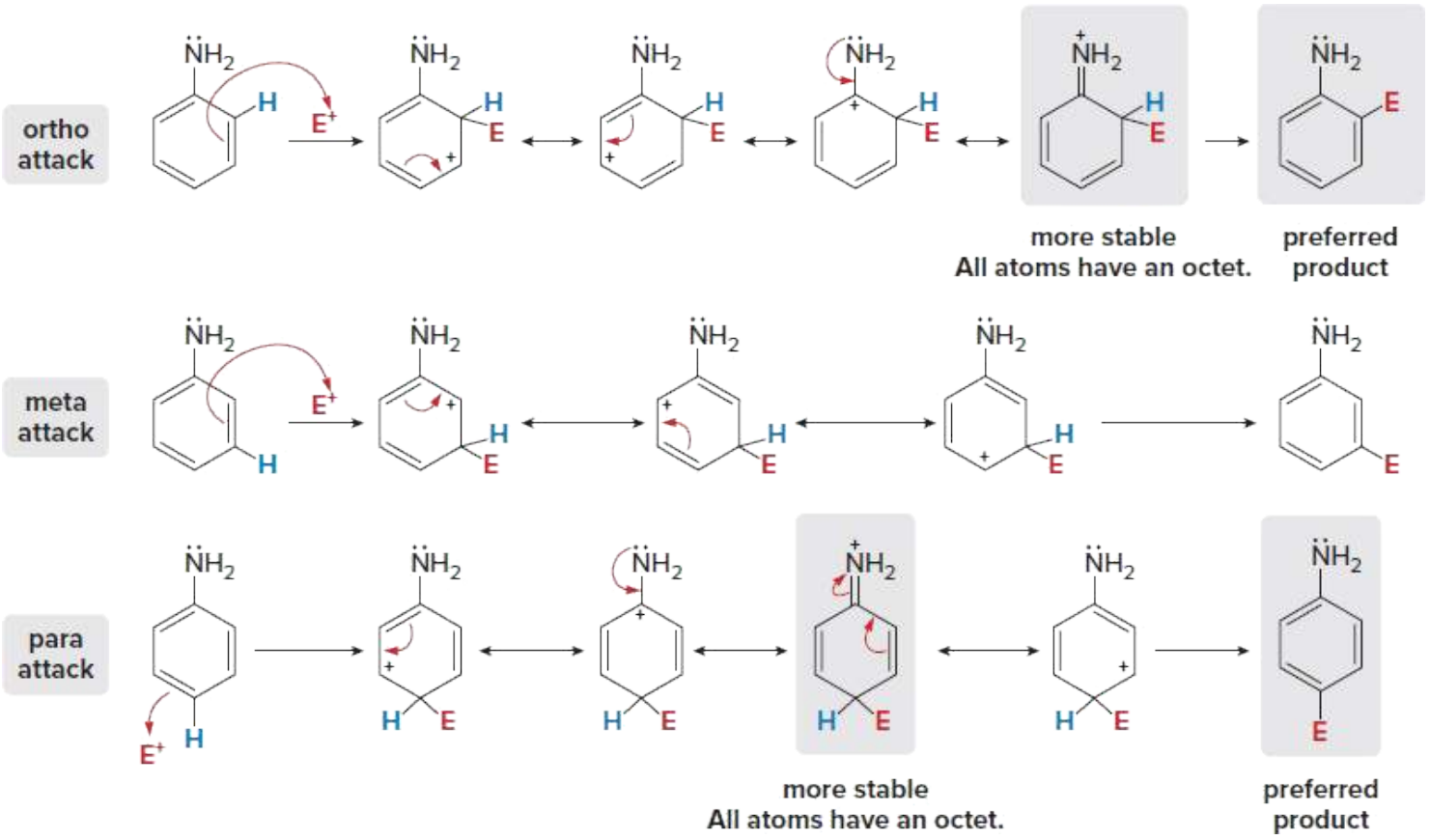
The positive charge in all resonance structures is always ortho or para to the new C–E bond. It is *not* necessarily ortho or para to the CH_3 group.

To evaluate the stability of the resonance structures, determine whether any are especially stable or unstable. In this example, attack ortho or para to CH_3 generates a resonance structure that places a positive charge on a carbon atom with the CH_3 group. The electron-donating CH_3 group *stabilizes* the adjacent positive charge. In contrast, attack meta to the CH_3 group does *not* generate any resonance structure stabilized by electron donation. Other alkyl groups are ortho, para directors for the same reason.

- **The CH_3 group directs electrophilic attack ortho and para to itself because an electron-donating inductive effect stabilizes the carbocation intermediate.**

16.9B The NH_2 Group—An ortho, para Director

To understand why an amino group (NH_2) directs electrophilic aromatic substitution to the ortho and para positions, follow the same procedure.

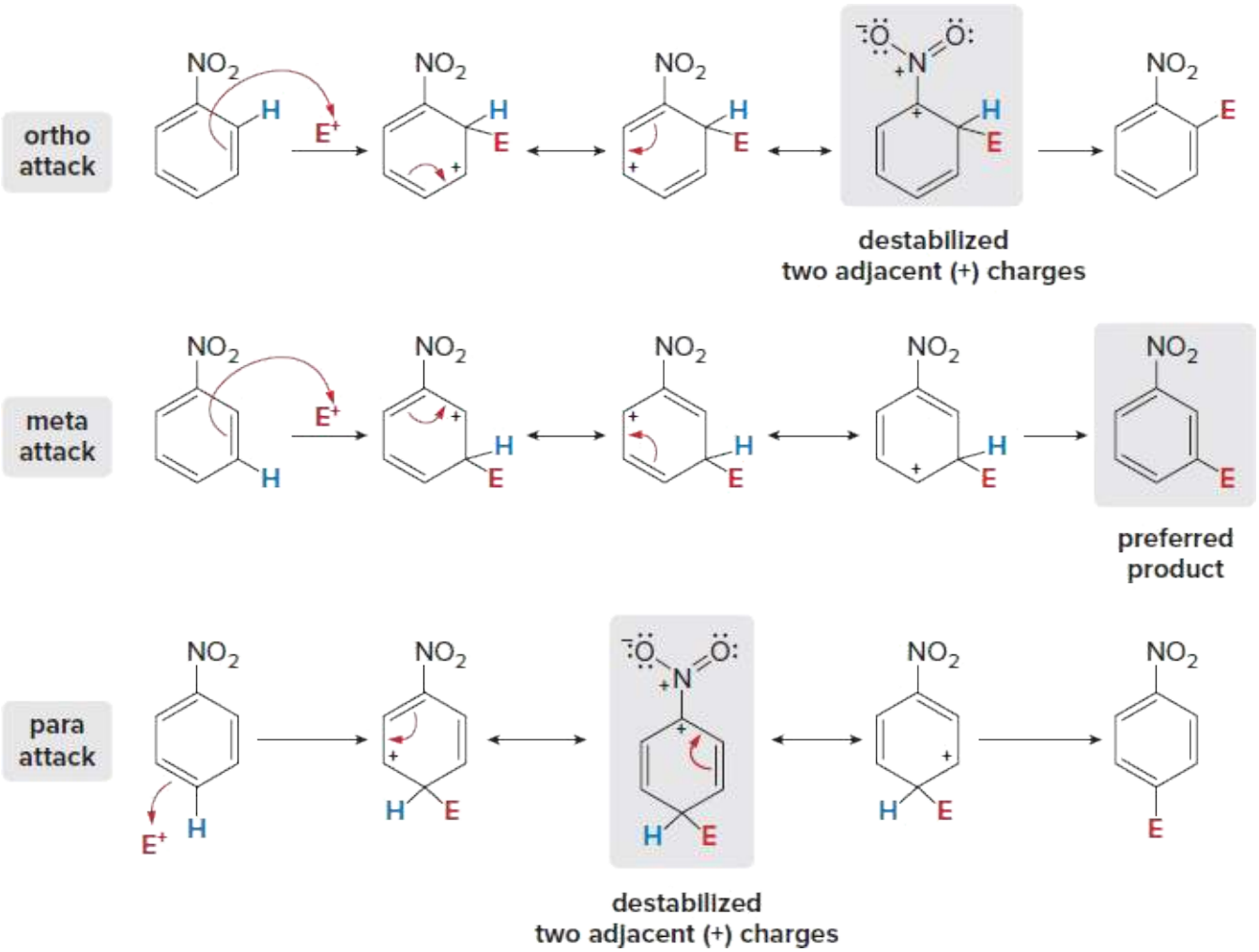


Attack at the meta position generates the usual three resonance structures. Because of the lone pair on the N atom, attack at the ortho and para positions generates a fourth resonance structure, which is stabilized because every atom has an octet of electrons. This additional resonance structure can be drawn for all substituents that have an N, O, or halogen atom bonded directly to the benzene ring.

- **The NH_2 group directs electrophilic attack ortho and para to itself because the carbocation intermediate has additional resonance stabilization.**

16.9C The NO_2 Group—A meta Director

To understand why a nitro group (NO_2) directs electrophilic aromatic substitution to the meta position, follow the same procedure.



Attack at each position generates three resonance structures. One resonance structure resulting from attack at the ortho and para positions is especially *destabilized*, because it contains a positive charge on two adjacent atoms. Attack at the meta position does not generate any particularly unstable resonance structures.

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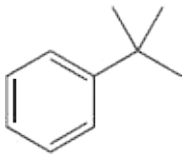
- **With the NO_2 group (and all meta directors), meta attack occurs because attack at the ortho or para position gives a destabilized carbocation intermediate.**

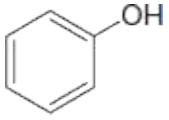
Problem 16.22

Draw all resonance structures for the carbocation formed by ortho attack of the electrophile $^{+}NO_2$ on each starting material. Label any resonance structures that are especially stable or unstable.

a.



b.



c.

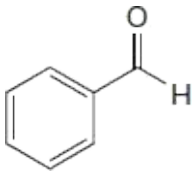
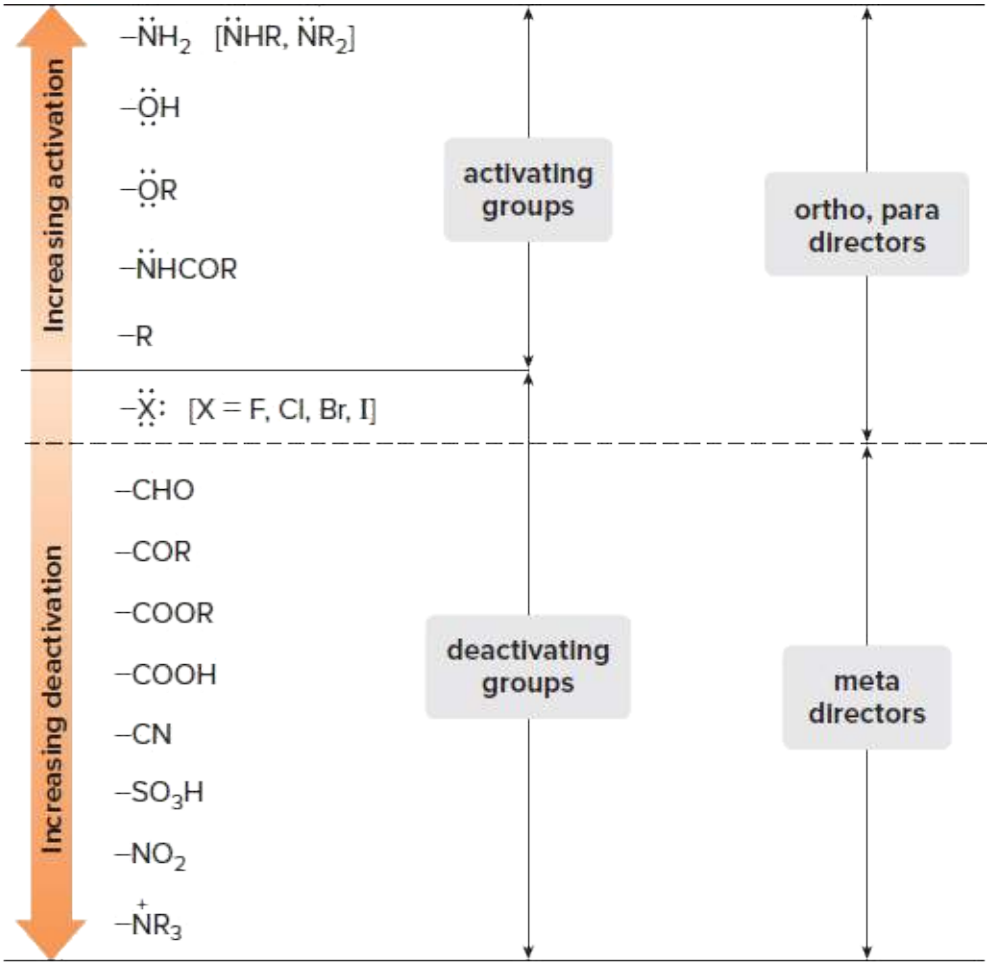


Figure 16.8 summarizes the reactivity and directing effects of the common substituents on benzene rings.

Figure 16.8 **The reactivity and directing effects of common substituted benzenes**



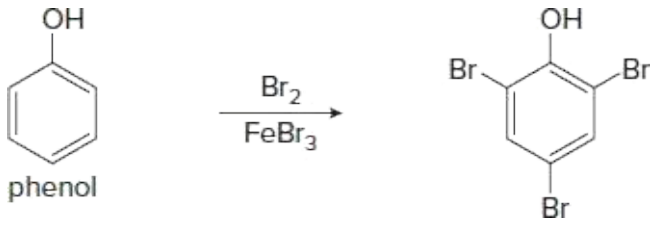
In summary:
[1] All ortho, para directors except the halogens activate the benzene ring.
[2] All meta directors deactivate the benzene ring.
[3] The halogens deactivate the benzene ring.

16.10 Limitations on Electrophilic Substitution Reactions with Substituted Benzenes

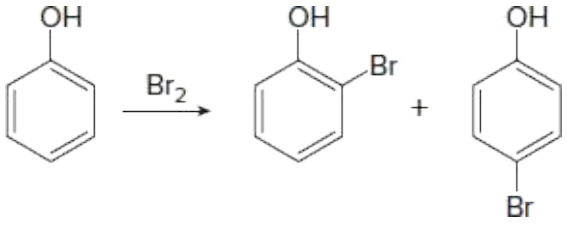
Although electrophilic aromatic substitution works well with most substituted benzenes, halogenation and the Friedel–Crafts reactions have some additional limitations that must be kept in mind.

16.10A Halogenation of Activated Benzenes

Considering all electrophilic aromatic substitution reactions, halogenation occurs the most readily. As a result, benzene rings activated by strong electron-donating groups—OH, NH_2, and their alkyl derivatives (OR, NHR, and NR_2)—undergo polyhalogenation when treated with X_2 and FeX_3. Aniline ($C_6H_5NH_2$) and phenol (C_6H_5OH) both give a tribromo derivative when treated with Br_2 and $FeBr_3$. Substitution occurs at all hydrogen atoms ortho and para to the NH_2 and OH groups.



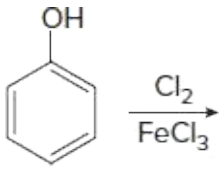
Monosubstitution of H by Br occurs with Br_2 *alone* without added catalyst to form a mixture of ortho and para products.



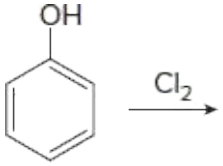
Problem 16.23

Draw the products of each reaction.

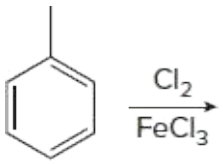
a.



b.



c.

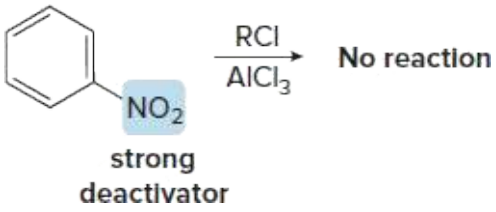


16.10B Limitations in Friedel–Crafts Reactions

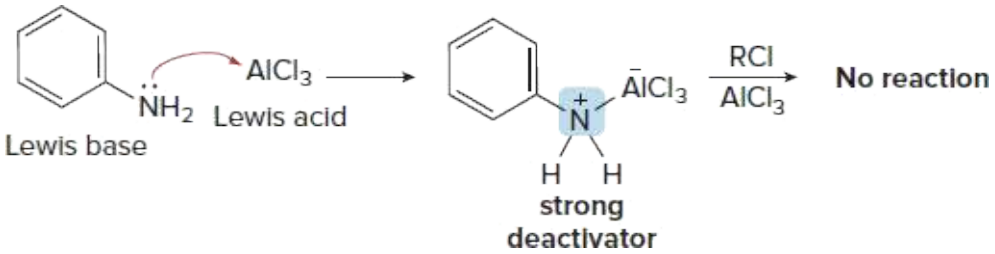
Friedel–Crafts reactions are the most difficult electrophilic aromatic substitution reactions to carry out in the laboratory. They do not occur when the benzene ring is

substituted with NO_2 (or any meta deactivator) or with NH_2, NHR, or NR_2 (strong activators).

A benzene ring deactivated by a strong electron-withdrawing group—that is, any of the meta directors—is not electron rich enough to undergo Friedel–Crafts reactions.

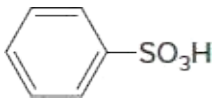


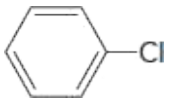
Friedel–Crafts reactions also do not occur with NH_2 groups, which are strong activating groups. NH_2 groups are strong Lewis bases (due to the nonbonded electron pair on N), so they react with $AlCl_3$, the Lewis acid needed for alkylation or acylation. The resulting product contains a positive charge adjacent to the benzene ring, so the ring is now strongly deactivated and therefore unreactive in Friedel–Crafts reactions.

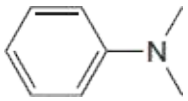


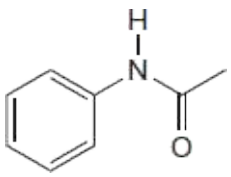
Problem 16.24

Which of the following compounds undergo Friedel–Crafts alkylation with CH_3Cl and $AlCl_3$? Draw the products formed when a reaction occurs.

a. 

b. 

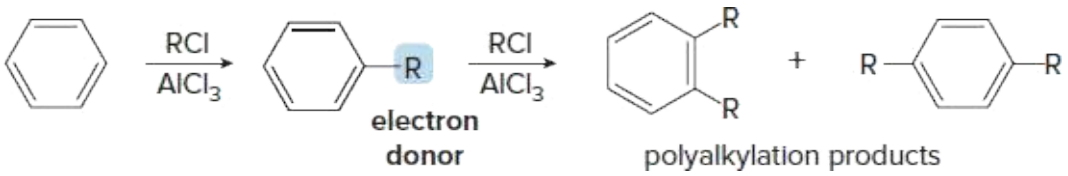
c. 

d. 

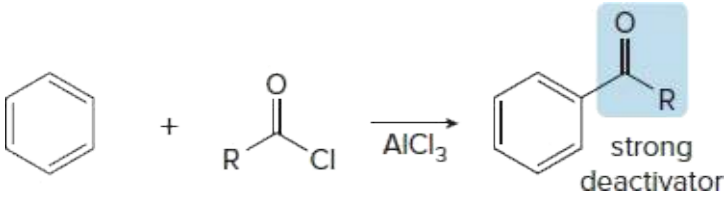
Another limitation of the Friedel–Crafts alkylation arises because of polyalkylation. Treatment of benzene with an alkyl halide and $AlCl_3$ places an electron-donor R group on the ring. Because R groups *activate* a ring, the alkylated product (C_6H_5R) is now *more reactive* than benzene itself toward further substitution, and it reacts again with

RCl to give products of polyalkylation.

To minimize polyalkylation, a large excess of benzene is used relative to the amount of alkyl halide.



Polysubstitution does not occur with Friedel–Crafts acylation, because the product now has an electron-withdrawing group that deactivates the ring toward another electrophilic substitution.

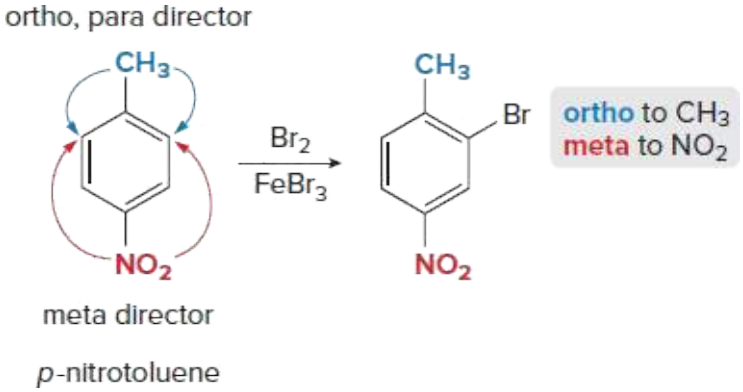


16.11 Disubstituted Benzenes

What happens in electrophilic aromatic substitution when a disubstituted benzene ring is used as starting material? To predict the products, look at the directing effects of *both* substituents and then determine the net result, using three guidelines.

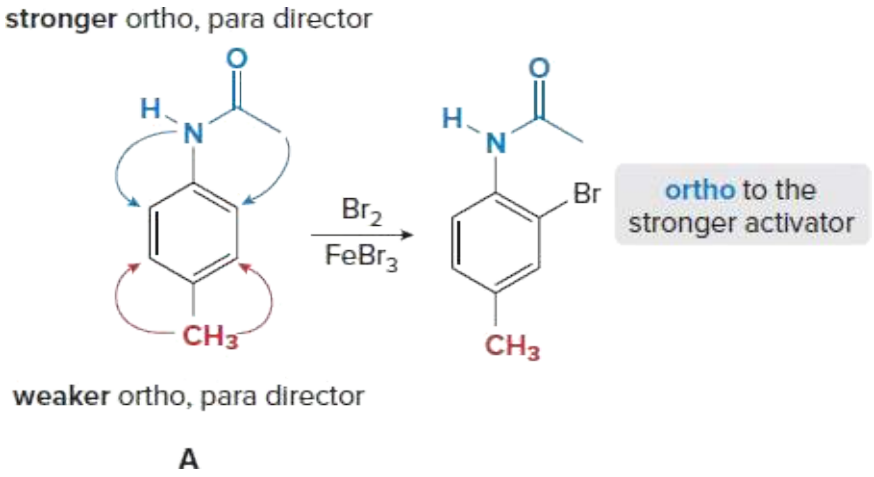
Rule [1] **When the directing effects of two groups *reinforce*, the new substituent is located on the position directed by both groups.**

The CH_3 group in *p*-nitrotoluene is an ortho, para director and the NO_2 group is a meta director. These two effects reinforce each other so that one product is formed on treatment with Br_2 and $FeBr_3$. The position para to the CH_3 group is "blocked" by a nitro group, so no substitution can occur on that carbon.



Rule [2] **If the directing effects of two groups *oppose* each other, the more powerful activator "wins out."**

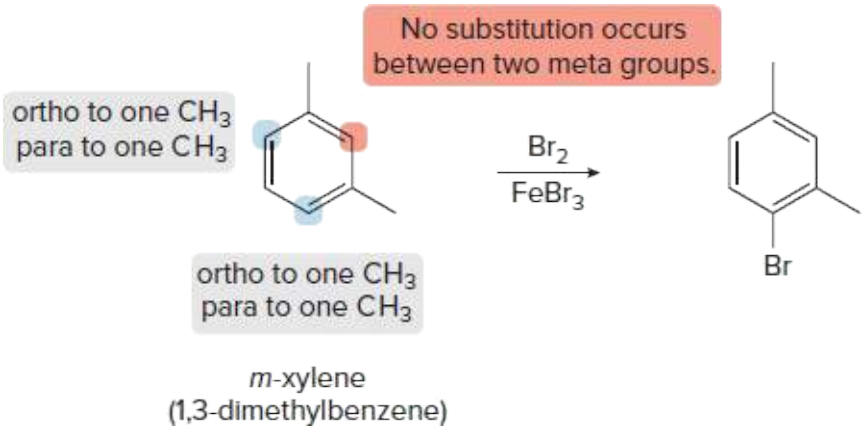
In compound A, the $NHCOCH_3$ group activates its two ortho positions, and the CH_3 group activates its two ortho positions to reaction with electrophiles. Because the $NHCOCH_3$ is a stronger activator, substitution occurs ortho to it.



A

Rule [3] **No substitution occurs between two meta substituents because of crowding.**

For example, no substitution occurs at the carbon atom between the two CH_3 groups in *m*-xylene, even though two CH_3 groups activate that position.

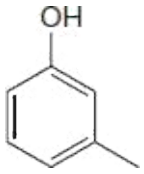


Sample Problem 16.6 **Drawing the Substitution Products from a Disubstituted Benzene**

Draw the products formed from nitration of each compound.

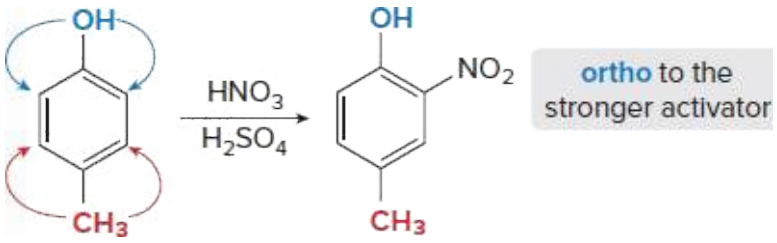
a.

b.

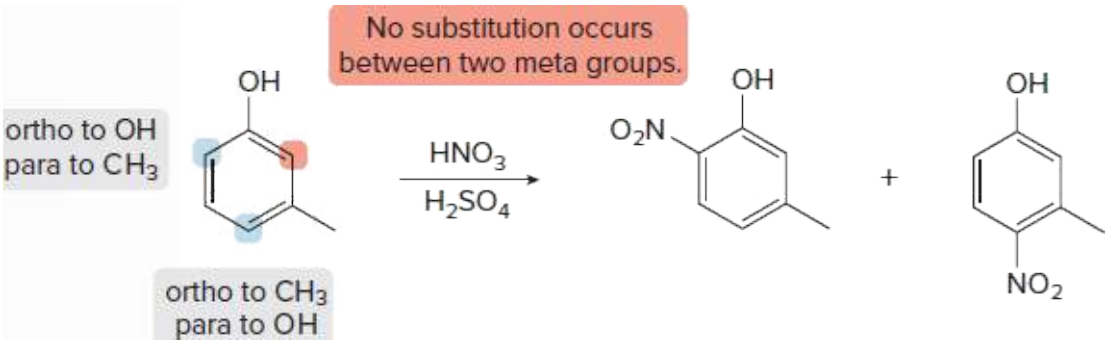


Solution

a. Both the OH and CH_3 groups are ortho, para directors. Because the OH group is a stronger activator, substitution occurs ortho to it.



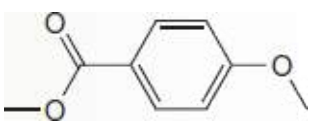
b. Both the OH and CH_3 groups are ortho, para directors whose directing effects reinforce each other in this case. No substitution occurs between the two meta substituents, however, so two products result.



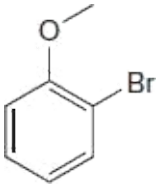
Problem 16.25

Draw the products formed when each compound is treated with HNO_3 and H_2SO_4.

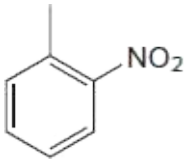
a.



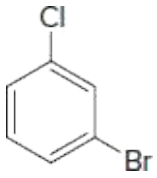
b.



c.



d.



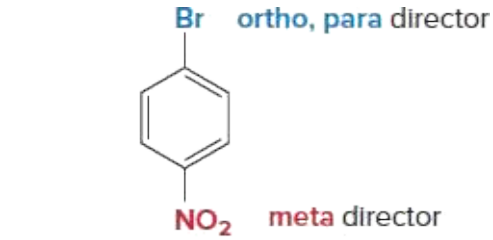
More Practice:

Try Problems 16.37, 16.41a–e, 16.43a–c.

16.12 Synthesis of Benzene Derivatives

To synthesize benzene derivatives with more than one substituent, we must always take into account the directing effects of each substituent. In a disubstituted benzene, the directing effects indicate which substituent must be added to the ring first.

For example, the Br group in *p*-bromonitrobenzene is an ortho, para director and the NO_2 group is a meta director. Because the two substituents are para to each other, the ortho, para director must be introduced *first* when synthesizing this compound from benzene.

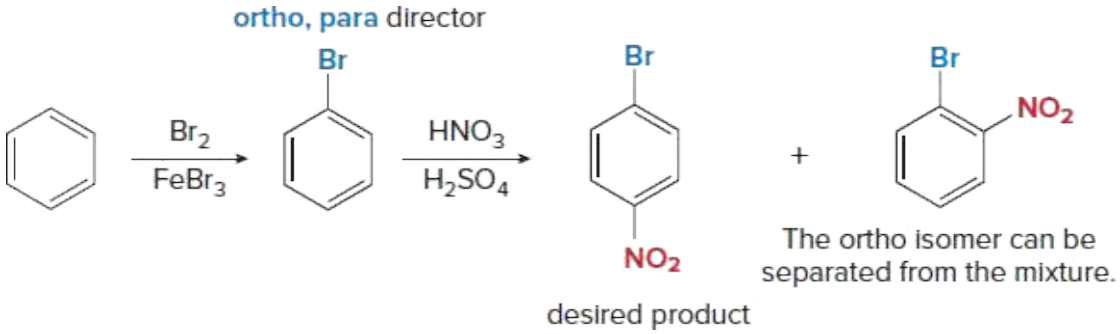


p-bromonitrobenzene

With two para substituents, add the ortho, para director first.

Thus, Pathway [1], in which bromination precedes nitration, yields the desired para product, whereas Pathway [2], in which nitration precedes bromination, yields the undesired meta isomer.

Pathway [1] Bromination before nitration: The desired para product is formed.



Pathway [2] Nitration before bromination: The undesired meta isomer is formed.

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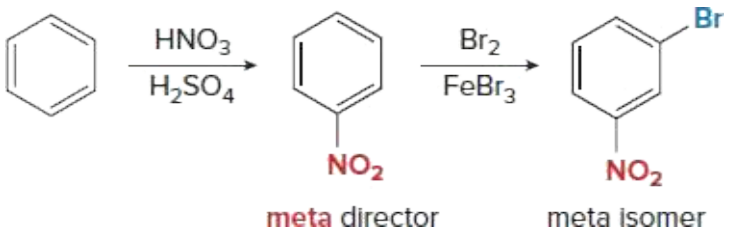
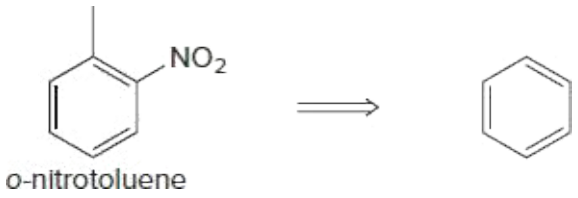


Pathway [1] yields both the desired para product and the undesired ortho isomer. Because these compounds are constitutional isomers, they are separable. Obtaining such a mixture of ortho and para isomers is often unavoidable.

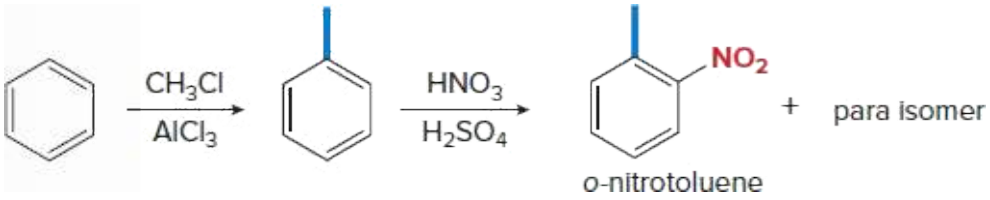
Sample Problem 16.7 Synthesizing a Disubstituted Benzene

Devise a synthesis of *o*-nitrotoluene from benzene.



Solution

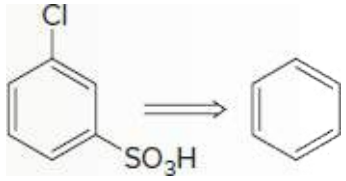
The CH_3 group in *o*-nitrotoluene is an ortho, para director and the NO_2 group is a meta director. Because the two substituents are ortho to each other, the ortho, para director must be introduced first. The synthesis thus involves two steps: Friedel–Crafts alkylation followed by nitration.



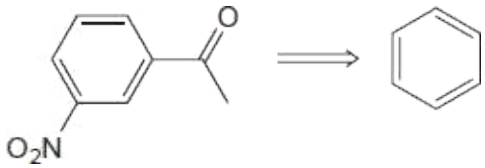
Problem 16.26

Devise a synthesis of each compound from the indicated starting material.

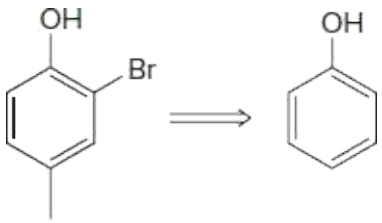
a.



b.

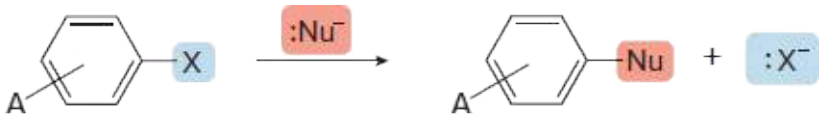


c.



16.13 Nucleophilic Aromatic Substitution

Although most reactions of aromatic compounds occur by way of electrophilic aromatic substitution, aryl halides undergo a limited number of substitution reactions with strong nucleophiles.



X = F, Cl, Br, I
A = H or electron-withdrawing group

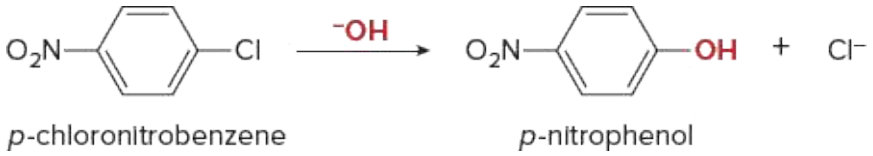
- **Nucleophilic aromatic substitution results in the substitution of a halogen X on a benzene ring by a nucleophile ($:Nu^-$).**

As we learned in Section 7.17, these reactions *cannot* occur by an S_N1 or S_N2 mechanism, which take place only at sp^3 hybridized carbons. Instead, two different mechanisms are proposed to explain the results: addition–elimination (Section 16.13A) and elimination–addition (Section 16.13B).

16.13A Nucleophilic Aromatic Substitution by Addition–Elimination

Aryl halides with strong electron-withdrawing groups (such as NO_2) on the ortho or para positions react with nucleophiles to afford substitution products. Treatment of *p*-chloronitrobenzene with hydroxide (^-OH) affords *p*-nitrophenol by replacement of Cl

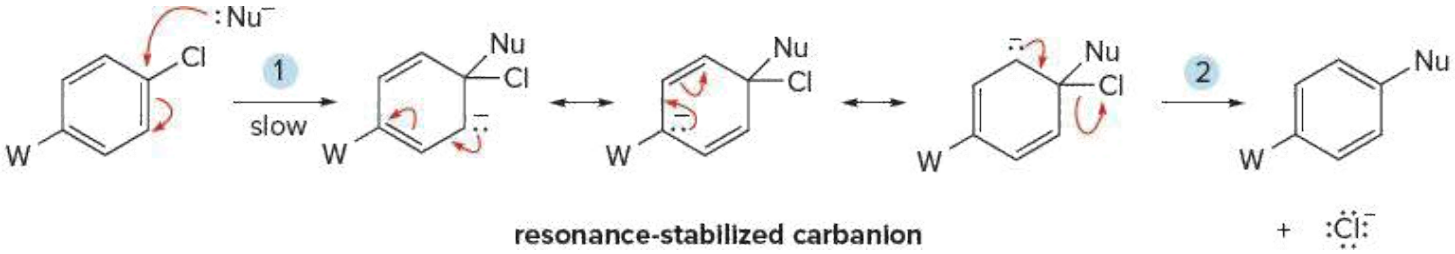
by OH.



p-chloronitrobenzene *p*-nitrophenol

Nucleophilic aromatic substitution occurs with a variety of strong nucleophiles, including ^-OH, ^-OR, $^-NH_2$, ^-SR, and in some cases, neutral nucleophiles such as NH_3 and RNH_2. The mechanism of these reactions has two steps: addition of the nucleophile to form a resonance-stabilized carbanion, followed by elimination of the halogen leaving group. Mechanism 16.10 is drawn with an aryl chloride containing a general electron-withdrawing group W.

Mechanism 16.10 Nucleophilic Aromatic Substitution by Addition–Elimination



1 **Addition of the nucleophile forms a resonance-stabilized carbanion and a new C–Nu bond in the rate-determining step.**

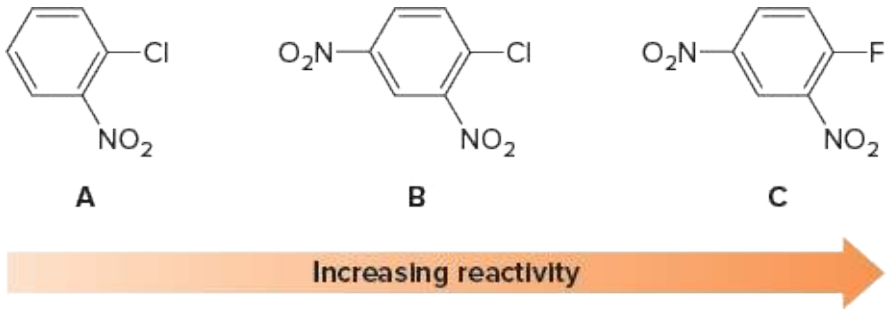
2 **Loss of the leaving group re-forms the aromatic ring.**

In nucleophilic aromatic substitution, the following trends in reactivity are observed.

- **Increasing the number of electron-withdrawing groups *increases* the reactivity of the aryl halide. Electron-withdrawing groups stabilize the intermediate carbanion and, by the Hammond postulate, lower the energy of the transition state that forms it.**
- **Increasing the electronegativity of the halogen *increases* the reactivity of the aryl halide. A more electronegative halogen stabilizes the intermediate carbanion by an inductive effect, making aryl fluorides (ArF) much *more* reactive than other aryl halides, which contain less electronegative halogens.**

Thus, aryl chloride B is more reactive than *o*-chloronitrobenzene (A) because it

contains *two* electron-withdrawing NO_2 groups. Aryl fluoride C is more reactive than B because C contains the *more electronegative* halogen, fluorine.



The location of the electron-withdrawing group greatly affects the rate of nucleophilic aromatic substitution. When a nitro group is located ortho or para to the halogen, the negative charge of the intermediate carbanion can be delocalized onto the NO_2 group, thus stabilizing it. With a meta NO_2 group, no such additional delocalization onto the NO_2 group occurs.

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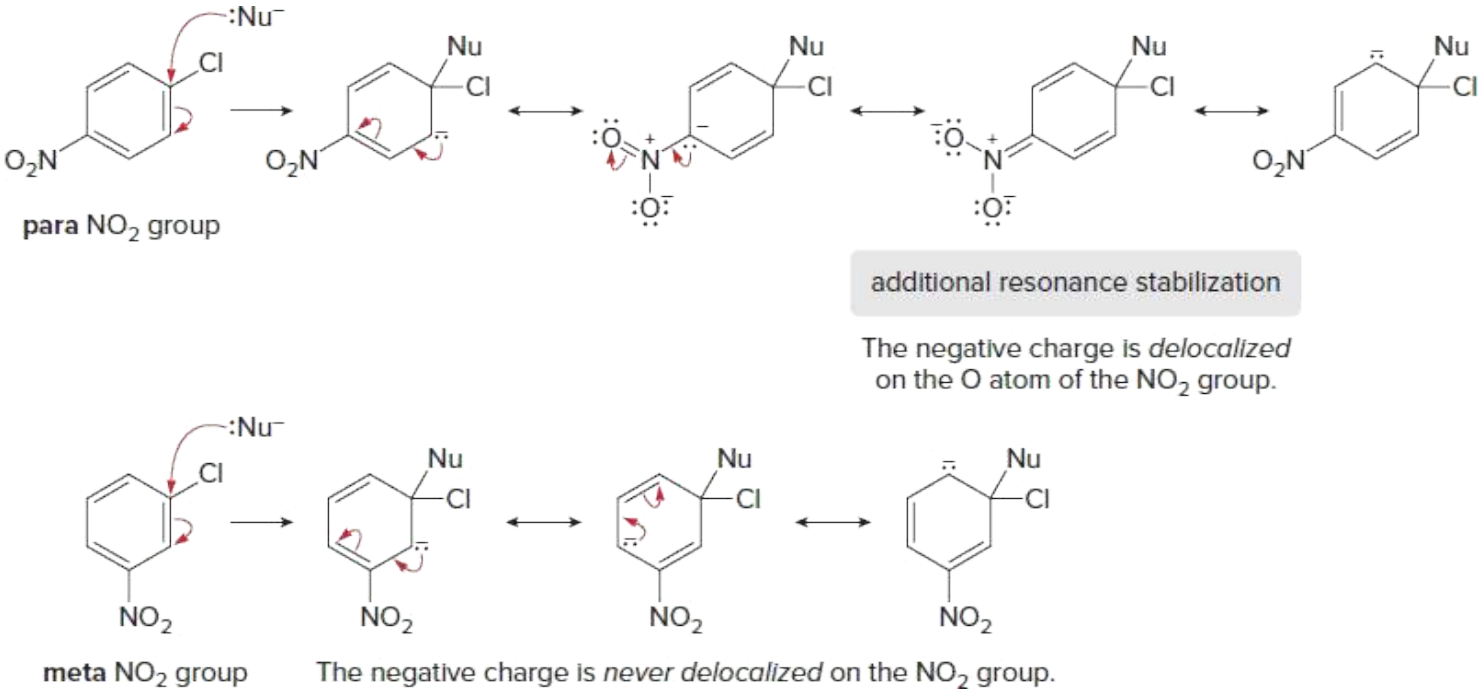
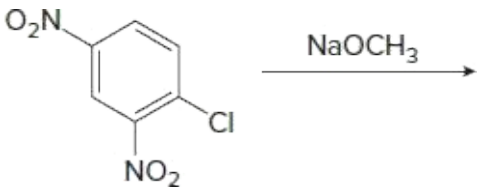
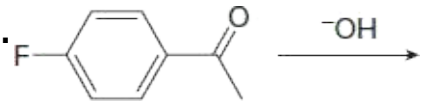


Thus, nucleophilic aromatic substitution by an addition–elimination mechanism occurs only with aryl halides that contain electron-withdrawing substituents at the ortho or para position.

Problem 16.27

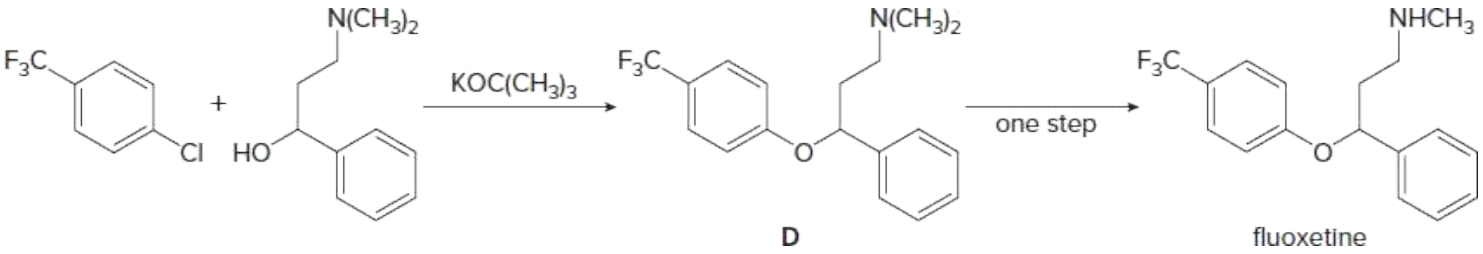
Draw the products of each reaction.

a. 

b. 

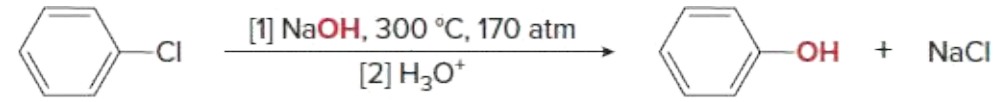
Problem 16.28

Draw a stepwise mechanism for the following reaction that forms ether D. D can be converted to the antidepressant fluoxetine (trade name Prozac) in a single step.



16.13B Nucleophilic Aromatic Substitution by Elimination–Addition: Benzyne

Aryl halides that do not contain an electron-withdrawing group generally do *not* react with nucleophiles. Under extreme reaction conditions, however, nucleophilic aromatic substitution can occur with aryl halides. For example, heating chlorobenzene with NaOH above 300 °C and 170 atmospheres of pressure affords phenol.



chlorobenzene phenol

The mechanism proposed to explain this result involves formation of a benzyne intermediate (C_6H_4) by elimination–addition. As shown in Mechanism 16.11, benzyne is a highly reactive, unstable intermediate formed by elimination of HX from an aryl halide.

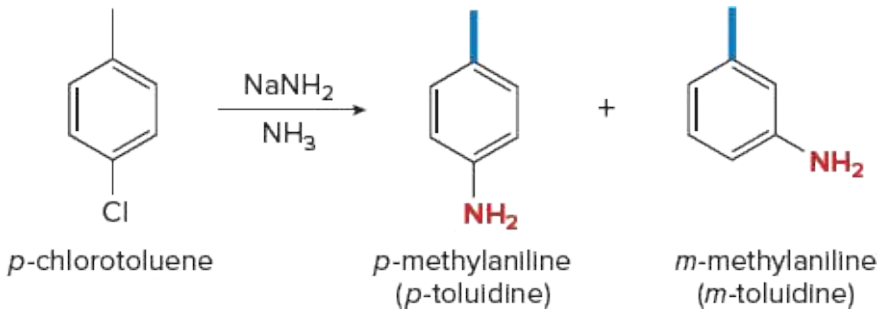
Page 758

Mechanism 16.11 Nucleophilic Aromatic Substitution by Elimination–Addition: Benzyne

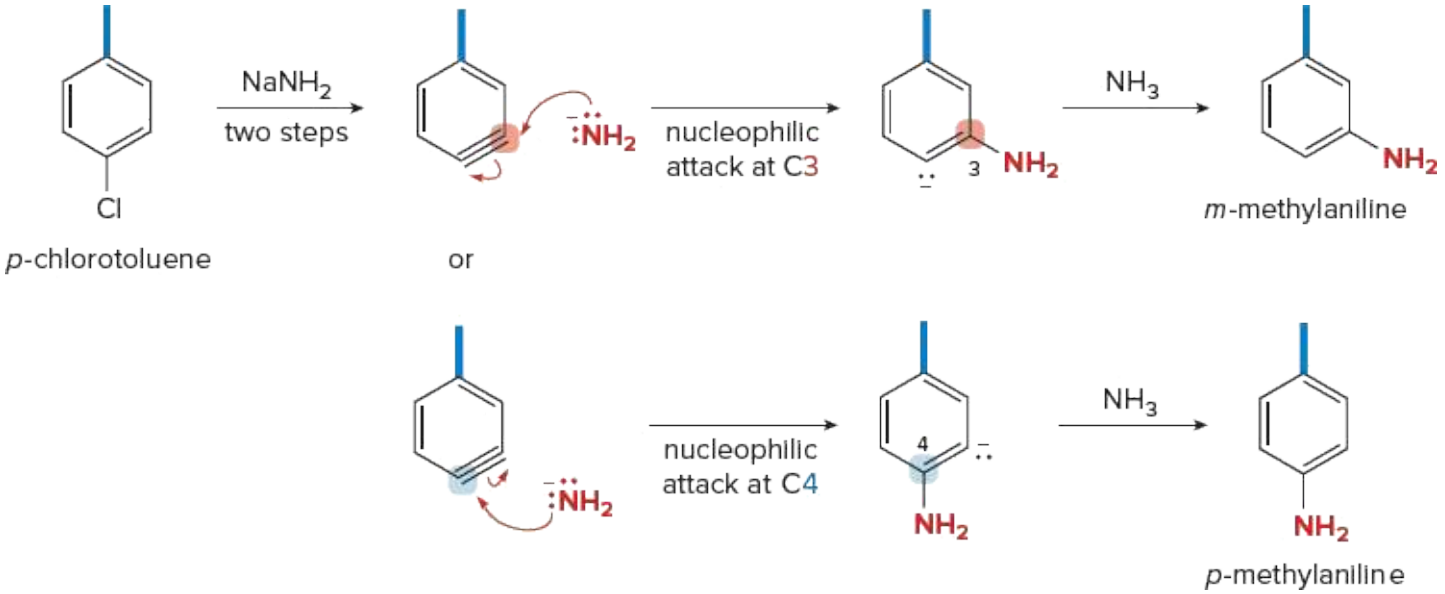
1 – 2 Elimination of H and X from two adjacent atoms forms a reactive benzyne intermediate.

3 – 4 Nucleophilic attack and protonation form the substitution product.

Formation of a benzyne intermediate explains why substituted aryl halides form mixtures of products. Nucleophilic aromatic substitution by an elimination–addition mechanism affords substitution on the carbon bonded directly to the leaving group and the carbon adjacent to it. As an example, treatment of *p*-chlorotoluene with $NaNH_2$ forms para- and meta-substitution products.

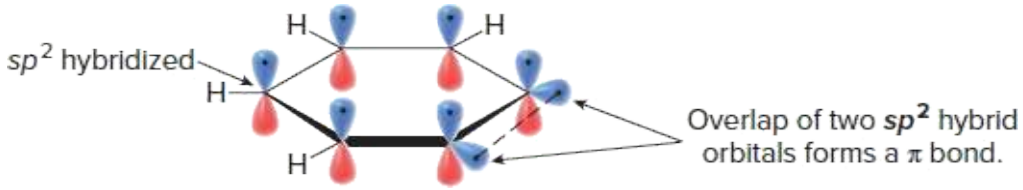


This result is explained by the fact that nucleophilic attack on the benzyne intermediate may occur at either C3 to form *m*-methylaniline, or C4 to form *p*-methylaniline.



As you might expect, the triple bond in benzyne is unusual. Each carbon of the six-membered ring is sp^2 hybridized, and as a result, the σ bond and two π bonds of the triple bond are formed with the following orbitals:

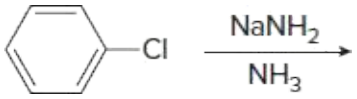
- **The σ bond is formed by overlap of two sp^2 hybrid orbitals.**
- **One π bond is formed by overlap of two *p* orbitals perpendicular to the plane of the molecule.**
- **The second π bond is formed by overlap of two sp^2 hybrid orbitals.**

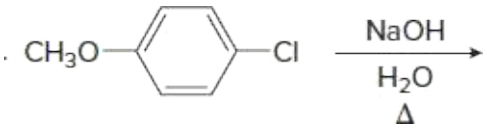


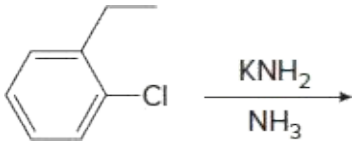
Thus, the second π bond of benzyne differs from all other π bonds seen thus far, because it is formed by the side-by-side overlap of *sp² hybrid orbitals*, not *p* orbitals. This π bond, located in the plane of the molecule, is extremely weak.

Problem 16.29

Draw the products of each reaction.

a. 

b. 

c. 

Problem 16.30

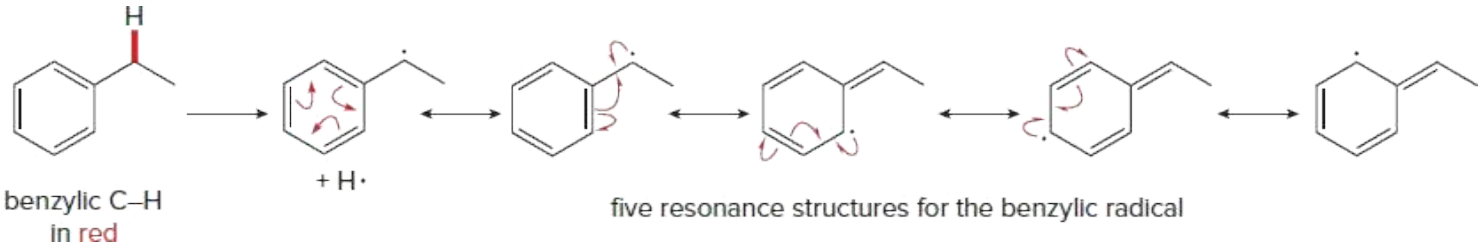
Draw all products formed when *m*-chlorotoluene is treated with KNH_2 in NH_3.

16.14 Halogenation of Alkyl Benzenes

Radical halogenation of alkanes was discussed in Chapter 13. The mechanism of radical halogenation at an allylic carbon was given in Section 13.10.

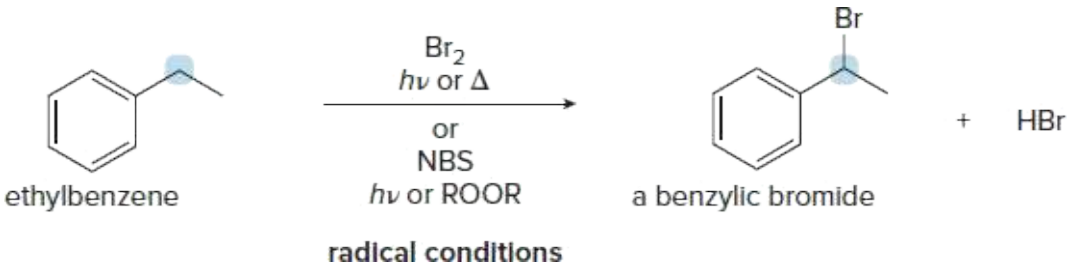
We finish Chapter 16 by learning some additional reactions of substituted benzenes that greatly expand the ability to synthesize benzene derivatives. In Section 16.14 we return to radical halogenation, and in Section 16.15 we examine useful oxidation and reduction reactions.

Benzylic C–H bonds are weaker than most other sp^3 hybridized C–H bonds, because homolysis forms a resonance-stabilized benzylic radical.



The bond dissociation energy for a benzylic C–H bond (356 kJ/mol) is even less than the bond dissociation energy for a 3° C–H bond (381 kJ/mol).

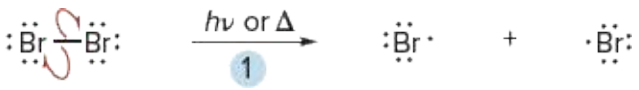
As a result, an alkyl benzene undergoes selective bromination at the weak benzylic C–H bond under radical conditions to form a benzylic halide. For example, radical bromination of ethylbenzene using either Br_2 (in the presence of light or heat) or *N*-bromosuccinimide (NBS, in the presence of light or peroxides) forms a benzylic bromide as the sole product.



The mechanism for halogenation at the benzylic position resembles other radical halogenation reactions, so it involves initiation, propagation, and termination. Mechanism 16.12 illustrates the radical bromination of ethylbenzene using Br_2 (*hν* or Δ).

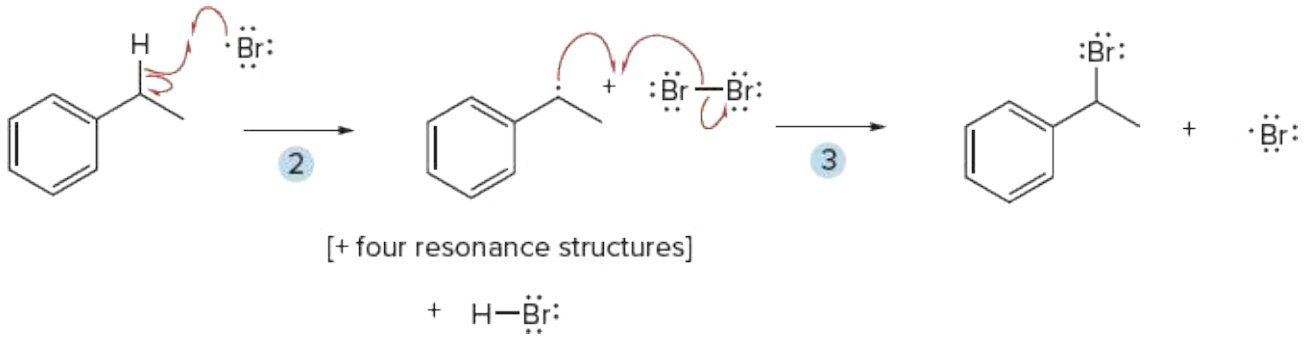
Mechanism 16.12 Benzylic Bromination

Part [1] Initiation



1 Homolysis of the Br–Br bond requires light or heat and forms two bromine radicals.

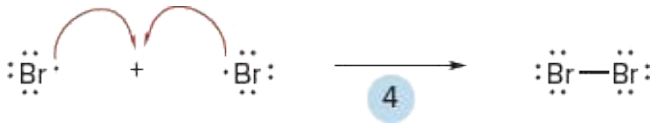
Part [2] Propagation



2 **Abstraction of a benzylic hydrogen by Br• forms the resonance-stabilized benzylic radical.**

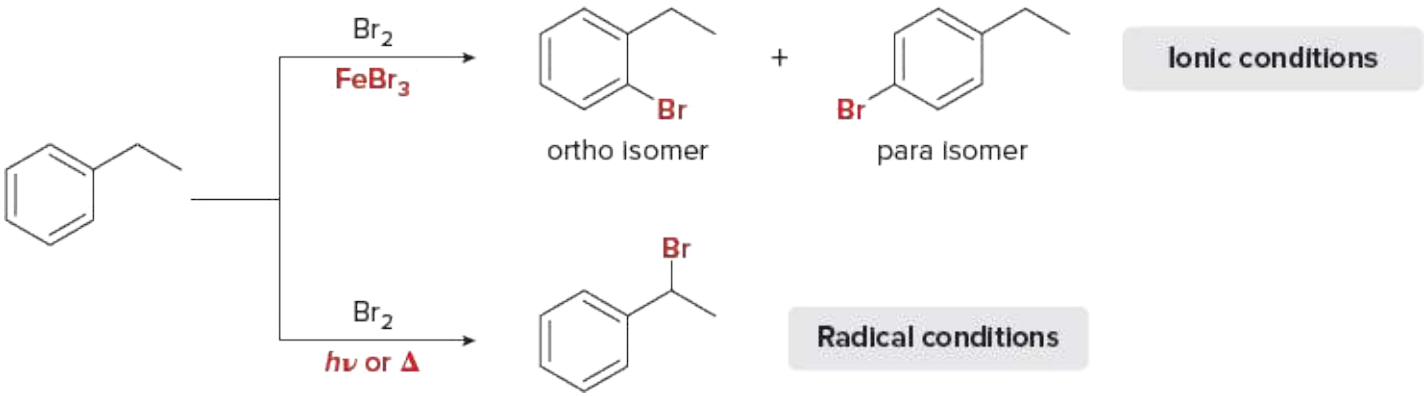
3 **The benzylic radical abstracts a bromine atom to form the benzylic bromide. Because Br• is also formed, Steps [2] and [3] can occur repeatedly without additional initiation.**

Part [3] Termination



4 **Termination of the chain occurs when any two radicals combine to form a bond.**

Thus, an alkyl benzene undergoes two different reactions with Br_2, depending on the reaction conditions.



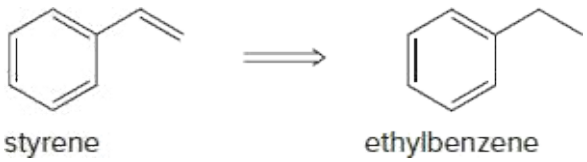
- With Br_2 and $FeBr_3$ (ionic conditions), electrophilic aromatic substitution occurs, resulting in replacement of H by Br on the aromatic ring to form ortho and para isomers.
- With Br_2 and light or heat (radical conditions), substitution of H by Br occurs at the *benzylic* carbon of the alkyl group.

The radical bromination of alkyl benzenes is a useful reaction because the resulting benzylic halide can serve as starting material for a variety of substitution and

elimination reactions, thus making it possible to form many new substituted benzenes. Sample Problem 16.8 illustrates one possibility.

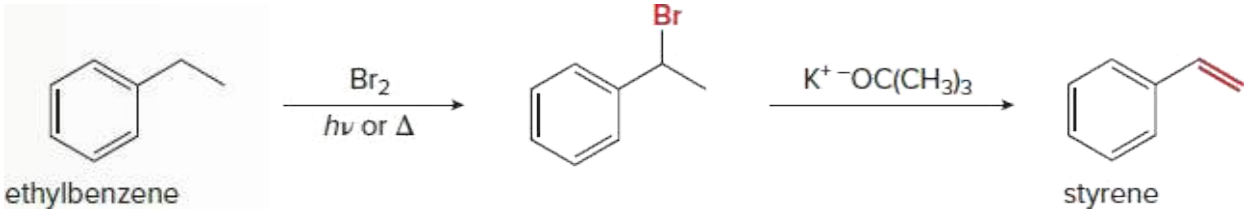
Sample Problem 16.8 Using Benzylic Bromination to Introduce a Double Bond

Design a synthesis of styrene from ethylbenzene.



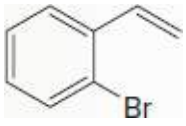
Solution

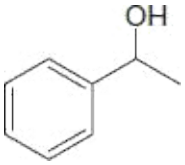
The double bond can be introduced by a two-step reaction sequence: bromination at the benzylic position under radical conditions, followed by elimination of HBr with strong base to form the π bond.

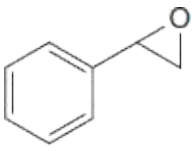


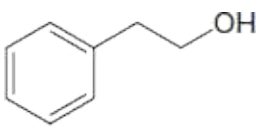
Problem 16.31

How could you use ethylbenzene to prepare each compound? More than one step is required.

a. 

b. 

c. 

d. 

More Practice:

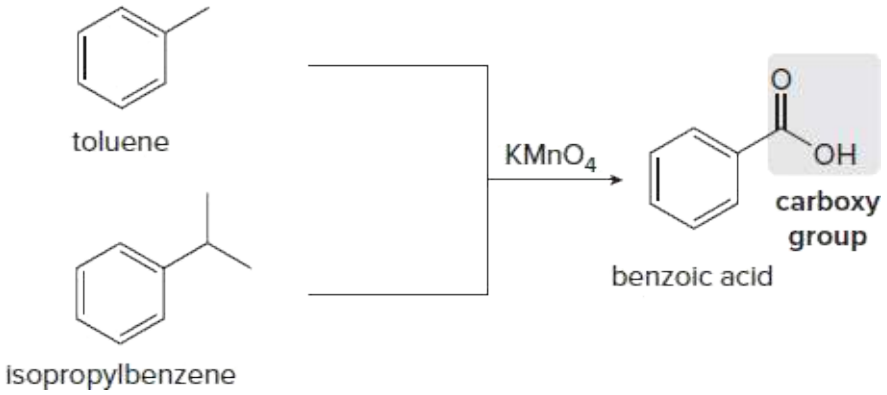
Try Problems 16.67a, e, f; 16.68a, c; 16.69.

16.15 Oxidation and Reduction of Substituted Benzenes

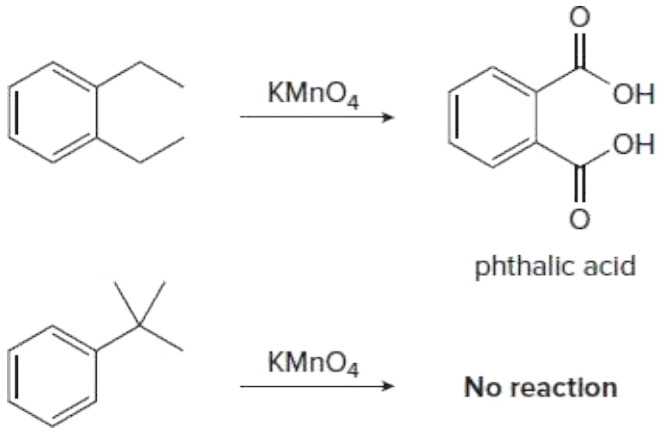
Oxidation and reduction reactions are valuable tools for preparing many other benzene derivatives. Because the mechanisms are complex and do not have general applicability, only reagents and reactions are presented, without reference to the detailed mechanism.

16.15A Oxidation of Alkyl Benzenes

Arenes containing at least one benzylic C–H bond are oxidized with $KMnO_4$ to benzoic acid, a carboxylic acid with the carboxy group (COOH) bonded directly to the benzene ring. With some alkyl benzenes, this also results in the cleavage of carbon–carbon bonds, so the product has fewer carbon atoms than the starting material.

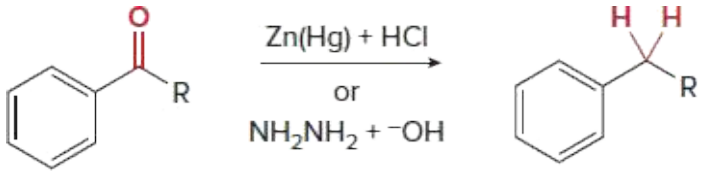


Substrates with more than one alkyl group are oxidized to dicarboxylic acids. Page 762 Compounds without a benzylic C–H bond are inert to oxidation.



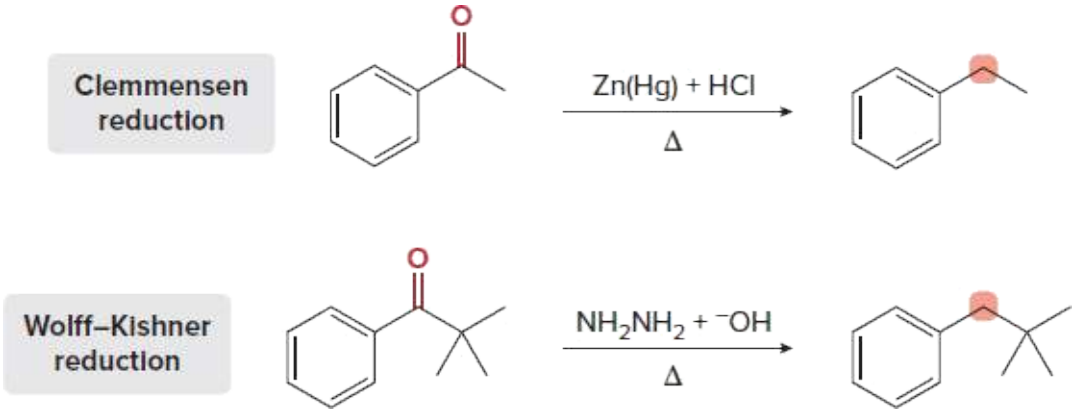
16.15B Reduction of Aryl Ketones to Alkyl Benzenes

Ketones formed as products in Friedel–Crafts acylation can be reduced to alkyl benzenes by two different methods.



- **The Clemmensen reduction uses zinc and mercury in the presence of strong acid.**
- **The Wolff–Kishner reduction uses hydrazine (NH_2NH_2) and strong base (KOH).**

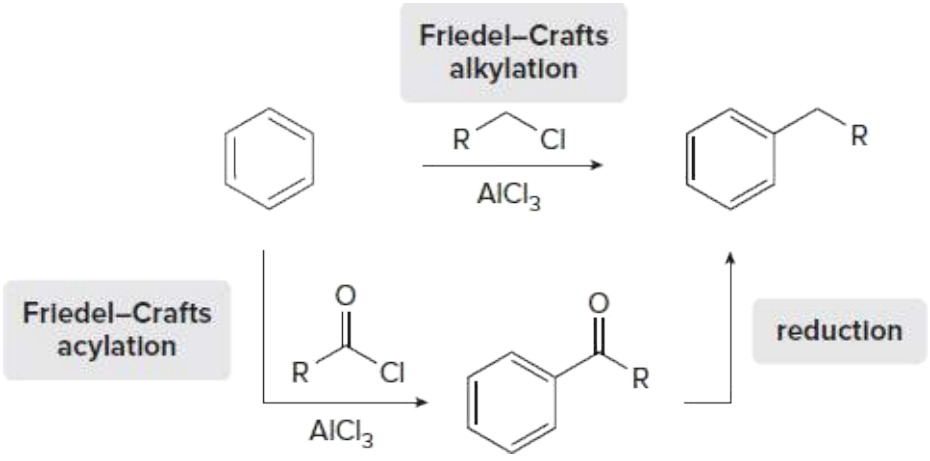
Because both C–O bonds in the starting material are converted to C–H bonds in the product, the reduction is difficult and the reaction conditions must be harsh.



We now know two different ways to introduce an alkyl group on a benzene ring (Figure 16.9):

- A one-step method using Friedel–Crafts alkylation
- A two-step method using Friedel–Crafts acylation to form a ketone, followed by reduction

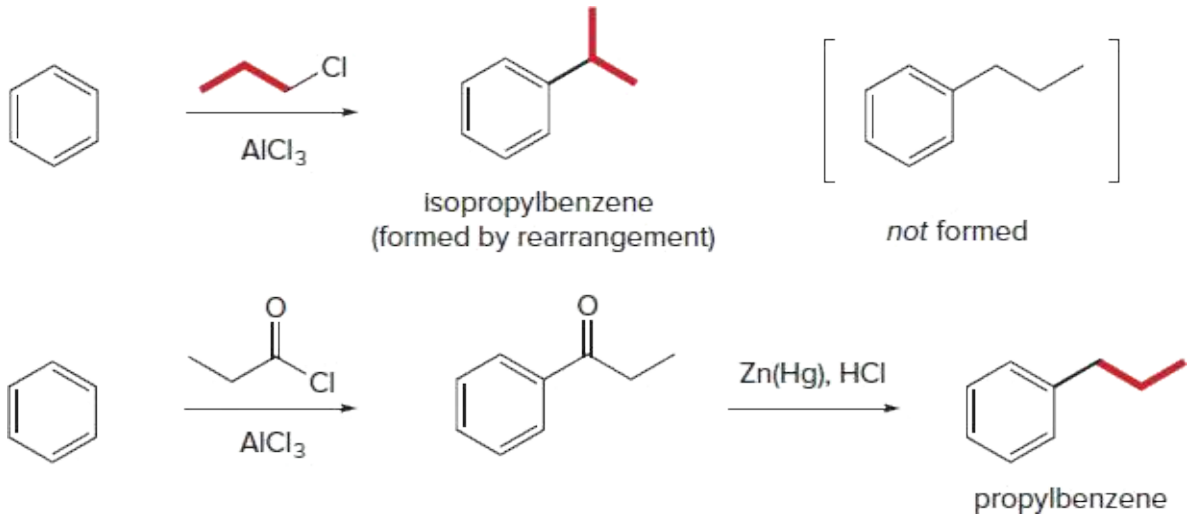
Figure 16.9 **Two methods to prepare an alkyl benzene**



Although the two-step method seems more roundabout, it must be used to

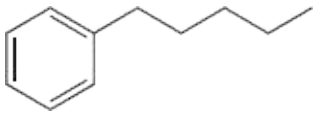
synthesize certain alkyl benzenes that cannot be prepared by the one-step Friedel–Crafts alkylation because of rearrangements.

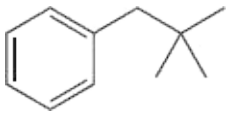
Recall from Section 16.5C that propylbenzene cannot be prepared by a Friedel–Crafts alkylation. Instead, when benzene is treated with 1-chloropropane and $AlCl_3$, isopropylbenzene is formed by a rearrangement reaction. Propylbenzene can be made, however, by a two-step procedure using Friedel–Crafts acylation followed by reduction.



Problem 16.32

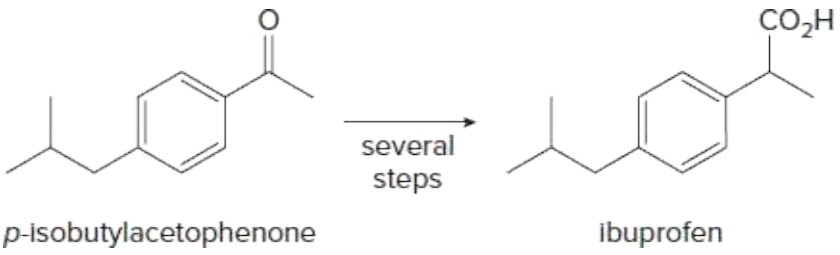
Write out the two-step sequence that converts benzene to each compound.

a. 

b. 

Problem 16.33

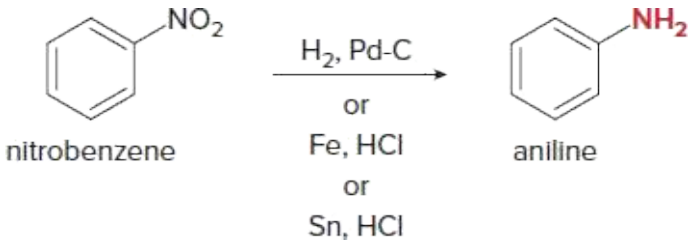
What steps are needed to convert benzene to *p*-isobutylacetophenone, a synthetic intermediate used in the synthesis of the anti-inflammatory agent ibuprofen.



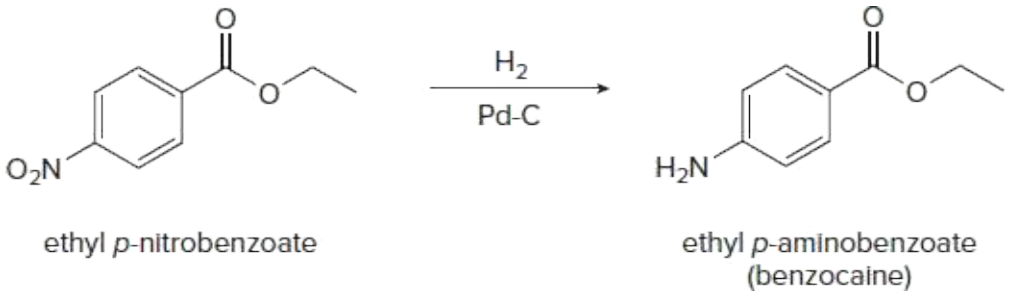
16.15C Reduction of Nitro Groups

A nitro group (NO_2) is easily introduced on a benzene ring by nitration with strong acid (Section 16.4). This process is useful because the nitro group is readily reduced to an amino group (NH_2) under a variety of conditions. The most common methods use H_2 and a catalyst, or a metal (such as Fe or Sn) and a strong acid like HCl.

Benzocaine is the active ingredient in the over-the-counter topical anesthetic Orajel. ©*McGraw-Hill Education/Jill Braaten, photographer*



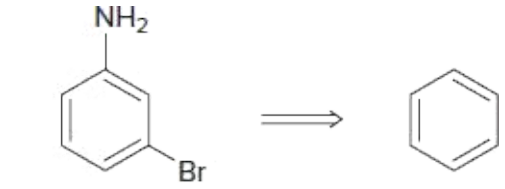
For example, reduction of ethyl *p*-nitrobenzoate with H_2 and a palladium catalyst forms ethyl *p*-aminobenzoate, a local anesthetic commonly called benzocaine.



Sample Problem 16.9 illustrates the utility of this process in a short synthesis. Page 764

Sample Problem 16.9 Introducing an NH_2 Group in a Synthesis

Design a synthesis of *m*-bromoaniline from benzene.



m-bromoaniline

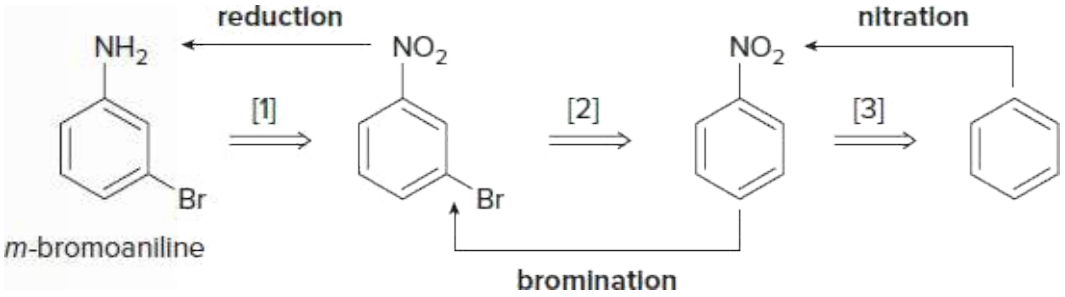
Solution

To devise a retrosynthetic plan, keep in mind:

- **The NH_2 group cannot be introduced directly on the ring by electrophilic aromatic substitution. It must be added by a two-step process: nitration followed by reduction.**
- **Both the Br and NH_2 groups are ortho, para directors, but they are located meta to each other on the ring. However, an NO_2 group (from which an NH_2 group is made) *is* a meta director, and we can use this fact to our advantage.**

Retrosynthetic Analysis

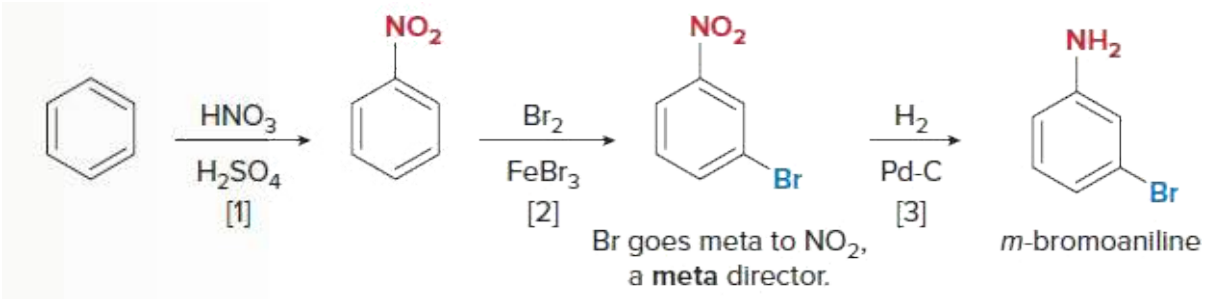
Working backwards gives the following three-step retrosynthetic analysis:



- **[1] Form the NH_2 group by reduction of NO_2.**
- **[2] Introduce the Br group meta to the NO_2 group by halogenation.**
- **[3] Add the NO_2 group by nitration.**

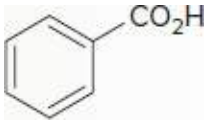
Synthesis

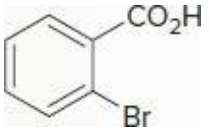
The synthesis involves three steps, and the order is crucial for success. Halogenation (Step [2] of the synthesis) must occur *before* reduction (Step [3]) in order to form the meta-substitution product.

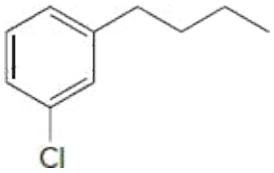


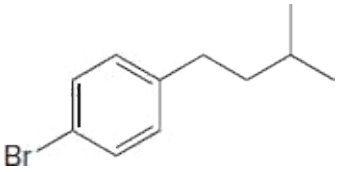
Problem 16.34

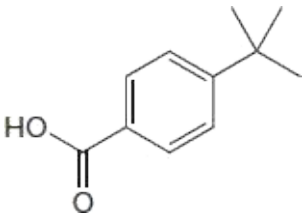
Synthesize each compound from benzene.

a. 

b. 

c. 

d. 

e. 

More Practice:

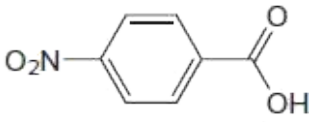
Try Problems 16.67b–d, 16.68b.

16.16 Multistep Synthesis

The reactions learned in Chapter 16 make it possible to synthesize a wide variety of substituted benzenes, as shown in Sample Problems 16.10 and 16.11.

Sample Problem 16.10 Designing a Multistep Synthesis

Synthesize *p*-nitrobenzoic acid from benzene.

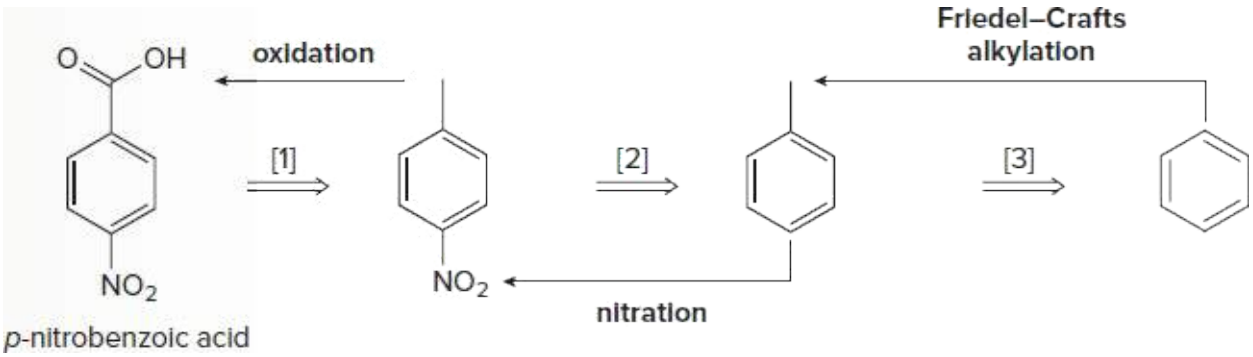


p-nitrobenzoic acid

Solution

Both groups on the ring (NO_2 and COOH) are meta directors. To place these two groups para to each other, remember that the COOH group is prepared by oxidizing an alkyl group, which is an ortho, para director.

Retrosynthetic Analysis

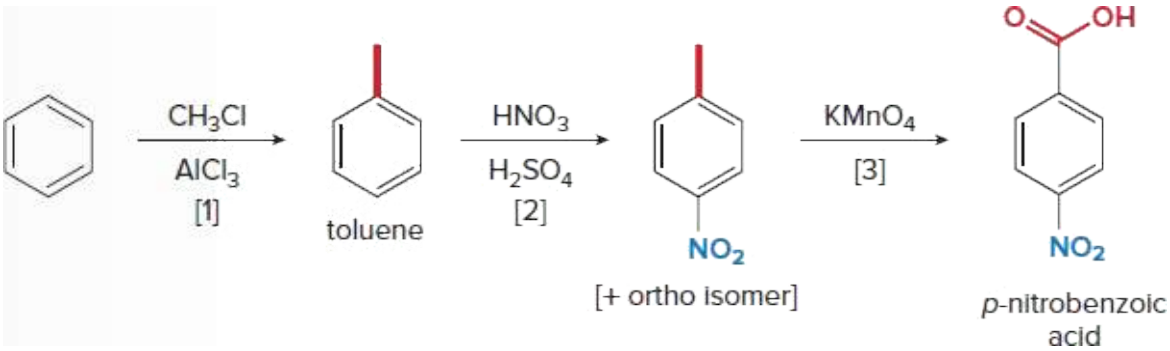


p-nitrobenzoic acid

Working backwards:

- **[1] Form the COOH group by oxidation of an alkyl group.**
- **[2] Introduce the NO_2 group para to the CH_3 group (an ortho, para director) by nitration.**
- **[3] Add the CH_3 group by Friedel–Crafts alkylation.**

Synthesis

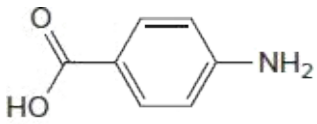


- **Friedel–Crafts alkylation with CH_3Cl and $AlCl_3$ forms toluene in Step [1]. Because CH_3 is an ortho, para director, nitration yields the desired para product, which can be separated from its ortho isomer (Step [2]).**
- **Oxidation with $KMnO_4$ converts the CH_3 group to a COOH group, giving the desired product in Step [3].**

Problem 16.35

Synthesize each compound from benzene.

a.

b. 

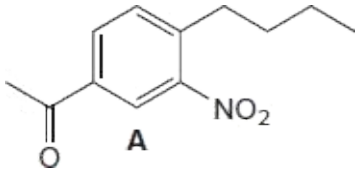
PABA
sunscreen component

More Practice:

Try Problems 16.70, 16.71.

Sample Problem 16.11 Synthesizing a Trisubstituted Benzene

Synthesize the trisubstituted benzene A from benzene.



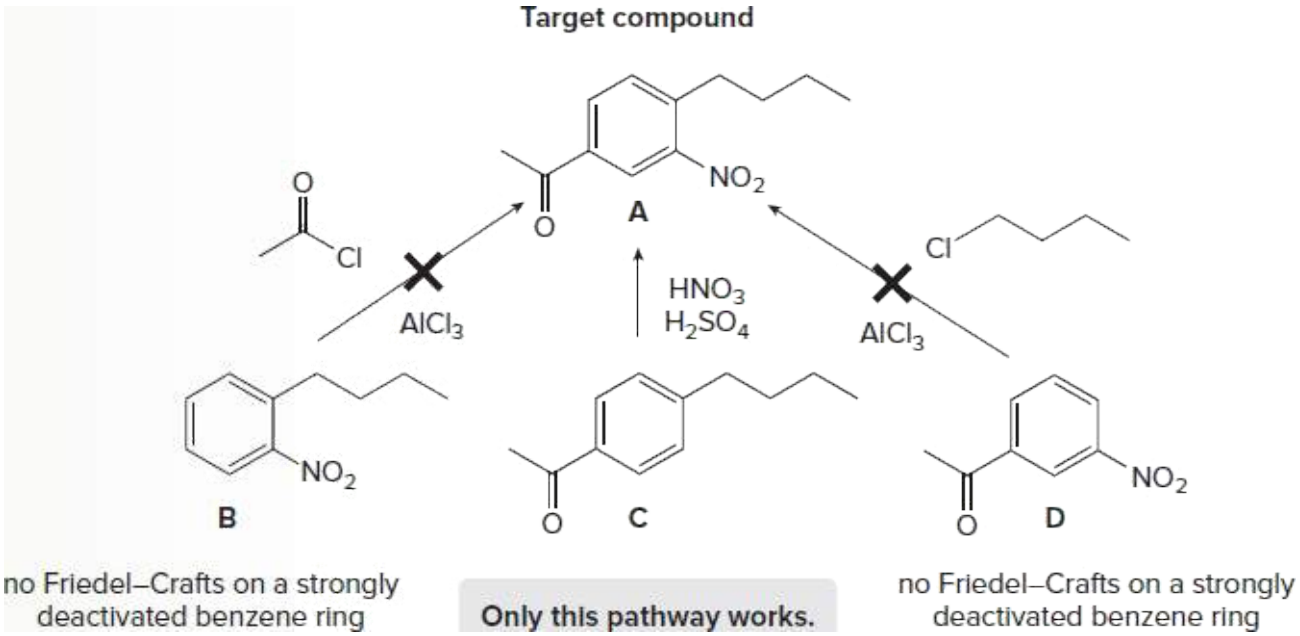
A

Solution

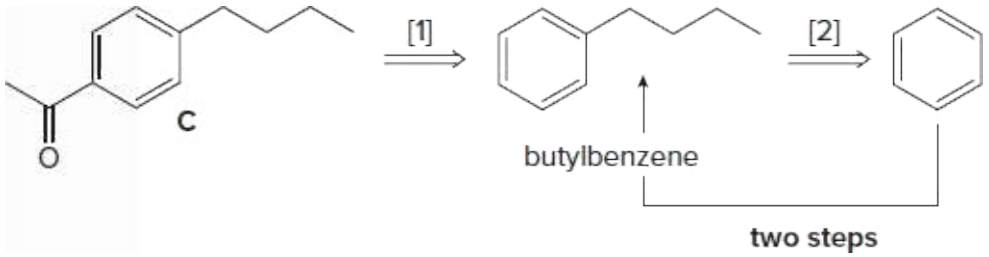
Two groups (CH_3CO and NO_2) in A are meta directors located meta to each other, and the third substituent, an alkyl group, is an ortho, para director.

Retrosynthetic Analysis

With three groups on the benzene ring, begin by determining the possible disubstituted benzenes that are immediate precursors of the target compound, and then eliminate any that cannot be converted to the desired product. For example, three different disubstituted benzenes (B–D) can theoretically be precursors to A. However, conversion of compounds B or D to A would require a Friedel–Crafts reaction on a deactivated benzene ring, a reaction that does not occur. Thus, only C is a feasible precursor of A.

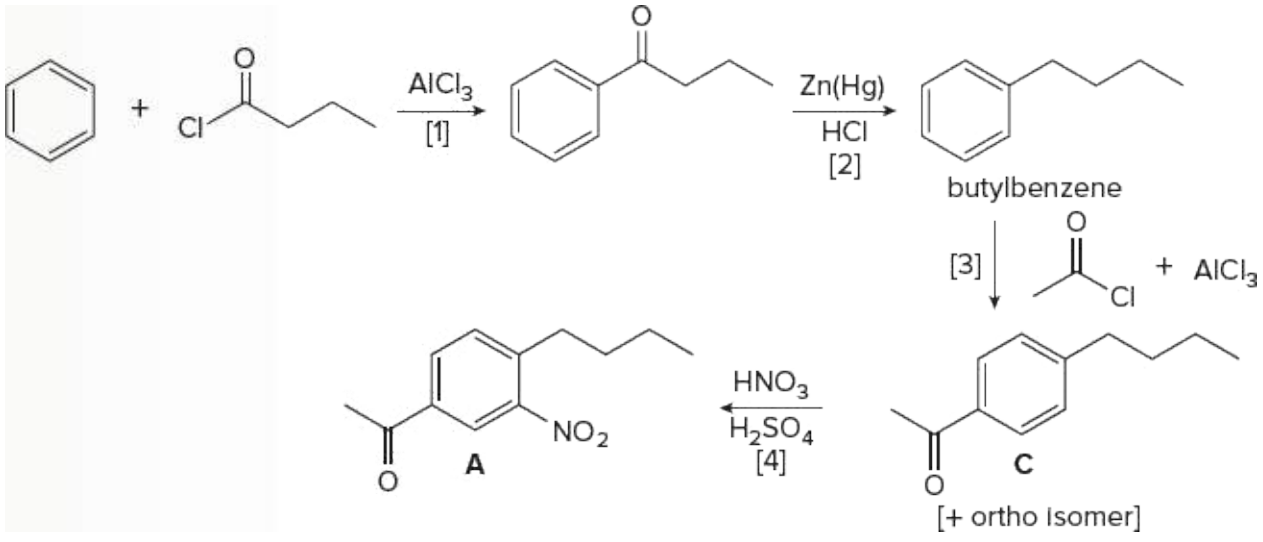


To complete the retrosynthetic analysis, prepare C from benzene:



- **[1] Add the ketone by Friedel–Crafts acylation.**
- **[2] Add the alkyl group by the two-step process—Friedel–Crafts acylation followed by reduction. It is not possible to prepare butylbenzene by a one-step Friedel–Crafts alkylation because of a rearrangement reaction (Section 16.15B).**

Synthesis



- **Friedel–Crafts acylation followed by reduction with Zn(Hg), HCl yields**

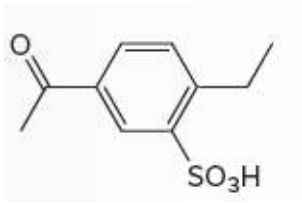
butylbenzene (Steps [1]–[2]).

- Friedel–Crafts acylation gives the para product C, which can be separated from its ortho isomer (Step [3]).
- Nitration in Step [4] introduces the NO_2 group ortho to the alkyl group (an ortho, para director) and meta to the CH_3CO group (a meta director).

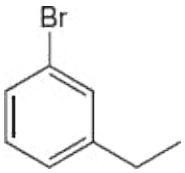
Problem 16.36

Synthesize each compound from benzene.

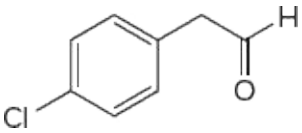
a.



b.



c.



More Practice:

Try Problems 16.67–16.71.

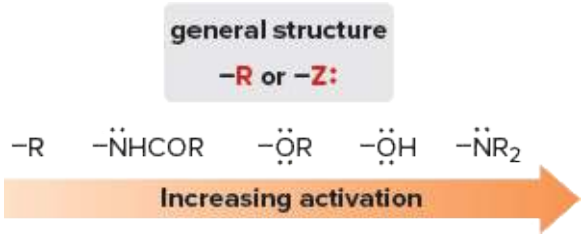
Chapter 16 REVIEW

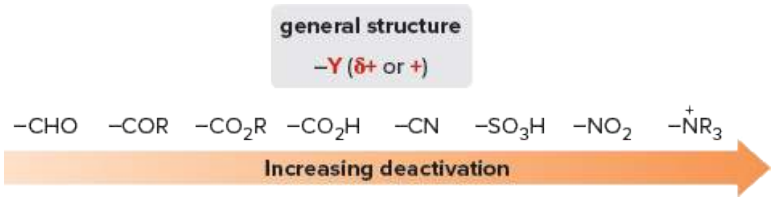
KEY CONCEPTS

[1] Three rules describing the reactivity and directing effects of common substituents (16.7–16.9)

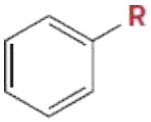
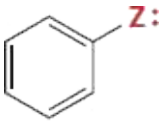
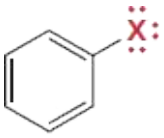
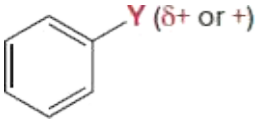
1 Ortho, para directors	2 Meta directors
• All ortho, para directors except the halogens	• All meta directors deactivate the benzene ring.

activate the benzene ring.





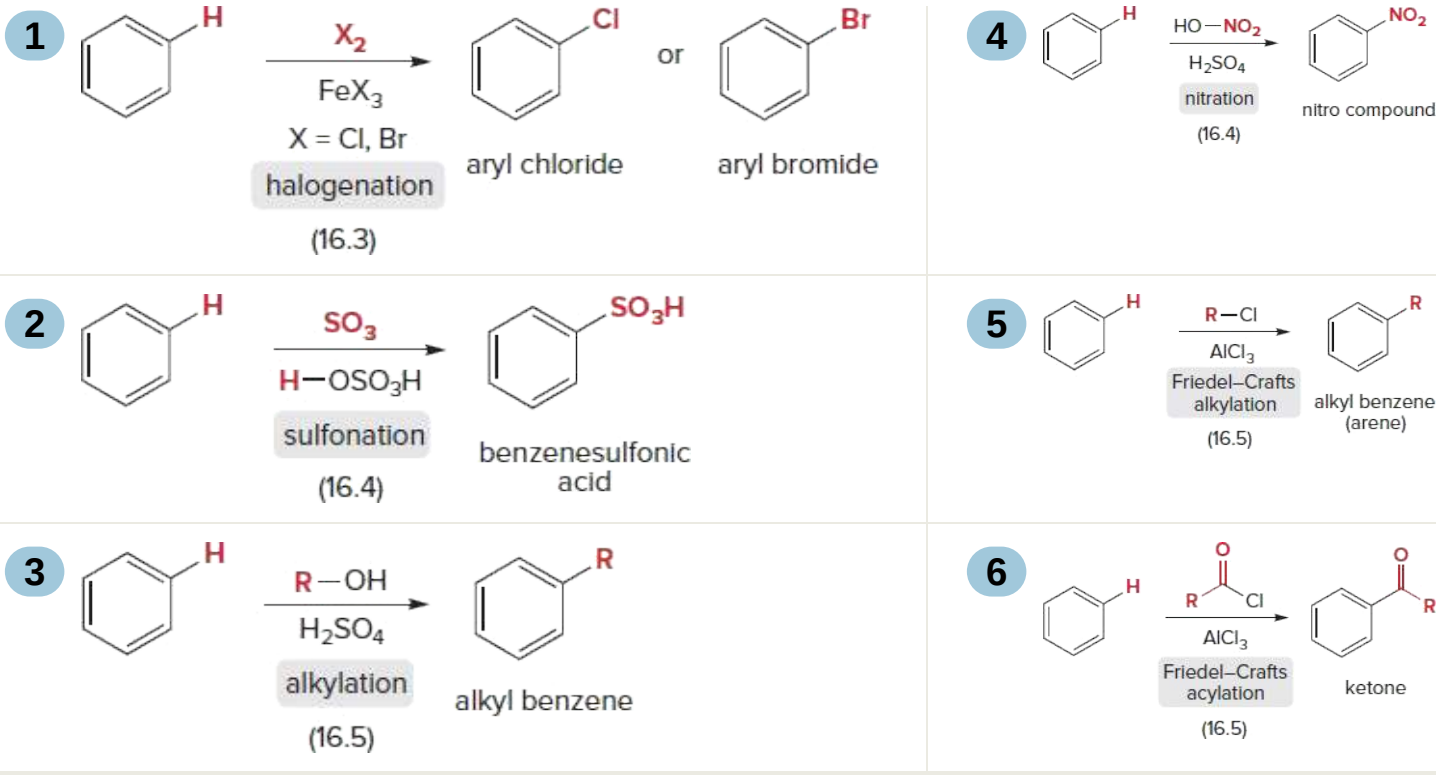
[2] Summary of substituent effects in electrophilic aromatic substitution (16.6–16.9)

1 Substituent	2 Inductive effect	3 Resonance effect	4 Reactivity
 R = alkyl	donating	none	activating
 Z = N or O	withdrawing	donating	activating
 X = halogen	withdrawing	donating	deactivating
	withdrawing	withdrawing	deactivating

Try Problems 16.49, 16.50.

KEY REACTIONS

[1] Electrophilic aromatic substitution



Try Problems 16.37, 16.38, 16.41a–e.

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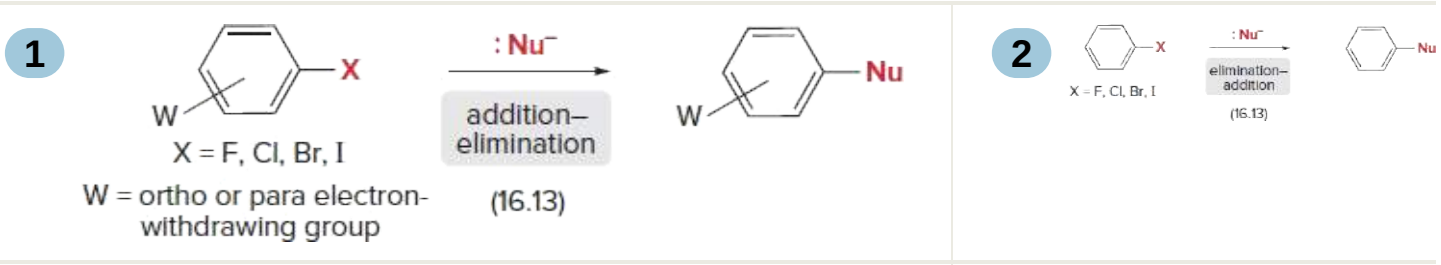
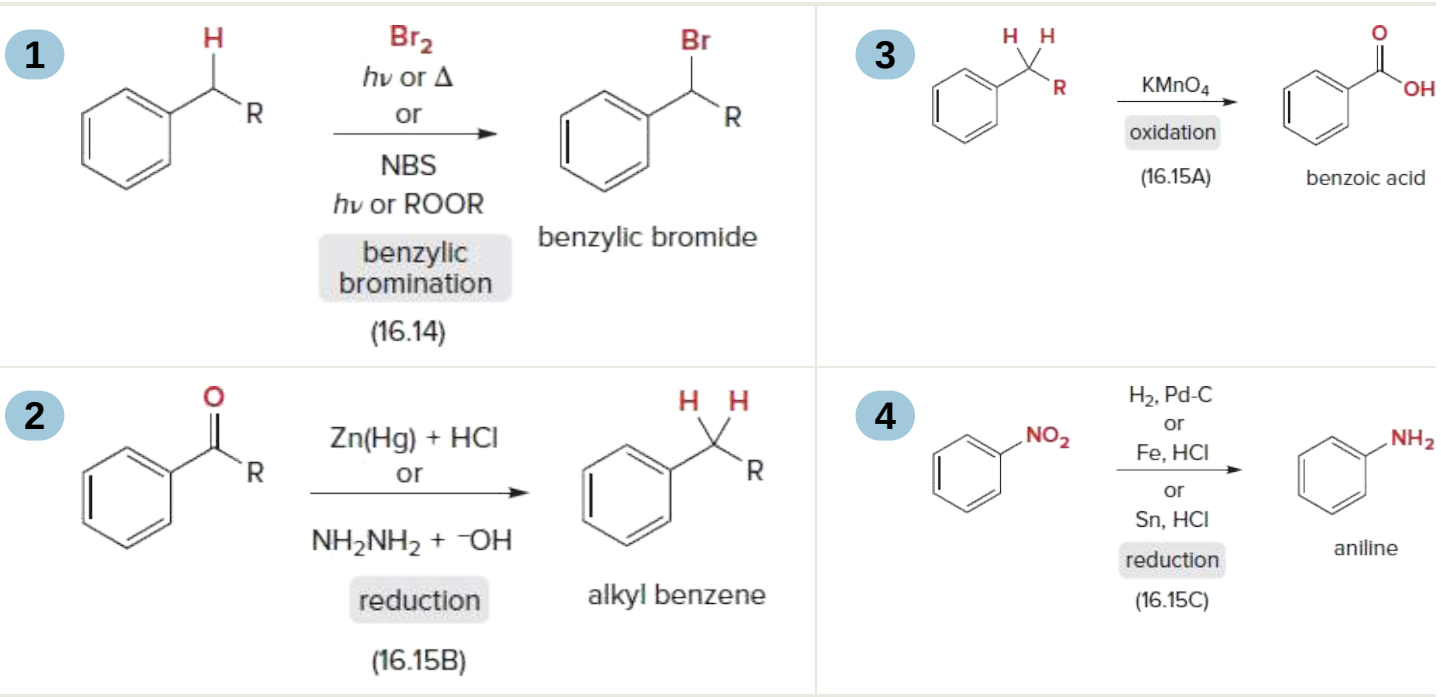
[2] Nucleophilic aromatic substitution



Try Problems 16.41f, 16.43d, 16.45.

[3] Other reactions of benzene derivatives



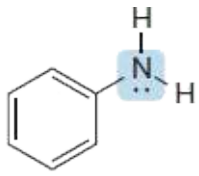
Try Problems 16.39, 16.43a–c.

KEY SKILLS

[1] Classifying substituents as electron donating or electron withdrawing (16.6); two considerations

Draw out the atoms, bonds, and electrons of the substituent, and look at the atom bonded directly to the benzene ring.

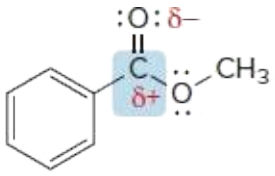
1



electron-donating group

- An O or N atom with a lone pair of electrons makes a substituent electron donating.

2



electron-withdrawing group

- A halogen or an atom with a partial positive charge makes a substituent electron withdrawing.

See Sample Problem 16.3. Try Problems 16.50–16.53.

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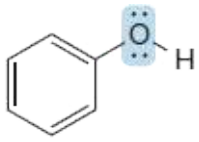
[2] Drawing the product(s) from reaction of a monosubstituted benzene with an electrophile (16.7)

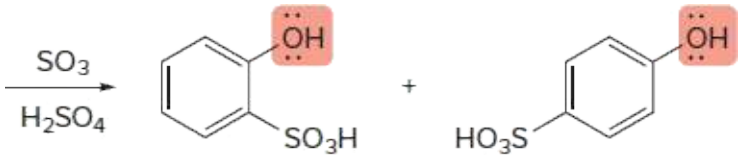
1 Evaluate the directing effect of the substituent.



electron-donating group

- The O atom has a lone pair on the atom bonded to the

2 Classify the substituent, draw the products, and identify whether the reaction is faster or slower than a reaction with benzene.



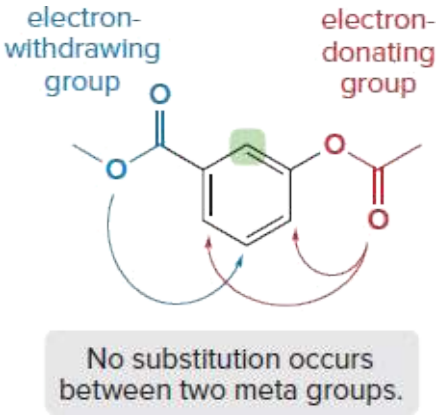
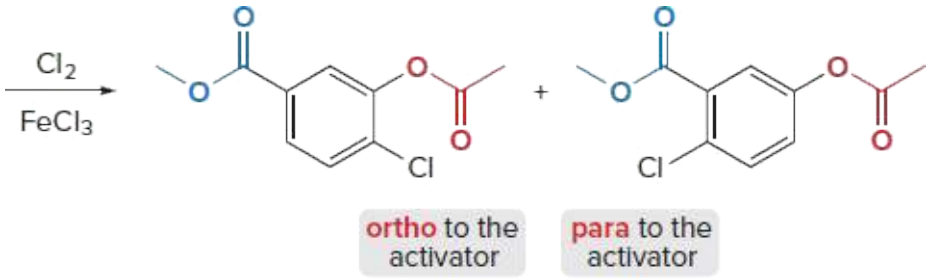
ortho para

- The OH group is ortho, para activating.
- The compound reacts faster than benzene.

benzene ring.

See Sample Problem 16.4. Try Problems 16.39, 16.40, 16.43a.

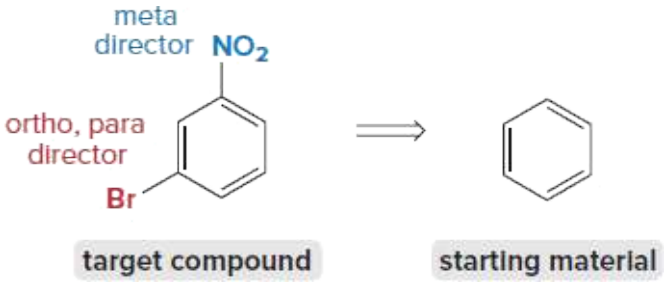
[3] Drawing the product(s) from reaction of a disubstituted benzene with an electrophile (16.11)

1 Evaluate the directing effects, and classify the substituents.	**2** Determine the net result.
	
• The $OCOCH_3$ group is an ortho, para director. • The CO_2CH_3 group is a meta director.	• If the directing effects of two groups oppose each other, the more powerful activator "wins." • No substitution occurs between two meta substituents because of crowding.

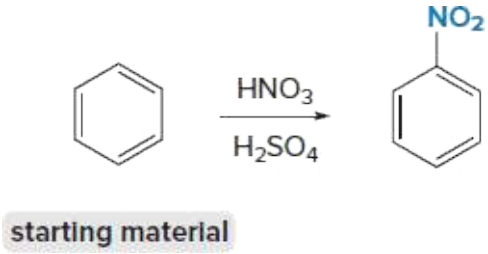
See Sample Problem 16.6. Try Problems 16.37, 16.41a–e, 16.43c.

[4] Devising a synthesis of a disubstituted benzene (16.12)

1 Classify the substituents, and determine the substitution pattern.	**2** Use the substitution pattern of the product to determine which substituent to add first.	**3** Co syr



- The two substituents are meta to each other.



- The meta director must be introduced first to place the second group meta to the first.

- Th
sy
in
st
ni
fo
br

See Sample Problems 16.7, 16.9, 16.10.

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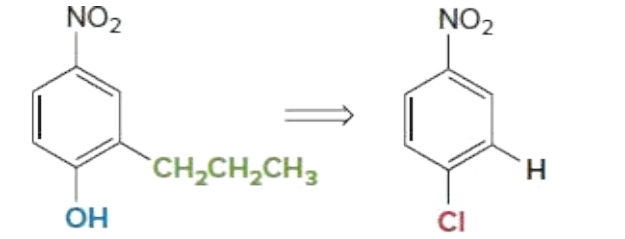
[5] Devising a synthesis of a trisubstituted benzene (16.16); example: 4-nitro-2-propylphenol from 1-chloro-4-nitrobenzene

1 Compare the carbon skeletons and functional groups.

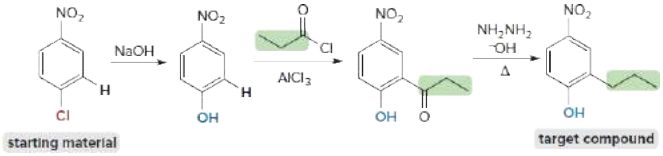
- The Cl group is converted to an OH group.
- The H atom is converted to a $CH_2CH_2CH_3$ group.



4-nitro-2-propylphenol target compound | 1-chloro-4-nitrobenzene starting material

2 Complete the synthesis.

- [1] Convert the Cl group to the group using addition–eliminati
- [2] Form the propyl group by tw steps: Friedel–Crafts acylation followed by reduction.



- The Friedel–Crafts acylation wi occur despite the strong NO_2 deactivator because the OH gr is a strong activator.

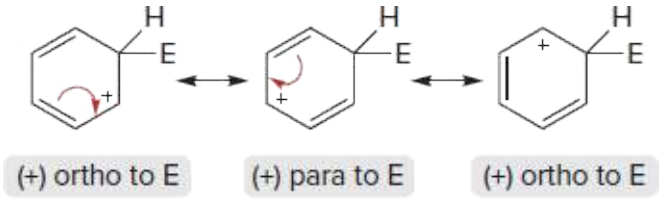
See Sample Problem 16.11. Try Problems 16.67–16.71.

KEY MECHANISM CONCEPTS

1 Electrophilic aromatic

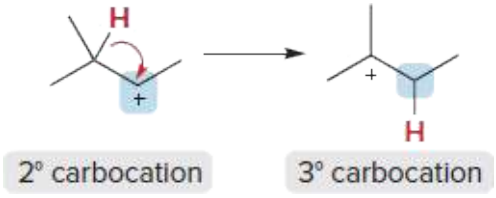
3 A rearrangement reaction

substitution



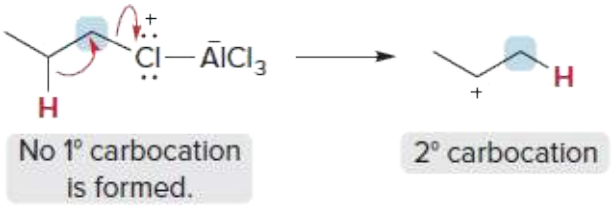
- See Mechanisms 16.1, 16.2, and 16.6.
- The mechanism has two steps.
- The first step is rate-determining.

2 Friedel–Crafts alkylation involving carbocation rearrangement



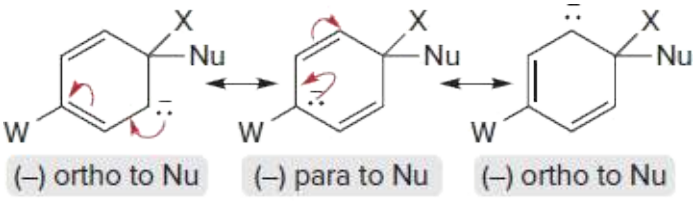
- See Mechanism 16.8.

beginning with a 1° alkyl chloride



- See Mechanism 16.9.

4 Nucleophilic aromatic substitution by addition–elimination



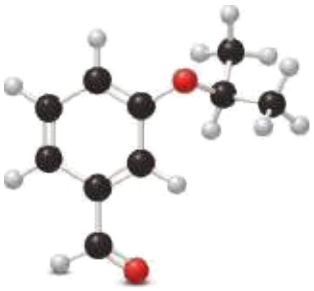
- See Mechanism 16.10.
- The mechanism has two steps.
- Strong electron-withdrawing groups (W) at the ortho and para positions are required.
- The rate is increased by increasing the number of electron-withdrawing groups and increasing the electronegativity of the halogen (X).

Try Problems 16.58–16.66.

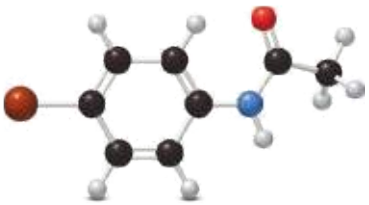
PROBLEMS

Problems Using Three-Dimensional Models

16.37 Draw the products formed when A and B are treated with each of the following reagents: (a) Br_2, $FeBr_3$; (b) HNO_3, H_2SO_4; (c) CH_3CH_2COCl, $AlCl_3$.

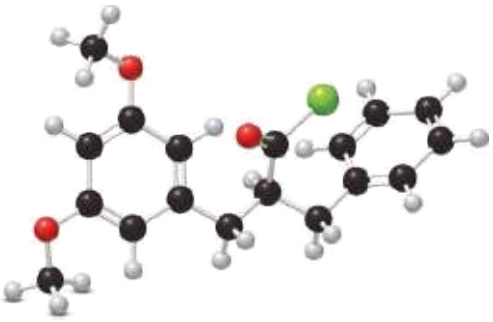


A



B

16.38 What is the major product formed by an intramolecular Friedel–Crafts acylation of the following compound?



Reactions

16.39 Draw the products formed when phenol (C_6H_5OH) is treated with each set of reagents.

a. [1] HNO_3, H_2SO_4; [2] Sn, HCl

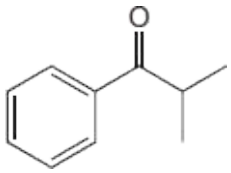
b. [1] $(CH_3CH_2)_2CHCOCl$, $AlCl_3$; [2] Zn(Hg), HCl

c. [1] CH_3CH_2Cl, $AlCl_3$; [2] Br_2, *hν*

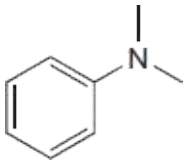
d. [1] $(CH_3)_2CHCl$, $AlCl_3$; [2] $KMnO_4$

16.40 Draw the products formed when each compound is treated with CH_3CH_2COCl, $AlCl_3$.

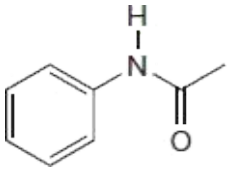
a.



b.

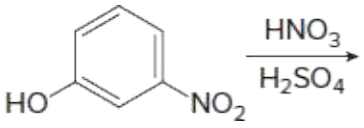


c.

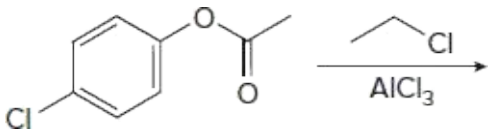


16.41 Draw the products of each reaction.

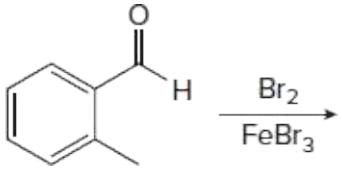
a.



b.



c.



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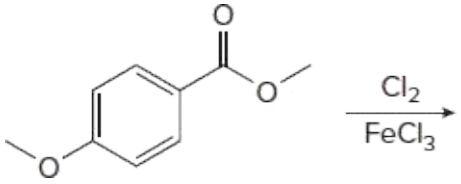

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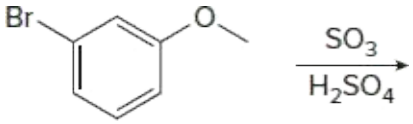

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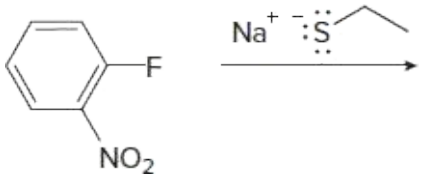
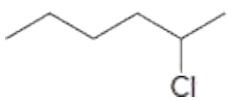


16.42 What products are formed when benzene is treated with each alkyl chloride and $AlCl_3$?

a.



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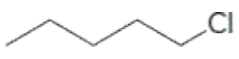

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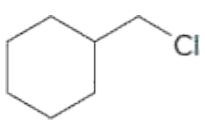
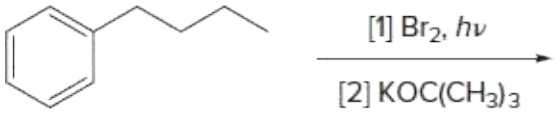


16.43 Draw the products of each reaction.

a.

b.



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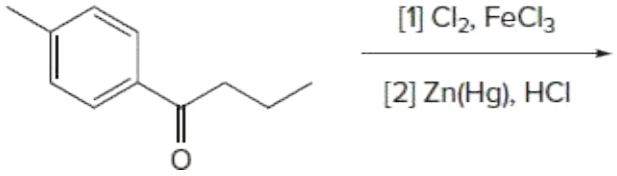

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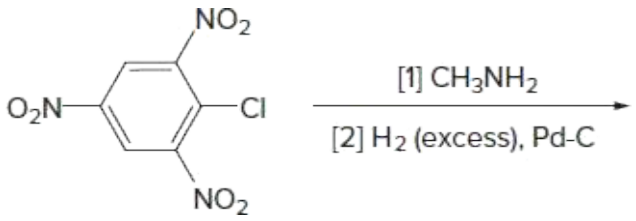
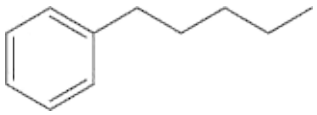
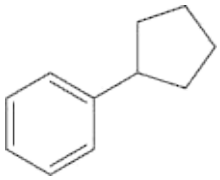


16.44 You have learned two ways to make an alkyl benzene: Friedel–Crafts alkylation, and Friedel–Crafts acylation followed by reduction. Although some alkyl benzenes can be prepared by both methods, it is often true that only one method can be used to prepare a given alkyl benzene. Which method(s) can be used to prepare each of the following compounds from benzene? Show the steps that would be used.

a.



b.



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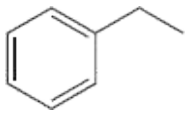
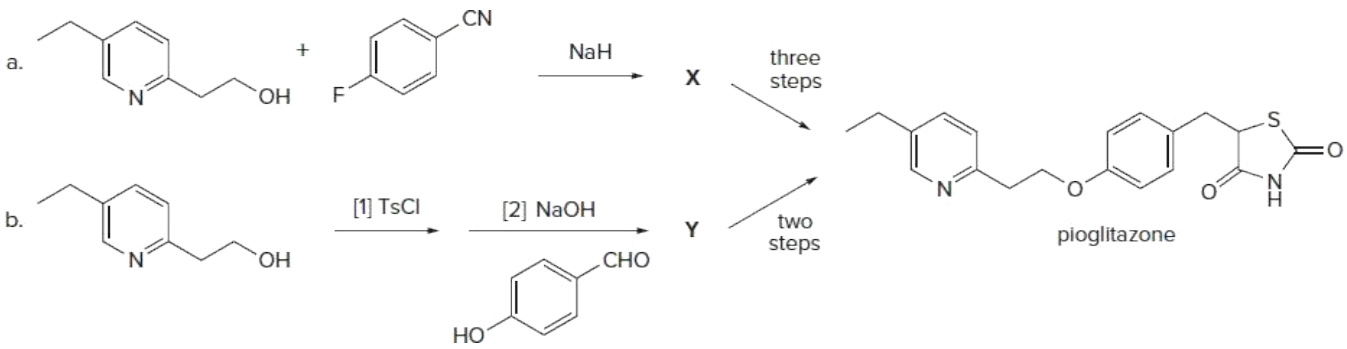
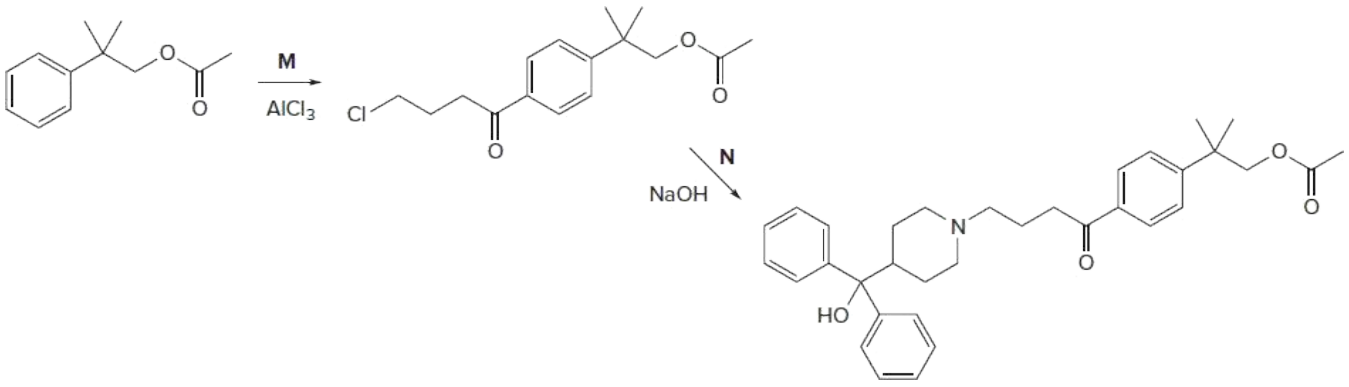


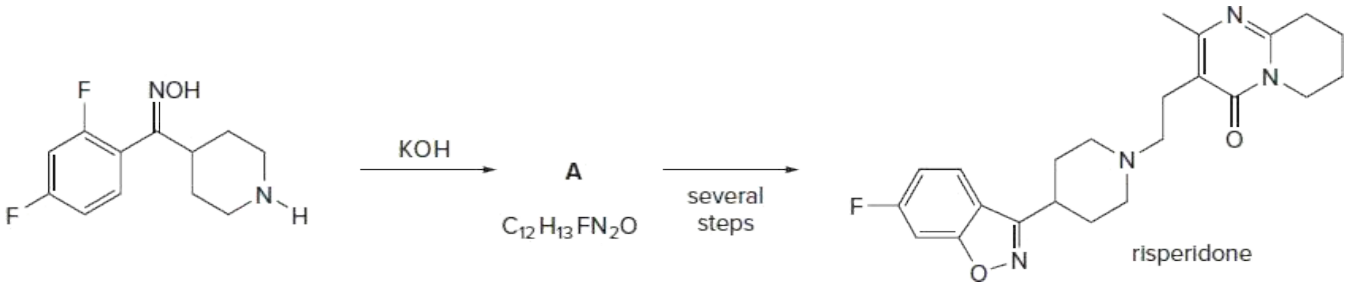
16.45 Identify X and Y, the products of key steps in two syntheses of pioglitazone, a drug used to treat diabetes.



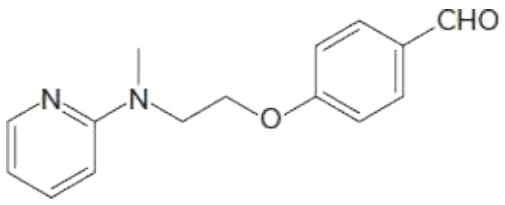
16.46 Identify M and N in the following reaction sequence, two steps in the original synthesis of the non-sedating antihistamine fexofenadine (Section 23.5B).



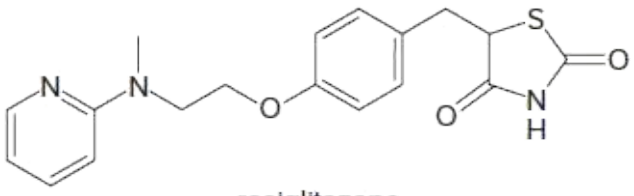
16.47 **Draw the structure of A, an intermediate in the synthesis of the antipsychotic drug risperidone. Explain why three rings in risperidone are considered aromatic.**



16.48 **D is an intermediate in the synthesis of rosiglitazone (trade name Avandia), a drug used to treat type 2 diabetes. Suggest two different methods to prepare the ether in D by substitution reactions.**



D



rosiglitazone

Substituent Effects

16.49 **Rank the compounds in each group in order of increasing reactivity in electrophilic aromatic substitution: (a) C_6H_6, C_6H_5Cl, C_6H_5CHO, $C_6H_5OCH_3$; (b) $C_6H_5CH_3$, $C_6H_5NH_2$, $C_6H_5CH_2NH_2$, $C_6H_5CONH_2$.**

16.50 **For each of the following substituted benzenes: [1] C_6H_5Br; [2] C_6H_5CN; [3] $C_6H_5OCOCH_3$:**

a. Does the substituent donate or withdraw electron density by an inductive effect?

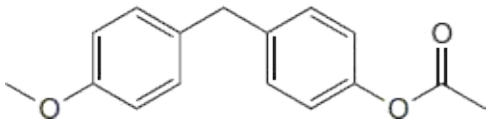
b. Does the substituent donate or withdraw electron density by a resonance effect?

c. On balance, does the substituent make a benzene ring more or less electron rich than benzene itself?

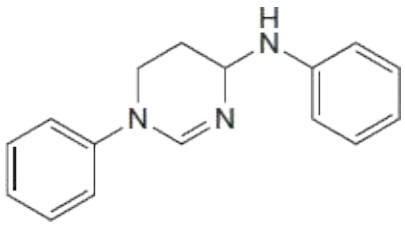
d. Does the substituent activate or deactivate the benzene ring in electrophilic aromatic substitution?

16.51 Determine which ring in each compound is more reactive in electrophilic aromatic substitution, and draw the product(s) formed when each compound is treated with the general electrophile E^+.

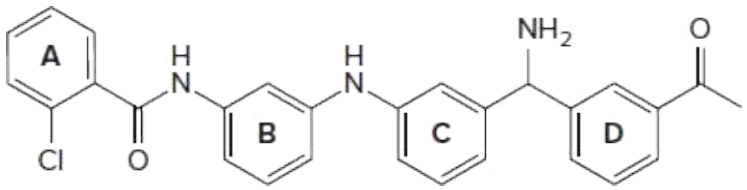
a.



b.

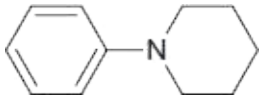


16.52 Consider the tetracyclic aromatic compound drawn below, with rings labeled as A, B, C, and D. (a) Which of the four rings is *most* reactive in electrophilic aromatic substitution? (b) Which of the four rings is *least* reactive in electrophilic aromatic substitution? (c) What are the major product(s) formed when this compound is treated with one equivalent of Br_2?

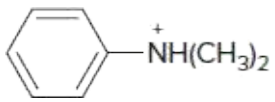


16.53 For each N-substituted benzene, predict whether the compound reacts faster than, slower than, or at a similar rate to benzene in electrophilic aromatic substitution. Then draw the major product(s) formed when each compound reacts with a general electrophile E^+.

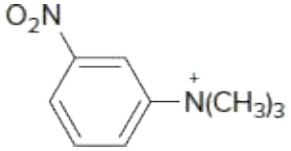
a.



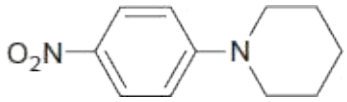
b.



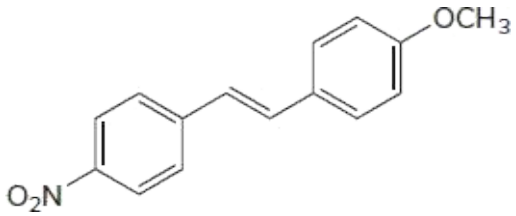
c.



d.



16.54 What is the major product of electrophilic addition of HBr to the following alkene? Explain your choice.



16.55 Using resonance structures, explain why a nitroso group (–NO) is an ortho, para director that deactivates a benzene ring toward electrophilic attack.

16.56 Explain this observation: Ethyl 3-phenylpropanoate ($C_6H_5CH_2CH_2CO_2CH_2CH_3$) reacts with electrophiles to afford ortho- and para-disubstituted arenes, but ethyl 3-phenylprop-2-enoate ($C_6H_5CH{=}CHCO_2CH_2CH_3$) reacts with electrophiles to afford meta-disubstituted arenes.

16.57 Rank the aryl halides in each group in order of increasing reactivity in nucleophilic aromatic substitution by an addition–elimination mechanism.

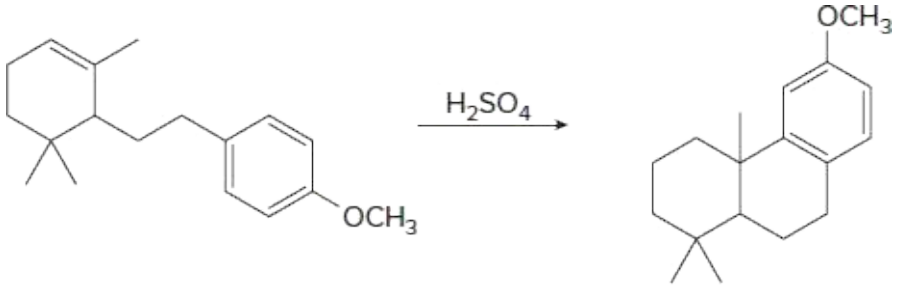
a. chlorobenzene, *p*-fluoronitrobenzene, *m*-fluoronitrobenzene

b. 1-fluoro-2,4-dinitrobenzene, 1-fluoro-3,5-dinitrobenzene, 1-fluoro-3,4-dinitrobenzene

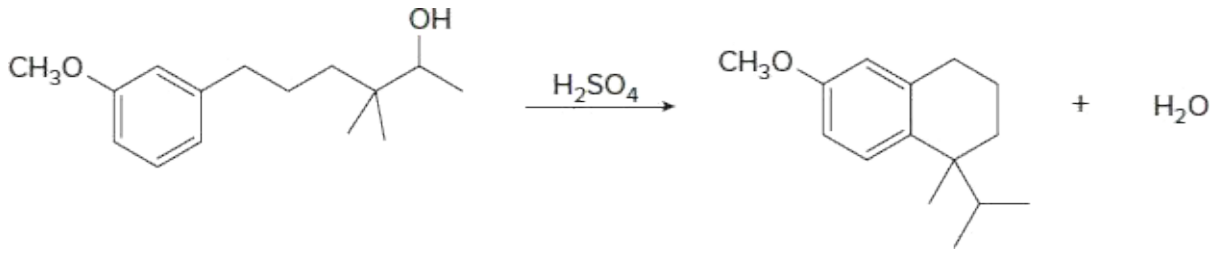
c. 1-fluoro-2,4-dinitrobenzene, 4-chloro-3-nitrotoluene, 4-fluoro-3-nitrotoluene

Mechanisms

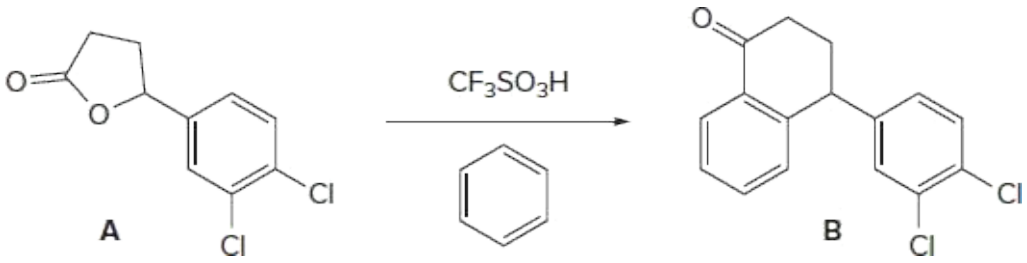
16.58 Draw a stepwise, detailed mechanism for the following intramolecular reaction.



16.59 Draw a stepwise, detailed mechanism for the following reaction.



16.60 **Draw a stepwise mechanism for the following reaction, which involves two Friedel–Crafts reactions. B was an intermediate in the synthesis of the antidepressant sertraline (Problem 16.11).**

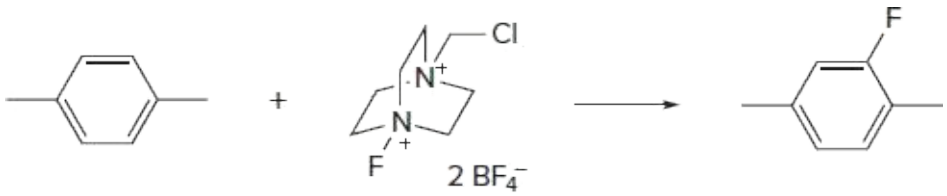


16.61 **Friedel–Crafts alkylation of benzene with (*R*)-2-chlorobutane and $AlCl_3$ affords sec-butylbenzene.**

a. How many stereogenic centers are present in the product?

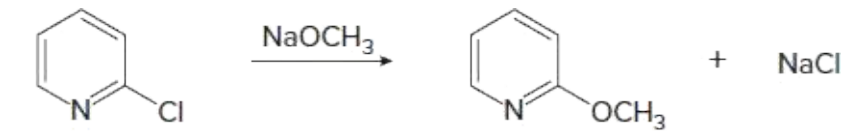
b. Would you expect the product to exhibit optical activity? Explain, with reference to the mechanism.

16.62 **Fluorination of a benzene ring can be accomplished with Selectfluor, a reagent that contains a fluorine bonded to a positively charged nitrogen atom. Fluorination is a useful reaction because several common drugs, such as the cholesterol-lowering drug atorvastatin, contain a fluorine bonded to an aromatic ring. Assuming that fluorination is analogous to other examples of electrophilic aromatic substitution, draw a stepwise mechanism for the following reaction.**



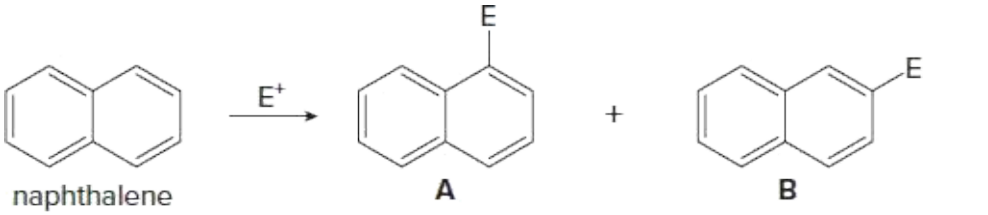
Selectfluor

16.63 **Draw a stepwise mechanism for the following substitution. Explain why 2-chloropyridine reacts faster than chlorobenzene in this type of reaction.**



2-chloropyridine

16.64 **Although two products (A and B) are possible when naphthalene undergoes electrophilic aromatic substitution, only A is formed. Draw resonance structures for the intermediate carbocation to explain why this is observed.**

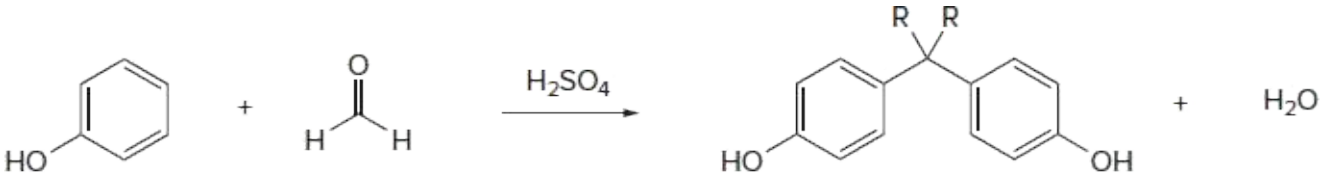


naphthalene

A This product is formed.

B This product is *not* formed.

16.65 **Draw a stepwise mechanism for the following reaction, which results in the synthesis of bisphenol F (R = H), an additive used in a variety of packaging materials. Bisphenol F is related to BPA (bisphenol A, R = CH_3), a reagent used to harden some plastics, now removed from certain baby products because of its estrogen-like activity that can disrupt endocrine pathways.**



bisphenol F

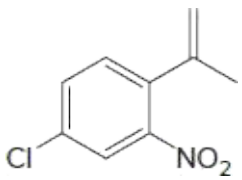
R = H

16.66 **Benzyl bromide ($C_6H_5CH_2Br$) reacts rapidly with CH_3OH to afford benzyl methyl ether ($C_6H_5CH_2OCH_3$). Draw a stepwise mechanism for the reaction, and explain why this 1° alkyl halide reacts rapidly with a weak nucleophile under conditions that favor an S_N1 mechanism. Would you expect the para-substituted benzylic halides $CH_3OC_6H_4CH_2Br$ and $O_2NC_6H_4CH_2Br$ to each be more or less reactive than benzyl bromide in this reaction? Explain your reasoning.**

Synthesis

16.67 **Synthesize each compound from benzene, organic halides with < 5 C's, and any other organic or inorganic reagents.**

a.



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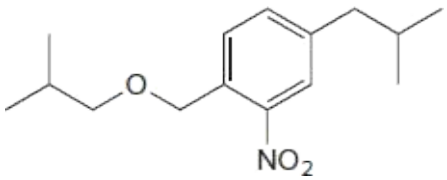
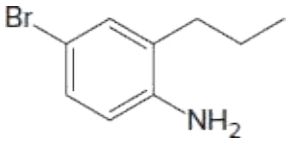
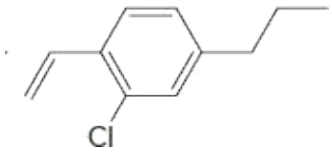
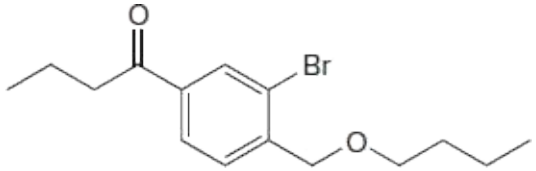
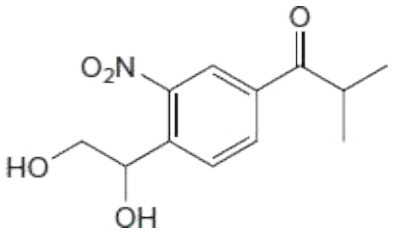


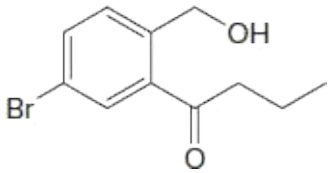
c. 

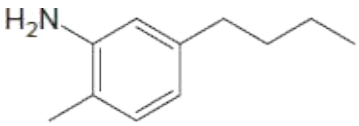
d. 

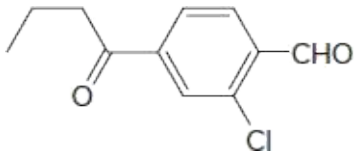
e. 

f. 

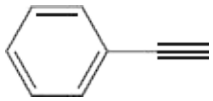
16.68 Synthesize each compound from toluene ($C_6H_5CH_3$) and any other organic or inorganic reagents.

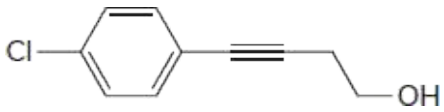
a. 

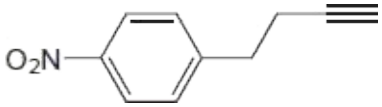
b. 

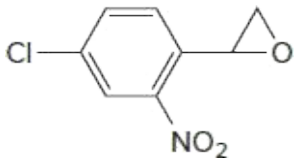
c. 

16.69 Use the reactions in this chapter along with those learned in Chapters 11 and 12 to synthesize each compound. You may use benzene, acetylene (HC≡CH), ethanol, ethylene oxide, and any inorganic reagents.

a. 

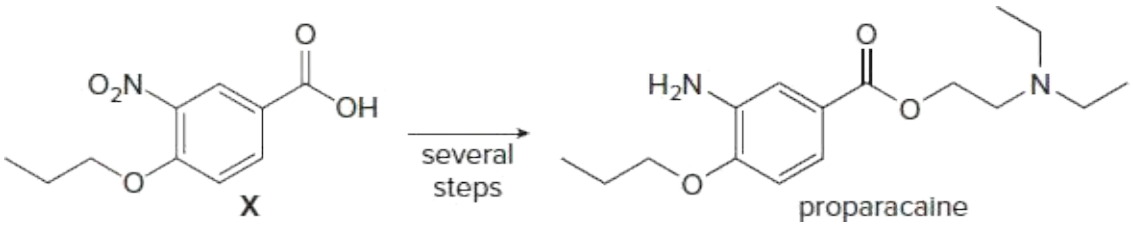
b. 

c. 

d. 

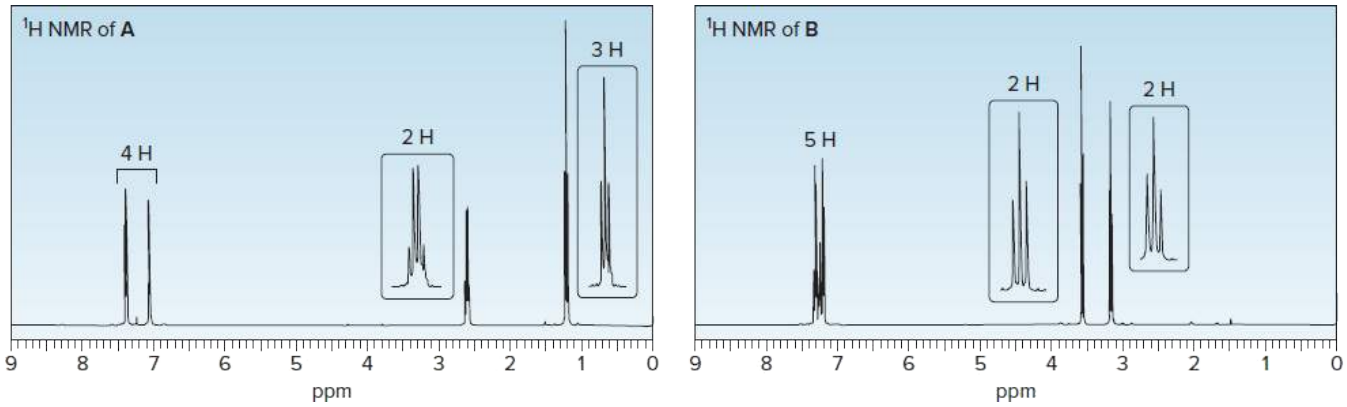
16.70 **Ibufenac, a para-disubstituted arene with the structure $HO_2CCH_2C_6H_4CH_2CH(CH_3)_2$, is a much more potent analgesic than aspirin, but it was never sold commercially because it caused liver toxicity in some clinical trials. Devise a synthesis of ibufenac from benzene and organic halides having fewer than five carbons.**

16.71 **Carboxylic acid X is an intermediate in the multistep synthesis of proparacaine, a local anesthetic. Devise a synthesis of X from phenol and any needed organic or inorganic reagents.**



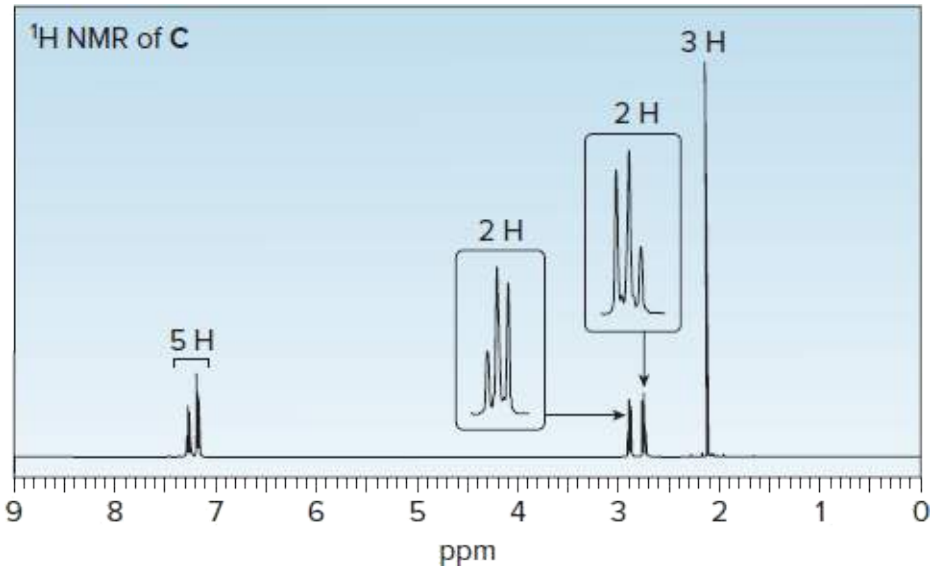
Spectroscopy

16.72 **Identify the structures of isomers A and B (molecular formula C_8H_9Br).**

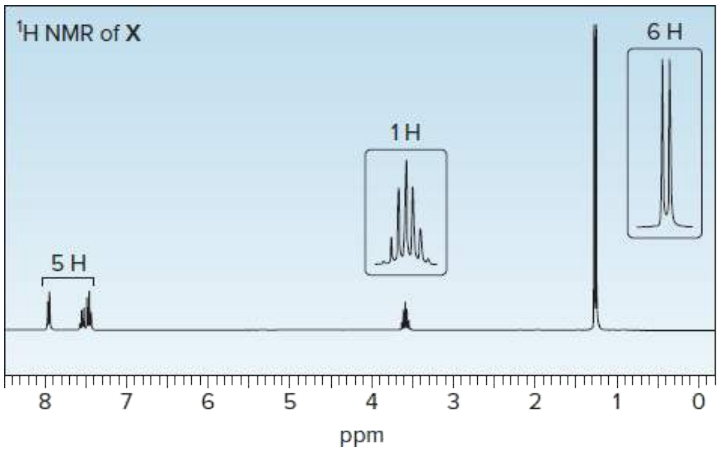


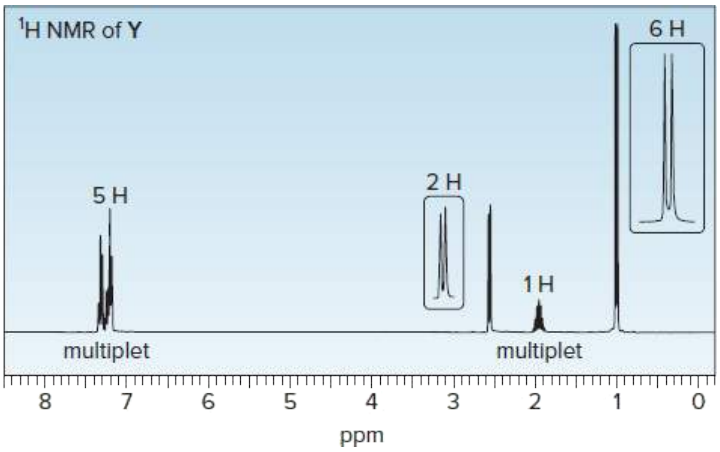
16.73 **Propose a structure of compound C (molecular formula $C_{10}H_{12}O$) consistent with the following data. C is partly responsible for the odor and flavor of raspberries.**

Compound C: IR absorption at 1717 cm^{-1}

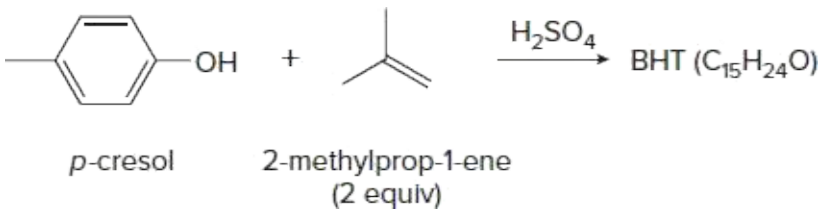


16.74 **Compound X (molecular formula $C_{10}H_{12}O$) was treated with NH_2NH_2, ^-OH to yield compound Y (molecular formula $C_{10}H_{14}$). Based on the ^1H NMR spectra of X and Y given below, what are the structures of X and Y?**



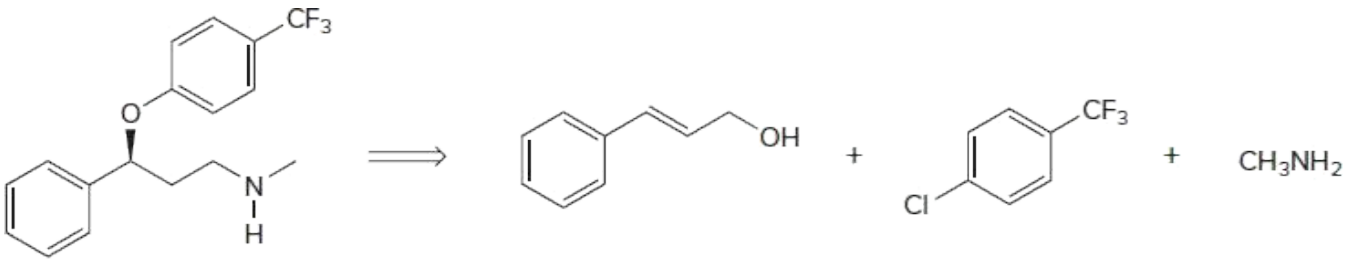


16.75 **Reaction of *p*-cresol with two equivalents of 2-methylprop-1-ene affords BHT, a preservative with molecular formula $C_{15}H_{24}O$. BHT gives the following ^1H NMR spectral data: 1.4 (singlet, 18 H), 2.27 (singlet, 3 H), 5.0 (singlet, 1 H), and 7.0 (singlet, 2 H) ppm. What is the structure of BHT? Draw a stepwise mechanism illustrating how it is formed.**



Challenge Problems

16.76 **Devise a synthesis of optically active (*S*)-fluoxetine (trade name Prozac) from the given starting materials and any other needed reagents.**



(*S*)-fluoxetine

16.77 **The ^{1}H NMR spectrum of phenol (C_6H_5OH) shows three absorptions in the aromatic region: 6.70 (2 ortho H's), 7.14 (2 meta H's), and 6.80 (1 para H) ppm. Explain why the ortho and para absorptions occur at lower chemical shift than the meta absorption.**

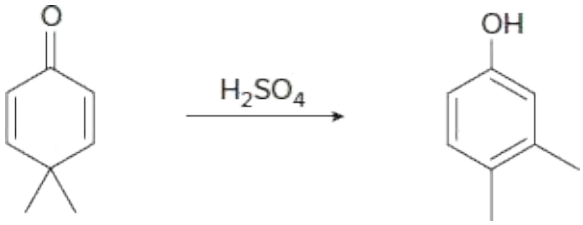
16.78 **Explain the reactivity and orientation effects observed in each heterocycle.**

pyridine pyrrole

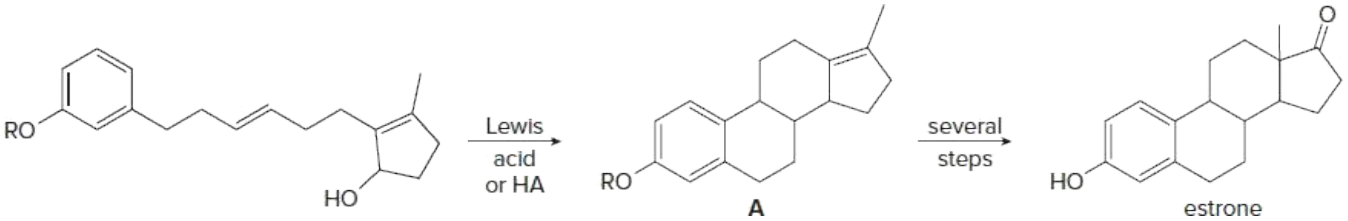
a. Pyridine is less reactive than benzene in electrophilic aromatic substitution and yields 3-substituted products.

b. Pyrrole is more reactive than benzene in electrophilic aromatic substitution and yields 2-substituted products.

16.79 **Draw a stepwise mechanism for the dienone–phenol rearrangement, a reaction that forms alkyl-substituted phenols from cyclohexadienones.**



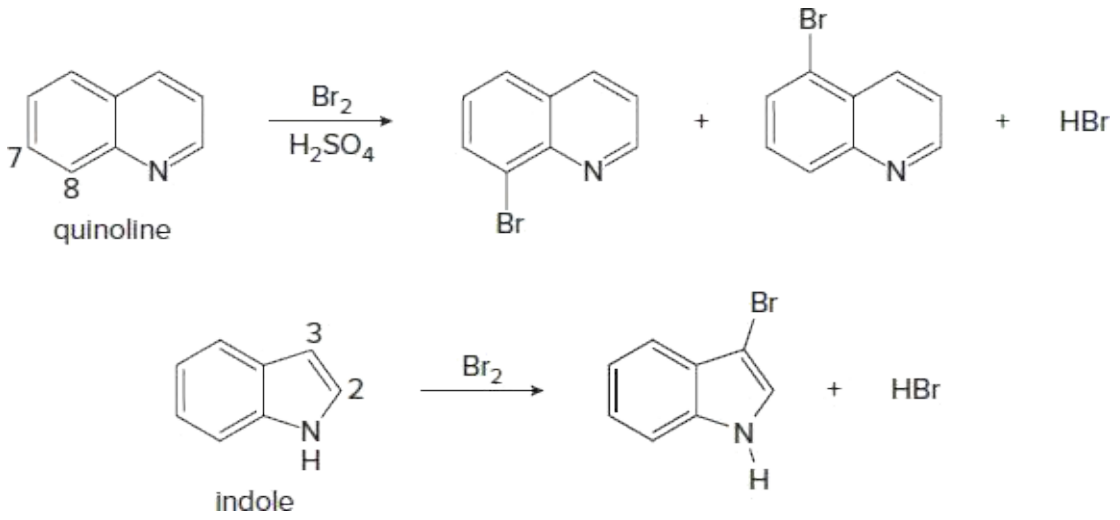
16.80 **Draw a stepwise mechanism for the following intramolecular reaction, which is used in the synthesis of the female sex hormone estrone.**



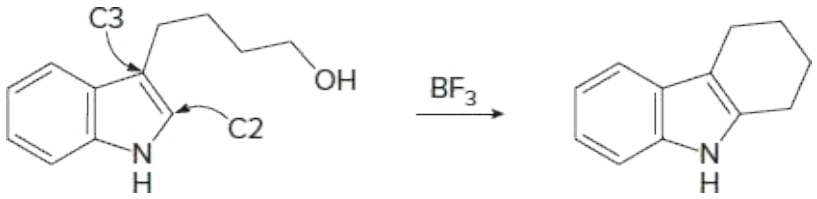
16.81 **The bicyclic heterocycles quinoline and indole undergo electrophilic**

aromatic substitution to give the products shown.

(a) Explain why electrophilic substitution occurs on the ring without the N atom for quinoline, but occurs on the ring with the N atom in indole. (b) Explain why electrophilic substitution occurs more readily at C8 than C7 in quinoline. (c) Explain why electrophilic substitution occurs more readily at C3 rather than C2 of indole.

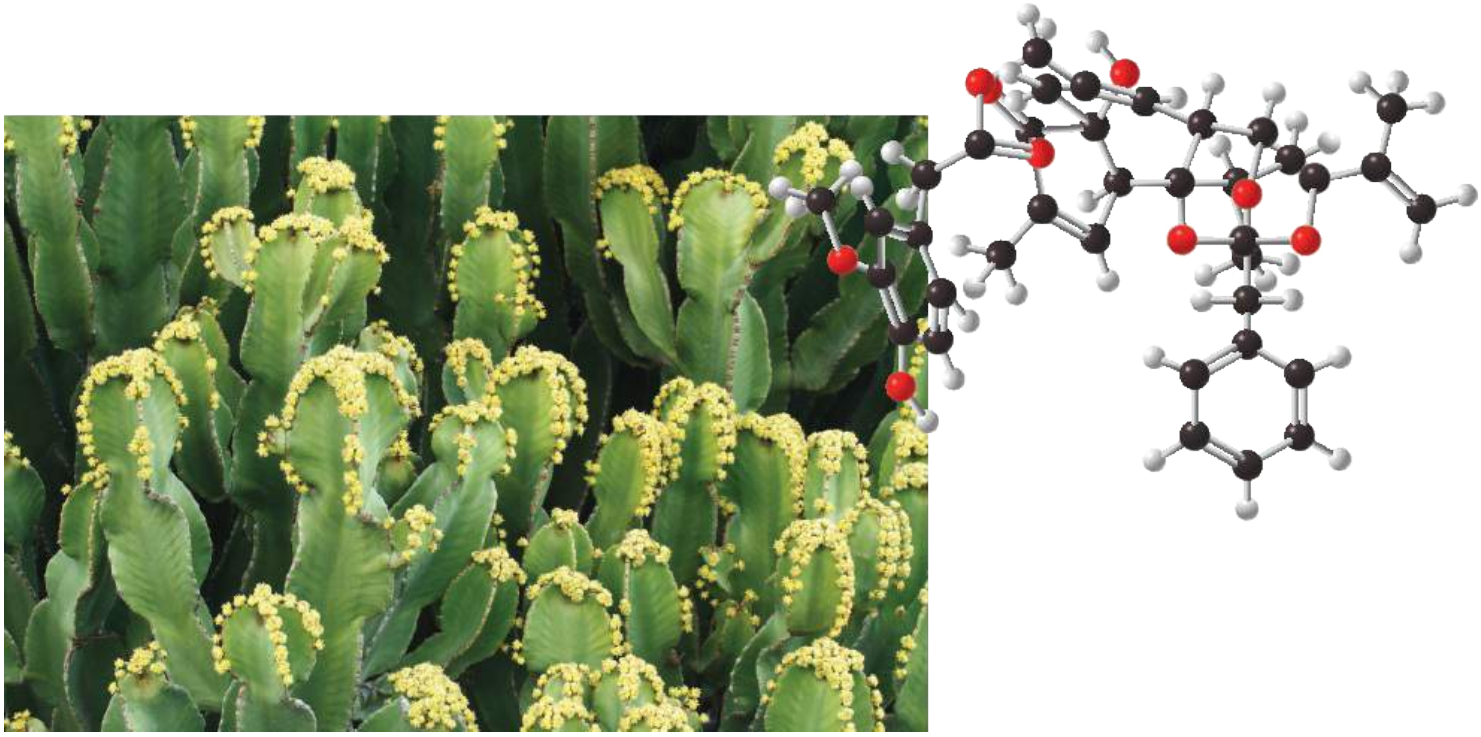


16.82 Devise a stepwise mechanism for the following reaction. The reaction does not take place by direct electrophilic aromatic substitution at C2. (Hint: The mechanism begins with addition of an electrophile at C3.)



Introduction to Carbonyl Chemistry; Organometallic Reagents; Oxidation and Reduction

17



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17.1 Introduction

17.2 General reactions of carbonyl compounds

17.3 A preview of oxidation and reduction

17.4 Reduction of aldehydes and ketones

17.5 The stereochemistry of carbonyl reduction

17.6 Enantioselective carbonyl reductions

17.7 Reduction of carboxylic acids and their derivatives

17.8 Oxidation of aldehydes

17.9 Organometallic reagents

17.10 Reaction of organometallic reagents with aldehydes and ketones

17.11 Retrosynthetic analysis of Grignard products
17.12 Protecting groups
17.13 Reaction of organometallic reagents with carboxylic acid derivatives
17.14 Reaction of organometallic reagents with other compounds
17.15 α,β-Unsaturated carbonyl compounds
17.16 Summary—The reactions of organometallic reagents
17.17 Synthesis

Resiniferatoxin, obtained from the flowering cactus *Euphorbia resinifera*, is a compound that produces the same hot, numbing sensation in the mouth that the capsaicin in chili peppers triggers, but it is 1000 times more potent. Like capsaicin, resiniferatoxin desensitizes neurons to pain, so it has potential as an analgesic for treating pain and inflammation. In fact, a thirteenth-century manuscript illustrates that extracts of *Euphorbia resinifera* were used for pain management over 1000 years ago. Although its complex structure was not elucidated until 1975, resiniferatoxin has now been synthesized in the laboratory by a multistep method that utilizes some of the key reactions presented in Chapter 17.

Why Study…

Carbonyl Compounds and Their Reactions?

Chapters 17 through 22 of this text discuss carbonyl compounds—aldehydes, ketones, acid halides, esters, amides, and carboxylic acids. The carbonyl group is perhaps the most important functional group in organic chemistry, because its electron-deficient carbon and easily broken π bond make it susceptible to a wide variety of useful reactions.

We begin by examining the similarities and differences between two broad classes of carbonyl compounds. We will then spend the remainder of Chapter 17 on reactions that are especially important in organic synthesis. Chapters 18 and 20 present specific reactions that occur at the carbonyl carbon, and Chapters 21 and 22 concentrate on reactions occurring at the α carbon to the carbonyl group. Chapter 19 covers carboxylic

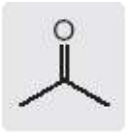
acids, which can react at both their OH and C=O groups, and nitriles (RCN), which undergo reactions similar to those of carbonyl compounds.

Although Chapter 17 is "jam-packed" with reactions, most of them follow one of two general pathways, so they can be classified in a well-organized fashion, provided you remember a few basic principles. Keep in mind these fundamental themes about reactions:

- Nucleophiles attack electrophiles.
- π Bonds are easily broken.
- Bonds to good leaving groups are easily cleaved.

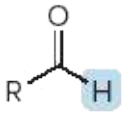
17.1 Introduction

Two broad classes of compounds contain a *carbonyl group*:

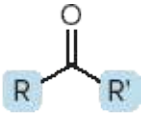


carbonyl group

[1] Compounds that have only carbon and hydrogen atoms bonded to the carbonyl group



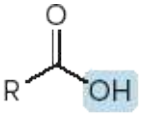
aldehyde



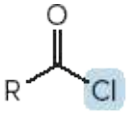
ketone

- **An aldehyde has at least one H atom bonded to the carbonyl group.**
- **A ketone has two alkyl or aryl groups bonded to the carbonyl group.**

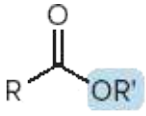
[2] Compounds that contain an electronegative atom bonded to the carbonyl group



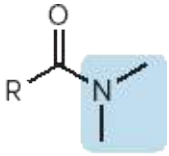
carboxylic acid



acid chloride



ester



amide

These include carboxylic acids, acid chlorides, esters, and amides, as well as other similar compounds discussed in Chapter 20. Each of these compounds contains an atom (Cl, O, or N) more electronegative than carbon, capable of acting as a leaving group. Acid chlorides, esters, and amides are often called carboxylic acid derivatives, because they can be synthesized from carboxylic acids (Chapter 20). Each compound

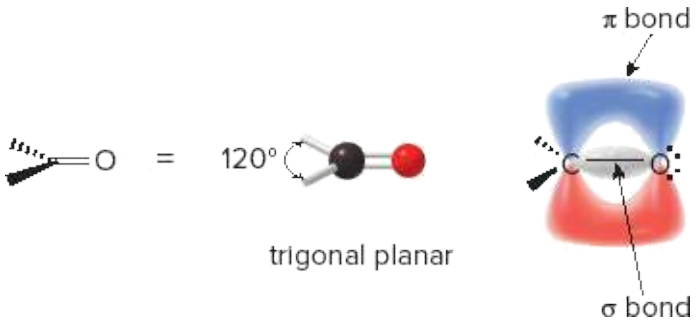
contains an acyl group (RCO″), so they are also called acyl derivatives.

- **The presence or absence of a leaving group on the carbonyl carbon determines the type of reactions these compounds undergo (Section 17.2).**

The carbonyl carbon atom is sp^2 hybridized and trigonal planar, and all bond angles are ~120°. The double bond of a carbonyl group consists of one σ bond and one π bond. The π bond is formed by the overlap of two *p* orbitals, and extends above and below the plane. In these features the carbonyl group resembles the trigonal planar, sp^2 hybridized carbons of a C–C double bond.

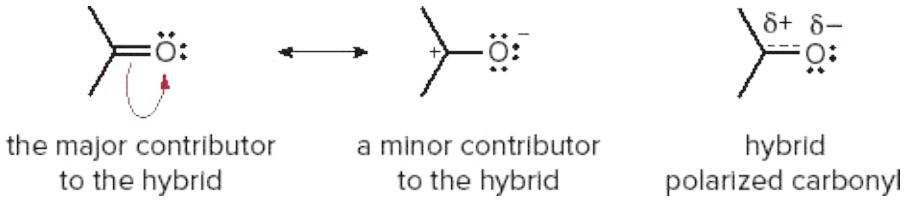
Page 782

The aldehyde α-sinensal (Problem 17.1) is the major compound responsible for the orange-like odor of mandarin oil, obtained from the mandarin tree in southern China.
©Gerald D. Carr, PhD

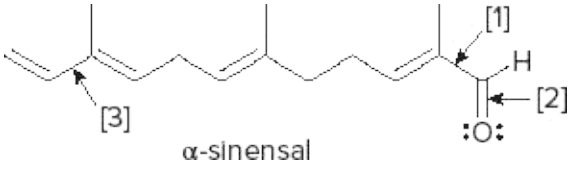


In one important way, though, a C=O and a C=C are very different. The electronegative

oxygen atom in the carbonyl group means that the bond is polarized, making the carbonyl carbon electron deficient. Using a resonance description, the carbonyl group is represented by two resonance structures, with a charge-separated resonance structure a minor contributor to the hybrid. An electrostatic potential plot for formaldehyde, the simplest aldehyde, is shown in Figure 17.1. It clearly indicates the polarized carbonyl group.

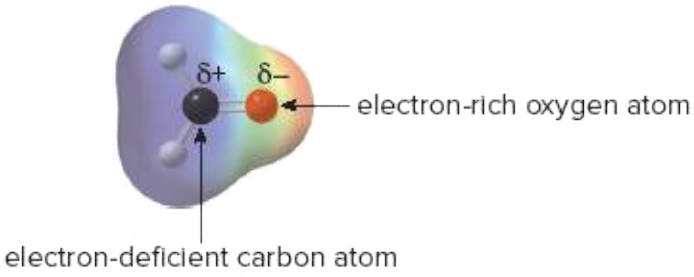


Problem 17.1



a. What orbitals are used to form the indicated bonds in α-sinensal?

b. In what type of orbitals do the lone pairs on O reside?

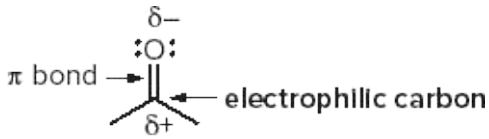


- An electrostatic potential map shows the electron-deficient carbon atom and the electron-rich oxygen atom of the carbonyl group.

Figure 17.1 **Electrostatic potential map of formaldehyde, $CH_2=O$**

17.2 General Reactions of Carbonyl Compounds

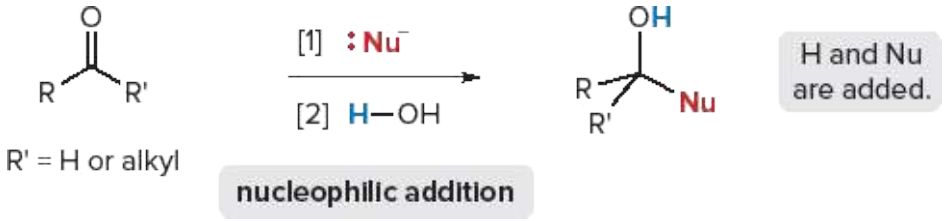
With what types of reagents should a carbonyl group react? The electronegative oxygen makes the carbonyl carbon electrophilic, and because it is trigonal planar, a carbonyl carbon is uncrowded. Moreover, a carbonyl group has an easily broken π bond.



uncrowded
sp^2 hybridized carbon

As a result, carbonyl compounds react with nucleophiles. The outcome of nucleophilic attack, however, depends on the identity of the carbonyl starting material.

- **Aldehydes and ketones undergo nucleophilic *addition.***



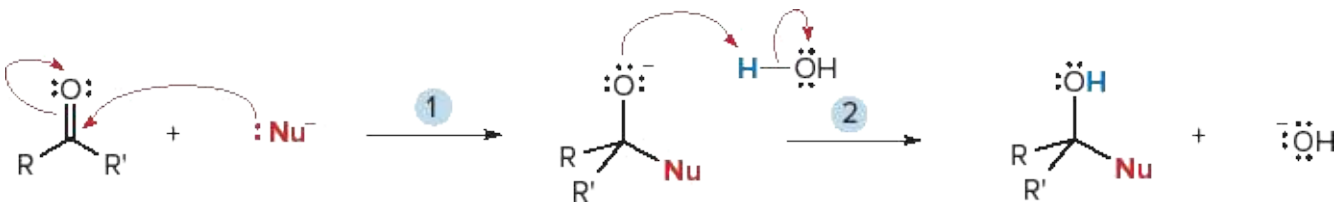
- **Carbonyl compounds that contain leaving groups undergo nucleophilic *substitution.***

Let's examine each of these general reactions individually.

17.2A Nucleophilic Addition to Aldehydes and Ketones

Aldehydes and ketones react with nucleophiles to form addition products by the two-step process shown in Mechanism 17.1: nucleophilic attack followed by protonation.

Mechanism 17.1 Nucleophilic Addition—A Two-Step Process



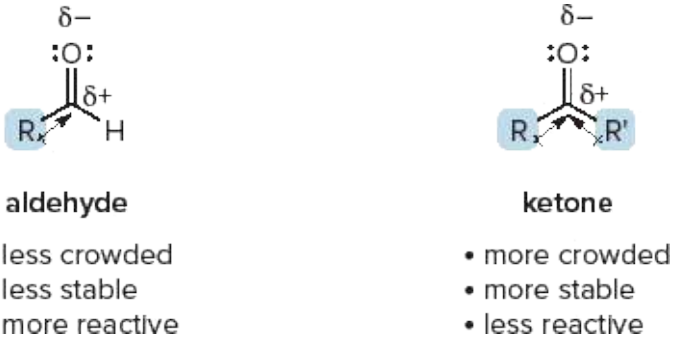
1 **The nucleophile attacks the electrophilic carbonyl. The π bond is broken, moving an electron pair out on oxygen and forming an sp^3 hybridized carbon.**

2 **Protonation of the negatively charged oxygen by H_2O forms the addition product.**

More examples of nucleophilic addition to aldehydes and ketones are discussed in Chapter 18.

The net result is that the π bond is broken, two new σ bonds are formed, and the elements of H and Nu are *added* across the π bond. Nucleophilic addition with two different nucleophiles—hydride ($H:^-$) and carbanions ($R:^-$)—is discussed in Chapter 17.

Aldehydes are more reactive than ketones toward nucleophilic attack for both steric and electronic reasons.

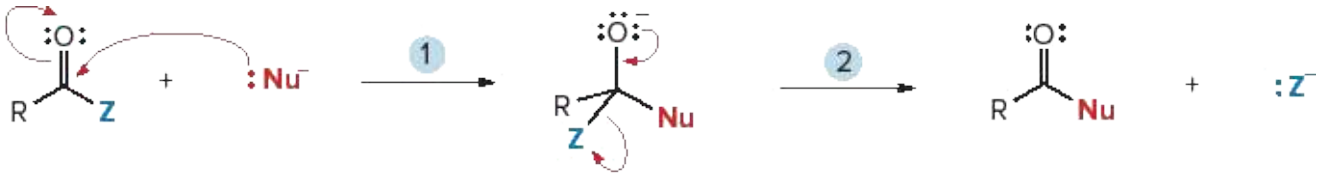


- **The two R groups bonded to the ketone carbonyl group make it *more crowded*, so nucleophilic attack is more difficult.**
- **The two electron-donor R groups stabilize the partial charge on the carbonyl carbon of a ketone, making it *more stable* and less reactive.**

17.2B Nucleophilic Substitution of RCOZ (Z = Leaving Group)

Carbonyl compounds with leaving groups react with nucleophiles to form substitution products by the two-step process shown in Mechanism 17.2: nucleophilic attack, followed by loss of the leaving group.

Mechanism 17.2 Nucleophilic Substitution—A Two-Step Process



Z = OH, Cl, OR', NH_2

1. **The nucleophile attacks the electrophilic carbonyl. The π bond is broken, moving an electron pair out on oxygen and forming an sp^3 hybridized carbon.**
2. **An electron pair on oxygen re-forms the π bond and Z comes off as a leaving group with the electron pair in the C–Z bond.**

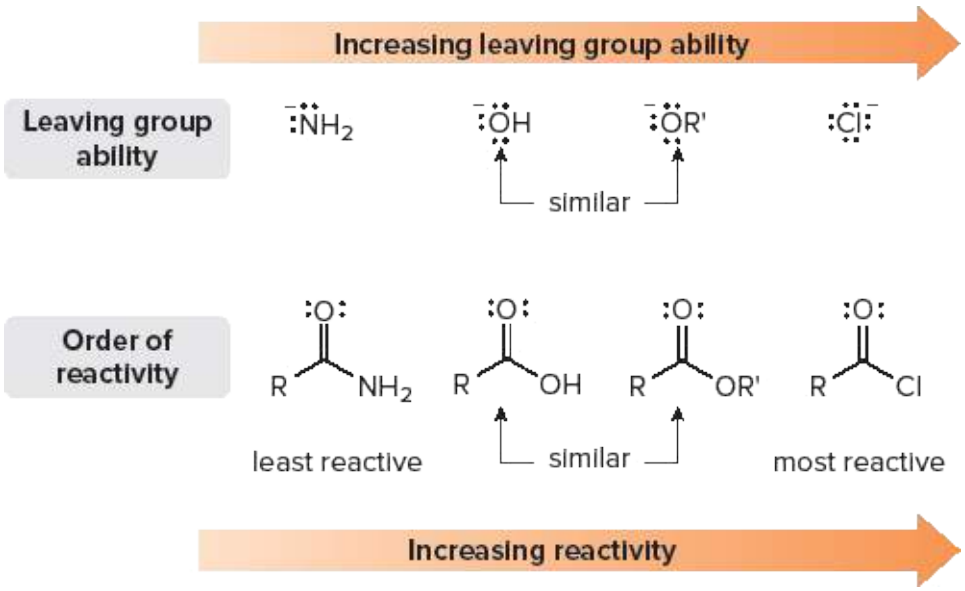
The net result is that Nu replaces Z—a nucleophilic substitution reaction. This reaction is often called nucleophilic *acyl* substitution to distinguish it from the nucleophilic substitution reactions at sp^3 hybridized carbons discussed in Chapter 7. Nucleophilic substitution with two different nucleophiles—hydride ($H:^-$) and carbanions ($R:^-$)—is discussed in Chapter 17. Other nucleophiles are examined in Chapter 20.

Carboxylic acid derivatives differ greatly in their reactivity toward nucleophiles. The order in which they react parallels the leaving group ability of the group Z bonded to the carbonyl carbon.

- **The *better* the leaving group Z, the *more reactive* RCOZ is in nucleophilic acyl substitution.**

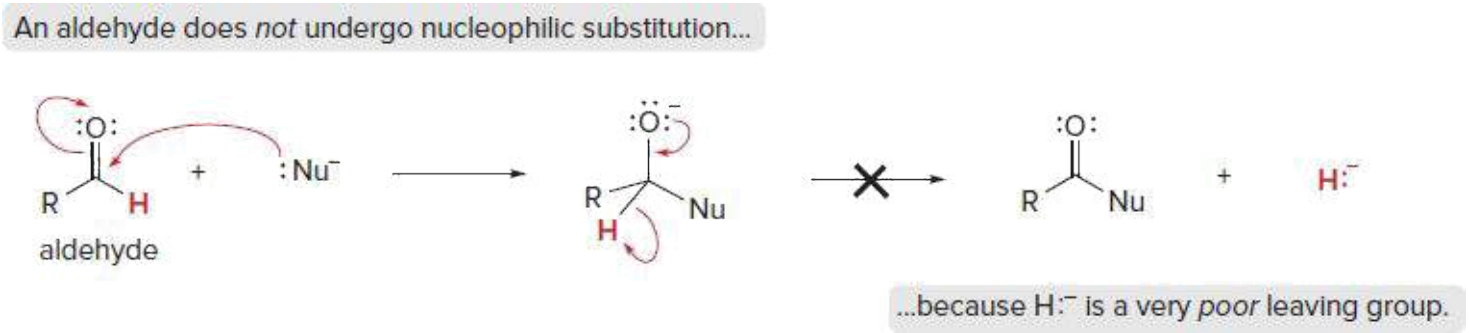
Recall from Section 7.7 that the *weaker* the base, the *better* the leaving group.

Thus, the following trends result:



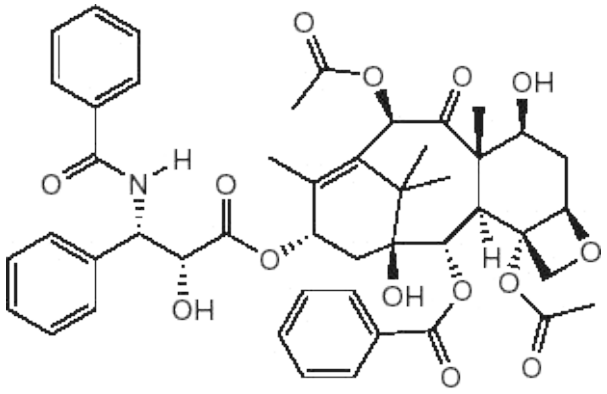
- **Acid chlorides (RCOCl), which have the best leaving group (Cl^-), are the most reactive carboxylic acid derivatives, and amides ($RCONH_2$), which have the worst leaving group ($^-NH_2$), are the least reactive.**
- **Carboxylic acids (RCOOH) and esters (RCOOR′), which have leaving groups of similar basicity (^-OH and $^-OR'$), fall in the middle.**

Nucleophilic addition and nucleophilic acyl substitution involve the *same* Page 785 first step—nucleophilic attack on the electrophilic carbonyl group to form a tetrahedral intermediate. The difference between them is what then happens to this intermediate. Aldehydes and ketones cannot undergo substitution because they have no leaving group bonded to the newly formed sp^3 hybridized carbon. Nucleophilic substitution with an aldehyde, for example, would form $H:^-$, an extremely strong base and therefore a very poor (and highly unlikely) leaving group.



Problem 17.2

Which carbonyl groups in the anticancer drug Taxol (Section 5.5) will undergo nucleophilic addition, and which will undergo nucleophilic substitution?

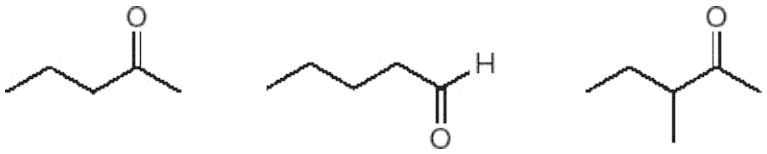


Taxol

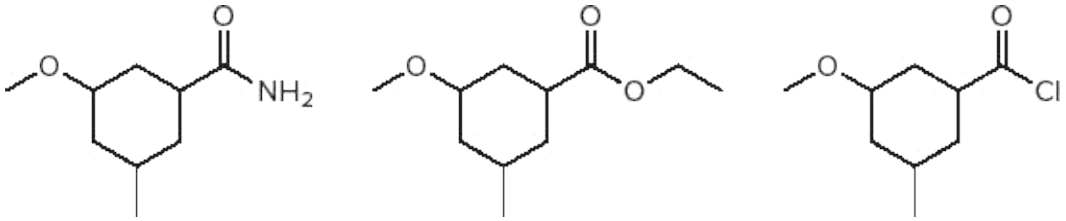
Problem 17.3

Rank the compounds in each group in order of increasing reactivity toward nucleophilic attack.

a.



b.



To show how these general principles of nucleophilic substitution and addition apply to carbonyl compounds, we are going to discuss oxidation and reduction reactions, and reactions with organometallic reagents—compounds that contain carbon–metal bonds. We begin with reduction to build on what you learned previously in Chapter 12.

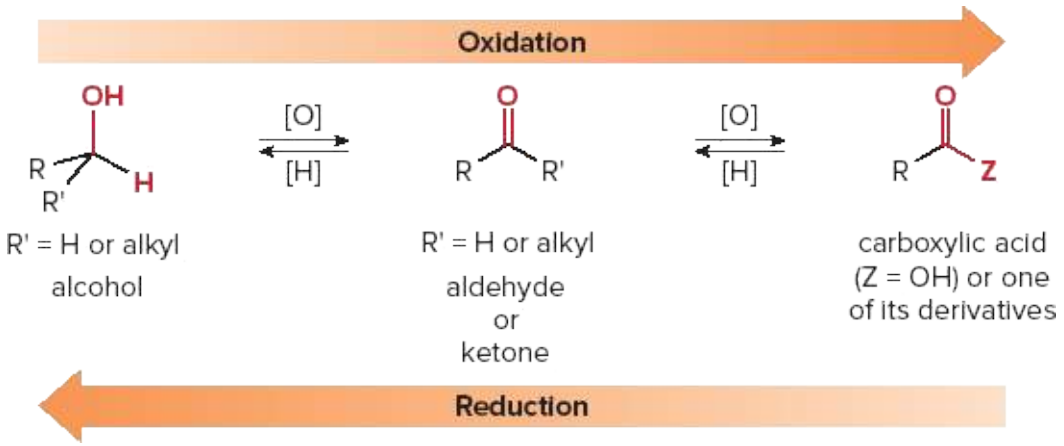
17.3 A Preview of Oxidation and Reduction

Recall the definitions of oxidation and reduction presented in Section 12.1:

- **Oxidation results in an *increase* in the number of C–Z bonds (usually C–O bonds) or a *decrease* in the number of C–H bonds.**
- **Reduction results in a *decrease* in the number of C–Z bonds (usually C–O bonds) or an *increase* in the number of C–H bonds.**

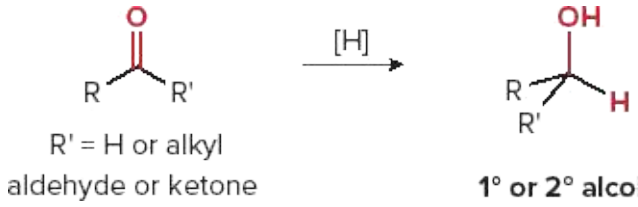
Carbonyl compounds are either reactants or products in many of these reactions, as illustrated in the accompanying diagram. For example, because aldehydes fall in the middle of this scheme, they can be both oxidized and reduced. Carboxylic acids and their derivatives (RCOZ), on the other hand, are already highly

oxidized, so their only useful reaction is reduction.



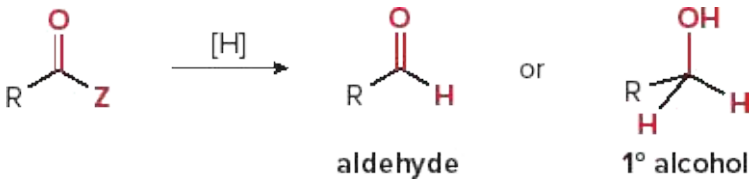
The three most useful oxidation and reduction reactions of carbonyl starting materials can be summarized as follows:

[1] Reduction of aldehydes and ketones to alcohols (Sections 17.4–17.6)



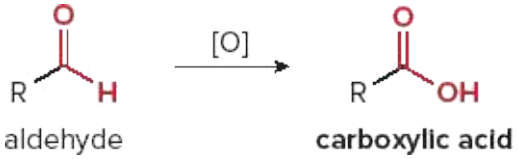
Aldehydes and ketones are reduced to 1° and 2° alcohols, respectively.

[2] Reduction of carboxylic acids and their derivatives (Section 17.7)



The reduction of carboxylic acids and their derivatives gives a variety of products, depending on the identity of Z and the nature of the reducing agent. The usual products are aldehydes or 1° alcohols.

[3] Oxidation of aldehydes to carboxylic acids (Section 17.8)



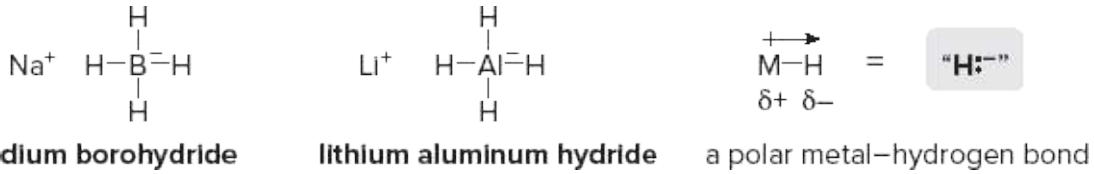
The most useful oxidation reaction of carbonyl compounds is the oxidation of aldehydes to carboxylic acids.

We begin with reduction, because the mechanisms of reduction reactions follow directly from the general mechanisms for nucleophilic addition and substitution.

$LiAlH_4$ and $NaBH_4$ serve as a source of $H:^-$, but there are no free $H:^-$ ions present in reactions with these reagents.

17.4 Reduction of Aldehydes and Ketones

The most useful reagents for reducing aldehydes and ketones are the metal hydride reagents (Section 12.2). The two most common metal hydride reagents are sodium borohydride ($NaBH_4$) and lithium aluminum hydride ($LiAlH_4$). These reagents contain a polar metal–hydrogen bond that serves as a source of the nucleophile hydride, $H:^-$. $LiAlH_4$ is a stronger reducing agent than $NaBH_4$, because the Al–H bond is more polar than the B–H bond.

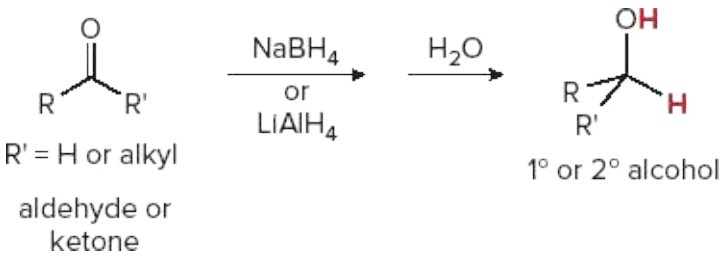


sodium borohydride | lithium aluminum hydride | a polar metal–hydrogen bond

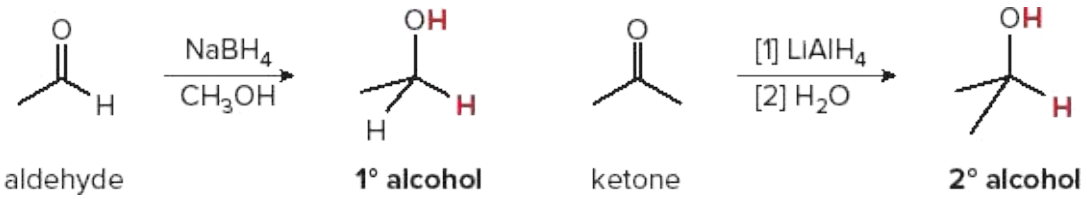
$LiAlH_4$ reductions must be carried out under anhydrous conditions, because water reacts violently with the reagent. Water is added to the reaction mixture (to serve as a proton source) *after* the reduction with $LiAlH_4$ is complete.

17.4A Reduction with Metal Hydride Reagents

Treating an aldehyde or a ketone with $NaBH_4$ or $LiAlH_4$, followed by water or some other proton source, affords an alcohol. This is an addition reaction because the elements of H_2 are added across the π bond, but it is also a reduction because the product alcohol has fewer C–O bonds than the starting carbonyl compound.



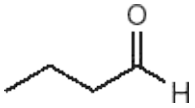
The product of this reduction reaction is a 1° alcohol when the starting carbonyl compound is an aldehyde, and a 2° alcohol when it is a ketone.

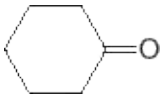


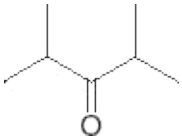
$NaBH_4$ selectively reduces aldehydes and ketones in the presence of most other functional groups. Reductions with $NaBH_4$ are typically carried out in CH_3OH as solvent. $LiAlH_4$ reduces aldehydes and ketones and many other functional groups as well (Sections 12.6 and 17.7).

Problem 17.4

What alcohol is formed when each compound is treated with $NaBH_4$ in CH_3OH?

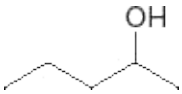
a.


b.


c.


Problem 17.5

What aldehyde or ketone is needed to prepare each alcohol by metal hydride reduction?

a.


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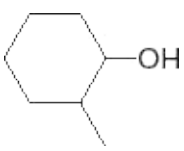

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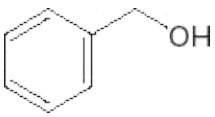

17.4B The Mechanism of Hydride Reduction

Hydride reduction of aldehydes and ketones occurs via the general mechanism of nucleophilic addition—that is, nucleophilic attack followed by protonation. Mechanism 17.3 is shown using $LiAlH_4$, but an analogous mechanism can be written for $NaBH_4$.

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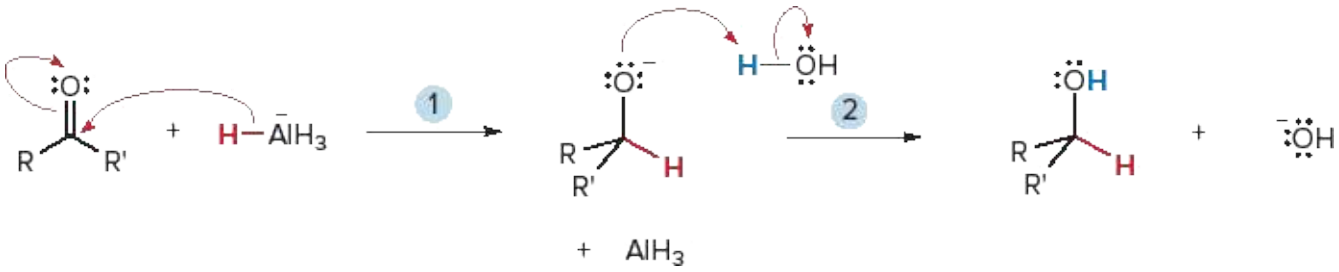
Mechanism 17.3 $LiAlH_4$ Reduction of RCHO and $R_2C{=}O$



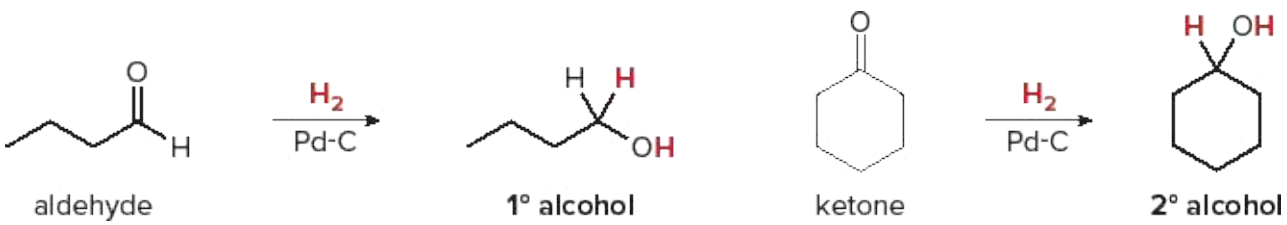
1 **The nucleophile (AlH_4^-) donates $H:^-$ to the carbonyl group, breaking the p bond and moving an electron pair out on oxygen. This forms a new C–H bond.**

2 **Protonation of the negatively charged oxygen by H_2O (or CH_3OH) forms the reduction product with a new O–H bond.**

- **The net result of adding $H:^-$ (from $NaBH_4$ or $LiAlH_4$) and H^+ (from H_2O) is the addition of the elements of H_2 to the carbonyl π bond.**

17.4C Catalytic Hydrogenation of Aldehydes and Ketones

Catalytic hydrogenation also reduces aldehydes and ketones to 1° and 2° alcohols, respectively, using H_2 and Pd-C (or another metal catalyst). H_2 adds to the C=O in much the same way that it adds to the C=C of an alkene (Section 12.3). The metal catalyst (Pd-C) provides a surface that binds the carbonyl starting material and H_2, and two H atoms are sequentially transferred with cleavage of the π bond.

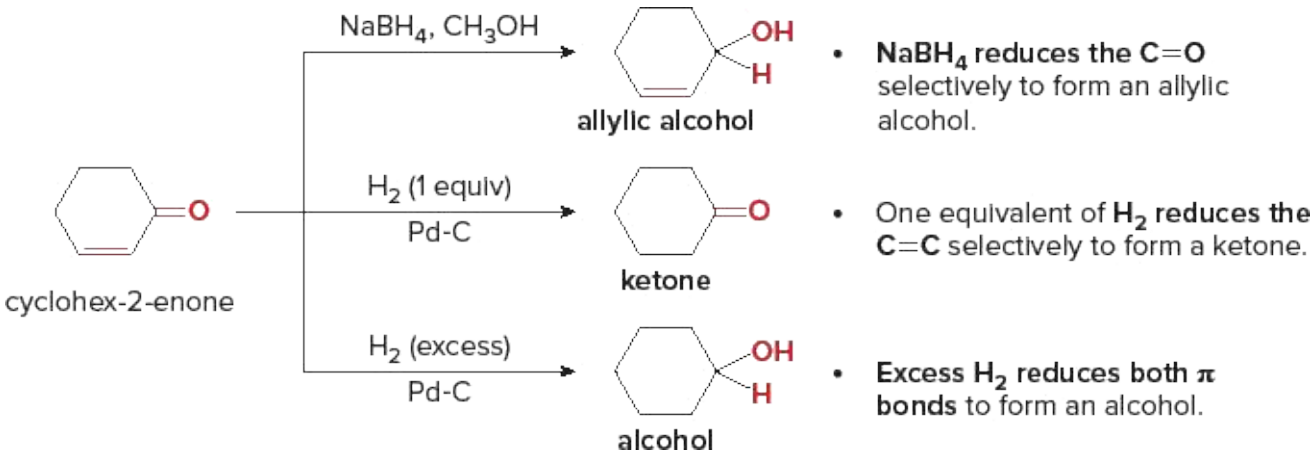


aldehyde — 1° alcohol — ketone — 2° alcohol

When a compound contains both a carbonyl group and a carbon–carbon double bond, selective reduction of one functional group can be achieved by proper choice of reagent.

- **A C=C is reduced faster than a C=O with H_2 (Pd-C).**
- **A C=O is readily reduced with $NaBH_4$ and $LiAlH_4$, but a C=C is inert.**

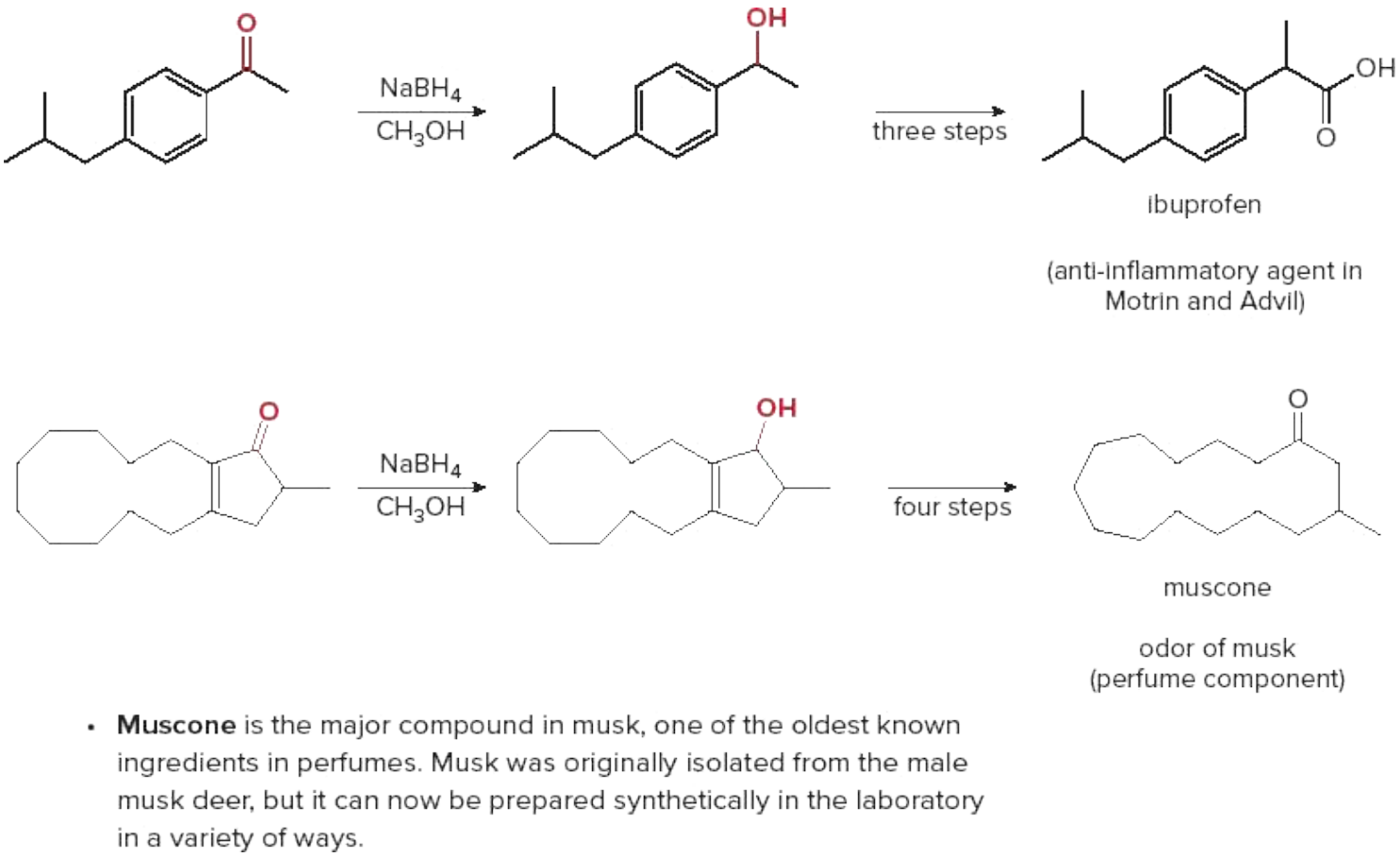
Thus, cyclohex-2-enone, a compound that contains both a carbon–carbon double bond and a carbonyl group, can be reduced to three different compounds—an allylic alcohol, a carbonyl compound, or an alcohol—depending on the reagent.



Problem 17.6

Draw the products formed when $CH_3COCH_2CH_2CH{=}CH_2$ is treated with each reagent: (a) $LiAlH_4$, then H_2O; (b) $NaBH_4$ in CH_3OH; (c) H_2 (1 equiv), Pd-C; (d) H_2 (excess), Pd-C; (e) $NaBH_4$ (excess) in CH_3OH; (f) $NaBD_4$ in CH_3OH.

The male musk deer, a small antlerless deer found in the mountain regions of China and Tibet, has long been hunted for its musk, a strongly scented liquid used in early medicine and later in perfumery. ©*Aleksey Suvorov/Alamy Stock Photo*



- **Muscone** is the major compound in musk, one of the oldest known ingredients in perfumes. Musk was originally isolated from the male musk deer, but it can now be prepared synthetically in the laboratory in a variety of ways.

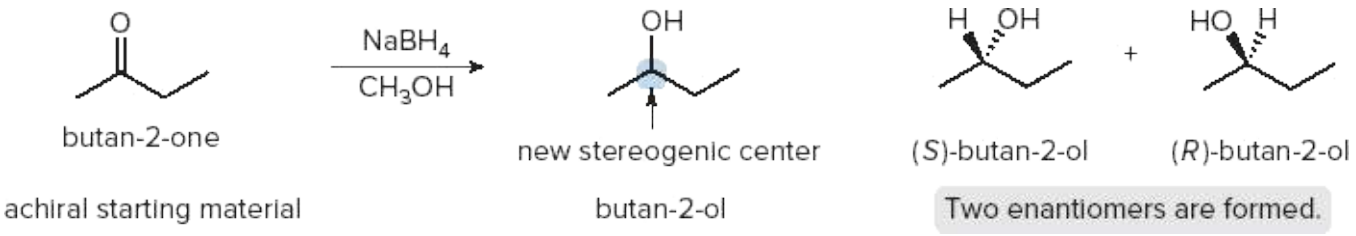
Figure 17.2 **$NaBH_4$ reductions used in organic synthesis**

The reduction of aldehydes and ketones is a common reaction used in the synthesis of many useful natural products. Two examples are shown in Figure 17.2.

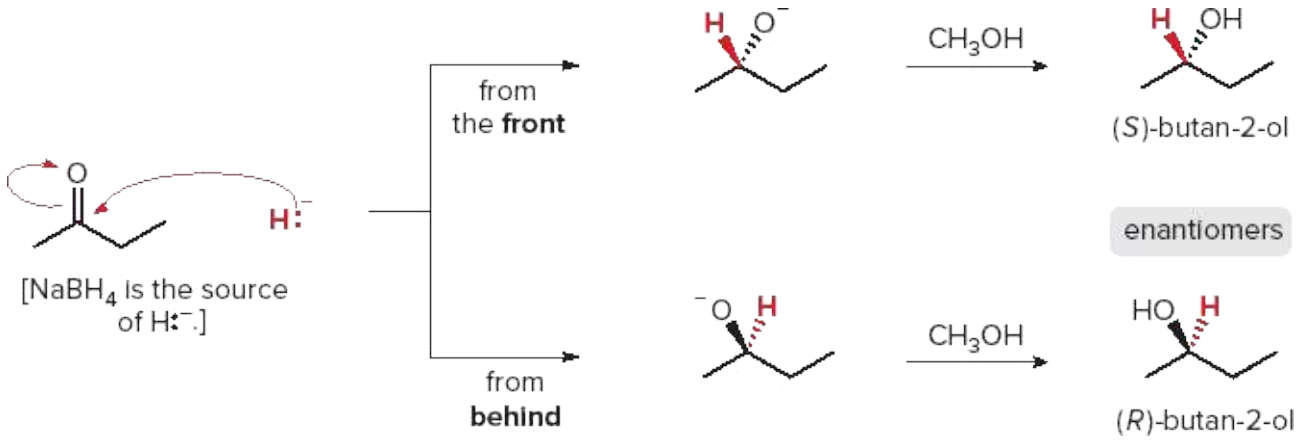
Recall from Section 9.16 that an achiral starting material gives a racemic mixture when a new stereogenic center is formed.

17.5 The Stereochemistry of Carbonyl Reduction

The stereochemistry of carbonyl reduction follows the same principles we have previously learned. Reduction converts a planar sp^2 hybridized carbonyl carbon to a tetrahedral sp^3 hybridized carbon. What happens when a new stereogenic center is formed in this process? With an achiral reagent like $NaBH_4$ or $LiAlH_4$, a racemic product is obtained. For example, $NaBH_4$ in CH_3OH solution reduces butan-2-one, an achiral ketone, to butan-2-ol, an alcohol that contains a new stereogenic center. Both enantiomers of butan-2-ol are formed in equal amounts.



Why is a racemic mixture formed? Because the carbonyl carbon is sp^2 hybridized and planar, hydride can approach the double bond with equal probability from both sides of the plane, forming two alkoxides, which are enantiomers of each other. Protonation of the alkoxides gives an equal amount of two alcohols, which are also enantiomers.

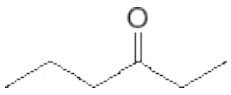


- **Conclusion: Hydride reduction of an achiral ketone with $LiAlH_4$ or $NaBH_4$ gives a racemic mixture of two alcohols when a new stereogenic center is formed.**

Problem 17.7

Draw the products formed (including stereoisomers) when each compound is reduced with $NaBH_4$ in CH_3OH.

a.



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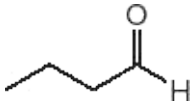
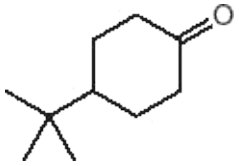


c.

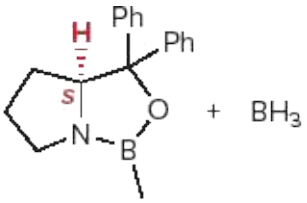


17.6 Enantioselective Carbonyl Reductions

17.6A CBS Reagents

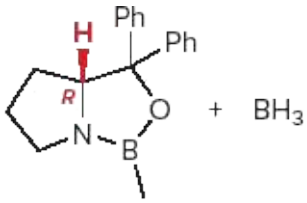
One enantiomer can be formed selectively from the reduction of a carbonyl group, provided a chiral reducing agent is used. This strategy is identical to that employed in the Sharpless asymmetric epoxidation reaction (Section 12.15). A reduction that forms one enantiomer predominantly or exclusively is an enantioselective or asymmetric reduction.

Many different chiral reducing agents have now been prepared for this purpose. One such reagent, formed by reacting borane (BH_3) with a heterocycle called an oxazaborolidine, has one stereogenic center (and thus two enantiomers).



(*S*)-2-methyl-**CBS**-oxazaborolidine

(*S*)-CBS reagent

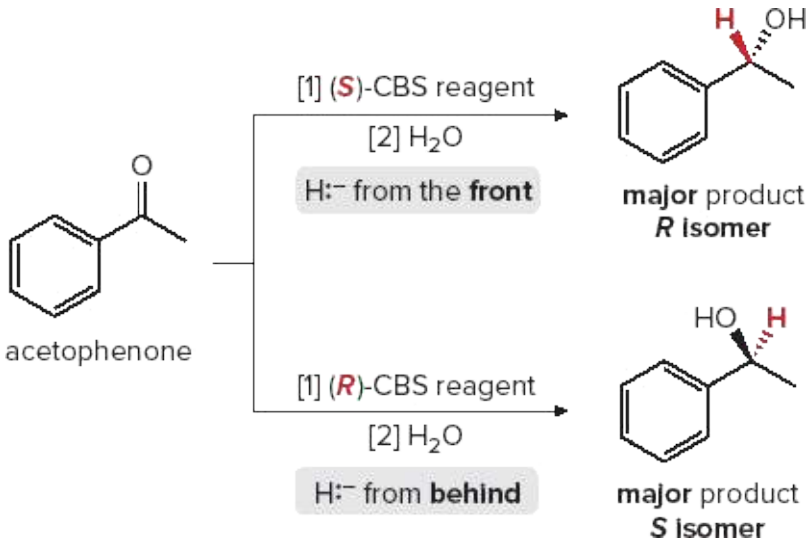


(*R*)-2-methyl-**CBS**-oxazaborolidine

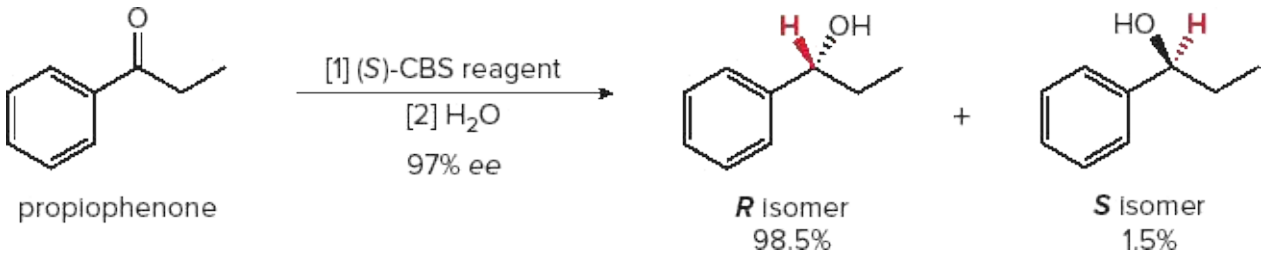
(*R*)-CBS reagent

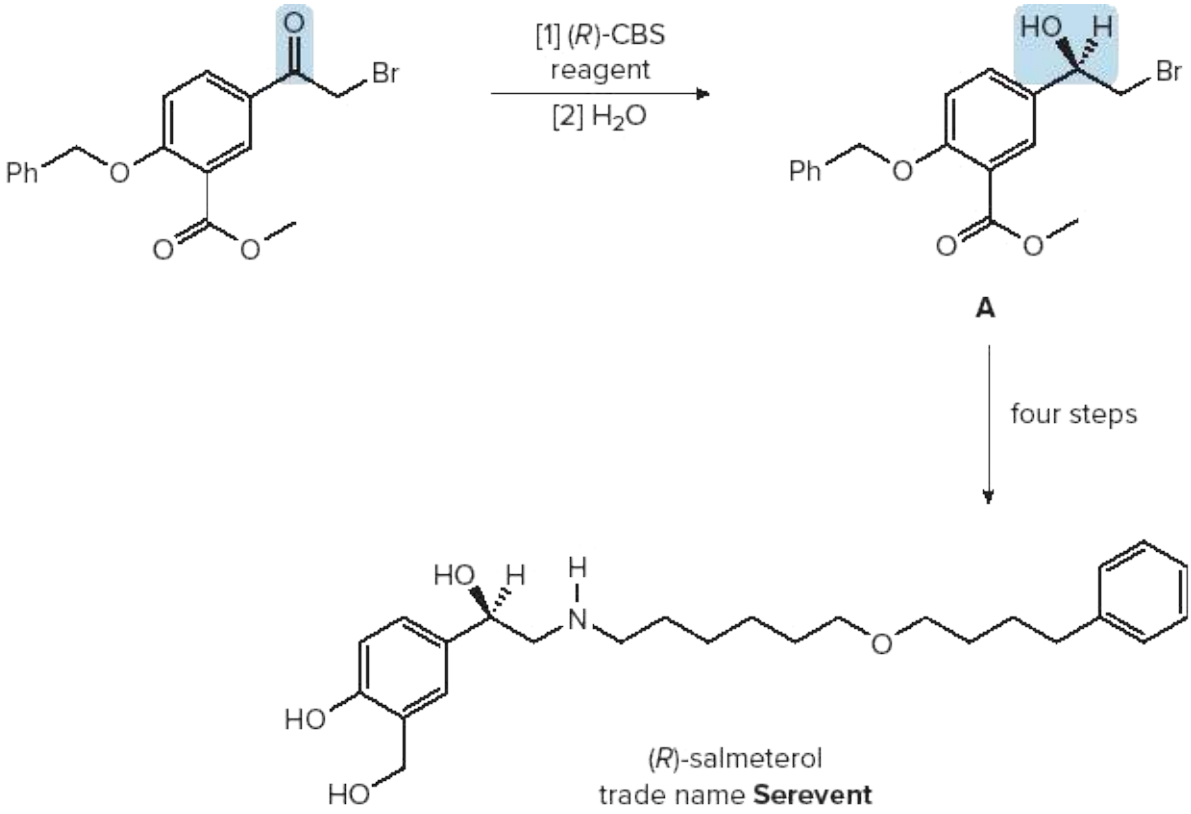
These reagents are called the (*S*)-CBS reagent and the (*R*)-CBS reagent, named for Corey, *B*akshi, and *S*hibata, the chemists who developed these versatile reagents. One B–H bond of BH_3 serves as the source of hydride in this reduction. The stereochemistry of the new stereogenic center in the product is often predictable. For ketones having the general structure C_6H_5COR, draw the starting material with the aryl group on the left side of the carbonyl, as shown with acetophenone. Then, to draw the product, keep in mind:

- **The (*S*)-CBS reagent delivers hydride ($H:^-$) from the *front* side of the C=O. This generally affords the *R* alcohol as the major product.**
- **The (*R*)-CBS reagent delivers hydride ($H:^-$) from the *back* side of the C=O. This generally affords the *S* alcohol as the major product.**



These reagents are highly enantioselective. Treatment of propiophenone with Page 791 the (*S*)-CBS reagent forms the *R* alcohol in 97% enantiomeric excess (*ee*). Enantioselective reductions are key steps in the synthesis of several widely used drugs, including salmeterol, a long-acting bronchodilator shown in Figure 17.3. This new technology provides access to single enantiomers of biologically active compounds, often previously available only as a racemic mixture.





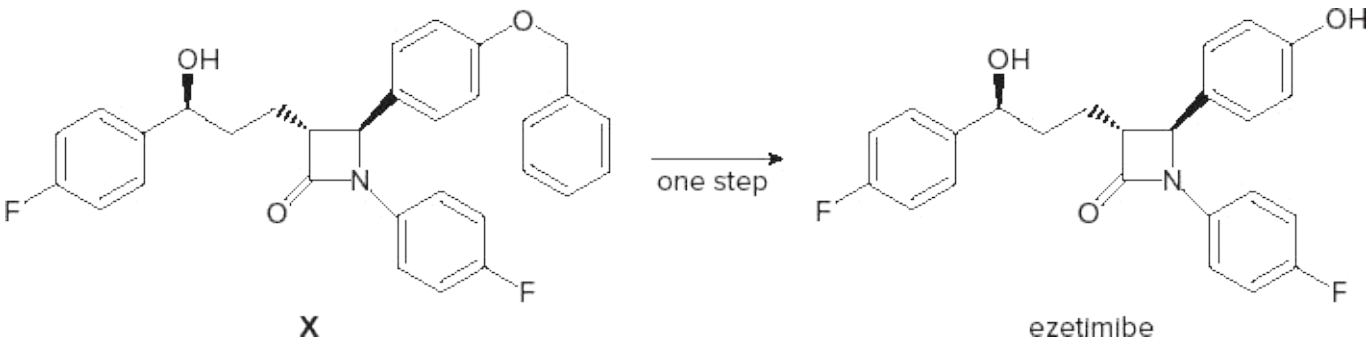
- (*R*)-Salmeterol is a long-acting bronchodilator used for the treatment of asthma.
- In this example, the **(*R*)-CBS reagent adds the new H atom from behind,** the same result observed with acetophenone and propiophenone. In this case, however, alcohol **A** has the *R* configuration using the rules for assigning priority in Chapter 5.

Figure 17.3 **Enantioselective reduction—A key step in the synthesis of salmeterol**

Ezetimibe (Problem 17.8) is sold as a single medication under the trade name of Zetia, or in combination with simvastatin, another cholesterol-lowering medication, and marketed as Vytorin. These drugs are prescribed for individuals who cannot tolerate or derive no benefit from other cholesterol-lowering medications. ©*John Kaprielian/Science Source*

Problem 17.8

What carbonyl compound and CBS reagent are needed to prepare X, an intermediate in the synthesis of ezetimibe (trade name Zetia), a drug that lowers cholesterol levels by inhibiting its absorption in the intestines?



17.6B Enantioselective Biological Reduction

Although laboratory reduction reactions often do not proceed with 100% enantioselectivity, biological reductions that occur in cells *always* proceed with complete selectivity, forming a single enantiomer. In cells, the reducing agent is NADH, nicotinamide adenine dinucleotide (reduced form), the coenzyme introduced in Section 12.14.

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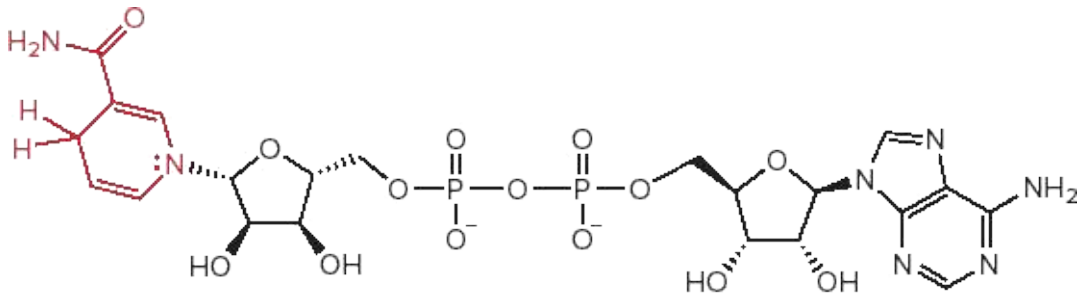
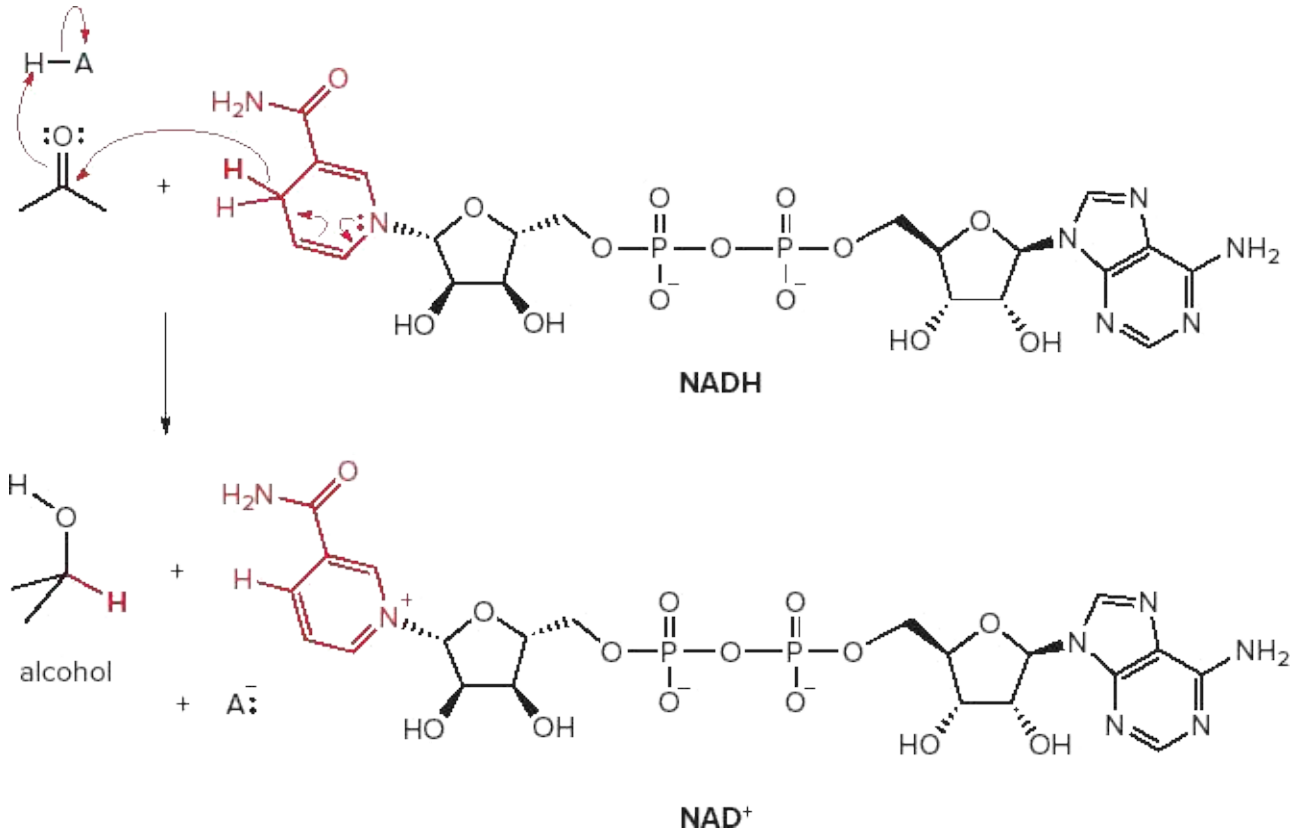


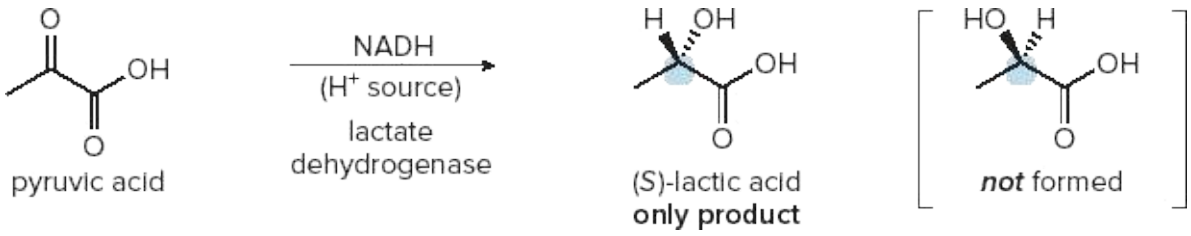
nicotinamide adenine dinucleotide
(reduced form)
NADH

In biological reduction, NADH donates $H:^-$, in much the same way as a metal hydride reagent. Nucleophilic attack of hydride and protonation thus form an alcohol from a carbonyl group, and NADH is converted to NAD^+.



This reaction is completely enantioselective. Reduction of pyruvic acid with NADH catalyzed by lactate dehydrogenase affords a single enantiomer of lactic acid with the *S* configuration. NADH reduces a variety of different carbonyl compounds in biological systems. The configuration of the product (*R* or *S*) depends on the enzyme used to catalyze the process.

Pyruvic acid is formed during the metabolism of glucose. During periods of strenuous exercise, when there is insufficient oxygen to metabolize pyruvic acid to CO_2, pyruvic acid is reduced to lactic acid. The tired feeling of sore muscles is a result of lactic acid accumulation.

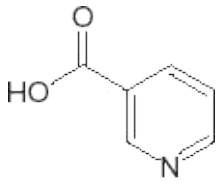


As we learned in Section 12.14, NAD^+, the oxidized form of NADH, is a biological oxidizing agent capable of oxidizing alcohols to carbonyl compounds, forming NADH in the process. NAD^+ is synthesized from the vitamin niacin, which can be obtained from soybeans among other dietary sources.

Niacin can be obtained from foods such as soybeans, which contain it naturally, and from breakfast cereals, which are fortified with it to help people consume their recommended daily allowance of this B vitamin.

©C Squared Studios/Getty Images

$LiAlH_4$ is a strong, nonselective reducing agent. DIBAL-H and $LiAlH[OC(CH_3)_3]_3$ are milder, more selective reducing agents.



niacin
vitamin B_3

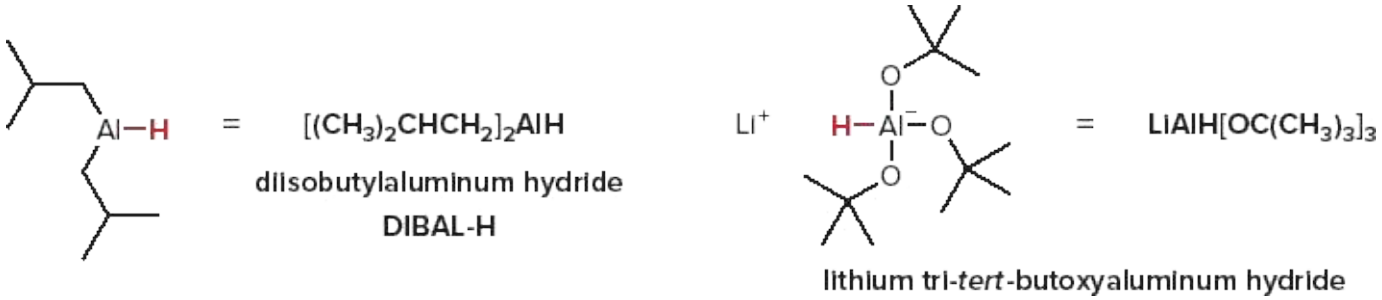
17.7 Reduction of Carboxylic Acids and Their Derivatives

The reduction of carboxylic acids and their derivatives (RCOZ) is complicated because the products obtained depend on the identity of both the leaving group (Z) and the reducing agent. Metal hydride reagents are the most useful reducing reagents. Lithium aluminum hydride is a strong reducing agent that reacts with *all* carboxylic acid derivatives. Two other related but more selective reducing agents are also used:

[1] Diisobutylaluminum hydride, $[(CH_3)_2CHCH_2]_2AlH$, abbreviated as DIBAL-H, has two bulky isobutyl groups, which make this reagent less reactive than $LiAlH_4$.

[2] Lithium tri-*tert*-butoxyaluminum hydride, $LiAlH[OC(CH_3)_3]_3$, has three electronegative oxygen atoms bonded to aluminum, which make this reagent less

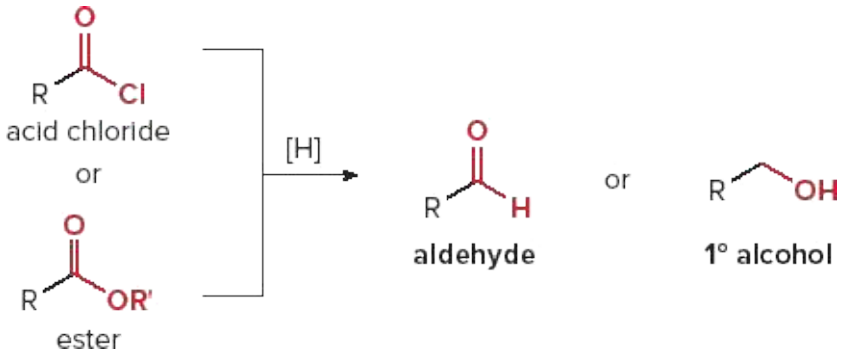
nucleophilic than $LiAlH_4$.



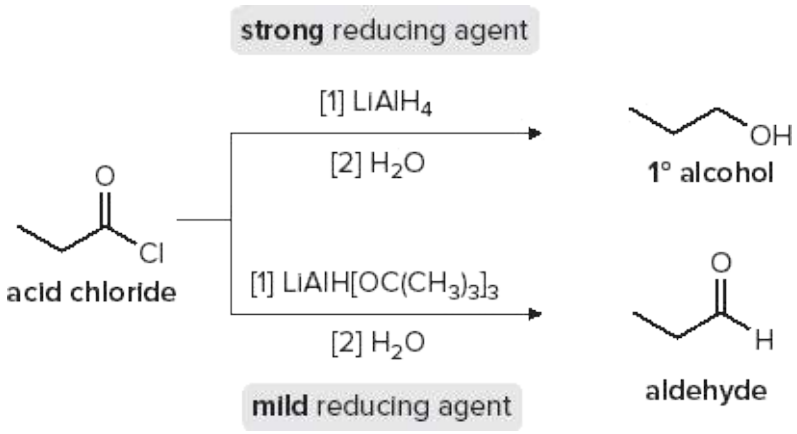
In both reagents, the single H atom bonded to Al is donated as $H:^-$ in hydride reductions.

17.7A Reduction of Acid Chlorides and Esters

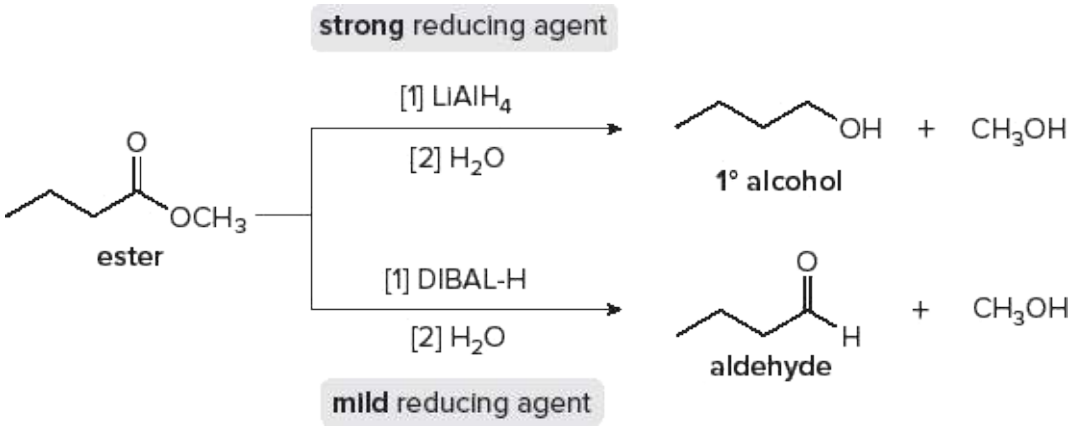
Acid chlorides and esters can be reduced to either aldehydes or alcohols, depending on the reagent.



- **$LiAlH_4$ converts RCOCl and RCOOR′ to alcohols.**
- **A milder reducing agent (DIBAL-H or $LiAlH[OC(CH_3)_3]_3$) converts RCOCl or RCOOR′ to RCHO at low temperatures.**



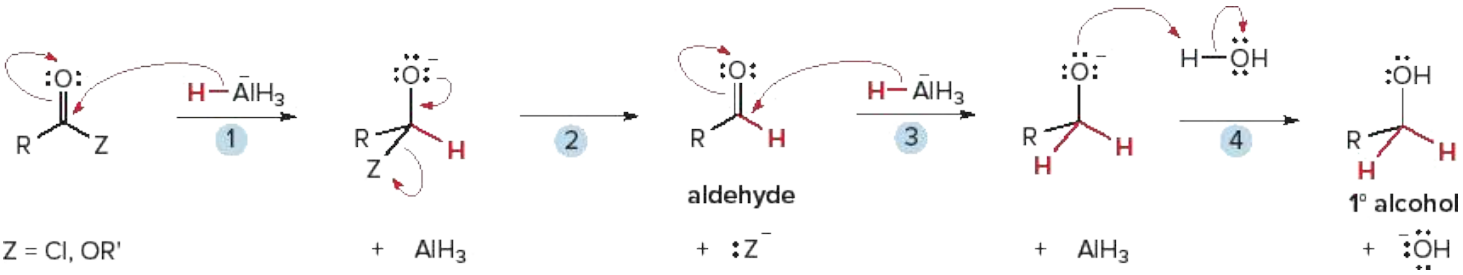
In the reduction of an acid chloride, Cl^- comes off as the leaving group.



In the reduction of the ester, CH_3O^- comes off as the leaving group, which is then protonated by H_2O to form CH_3OH.

Mechanism 17.4 illustrates why two different products are possible. It can be conceptually divided into two parts: nucleophilic substitution to form an aldehyde (Steps [1] and [2]), followed by nucleophilic addition to the aldehyde to form an alcohol (Steps [3] and [4]). A general mechanism is drawn using $LiAlH_4$ as reducing agent.

Mechanism 17.4 Reduction of RCOCl and RCOOR' with a Metal Hydride Reagent

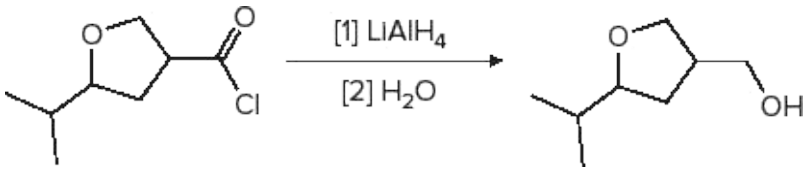


1. **Nucleophilic attack of $H:^-$ forms a tetrahedral intermediate with a leaving group Z.**
2. **The π bond is re-formed and the leaving group Z departs. The overall result of addition of $H:^-$ and elimination of $Z:^-$ is substitution of H for Z.**
3. **Nucleophilic attack of $H:^-$ forms an alkoxide with no leaving group.**
4. **Protonation of the alkoxide by H_2O forms the alcohol reduction product. The overall result of Steps [3] and [4] is addition of H_2.**

With less nucleophilic reducing agents such as DIBAL-H and $LiAlH[OC(CH_3)_3]_3$, the process stops after reaction with one equivalent of $H:^-$ and the aldehyde is formed as product (Steps [1] and [2] of Mechanism 17.4). With a stronger reducing agent like $LiAlH_4$, two equivalents of $H:^-$ are added and an alcohol is formed.

Problem 17.9

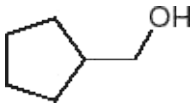
Draw a stepwise mechanism for the following reaction.



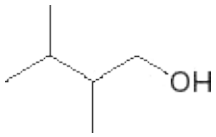
Problem 17.10

Draw the structure of both an acid chloride and an ester that can be used to prepare each compound by reduction.

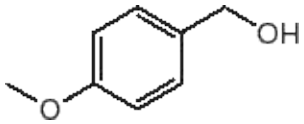
a.



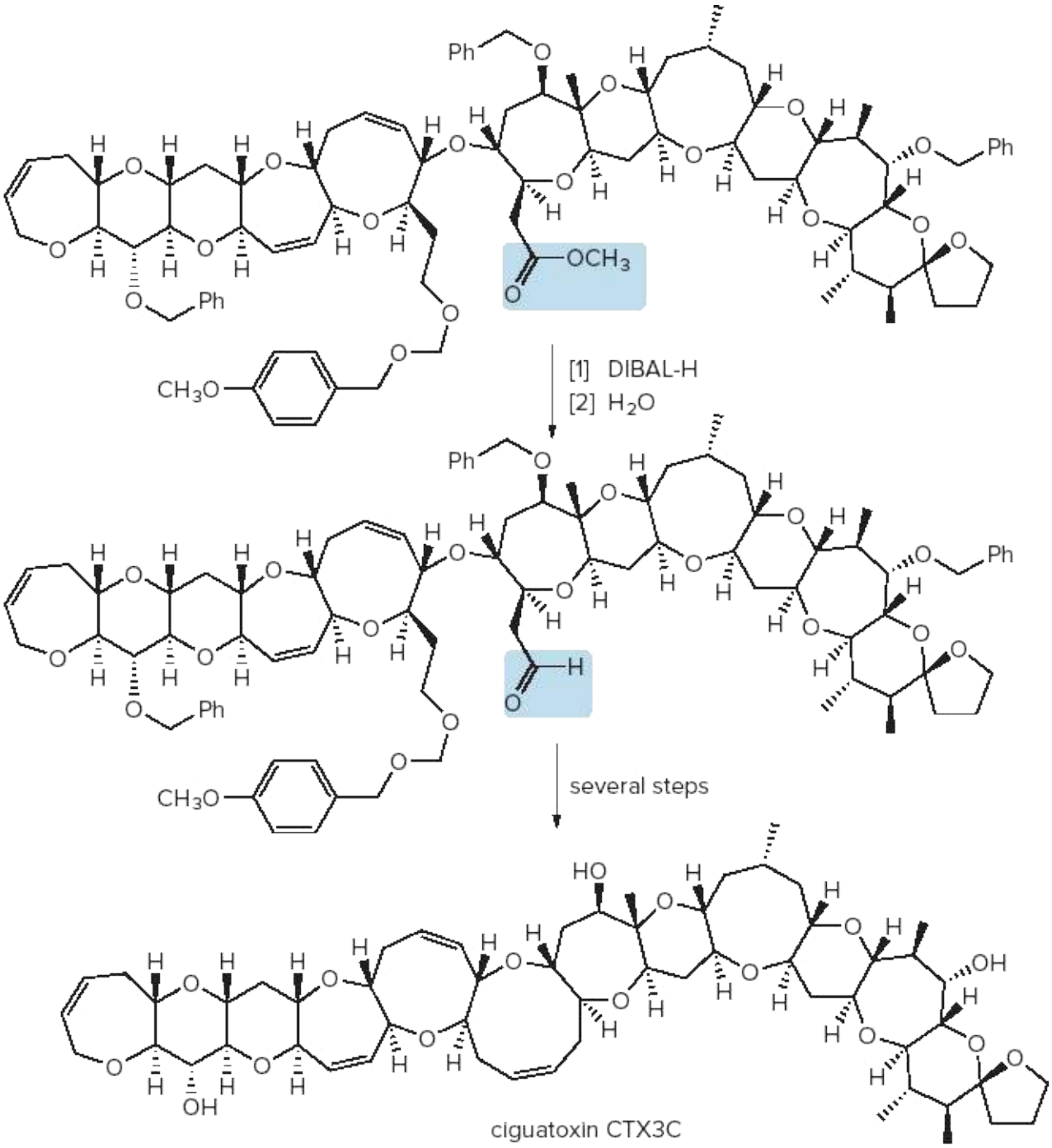
b.



c.



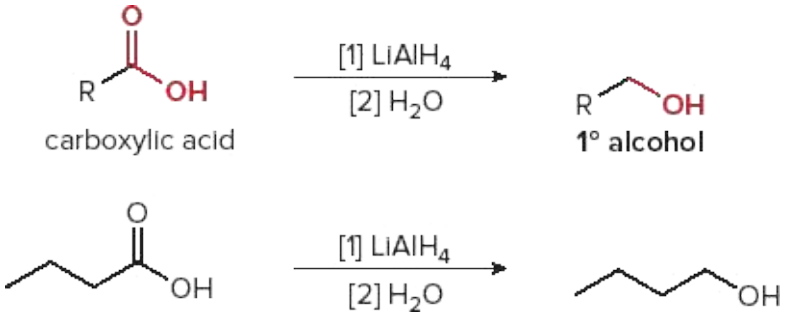
Selective reductions are routinely used in the synthesis of highly complex natural products such as ciguatoxin CTX3C, a potent neurotoxin found in more than 400 species of warm-water fish. One reaction in a synthesis of ciguatoxin CTX3C involved the reduction of an ester to an aldehyde using DIBAL-H, as shown in Figure 17.4.


Ph
O
H
O
H
H
O
H
H
O
H

Interest in providing a practical supply of ciguatoxin CTX3C, a potent neurotoxin, for biological testing led to a laboratory synthesis in 2001. ©*Daniel C. Smith*

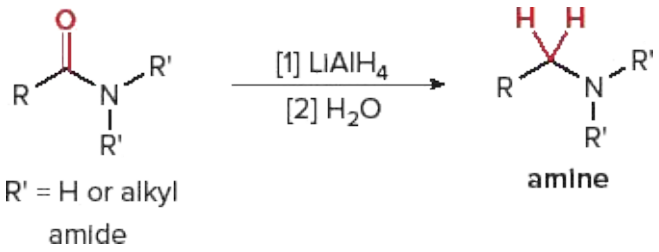
17.7B Reduction of Carboxylic Acids and Amides

Carboxylic acids are reduced to alcohols with $LiAlH_4$. $LiAlH_4$ is too strong a reducing agent to stop the reaction at the aldehyde stage, but milder reagents are not strong enough to initiate the reaction in the first place, so this is the only useful reduction reaction of carboxylic acids.

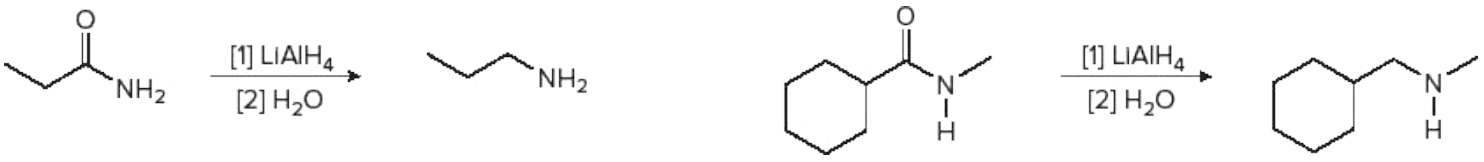


Unlike the $LiAlH_4$ reduction of all other carboxylic acid derivatives, which affords alcohols, the $LiAlH_4$ reduction of amides forms amines.

Page 796



Both C–O bonds are reduced to C–H bonds by $LiAlH_4$, and any H atom or R group bonded to the amide nitrogen atom remains bonded to it in the product. Because $^-NH_2$ (or ^-NHR or $^-NR_2$) is a *poorer* leaving group than Cl^- or ^-OR, $^-NH_2$ is never lost during reduction, and therefore it forms an amine in the final product.

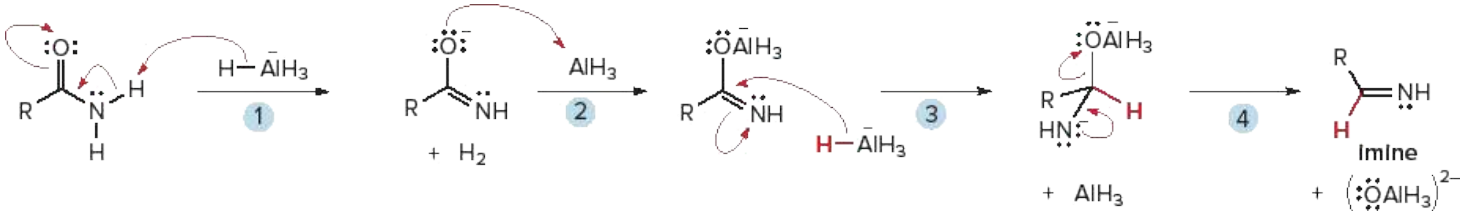


Imines and related compounds are discussed in Chapter 18.

The mechanism, illustrated in Mechanism 17.5 with $RCONH_2$ as starting material, is somewhat different than the previous reductions of carboxylic acid derivatives. Amide reduction proceeds with formation of an intermediate *imine*, a compound containing a C–N double bond, which is then further reduced to an amine.

Mechanism 17.5 Reduction of an Amide to an Amine with $LiAlH_4$

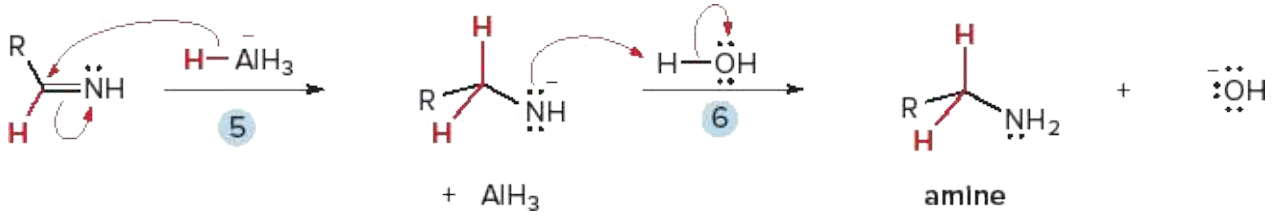
Part [1] Reduction of an amide to an imine



1 – 2 AlH_4^- removes a proton from the amide to form a Lewis base that complexes with AlH_3 in Step [2].

3 – 4 Nucleophilic attack of $H:^-$ and loss of a leaving group, $(OAlH3)^{2-}$, form an imine.

Part [2] Reduction of an imine to an amine

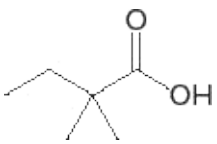


5 – 6 Nucleophilic addition of $H:^-$ and protonation form the amine.

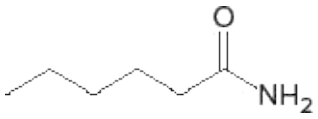
Problem 17.11

Draw the products formed from $LiAlH_4$ reduction of each compound.

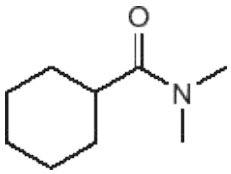
a.



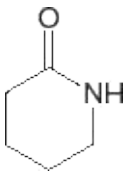
b.



c.

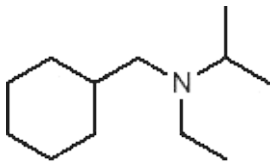


d.



Sample Problem 17.1 Determining the Amide That Forms an Amine by Reduction

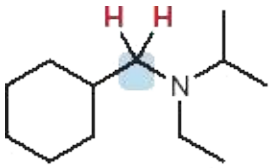
What amide(s) form amine X on treatment with $LiAlH_4$?

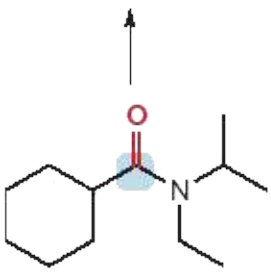


X

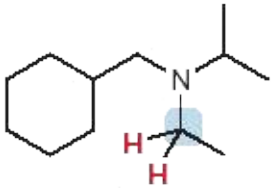
Solution

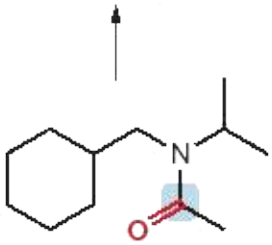
$LiAlH_4$ reduction of an amide converts a C=O to a CH_2 group, so we must examine the alkyl groups bonded to the amine nitrogen. Any alkyl group with a CH_2 group bonded *directly* to the N can be formed by reduction of a C=O. An alkyl group with zero or one H atom *cannot* be formed by reduction of a C=O. For amine X, the CH_2 groups in blue can be formed from C=O's, but the CH group labeled in red cannot be formed from a C=O.



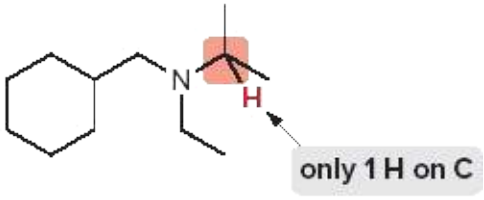


A





B

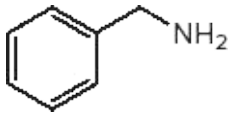


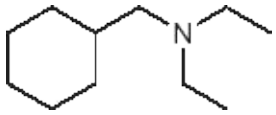
The CH bond in red *cannot* be formed from a C=O.

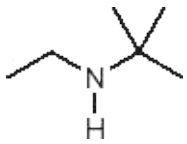
Thus, amides A and B can be converted to amine X by reduction of a C=O with $LiAlH_4$.

Problem 17.12

What amide(s) will form each of the following amines on treatment with $LiAlH_4$?

a. 

b. 

c. 

More Practice:

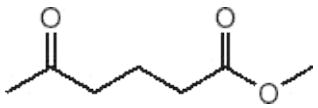
Try Problem 17.56.

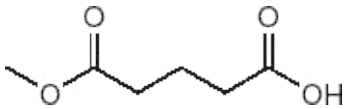
17.7C A Summary of the Reagents for Reduction

The many available metal hydride reagents reduce a wide variety of functional groups. Keep in mind that $LiAlH_4$ is such a strong reducing agent that it *nonselectively* reduces most polar functional groups. All other metal hydride reagents are more selective, and each has its particular reactions that best utilize its reduced reactivity. The reagents and their uses are summarized in Table 17.1.

Problem 17.13

What product is formed when each compound is treated with either $LiAlH_4$ (followed by H_2O), or $NaBH_4$ in CH_3OH?

a. 

b. 

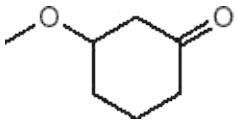
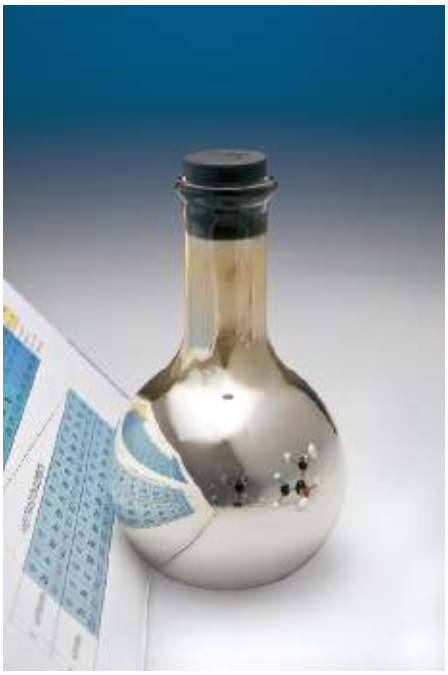
c. 

Table 17.1 A Summary of Metal Hydride Reducing Agents

	Reagent	Starting material	→	Product
Strong	**$LiAlH_4$**	**RCHO**	**→**	**RCH_2OH**

reagent				
		R_2CO	→	R_2CHOH
		RCOOH	→	RCH_2OH
		RCOOR′	→	RCH_2OH
		RCOCl	→	RCH_2OH
		$RCONH_2$	→	RCH_2NH_2
Milder reagents	$NaBH_4$	RCHO	→	RCH_2OH
		R_2CO	→	R_2CHOH
	$LiAlH[OC(CH_3)_3]_3$	RCOCl	→	RCHO
	DIBAL-H	RCOOR′	→	RCHO

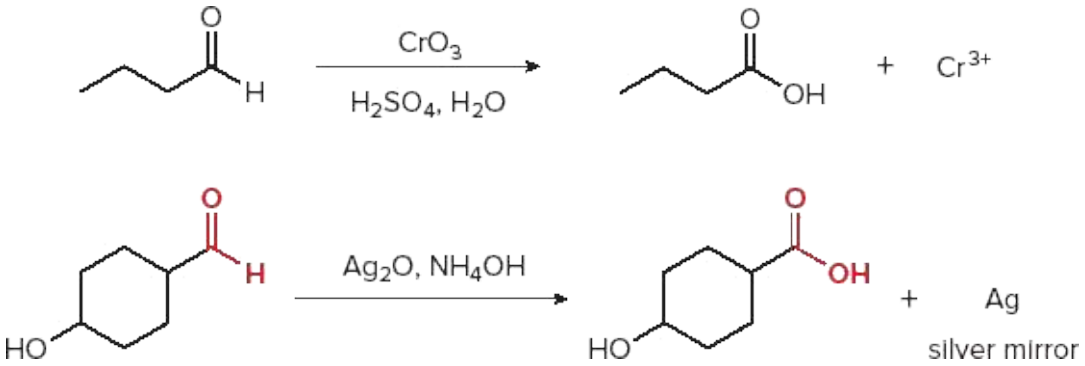


Aldehydes give a positive Tollens test; that is, they react with Ag^+ to form RCOOH and Ag. When the reaction is carried out in a glass flask, a silver mirror is formed on its walls. Other functional groups give a negative Tollens test, because no silver mirror forms. ©*McGraw-Hill Education/Charles D. Winters, photographer*

17.8 Oxidation of Aldehydes

The most common oxidation reaction of carbonyl compounds is the oxidation of aldehydes to carboxylic acids. A variety of oxidizing agents can be used, including CrO_3, $Na_2Cr_2O_7$, $K_2Cr_2O_7$, and $KMnO_4$. Cr^{6+} reagents are also used to oxidize 1° and 2° alcohols, as discussed in Section 12.12. Because ketones have no H on the carbonyl carbon, they do *not* undergo this oxidation reaction.

Aldehydes are oxidized selectively in the presence of other functional groups using silver(I) oxide in aqueous ammonium hydroxide (Ag_2O in NH_4OH). This is called Tollens reagent. Oxidation with Tollens reagent provides a distinct color change, because the Ag^+ reagent is reduced to silver metal (Ag), which precipitates out of solution.

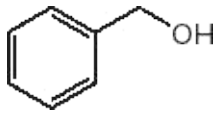


Only the aldehyde is oxidized.

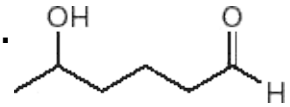
Problem 17.14

What product is formed when each compound is treated with either Ag_2O, NH_4OH or $Na_2Cr_2O_7$, H_2SO_4, H_2O?

a.

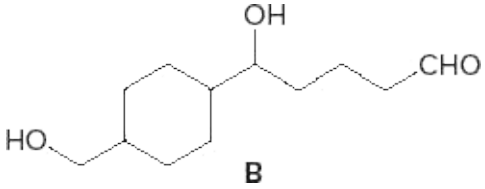


b.



Problem 17.15

Review the oxidation reactions using Cr^{6+} reagents in Section 12.12. Then draw the product formed when compound B is treated with each reagent.



B

a. $NaBH_4$, CH_3OH

b. [1] $LiAlH_4$; [2] H_2O

c. PCC

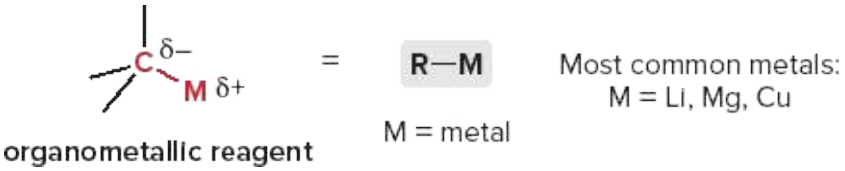
d. Ag_2O, NH_4OH

e. CrO_3, H_2SO_4, H_2O

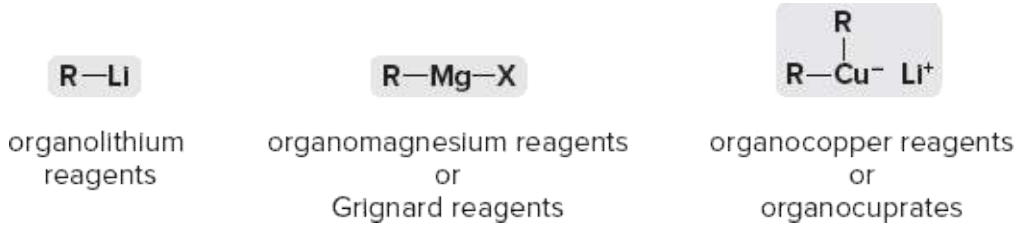
17.9 Organometallic Reagents

We will now discuss the reactions of carbonyl compounds with organometallic reagents, another class of nucleophiles.

- ***Organometallic reagents*** **contain a carbon atom bonded to a metal.**



Lithium, magnesium, and copper are the most commonly used metals in organometallic reagents, but others (such as Sn, Si, Tl, Al, Ti, and Hg) are known. General structures of the three common organometallic reagents are shown. R can be alkyl, aryl, allyl, benzyl, sp^2 hybridized, and with M = Li or Mg, *sp* hybridized. Because metals are *more electropositive* (less electronegative) than carbon, they donate electron density toward carbon, so that carbon bears a partial negative charge.



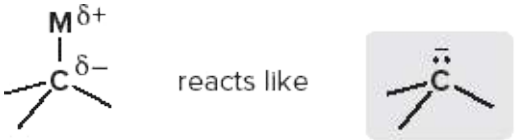
- **The *more polar* the carbon–metal bond, the *more reactive* the organometallic reagent.**

Because both Li and Mg are very electropositive metals, organolithium (RLi) and organomagnesium reagents (RMgX) contain very polar carbon–metal bonds and are therefore *very reactive* reagents. Organomagnesium reagents are called Grignard reagents, after Victor Grignard, who received the Nobel Prize in Chemistry in 1912 for his work with them.

Electronegativity values for carbon and the common metals in R–M reagents are C (2.5), Li (1.0), Mg (1.3), and Cu (1.8).

Organocopper reagents (R_2CuLi), also called organocuprates, have a less polar carbon–metal bond and are therefore *less reactive*. Although organocuprates contain two alkyl groups bonded to copper, only one R group is utilized in a reaction.

Regardless of the metal, organometallic reagents are useful synthetically because they react as if they were free carbanions; that is, carbon bears a partial *negative* charge, so the reagents react as bases and nucleophiles.

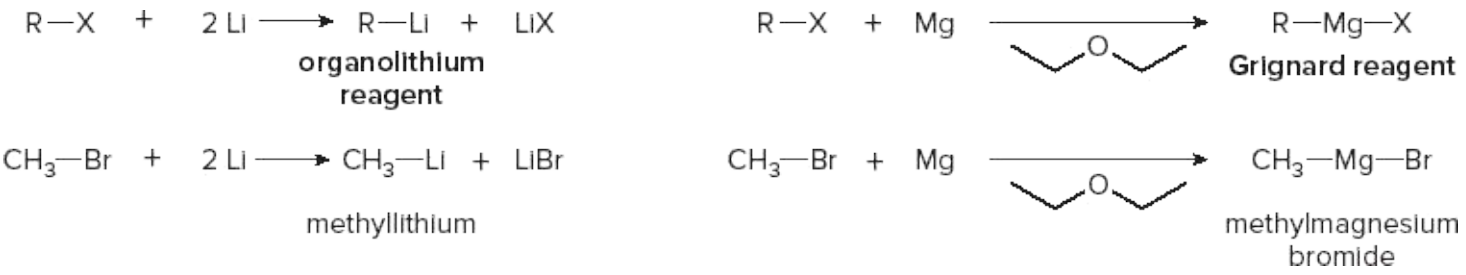


carbanion

a base and a nucleophile

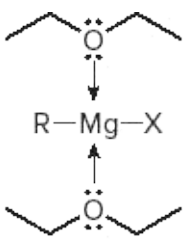
17.9A Preparation of Organometallic Reagents

Organolithium and Grignard reagents are typically prepared by reaction of an organic halide with the corresponding metal, as shown in the accompanying equations.



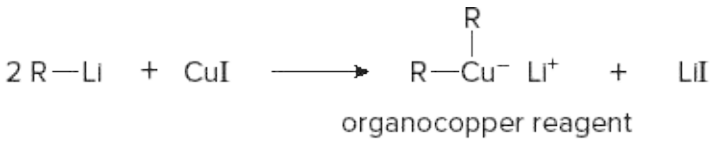
With lithium, the halogen and metal exchange to form the organolithium reagent. With magnesium, the metal inserts in the carbon–halogen bond, forming the Grignard reagent. Grignard reagents are usually prepared in diethyl ether ($CH_3CH_2OCH_2CH_3$) as solvent. It is thought that two ether oxygen atoms complex with the magnesium atom, stabilizing the reagent.

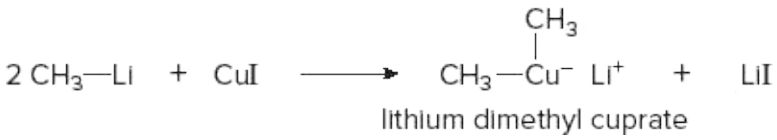
Page 800



Two molecules of diethyl ether complex with the Mg atom of the Grignard reagent.

Organocuprates are prepared from organolithium reagents by reaction with a Cu^+ salt, often CuI.



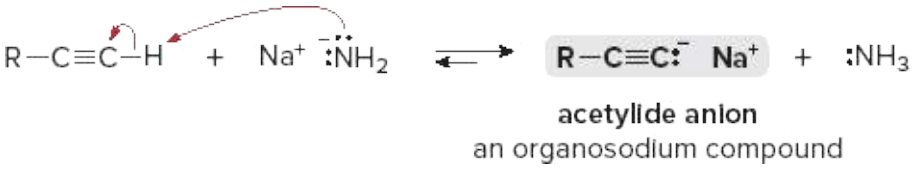


Problem 17.16

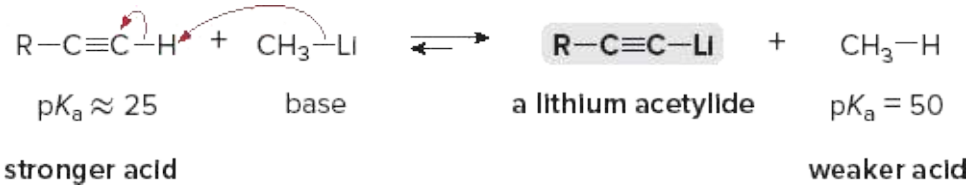
Write the step(s) needed to convert CH_3CH_2Br to each reagent: (a) CH_3CH_2Li; (b) CH_3CH_2MgBr; (c) $(CH_3CH_2)_2CuLi$.

17.9B Acetylide Anions

The acetylide anions discussed in Chapter 11 are another example of organometallic compounds. These reagents are prepared by an acid–base reaction of an alkyne with a base such as $NaNH_2$ or NaH. We can think of these compounds as organosodium reagents. Because sodium is even more electropositive (less electronegative) than lithium, the C–Na bond of these organosodium compounds is best described as ionic, rather than polar covalent.



An acid–base reaction can also be used to prepare *sp* hybridized organolithium compounds. Treatment of a terminal alkyne with CH_3Li affords a lithium acetylide. Equilibrium favors the products because the *sp* hybridized C–H bond of the terminal alkyne is more acidic than the sp^3 hybridized conjugate acid, CH_4, that is formed.



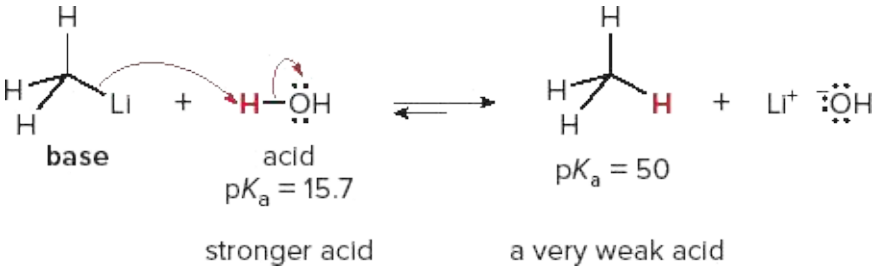
Problem 17.17

Which of the following species represent organometallic compounds: (a) $BrMgC{\equiv}CCH_2CH_3$; (b) $NaOCH_2CH_3$; (c) $KOC(CH_3)_3$; (d) PhLi?

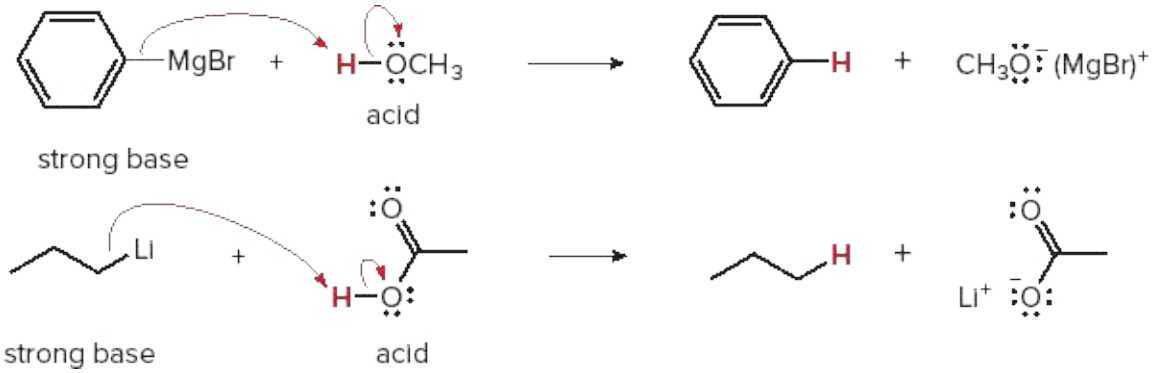
17.9C Reaction as a Base

- **Organometallic reagents are strong bases that readily abstract a proton from water to form hydrocarbons.**

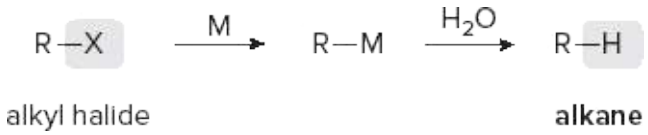
The electron pair in the carbon–metal bond is used to form a new bond to the proton. Equilibrium favors the products of this acid–base reaction because H_2O is a much stronger acid than the alkane product.



Similar reactions occur for the same reason with the O–H proton in alcohols and carboxylic acids, and the N–H protons of amines.



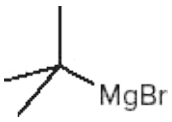
Because organolithium and Grignard reagents are themselves prepared from alkyl halides, a two-step method converts an alkyl halide to an alkane (or another hydrocarbon).

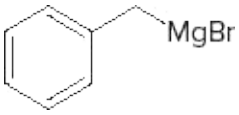


Problem 17.18

Draw the product formed when each organometallic reagent is treated with H_2O.

a.

b. 

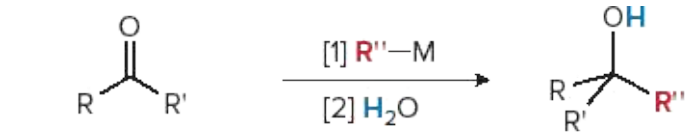
c. 

d.

17.9D Reaction as a Nucleophile

Organometallic reagents are also strong nucleophiles that react with electrophilic carbon atoms to form new carbon–carbon bonds. These reactions are very valuable in forming the carbon skeletons of complex organic molecules. The following reactions of organometallic reagents are examined in Sections 17.10, 17.13, and 17.14:

[1] Reaction of R–M with aldehydes and ketones to afford alcohols (Section 17.10)

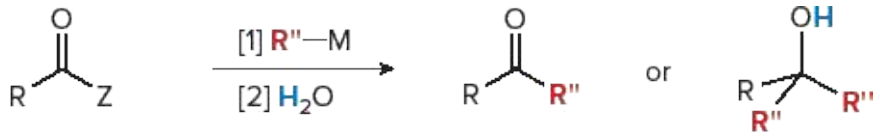


R' = H or alkyl
aldehyde or ketone

1°, 2°, or 3° alcohol

Aldehydes and ketones are converted to 1°, 2°, or 3° alcohols with R″Li or R″MgX.

[2] Reaction of R–M with carboxylic acid derivatives (Section 17.13)



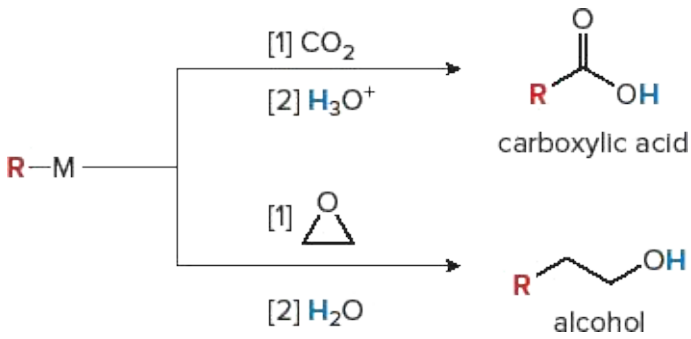
Z = Cl or OR'

ketone

3° alcohol

Acid chlorides and esters can be converted to ketones or 3° alcohols with organometallic reagents. The identity of the product depends on the identity of R″–M and the leaving group Z.

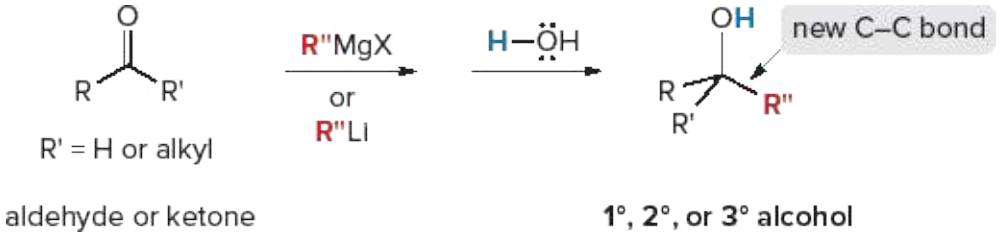
[3] Reaction of R–M with other electrophilic functional groups (Section 17.14)



Organometallic reagents also react with CO_2 to form carboxylic acids and with epoxides to form alcohols.

17.10 Reaction of Organometallic Reagents with Aldehydes and Ketones

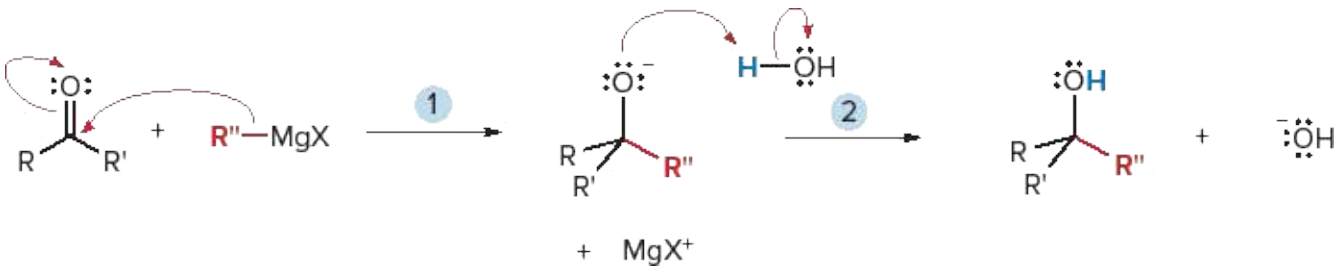
Treatment of an aldehyde or ketone with either an organolithium or Grignard reagent followed by water forms an alcohol with a new carbon–carbon bond. This reaction is an addition reaction because the elements of R″ and H are added across the π bond.



17.10A General Features

This reaction follows the general mechanism for nucleophilic addition (Section 17.2A)—that is, nucleophilic attack by a carbanion followed by protonation. Mechanism 17.6 is shown using R″MgX, but the same steps occur with organolithium reagents and acetylide anions.

Mechanism 17.6 Nucleophilic Addition of R″MgX to RCHO and R_2C=O

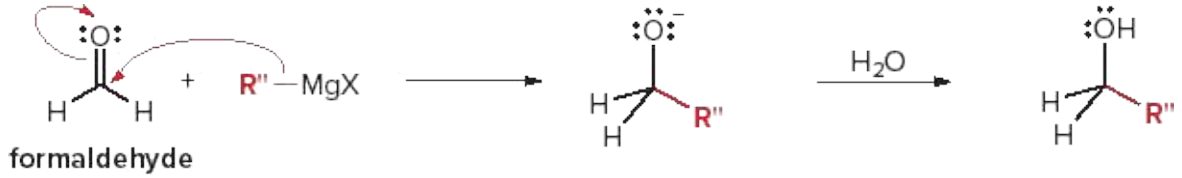


1 The nucleophile $(R")^-$ attacks the carbonyl group, breaking the π bond and yielding an alkoxide. This forms a new carbon–carbon bond.

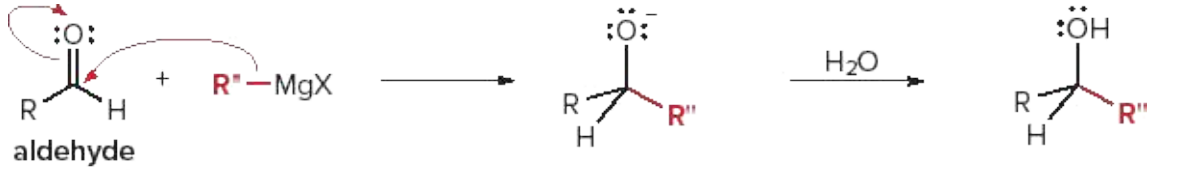
2 **Protonation of the alkoxide by H2O forms the addition product with a new O–H bond. The overall result is addition of R" and H to the carbonyl group.**

This reaction is used to prepare 1°, 2°, and 3° alcohols, depending on the number of alkyl groups bonded to the carbonyl carbon of the aldehyde or ketone. Page 803

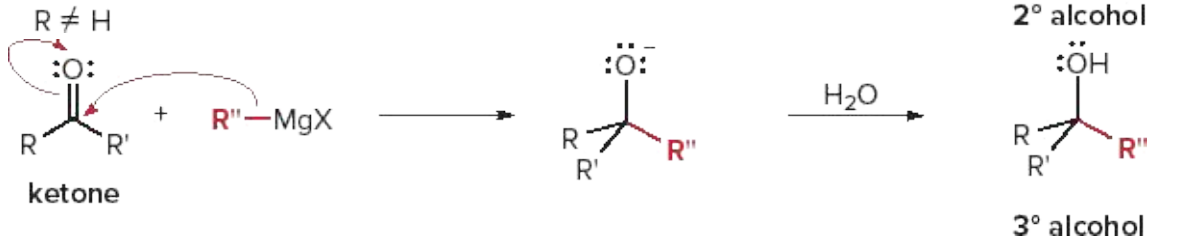
[1]



[2]



[3]



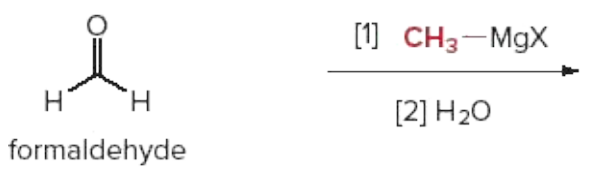
[1] Addition of R″MgX to formaldehyde (CH_2=O) forms a 1° alcohol.

[2] Addition of R″MgX to all other aldehydes forms a 2° alcohol.

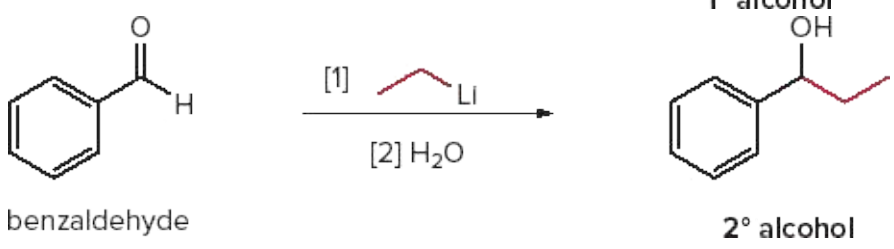
[3] Addition of R″MgX to ketones forms a 3° alcohol.

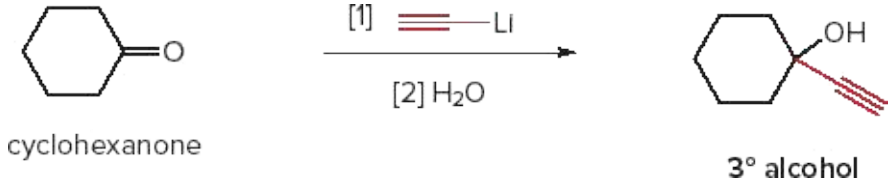
Each reaction results in addition of one new alkyl group to the carbonyl carbon, and forms one new carbon–carbon bond. The reaction is general for all organolithium and Grignard reagents, and works for acetylide anions as well, as illustrated in Equations [1]–[3].

[1]



[2]



[3] 

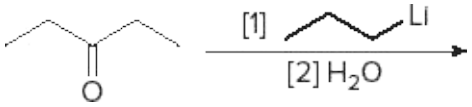
cyclohexanone

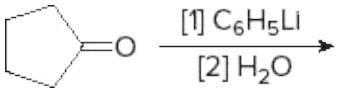
3° alcohol

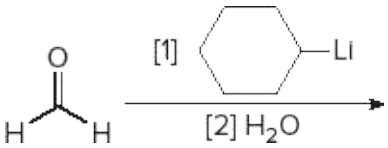
Because organometallic reagents are strong bases that rapidly react with H_2O (Section 17.9C), the addition of the new alkyl group must be carried out under anhydrous conditions to prevent traces of water from reacting with the reagent, thus reducing the yield of the desired alcohol. Water is added *after* the addition to protonate the alkoxide.

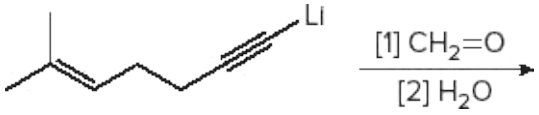
Problem 17.19

Draw the product of each reaction.

a. 

b. 

c. 

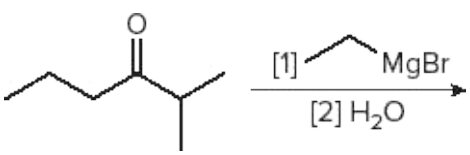
d. 

17.10B Stereochemistry

Like reduction, addition of organometallic reagents converts an sp^2 hybridized carbonyl carbon to a tetrahedral sp^3 hybridized carbon. Addition of R–M always occurs from both sides of the trigonal planar carbonyl group. When a new stereogenic center is formed from an achiral starting material, an equal mixture of enantiomers results, as shown in Sample Problem 17.2.

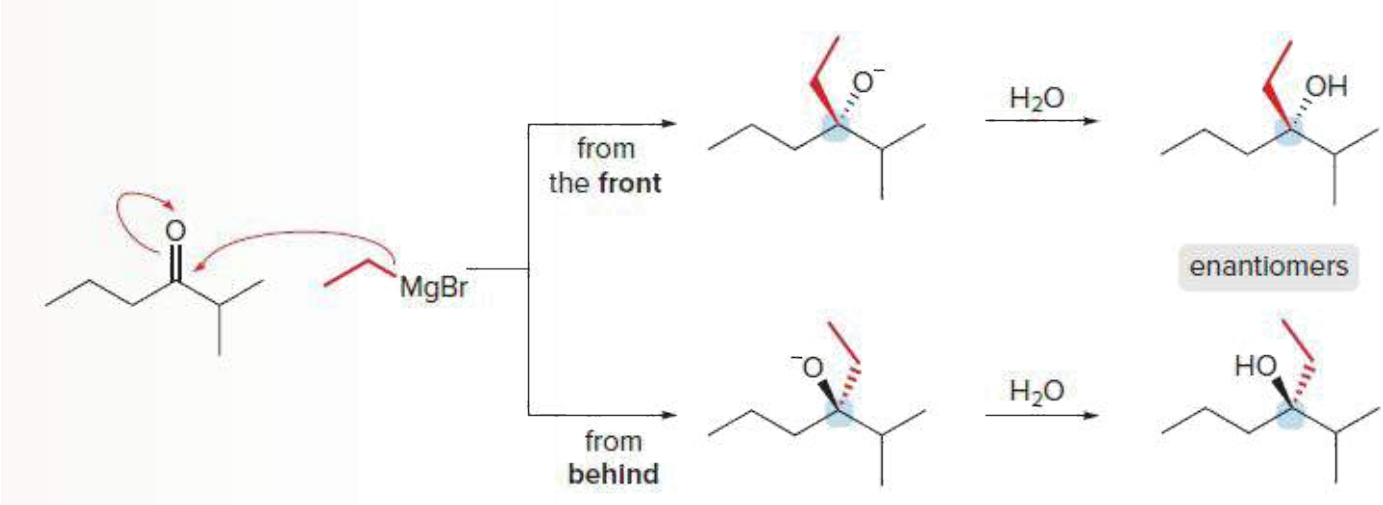
Sample Problem 17.2 Drawing the Stereoisomers Formed During Grignard Addition

Draw all stereoisomers formed in the following reaction.



Solution

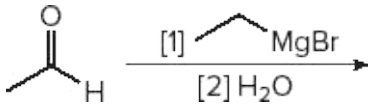
The Grignard reagent adds from both sides of the trigonal planar carbonyl group, forming two alkoxides, each containing a new stereogenic center labeled in blue. Protonation with water yields an equal amount of two enantiomers—a racemic mixture.



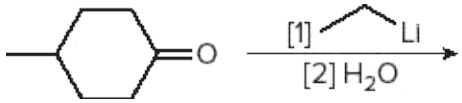
Problem 17.20

Draw the products (including stereochemistry) of the following reactions.

a.



b.



More Practice:

Try Problems 17.35c, d; 17.45a.

17.10C Applications in Synthesis

Many syntheses of useful compounds utilize the nucleophilic addition of a Grignard or organolithium reagent to form carbon–carbon bonds. For example, a key step in the synthesis of ethynylestradiol (Section 11.4), an oral contraceptive component, is the addition of lithium acetylide to a ketone, as shown in Figure 17.5.

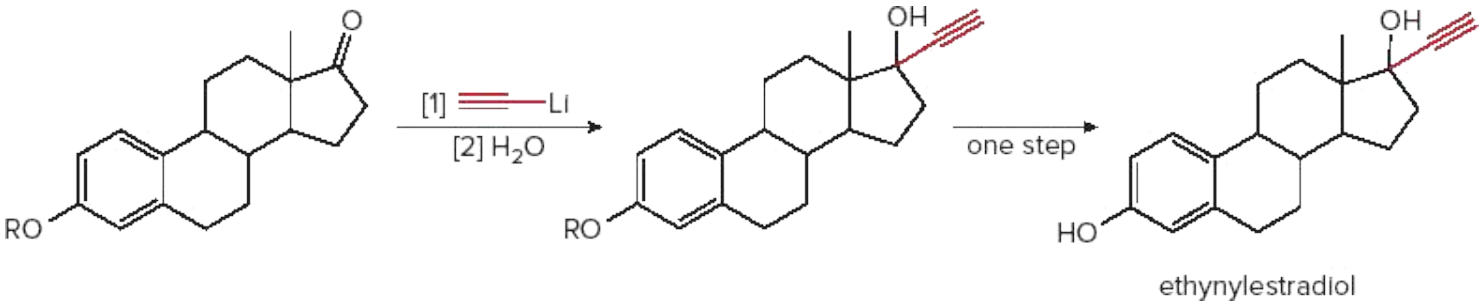
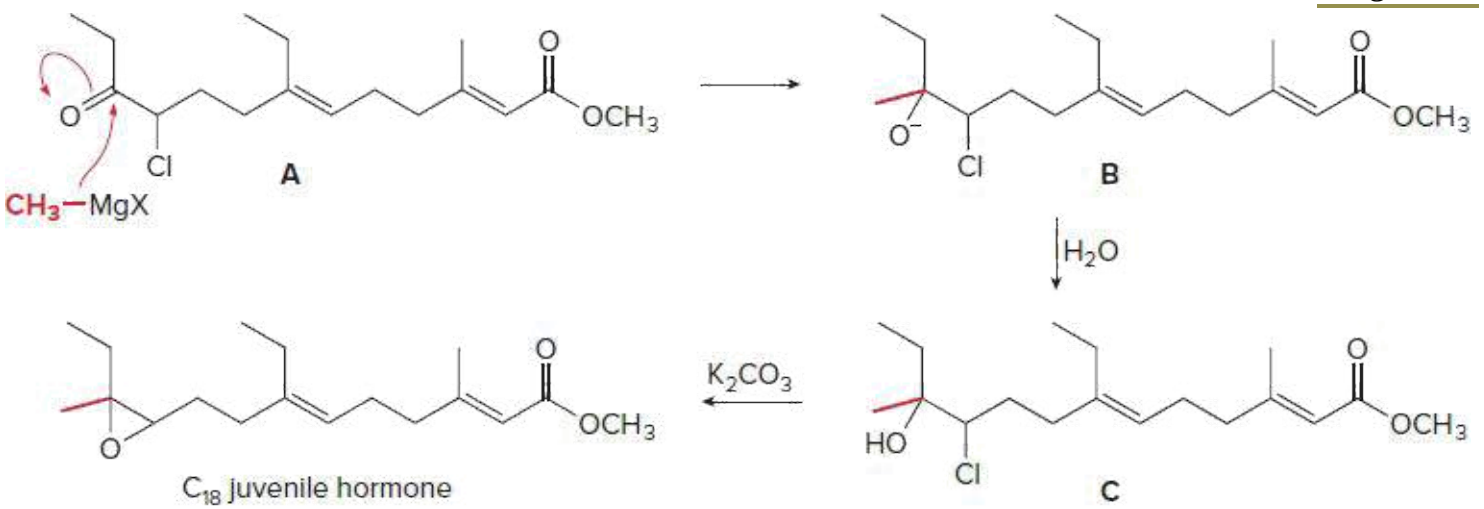


Figure 17.5 The synthesis of ethynylestradiol



- Addition of CH_3MgX to ketone **A** gives an alkoxide, **B**, which is protonated with H_2O to form 3° alcohol **C**. Although the ester group (–$COOCH_3$) can also react with the Grignard reagent (Section 17.13), it is less reactive than the ketone carbonyl. Thus, with control of reaction conditions, nucleophilic addition occurs selectively at the ketone.
- Treatment of halohydrin **C** with K_2CO_3 forms the C_{18} juvenile hormone in one step. Conversion of a halohydrin to an epoxide was discussed in Section 9.6.

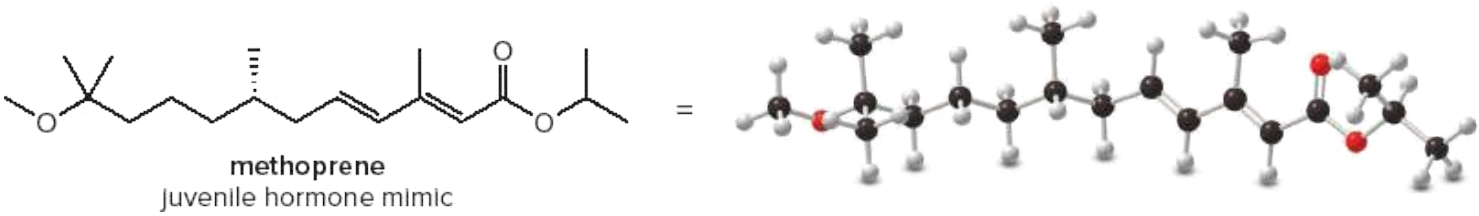
Figure 17.6 **C_{18} juvenile hormone**

Juvenile hormones regulate the life cycle of the cecropia moth.

©Matt Jeppson/Shutterstock

The synthesis of C_{18} juvenile hormone, a member of a group of structurally related molecules that regulate the complex life cycle of an insect, is another example. The last steps of the synthesis are outlined in Figure 17.6.

Juvenile hormones maintain the juvenile stage of an insect until it is ready for adulthood. This property has been exploited to control mosquitoes and other insects infecting livestock and crops. Although juvenile hormone itself is too unstable in light and too expensive to synthesize for use in controlling insect populations, related compounds, called juvenile hormone *mimics*, have been used effectively. Application of these synthetic hormones to an egg or larva of an insect prevents maturation. With no sexually mature adults to propagate the next generation, the insect population is reduced. The best-known example of a synthetic juvenile hormone is called methoprene, sold under such trade names as Altocid, Precor, and Diacon. Methoprene is used in cattle salt blocks to control hornflies, in stored tobacco to control pests, and on dogs and cats to control fleas.



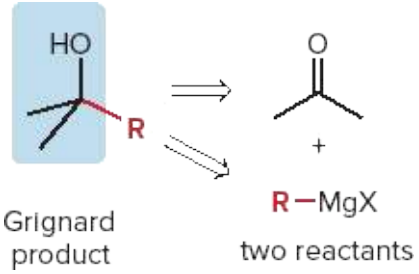
methoprene
juvenile hormone mimic

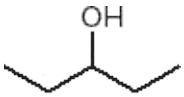
17.11 Retrosynthetic Analysis of Grignard Products

To use the Grignard addition in synthesis, you must be able to determine what carbonyl and Grignard components are needed to prepare a given compound—that is, you must work backwards, in the retrosynthetic direction. This involves a two-step process:

Step [1] **Find the carbon bonded to the OH group in the product.**

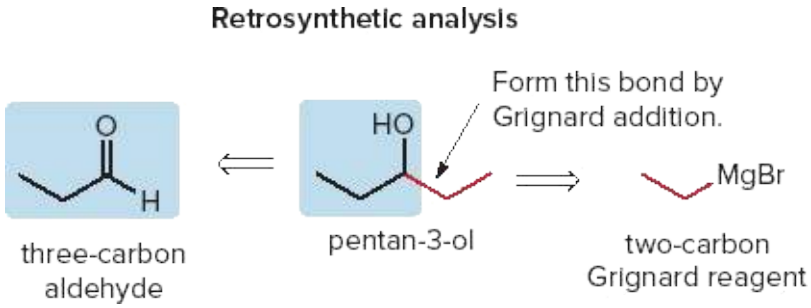
Step [2] **Break the molecule into two components: One alkyl group bonded to the carbon with the OH group comes from the organometallic reagent. The rest of the molecule comes from the carbonyl component.**



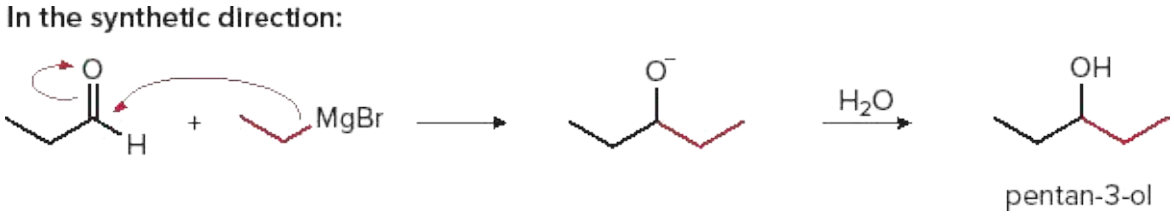


pentan-3-ol

To synthesize pentan-3-ol [$(CH_3CH_2)_2CHOH$] by a Grignard reaction, locate the carbon bonded to the OH group, and then break the molecule into two components at this carbon. Thus, retrosynthetic analysis shows that one of the ethyl groups on this carbon comes from a Grignard reagent (CH_3CH_2MgX), and the rest of the molecule comes from the carbonyl component, a three-carbon aldehyde.



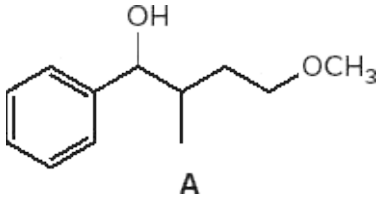
Then, writing the reaction in the synthetic direction—that is, from starting material to product—shows whether the analysis is correct. In this example, a three-carbon aldehyde reacts with CH_3CH_2MgBr to form an alkoxide, which can then be protonated by H_2O to form pentan-3-ol, the desired alcohol.



There is often more than one way to synthesize a 2° alcohol by Grignard addition, as shown in Sample Problem 17.3.

Sample Problem 17.3 Determining the Starting Materials in a Grignard Synthesis

Show two different methods to synthesize alcohol A using a Grignard reaction.

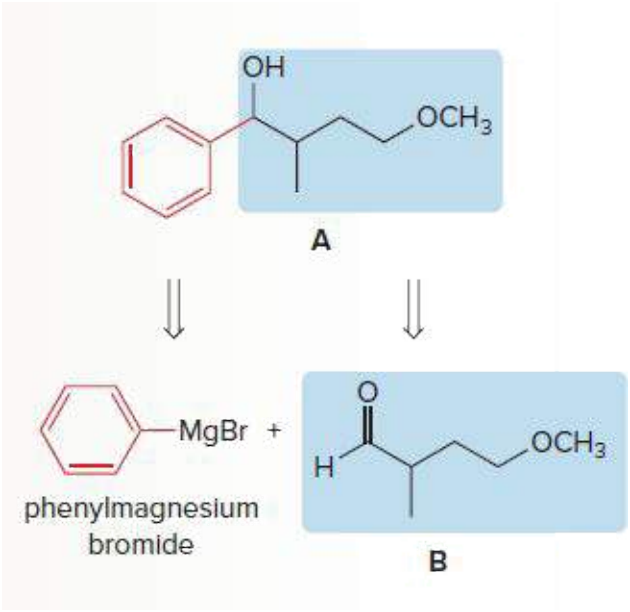


A

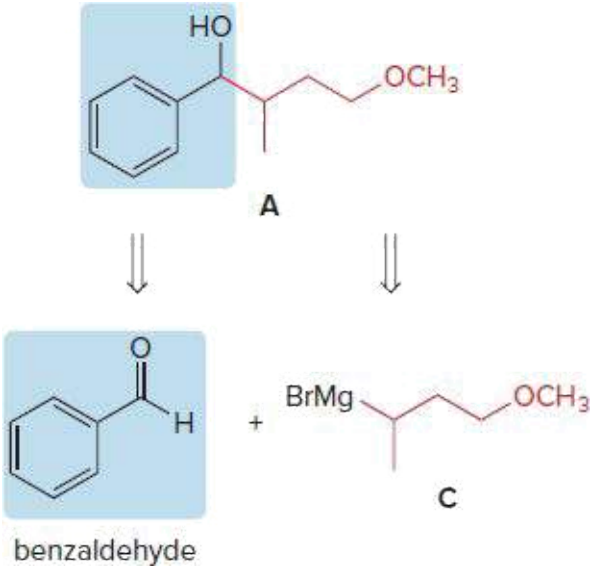
Solution

Because A has two different R groups bonded to the carbon bearing the OH group, there are two different ways to form a new carbon–carbon bond by Grignard addition.

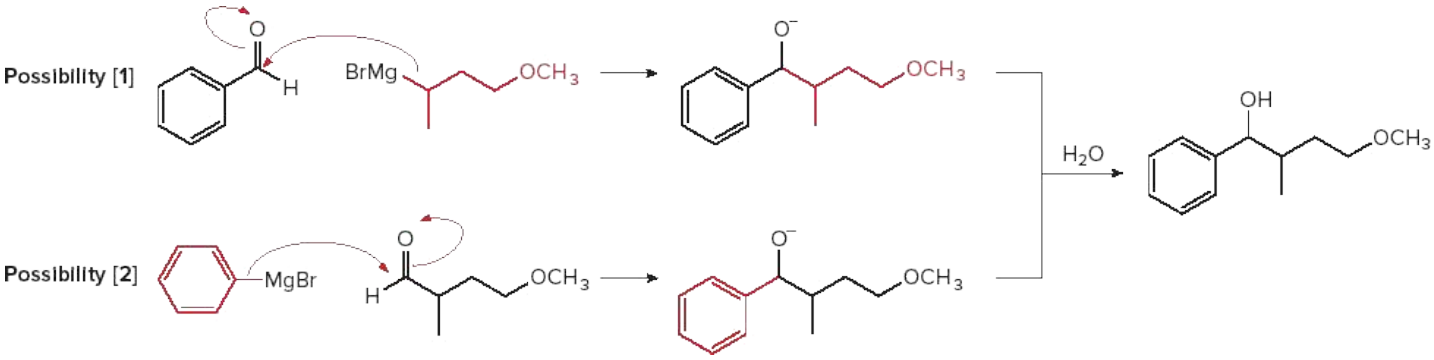
Possibility [1] Use $C_6H_5M_gBr$ and aldehyde B.



Possibility [2] Use Grignard reagent C and benzaldehyde.



Both methods give the desired product A, as can be seen by writing the reactions from starting material to product.

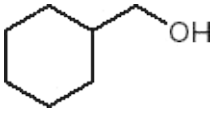


Problem 17.21

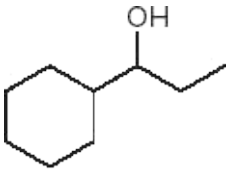
What Grignard reagent and carbonyl compound are needed to prepare each alcohol? As shown in part (d), 3° alcohols with three different R groups on the carbon bonded to the OH group can be prepared by three different Grignard reactions.

a.

b.

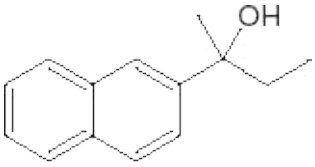


c.



(two methods)

d.



(three methods)

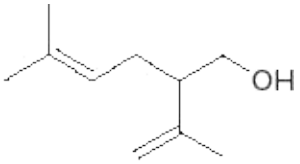
More Practice:

Try Problems 17.57, 17.58, 17.60.

Problem 17.22

Linalool (the Chapter 9 opening molecule) and lavandulol are two of the major components of lavender oil. (a) What organolithium reagent and carbonyl compound can be used to make each alcohol? (b) How might lavandulol be formed by reduction of a carbonyl compound? (c) Why can't linalool be prepared by a similar pathway?

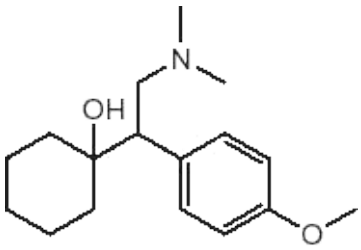
linalool
(three methods)



lavandulol

Problem 17.23

What Grignard reagent and carbonyl compound can be used to prepare the antidepressant venlafaxine (trade name Effexor)?



venlafaxine

Rapid acid–base reactions occur between organometallic reagents and all of the following functional groups: ROH, RCOOH, RNH_2, R_2NH, $RCONH_2$, RCONHR, and RSH.

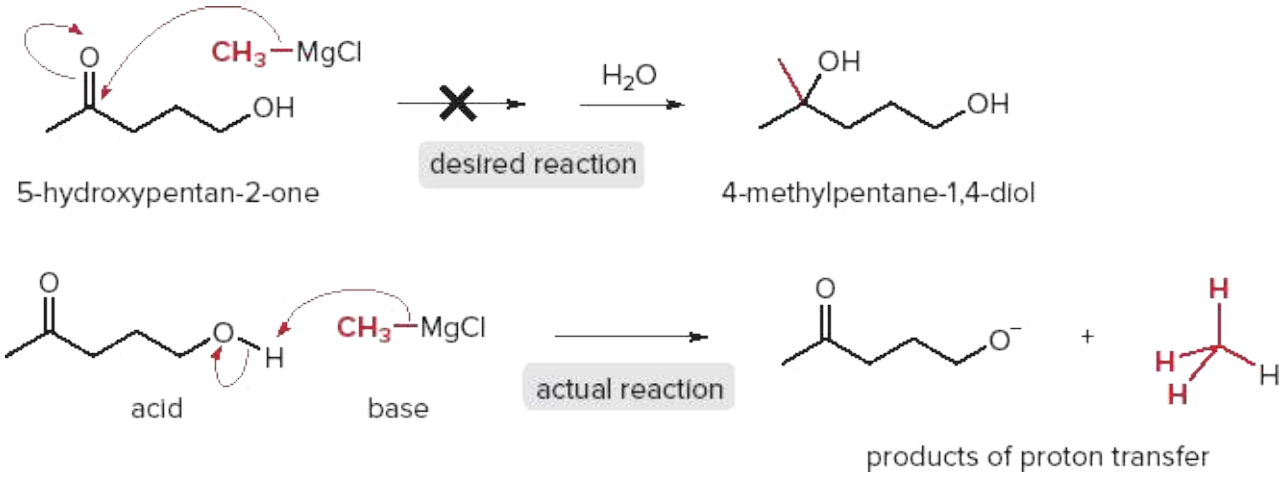
17.12 Protecting Groups

Although the addition of organometallic reagents to carbonyls is a very versatile reaction, it cannot be used with molecules that contain both a carbonyl group and N–H or O–H bonds.

- **Carbonyl compounds that also contain N–H or O–H bonds undergo an acid–base reaction with organometallic reagents, *not* nucleophilic addition.**

Suppose, for example, that you wanted to add methylmagnesium chloride (CH_3MgCl) to the carbonyl group of 5-hydroxypentan-2-one to form a diol. Nucleophilic addition will *not* occur with this substrate. Instead, because Grignard reagents are strong bases and proton transfer reactions are fast, CH_3MgCl removes the O–H proton before nucleophilic addition takes place. The stronger acid and base react to form the weaker conjugate acid and conjugate base, as we learned in Section 17.9C.

Page 808



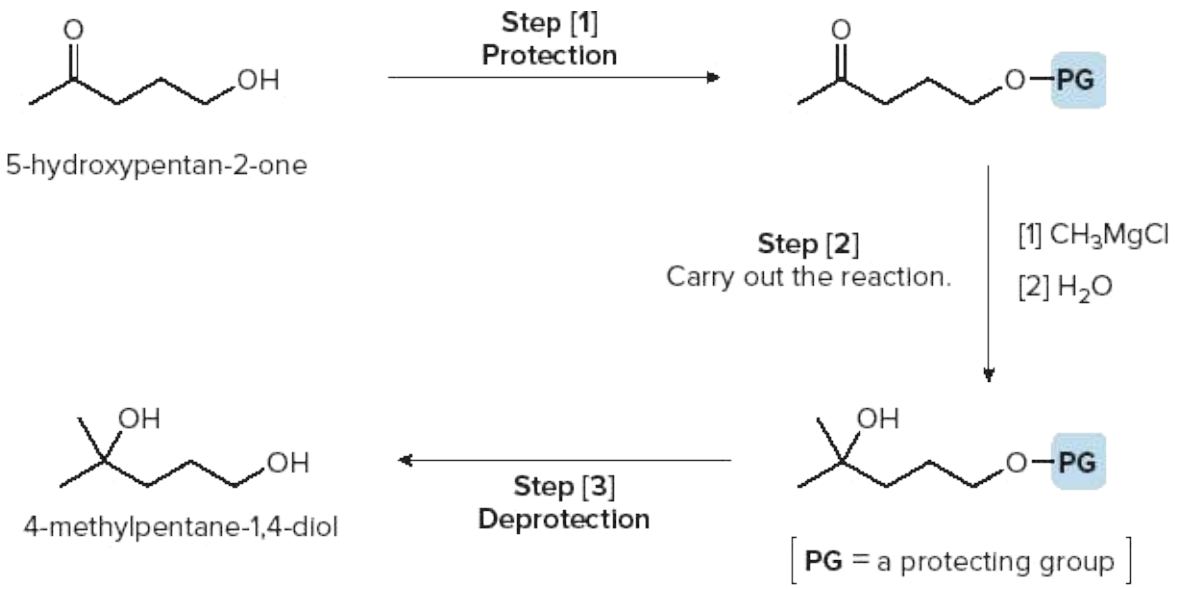
Solving this problem requires a three-step strategy:

Step [1] **Convert the OH group to another functional group that does not interfere with the desired reaction. This new blocking group is called a protecting group, and the reaction that creates it is called *protection.***

Step [2] **Carry out the desired reaction.**

Step [3] **Remove the protecting group. This reaction is called *deprotection*.**

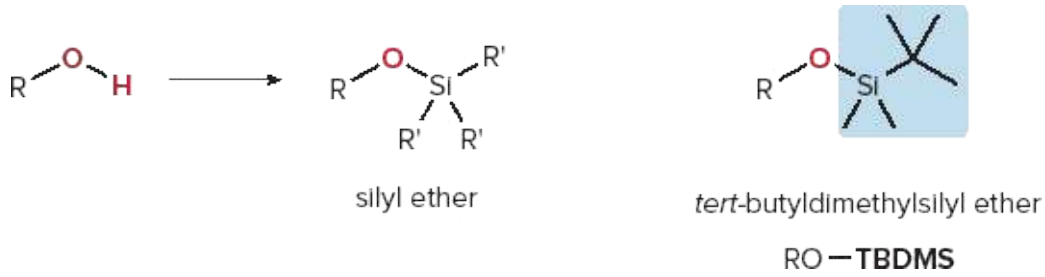
Application of the general strategy to the Grignard addition of CH_3MgCl to 5-hydroxypentan-2-one is illustrated in Figure 17.7.



- In Step [1], the OH proton in 5-hydroxypentan-2-one is replaced with a protecting group, written as **PG.** Because the product of Step [1] no longer has an OH proton, it can now undergo nucleophilic addition.
- In Step [2], CH_3MgCl adds to the carbonyl group to yield a 3° alcohol after protonation with water.
- Removal of the protecting group in Step [3] forms the desired product, 4-methylpentane-1,4-diol.

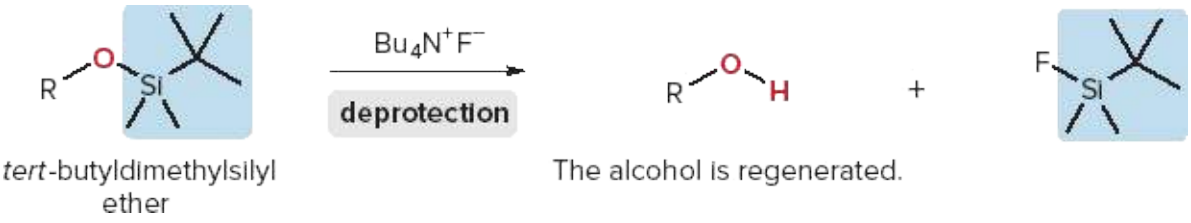
Figure 17.7 **General strategy for using a protecting group**

A common OH protecting group is a silyl ether. A silyl ether has a new O–Si bond in place of the O–H bond of the alcohol. The most widely used silyl ether protecting group is the *tert*-butyldimethylsilyl ether, abbreviated as TBDMS.



tert-Butyldimethylsilyl ethers are prepared from alcohols by reaction with *tert*-butyldimethylsilyl chloride and an amine base, usually imidazole.

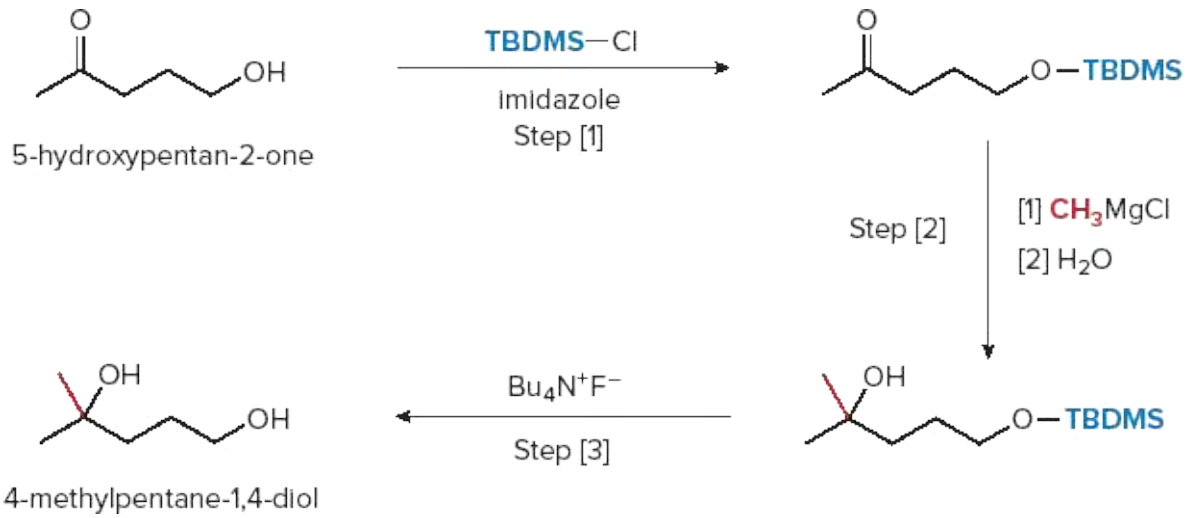
The silyl ether is typically removed with a fluoride salt, usually tetrabutylammonium fluoride $(CH_3CH_2CH_2CH_2)_4N^+F^-$, drawn as $Bu_4N^+F^-$ (Bu = butyl).



tert-butyldimethylsilyl ether

The alcohol is regenerated.

The use of a *tert*-butyldimethylsilyl ether as a protecting group makes possible the synthesis of 4-methylpentane-1,4-diol by a three-step sequence.

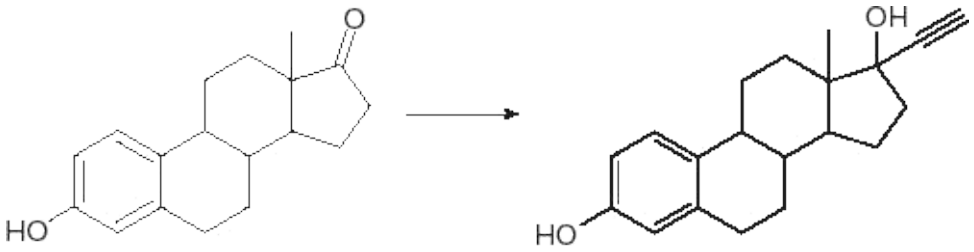


- Step [1] Protect the OH group as a *tert*-butyldimethylsilyl ether by reaction with *tert*-butyldimethylsilyl chloride and imidazole.
- Step [2] Carry out nucleophilic addition by using CH_3MgCl, followed by protonation.
- Step [3] Remove the protecting group with tetrabutylammonium fluoride to form the desired addition product.

Protecting groups block interfering functional groups, and in this way, a wider variety of reactions can take place with a particular substrate. For more on protecting groups, see the discussion of acetals in Section 18.14.

Problem 17.24

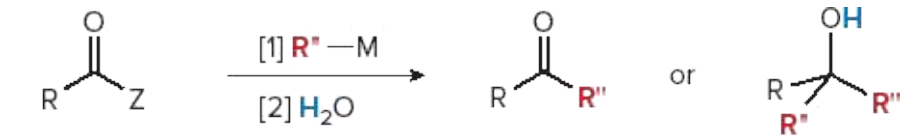
Using protecting groups, show how estrone can be converted to ethynylestradiol, a widely used oral contraceptive.



estrone ethynylestradiol

17.13 Reaction of Organometallic Reagents with Carboxylic Acid Derivatives

Organometallic reagents react with carboxylic acid derivatives (RCOZ) to form two different products, depending on the identity of both the leaving group Z and the reagent R–M. The most useful reactions are carried out with esters and acid chlorides, forming either ketones or 3° alcohols.

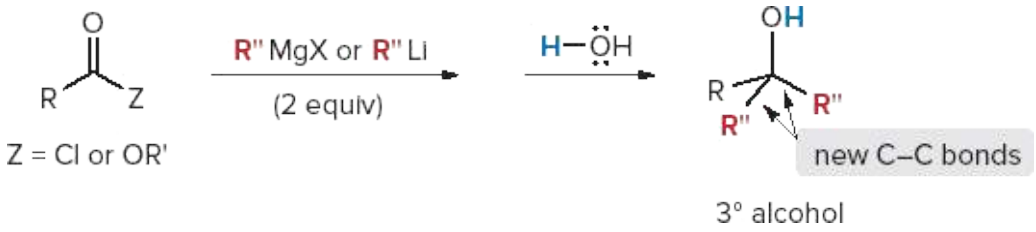


Z = Cl or OR' ketone 3° alcohol

- **Keep in mind that RLi and RMgX are very reactive reagents, whereas R_2CuLi is much less reactive. This reactivity difference makes selective reactions possible.**

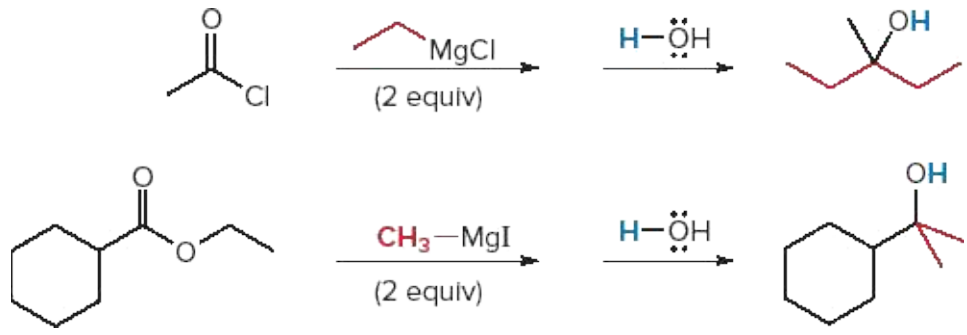
17.13A Reaction of RLi and RMgX with Esters and Acid Chlorides

Both esters and acid chlorides form 3° alcohols when treated with two equivalents of either Grignard or organolithium reagents. Two new carbon–carbon bonds are formed in the product.



Z = Cl or OR' 3° alcohol

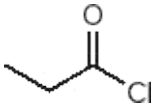
Two examples using Grignard reagents are shown.



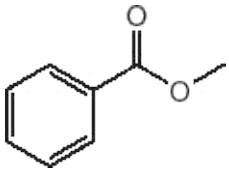
Problem 17.25

Draw the product formed when each compound is treated with two equivalents of $CH_3CH_2CH_2CH_2MgBr$ followed by H_2O.

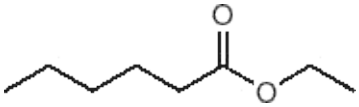
a.



b.



c.



The mechanism for this addition reaction resembles the mechanism for the metal hydride reduction of acid chlorides and esters discussed in Section 17.7A. The mechanism is conceptually divided into two parts: nucleophilic substitution to form a ketone (Steps [1] and [2]), followed by nucleophilic addition to form a 3° alcohol (Steps [3] and [4]), as shown in Mechanism 17.7.

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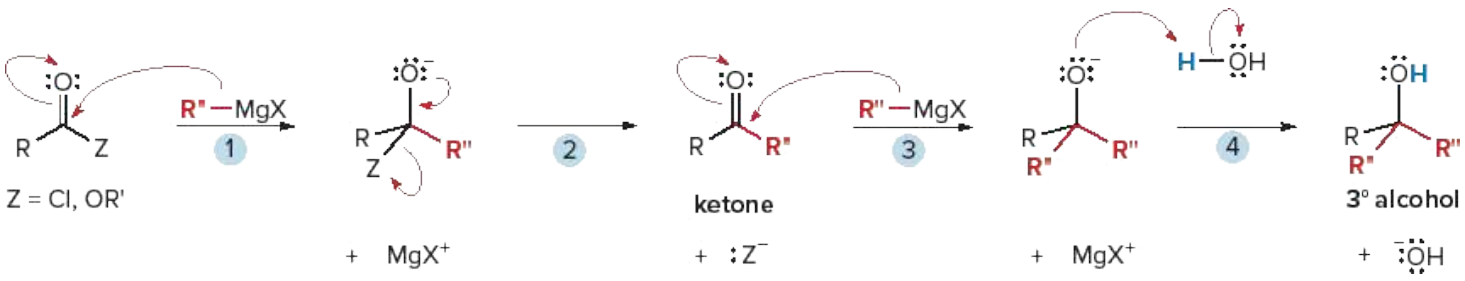
Mechanism 17.7 Reaction of R″MgX or R″Li with RCOCl and RCOOR′



1 **Nucleophilic attack of $(R'')^-$ forms a tetrahedral intermediate with a leaving group Z.**

2 **The π bond is re-formed and the leaving group Z departs to form a ketone. The overall result of addition of $(R'')^-$ and elimination of $Z:^-$ is substitution of R″ for Z.**

3 **Nucleophilic attack of $(R'')^-$ forms an alkoxide with no leaving group.**

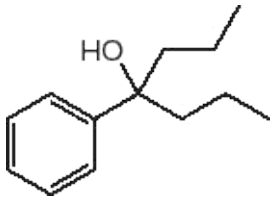
4 **Protonation of the alkoxide by H_2O forms a 3° alcohol.**

Organolithium and Grignard reagents afford 3° alcohols when they react with esters and acid chlorides. As soon as the ketone forms by addition of one equivalent of reagent to RCOZ (Steps [1] and [2] of the mechanism), it reacts with a second equivalent of reagent to form the 3° alcohol.

This reaction is more limited than the Grignard addition to aldehydes and ketones, because only 3° alcohols having two identical alkyl groups can be prepared. Nonetheless, it is still a valuable reaction because it forms two new carbon–carbon bonds.

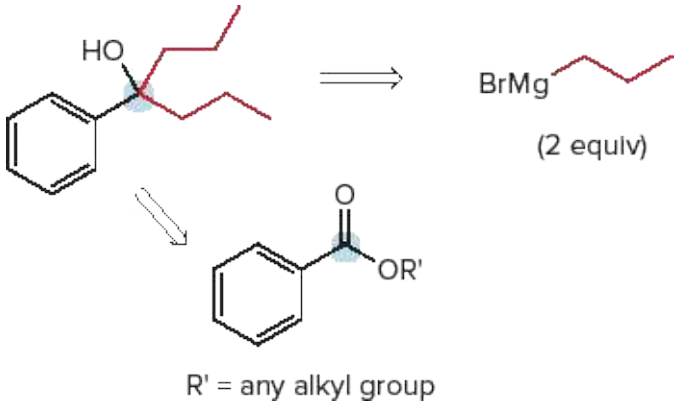
Sample Problem 17.4 Identifying the Ester and Grignard Reagent Needed to Prepare an Alcohol

What ester and Grignard reagent are needed to prepare the following alcohol?

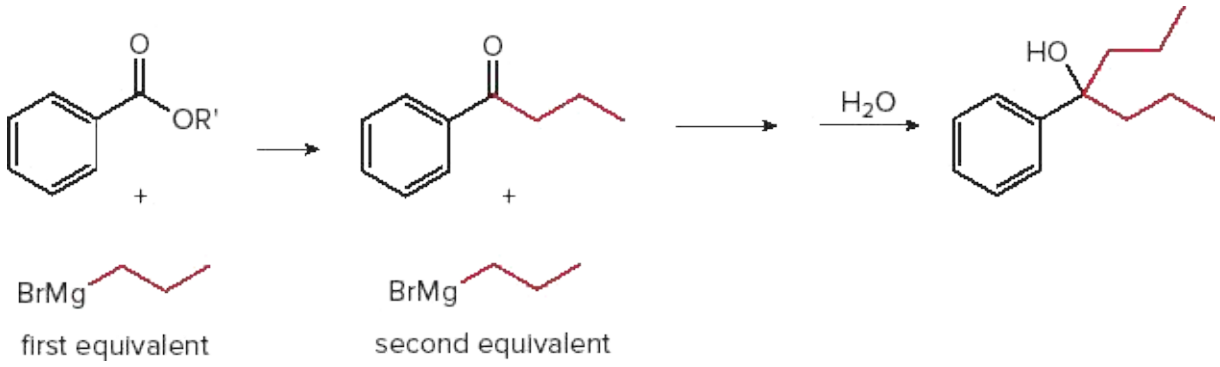


Solution

A 3° alcohol formed from an ester and Grignard reagent must have two identical R groups, and these R groups come from RMgX. The remainder of the molecule comes from the ester. The carbon (labeled in blue) bonded to the OH group comes from the carbonyl carbon.



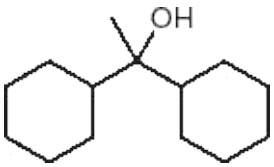
Checking in the synthetic direction:



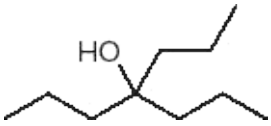
Problem 17.26

What ester and Grignard reagent are needed to prepare each alcohol?

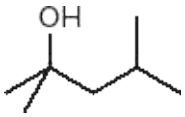
a.



b.



c.

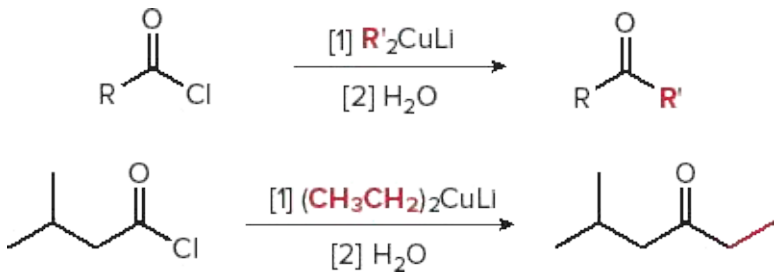


More Practice:

Try Problem 17.59.

17.13B Reaction of R_2CuLi with Acid Chlorides

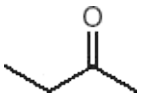
To form a ketone from a carboxylic acid derivative, a less reactive organometallic reagent—namely, an organocuprate—is needed. Acid chlorides, which have the best leaving group (Cl^-) of the carboxylic acid derivatives, react with R'_2CuLi, to give a ketone as product. Esters, which contain a poorer leaving group (^-OR), do *not* react with R'_2CuLi.

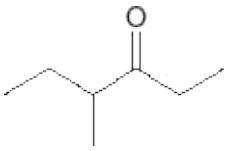


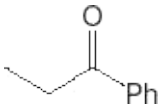
This reaction results in nucleophilic substitution of an alkyl group R′ for the leaving group Cl, forming one new carbon–carbon bond.

Problem 17.27

What organocuprate reagent is needed to convert CH_3CH_2COCl to each ketone?

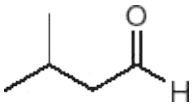
a. 

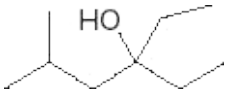
b. 

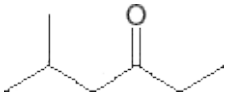
c. 

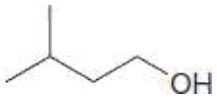
Problem 17.28

What reagent is needed to convert $(CH_3)_2CHCH_2COCl$ to each compound?

a. 

b. 

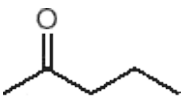
c. 

d. 

A ketone with two different R groups bonded to the carbonyl carbon can be made by two different methods, as illustrated in Sample Problem 17.5.

Sample Problem 17.5 Determining the Acid Chloride and Organocuprate Needed to Prepare a Ketone

Show two different ways to prepare pentan-2-one from an acid chloride and an organocuprate reagent.

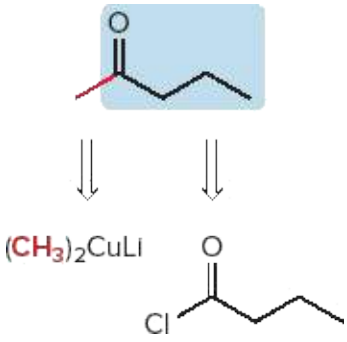


pentan-2-one

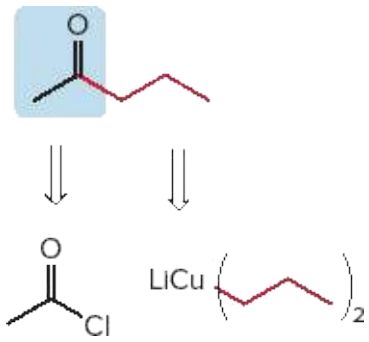
Solution

In each case, one alkyl group comes from the organocuprate and one comes from the acid chloride.

Possibility [1] **Use $(CH_3)_2CuLi$ and a four-carbon acid chloride.**



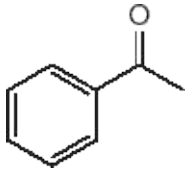
Possibility [2] Use $(CH_3CH_2CH_2)_2CuLi$ and a two-carbon acid chloride.



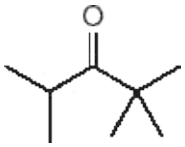
Problem 17.29

Draw two different ways to prepare each ketone from an acid chloride and an organocuprate reagent.

a.



b.



More Practice:

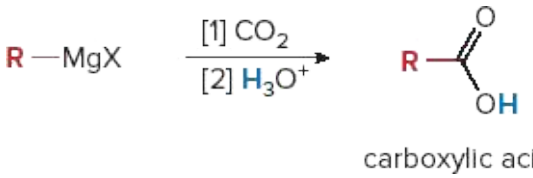
Try Problem 17.38a.

17.14 Reaction of Organometallic Reagents with Other Compounds

Because organometallic reagents are strong nucleophiles, they react with many other electrophiles in addition to carbonyl groups. Because these reactions always lead to the formation of new carbon–carbon bonds, they are also valuable in organic synthesis. In Section 17.14, we examine the reactions of organometallic reagents with carbon dioxide and epoxides.

17.14A Reaction of Grignard Reagents with Carbon Dioxide

Grignard reagents react with CO_2 to give carboxylic acids after protonation with aqueous acid. This reaction, called carboxylation, forms a carboxylic acid with one more carbon atom than the Grignard reagent from which it is prepared.



carboxylic acid

Because Grignard reagents are made from alkyl or aryl halides, an organic halide can be converted to a carboxylic acid having one more carbon atom by a two-step reaction sequence: formation of a Grignard reagent, followed by reaction with CO_2.

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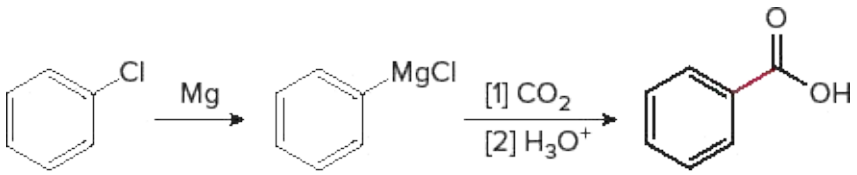
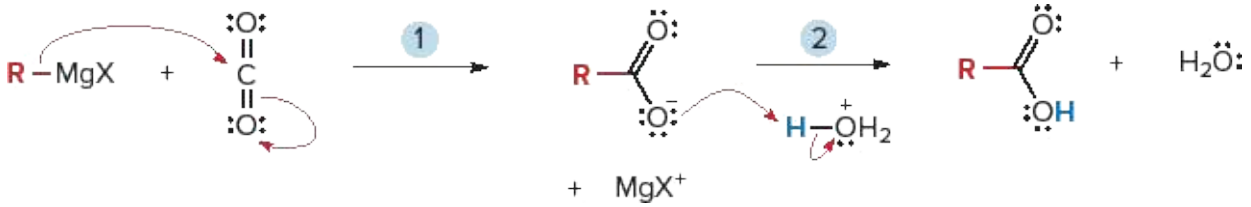


new C–C bond in red

The mechanism resembles earlier reactions of nucleophilic Grignard reagents with carbonyl groups, as shown in Mechanism 17.8.

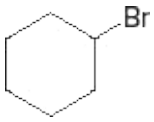
Mechanism 17.8 Carboxylation—Reaction of RMgX with CO_2



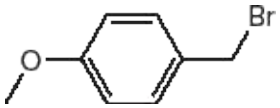
1. **The nucleophilic Grignard reagent attacks the electrophilic carbon of CO_2, cleaving the π bond and forming a new carbon–carbon bond.**
2. **Protonation of the carboxylate anion with aqueous acid forms the carboxylic acid.**

Problem 17.30

What carboxylic acid is formed from each alkyl halide on treatment with [1] Mg; [2] CO_2; [3] H_3O^+?

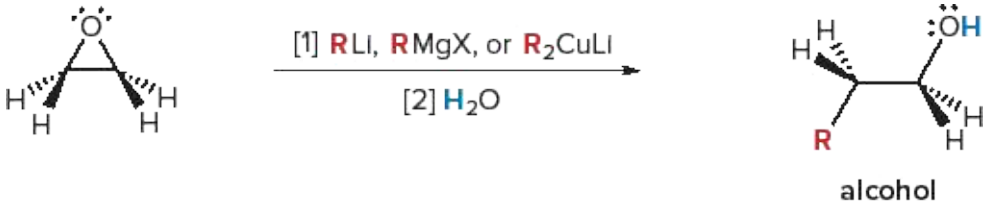
a. 

b.

c. 

17_14BReaction of Organometallic Reagents with Epoxides

Like other strong nucleophiles, organometallic reagents—RLi, RMgX, and R_2CuLi—open epoxide rings to form alcohols.



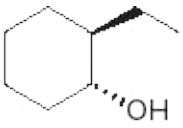
The opening of epoxide rings with negatively charged nucleophiles was discussed in Section 9.16A.

The reaction follows the same two-step process as the opening of epoxide rings with other negatively charged nucleophiles—that is, nucleophilic attack from the back side of the epoxide ring, followed by protonation of the resulting alkoxide. In unsymmetrical epoxides, nucleophilic attack occurs at the *less* substituted carbon atom.

Problem 17.31

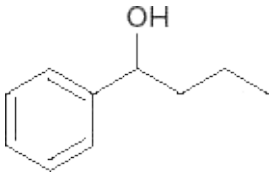
What epoxide is needed to convert CH_3CH_2MgBr to each of the following alcohols, after quenching with water?

a.



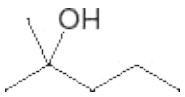
(+ enantiomer)

b.



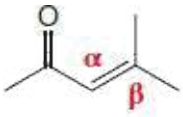
c.

d.



17.15 α,β-Unsaturated Carbonyl Compounds

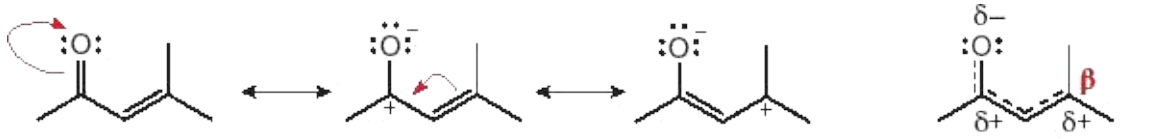
α,β-Unsaturated carbonyl compounds are conjugated molecules containing a carbonyl group and a carbon–carbon double bond, separated by a single σ bond.



α,β-unsaturated carbonyl compound

Both functional groups of α,β-unsaturated carbonyl compounds have π bonds, but individually, they react with very different kinds of reagents. Carbon–carbon double bonds react with electrophiles (Chapter 10) and carbonyl groups react with nucleophiles (Section 17.2). What happens, then, when these two functional groups having opposite reactivity are in close proximity?

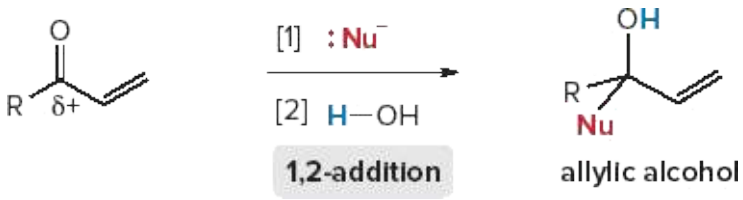
Because the two π bonds are conjugated, the electron density in an α,β-unsaturated carbonyl compound is *delocalized over four atoms*. Three resonance structures show that the carbonyl carbon and the β carbon bear a partial positive charge. This means that α,β-unsaturated carbonyl compounds can react with nucleophiles at two different sites.



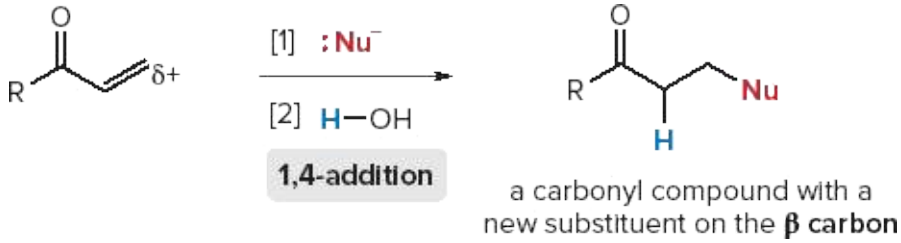
three resonance structures for an α,β-unsaturated carbonyl compound

hybrid
two electrophilic sites

- **Addition of a nucleophile to the carbonyl carbon, called 1,2-addition, adds the elements of H and Nu across the C=O, forming an allylic alcohol.**



- **Addition of a nucleophile to the β carbon, called 1,4-addition or conjugate addition, forms a carbonyl compound.**

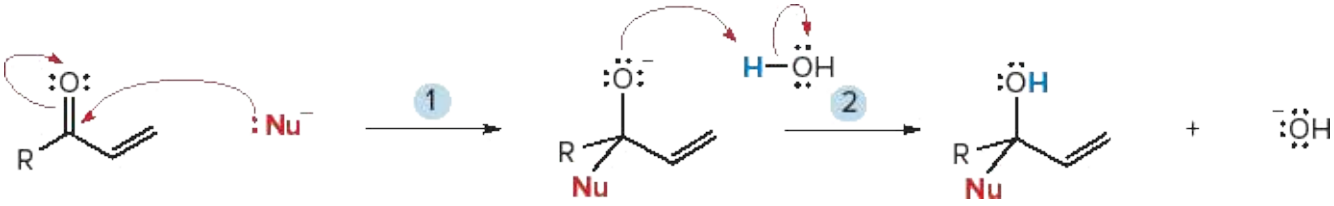


Both 1,2- and 1,4-addition result in nucleophilic addition of the elements of H and Nu.

17.15A The Mechanisms for 1,2-Addition and 1,4-Addition

The steps for the mechanism of 1,2-addition are exactly the same as those for the nucleophilic addition to an aldehyde or ketone—that is, nucleophilic attack, followed by protonation (Section 17.2A), as shown in Mechanism 17.9.

Mechanism 17.9 1,2-Addition to an α,β-Unsaturated Carbonyl Compound

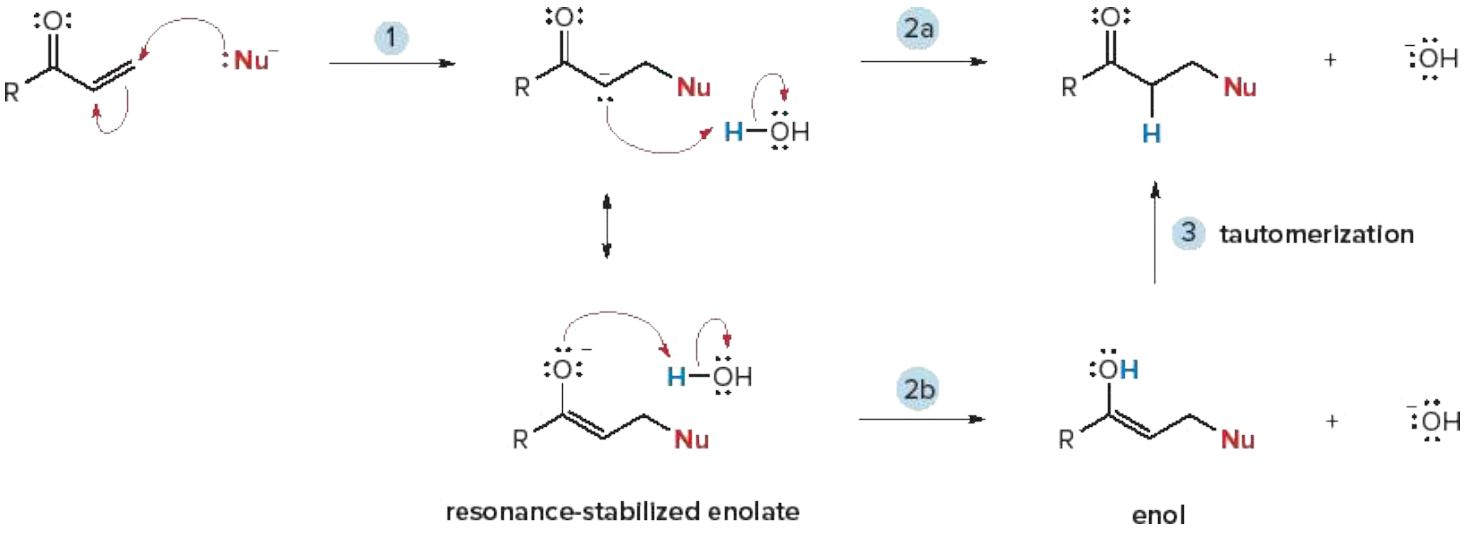


1. **The nucleophile attacks the electrophilic carbonyl. The π bond is broken, moving an electron pair out on oxygen.**
2. **Protonation of the negatively charged oxygen by H_2O forms the addition product. H and Nu are added to the carbonyl group.**

The mechanism for 1,4-addition also begins with nucleophilic attack, and then protonation and tautomerization add the elements of H and Nu to the α and β carbons of the carbonyl compound, as shown in Mechanism 17.10.

Mechanism 17.10 1,4-Addition to an α,β-Unsaturated Carbonyl

Compound



1 **Nucleophilic attack at the electrophilic β carbon forms a resonance-stabilized enolate anion, which can react on either carbon or oxygen in the second step.**

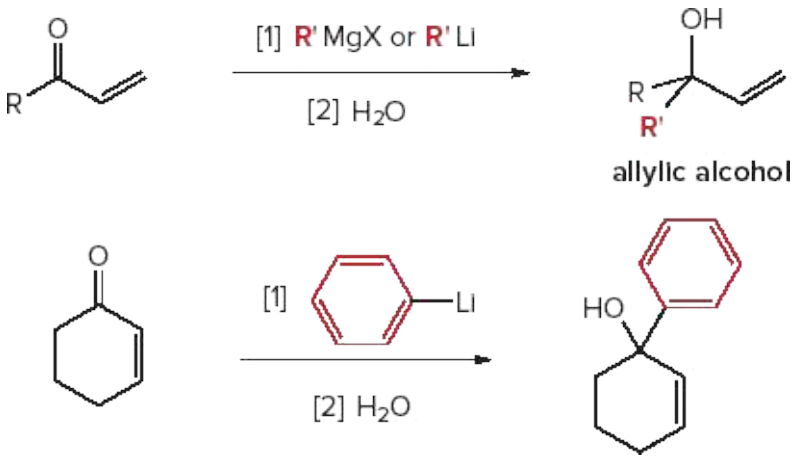
2a **Protonation of the carbon end of the enolate forms the 1,4-addition product directly.**

2b – 3 **Protonation of the oxygen end of the enolate forms an enol, which undergoes tautomerization by the two-step process described in Section 11.9. This forms the same 1,4-addition product that results from protonation on carbon.**

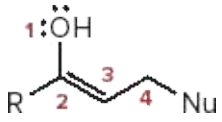
17.15B Reaction of α,β-Unsaturated Carbonyl Compounds with Organometallic Reagents

The identity of the metal in an organometallic reagent determines whether it reacts with an α,β-unsaturated aldehyde or ketone by 1,2-addition or 1,4-addition.

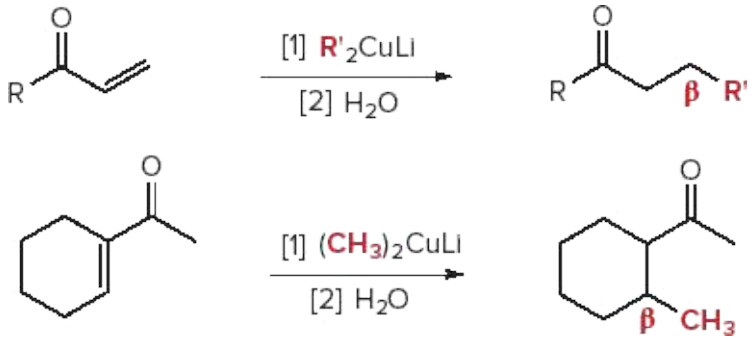
- **Organolithium and Grignard reagents form 1,2-addition products.**



Why is conjugate addition also called 1,4-addition? If the atoms of the enol are numbered beginning with the O atom, then the elements of H and Nu are bonded to atoms "1" and "4," respectively.



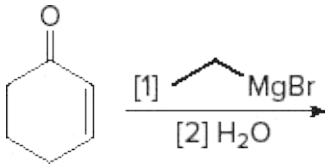
- **Organocuprate reagents form 1,4-addition products.**



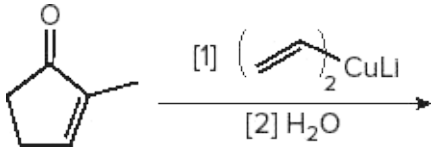
Sample Problem 17.6 Drawing the Products of 1,2-and 1,4-Addition

Draw the products of each reaction.

a.



b.



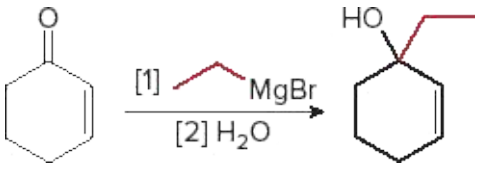
Solution

The characteristic reaction of α,β-unsaturated carbonyl compounds is

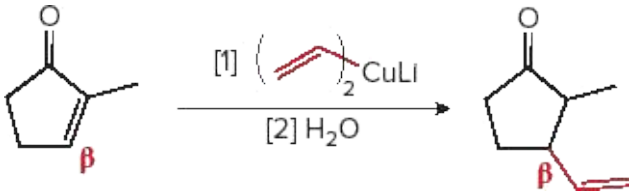
nucleophilic addition.

The reagent determines the mode of addition (1,2- or 1,4-).

a. Grignard reagents undergo 1,2-addition. CH_3CH_2MgBr adds a new CH_3CH_2 group at the carbonyl carbon.



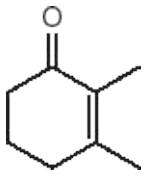
b. Organocuprate reagents undergo 1,4-addition. The cuprate reagent adds a new vinyl group (CH_2=CH) at the β carbon.



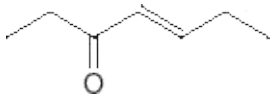
Problem 17.32

Draw the product when each compound is treated with either $(CH_3)_2CuLi$, followed by H_2O, or HC≡CLi, followed by H_2O.

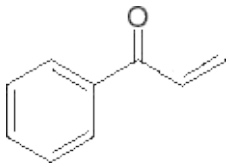
a.



b.



c.



More Practice:

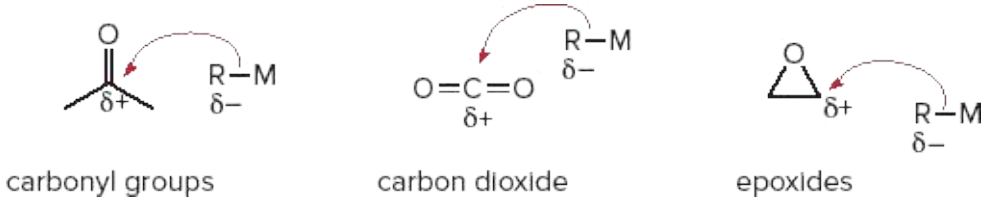
Try Problems 17.38c; 17.40d–f; 17.43b, e.

17.16 Summary—The Reactions of Organometallic Reagents

We have now seen many different reactions of organometallic reagents with a variety of functional groups, and you may have some difficulty keeping them all straight.

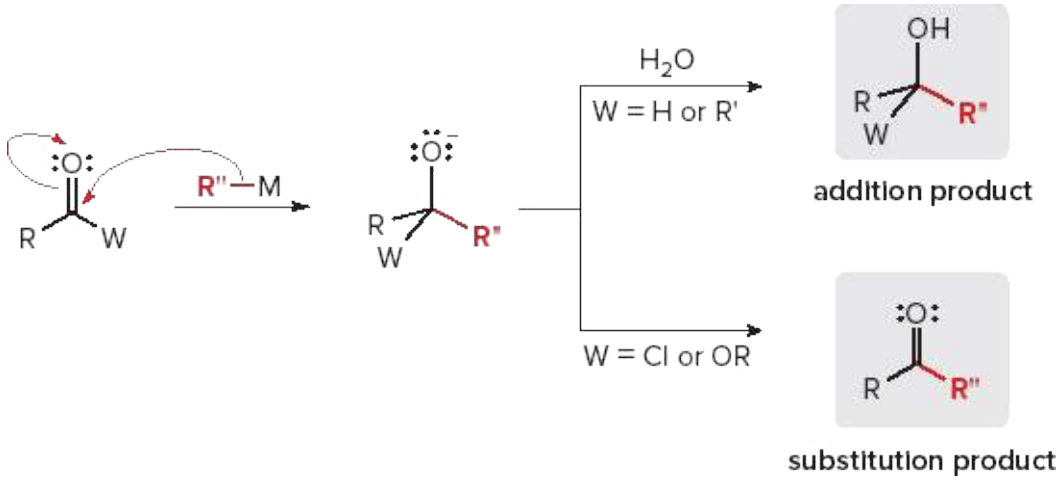
Rather than memorizing them all, keep in mind the following three concepts:

[1] Organometallic reagents (R–M) attack electrophilic carbon atoms, especially the carbonyl carbon.



[2] After an organometallic reagent adds to a carbonyl group, the fate of the intermediate depends on the presence or absence of a leaving group.

- Without a leaving group, the characteristic reaction is *nucleophilic addition*.
- With a leaving group, the reaction is *nucleophilic substitution*.



[3] The polarity of the R–M bond determines the reactivity of the reagents.

- RLi and RMgX are very reactive reagents.
- R_2CuLi is much less reactive.

17.17 Synthesis

The reactions learned in Chapter 17 have proven extremely useful in organic synthesis. Oxidation and reduction reactions interconvert two functional groups that differ in oxidation state. Organometallic reagents form new carbon–carbon bonds.

Synthesis is perhaps the most difficult aspect of organic chemistry. It requires you to

remember both the new reactions you've just learned and the ones you've encountered in previous chapters. In a successful synthesis, you must also put these reactions in a logical order. Don't be discouraged. Learn the basic reactions and then practice them over and over again with synthesis problems.

In Sample Problems 17.7 and 17.8 that follow, keep in mind that the products formed by the reactions of Chapter 17 can themselves be transformed into many other functional groups. For example, hexan-2-ol, the product of Grignard addition of butylmagnesium chloride to acetaldehyde, can be transformed into a variety of other compounds, as shown in Figure 17.8.

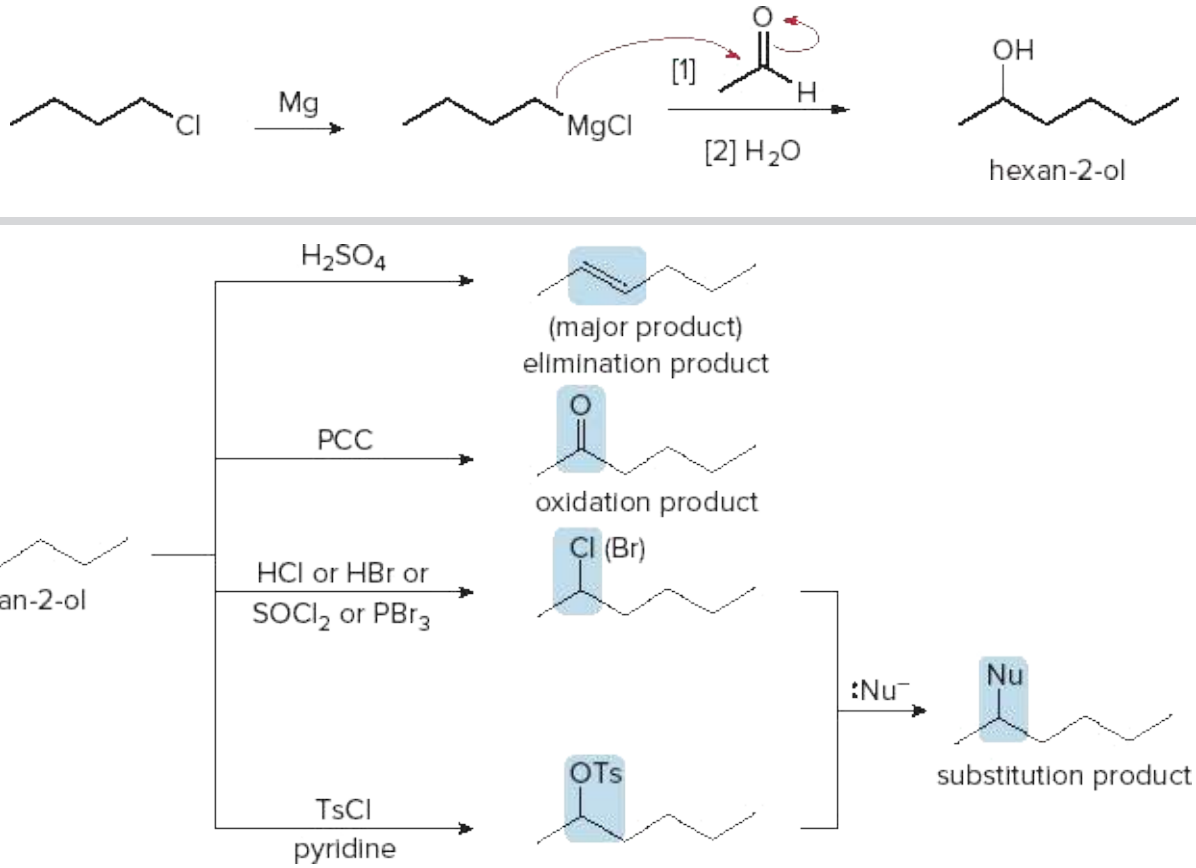
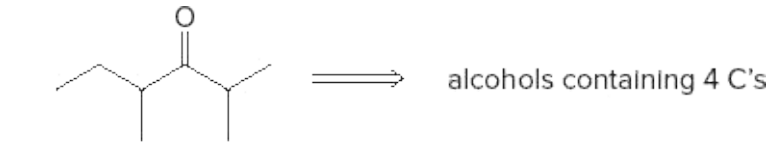


Figure 17.8 **Conversion of hexan-2-ol to other compounds**

Before proceeding with Sample Problems 17.7 and 17.8, you should review the stepwise strategy for designing a synthesis found in Section 11.12.

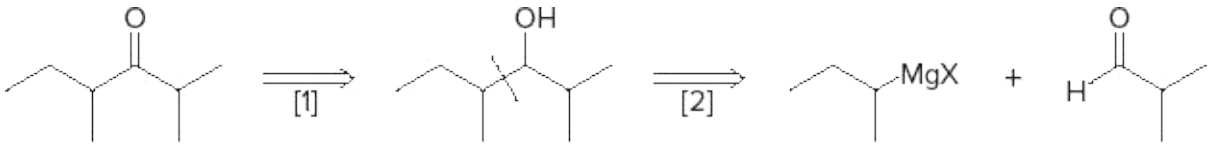
Sample Problem 17.7 Devising a Synthesis with a Carbon–Carbon Bond-Forming Reaction

Synthesize 2,4-dimethylhexan-3-one from four-carbon alcohols.



2,4-dimethylhexan-3-one

Retrosynthetic Analysis



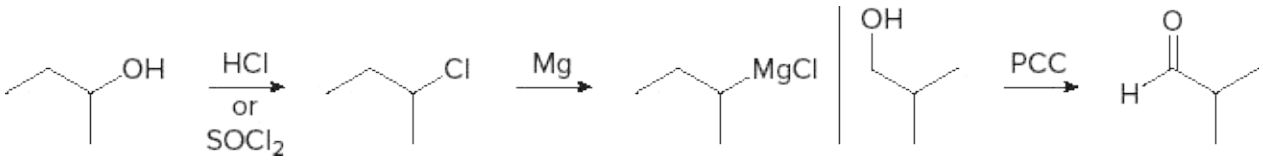
Synthesize each of these components.

Thinking backwards:

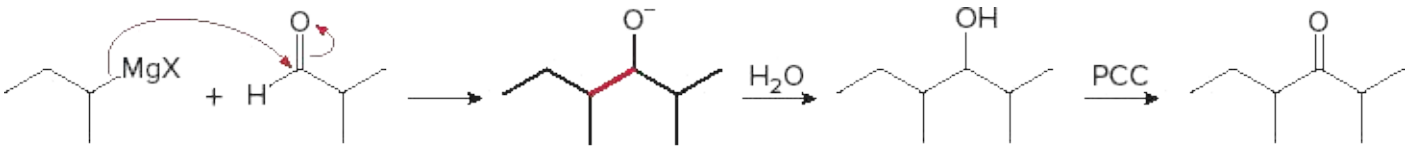
- **[1] Form the ketone by oxidation of a 2° alcohol.**
- **[2] Make the 2° alcohol by Grignard addition to an aldehyde. Both of these compounds have 4 C's, and each must be synthesized from an alcohol.**

Synthesis

First, make both components needed for the Grignard reaction.



Then complete the synthesis with Grignard addition, followed by oxidation of the alcohol to the ketone.

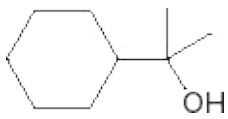


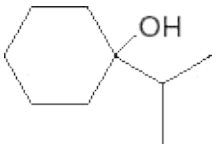
new C–C bond in red

Problem 17.33

Convert propan-2-ol [$(CH_3)_2CHOH$] to each compound. You may use any other organic or inorganic compounds.

a.



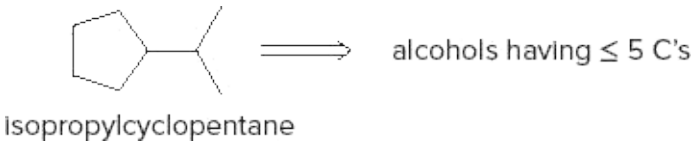
b. 

More Practice:

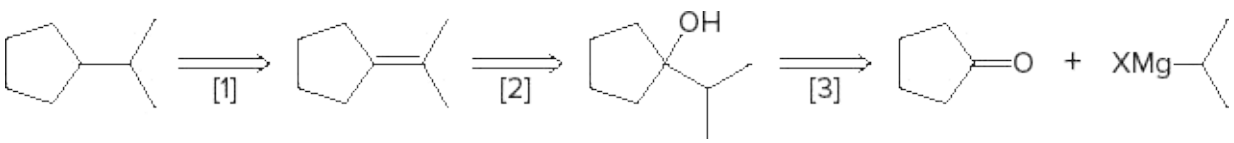
Try Problems 17.36; 17.63a, d; 17.64a.

Sample Problem 17.8 Devising a Synthesis with a Grignard Addition

Synthesize isopropylcyclopentane from alcohols having ≤ 5 C's.



Retrosynthetic Analysis



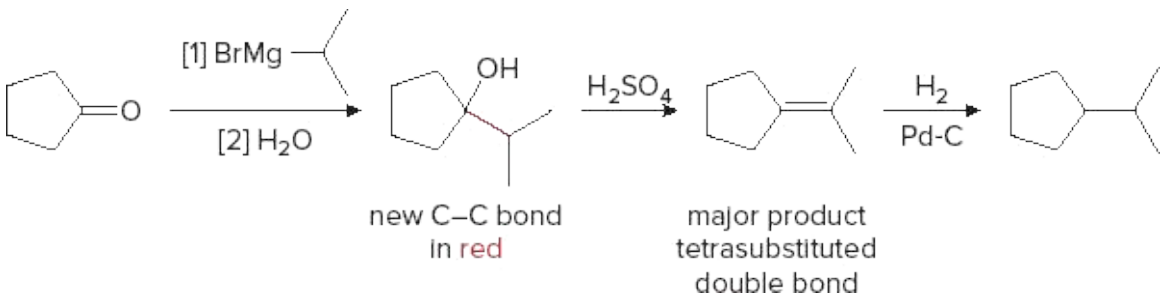
Thinking backwards:

- **[1] Form the alkane by hydrogenation of an alkene.**
- **[2] Introduce the double bond by dehydration of an alcohol.**
- **[3] Form the 3° alcohol by Grignard addition to a ketone. Both components of the Grignard reaction must then be synthesized.**

Synthesis

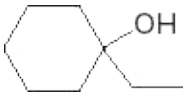
First, make both components needed for the Grignard reaction.

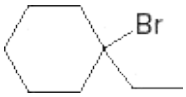
Complete the synthesis with Grignard addition, dehydration, and hydrogenation.

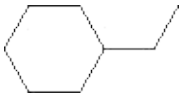


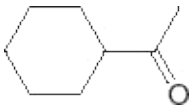
Problem 17.34

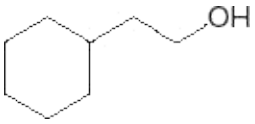
Synthesize each compound from cyclohexanol, ethanol, and any other needed reagents.

a. 

b. 

c. 

d. 

e. 

More Practice:

Try Problems 17.62; 17.63b, c; 17.64b, c; 17.65–17.68.

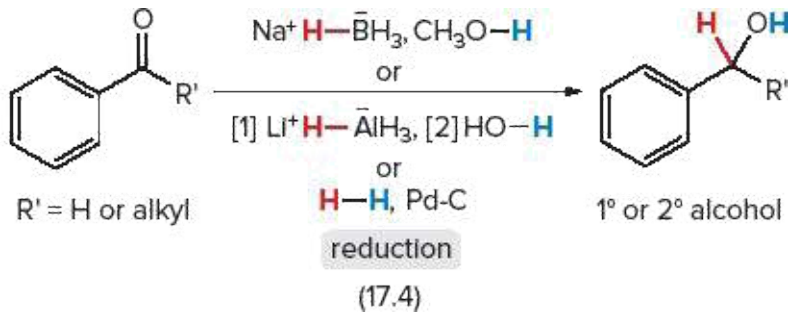
Chapter 17 REVIEW

KEY REACTIONS

Reduction Reactions

[1] Reduction of aldehydes and ketones

1



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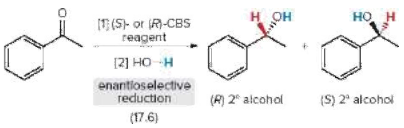
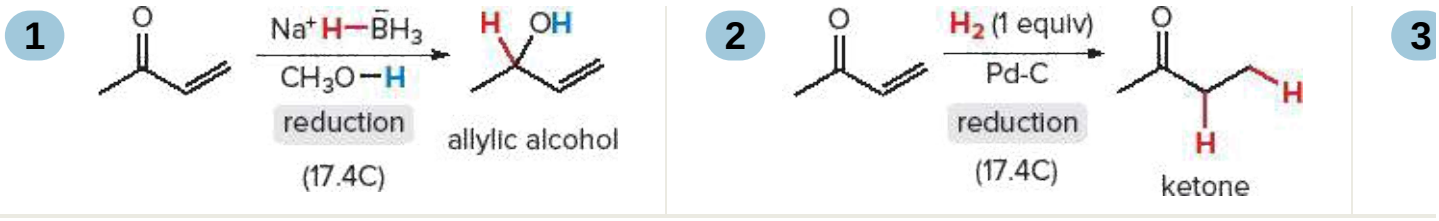


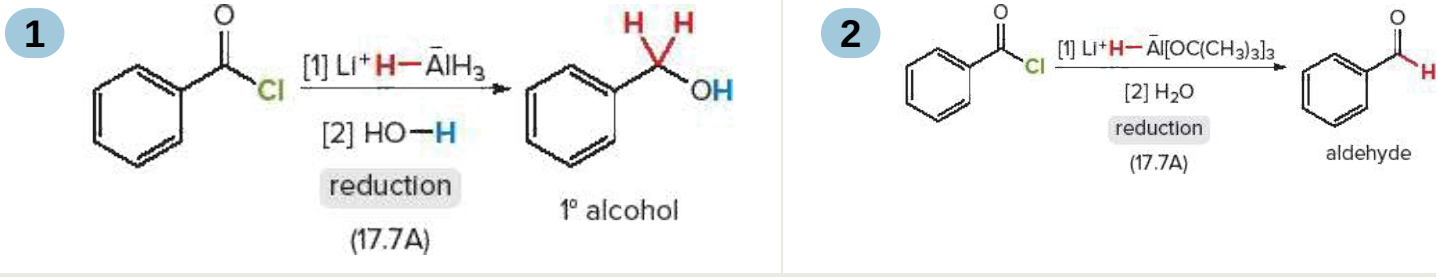
Try Problems 17.35(A) a, b; 17.37a, b, c; 17.39; 17.45c.

[2] Reduction of α,β-unsaturated aldehydes and ketones



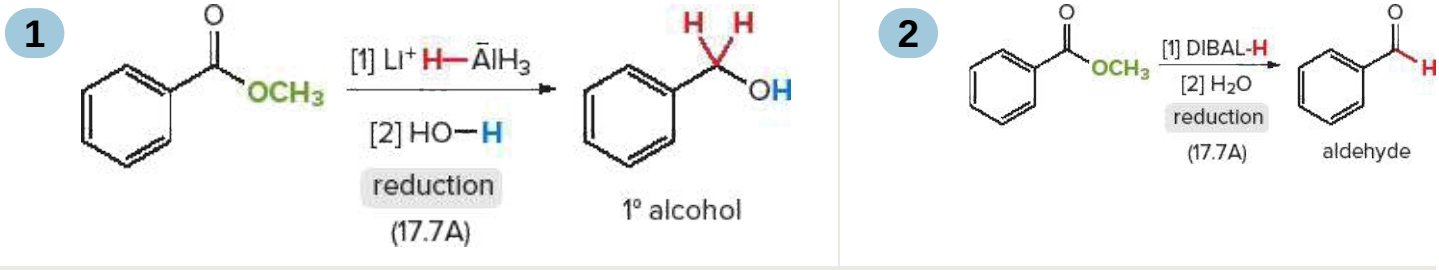
Try Problem 17.40a, b, c.

[3] Reduction of acid chlorides



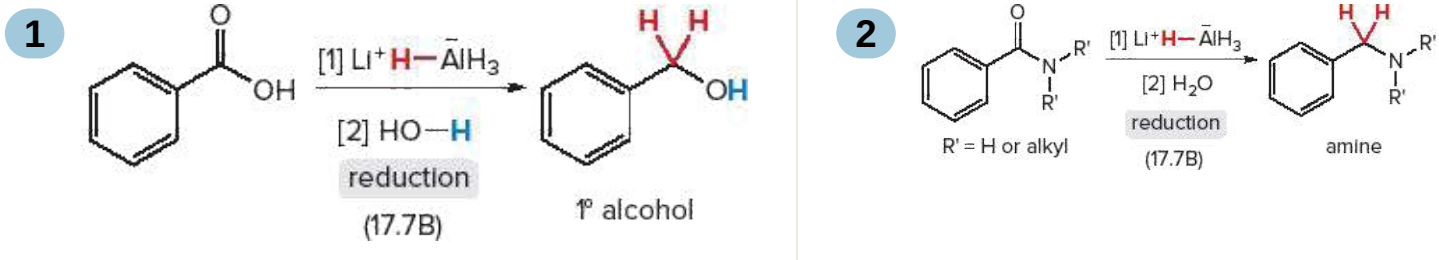
Try Problem 17.41d.

[4] Reduction of esters



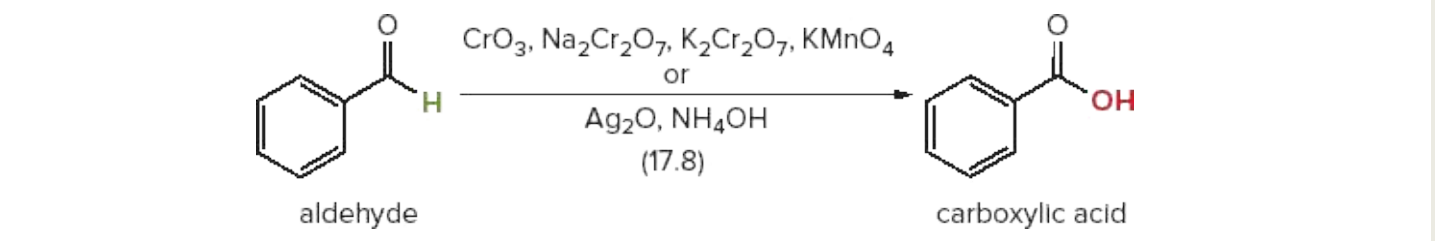
Try Problems 17.35(B) a, b; 17.41a, b; 17.45d.

[5] Reduction of carboxylic acids and amides



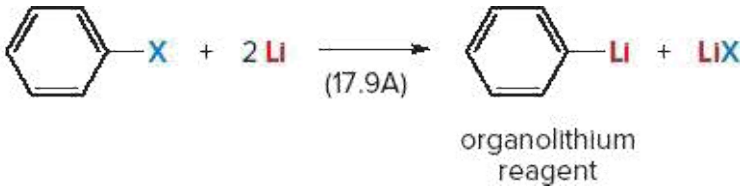
Try Problems 17.41c, 17.56.

Oxidation of Aldehydes to Carboxylic Acids



Preparation of Organometallic Reagents

1



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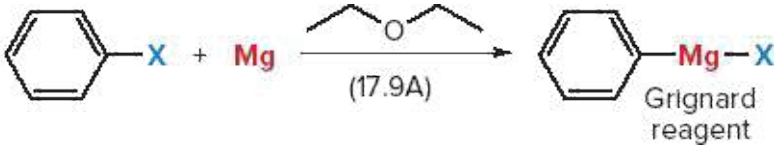

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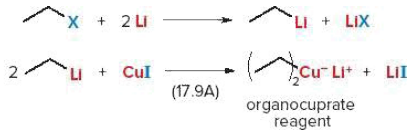

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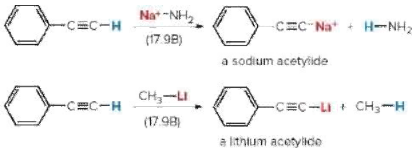
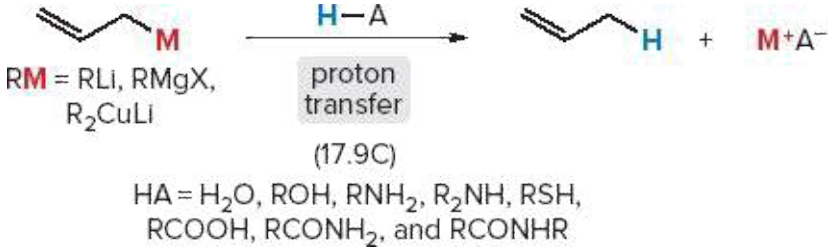


Reactions with Organometallic Reagents

1



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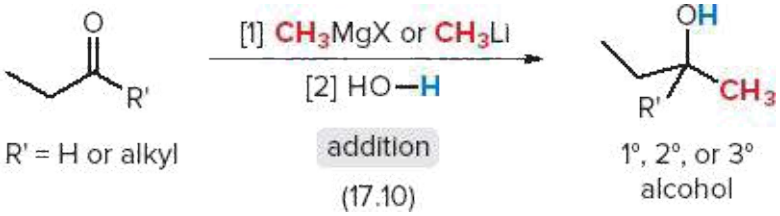

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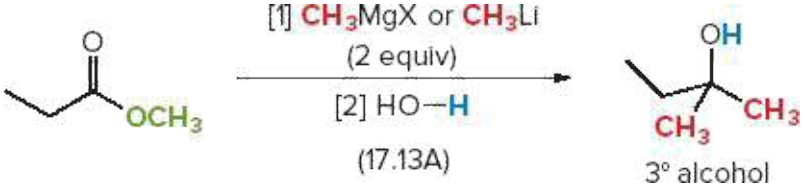

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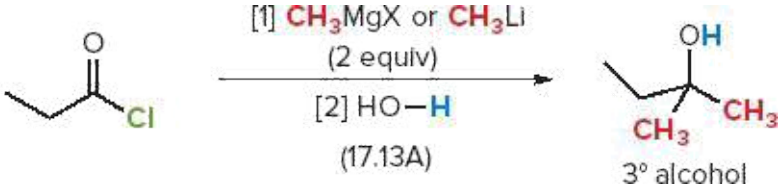

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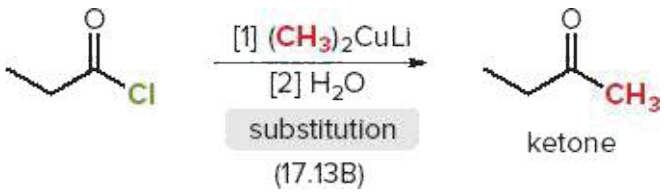

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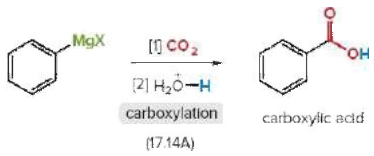

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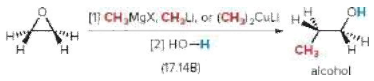

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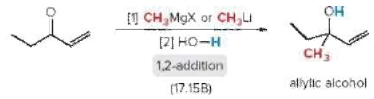

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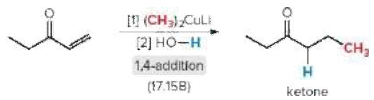
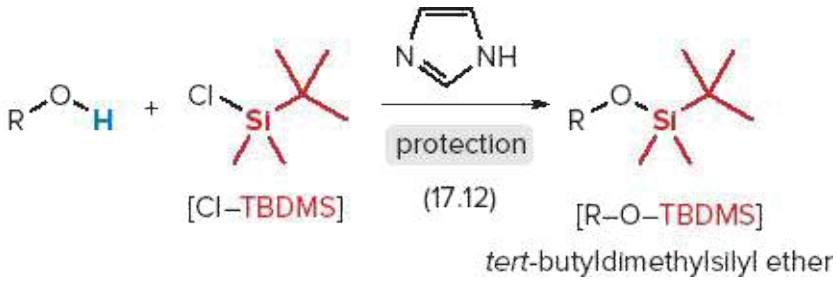


Try Problems 17.35c, d; 17.37g–k; 17.38; 17.40d–f; 17.43; 17.45a, b.

Protecting Groups

1



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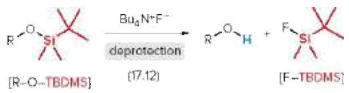
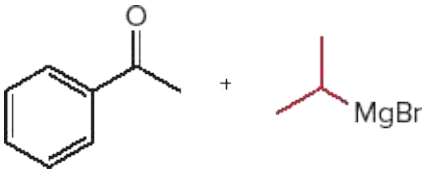
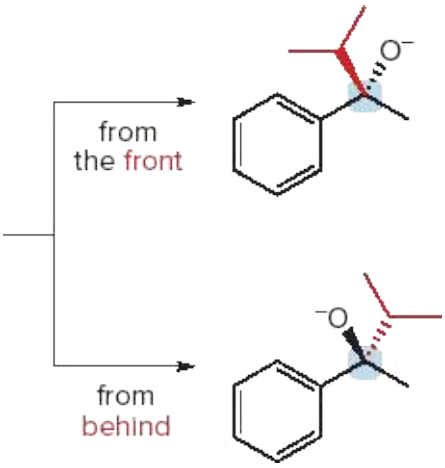
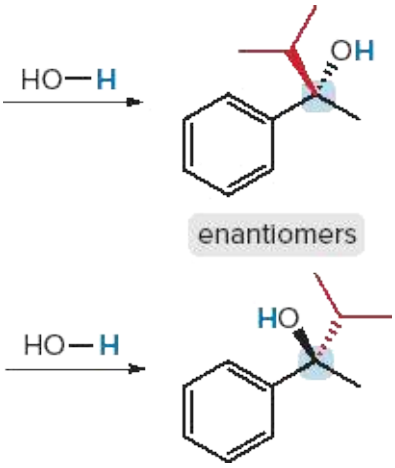


Try Problems 17.37l, 17.48.

KEY SKILLS

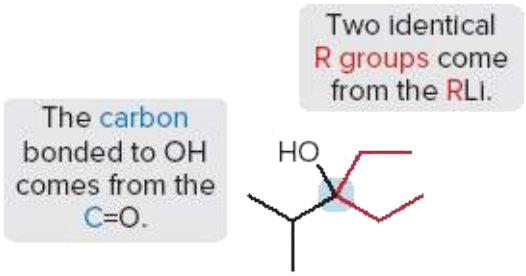
[1] Drawing all stereoisomers that form in a Grignard reaction (17.10B)

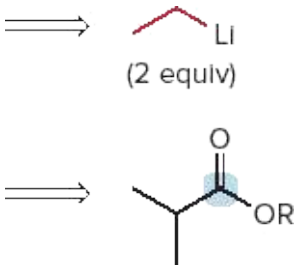
1 Use the reagents to identify the group added to the C=O.	**2** Use the mechanism to determine the stereochemistry.	**3** Protonate the alkoxide to draw the product(s).
		

See Sample Problem 17.2. Try Problem 17.45a.

[2] Determining the starting materials for the preparation of an alcohol from an organolithium reagent and an ester (17.13); example: 3-ethyl-2-methylpentan-3-ol

1 Determine which parts of the molecule come from each of the starting materials.	**2** Draw the starting materials.



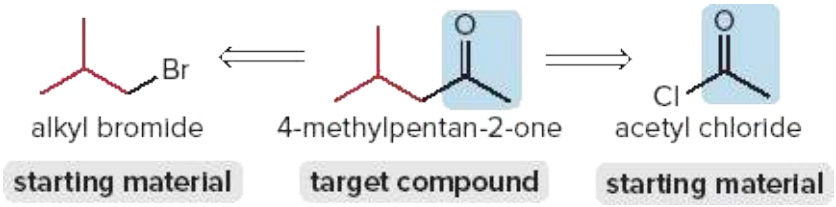


See Sample Problem 17.4. Try Problem 17.59.

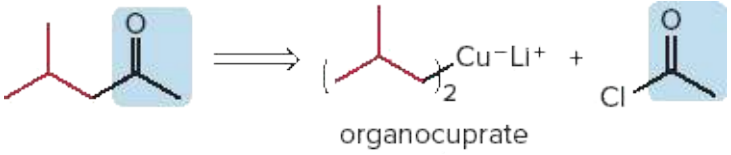
Page 824

[3] Devising a synthesis of a ketone (17.11); example: 4-methylpentan-2-one from acetyl chloride and an alkyl bromide

1 Compare the carbon skeletons.

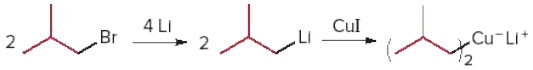


2 Work backwards.



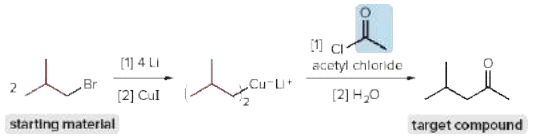
A **ketone** is made from the reaction between an **organocuprate** and an **acid chloride.**

3 Work forwards.



An **alkyl bromide** is converted to an **organocuprate** using a two-step process.

4 Complete the synthesis.



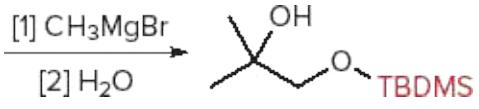
See Sample Problem 17.5. Try Problems 17.63d; 17.64a, b; 17.65a.

[4] Using a protecting group (17.12)

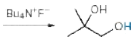
1 Protect the OH group.

- **The OH group is converted to another functional group that does not interfere with the**

2 Carry out the reaction.



3 Re the pro gro

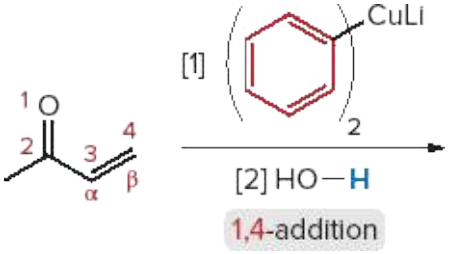


reaction at the C=O.

See Figure 17.7. Try Problem 17.48.

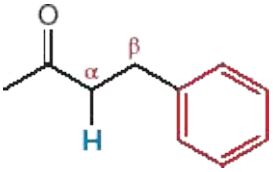
[5] Drawing the product that forms in the reaction of an α,β-unsaturated carbonyl compound with an organometallic reagent (17.10B)

1 Identify whether the reagent will undergo 1,2- or 1,4-addition.



- Organocuprate reagents add to the β carbon to afford the 1,4-addition product.

2 Draw the product.

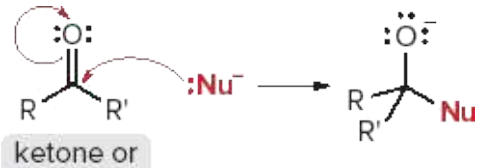


- The phenyl group is attached to the β carbon.
- The α carbon is protonated.

See Sample Problem 17.6. Try Problems 17.38c; 17.40d–f; 17.43b, e.

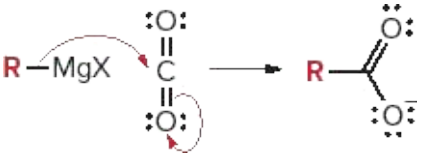
KEY MECHANISM CONCEPTS

1 Nucleophilic addition



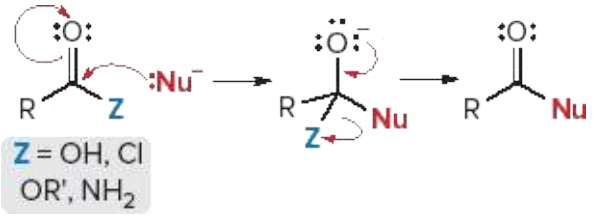
- See Mechanisms 17.1, 17.3, 17.6, and 17.9.
- Nucleophilic addition occurs because ketones and aldehydes have no leaving group.
  Addition followed by
- protonation gives an alcohol.

3 Carboxylation—Reaction of RMgX with CO_2



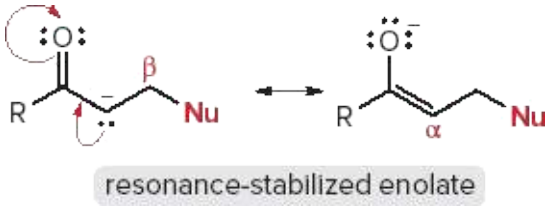
- See Mechanism 17.8.
- Nucleophilic attack followed by protonation gives a carboxylic acid.

2 **Nucleophilic substitution**



- **See Mechanism 17.2.**
- **Nucleophilic substitution occurs because of the leaving group Z.**
- **Substitution involves addition followed by loss of Z to give a new carbonyl compound.**

4 **1,4-Addition to an α,β-unsaturated carbonyl compound**



- **See Mechanism 17.10.**
- **Nucleophilic attack at the β position gives an enolate.**
- **Protonation at the α position gives a carbonyl compound.**

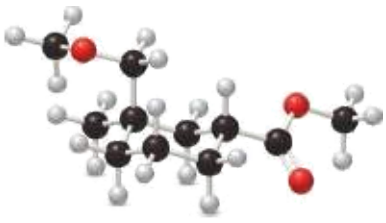
Try Problems 17.51–17.55.

PROBLEMS

Problems Using Three-Dimensional Models

17.35 **Draw the products formed when A or B is treated with each reagent. In some cases, no reaction occurs.**

A



B

a. $NaBH_4$, CH_3OH

b. [1] $LiAlH_4$; [2] H_2O

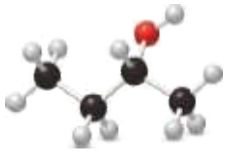
c. [1] CH_3MgBr (excess); [2] H_2O

d. [1] C_6H_5Li (excess); [2] H_2O

e. $Na_2Cr_2O_7$, H_2SO_4, H_2O

17.36 Devise a synthesis of each alcohol from organic alcohols having one or two carbons and any required reagents.

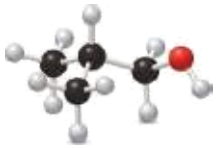
a.



(+ enantiomer)

b.

c.



d.

Reactions and Reagents

17.37 Draw the product formed when pentanal ($CH_3CH_2CH_2CH_2CHO$) is treated with each reagent. With some reagents, no reaction occurs.

a. $NaBH_4$, CH_3OH

b. [1] $LiAlH_4$; [2] H_2O

c. H_2, Pd-C

d. PCC

e. $Na_2Cr_2O_7$, H_2SO_4, H_2O

f. Ag_2O, NH_4OH

g. [1] CH_3MgBr; [2] H_2O

h. [1] C_6H_5Li; [2] H_2O

i. [1] $(CH_3)_2CuLi$; [2] H_2O

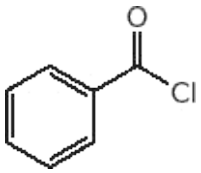
j. [1] $HC{\equiv}CNa$; [2] H_2O

k. [1] $CH_3C{\equiv}CLi$; [2] H_2O

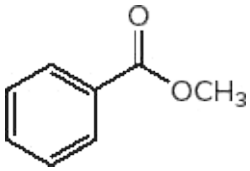
l. The product in (a), then TBDMS—Cl, imidazole

17.38 **Draw the product formed when $(CH_3CH_2CH_2CH_2)_2CuLi$ is treated with each compound. In some cases, no reaction occurs.**

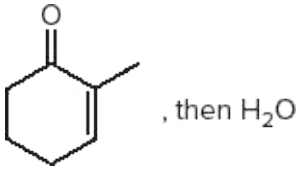
a.



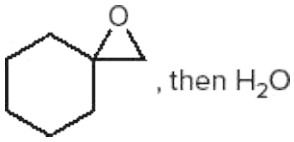
b.



c.

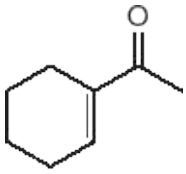


d.



17.39 **The stereochemistry of the products of reduction depends on the reagent used, as you learned in Sections 17.5 and 17.6. With this in mind, how would you convert 3,3-dimethylbutan-2-one $[CH_3COC(CH_3)_3]$ to: (a) racemic 3,3-dimethylbutan-2-ol $[CH_3CH(OH)C(CH_3)_3]$; (b) only (*R*)-3,3-dimethylbutan-2-ol; (c) only (*S*)-3,3-dimethylbutan-2-ol?**

17.40 **Draw the product formed when the α,β-unsaturated ketone A is treated with each reagent.**



A

a. $NaBH_4$, CH_3OH

b. H_2 (1 equiv), Pd-C

c. H_2 (excess), Pd-C

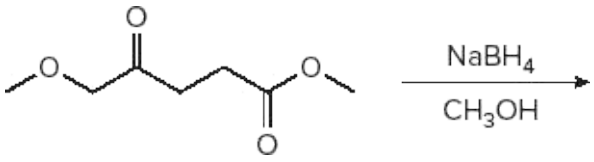
d. [1] CH_3Li; [2] H_2O

e. [1] CH_3CH_2MgBr; [2] H_2O

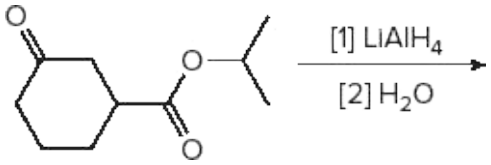
f. [1] $(CH_2{=}CH)_2CuLi$; [2] H_2O

17.41 **Draw the products of each reduction reaction.**

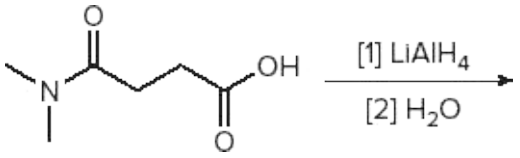
a.



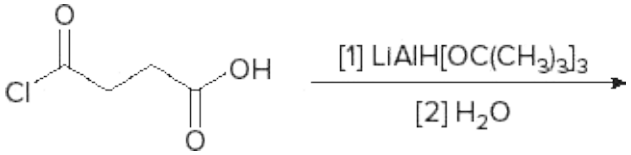
b.



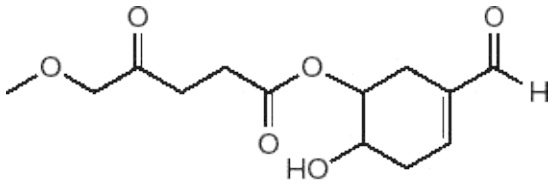
c.



d.



17.42 Draw the product(s) formed when A is treated with each reagent.



A

a. $NaBH_4$, CH_3OH

b. $LiAlH_4$, then H_2O

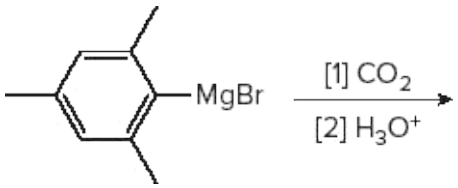
c. Ag_2O, NH_4OH

d. CrO_3, H_2SO_4, H_2O

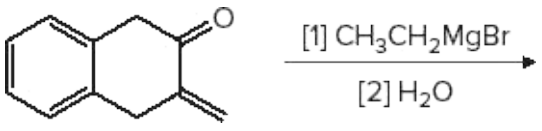
e. PCC

17.43 Draw the products of the following reactions with organometallic reagents.

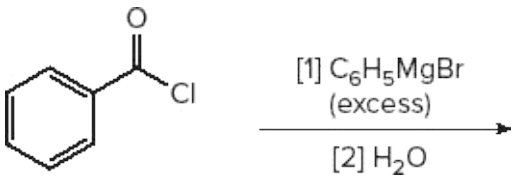
a.



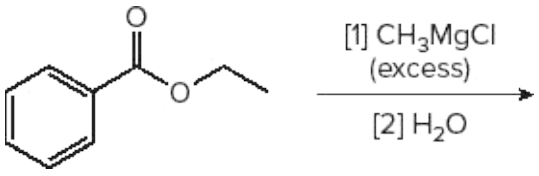
b.



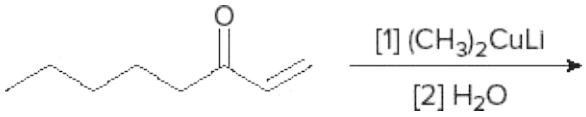
c.



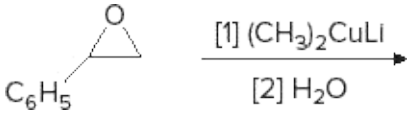
d.



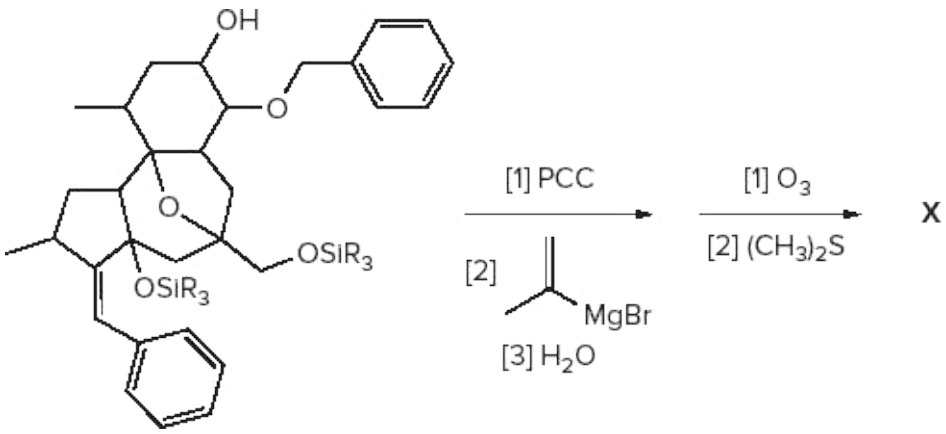
e.



f.

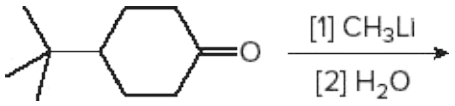


17.44 Identify the product X, formed by the reaction sequence shown. These steps were used in the synthesis of resiniferatoxin, the complex chapter-opening molecule.

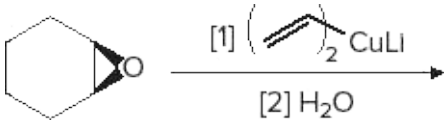


17.45 Draw all stereoisomers formed in each reaction.

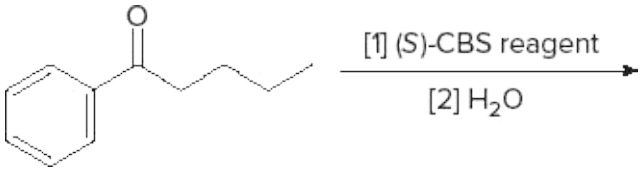
a.



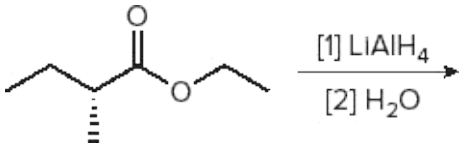
b.



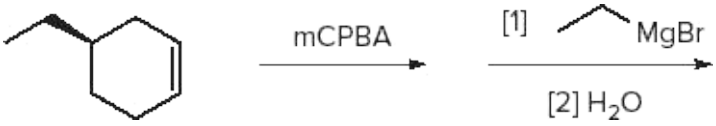
c.



d.



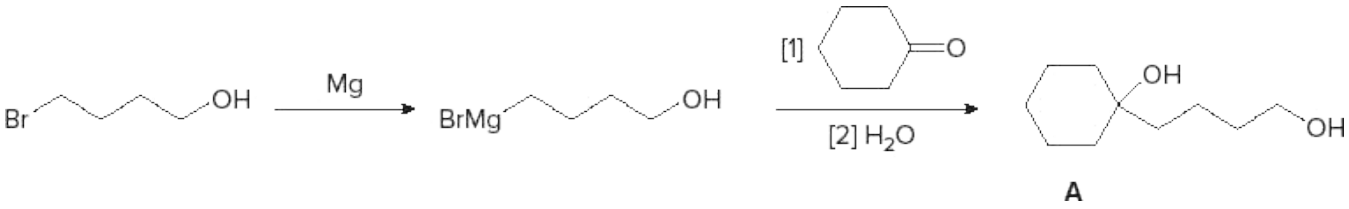
17.46 Draw all stereoisomers formed in the following two-step reaction sequence.



17.47 Explain why metal hydride reduction gives an endo alcohol as the major

product in one reaction and an exo alcohol as the major product in the other reaction.

17.48 A student tried to carry out the following reaction sequence, but none of diol A was formed. Explain what was wrong with this plan, and design a successful stepwise synthesis of A.



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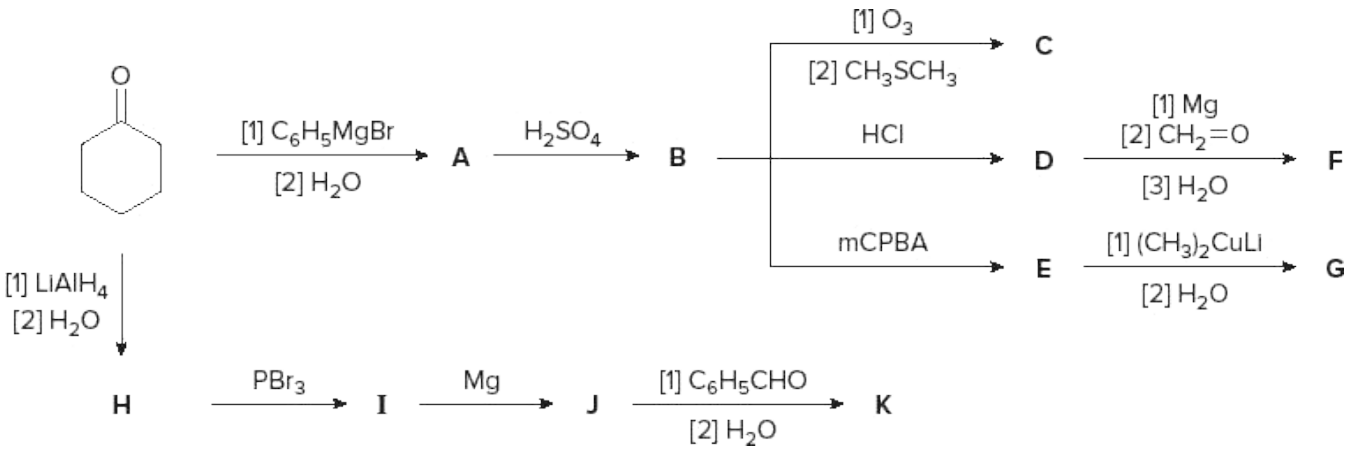
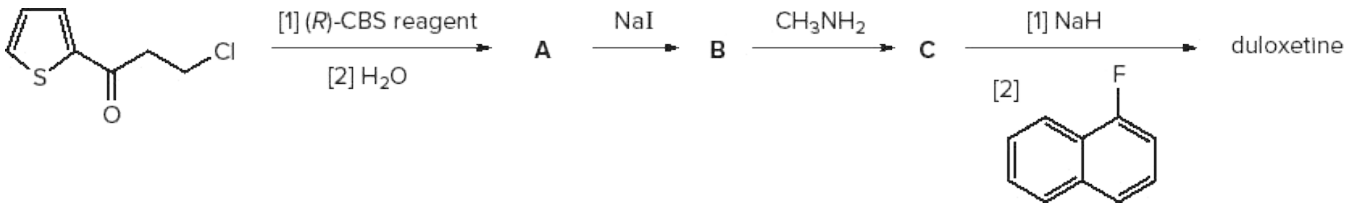
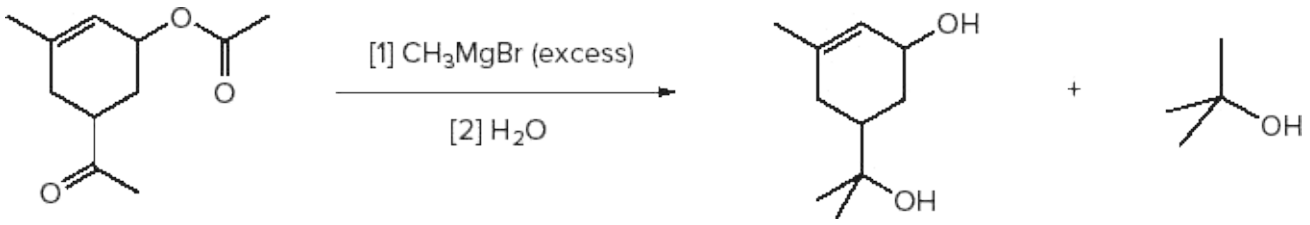
17.49 Identify the lettered compounds in the following reaction scheme. Compounds F, G, and K are isomers of molecular formula $C_{13}H_{18}O$. How could ^1H NMR spectroscopy distinguish these three compounds from each other?



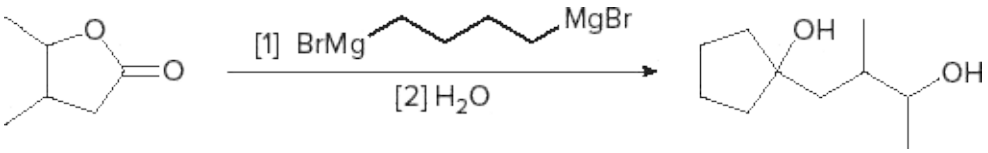
17.50 Several steps in the synthesis of optically active duloxetine, an antidepressant sold under the trade name Cymbalta, are shown. Identify the structure of intermediates A–C and the final product duloxetine, including stereochemistry, in this reaction sequence.



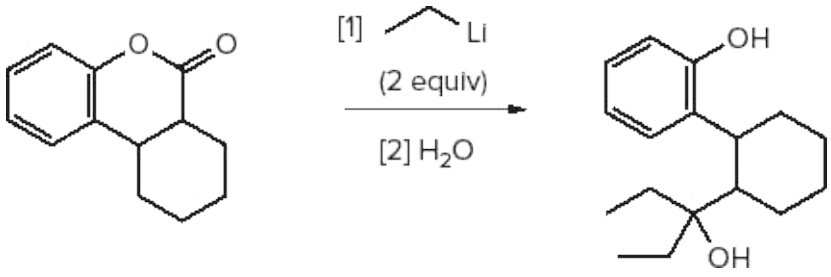
17.51 Draw a stepwise mechanism for the following reaction. Your mechanism must show how both organic products are formed.



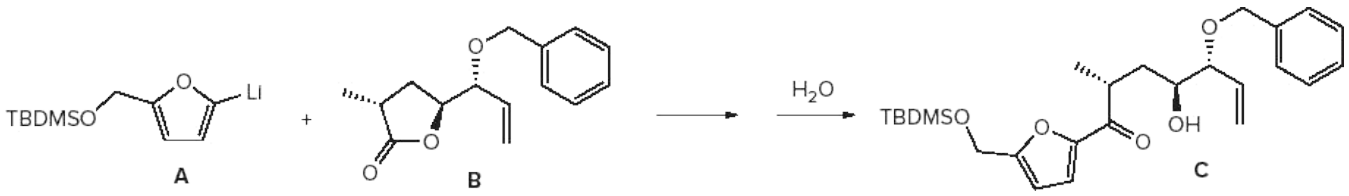
17.52 Draw a stepwise mechanism for the following reaction.



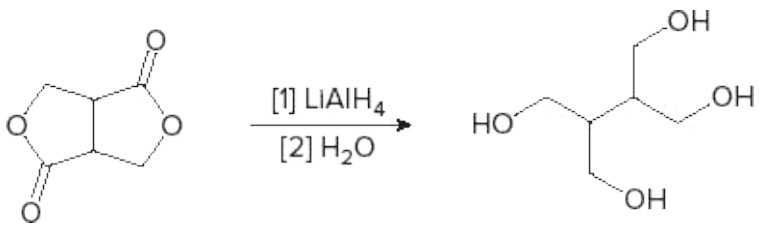
17.53 Draw a stepwise mechanism for the following reaction.



17.54 Slow addition of organolithium reagent A to B afforded C, an intermediate in the synthesis of the chapter-opening molecule, resiniferatoxin. Draw a stepwise mechanism for this process.



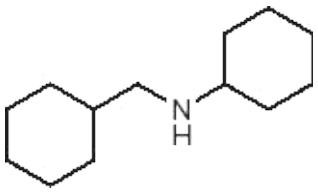
17.55 Draw a stepwise mechanism for the following reaction.



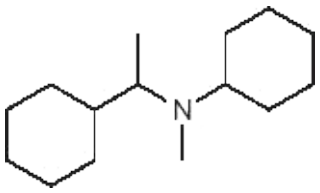
Synthesis

17.56 What amides will form each amine on treatment with $LiAlH_4$?

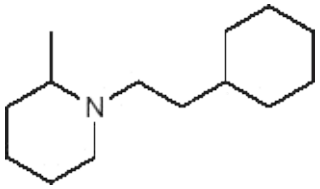
a.



b.

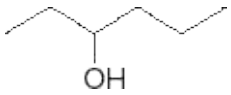


c.

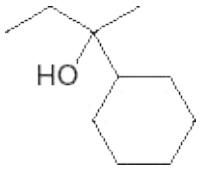


17.57 What Grignard reagent and aldehyde (or ketone) are needed to prepare each alcohol? Show all possible routes.

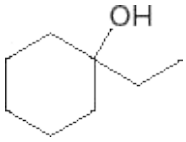
a.



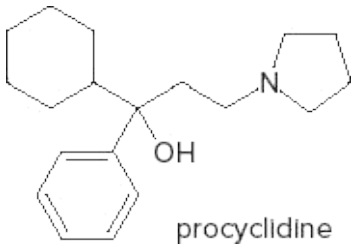
b.



c.



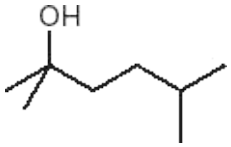
17.58 Procyclidine is a drug that has been used to treat the uncontrolled body movements associated with Parkinson's disease. Draw three different methods to prepare procyclidine using a Grignard reagent.



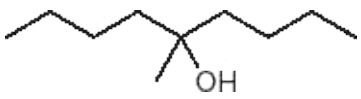
procyclidine

17.59 What ester and Grignard reagent are needed to synthesize each alcohol?

a.

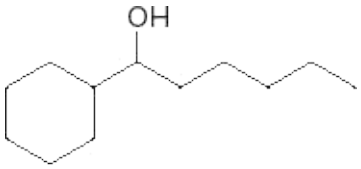


b.



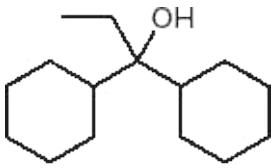
17.60 What organolithium reagent and carbonyl compound can be used to prepare each of the following compounds? You may use aldehydes, ketones, or esters as carbonyl starting materials.

a.



(two ways)

b.

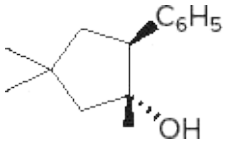


(three ways)

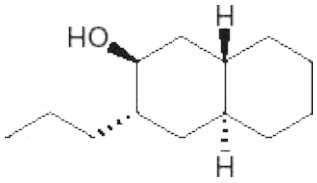
17.61 What epoxide and organometallic reagent are needed to synthesize each alcohol?

a.

b.



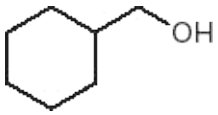
c.



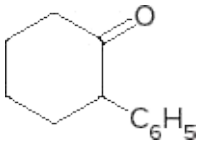
17.62 Propose at least three methods to convert $C_6H_5CH_2CH_2Br$ to $C_6H_5CH_2CH_3$.

17.63 Synthesize each compound from cyclohexanol using any other organic or inorganic compounds.

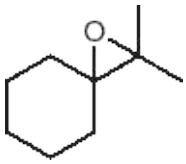
a.



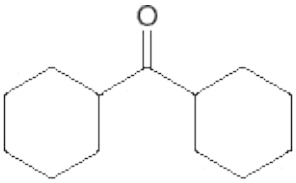
b.



c.



d.

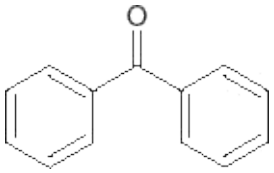


(Each cyclohexane ring must come from cyclohexanol.)

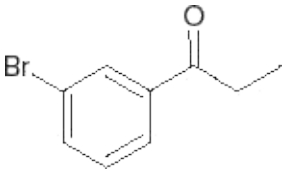
17.64 Convert benzene into each compound. You may also use any inorganic reagents and organic alcohols having four or fewer carbons. One step of

the synthesis must use a Grignard reagent.

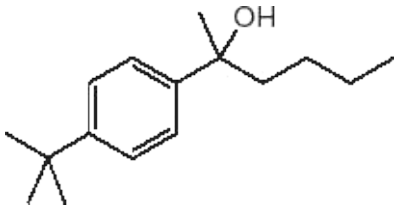
a.



b.

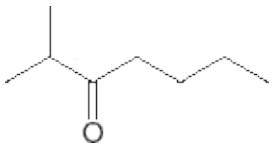


c.

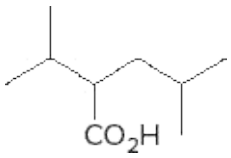


17.65 Design a synthesis of each compound from alcohols having four or fewer carbons as the only organic starting materials. You may use any other inorganic reagents you choose.

a.



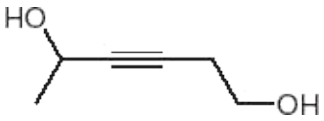
b.



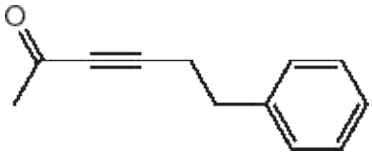
c.

17.66 Devise a synthesis of each alkyne. You may use acetylene, benzene, organic halides, ethylene oxide, and any other required inorganic reagents.

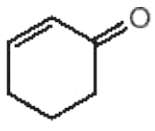
a.



b.

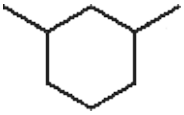


17.67 Devise a synthesis of each compound from cyclohex-2-enone and organic halides having one or two carbons. You may use any other required inorganic reagents.

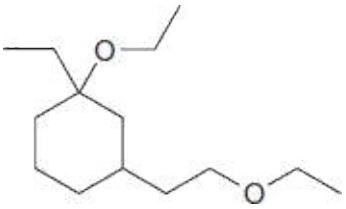


cyclohex-2-enone

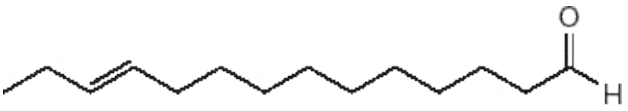
a.



b.



17.68 **Devise a synthesis of (*E*)-tetradec-11-enal, a sex pheromone of the spruce budworm, a pest that destroys fir and spruce forests, from acetylene, $Br(CH_2)_{10}OH$, and any needed organic compounds or inorganic reagents.**



(*E*)-tetradec-11-enal

Spectroscopy

17.69 **An unknown compound A (molecular formula $C_7H_{14}O$) was treated with $NaBH_4$ in CH_3OH to form compound B (molecular formula $C_7H_{16}O$). Compound A has a strong absorption in its IR spectrum at 1716 cm^{-1}. Compound B has a strong absorption in its IR spectrum at 3600–3200 cm^{-1}. The ^1H NMR spectra of A and B are given. What are the structures of A and B?**

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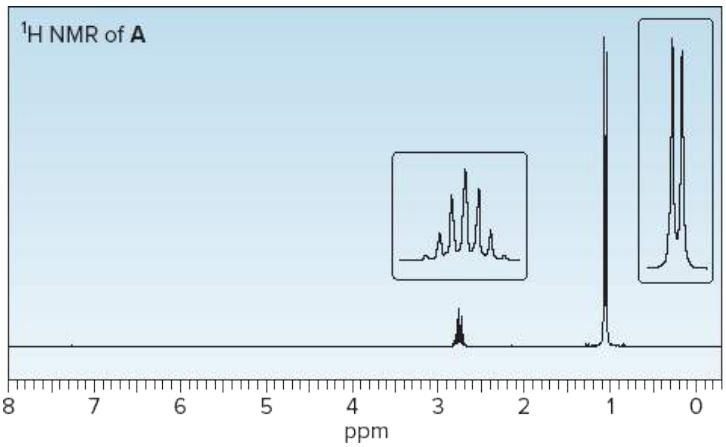
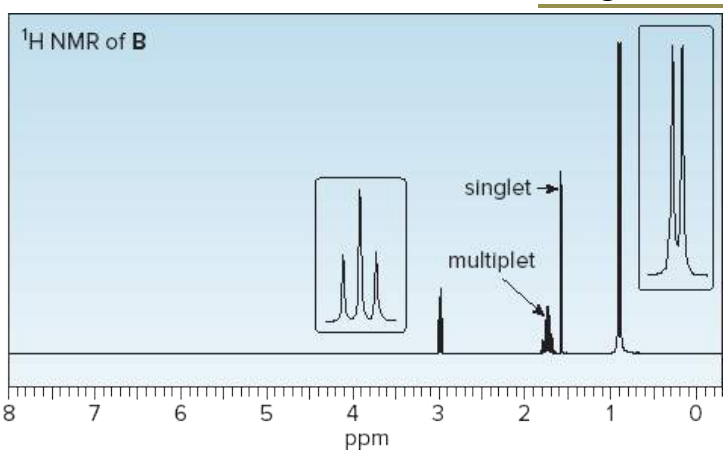




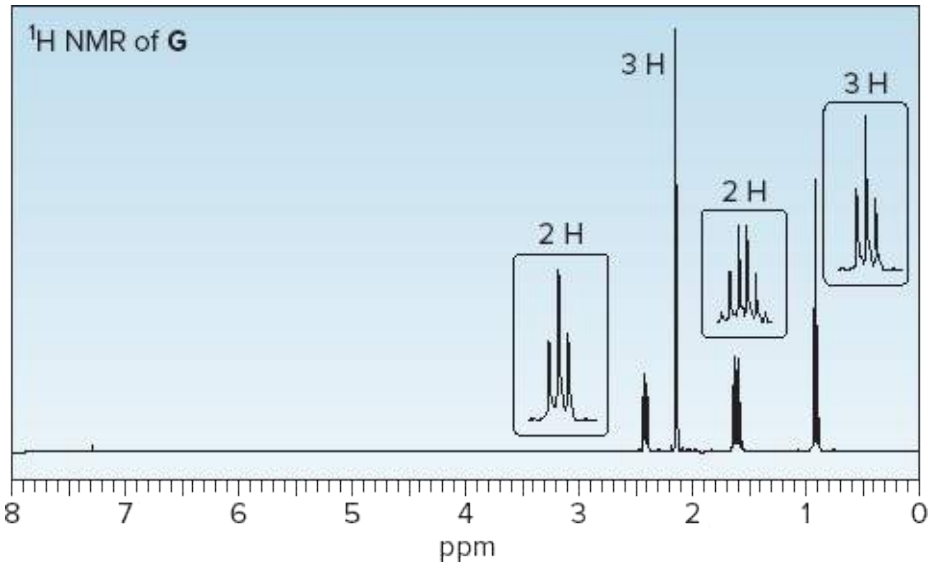
17.70 **Treatment of compound E (molecular formula $C_4H_8O_2$) with excess CH_3CH_2MgBr yields compound F (molecular formula $C_6H_{14}O$) after protonation with H_2O. E shows a strong absorption in its IR spectrum at 1743 cm^{-1}. F shows a strong IR absorption at 3600–3200 cm^{-1}. The ^1H NMR spectral data of E and F are given. What are the structures of E and F?**

Compound E signals at 1.2 (triplet, 3 H), 2.0 (singlet, 3 H), and 4.1

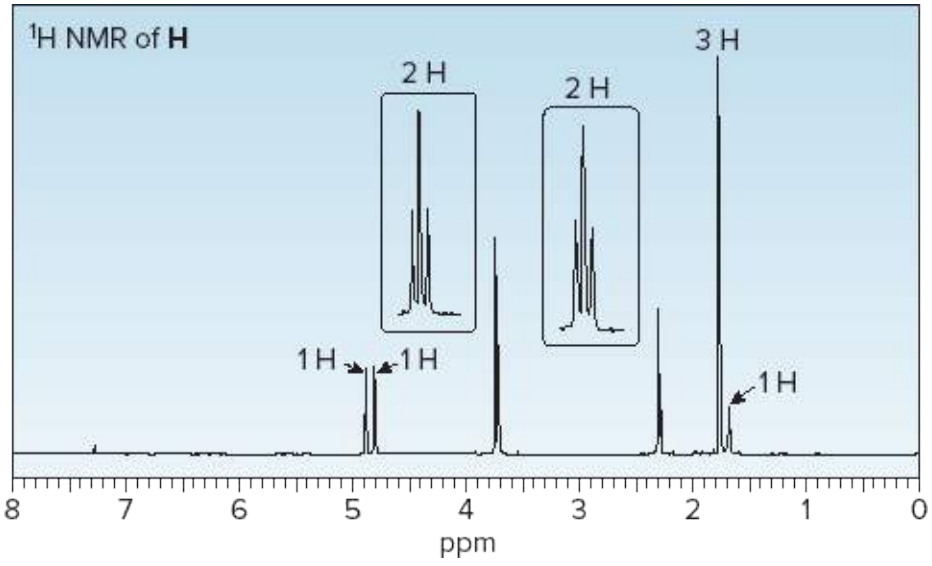
(quartet, 2 H) ppm

Compound F signals at 0.9 (triplet, 6 H), 1.1 (singlet, 3 H), 1.5 (quartet, 4 H), and 1.55 (singlet, 1 H) ppm

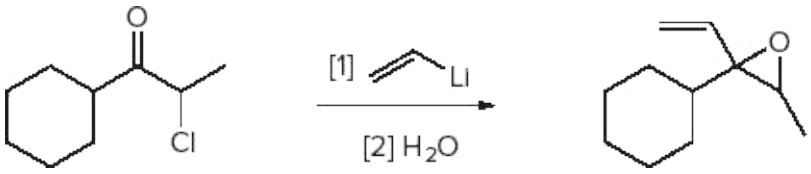
17.71 **Reaction of butanenitrile ($CH_3CH_2CH_2CN$) with methylmagnesium bromide (CH_3MgBr), followed by treatment with aqueous acid, forms compound G. G has a molecular ion in its mass spectrum at *m/z* = 86 and a base peak at *m/z* = 43. G exhibits a strong absorption in its IR spectrum at 1721 cm^{-1} and has the ^1H NMR spectrum given below. What is the structure of G? We will learn about the details of this reaction in Chapter 19.**



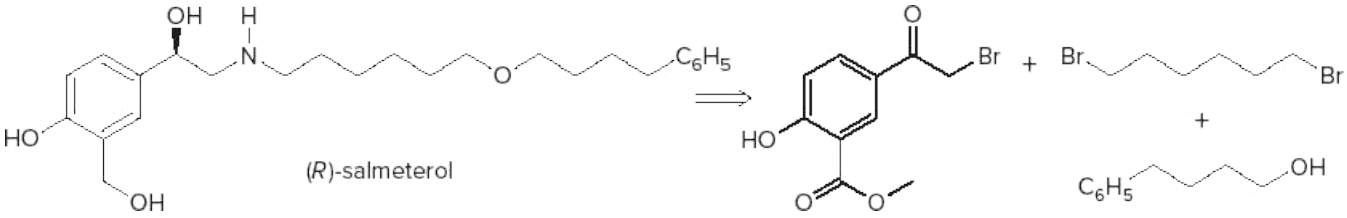
17.72 **Treatment of isobutene [$(CH_3)_2C=CH_2$] with $(CH_3)_3CLi$ forms a carbanion that reacts with $CH_2=O$ to form H after water is added to the reaction mixture. H has a molecular ion in its mass spectrum at *m/z* = 86, and shows fragments at 71 and 68. H exhibits absorptions in its IR spectrum at 3600−3200 and 1651 cm^{-1}, and has the ^1H NMR spectrum given below. What is the structure of H?**



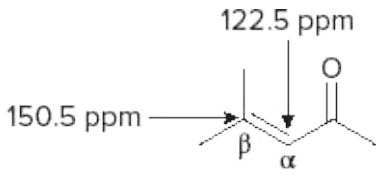
17.73 Draw a stepwise mechanism for the following reaction.



17.74 Design a synthesis of (*R*)-salmeterol (Figure 17.3) from the following starting materials.

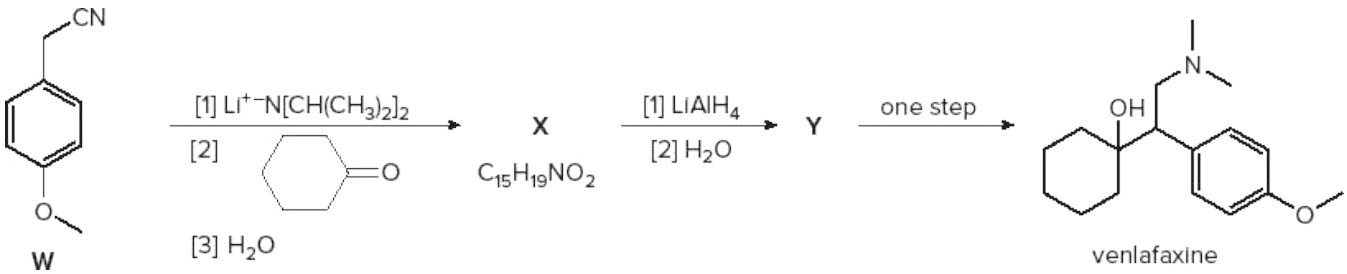


17.75 Explain why the β carbon of an α,β-unsaturated carbonyl compound absorbs farther downfield in the ^{13}C NMR spectrum than the α carbon, even though the α carbon is closer to the electron-withdrawing carbonyl group. For example, the β carbon of mesityl oxide absorbs at 150.5 ppm, whereas the α carbon absorbs at 122.5 ppm.



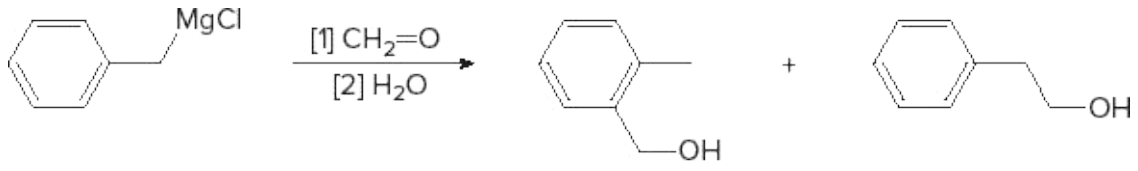
mesityl oxide

17.76 Identify X and Y, two of the intermediates in a synthesis of the antidepressant venlafaxine (trade name Effexor), in the following reaction scheme. Write a mechanism for the formation of X from W.



venlafaxine

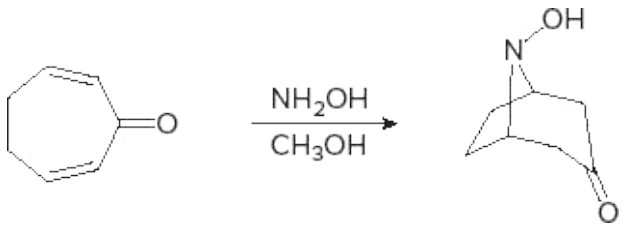
17.77 Reaction of benzylmagnesium chloride with formaldehyde yields alcohols N and P after protonation. Draw a stepwise mechanism that shows how both products are formed.



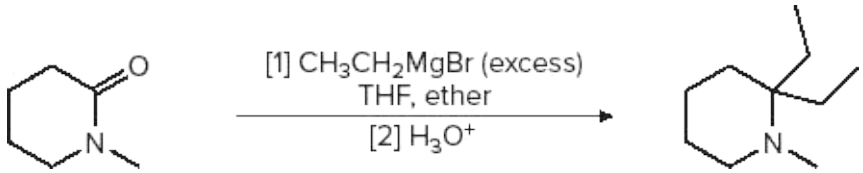
N
major product

P
minor product

17.78 Draw a stepwise mechanism for the following reaction. (Hint: Conjugate addition can occur with heteroatoms as well as carbon nucleophiles.)



17.79 Draw a stepwise mechanism for the following reaction of a Grignard reagent with a cyclic amide.



18

Aldehydes and Ketones—Nucleophilic Addition

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18.1 Introduction
18.2 Nomenclature
18.3 Properties of aldehydes and ketones
18.4 Interesting aldehydes and ketones
18.5 Preparation of aldehydes and ketones
18.6 Reactions of aldehydes and ketones—General considerations
18.7 Nucleophilic addition of H^- and R^-—A review
18.8 Nucleophilic addition of ^-CN
18.9 The Wittig reaction
18.10 Addition of 1° amines
18.11 Addition of 2° amines
18.12 Addition of H_2O—Hydration
18.13 Addition of alcohols—Acetal formation
18.14 Acetals as protecting groups
18.15 Cyclic hemiacetals
18.16 An introduction to carbohydrates

Extracts of the oleander plant *Nerium oleander*, a common ornamental shrub that grows in tropical and subtropical regions, contain oleandrin ($C_{32}H_{48}O_9$). Although oleandrin and related compounds are responsible for the toxicity of the sap of oleander, oleander has been used in China and Russia for the treatment of congestive heart failure. Oleandrin contains an acetal, which is formed by an addition reaction to a carbonyl group. In Chapter 18, we learn about nucleophilic addition, the characteristic reaction of aldehydes and ketones.

Why Study…

Aldehydes and Ketones?

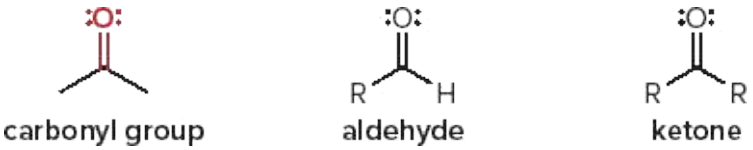
In Chapter 18, we continue the study of carbonyl compounds with a detailed look at aldehydes and ketones. We will first learn about the nomenclature, physical properties, and spectroscopic absorptions that characterize aldehydes and ketones. The remainder of Chapter 18 is devoted to nucleophilic addition reactions. Although we have already learned two examples of this reaction in Chapter 17, nucleophilic addition to aldehydes and ketones is a general reaction that occurs with many nucleophiles, forming a wide variety of products, including carbohydrates and molecules central to the process of vision.

Every new reaction in Chapter 18 involves nucleophilic addition, so the challenge lies in learning the specific reagents and mechanisms that characterize each reaction.

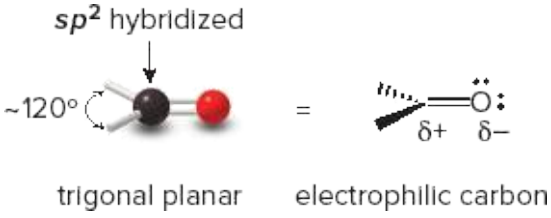
18.1 Introduction

An aldehyde is often written as RCHO. Remember that the H atom is bonded to the carbon atom, *not* the oxygen. Likewise, a ketone is written as RCOR or, if both alkyl groups are the same, R_2CO. Each structure must contain a C=O for every atom to have an octet.

As we learned in Chapter 17, aldehydes and ketones contain a carbonyl group. An aldehyde contains at least one H atom bonded to the carbonyl carbon, whereas a ketone has two alkyl or aryl groups bonded to it.

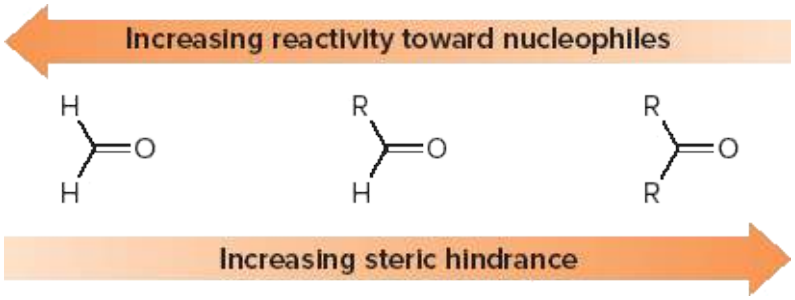


Two structural features determine the chemistry and properties of aldehydes and ketones.



- **The carbonyl group is sp^2 hybridized and trigonal planar, making it relatively *uncrowded.***
- **The electronegative oxygen atom polarizes the carbonyl group, making the carbonyl carbon *electrophilic.***

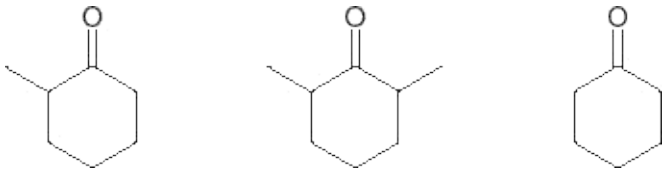
As a result, aldehydes and ketones react with nucleophiles. The relative reactivity of the carbonyl group is determined by the number of R groups bonded to it. As the number of R groups around the carbonyl carbon *increases*, the reactivity of the carbonyl compound *decreases*, resulting in the following order of reactivity:



Increasing the number of alkyl groups on the carbonyl carbon decreases reactivity for both steric and electronic reasons, as discussed in Section 17.2B.

Problem 18.1

Rank the following compounds in order of increasing reactivity toward nucleophilic attack.



Problem 18.2

Explain why benzaldehyde is less reactive than cyclohexanecarbaldehyde toward nucleophilic attack.

benzaldehyde cyclohexanecarbaldehyde

18.2 Nomenclature

Both IUPAC and common names are used for aldehydes and ketones.

18.2A Naming Aldehydes in the IUPAC System

In IUPAC nomenclature, aldehydes are identified by a suffix added to the parent name of the longest chain. Two different suffixes are used, depending on whether the CHO group is bonded to a chain or a ring.

To name an aldehyde using the IUPAC system:

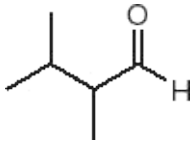
[1] If the CHO is bonded to a chain of carbons, find the longest chain containing the CHO group, and change the *-e* ending of the parent alkane to the suffix *-al*. If the CHO group is bonded to a ring, name the ring and add the suffix *-carbaldehyde*.

[2] Number the chain or ring to put the CHO group at C1, but omit this number from the name. Apply all of the other usual rules of nomenclature.

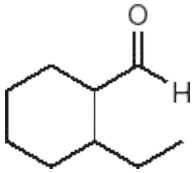
Sample Problem 18.1 Naming an Aldehyde Using the IUPAC System

Give the IUPAC name for each compound.

a.

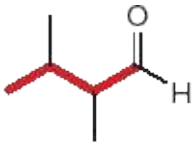


b.



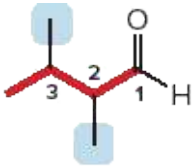
Solution

a. [1] Find and name the longest chain containing the CHO:



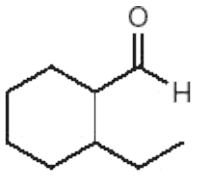
butane ⟶ butan*al*
(4 C's)

[2] Number and name substituents:



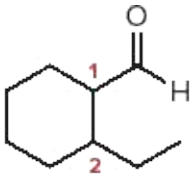
Answer: 2,3-dimethylbutanal

b. [1] Find and name the ring bonded to the CHO group:



cyclohexane + carbaldehyde
(6 C's)

[2] Number and name substituents:

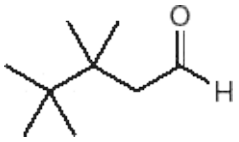


Answer:
2-ethylcyclohexanecarbaldehyde

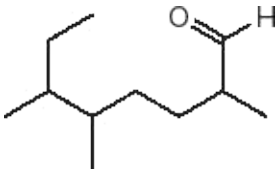
Problem 18.3

Give the IUPAC name for each aldehyde.

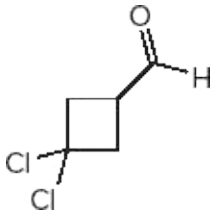
a.



b.



c.



More Practice:

Try Problems 18.37a; 18.40b, d.

Problem 18.4

Give the structure corresponding to each IUPAC name.

a. 2-isobutyl-3-isopropylhexanal

b. *trans*-3-methylcyclopentanecarbaldehyde

c. 1-methylcyclopropanecarbaldehyde

d. 3,6-diethylnonanal

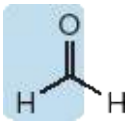
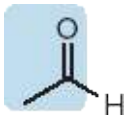
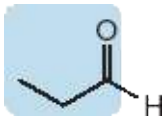
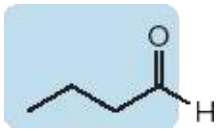
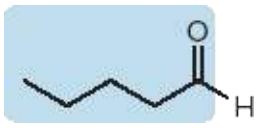
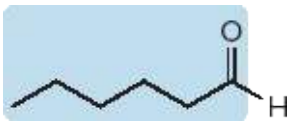
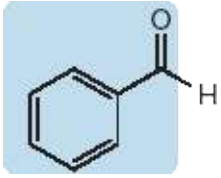
18.2B Common Names for Aldehydes

Many simple aldehydes have common names that are widely used.

- **A common name for an aldehyde is formed by taking the common parent name and adding the suffix *-aldehyde.***

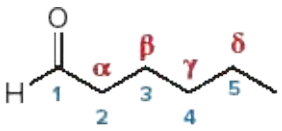
Table 18.1 lists common parent names for some simple aldehydes. These parent names are used in the nomenclature of many other carbonyl compounds (Chapters 19 and 20). The common names formaldehyde, acetaldehyde, and benzaldehyde are virtually always used instead of their IUPAC names.

Table 18.1 Common Names for Some Simple Aldehydes

Number of C atoms	Structure	Parent name	Common name
1		form-	formaldehyde
2		acet-	acetaldehyde
3		propion-	propionaldehyde
4		butyr-	butyraldehyde
5		valer-	valeraldehyde
6		capro-	caproaldehyde
		benz-	benzaldehyde

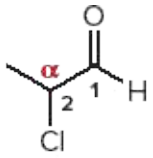
Greek letters are used to designate the location of substituents in common names.

- **The carbon adjacent to the CHO is called the a carbon.**
- **The carbon bonded to the a carbon is the β carbon, followed by the γ (gamma) carbon, the δ (delta) carbon, and so forth down the chain. The last carbon in the chain is sometimes called the Ω (omega) carbon.**

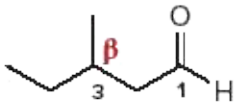


IUPAC numbering begins at the C=O.
Greek lettering begins at the C bonded to the C=O.

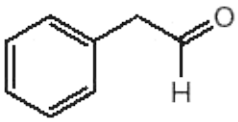
Figure 18.1 gives the common and IUPAC names for three aldehydes.



2-chloropropanal
(α-chloropropionaldehyde)



3-methylpentanal
(β-methylvaleraldehyde)



phenylethanal
(phenylacetaldehyde)

(Common names are in parentheses.)

Figure 18.1 **Three examples of aldehyde nomenclature**

18.2C Naming Ketones in the IUPAC System

- **In the IUPAC system, all ketones are identified by the suffix *-one.***

To name an acyclic ketone using IUPAC rules:

[1] Find the longest chain containing the carbonyl group, and change the *-e* ending of the parent alkane to the suffix *-one*.

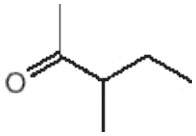
[2] Number the carbon chain to give the carbonyl carbon the lower number. Apply all of the other usual rules of nomenclature.

With cyclic ketones, numbering always begins at the carbonyl carbon, but the "1" is usually omitted from the name. The ring is then numbered clockwise or counterclockwise to give the

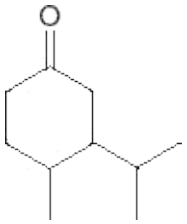
Sample Problem 18.2 **Naming a Ketone Using the IUPAC System**

Give the IUPAC name for each ketone.

a.

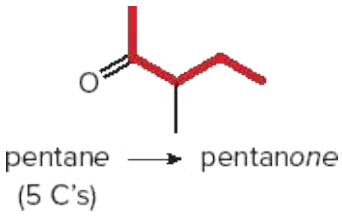


b.

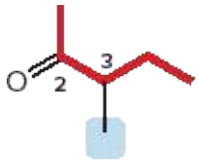


Solution

a. [1] Find and name the longest chain containing the carbonyl group:

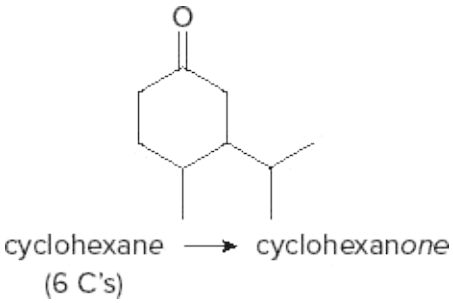


[2] Number and name substituents:

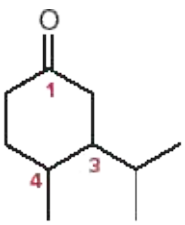


Answer: 3-methylpentan-2-one

b. [1] Name the ring:



[2] Number and name substituents:

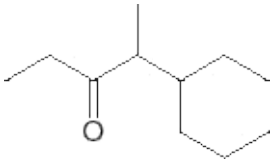


Answer:
3-isopropyl-4-methylcyclohexanone

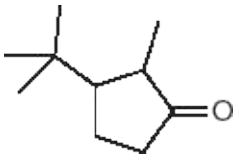
Problem 18.5

Give the IUPAC name for each ketone.

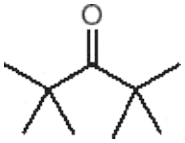
a.



b.



c.

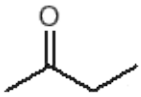


More Practice:

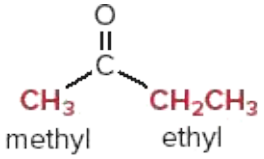
Try Problems 18.37a; 18.40a, c.

18.2D Common Names for Ketones

Most common names for ketones are formed by naming both alkyl groups on the carbonyl carbon, arranging them alphabetically, and adding the word *ketone*. Using this method, the common name for butan-2-one becomes ethyl methyl ketone.



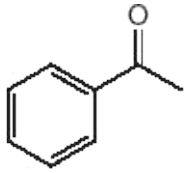
IUPAC name: **butan-2-one**



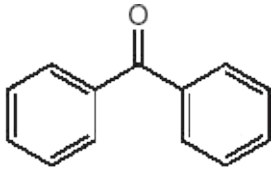
Common name: **ethyl methyl ketone**

Three widely used common names for some simple ketones do not follow this convention:

acetone

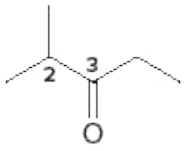


acetophenone

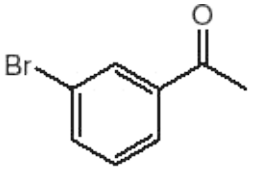


benzophenone

Figure 18.2 gives acceptable names for two ketones.



IUPAC name: 2-methylpentan-3-one
Common name: ethyl isopropyl ketone



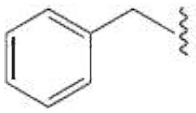
m-bromoacetophenone
or
3-bromoacetophenone

Figure 18.2 **Two examples of ketone nomenclature**

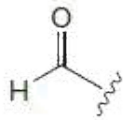
18.2E Additional Nomenclature Facts

Do not confuse a benzyl group with a benzoyl group.

Sometimes acyl groups (RCO–) must be named as substituents. To name an acyl group, take either the IUPAC or common parent name and add the suffix *-yl* or *-oyl*. The three most common acyl groups are drawn below.

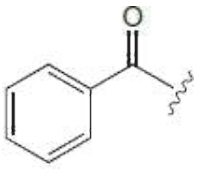


benzyl group



formyl group

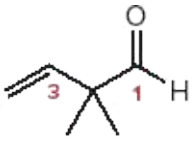
acetyl group



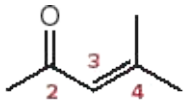
benzoyl group

Compounds containing both a C–C double bond and an aldehyde are named as enals, and compounds that contain both a C–C double bond and a ketone are named as enones. The chain is numbered to give the carbonyl group the *lower* number.

Page 839



2,2-dimethylbut-3-enal



4-methylpent-3-en-2-one

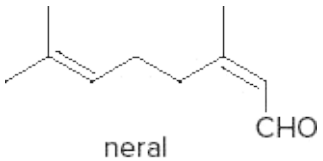
Problem 18.6

Give the structure corresponding to each name: (a) sec-butyl ethyl ketone; (b) methyl vinyl ketone; (c) p-ethylacetophenone; (d) 3-benzoyl-2-benzylcyclopentanone; (e) 6,6-dimethylcyclohex-2-enone; (f) 3-ethylhex-5-enal.

Problem 18.7

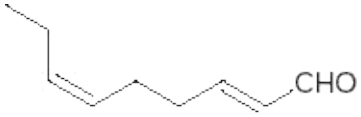
Give the IUPAC name (including any *E*,*Z* designation) for each unsaturated aldehyde.

a.



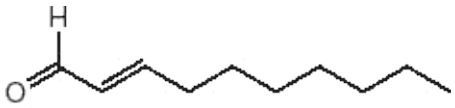
neral
found in lemongrass

b.



cucumber aldehyde

c.



found in stinkbugs and cilantro

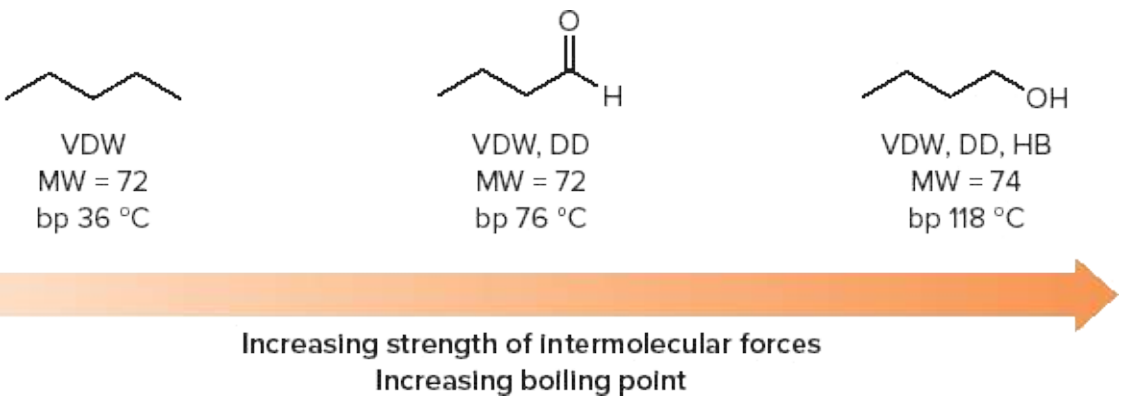
18.3 Properties of Aldehydes and Ketones

18.3A Physical Properties

Aldehydes and ketones exhibit dipole–dipole interactions because of their polar carbonyl group. Because they have no O–H bond, two molecules of RCHO or RCOR are incapable of intermolecular hydrogen bonding, making them *less polar* than alcohols. How these intermolecular forces affect the physical properties of aldehydes and ketones is summarized in Table 18.2.

Table 18.2 Physical Properties of Aldehydes and Ketones

Property	Observation
Boiling point and melting point	• For compounds of comparable molecular weight, bp's and m follow the usual trend: The stronger the intermolecular forces, higher the bp or mp.
Solubility	• RCHO and RCOR are soluble in organic solvents regardless of siz • RCHO and RCOR having ≤ 5 C's are H_2O soluble because they



	hydrogen bond with H_2O (Section 3.4C). • RCHO and RCOR having > 5 C's are H_2O insoluble because nonpolar alkyl portion is too large to dissolve in the polar H solvent.

Key: VDW = van der Waals, DD = dipole–dipole, HB = hydrogen bonding, MW = molecular weight

Problem 18.8

The boiling point of butan-2-one (80 °C) is significantly higher than the boiling point of diethyl ether (35 °C), even though both compounds exhibit dipole–dipole interactions and have comparable molecular weights. Offer an explanation.

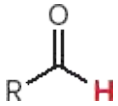
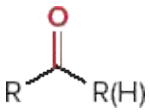
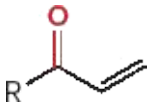
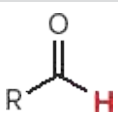
18.3B Spectroscopic Properties

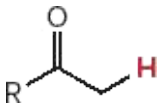
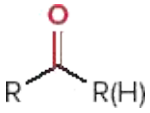
Many details of the spectroscopy of aldehydes and ketones have been presented in Spectroscopy Parts A, B, and C:

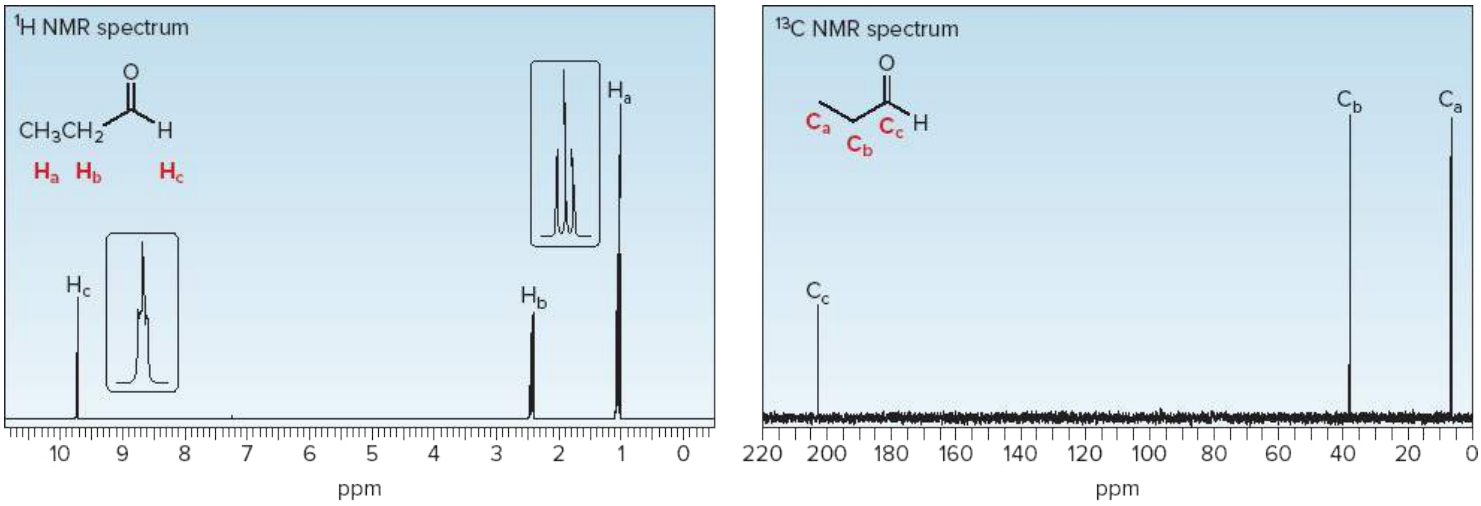
- Fragmentation patterns in mass spectra: Section A.4A and Sample Problem A.7
- The carbonyl absorption in infrared spectra: Sections B.3C and B.4B
- ^1H and ^{13}C NMR absorptions: Section C.11B and Tables C.1 and C.5

Key NMR and IR absorptions for aldehydes and ketones are summarized in Table 18.3, and Figure 18.3 illustrates ^1H and ^{13}C NMR spectra for a simple aldehyde.

Table 18.3 Characteristic Spectroscopic Absorptions of Aldehydes and Ketones

Type of spectroscopy IR absorptions	Type of C, H	Absorption
IR absorptions		2700–2830 cm^{-1} (one or two peaks)
		**~1700 cm^{-1} (increasing ν with decreasing ring size)**
		**1680 cm^{-1}**
^1H NMR absorptions		**9–10 ppm**

		**2–2.5 ppm**
^{13}C NMR absorption		**190–215 ppm**

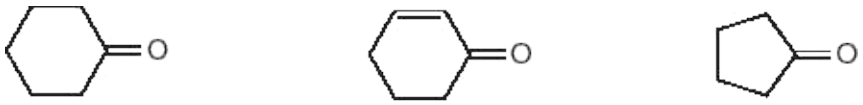


- **^{1}H NMR:** There are three signals due to the three different kinds of hydrogens, labeled H_a, H_b, and H_c. The **deshielded CHO proton** occurs downfield at 9.8 ppm. The H_c signal is split into a triplet by the adjacent CH_2 group, but the coupling constant is small.
- **^{13}C NMR:** There are three signals due to the three different kinds of carbons, labeled C_a, C_b, and C_c. The **deshielded carbonyl carbon** absorbs downfield at 203 ppm.

Figure 18.3 **The ^{1}H and ^{13}C NMR spectra of propanal, CH_3CH_2CHO**

Problem 18.9

Rank the following compounds in order of increasing frequency of their carbonyl absorption in the infrared.



A B C

18.4 Interesting Aldehydes and Ketones

formaldehyde
$CH_2=O$

acetone
$(CH_3)_2C=O$

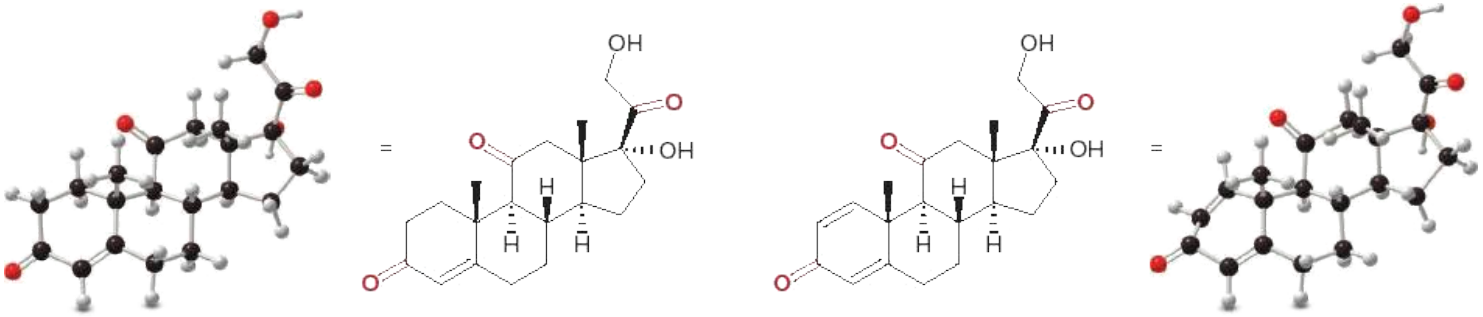
Because it is a starting material for the synthesis of many resins and plastics, billions of pounds of formaldehyde are produced annually in the United States by the oxidation of methanol (CH_3OH). Formaldehyde is also sold as a 37% aqueous solution called formalin, which has been used as a disinfectant, antiseptic, and preservative for biological specimens. Formaldehyde, a product of the incomplete combustion of coal and other fossil fuels, is partly responsible for the irritation caused by smoggy air.

Acetone is an industrial solvent and a starting material in the synthesis of some organic polymers. Acetone is produced in vivo during the breakdown of fatty acids. In diabetes, a common endocrine disease in which normal metabolic processes are altered because of the inadequate secretion of insulin, individuals often have unusually high levels of acetone in their bloodstreams. The characteristic odor of acetone can be detected on the breath of diabetic patients when their disease is poorly controlled.

Many aldehydes with characteristic odors occur in nature, including vanillin from vanilla beans and cinnamaldehyde from cinnamon.

McGraw-Hill Education/Jill Braaten, photographer

Many steroid hormones contain a carbonyl along with other functional groups. Cortisone and prednisone are two anti-inflammatory steroids with closely related structures. Cortisone is secreted by the body's adrenal gland, whereas prednisone is a synthetic analogue used in the treatment of inflammatory diseases such as arthritis and asthma.

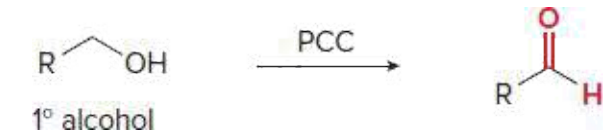
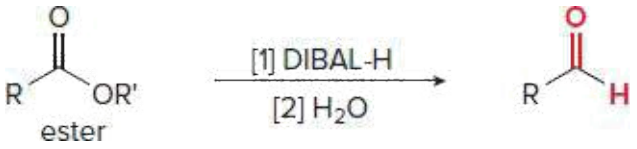
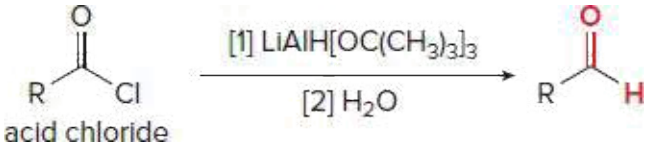
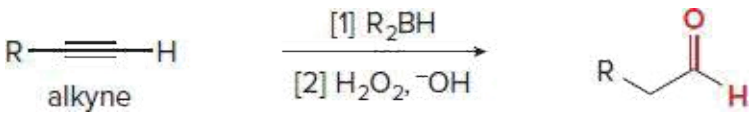


18.5 Preparation of Aldehydes and Ketones

Aldehydes and ketones can be prepared by a variety of methods. Because these reactions are needed for many multistep syntheses, Section 18.5 briefly summarizes earlier reactions that synthesize an aldehyde or ketone.

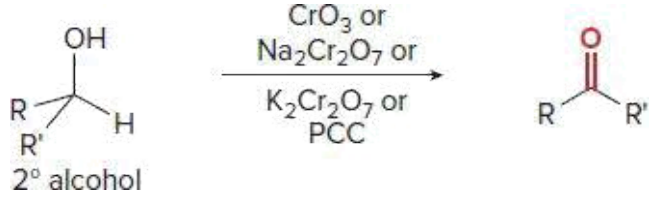
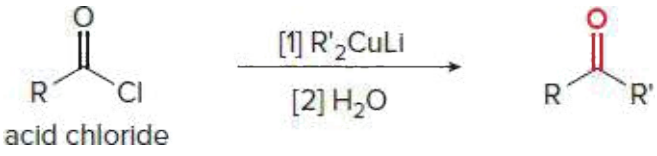
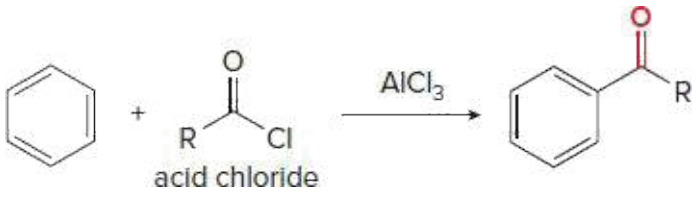
Aldehydes are prepared from 1° alcohols, esters, acid chlorides, and alkynes (Table 18.4).

Table 18.4 Common Methods to Synthesize Aldehydes

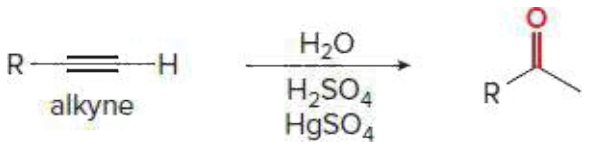
Method	Reaction
[1] Oxidation of 1° alcohols with PCC (Section 12.12B)	
[2] Reduction of esters (Section 17.7A)	
[3] Reduction of acid chlorides (Section 17.7A)	
[4] Hydroboration–oxidation of an alkyne (Section 11.10)	

Ketones are prepared from 2° alcohols, acid chlorides, and alkynes (Table 18.5).

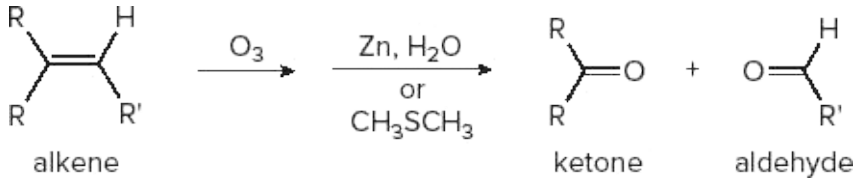
Table 18.5 Common Methods to Synthesize Ketones

Method	Reaction
[1] Oxidation of 2° alcohols with Cr^{6+} reagents (Section 12.12A)	
[2] Reaction of acid chlorides with organocuprates (Section 17.13)	
[3] Friedel–Crafts acylation (Section 16.5)	

[4] Hydration of an alkyne (Section 11.9)

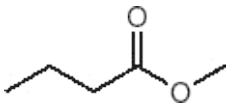


Aldehydes and ketones are also both obtained as products of the oxidative cleavage of alkenes (Section 12.10).

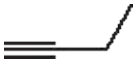


Problem 18.10

What reagents are needed to convert each compound to butanal ($CH_3CH_2CH_2CHO$)?

a. 

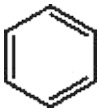
b.

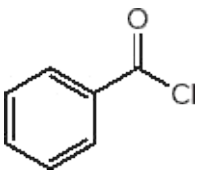
c. 

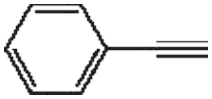
d.

Problem 18.11

What reagents are needed to convert each compound to acetophenone ($C_6H_5COCH_3$)?

a. 

b. 

c. 

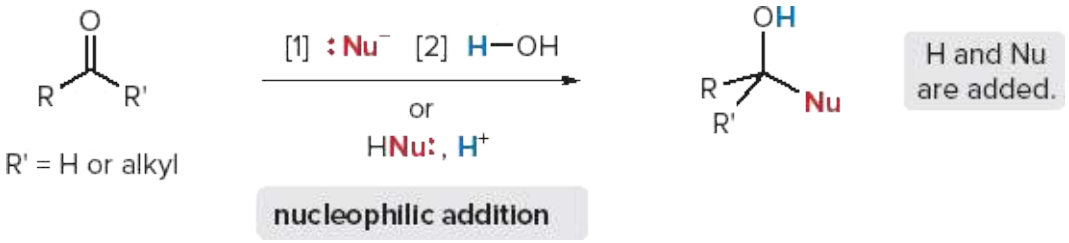
18.6 Reactions of Aldehydes and Ketones–General

Considerations

Let's begin our discussion of carbonyl reactions by looking at the two general kinds of reactions that aldehydes and ketones undergo.

[1] Reaction at the carbonyl carbon

Recall from Chapter 17 that the uncrowded, electrophilic carbonyl carbon makes aldehydes and ketones susceptible to nucleophilic addition reactions.

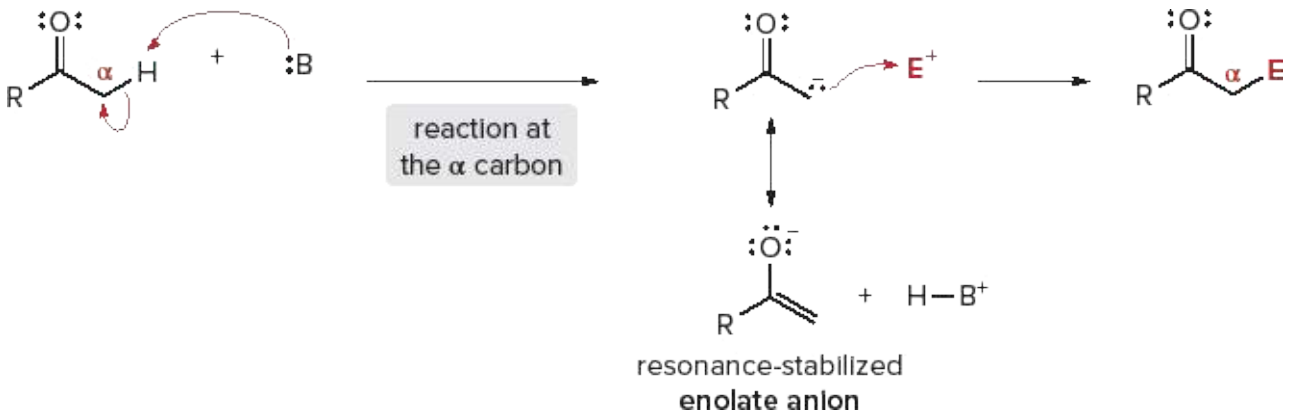


The elements of H and Nu are added to the carbonyl group. In Chapter 17, you learned about this reaction with hydride ($H:^-$) and carbanions ($R:^-$) as nucleophiles. In Chapter 18, we will discuss similar reactions with other nucleophiles.

[2] Reaction at the a carbon

A second general reaction of aldehydes and ketones involves reaction at the a carbon. A C–H bond on the a carbon to a carbonyl group is more acidic than many other C–H bonds, because reaction with base forms a resonance-stabilized enolate anion.

- **Enolates are nucleophiles, so they react with electrophiles (E^+) to form new bonds on the a carbon.**



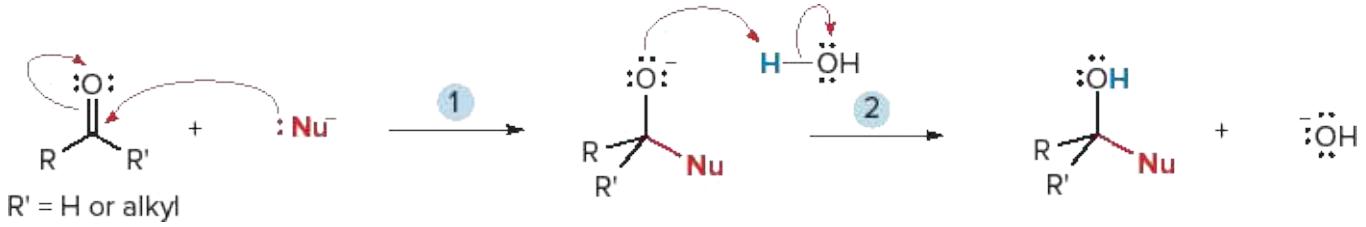
Chapters 21 and 22 are devoted to reactions at the a carbon to a carbonyl group.

- **Aldehydes and ketones react with nucleophiles at the carbonyl carbon.**
- **Aldehydes and ketones form enolates that react with electrophiles at the a carbon.**

18.6A The General Mechanism of Nucleophilic Addition

Two general mechanisms are usually drawn for nucleophilic addition, depending on the nucleophile (negatively charged versus neutral) and the presence or absence of an acid catalyst. With negatively charged nucleophiles, nucleophilic addition follows the two-step process first discussed in Chapter 17—nucleophilic attack followed by protonation, as shown in Mechanism 18.1.

Mechanism 18.1 General Mechanism–Nucleophilic Addition



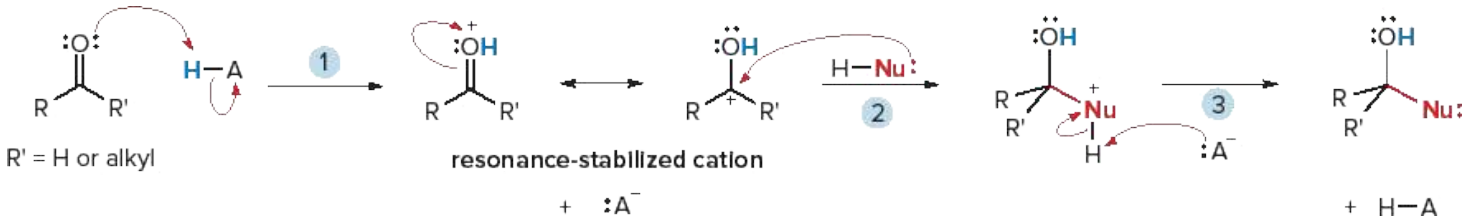
1 **The nucleophile attacks the electrophilic carbonyl. The π bond is broken, moving an electron pair out on oxygen and forming an sp^3 hybridized carbon.**

2 **Protonation of the negatively charged oxygen by H_2O forms the addition product.**

In this mechanism, nucleophilic attack *precedes* protonation. This process occurs with strong neutral or negatively charged nucleophiles.

With some neutral nucleophiles, however, nucleophilic addition does not occur unless an acid catalyst is added. The general mechanism for this reaction consists of three steps (not two), but the same product results because H and Nu add across the carbonyl π bond. In this mechanism, protonation *precedes* nucleophilic attack. Mechanism 18.2 is shown with the neutral nucleophile H–Nu: and a general acid H–A.

Mechanism 18.2 General Mechanism–Acid-Catalyzed Nucleophilic Addition

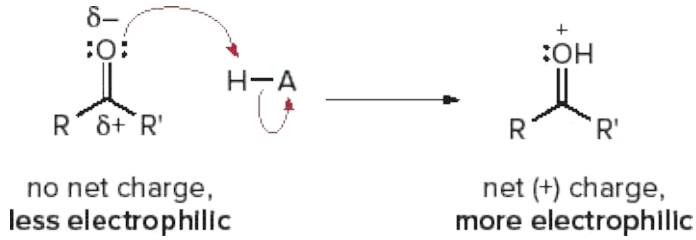


1 **Protonation of the carbonyl oxygen forms a resonance-stabilized**

cation.

2 – 3 Nucleophilic attack and deprotonation form the neutral addition product. The overall result is addition of H and Nu to the carbonyl group.

The effect of protonation is to convert a neutral carbonyl group to one having a net positive charge. This protonated carbonyl group is much more electrophilic, and much more susceptible to attack by a nucleophile. This step is unnecessary with strong nucleophiles like hydride ($H:^-$) that were used in Chapter 17. With weaker nucleophiles, however, nucleophilic attack does not occur unless the carbonyl group is first protonated.



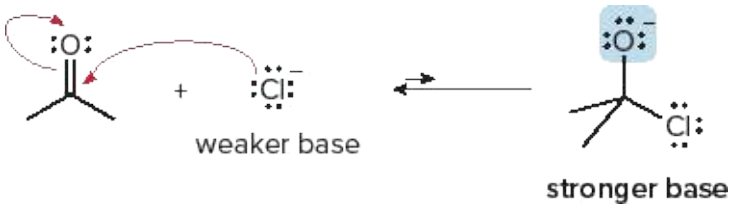
This step is a specific example of a general phenomenon:

- **Any reaction involving a carbonyl group and a strong acid begins with the same first step—protonation of the carbonyl oxygen.**

18.6B The Nucleophile

What nucleophiles add to carbonyl groups? This cannot be predicted solely on the trends in nucleophilicity learned in Chapter 7. Only *some* of the nucleophiles that react well in nucleophilic substitution at sp^3 hybridized carbons give reasonable yields of nucleophilic addition products.

Cl^-, Br^-, and I^- are good nucleophiles in substitution reactions at sp^3 hybridized carbons, but they are *ineffective* nucleophiles in addition. Addition of Cl^- to a carbonyl group, for example, would cleave the C–O π bond, forming an alkoxide. Because Cl^- is a much *weaker* base than the alkoxide formed, equilibrium favors the starting materials (the weaker base, Cl^-), *not* the addition product.



The situation is further complicated because some of the initial nucleophilic addition adducts are unstable and undergo elimination to form a stable product. For example, amines (RNH_2) add to carbonyl groups in the presence of mild acid to form unstable carbinolamines, which readily lose water to form imines. This addition–elimination sequence replaces a C=O by a C=N. The details of this process are discussed in Section 18.10A.

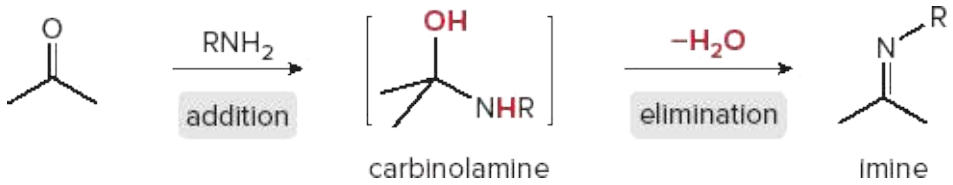


Figure 18.4 lists nucleophiles that add to a carbonyl group, as well as the products obtained from nucleophilic addition using cyclohexanone as a representative ketone. These reactions are discussed in the remaining sections of Chapter 18. In cases in which the initial addition adduct is unstable, it is enclosed within brackets, followed by the final product.

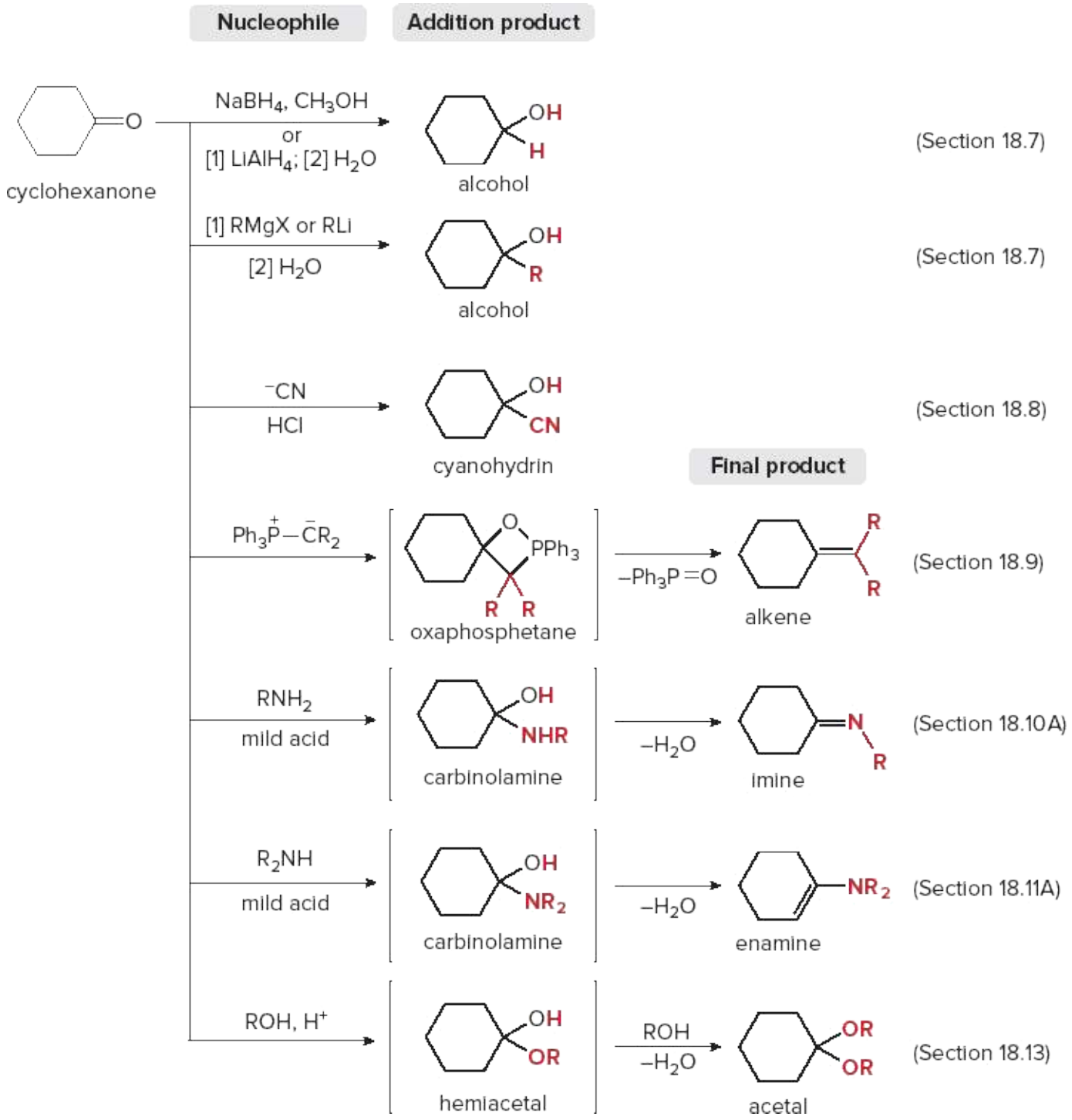


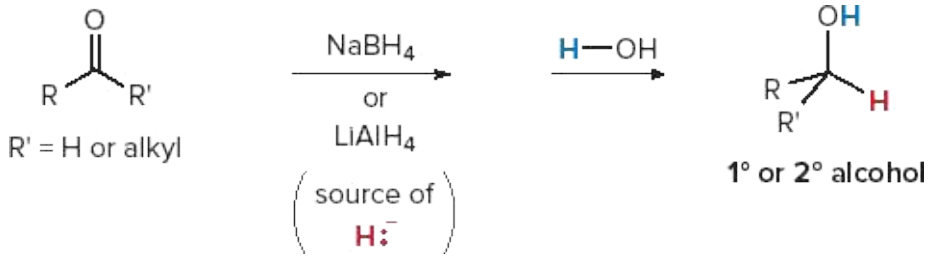
Figure 18.4 **Specific examples of nucleophilic addition**

18.7 Nucleophilic Addition of H and R —A Review

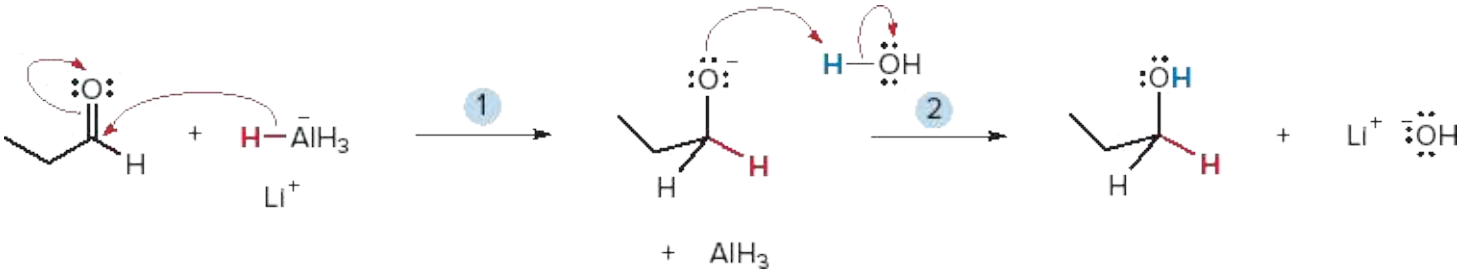
We begin our study of nucleophilic additions to aldehydes and ketones by briefly reviewing nucleophilic addition of hydride and carbanions, two reactions examined in Sections 17.4 and 17.10, respectively.

Treatment of an aldehyde or ketone with either $NaBH_4$ or $LiAlH_4$ followed by protonation forms a 1° or 2° alcohol. $NaBH_4$ and $LiAlH_4$ serve as a source of hydride, $H:^-$—the nucleophile—and the reaction results in addition of the elements of

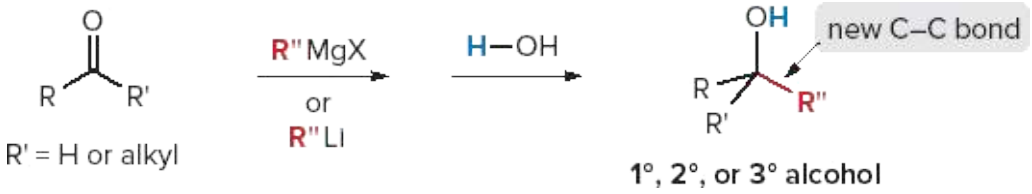
H_2 across the C–O π bond. Addition of H_2 reduces the carbonyl group to an alcohol.



Hydride reduction of aldehydes and ketones occurs via the two-step mechanism of nucleophilic addition—that is, nucleophilic attack of H:– followed by protonation—shown in Section 17.4B.

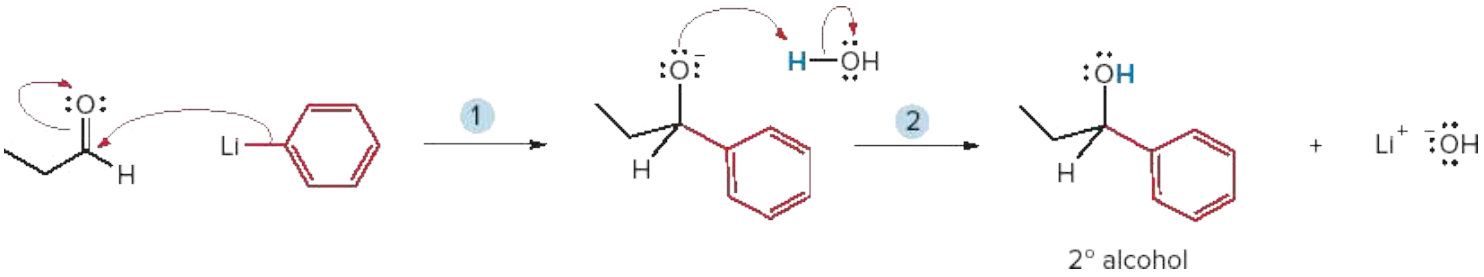


Treatment of an aldehyde or ketone with either an organolithium (R″Li) or Grignard reagent (R″MgX) followed by water forms a 1°, 2°, or 3° alcohol containing a new carbon–carbon bond. R″Li and R″MgX serve as a source of a carbanion (R″)−—the nucleophile—and the reaction results in addition of the elements of R″ and H across the C–O π bond.



The stereochemistry of hydride reduction and Grignard addition was discussed in Sections 17.5 and 17.10B, respectively.

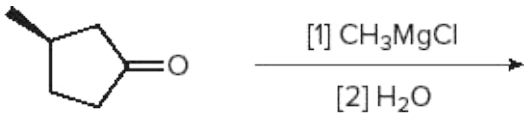
The nucleophilic addition of carbanions to aldehydes and ketones occurs via the two-step mechanism of nucleophilic addition—that is, nucleophilic attack of (R″)– followed by protonation—shown in Section 17.10A.



In both reactions, the nucleophile—either hydride or a carbanion—attacks the trigonal planar sp^2 hybridized carbonyl from both sides, so that when a new stereogenic center is formed, a mixture of stereoisomers results, as shown in Sample Problem 18.3.

Sample Problem 18.3 Drawing the Products with Stereochemistry in Nucleophilic Addition

Draw the products (including the stereochemistry) formed in the following reaction.



(*R*)-3-methylcyclopentanone

Solution

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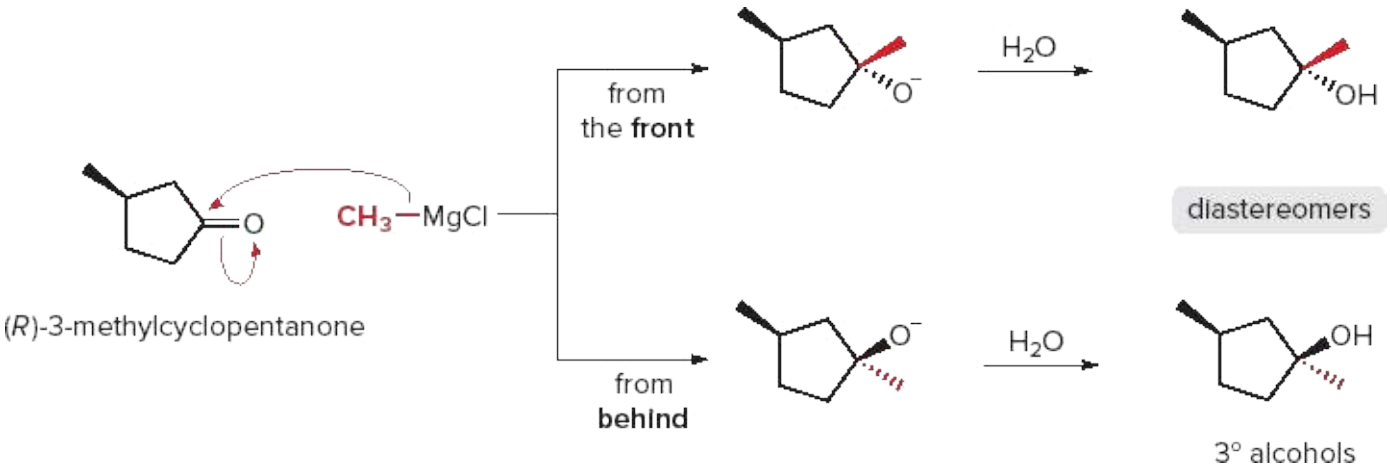
The Grignard reagent adds CH_3^- from both sides of the trigonal planar carbonyl group, yielding a mixture of 3° alcohols after protonation with water. In this example, the starting ketone and both alcohol products are chiral. The two products, which contain two stereogenic centers, are stereoisomers but not mirror images–that is, they are diastereomers.

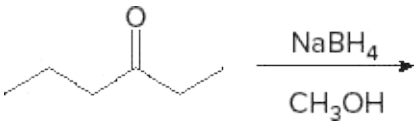


(*R*)-3-methylcyclopentanone

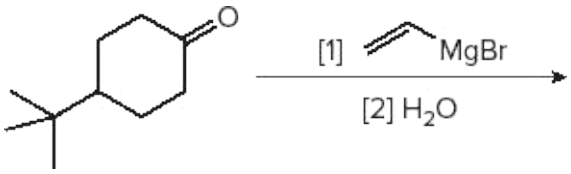
Problem 18.12

Draw the products of each reaction. Include all stereoisomers formed.

a.



b.

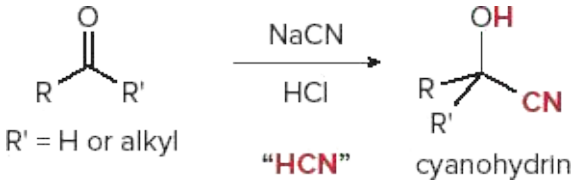


More Practice:

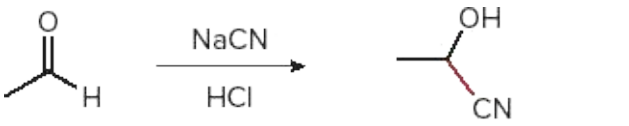
Try Problems 18.37b [1], [2]; 18.45c.

18.8 Nucleophilic Addition of ⁻CN

Treatment of an aldehyde or ketone with NaCN and a strong acid such as HCl adds the elements of HCN across the carbon–oxygen π bond, forming a cyanohydrin.



This reaction adds one carbon to the aldehyde or ketone, forming a new carbon–carbon bond.

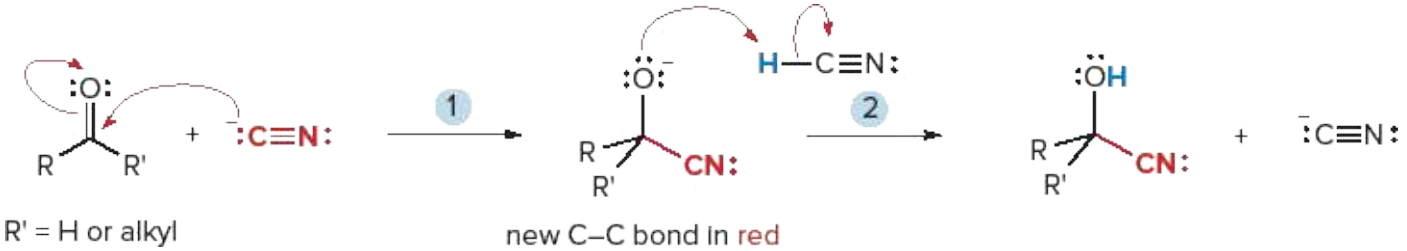


acetaldehyde cyanohydrin
new C–C bond in red

18.8A The Mechanism

The mechanism of cyanohydrin formation involves the usual two steps of nucleophilic addition: nucleophilic attack followed by protonation as shown in Mechanism 18.3.

Mechanism 18.3 Nucleophilic Addition of ⁻CN–Cyanohydrin Formation



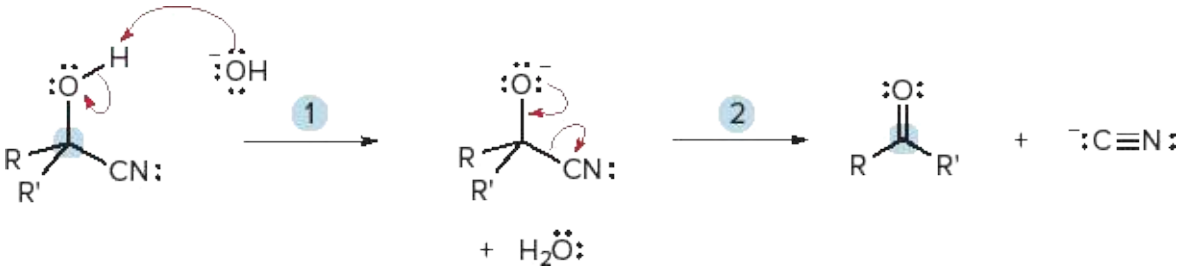
R' = H or alkyl

new C–C bond in red

1. **Nucleophilic attack of CN forms a new carbon–carbon bond with cleavage of the C–O π bond.**
2. **Protonation of the negatively charged oxygen by HCN forms the addition product. The HCN used in this step is formed by the acid–base reaction of $^{-}$CN with the strong acid, HCl.**

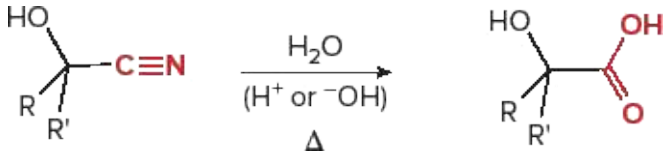
This reaction does not occur with HCN alone. The cyanide anion makes addition possible because it is a strong nucleophile that attacks the carbonyl group.

Cyanohydrins can be reconverted to carbonyl compounds by treatment with base. This process is just the reverse of the addition of HCN: deprotonation followed by elimination of $^{-}$CN.



Note the difference between two similar terms. Hydration results in *adding* water to a compound. Hydrolysis results in *cleaving bonds* with water.

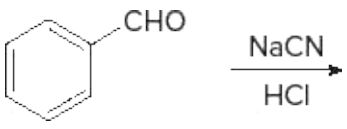
The cyano group (CN) of a cyanohydrin is readily hydrolyzed to a carboxy group (COOH) by heating with aqueous acid or base. Hydrolysis replaces the three C–N bonds by three C–O bonds.



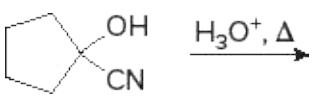
Problem 18.13

Draw the products of each reaction.

a.

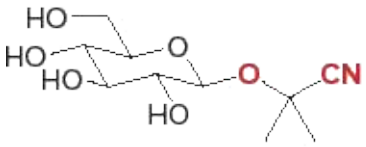


b.

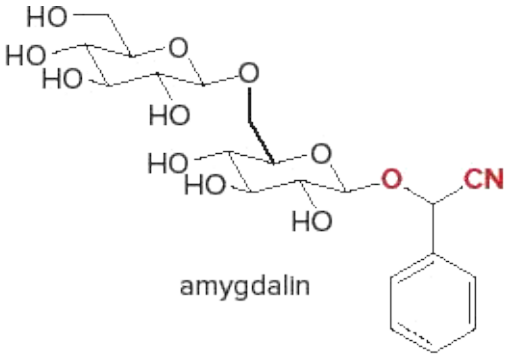


18.8B Application: Naturally Occurring Cyanohydrin Derivatives

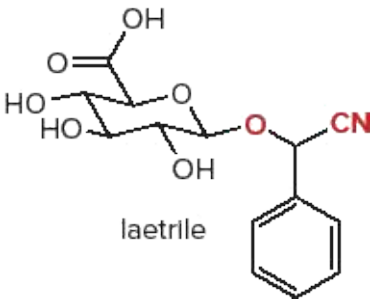
Although the cyanohydrin is an uncommon functional group, linamarin and amygdalin are two naturally occurring cyanohydrin derivatives. Both contain a carbon atom bonded to both an oxygen atom and a cyano group, analogous to a cyanohydrin.



linamarin



amygdalin



laetrile

Peach and apricot pits are a natural source of the cyanohydrin derivative amygdalin. ***©McGraw-Hill Education/Jill Braaten, photographer***

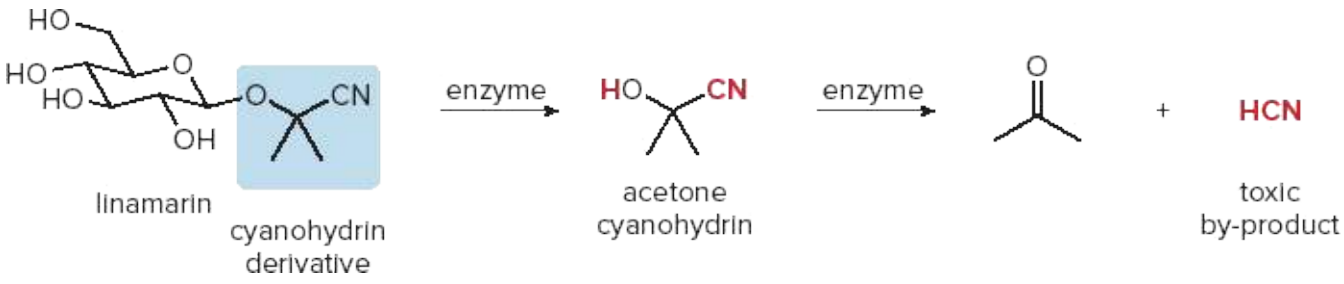
Cassava is a widely grown root crop, first introduced to Africa by Portuguese traders from Brazil in the sixteenth century. The peeled root is eaten after boiling or roasting. If the root is eaten without processing, illness and even death can result from high levels of HCN.

©Daniel C. Smith

Linamarin is isolated from cassava, a woody shrub grown as a root crop in the humid tropical regions of South America and Africa. Amygdalin is present in the seeds and

pits of apricots, peaches, and wild cherries. Amygdalin and the related synthetic compound laetrile were once touted as anticancer drugs, although their effectiveness is unproven.

Linamarin, amygdalin, and laetrile are toxic compounds because they are metabolized to cyanohydrins, which are hydrolyzed to carbonyl compounds and toxic HCN gas, a cellular poison with a characteristic almond odor. This second step is merely the reconversion of a cyanohydrin to a carbonyl compound, a process that occurs with base in reactions run in the laboratory (Section 18.8A). If cassava root is processed with care, linamarin is enzymatically metabolized by this reaction sequence and the toxic HCN is released before the root is ingested, making it safe to eat.



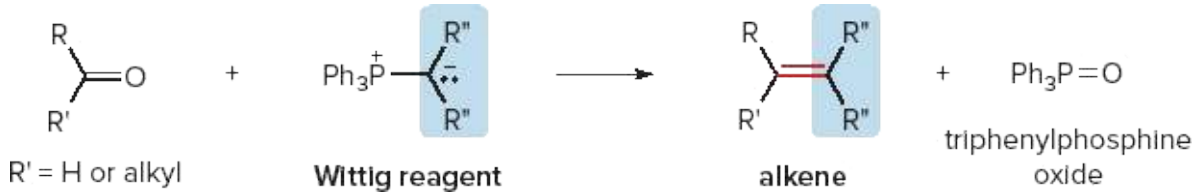
Problem 18.14

What cyanohydrin and carbonyl compound are formed when amygdalin is metabolized in a similar manner to linamarin?

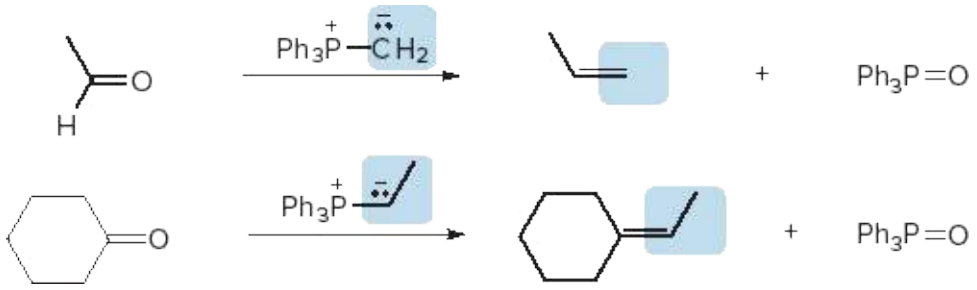
18.9 The Wittig Reaction

The additions of H^-, R^-, and ^-CN all involve the same two steps—nucleophilic attack followed by protonation. Other examples of nucleophilic addition in Chapter 18 are somewhat different. Although they still involve attack of a nucleophile, the initial addition adduct is converted to another product by one or more reactions.

The first reaction in this category is the Wittig reaction, named for German chemist Georg Wittig, who was awarded the Nobel Prize in Chemistry in 1979 for its discovery. The Wittig reaction uses a carbon nucleophile, the Wittig reagent, to form alkenes. When a carbonyl compound is treated with a Wittig reagent, the carbonyl oxygen atom is replaced by the negatively charged alkyl group bonded to the phosphorus—that is, the C=O is converted to a C=C.

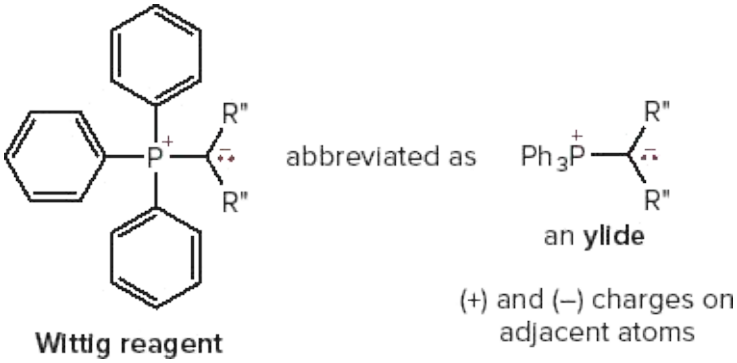


- **A Wittig reaction forms two new carbon–carbon bonds–one new σ bond and one new π bond–as well as a phosphorus by-product, $Ph_3P{=}O$ (triphenylphosphine oxide).**



18.9A The Wittig Reagent

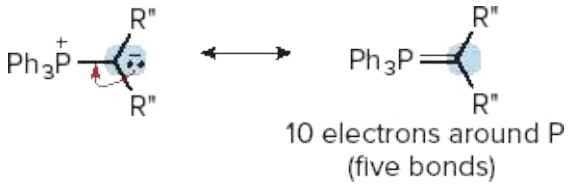
A Wittig reagent is an organophosphorus reagent—a reagent that contains a carbon–phosphorus bond. A typical Wittig reagent has a phosphorus atom bonded to three phenyl groups, plus another alkyl group that bears a negative charge.



Phosphorus ylides are also called phosphoranes.

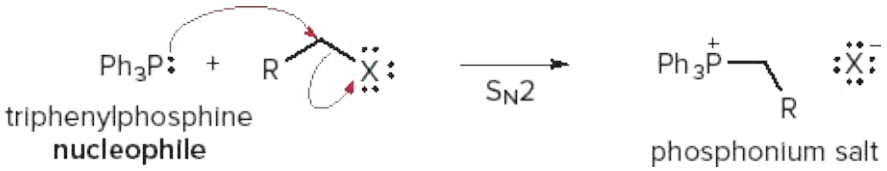
A Wittig reagent is an *ylide*, a species that contains two oppositely charged atoms bonded to each other, and both atoms have octets. In a Wittig reagent, a negatively charged carbon atom is bonded to a positively charged phosphorus atom.

Because phosphorus is a third-row element, it can be surrounded by more than eight electrons. As a result, a second resonance structure can be drawn that places a double bond between carbon and phosphorus. Regardless of which resonance structure is drawn, a Wittig reagent has no net charge. In one resonance structure, though, the carbon atom bonded to phosphorus (labeled in blue) bears a net negative charge, so it is *nucleophilic*.



Wittig reagents are synthesized by a two-step procedure.

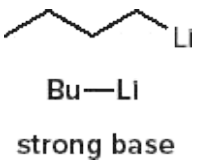
Step [1] **S_N2 reaction of triphenylphosphine with an alkyl halide forms a [phosphonium salt](#).**



Because phosphorus is located below nitrogen in the periodic table, a neutral phosphorus atom with three bonds also has a lone pair of electrons.

Triphenylphosphine (Ph_3P:), which contains a lone pair of electrons on P, is the nucleophile. Because the reaction follows an S_N2 mechanism, it works best with unhindered CH_3X and 1° alkyl halides (RCH_2X). Secondary alkyl halides (R_2CHX) can also be used, although yields are often lower.

Step [2] **Deprotonation of the phosphonium salt with a strong base (:B) forms the ylide.**



[Section 17.9C](#) discussed the reaction of organometallic reagents as strong bases.

Because removal of a proton from a carbon bonded to phosphorus generates a resonance-stabilized carbanion (the ylide), this proton is somewhat more acidic than other protons on an alkyl group in the phosphonium salt. Very strong bases are still needed, though, to favor the products of this acid–base reaction. Common bases used for this reaction are the organolithium reagents such as butyllithium, $CH_3CH_2CH_2CH_2Li$, abbreviated as BuLi.

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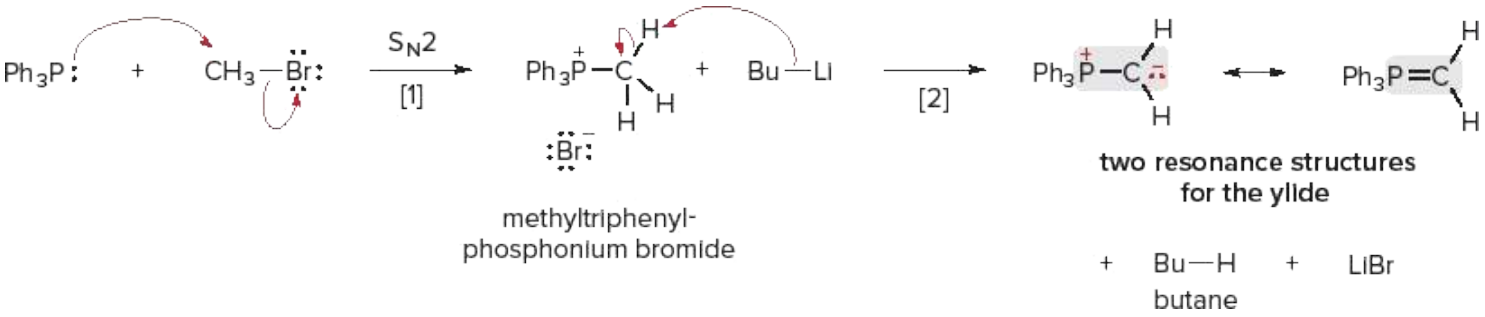
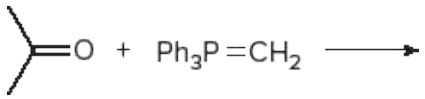
To synthesize the Wittig reagent, $Ph_3P{=}CH_2$, use these two steps:

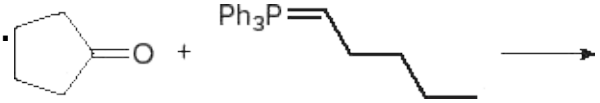


- Step [1] Form the phosphonium salt by S_N2 reaction of Ph_3P: and CH_3Br.
- Step [2] Form the ylide by removal of a proton using BuLi as a strong base.

Problem 18.15

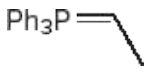
Draw the products of the following Wittig reactions.

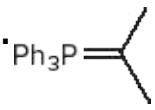
a. 

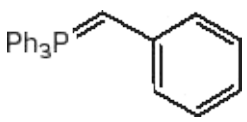
b. 

Problem 18.16

Outline a synthesis of each Wittig reagent from Ph_3P and an alkyl halide.

a. 

b. 

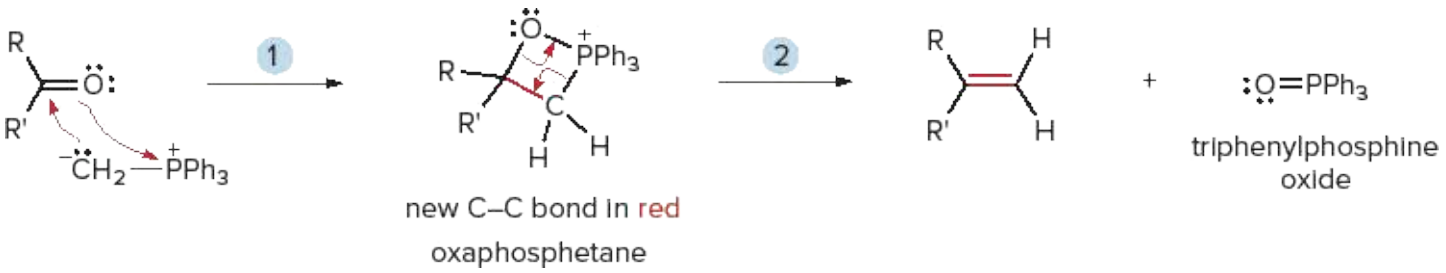
c. 

18.9B Mechanism of the Wittig Reaction

The currently accepted mechanism of the Wittig reaction involves two steps. Like other

nucleophiles, the Wittig reagent attacks an electrophilic carbonyl carbon, but then the initial addition adduct undergoes elimination to form an alkene. Mechanism 18.4 is drawn using $Ph_3P{=}CH_2$.

Mechanism 18.4 The Wittig Reaction

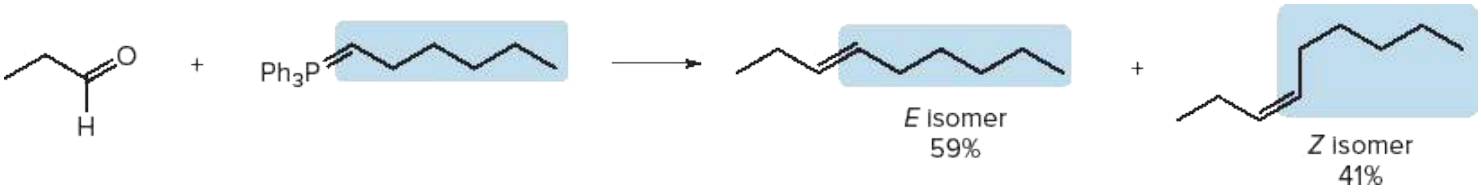


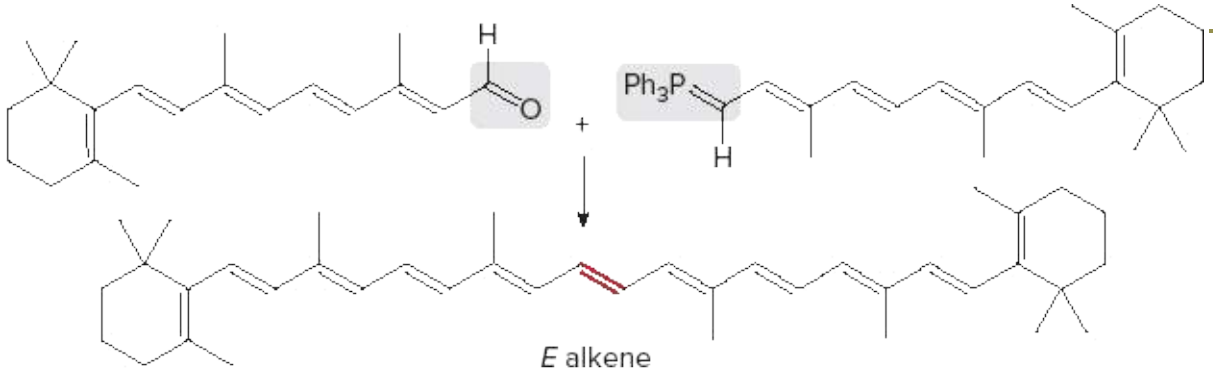
new C–C bond in red

oxaphosphetane

1. **The negatively charged carbon of the ylide attacks the carbonyl carbon as the carbonyl oxygen attacks the positively charged P atom. This step forms two bonds and generates a four-membered ring called an oxaphosphetane.**
2. **Elimination of triphenylphosphine oxide forms two new π bonds. The formation of the strong P=O provides the driving force for the Wittig reaction.**

One limitation of the Wittig reaction is that a mixture of alkene stereoisomers sometimes forms. For example, reaction of propanal (CH_3CH_2CHO) with a Wittig reagent forms the mixture of *E* and *Z* isomers shown.





β-carotene
orange pigment found in carrots
(vitamin A precursor)

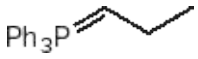
- The more stable *E* alkene is the major product in this Wittig reaction.

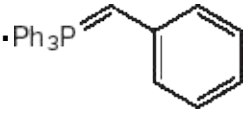
Figure 18.5 **A Wittig reaction used to synthesize β-carotene**

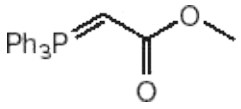
Because the Wittig reaction forms two carbon–carbon bonds in a single reaction, it has been used to synthesize many natural products, including β-carotene, shown in Figure 18.5.

Problem 18.17

Draw the products (including stereoisomers) formed when benzaldehyde (C_6H_5CHO) is treated with each Wittig reagent.

a. 

b. 

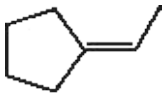
c. 

18.9C Retrosynthetic Analysis

To use the Wittig reaction in synthesis, you must be able to determine what carbonyl compound and Wittig reagent are needed to prepare a given compound—that is, you must work backwards, in the retrosynthetic direction. There can be two different Wittig routes to a given alkene, but one is often preferred on steric grounds.

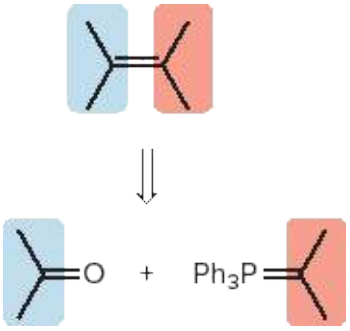
How To Determine the Starting Materials for a Wittig Reaction Using Retrosynthetic Analysis

Example What starting materials are needed to synthesize alkene X by a Wittig reaction?



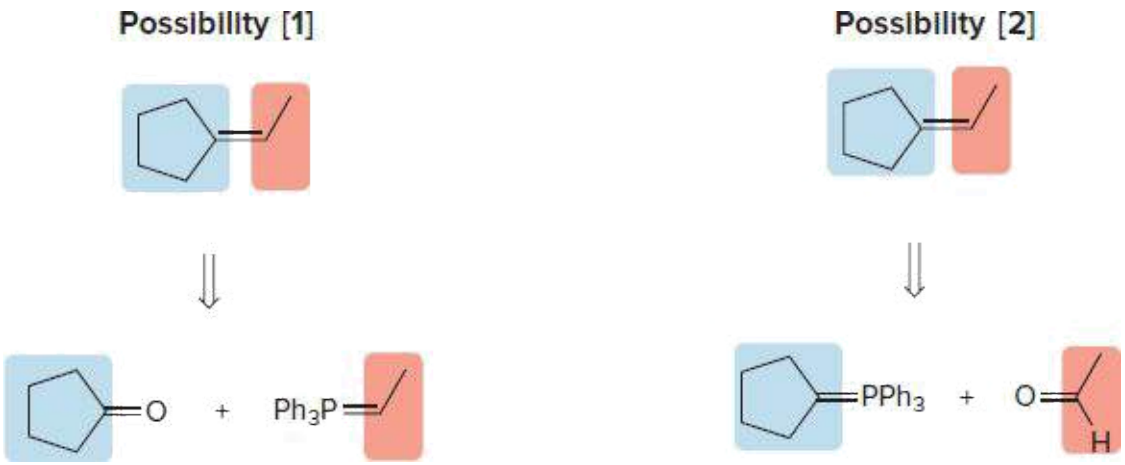
X

Step [1] Cleave the carbon–carbon double bond into two components.



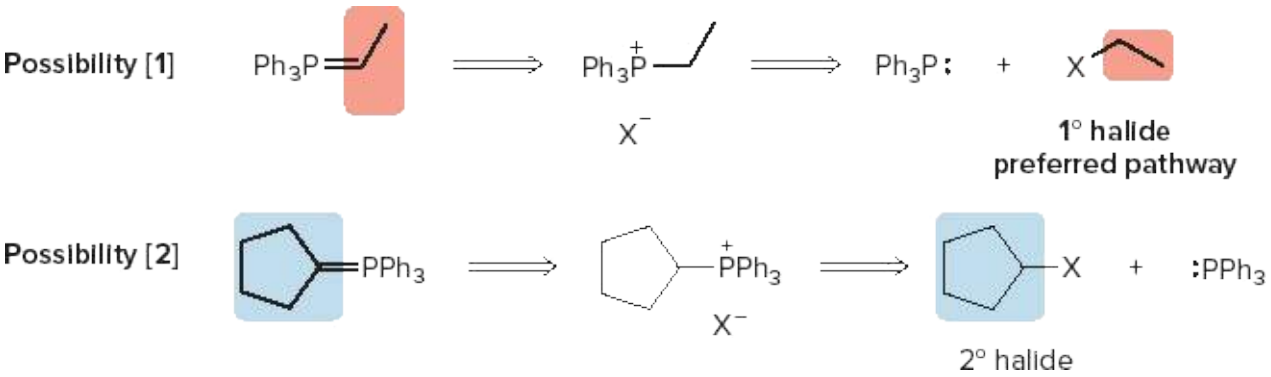
- **Part of the molecule becomes the carbonyl component, and the other part becomes the Wittig reagent.**

There are usually two routes to a given alkene using a Wittig reaction:



Step [2] **Compare the Wittig reagents. The preferred pathway uses a Wittig reagent derived from an unhindered alkyl halide–CH_3X or RCH_2X.**

Determine what alkyl halide is needed to prepare each Wittig reagent:



Because the synthesis of the Wittig reagent begins with an S_N2 reaction, the preferred pathway begins with an unhindered methyl halide or 1° alkyl halide. In this example, retrosynthetic analysis of both Wittig reagents indicates that only one of them ($Ph_3P{=}CHCH_3$)

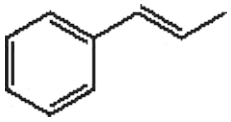
can be synthesized from a 1° alkyl halide, making Possibility [1] the preferred pathway.

Problem 18.18

What starting materials are needed to prepare each alkene by a Wittig reaction? When there are two possible routes, indicate which route, if any, is preferred.

a.

b.

c. 

18.9D Comparing Methods of Alkene Synthesis

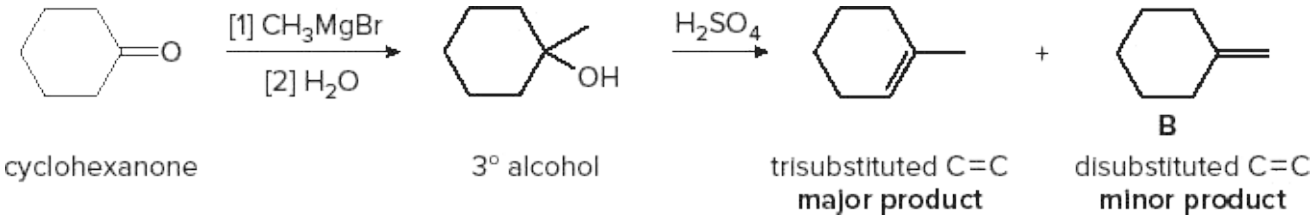
An advantage in using the Wittig reaction over other elimination methods to synthesize alkenes is that you always know the location of the double bond. Whereas other methods of alkene synthesis often give a mixture of constitutional isomers, the Wittig reaction always gives a *single* constitutional isomer.

For example, two methods can be used to convert cyclohexanone into alkene B (methylene-cyclohexane): a two-step method consisting of Grignard addition followed by dehydration, or a one-step Wittig reaction.

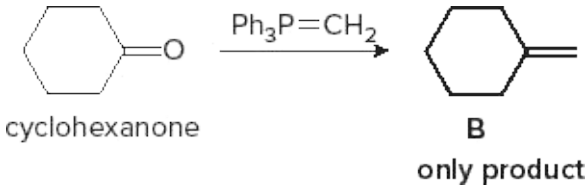
cyclohexanone B

Recall from Section 9.8 that the major product formed in acid-catalyzed dehydration of an alcohol is the more substituted alkene.

In a two-step method, treatment of cyclohexanone with CH_3MgBr forms a 3° alcohol after protonation. Dehydration of the alcohol with H_2SO_4 forms a mixture of alkenes, in which the desired disubstituted alkene is the minor product.



By contrast, reaction of cyclohexanone with $Ph_3P{=}CH_2$ affords the desired alkene as the only product. The newly formed double bond always joins the carbonyl carbon with the negatively charged carbon of the Wittig reagent. In other words, the position of the double bond is always unambiguous in the Wittig reaction. This makes the Wittig reaction an especially attractive method for preparing many alkenes.

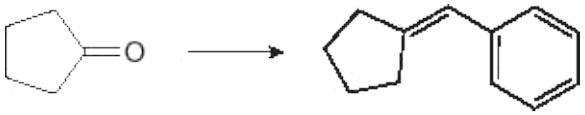


Problem 18.19

Show two methods to synthesize each alkene: a one-step method using a Wittig reagent, and a two-step method that forms a carbon–carbon bond with an organometallic reagent in one of the steps.

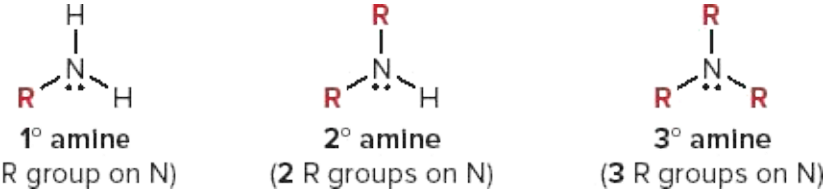
a.

b.



18.10 Addition of 1° Amines

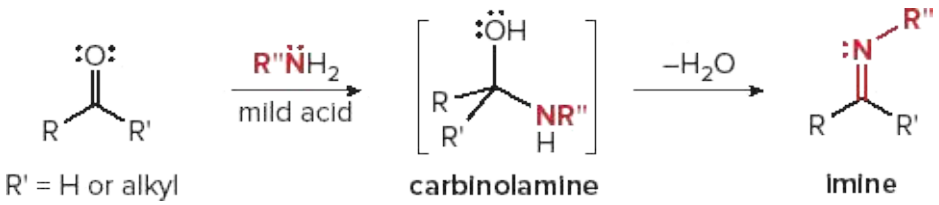
We now move on to the reaction of aldehydes and ketones with nitrogen and oxygen heteroatoms. Amines are organic nitrogen compounds that contain a nonbonded electron pair on the N atom. As we learned in Section 3.2, amines are classified as 1°, 2°, or 3° by the number of alkyl groups bonded to the *nitrogen* atom.



Both 1° and 2° amines react with aldehydes and ketones. We begin by examining the reaction of aldehydes and ketones with 1° amines.

18.10A Formation of Imines

Treatment of an aldehyde or ketone with a 1° amine affords an imine (also called a Schiff base). Nucleophilic attack of the 1° amine on the carbonyl group forms an unstable carbinolamine, which loses water to form an imine. The overall reaction results in replacement of C=O by C=NR.



Because the N atom of an imine is surrounded by three groups (two atoms and a lone pair), it is sp^2 hybridized, making the C–N–R" bond angle ~120° (*not* 180°). Imine formation is fastest when the reaction medium is weakly acidic.

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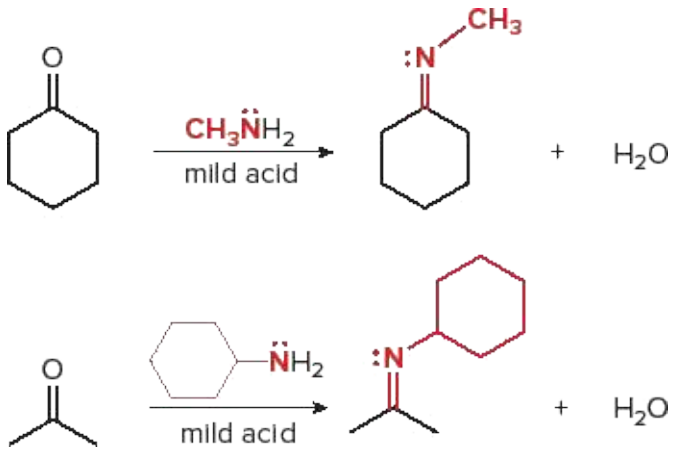
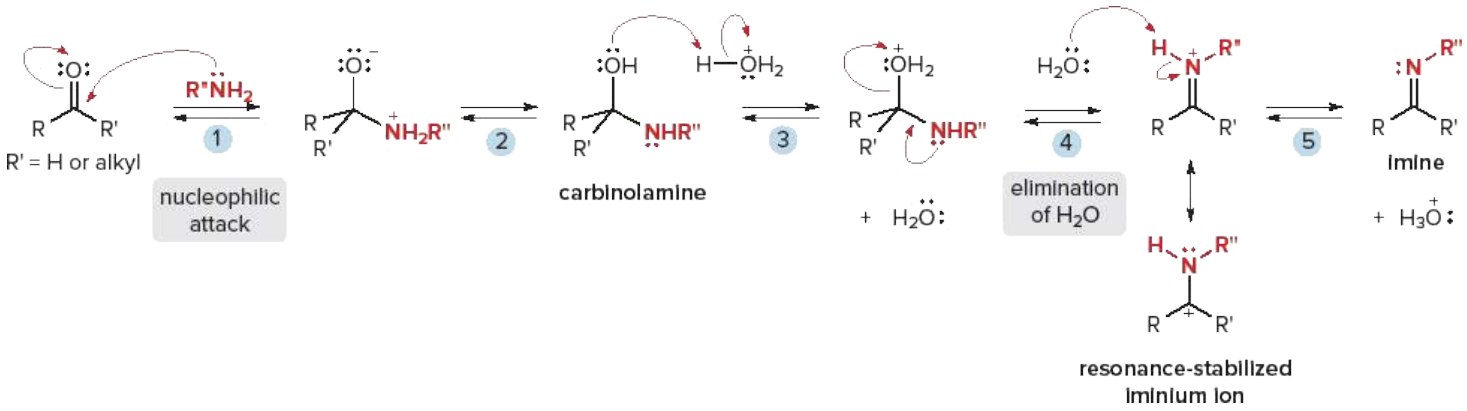


The mechanism of imine formation (Mechanism 18.5) can be divided into two distinct parts: nucleophilic addition of the 1° amine (Steps [1] and [2]), followed by elimination of H_2O (Steps [3]–[5]). Each step involves a reversible equilibrium, so that the reaction is driven to completion by removing H_2O.

Imine formation is most rapid at pH 4–5. Mild acid is needed for protonation of the hydroxy group in Step [3] to form a good leaving group. Under strongly acidic conditions, the reaction rate decreases because the amine nucleophile is protonated. With no free electron pair, it is no longer a nucleophile, and so nucleophilic addition cannot occur.

Mechanism 18.5 Imine Formation from an Aldehyde or a Ketone



1 – **2** **Nucleophilic attack of the amine followed by proton transfer forms the carbinolamine.**

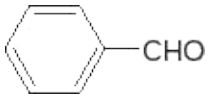
3 **Protonation of the OH group forms a good leaving group.**

4 **Loss of H_2O forms a resonance-stabilized [iminium ion](#).**

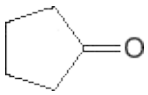
5 **Loss of a proton forms the imine.**

Problem 18.20

Draw the product formed when $CH_3CH_2CH_2CH_2NH_2$ reacts with each carbonyl compound in the presence of mild acid.

a. 

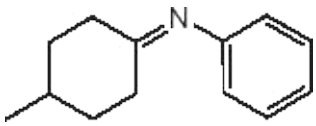
b.

c. 

Problem 18.21

What 1° amine and carbonyl compound are needed to prepare each imine?

a.

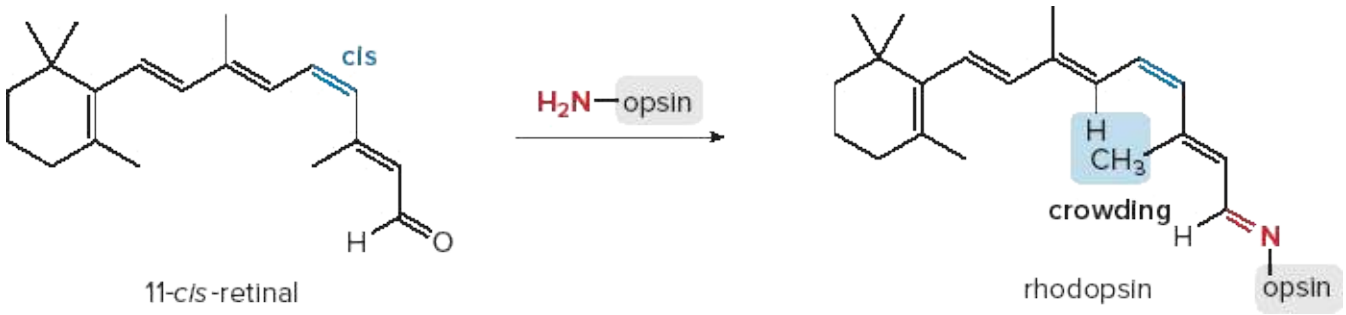
b. 

18.10B Application: Retinal, Rhodopsin, and the Chemistry of Vision

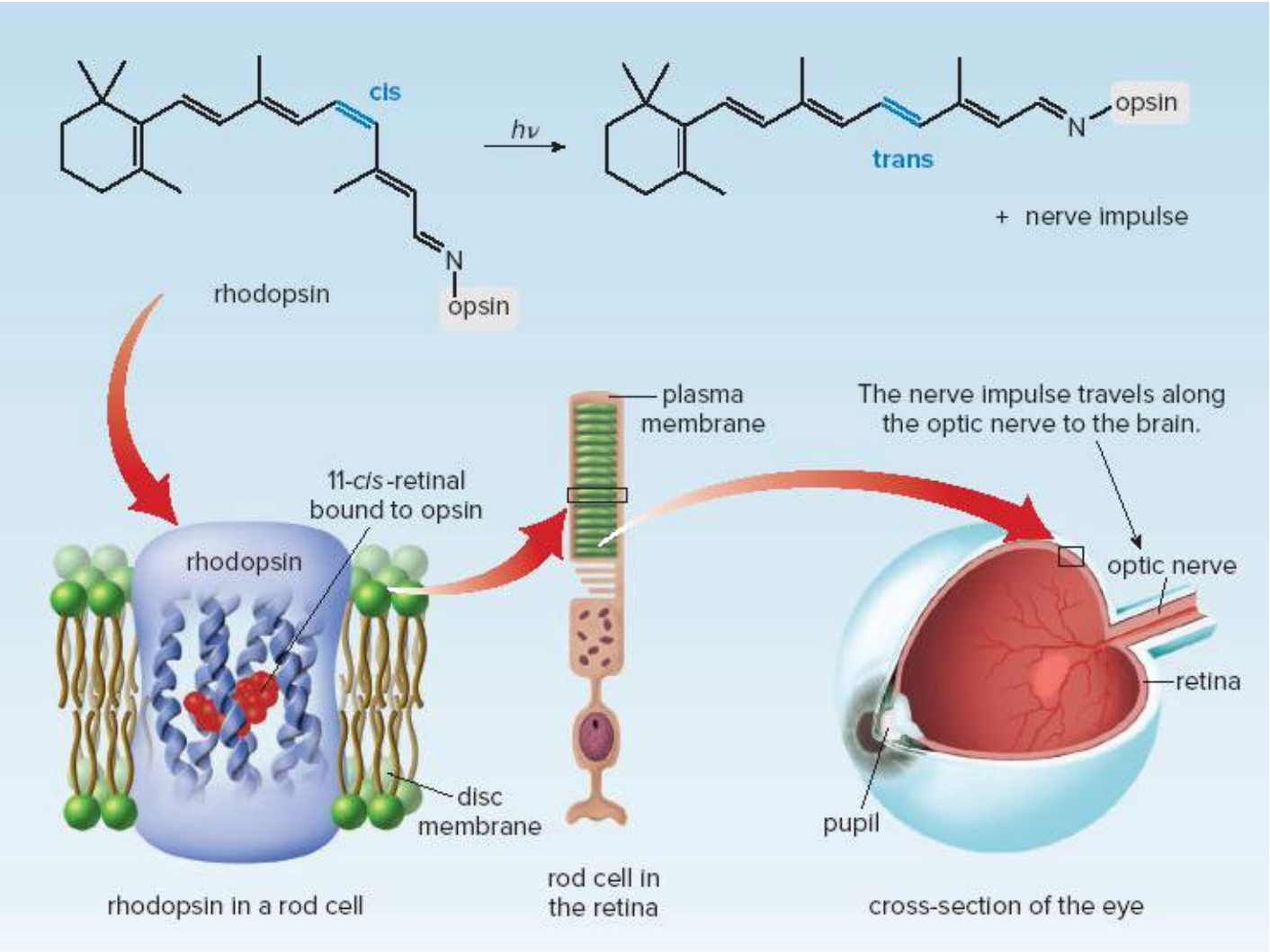
11-*cis*-Retinal is the light-sensitive aldehyde that plays a key role in the chemistry of vision for all vertebrates, arthropods, and mollusks. ***©©Daniel C. Smith***

The central role of rhodopsin in the visual process was delineated by Nobel Laureate George Wald of Harvard University.

Many imines play vital roles in biological systems. A key molecule in the chemistry of vision is the highly conjugated imine rhodopsin, which is synthesized in the rod cells of the eye from 11-*cis*-retinal and a 1° amine in the protein opsin.



The complex process of vision centers around this imine derived from retinal (Figure 18.6). The 11-cis double bond in rhodopsin creates crowding in the rather rigid side chain. When light strikes the rod cells of the retina, it is absorbed by the conjugated double bonds of rhodopsin, and the 11-cis double bond is isomerized to the 11-trans arrangement. This isomerization is accompanied by a drastic change in shape in the protein, altering the concentration of Ca^{2+} ions moving across the cell membrane, and sending a nerve impulse to the brain, which is then processed into a visual image.



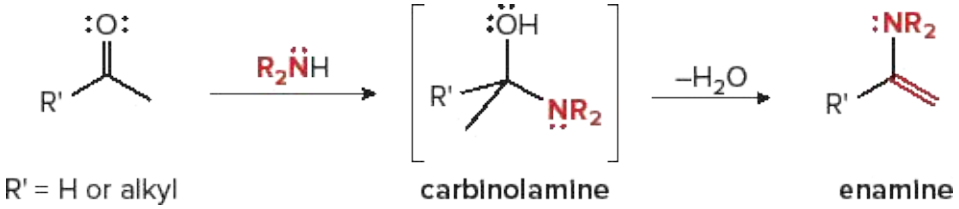
- Rhodopsin is a light-sensitive compound located in the membrane of the rod cells in the retina of the eye. Rhodopsin contains the protein opsin bonded to 11-*cis*-retinal via an imine linkage. When light strikes this molecule, the **crowded 11-cis double bond isomerizes to the 11-trans isomer,** and a nerve impulse is transmitted to the brain by the optic nerve.

Figure 18.6 **The key reaction in the chemistry of vision**

18.11 Addition of 2° Amines

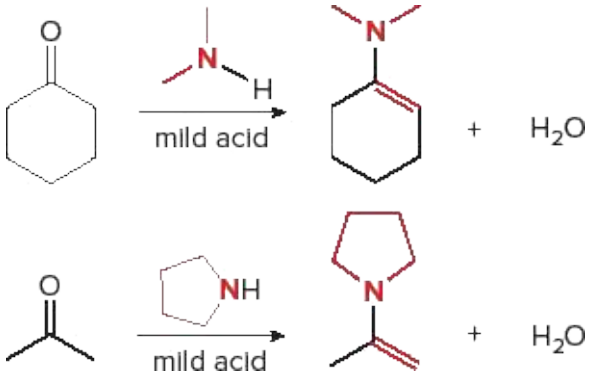
18.11A Formation of Enamines

A 2° amine reacts with an aldehyde or a ketone to give an enamine. *Enamines* have a nitrogen atom bonded to a double bond (alkene + *amine* = *enamine*).



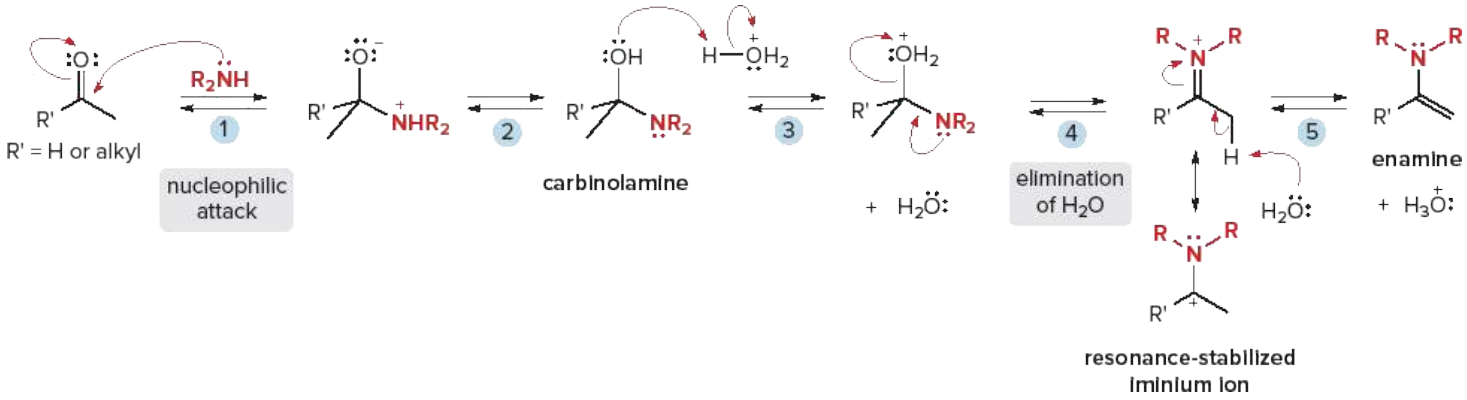
Like imines, enamines are also formed by the addition of a nitrogen nucleophile to a

carbonyl group followed by elimination of water. In this case, however, elimination occurs across two adjacent *carbon* atoms to form a new carbon–carbon π bond.



The mechanism for enamine formation (Mechanism 18.6) is identical to the mechanism for imine formation except for the *last step*, involving formation of the π bond. The mechanism can be divided into two distinct parts: nucleophilic addition of the 2° amine (Steps [1] and [2]), followed by elimination of H_2O (Steps [3]–[5]). Each step involves a reversible equilibrium once again, so that the reaction is driven to completion by removing H_2O.

Mechanism 18.6 Enamine Formation from an Aldehyde or a Ketone



1 – 2 Nucleophilic attack of the amine followed by proton transfer forms the carbinolamine.

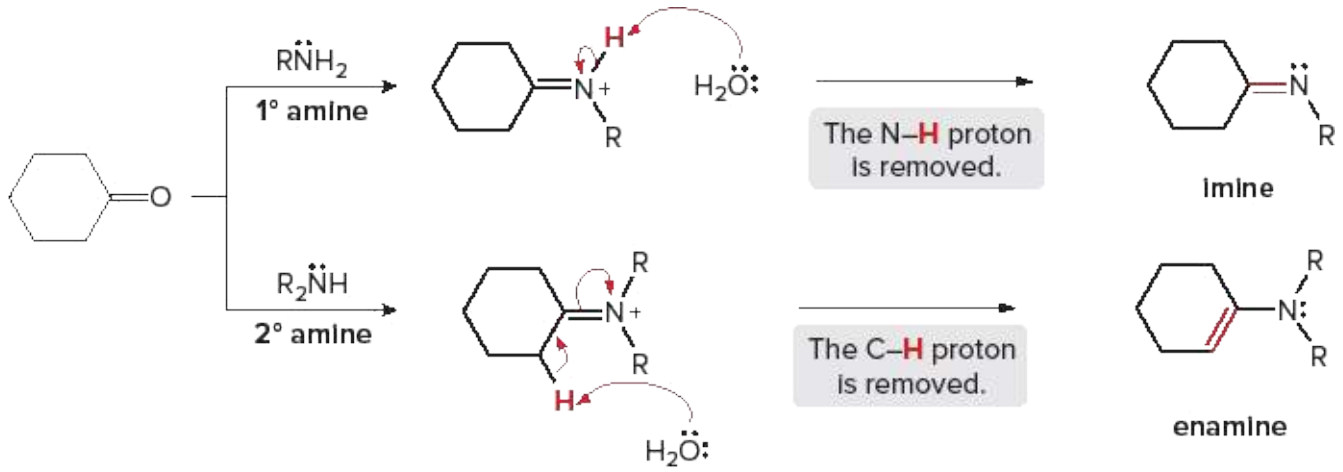
3 Protonation of the OH group forms a good leaving group.

4 Loss of H_2O forms a resonance-stabilized iminium ion.

5 Loss of a proton from the adjacent C–H bond forms the enamine.

The mechanisms illustrate why the reaction of 1° amines with carbonyl compounds forms *imines*, but the reaction with 2° amines forms *enamines*. In Figure 18.7, the last step of both mechanisms is compared using cyclohexanone as starting material. The position of the double bond depends on which proton is removed in the last step.

Removal of an N–H proton forms a C=N, whereas removal of a C–H proton forms a C=C.



- With a **1° amine,** the intermediate iminium ion still has a proton on the N atom that may be removed to form a C=N.
- With a **2° amine,** the intermediate iminium ion has *no* proton on the N atom. A proton must be removed from an adjacent C–H bond, and this forms a C=C.

Figure 18.7 **The formation of imines and enamines compared**

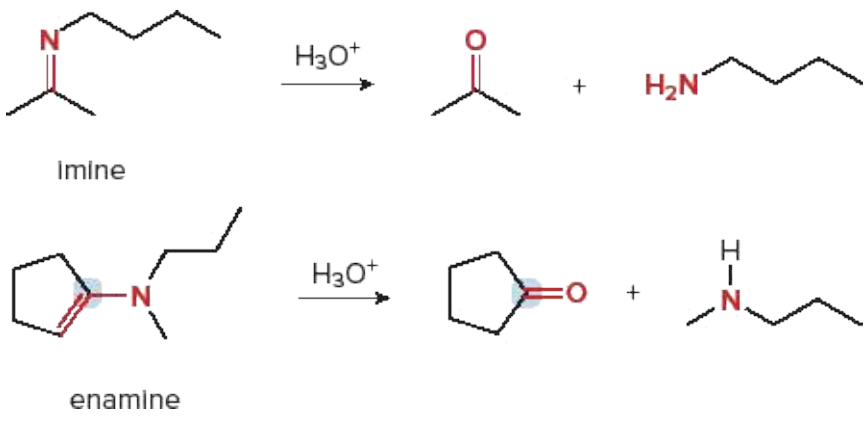
Problem 18.22

What two enamines are formed when 2-methylcyclohexanone is treated with $(CH_3)_2NH$?

18.11B Imine and Enamine Hydrolysis

Because imines and enamines are formed by a set of reversible reactions, both can be converted back to carbonyl compounds by hydrolysis with mild acid.

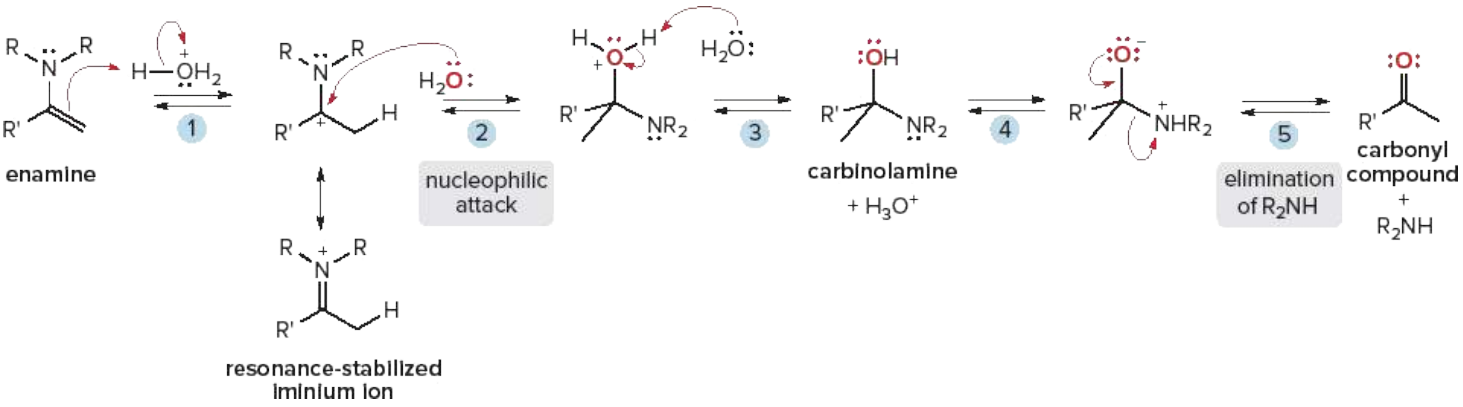
- **Hydrolysis of imines and enamines forms aldehydes and ketones.**



The mechanism of these reactions is exactly the *reverse* of the mechanism written for the formation of imines and enamines. In the hydrolysis of enamines shown in

Mechanism 18.7, the carbonyl carbon in the product comes from the sp^2 hybridized carbon bonded to the N atom in the starting material.

Mechanism 18.7 Hydrolysis of an Enamine



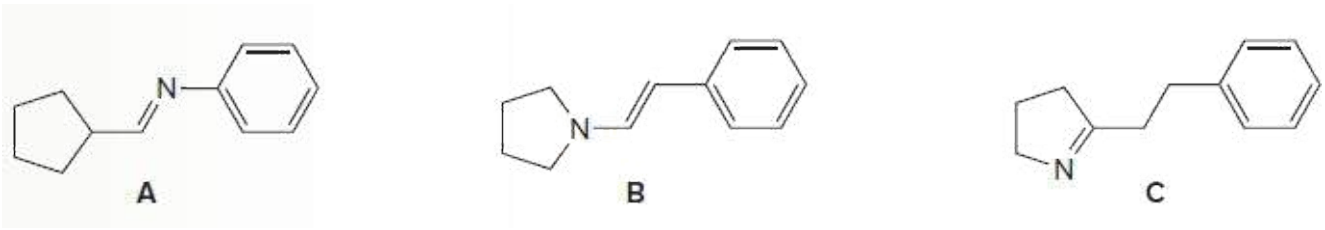
1 Protonation of the enamine forms a resonance-stabilized iminium ion.

2 – **3** Nucleophilic attack of H_2O and deprotonation form a carbinolamine.

4 – **5** Proton transfer and loss of R_2NH form the carbonyl group.

Sample Problem 18.4 Drawing the Products of Imine and Enamine Hydrolysis

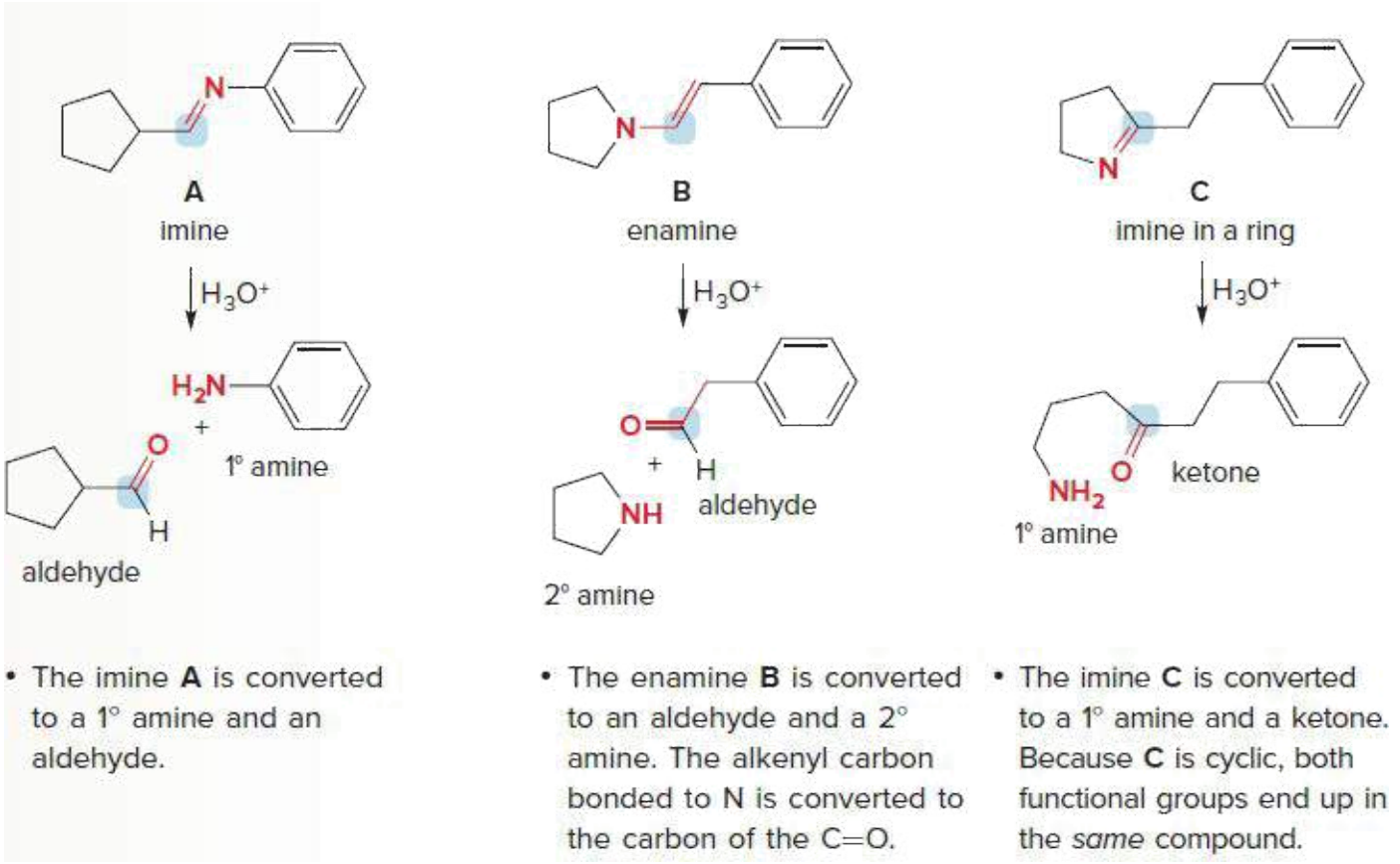
Draw the products formed by the hydrolysis of each compound.



Solution

- An imine contains a C=N, which is converted to a C=O and a 1° amine during hydrolysis.
- An enamine, which contains a N atom bonded to a C=C, is hydrolyzed to a 2° amine and a carbonyl compound.

The carbon in A, B, and C labeled in blue is converted to the carbonyl carbon.

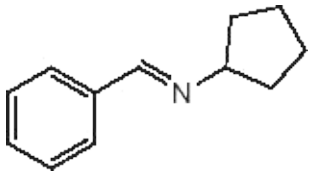


- The imine **A** is converted to a 1° amine and an aldehyde.
- The enamine **B** is converted to an aldehyde and a 2° amine. The alkenyl carbon bonded to N is converted to the carbon of the C=O.
- The imine **C** is converted to a 1° amine and a ketone. Because **C** is cyclic, both functional groups end up in the *same* compound.

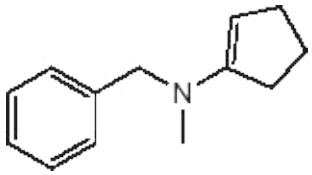
Problem 18.23

What carbonyl compound and amine are formed by the hydrolysis of each compound?

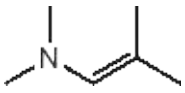
a.



b.



c.

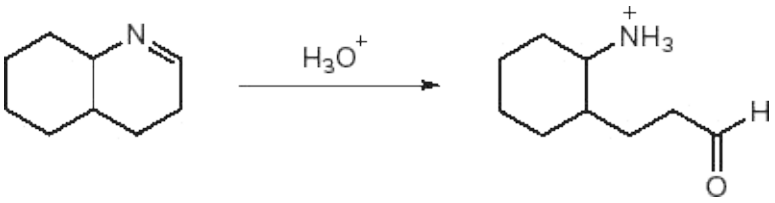


More Practice:

Try Problems 18.43c, g; 18.49; 18.51.

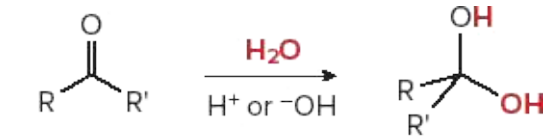
Problem 18.24

Draw a stepwise mechanism for the following imine hydrolysis.



18.12 Addition of H_2O—Hydration

Treatment of a carbonyl compound with H_2O in the presence of an acid or base catalyst adds the elements of H and OH across the carbon–oxygen π bond, forming a *gem*-diol or hydrate.



R' = H or alkyl

gem-diol (hydrate)

Hydration of a carbonyl group gives a good yield of *gem*-diol only with an unhindered aldehyde like formaldehyde, and with aldehydes containing nearby electron-withdrawing groups.

formaldehyde — formaldehyde hydrate

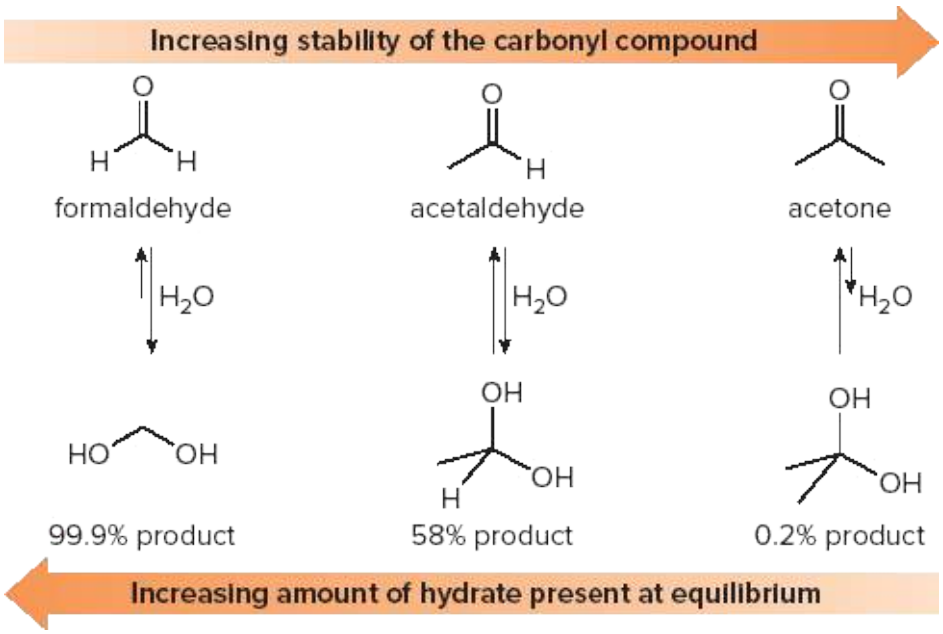
chloral — chloral hydrate

18.12A The Thermodynamics of Hydrate Formation

Whether addition of H_2O to a carbonyl group affords a good yield of the *gem*-diol depends on the relative energies of the starting material and the product. With *less stable* carbonyl starting materials, equilibrium favors the *hydrate* product, whereas with *more stable* carbonyl starting materials, equilibrium favors the *carbonyl starting material*. Because alkyl groups stabilize a carbonyl group (Section 17.2B):

- ***Increasing*** **the number of alkyl groups on the carbonyl carbon** ***decreases*** **the amount of hydrate at equilibrium.**

This can be illustrated by comparing the amount of hydrate formed from formaldehyde, acetaldehyde, and acetone.

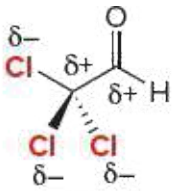


Formaldehyde, the least stable carbonyl compound, forms the largest percentage of hydrate. On the other hand, acetone and other ketones, which have two electron-donor R groups, form < 1% of the hydrate at equilibrium. Other electronic factors come into play as well:

- **Electron-*donating* groups near the carbonyl carbon stabilize the carbonyl group, *decreasing* the amount of the hydrate at equilibrium.**
- **Electron-*withdrawing* groups near the carbonyl carbon destabilize the carbonyl group, *increasing* the amount of hydrate at equilibrium.**

Chloral hydrate, a sedative sometimes administered to calm a patient prior to a surgical procedure, has also been used for less reputable purposes. Adding it to an alcoholic beverage makes a so-called knock-out drink, causing an individual who drinks it to pass out. Because it is addictive and care must be taken in its administration, chloral hydrate is a controlled substance.

This explains why chloral (trichloroacetaldehyde) forms a large amount of hydrate at equilibrium. Three electron-withdrawing Cl atoms place a partial positive charge on the a carbon to the carbonyl, destabilizing the carbonyl group, and therefore increasing the amount of hydrate at equilibrium.

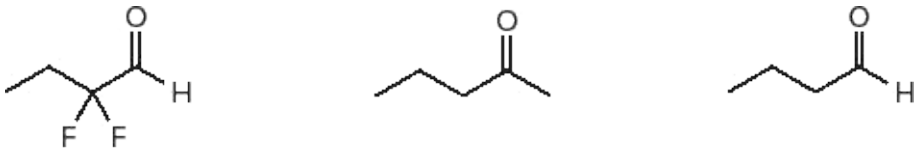


chloral

Adjacent like charges (δ+) *destabilize* the carbonyl and *increase* the amount of hydrate.

Problem 18.25

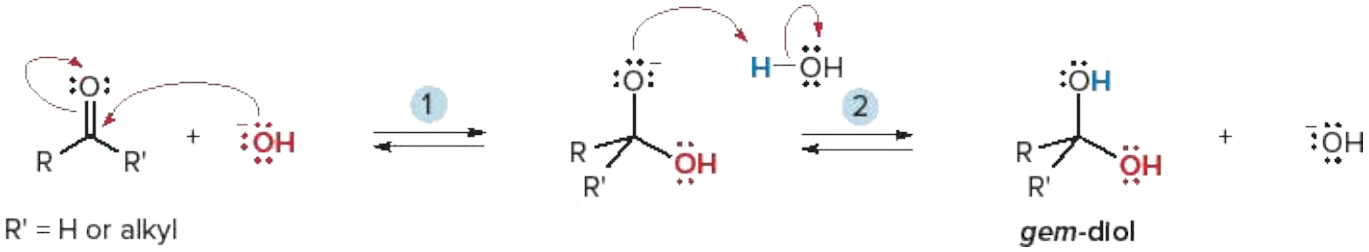
Rank the following carbonyl compounds in order of increasing percentage of hydrate present at equilibrium.



18.12B The Kinetics of Hydrate Formation

Although H_2O itself adds slowly to a carbonyl group, both acid and base catalyze the addition. In base, the nucleophile is ^-OH, and the mechanism follows the usual two steps for nucleophilic addition: nucleophilic attack followed by protonation, as shown in Mechanism 18.8.

Mechanism 18.8 Base-Catalyzed Addition of H_2O to a Carbonyl Group



R' = H or alkyl

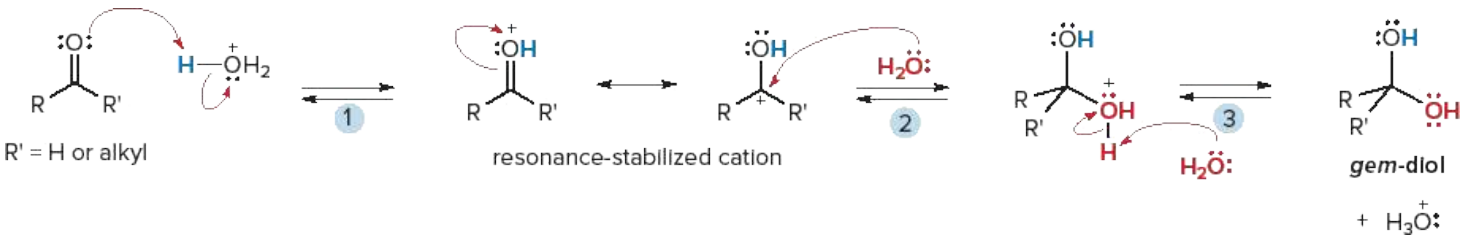
gem-diol

1. **The nucleophile (^-OH) attacks the carbonyl, breaking the π bond and moving an electron pair out on oxygen.**
2. **Protonation of the negatively charged oxygen by H_2O forms the hydration product.**

The acid-catalyzed addition follows the general mechanism presented in Section 18.6A. For a poorer nucleophile like H_2O to attack a carbonyl group, the carbonyl must be protonated by acid first; thus, protonation *precedes* nucleophilic attack. The overall

mechanism has three steps, as shown in Mechanism 18.9.

Mechanism 18.9 Acid-Catalyzed Addition of H_2O to a Carbonyl Group



1 **Protonation of the carbonyl oxygen forms a resonance-stabilized cation.**

2 – **3** **Nucleophilic attack and deprotonation form the *gem*-diol. The overall result is addition of H and OH to the carbonyl group.**

Acid and base increase the rate of reaction for different reasons:

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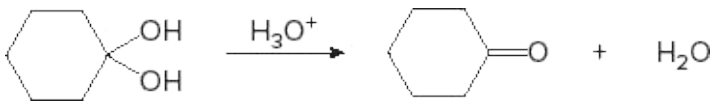
- Base converts H_2O to "OH, a *stronger nucleophile*.
- Acid protonates the carbonyl group, making it *more electrophilic* toward nucleophilic attack.

These catalysts increase the rate of the reaction, but they do not affect the equilibrium constant. Starting materials that give a low yield of *gem*-diol do so whether or not a catalyst is present. Because these reactions are reversible, the conversion of *gem*-diols to aldehydes and ketones is also catalyzed by acid and base, and the steps of the mechanism are reversed.

Problem 18.26

Draw a stepwise mechanism for the following reaction.

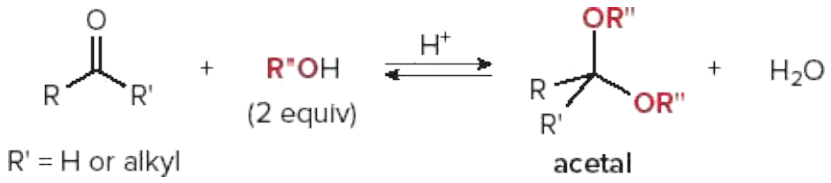


18.13 Addition of Alcohols—Acetal Formation

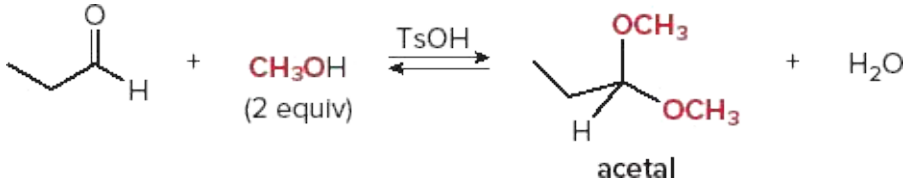
The term *acetal* refers to any compound derived from an aldehyde or ketone, having two OR groups bonded to a single carbon. The term *ketal* is sometimes used when the starting carbonyl compound is a ketone; that is, the carbon bonded to the alkoxy groups is *not* bonded to a H atom and the general

structure is $R_2C(OR')_2$. Because ketals are considered a subclass of acetals in the IUPAC system, we will use the single general term *acetal* for any compound having two OR groups on a carbon atom.

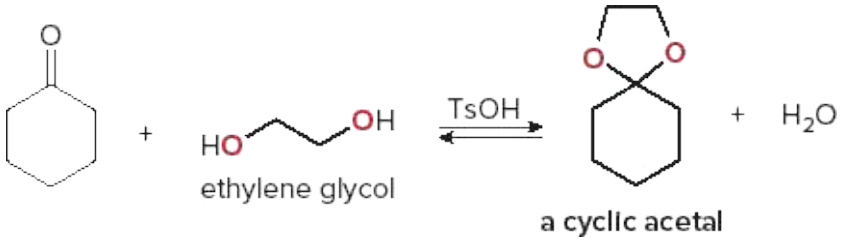
Aldehydes and ketones react with *two* equivalents of alcohol to form acetals. In an acetal, the carbonyl carbon from the aldehyde or ketone is now singly bonded to two OR″ (alkoxy) groups.



This reaction differs from other additions we have seen thus far, because two equivalents of alcohol are added to the carbonyl group, and two new C–O σ bonds are formed. Acetal formation is catalyzed by acids, commonly *p*-toluenesulfonic acid (TsOH).

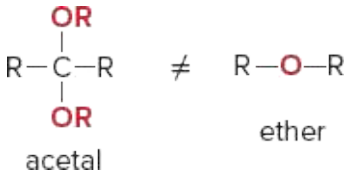


When a diol such as ethylene glycol is used in place of two equivalents of ROH, a cyclic acetal is formed. Both oxygen atoms in the cyclic acetal come from the diol.



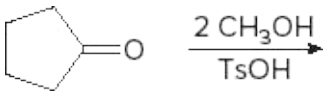
Like *gem*-diol formation, the synthesis of acetals is reversible, and often the equilibrium favors reactants, not products. In acetal synthesis, however, water is formed as a by-product, so the equilibrium can be driven to the right by removing the water as it is formed. This can be done in a variety of ways in the laboratory. A drying agent can be added that reacts with the water, or more commonly, the water can be distilled from the reaction mixture as it is formed. Driving an equilibrium to the right by removing one of the products is an application of Le Châtelier's principle (see Section 9.8).

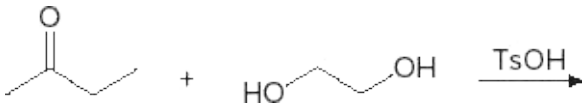
Acetals are *not* ethers, even though both functional groups contain a C–O σ bond. Having two C–O σ bonds on the *same* carbon atom makes an acetal very different from an ether.



Problem 18.27

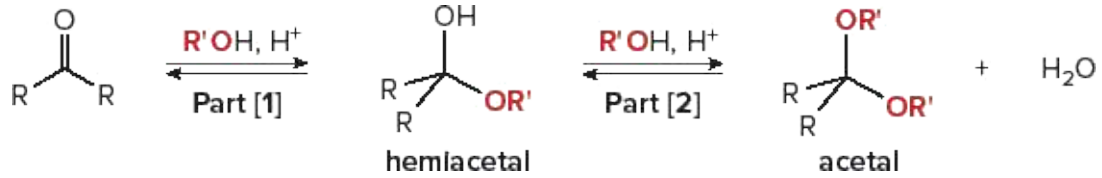
Draw the products of each reaction.

a. 

b. 

18.13A The Mechanism

The mechanism for acetal formation can be divided into two parts: the addition of one equivalent of alcohol to form a hemiacetal, followed by the conversion of the hemiacetal to the acetal. A hemiacetal has a carbon atom bonded to one OH group and one OR group.

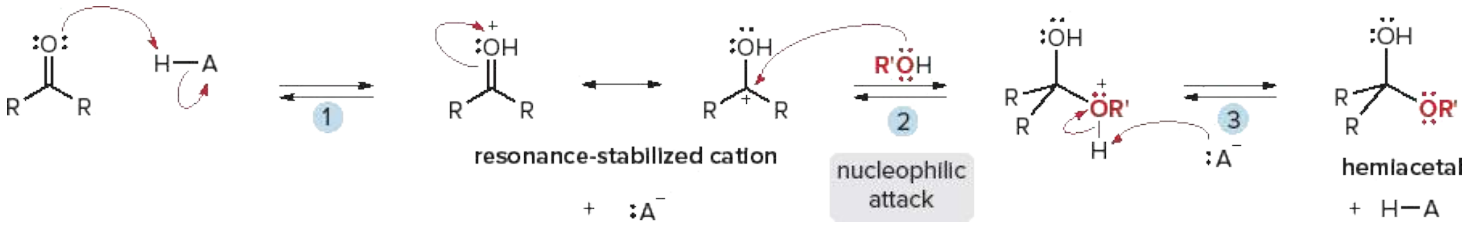


Like *gem*-diols, hemiacetals are often higher in energy than their carbonyl starting materials, making the direction of equilibrium unfavorable for hemiacetal formation. The elimination of H_2O, which can be removed from the reaction mixture to drive the equilibrium to favor product, occurs during the conversion of the hemiacetal to the acetal. This explains why two equivalents of ROH react with a carbonyl compound, forming the acetal as product.

Mechanism 18.10 is written in two parts with a general acid HA.

Mechanism 18.10 Acetal Formation

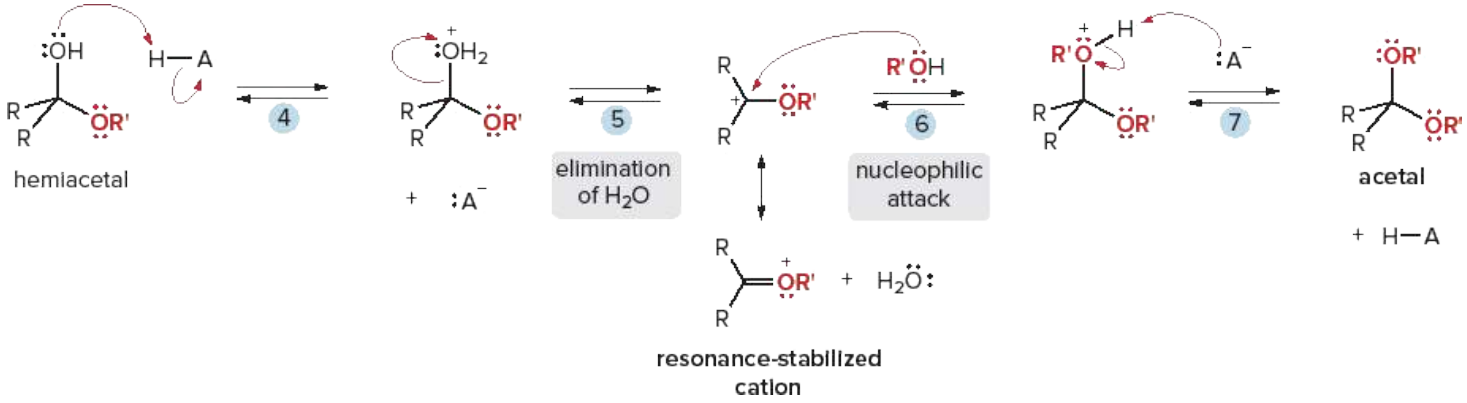
Part [1] Formation of a hemiacetal



1 Protonation of the carbonyl oxygen forms a resonance-stabilized cation.

2 – 3 Nucleophilic attack by R'OH and deprotonation form the hemiacetal. The overall result is addition of H and OR′ to the carbonyl group.

Part [2] Formation of an acetal



4 Protonation of the OH group of the hemiacetal forms a good leaving group.

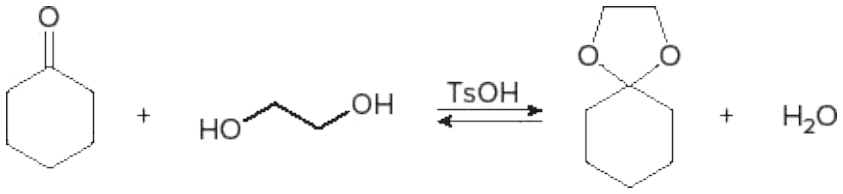
5 Loss of H_2O forms a resonance-stabilized cation.

6 – 7 Nucleophilic attack by R'OH followed by loss of a proton forms the acetal. The overall result of Part [2] is the addition of a second OR′ group to the carbonyl.

Although this mechanism is lengthy—there are seven steps—there are only three different kinds of reactions: addition of a nucleophile, elimination of a leaving group, and proton transfer. Steps [2] and [6] involve nucleophilic attack, and Step [5] eliminates H_2O. The other four steps in the mechanism shuffle protons from one oxygen atom to another, to make a better leaving group or a more electrophilic carbonyl group.

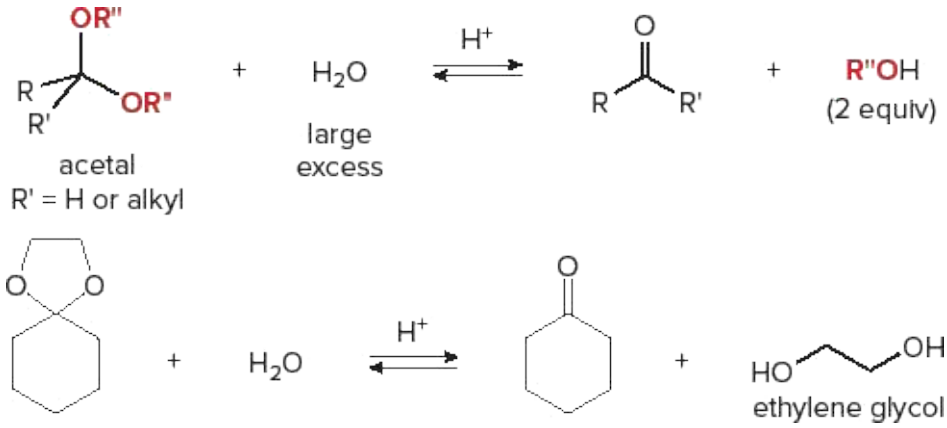
Problem 18.28

Draw a stepwise mechanism for the following reaction.



18.13B Hydrolysis of Acetals

Conversion of an aldehyde or ketone to an acetal is a reversible reaction, so an acetal can be hydrolyzed to an aldehyde or ketone by treatment with aqueous acid. Because this reaction is also an equilibrium process, it is driven to the right by using a large excess of water for hydrolysis.

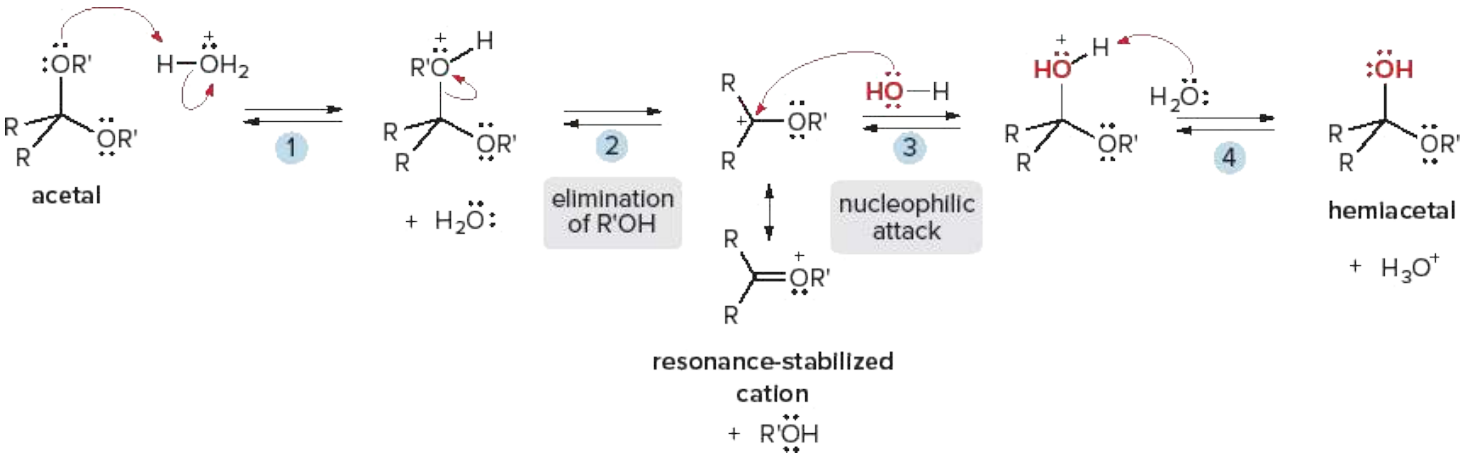


The mechanism for this reaction is the reverse of acetal synthesis, as shown in Mechanism 18.11.

Acetal hydrolysis requires a strong acid to make a good leaving group (ROH). Acetal hydrolysis does not occur in base.

Mechanism 18.11 Acetal Hydrolysis

Part [1] Conversion of an acetal to a hemiacetal



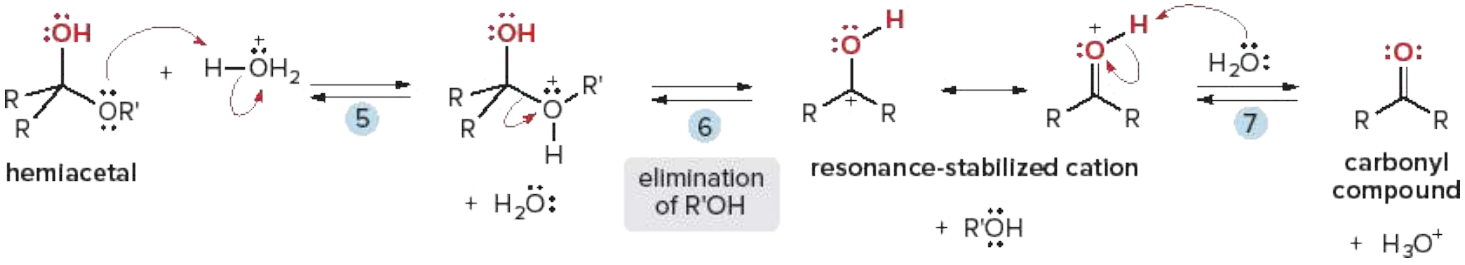
1 **Protonation of one OR′ group of the acetal forms a good leaving**

group.

2 Loss of R–OH forms a resonance-stabilized cation.

3 – 4 Nucleophilic attack by H_2O followed by loss of a proton forms the hemiacetal. The overall result of Part [1] is the substitution of one OR′ group by OH.

Part [2] Conversion of a hemiacetal to a carbonyl group

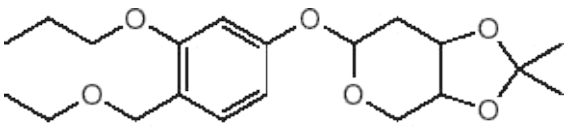


5 Protonation of the OR′ group of the hemiacetal forms a good leaving group.

6 – 7 Loss of R'OH and deprotonation form a carbonyl compound.

Sample Problem 18.5 Drawing the Products of Acetal Hydrolysis

Identify the acetal carbons in A, and draw the products formed by hydrolysis of A with aqueous acid.



A

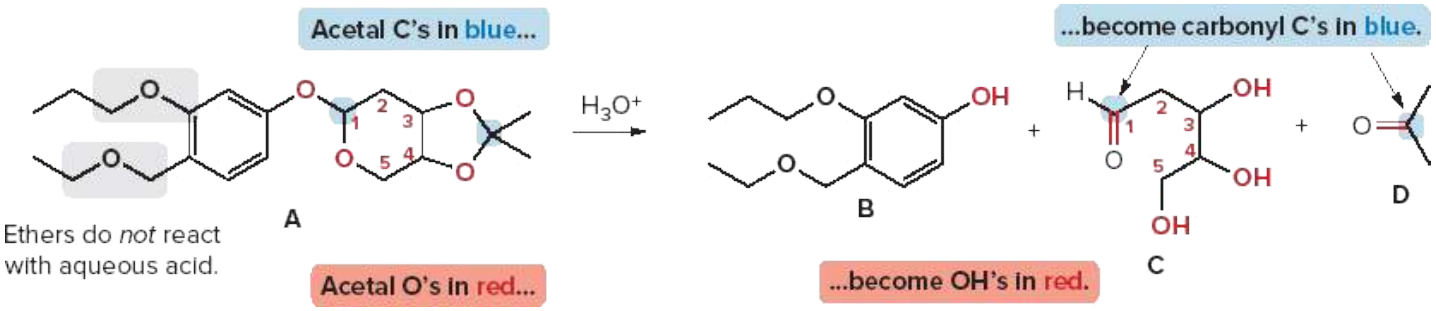
Solution

Determine the identity of the functional group that contains each O atom.

- **An acetal contains *two* oxygen atoms bonded to the *same* carbon.**
- **An ether contains *one* oxygen atom bonded to *two* carbons.**

A contains two ethers (in gray) and two acetals (with O atoms in red and acetal carbons labeled in blue).

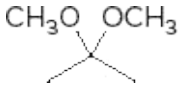
- **The acetal C bonded to two O's is converted to a carbonyl C during hydrolysis.**
- **The acetal O's are converted to OH groups.**

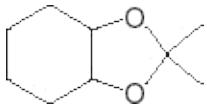


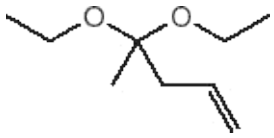
All C–O bonds of the acetals are broken and three products are formed.

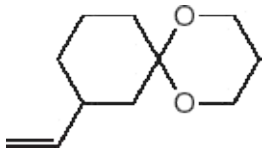
Problem 18.29

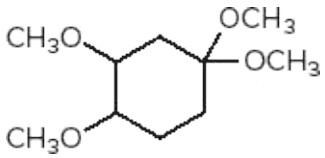
Draw the products formed when each acetal is treated with aqueous acid.

a. 

b. 

c. 

d. 

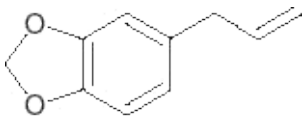
e. 

More Practice:

Try Problems 18.44, 18.48, 18.50, 18.52.

Problem 18.30

Safrole is a naturally occurring acetal isolated from sassafras plants. Once used as a common food additive in root beer and other beverages, it is now banned because it is carcinogenic. What compounds are formed when safrole is hydrolyzed with aqueous acid?

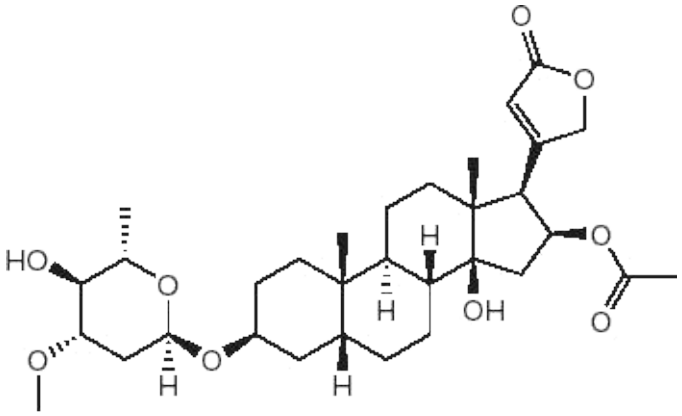


safrole

Sassafras, source of safrole (Problem 18.30) ***©Kj2011/Getty Images***

Problem 18.31

Identify the acetal in oleandrin, the chapter-opening molecule, and draw the products formed by acid-catalyzed hydrolysis of the acetal.

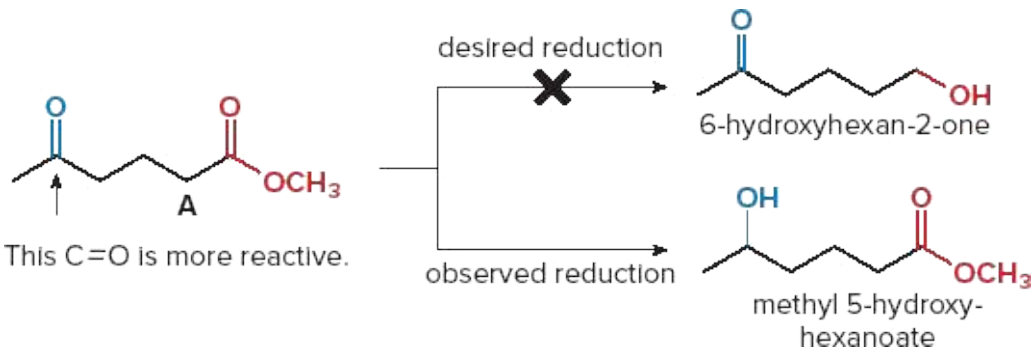


oleandrin

18.14 Acetals as Protecting Groups

Just as the *tert*-butyldimethylsilyl ethers are used as protecting groups for alcohols (Section 17.12), acetals are valuable protecting groups for aldehydes and ketones.

Suppose a starting material A contains both a ketone and an ester, and it is necessary to selectively reduce the ester to an alcohol (6-hydroxyhexan-2-one), leaving the ketone untouched. Such a selective reduction is *not* possible in one step. Because ketones are more readily reduced, methyl 5-hydroxyhexanoate is formed instead.



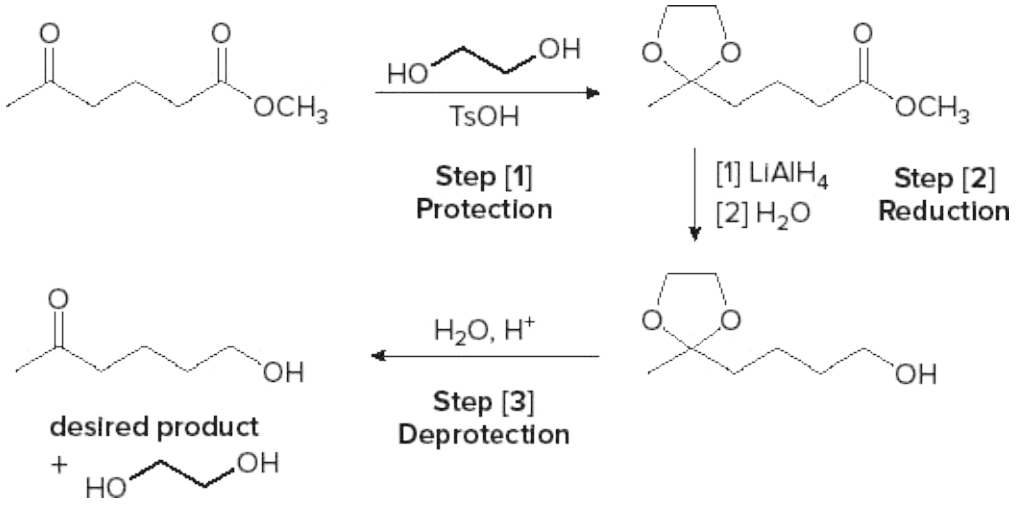
To solve this problem, we can use a protecting group to block the more reactive ketone carbonyl group. The overall process requires three steps.

[1] Protect the interfering functional group—the ketone carbonyl.

[2] Carry out the desired reaction—reduction.

[3] Remove the protecting group.

The following three-step sequence using a cyclic acetal leads to the desired product.

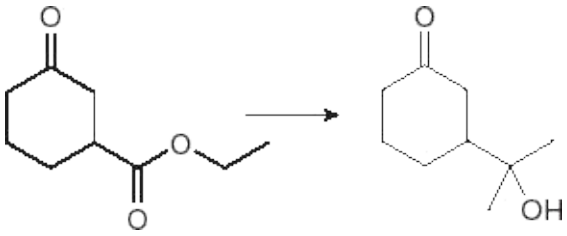


- Step [1] The ketone carbonyl is protected as a cyclic acetal by reaction of the starting material with $HOCH_2CH_2OH$ and TsOH.
- Step [2] Reduction of the ester is then carried out with $LiAlH_4$, followed by treatment with H_2O.
- Step [3] The acetal is then converted back to a ketone carbonyl group with aqueous acid.

Acetals are widely used protecting groups for aldehydes and ketones because they are easy to add and easy to remove, and they are stable to a wide variety of reaction conditions. Acetals do *not* react with base, oxidizing agents, reducing agents, or nucleophiles. Good protecting groups must survive a variety of reaction conditions that take place at other sites in a molecule, but they must also be selectively removed under mild conditions when needed.

Problem 18.32

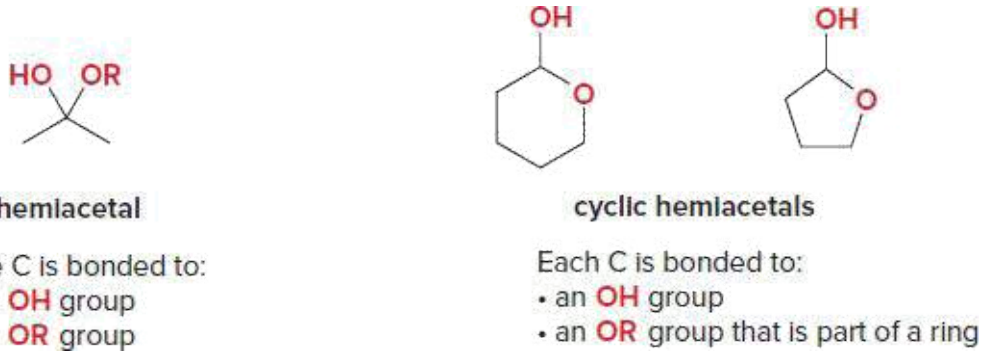
How would you use a protecting group to carry out the following transformation?



Cyclic hemiacetals are also called lactols.

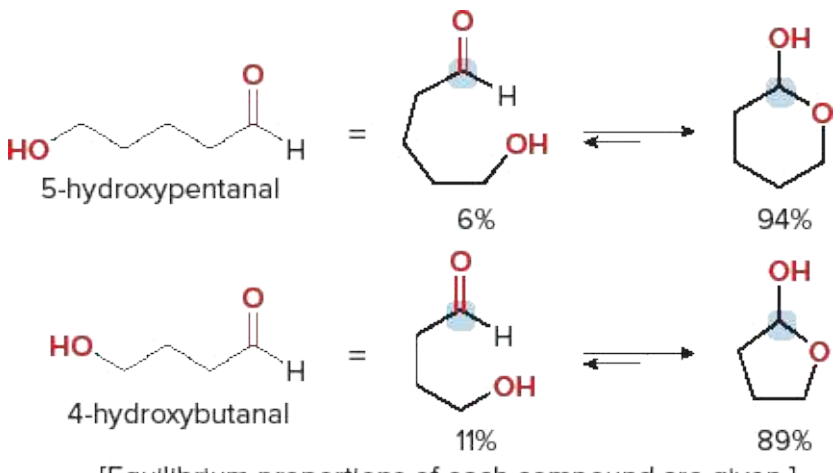
18.15 Cyclic Hemiacetals

Although acyclic hemiacetals are generally unstable and therefore not present in appreciable amounts at equilibrium, cyclic hemiacetals containing five- and six-membered rings are stable compounds that are readily isolated.



18.15A Forming Cyclic Hemiacetals

All hemiacetals are formed by nucleophilic addition of a hydroxy group to a carbonyl group. In the same way, cyclic hemiacetals are formed by intramolecular cyclization of hydroxy aldehydes.



[Equilibrium proportions of each compound are given.]

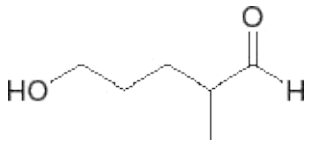
Such intramolecular reactions to form five- and six-membered rings are faster than the corresponding intermolecular reactions. The two reacting functional groups, in this

case OH and C=O, are held in close proximity, increasing the probability of reaction.

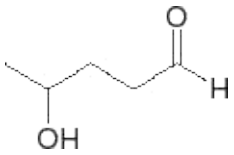
Problem 18.33

What lactol (cyclic hemiacetal) is formed from intramolecular cyclization of each hydroxy aldehyde?

a.

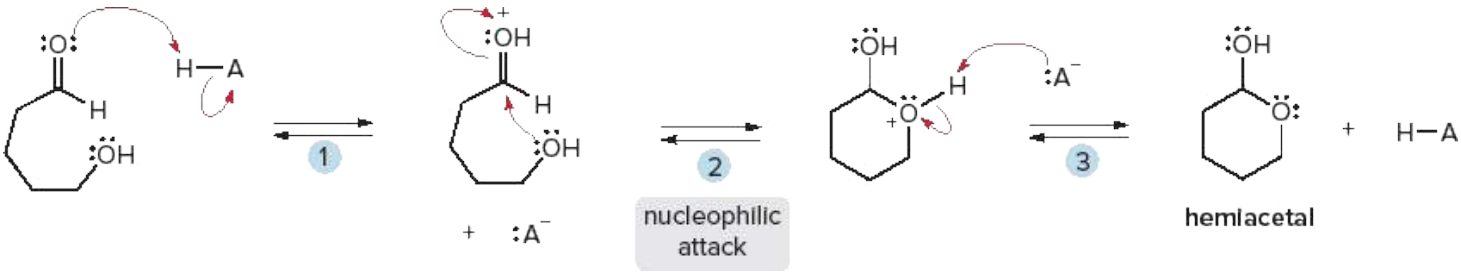


b.



Hemiacetal formation is catalyzed by both acid and base. The acid-catalyzed mechanism is identical to Part [1] of Mechanism 18.10, except that the reaction occurs in an intramolecular fashion, as shown for the acid-catalyzed cyclization of 5-hydroxypentanal to form a six-membered cyclic hemiacetal in Mechanism 18.12.

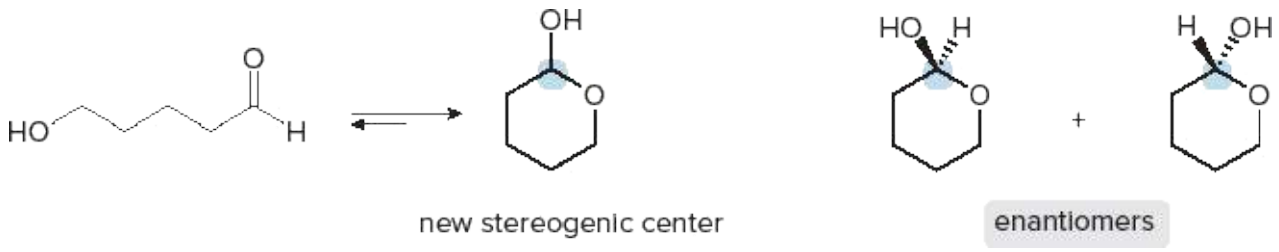
Mechanism 18.12 Acid-Catalyzed Cyclic Hemiacetal Formation



1 – 2 Protonation of the carbonyl oxygen followed by intramolecular nucleophilic attack forms the six-membered ring.

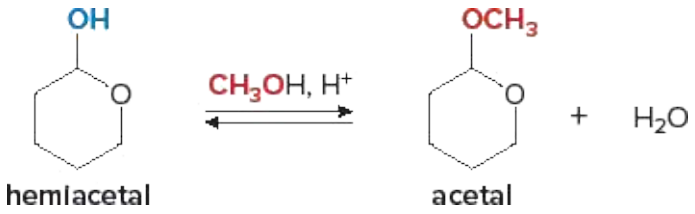
3 Deprotonation forms the neutral cyclic hemiacetal.

Intramolecular cyclization of a hydroxy aldehyde forms a hemiacetal with a new stereogenic center, so that an equal amount of two enantiomers results.



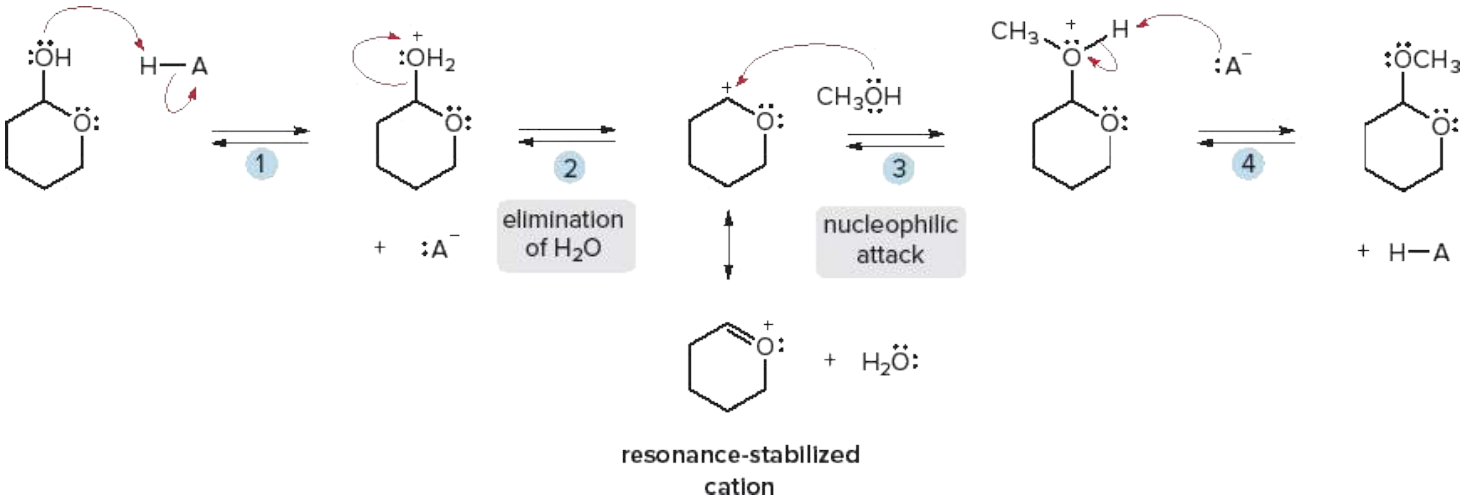
18.15B The Conversion of Hemiacetals to Acetals

Cyclic hemiacetals can be converted to acetals by treatment with an alcohol and acid. This reaction converts the OH group that is part of the hemiacetal to an OR group.



Mechanism 18.13, which is similar to Part [2] of Mechanism 18.10, illustrates the conversion of a cyclic hemiacetal to an acetal.

Mechanism 18.13 A Cyclic Acetal from a Cyclic Hemiacetal



1 Protonation of the OH group of the hemiacetal forms a good leaving group.

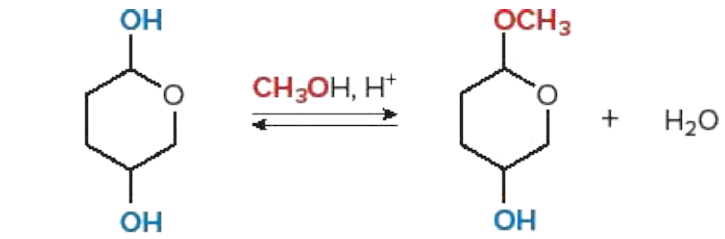
2 Loss of H_2O forms a resonance-stabilized cation.

3 – 4 Nucleophilic attack by CH_3OH followed by loss of a proton forms the acetal.

The overall result of this reaction is the replacement of the hemiacetal OH group by an OCH_3 group. This substitution reaction readily occurs because the carbocation formed in Step [2] is stabilized by resonance. This fact makes the OH group of a hemiacetal different from the hydroxy group in other alcohols.

The conversion of cyclic hemiacetals to acetals is an important reaction in carbohydrate chemistry, as discussed in Chapter 26.

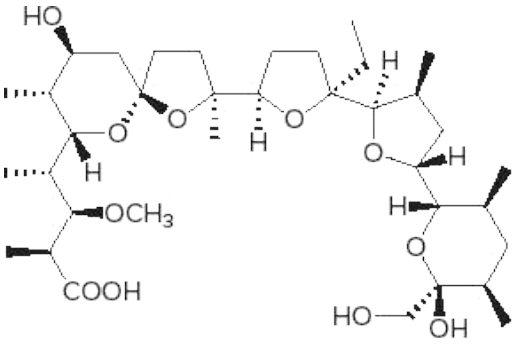
Thus, when a compound that contains both an alcohol OH group and a hemiacetal OH group is treated with an alcohol and acid, only the hemiacetal OH group reacts to form an acetal. The alcohol OH group does *not* react.



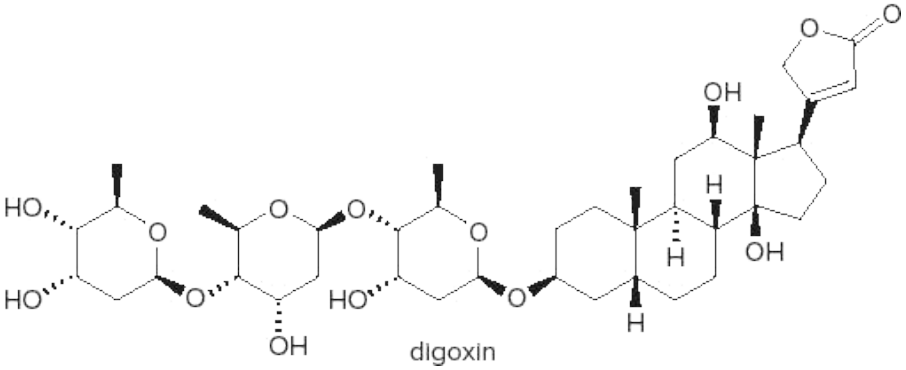
Only the hemiacetal OH reacts.

Problem 18.34

Two naturally occurring compounds that contain stable cyclic hemiacetals and acetals are monensin and digoxin. Monensin, a polyether antibiotic produced by *Streptomyces cinnamonensis*, is used as an additive in cattle feed. Digoxin is a widely prescribed cardiac drug used to increase the force of heart contractions. Label each acetal, hemiacetal, and ether in both compounds.



monensin



digoxin

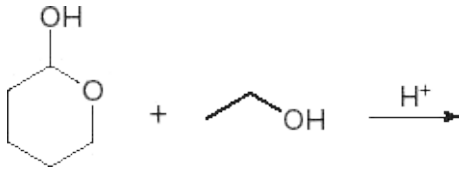
Digoxin (Problem 18.34) is obtained by extraction of the leaves of the woolly foxglove plant, which is grown in the Netherlands and shipped to the United States for processing.

©Richo Cech, Horizon Herbs, LLC

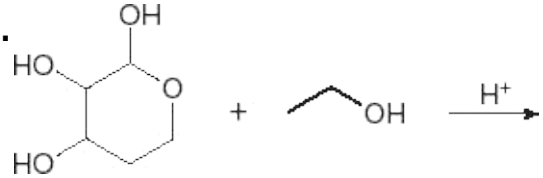
Problem 18.35

Draw the products of each reaction.

a.



b.

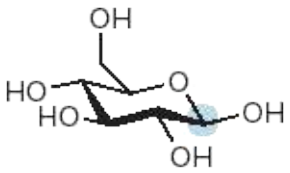


18.16 An Introduction to Carbohydrates

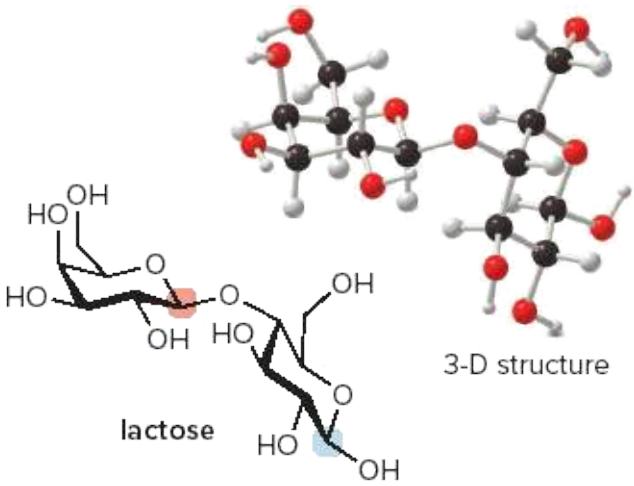
Carbohydrates, commonly referred to as sugars and starches, are polyhydroxy aldehydes and ketones, or compounds that can be hydrolyzed to them. Along with proteins, fatty acids, and nucleotides, they form one of the four main groups of biomolecules responsible for the structure and function of all living cells.

Many carbohydrates contain cyclic acetals or hemiacetals. Examples include glucose, the most common simple sugar, and lactose, the principal carbohydrate in milk. Hemiacetal carbons are labeled in blue, whereas the acetal carbon is labeled in red.

3-D structure



β-D-glucose
(one form of glucose)



3-D structure

lactose

Glucose is the carbohydrate that is transported in the blood to individual cells. The hormone insulin regulates the level of glucose in the blood. Diabetes is a common disease that results from a deficiency of insulin, resulting in increased glucose levels in the blood and other metabolic abnormalities. Insulin injections control glucose levels.

Hemiacetals in sugars are formed in the same way that other hemiacetals are formed—that is, by cyclization of hydroxy aldehydes. Thus, the hemiacetal of glucose is formed by cyclization of an acyclic *polyhydroxy* aldehyde A, as shown in the accompanying equation. This process illustrates two important features.

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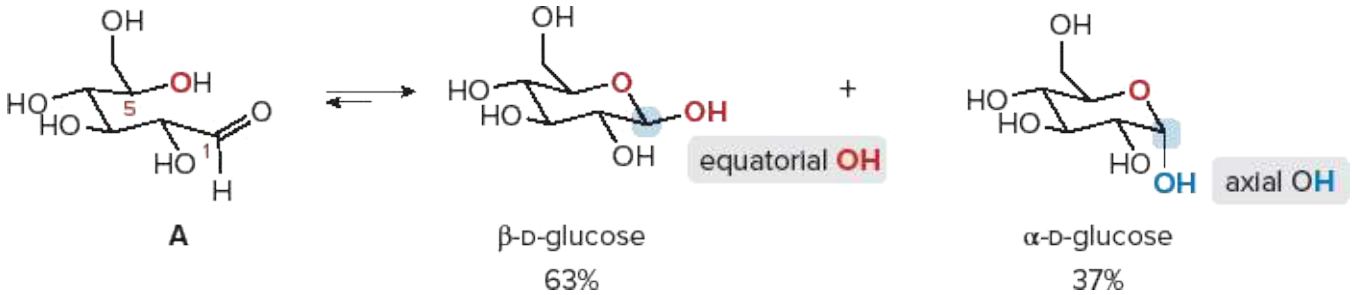


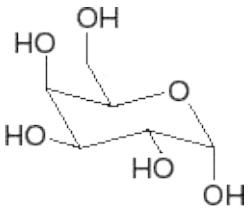
- When the OH group on C5 is the nucleophile, cyclization yields a six-membered ring, and this ring size is preferred.
- Cyclization forms a new stereogenic center (labeled in blue), exactly analogous to the cyclization of the simpler hydroxy aldehyde (5-hydroxypentanal) in Section 18.15A. The new OH group of the hemiacetal can occupy either the equatorial or

axial position.

For glucose, this results in two cyclic forms, called β-D-glucose (having an equatorial OH group) and α-D-glucose (having an axial OH group). Because β-D-glucose has the new OH group in the more roomy equatorial position, this cyclic form of glucose is the major product. At equilibrium, only a trace of the acyclic hydroxy aldehyde A is present.

Many more details on this process and other aspects of carbohydrate chemistry are presented in Chapter 26.

Problem 18.36



α-D-galactose

a. How many stereogenic centers are present in α-D-galactose?

b. Label the hemiacetal carbon in α-D-galactose.

c. Draw the structure of β-D-galactose.

d. Draw the structure of the polyhydroxy aldehyde that cyclizes to α- and β-D-galactose.

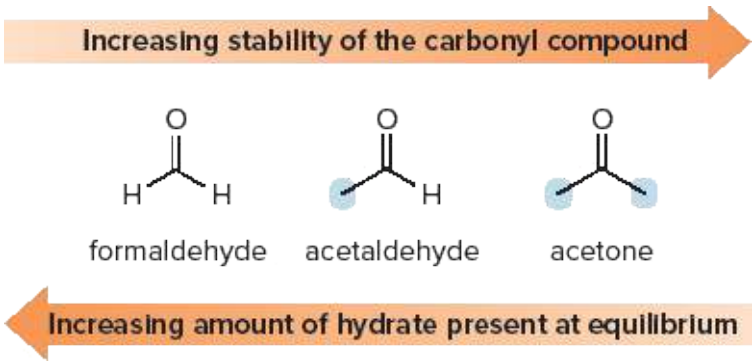
e. From what you learned in Section 18.15B, what product(s) is (are) formed when α-D-galactose is treated with CH3OH and an acid catalyst?

Chapter 18 REVIEW

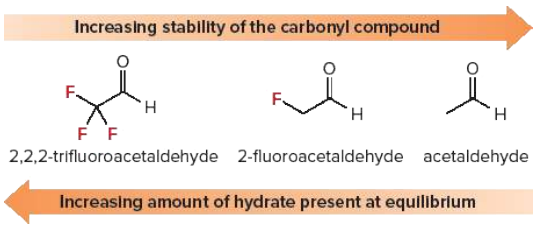
KEY CONCEPTS

The relationship between the stability of a carbonyl compound and hydrate formation (18.12)

1 **Aldehydes versus ketones**	2 **Electron-withdrawing groups**



- **Increasing the number of alkyl groups on the carbonyl carbon decreases the amount of hydrate at equilibrium.**



- **Increasing the number of electron-withdrawing groups near the carbonyl carbon increases the amount of hydrate at equilibrium.**

Try Problem 18.53a, b.

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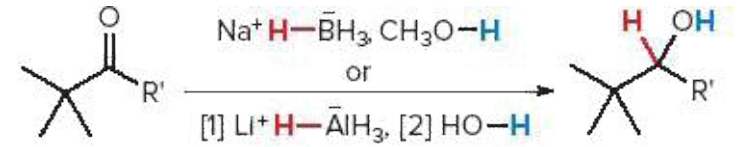
KEY REACTIONS

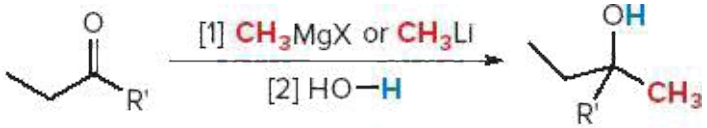
Nucleophilic Addition Reactions

1



R' = H or alkyl — addition (18.7) — 1° or 2° alcohol

2

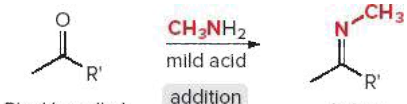


R' = H or alkyl — addition (18.7) — 1°, 2°, or 3° alcohol

3

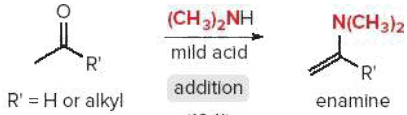
R' = H or alkyl — addition (18.8) — cyanohydrin

5



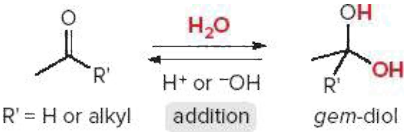
R' = H or alkyl — addition (18.10) — imine

6



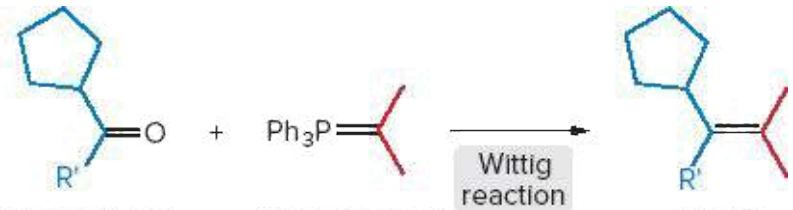
R' = H or alkyl — addition (18.11) — enamine

7



R' = H or alkyl — addition (18.12) — *gem*-diol

4



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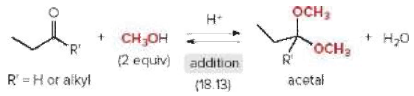
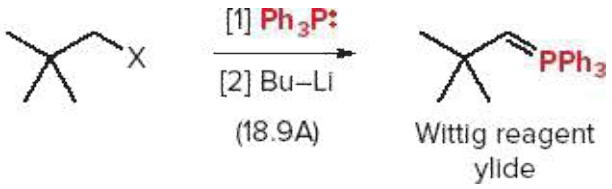


Try Problems 18.37b; 18.42; 18.43a, b, d, f, h; 18.45; 18.46.

Other Reactions

1



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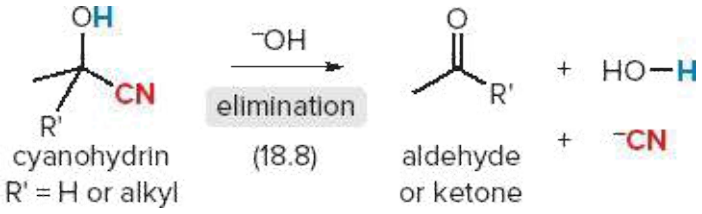

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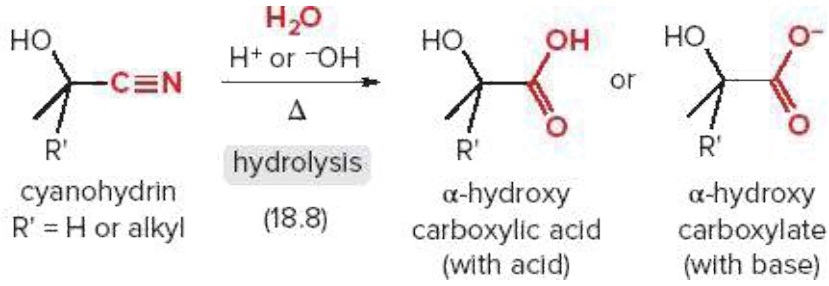

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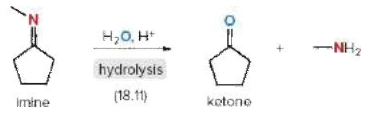

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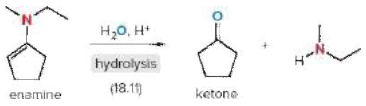

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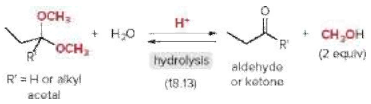
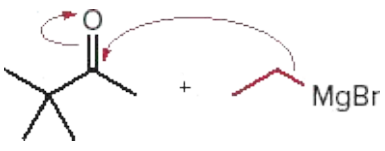
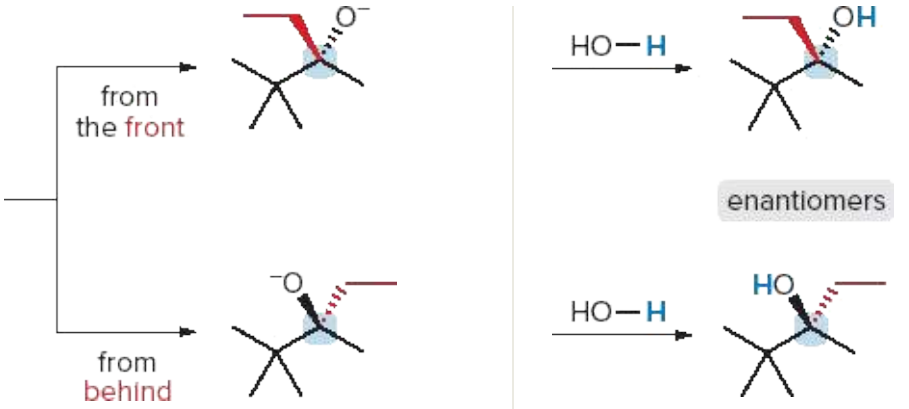


See Sample Problem 18.4. Try Problems 18.42; 18.43c, e, g; 18.44; 18.48; 18.49; 18.50b; 18.51; 18.52.

KEY SKILLS

[1] Drawing all stereoisomers that form in a Grignard reaction (18.7)

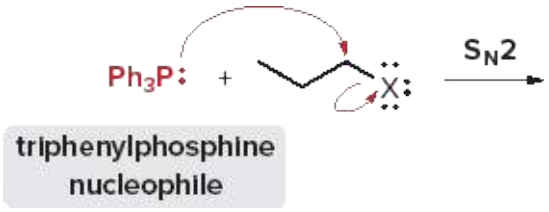
1 Use the reagents to identify the group added to the C=O.	**2** Use the mechanism to determine the stereochemistry.	**3** Draw the product(s).
		



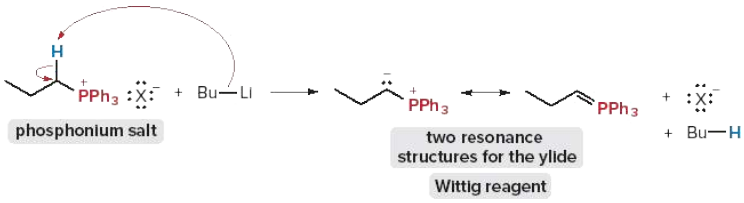
See Sample Problem 18.3. Try Problem 18.37b [2].

[2] Synthesizing Wittig reagents by a two-step procedure (18.9A)

1 **React triphenylphosphine with an alkyl halide.**



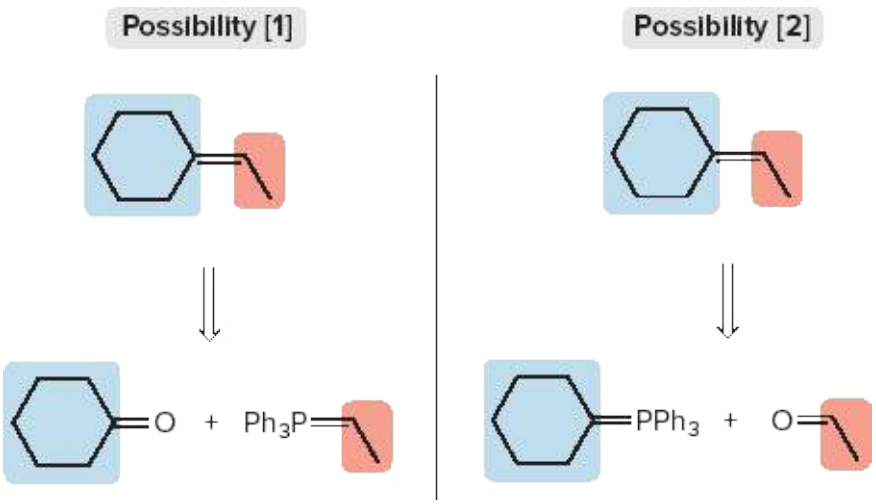
2 **Deprotonate the phosphonium salt v a strong base.**



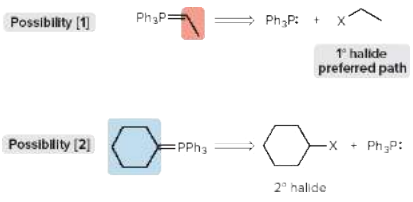
Try Problem 18.42.

[3] Determining the starting materials for a Wittig reaction using retrosynthetic analysis (18.9C)

1 **Cleave the carbon–carbon double bond into two components.**



2 **Compare the Witti reagents.**



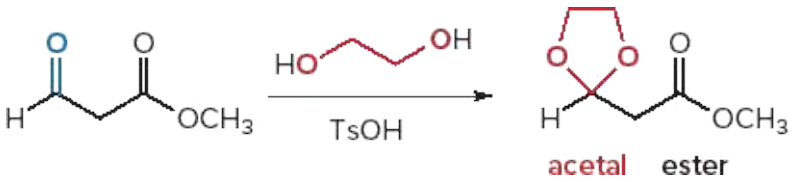
- **The preferred pathway uses a Wittig reagent derived from an**

unhindered alkyl halide–CH_3X or RCH_2X.

See *How To*, p. 853. Try Problems 18.54, 18.56.

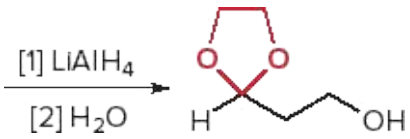
[4] Using an acetal as a protecting group (18.14)

1 **Protect the ketone.**



- The CHO is converted to an acetal, which does not interfere with the reduction of the ester.

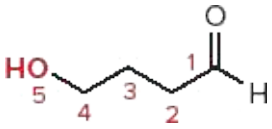
2 **Carry out the reaction.**



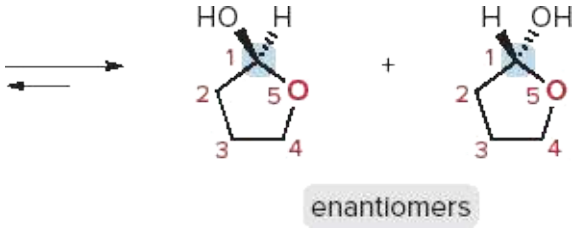
Try Problems 18.62, 18.63.

[5] Drawing the stereoisomers that form in the intramolecular cyclization of a hydroxy aldehyde (18.15A)

1 **Identify the OH group five or six atoms away from the C=O.**



2 **Use the mechanism to draw the products and determine the stereochemistry.**

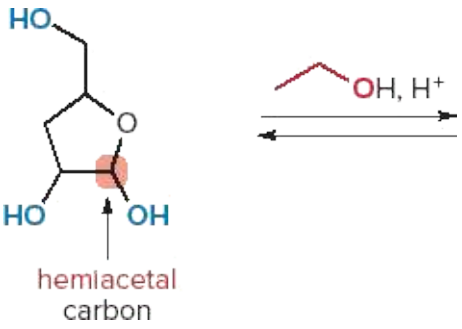


- A new stereogenic center is formed, so an equal amount of two enantiomers results.

Try Problems 18.47, 18.77.

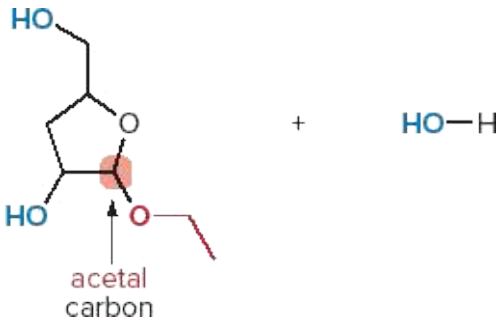
[6] Determining the reactive OH group that forms an acetal when treated with an alcohol and acid (18.15B)

1 Identify the hemiacetal.



- A hemiacetal carbon is bonded to an OH group and an OR group.
- When treated with an alcohol and acid, only the hemiacetal OH reacts.

2 Draw the product(s).



- The 1° and 2° OH's do *not* react under these conditions.
- The acetal carbon is bonded to two OR groups.

Try Problem 18.45d.

PROBLEMS

Problems Using Three-Dimensional Models

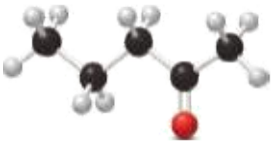
18.37 (a) Give the IUPAC name for A and B. (b) Draw the product formed when A or B is treated with each reagent: [1] $NaBH_4$, CH_3OH; [2] CH_3MgBr,

then H_2O; [3] $Ph_3P{=}CHOCH_3$; [4] $CH_3CH_2CH_2NH_2$, mild acid; [5] $HOCH_2CH_2CH_2OH$, H^+.

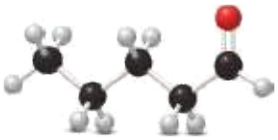
A

B

18.38 Rank the following compounds in order of increasing reactivity in nucleophilic addition.



C



D

E

18.39 What carbonyl compound and diol are needed to prepare each compound?

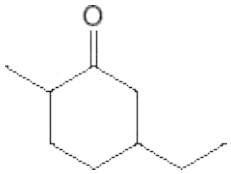
a.

b.

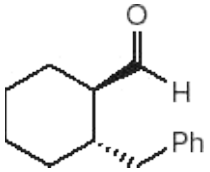
Nomenclature

18.40 Give the IUPAC name for each compound.

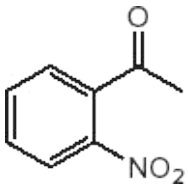
a.



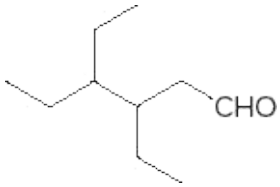
b.



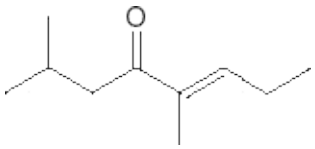
c.



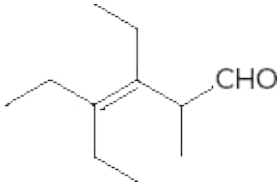
d.



e.



f.



18.41 Give the structure corresponding to each name.

a. 2-methyl-3-phenylbutanal

b. 3,3-dimethylcyclohexanecarbaldehyde

c. 3-benzoylcyclopentanone

d. 2-formylcyclopentanone

e. (*R*)-3-methylheptan-2-one

f. *m*-acetylbenzaldehyde

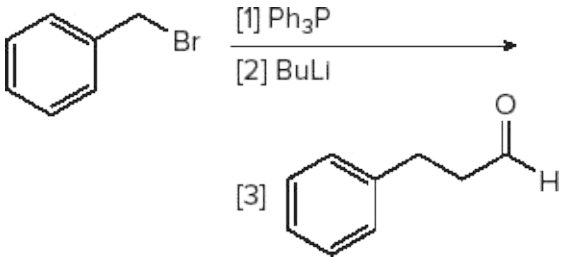
g. 2-sec-butylcyclopent-3-enone

h. 5,6-dimethylcyclohex-1-enecarbaldehyde

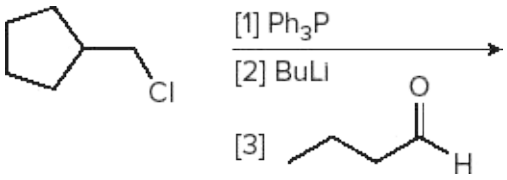
Reactions

18.42 Draw the products formed in each reaction sequence.

a.

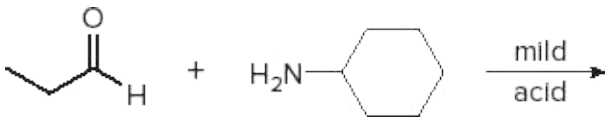


b.

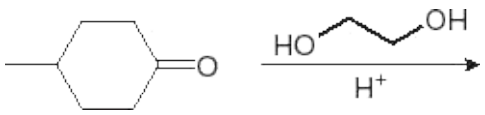


18.43 Draw the products of each reaction.

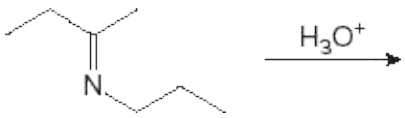
a.



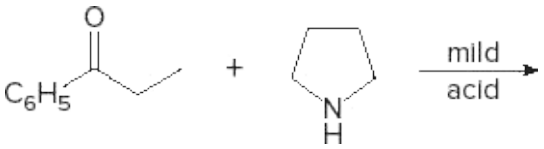
b.



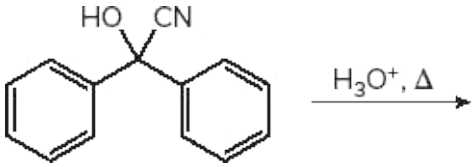
c.



d.



e.



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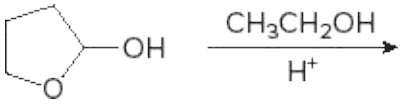

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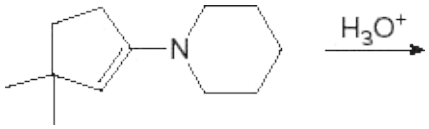

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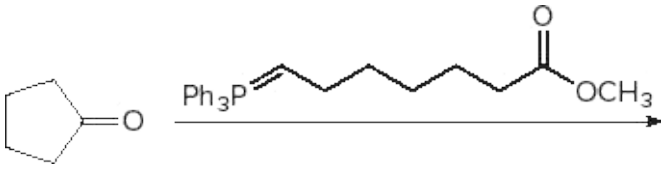
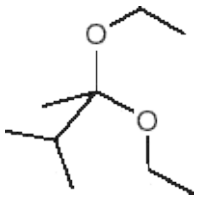
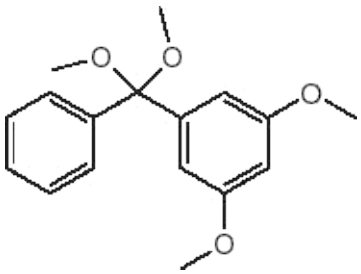


18.44 What carbonyl compound and alcohol are formed by hydrolysis of each acetal?

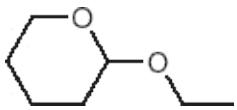
a.



b.

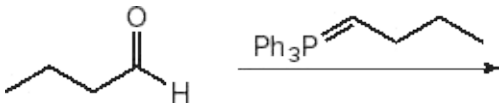


c.

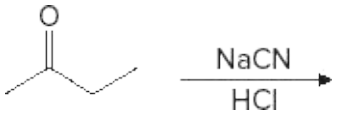


18.45 Draw all stereoisomers formed in each reaction.

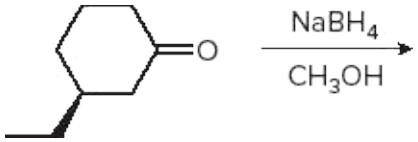
a.



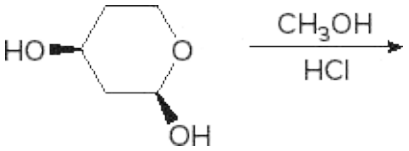
b.



c.

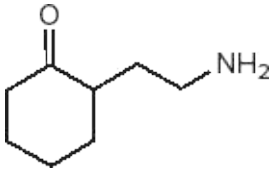


d.



18.46 What product is formed when each compound undergoes an intramolecular reaction in the presence of acid?

a.



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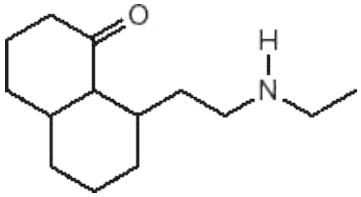
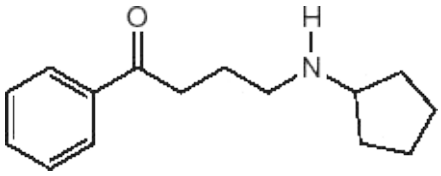
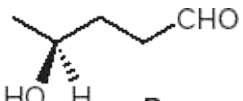


c.



18.47 Hydroxy aldehydes A and B readily cyclize to form hemiacetals. Draw the stereoisomers formed in this reaction from both A and B. Explain why this process gives an optically inactive product mixture from A and an optically active product mixture from B.

A



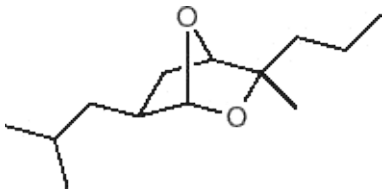
B

18.48 What products are formed when each acetal is hydrolyzed with aqueous acid?

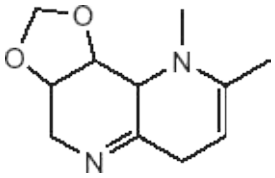
a.

b.

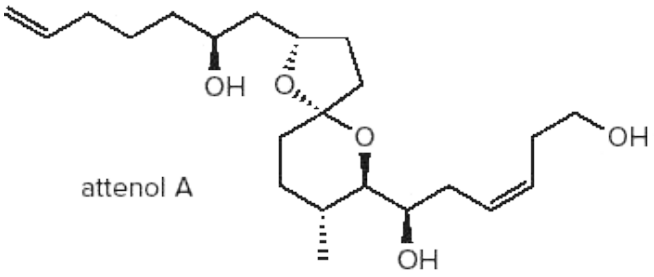
c.



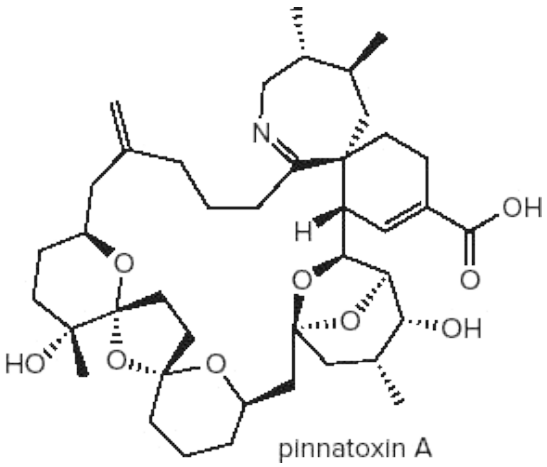
18.49 What hydrolysis products are formed when the following compound is treated with aqueous acid?



18.50 Attenol A and pinnatoxin A are natural products isolated from marine sources. (a) Locate the acetals, hemiacetals, imines, and enamines in both compounds. (b) Draw the hydrolysis product formed when attenol A is treated with aqueous acid. Include stereochemistry at all stereogenic centers.



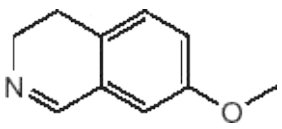
attenol A



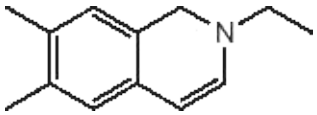
pinnatoxin A

18.51 What products are formed by hydrolysis of each imine or enamine?

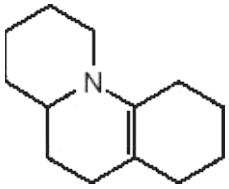
a.



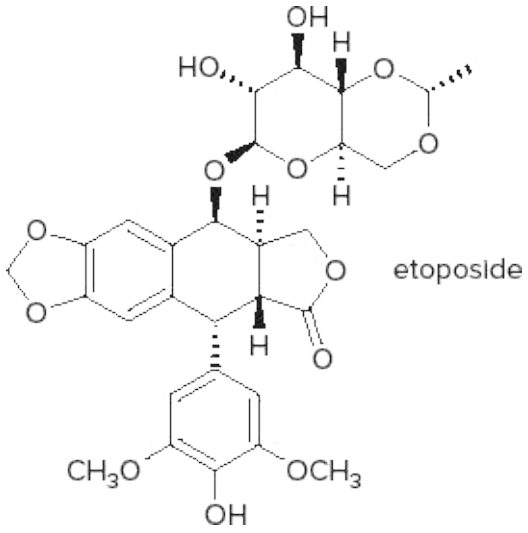
b.



c.

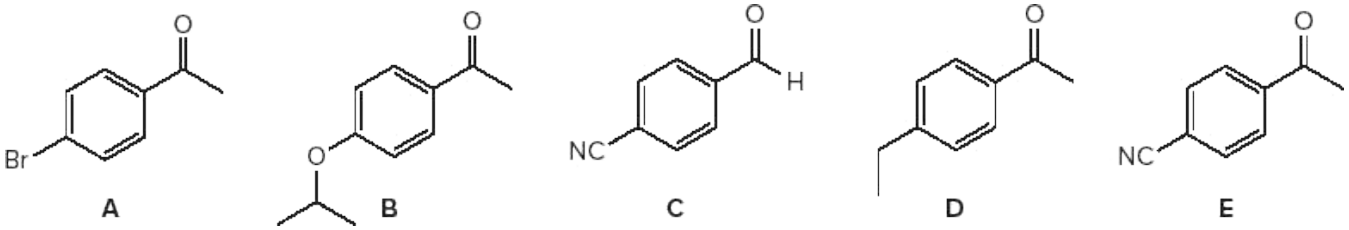


18.52 Etoposide, sold as a phosphate derivative with the trade name of Etopophos, is used for the treatment of lung cancer, testicular cancer, and lymphomas. (a) Locate the acetals in etoposide. (b) What products are formed when all of the acetals are hydrolyzed with aqueous acid?



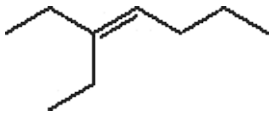
Properties of Aldehydes and Ketones

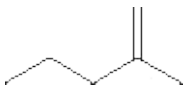
18.53 Consider carbonyl compounds A–E drawn below. (a) Rank A–E in order of increasing stability. (b) Rank A–E in order of increasing amount of hydrate formed when treated with aqueous acid. (c) Which compound is most reactive in nucleophilic addition? (d) From what you learned about the position of the carbonyl absorption in the IR in Sections B.3C and B.4B, which compound has a carbonyl absorption at lowest frequency?

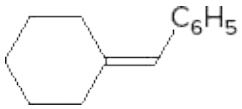


Synthesis

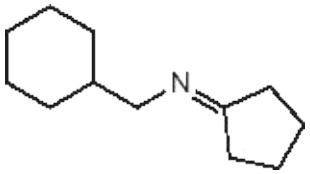
18.54 What Wittig reagent and carbonyl compound are needed to prepare each alkene? When two routes are possible, indicate which route, if any, is preferred.

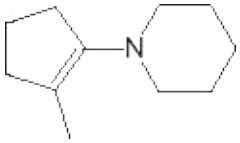
a. 

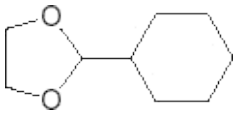
b. 

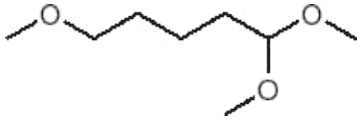
c. 

18.55 What carbonyl compound and amine or alcohol are needed to prepare each product?

a. 

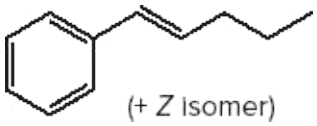
b. 

c. 

d. 

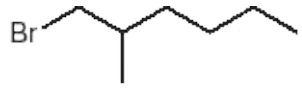
18.56 Show two different methods to carry out the following transformation: a one-step method using a Wittig reagent, and a two-step method using a Grignard reagent. Which route, if any, is preferred?

18.57 Devise a synthesis of each alkene using a Wittig reaction to form the double bond. You may use benzene and organic alcohols having four or fewer carbons as starting materials and any required reagents.

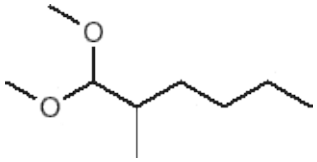
a. 

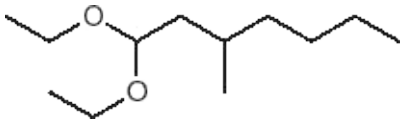
b.

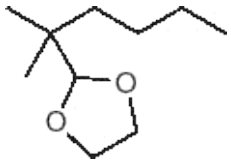
18.58 Devise a synthesis of each acetal from 1-bromo-2-methylhexane, alcohols (and diols) containing one or two carbons, and any needed inorganic reagents.



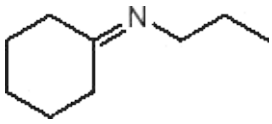
1-bromo-2-methylhexane

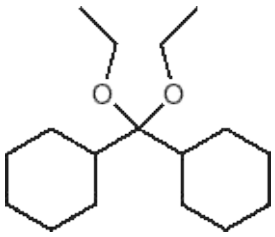
a. 

b. 

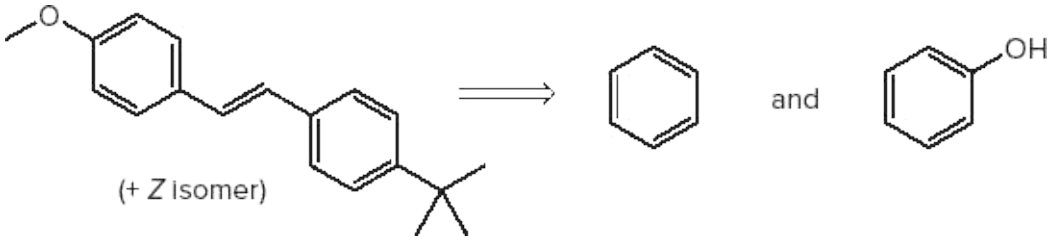
c. 

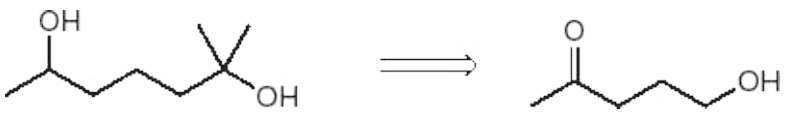
18.59 Devise a synthesis of each compound from cyclohexene and organic alcohols. You may use any other required organic or inorganic reagents.

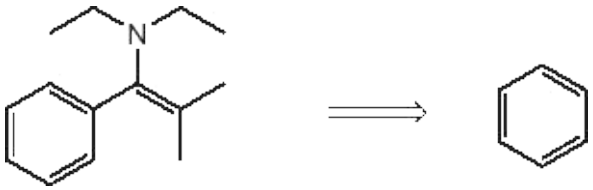
a. 

b. 

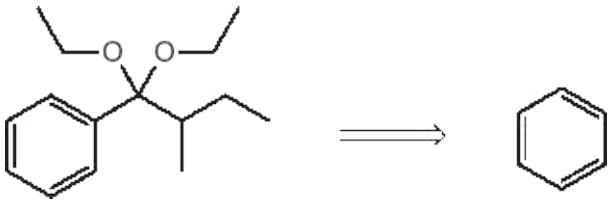
18.60 Devise a synthesis of each compound from the given starting materials. You may also use organic alcohols having four or fewer carbons, and any organic or inorganic reagents.

a. 

b. 

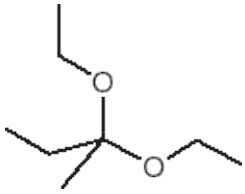
c. 

d.

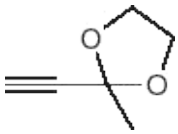


18.61 Devise a synthesis of each compound from ethanol (CH_3CH_2OH) as the only source of carbon atoms. You may use any other organic or inorganic reagents you choose.

a.

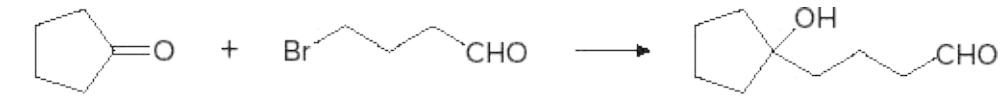


b.



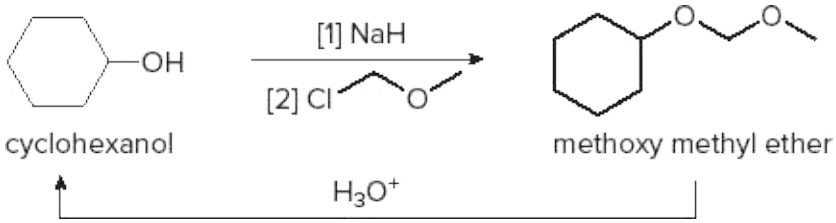
Protecting Groups

18.62 Design a stepwise synthesis to convert cyclopentanone and 4-bromobutanal to hydroxy aldehyde A.



cyclopentanone 4-bromobutanal **A**

18.63 Besides the tert-butyldimethylsilyl ethers introduced in Chapter 17, there are many other widely used alcohol protecting groups. For example, an alcohol such as cyclohexanol can be converted to a methoxy methyl ether (a MOM protecting group) by treatment with base and chloromethyl methyl ether, $ClCH_2OCH_3$. The protecting group can be removed by treatment with aqueous acid.



a. Write a stepwise mechanism for the formation of a MOM ether from cyclohexanol.

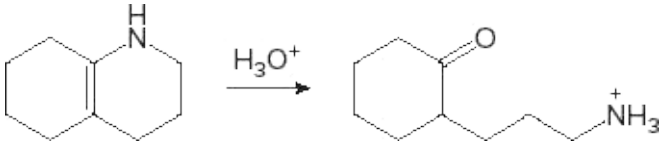
b. What functional group comprises a MOM ether?

c. Besides cyclohexanol, what other products are formed by aqueous

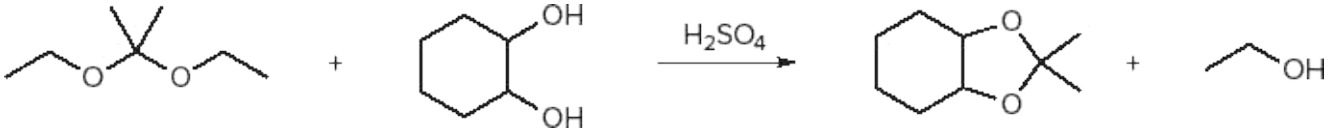
hydrolysis of the MOM ether? Draw a stepwise mechanism that accounts for formation of each product.

Mechanism

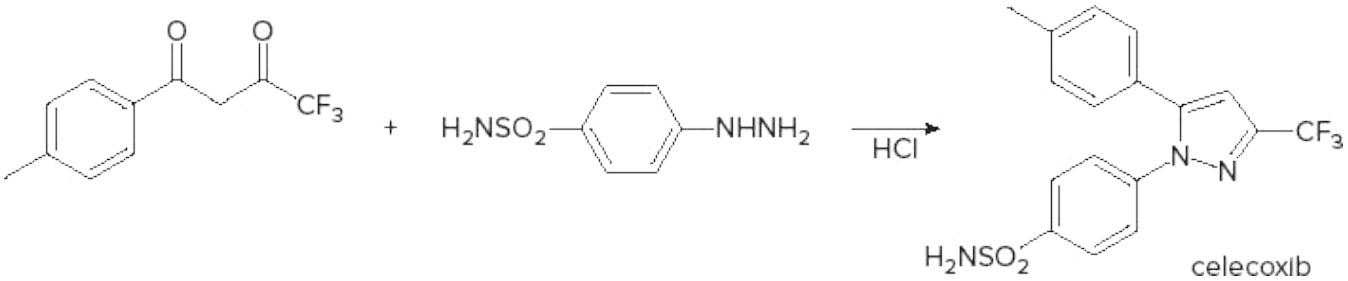
18.64 Draw a stepwise mechanism for the following reaction.



18.65 One acetal can be converted to a different acetal by reaction with a diol in the presence of acid, a process called transacetalization. Draw a stepwise mechanism for the following transacetalization.



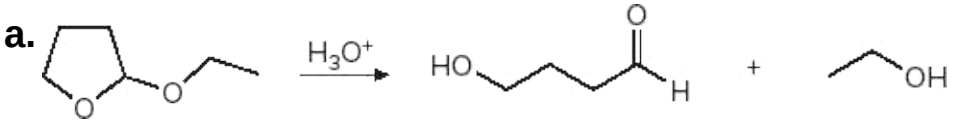
18.66 Draw a stepwise mechanism for the following reaction, a key step in the synthesis of the anti-inflammatory drug celecoxib (trade name Celebrex).



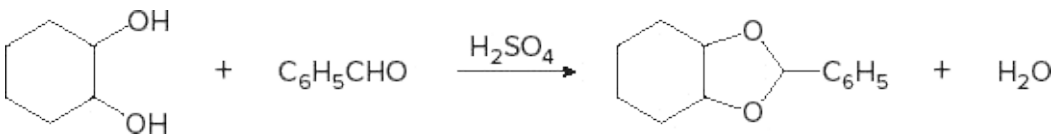
18.67 Treatment of $(HOCH_2CH_2CH_2CH_2)_2CO$ with acid forms a product of molecular formula $C_9H_{16}O_2$ and a molecule of water. Draw the structure of the product and explain how it is formed.

18.68 Draw a stepwise mechanism for each reaction.

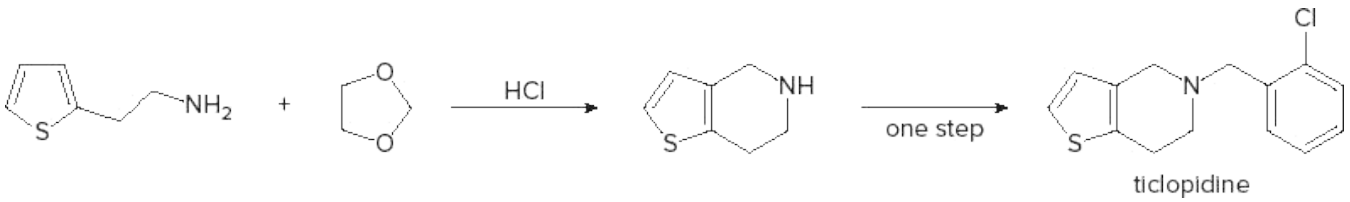
a.



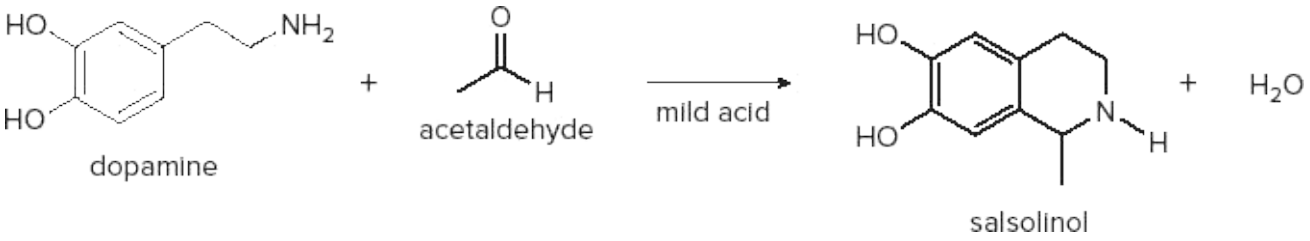
b.



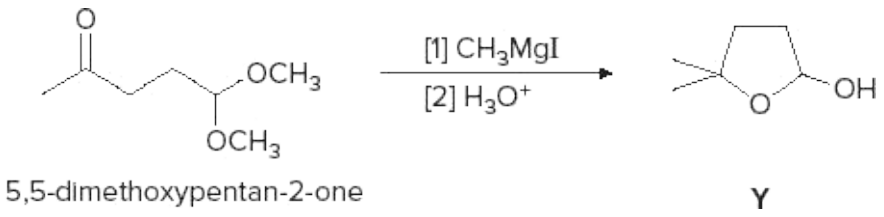
18.69 Draw a stepwise mechanism for the following reaction, a key step in the synthesis of ticlopidine, a drug that inhibits platelet aggregation. Ticlopidine has been used to reduce the risk of stroke in patients who cannot tolerate aspirin.



18.70 **Salsolinol is a naturally occurring compound found in bananas, chocolate, and several foods derived from plant sources. Salsolinol is also formed in the body when acetaldehyde, an oxidation product of the ethanol ingested in an alcoholic beverage, reacts with dopamine, a neurotransmitter. Draw a stepwise mechanism for the formation of salsolinol in the following reaction.**

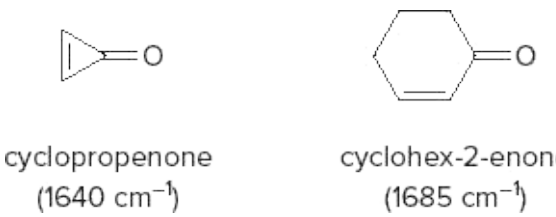


18.71 **Reaction of 5,5-dimethoxypentan-2-one with methylmagnesium iodide followed by treatment with aqueous acid forms cyclic hemiacetal Y. Draw a stepwise mechanism that illustrates how Y is formed.**



Spectroscopy

18.72 **Although the carbonyl absorption of cyclic ketones generally shifts to higher wavenumber with decreasing ring size (Section B.4B), the C=O of cyclopropenone absorbs at lower wavenumber in its IR spectrum than the C=O of cyclohex-2-enone. Explain this observation by using the principles of aromaticity learned in Chapter 15.**

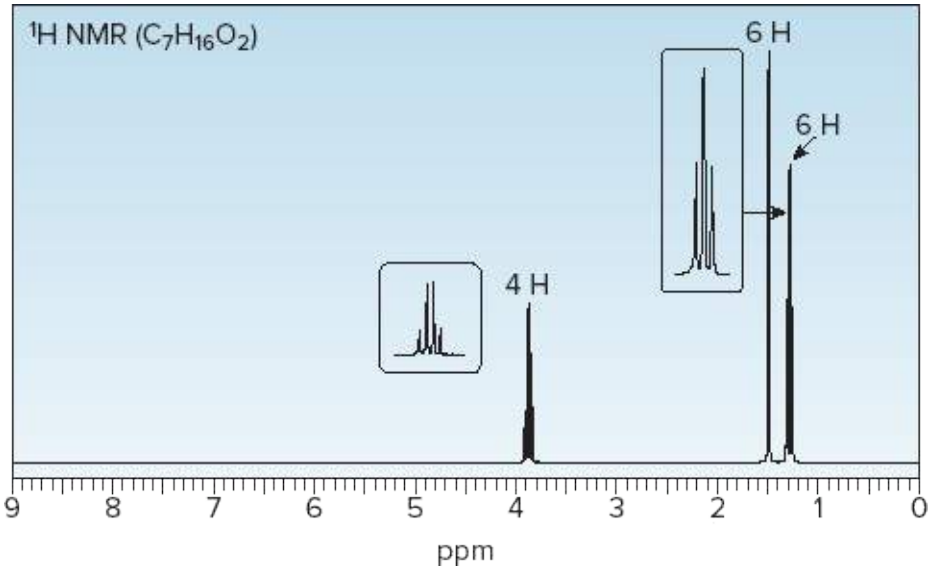


18.73 **Use the ^{1}H NMR and IR data to determine the structure of each compound.**

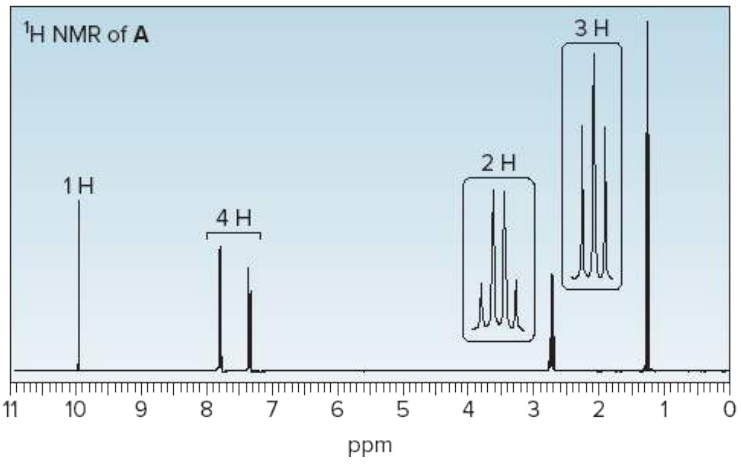
Compound A	**Molecular formula:**	**$C_5H_{10}O$**
		1728, 2791, and 2700 cm^{-1}

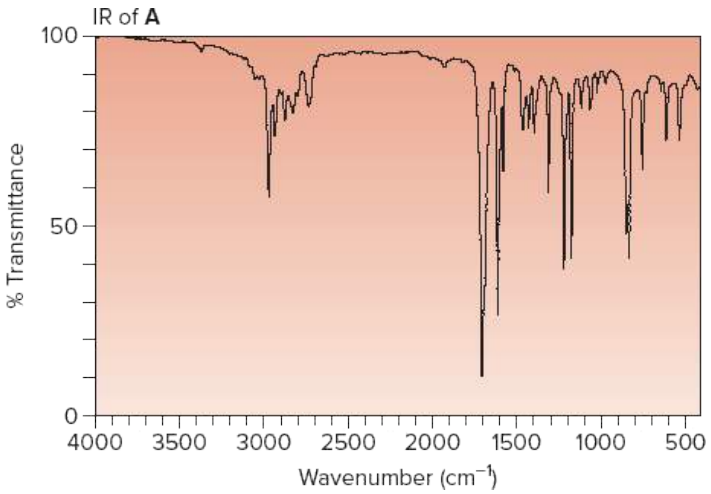
	IR absorptions at	**1.08 (singlet, 9 H) and 9.48**
	^{1}H NMR data:	**(singlet, 1 H) ppm**
Compound B	**Molecular formula:**	**$C_{10}H_{12}O$**
	IR absorption at	**1686 cm^{-1}**
	^{1}H NMR data:	**1.21 (triplet, 3 H), 2.39 (singlet, 3 H), 2.95 (quartet, 2 H), 7.24 (doublet, 2 H), and 7.85 (doublet, 2 H) ppm**
Compound C	**Molecular formula:**	**$C_{10}H_{12}O$**
	IR absorption at	**1719 cm^{-1}**
	^{1}H NMR data:	**1.02 (triplet, 3 H), 2.45 (quartet, 2 H), 3.67 (singlet, 2 H), and 7.06–7.48 (multiplet, 5 H) ppm**

18.74 **A solution of acetone [$(CH_3)_2C{=}O$] in ethanol (CH_3CH_2OH) in the presence of a trace of acid was allowed to stand for several days, and a new compound of molecular formula $C_7H_{16}O_2$ was formed. The IR spectrum showed only one major peak in the functional group region around 3000 cm^{-1}, and the ^{1}H NMR spectrum is given here. What is the structure of the product?**

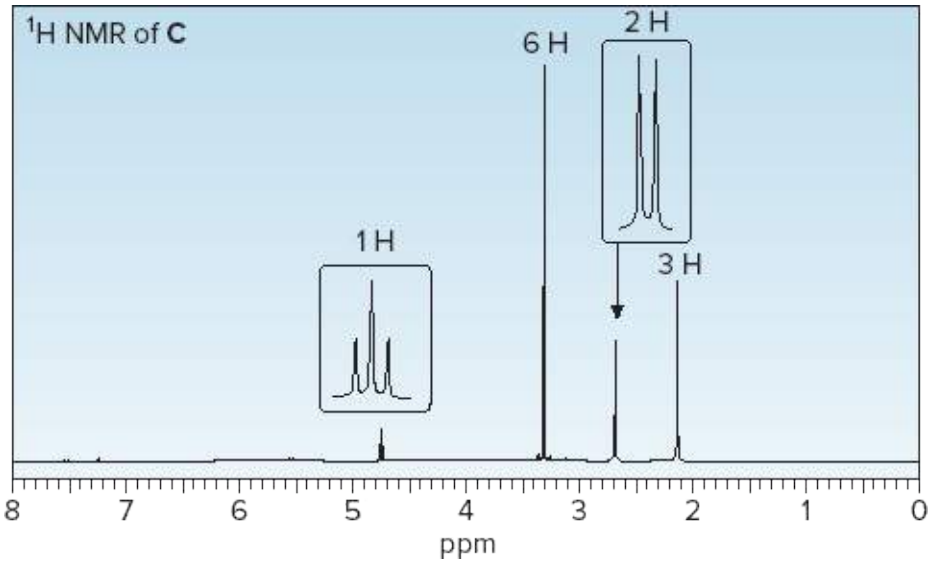


18.75 **Identify the structure of compound A (molecular formula $C_9H_{10}O$) from the ^{1}H NMR and IR spectra given.**





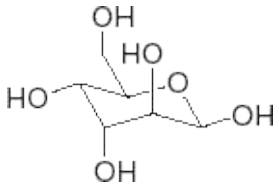
18.76 **An unknown compound C of molecular formula $C_6H_{12}O_3$ exhibits a strong absorption in its IR spectrum at 1718 cm^{-1} and the given ^1H NMR spectrum. What is the structure of C?**



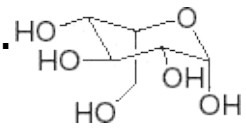
Carbohydrates

18.77 **Draw the structure of the acyclic polyhydroxy aldehyde that cyclizes to each hemiacetal.**

a.

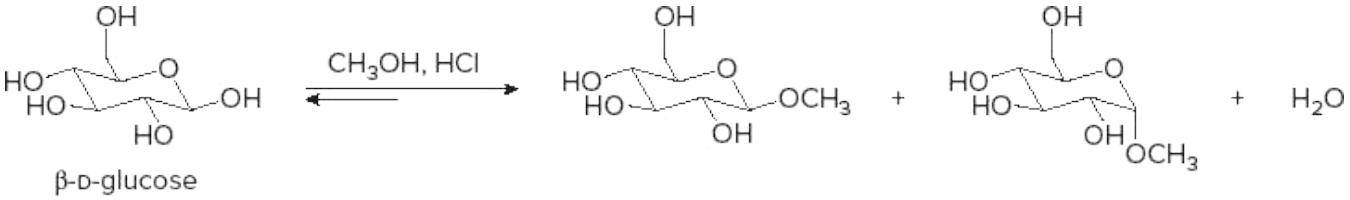


b.



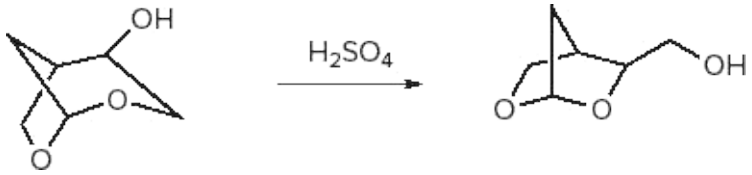
18.78 **β-D-Glucose, a hemiacetal, can be converted to a mixture of acetals on treatment with CH_3OH in the presence of acid. Draw a stepwise mechanism for this reaction. Explain why two acetals are formed from a**

single starting material.



Challenge Problems

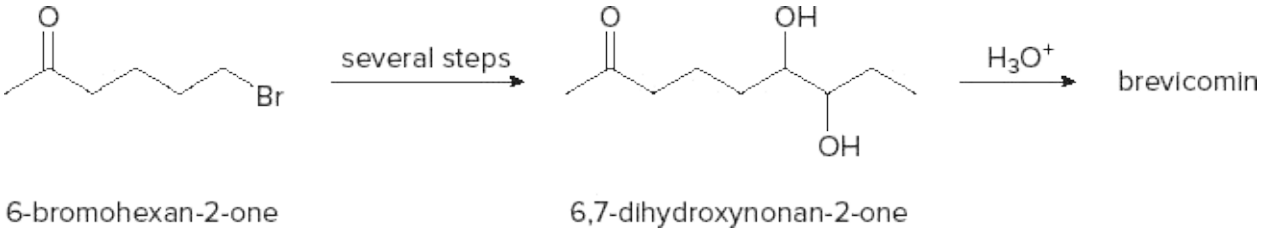
18.79 Draw a stepwise mechanism for the following isomerization.



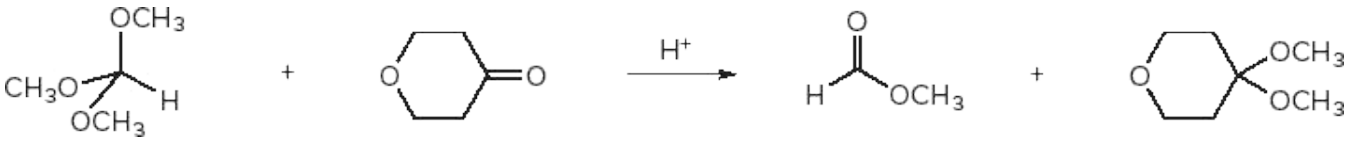
18.80 Brevicomin, the aggregation pheromone of the western pine bark beetle, contains a bicyclic bridged ring system and is prepared by the acid-catalyzed cyclization of 6,7-dihydroxy-nonan-2-one.

a. Suggest a structure for brevicomin.

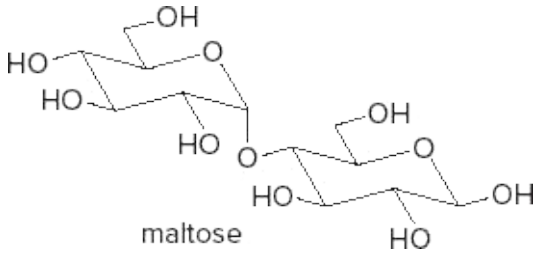
b. Devise a synthesis of 6,7-dihydroxynonan-2-one from 6-bromohexan-2-one. You may also use three-carbon alcohols and any required organic or inorganic reagents.



18.81 Draw a stepwise mechanism for the following reaction.



18.82 Maltose is a carbohydrate present in malt, the liquid obtained from barley and other grains. Although maltose has numerous functional groups, its reactions are explained by the same principles we have already encountered.



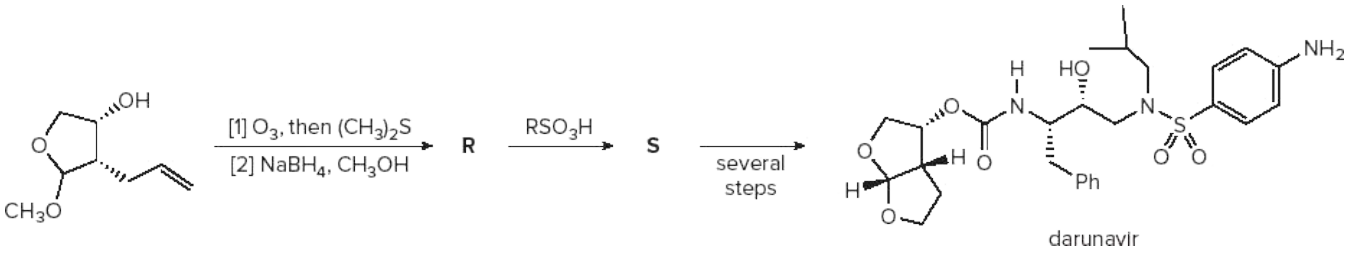
a. Label the acetal and hemiacetal carbons.

b. What products are formed when maltose is treated with each of these reagents: [1] $H3O^+$; [2] CH3OH and HCl; [3] excess NaH, then excess CH_3I?

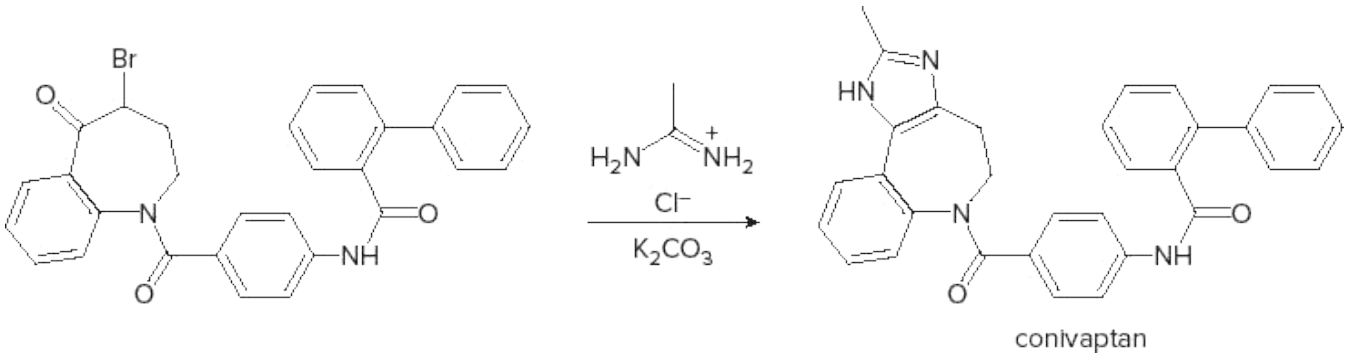
c. Draw the products formed when the compound formed in Reaction [3] of part (b) is treated with aqueous acid.

The reactions in parts (b) and (c) are used to determine structural features of carbohydrates like maltose. We will learn much more about maltose and similar carbohydrates in Chapter 26.

18.83 Identify R and S in the following reaction sequence, and draw a mechanism for the conversion of R to S (molecular formula $C_6H_{10}O_3$). S was used in the synthesis of darunavir (trade name Prezista), used to treat HIV.

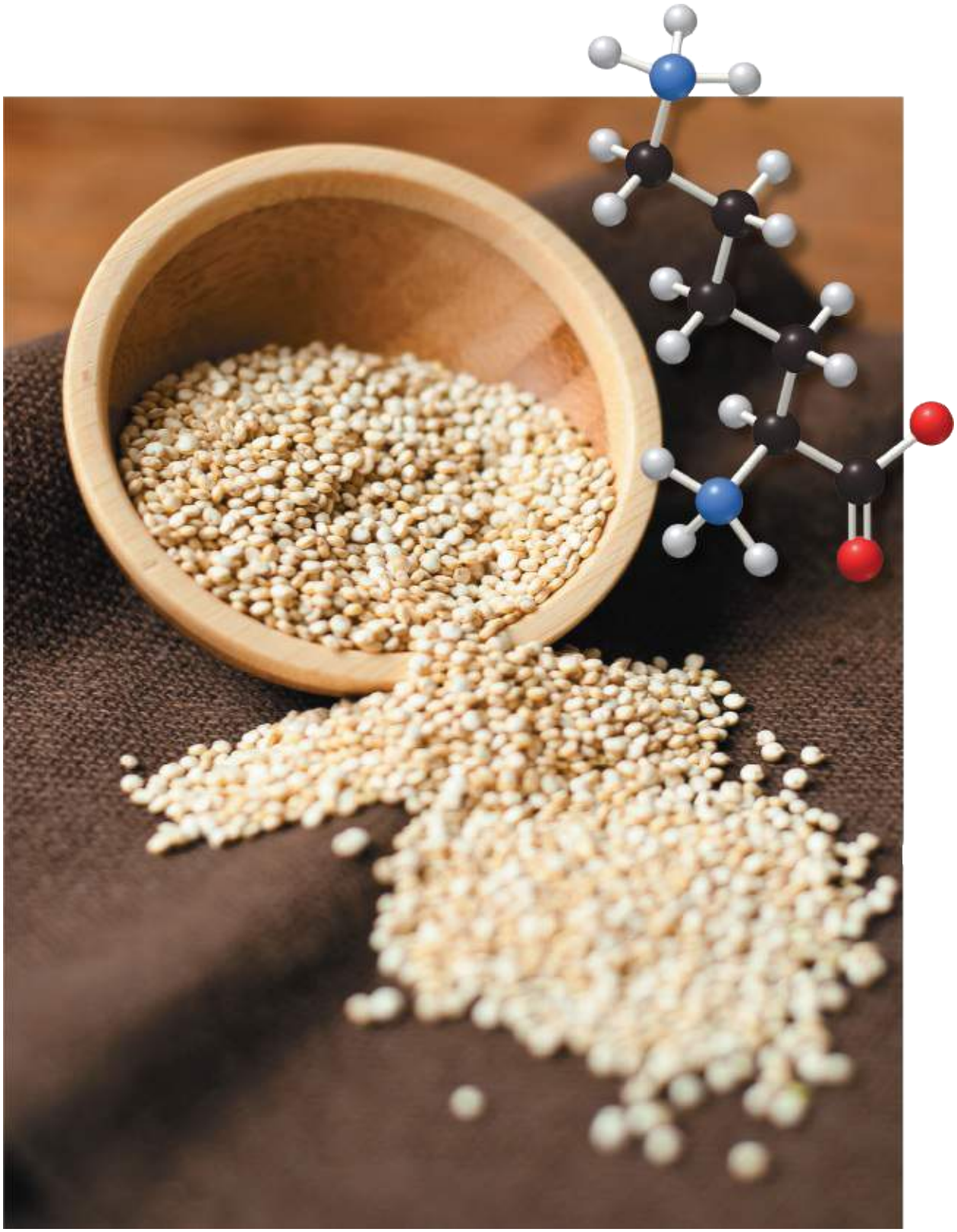


18.84 Draw a stepwise mechanism for the following reaction, a key step in the synthesis of conivaptan (trade name Vaprisol), a drug used in the treatment of low sodium levels.



19

Carboxylic Acids and Nitriles



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19.1 Structure and bonding
19.2 Nomenclature
19.3 Physical and spectroscopic properties
19.4 Interesting carboxylic acids and nitriles
19.5 Aspirin, arachidonic acid, and prostaglandins
19.6 Preparation of carboxylic acids
19.7 Carboxylic acids—Strong organic Brønsted–Lowry acids
19.8 Inductive effects in aliphatic carboxylic acids
19.9 Substituted benzoic acids
19.10 Extraction
19.11 Amino acids
19.12 Nitriles

Lysine is an essential amino acid that is needed for protein synthesis. Because lysine cannot be synthesized by humans and is not stored in the body, it must be ingested on a regular basis. Common food sources of lysine are meat, beans, peas, soy, and peanuts. Although most grains are low in lysine, quinoa is relatively high in lysine content and a good source of essential amino acids for a vegetarian diet. Like other amino acids, lysine contains both a carboxylic acid and an amine base. In Chapter 19, we learn about carboxylic acids and a related family of compounds, nitriles.

Why Study…

Carboxylic Acids and Nitriles?

Chapter 19 concentrates on two classes of compounds, carboxylic acids (RCO_2H) and nitriles (RCN). With a polarized C=O and an acidic O—H bond, carboxylic acids undergo a variety of reactions. In this chapter we concentrate on one feature only—the acidity of carboxylic acids. Aspirin, a synthetic pain reliever, and naturally occurring fatty acids and prostaglandins are all carboxylic acids.

Nitriles are less common, but this useful functional group can be transformed into many other common functional groups. Moreover, several drugs that contain one or more cyano groups (C≡N) are used in the treatment of breast cancer and depression.

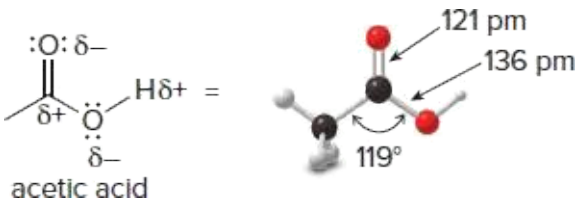
The word *carboxy* (for a COOH group) is derived from *carbo*nyl (C=O) + hydr*oxy* (OH).

19.1 Structure and Bonding

Carboxylic acids are organic compounds containing a carboxy group (COOH). Although the structure of a carboxylic acid is often abbreviated as RCOOH or RCO_2H, keep in mind that the central carbon atom of the functional group is doubly bonded to one oxygen atom and singly bonded to another.

carboxylic acid carboxy group

The carbon atom of a carboxy group is surrounded by three groups, making it sp^2 hybridized and trigonal planar, with bond angles of approximately 120°. The C=O of a carboxylic acid is *shorter* than its C—O. Because oxygen is more electronegative than either carbon or hydrogen, the C—O and O—H bonds are polar.



acetic acid

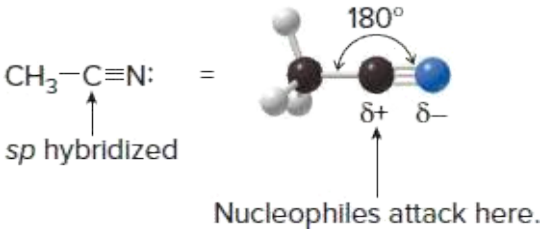
Nitriles are compounds that contain a cyano group, C≡N, bonded to an alkyl group. Nitriles have no carbonyl group, so they are structurally distinct from carboxylic acids. The carbon atom of the cyano group, however, has the same oxidation state as the carbonyl carbon of a carboxylic acid, so there are certain parallels in their chemistry.

nitrile

Each labeled C has three bonds to a more electronegative element.

The structure and bonding in nitriles is very different from that in carboxylic acids, and it resembles the carbon–carbon triple bond of alkynes. Unlike alkynes, however,

nitriles contain an electrophilic carbon atom, making them susceptible to nucleophilic attack.



- **The carbon atom of the C≡N group is *sp* hybridized, making it linear with a bond angle of 180°.**
- **The triple bond consists of one σ and two π bonds.**

19.2 Nomenclature

Both IUPAC and common names are used for carboxylic acids and nitriles.

19.2A Naming Carboxylic Acids

In IUPAC nomenclature, carboxylic acids are identified by a suffix added to the parent name of the longest chain, and two different endings are used depending on whether the carboxy group is bonded to a chain or a ring.

To name a carboxylic acid using the IUPAC system:

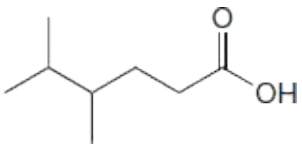
[1] If the COOH is bonded to a *chain* of carbons, find the longest chain containing the COOH group, and change the *-e* ending of the parent alkane to the suffix *-oic acid*. If the COOH group is bonded to a *ring*, name the ring and add the words *carboxylic acid*.

[2] Number the carbon chain or ring to put the COOH group at C1, but omit this number from the name. Apply all the other usual rules of nomenclature.

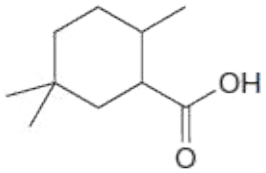
Sample Problem 19.1 Naming a Carboxylic Acid Using the IUPAC System

Give the IUPAC name of each compound.

a.



b.



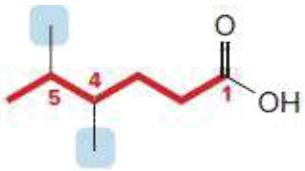
Solution

a. [1] Find and name the longest chain containing COOH:

hexane ⟶ hexan*oic acid*
(6 C's)

The COOH contributes one C to the longest chain.

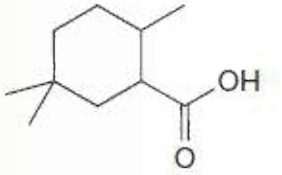
[2] Number and name the substituents:



two methyl substituents on C4 and C5

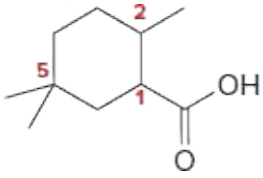
Answer: 4,5-dimethylhexanoic acid

b. [1] Find and name the ring bonded to COOH.



cyclohexane + carboxylic acid
(6 C's)

[2] Number and name the substituents:



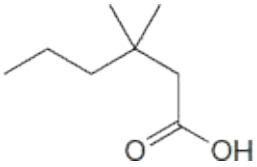
Number to put COOH at C1 and give the second substituent (CH_3) the lower number (C2).

Answer: 2,5,5-trimethylcyclohexanecarboxylic acid

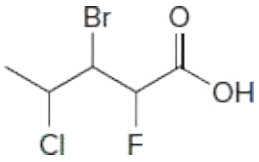
Problem 19.1

Give the IUPAC name for each compound.

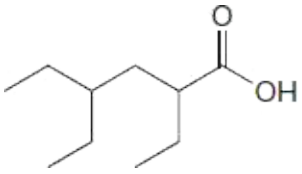
a.



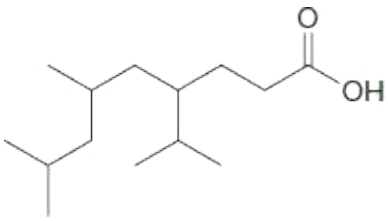
b.



c.



d.



More Practice:

Try Problems 19.31a; 19.34a, c, d, f.

Problem 19.2

Give the structure corresponding to each IUPAC name.

a. 2-bromobutanoic acid

b. 2,3-dimethylpentanoic acid

c. 3,3,4-trimethylheptanoic acid

d. 2-sec-butyl-4,4-diethylnonanoic acid

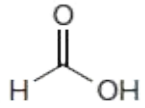
e. 3,4-diethylcyclohexanecarboxylic acid

f. 1-isopropylcyclobutanecarboxylic acid

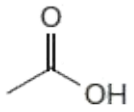
Most simple carboxylic acids have common names that are more widely used than their IUPAC names.

- **A common name is formed by using a common parent name followed by the suffix *-ic acid*.**

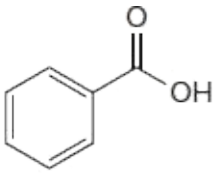
The common parent names for simple carboxylic acids are similar to those used for aldehydes (Table 18.1). The common names formic acid, acetic acid, and benzoic acid are virtually always used instead of their IUPAC names.



formic acid
(methanoic acid)



acetic acid
(ethanoic acid)



benzoic acid
(benzenecarboxylic acid)

Problem 19.3

Draw the structure corresponding to each common name:

a. α-methoxyvaleric acid

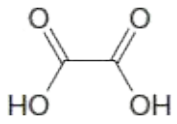
b. β-phenylpropionic acid

c. α,β-dimethylcaproic acid

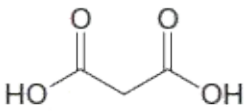
d. α-chloro-β-methylbutyric acid

19.2B Naming Dicarboxylic Acids and Carboxylates

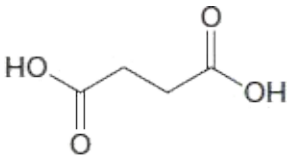
Many compounds containing two carboxy groups are also known. In the IUPAC system, diacids are named by adding the suffix *-dioic acid* to the name of the parent alkane. The three simplest diacids are most often identified by their common names, as shown.



oxalic acid
(ethanedioic acid)



malonic acid
(propanedioic acid)



succinic acid
(butanedioic acid)

Metal salts of carboxylate anions are formed from carboxylic acids in many reactions in Chapter 19. To name the metal salt of a carboxylate anion, change the *-ic acid* ending of the carboxylic acid to the suffix *-ate* and put three parts together:

name of the metal cation	+	parent	+	suffix
		common or IUPAC		*-ate*

Two examples are shown in Figure 19.1.

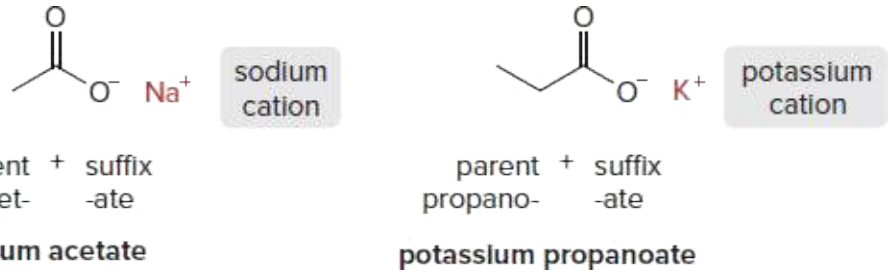
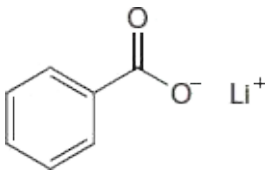


Figure 19.1 **Naming the metal salts of carboxylate anions**

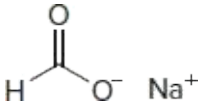
Problem 19.4

Give the IUPAC name for each metal salt of a carboxylate anion.

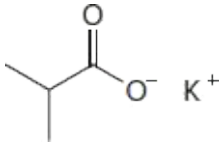
a.



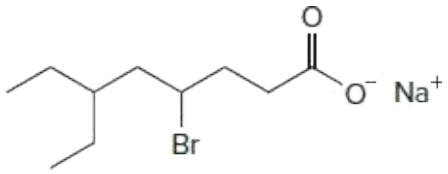
b.



c.



d.



Problem 19.5

Depakote, a drug used to treat seizures and bipolar disorder, consists of a mixture of valproic acid [$(CH_3CH_2CH_2)_2CHCO_2H$] and its sodium salt. Give IUPAC names for each of these compounds.

19.2C Naming Nitriles

In contrast to the carboxylic acids, nitriles are named as alkane derivatives. To name a nitrile using IUPAC rules:

In naming a nitrile, the CN carbon is one carbon atom of the longest chain. CH_3CH_2CN is propanenitrile, *not* ethanenitrile.

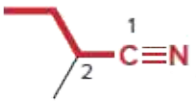
- **Find the longest chain that contains the CN and add the word *nitrile* to the name of the parent alkane. Number the chain to put CN at C1, but**

omit this number from the name.

Common names for nitriles are derived from the names of the carboxylic acid having the same number of carbon atoms by replacing the *-ic acid* ending of the carboxylic acid by the suffix *-onitrile*.

When CN is named as a substituent, it is called a *cyano* group. Figure 19.2 illustrates features of nitrile nomenclature.

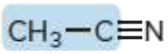
a. IUPAC name for a nitrile



butane + nitrile
(4 C's)

2-methylbutanenitrile

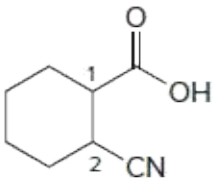
b. Common name for a nitrile



derived from
acetic *acid*

acetonitrile

c. CN as a substituent

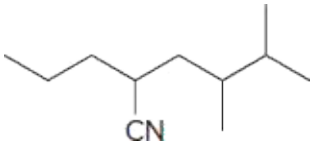


2-cyanocyclohexanecarboxylic acid

Figure 19.2 **Summary of nitrile nomenclature**

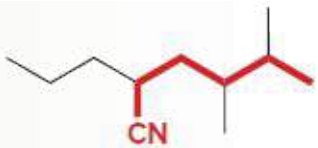
Sample Problem 19.2 Naming a Nitrile Using the IUPAC System

Give the IUPAC name for the following nitrile.



Solution

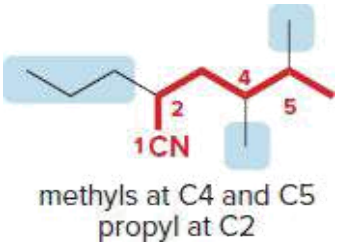
[1] Find and name the longest chain containing the CN.



hexane + nitrile
(6 C's)

The CN contributes
one C to the longest chain.

[2] Number and name the substituents.



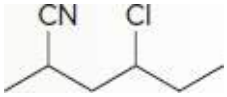
methyls at C4 and C5
propyl at C2

Answer: 4,5-dimethyl-2-propylhexanenitrile

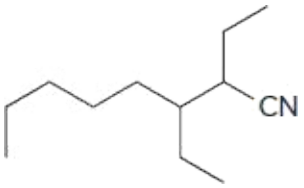
Problem 19.6

Give the IUPAC name for each nitrile.

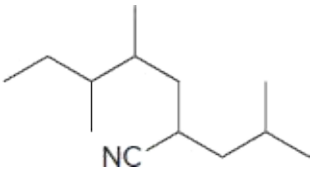
a.



b.



c.



More Practice:

Try Problems 19.33a; 19.34g, h.

19.3 Physical and Spectroscopic Properties

19.3A Physical Properties

Carboxylic acids and nitriles exhibit dipole–dipole interactions because they have polar C—O, C—N, and O—H bonds. Carboxylic acids also exhibit intermolecular hydrogen bonding because they possess a hydrogen atom bonded to an electronegative oxygen atom. Carboxylic acids often exist as dimers, held together by *two* intermolecular hydrogen bonds between the carbonyl oxygen atom of one molecule and the OH hydrogen atom of another molecule (Figure 19.3). Carboxylic acids are the most polar organic compounds we have studied so far.

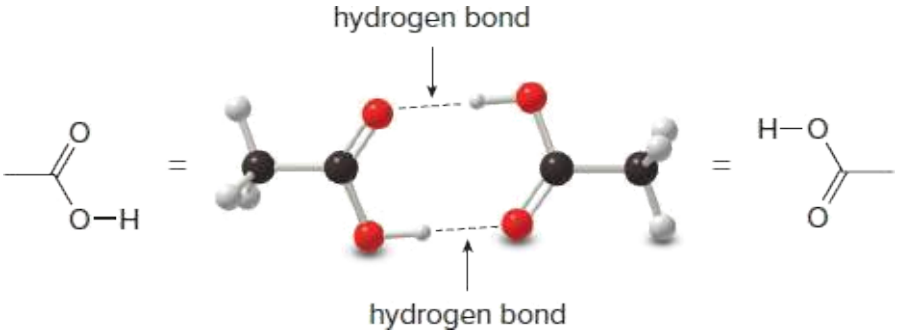
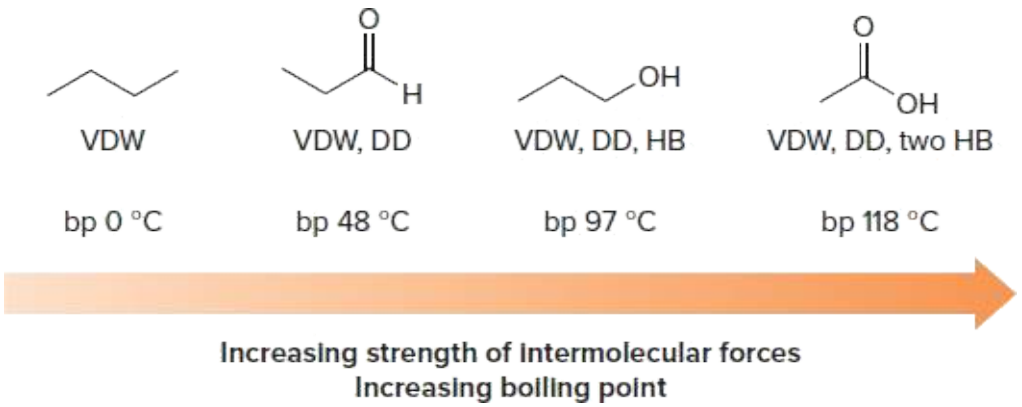


Figure 19.3 **Two molecules of acetic acid (CH_3COOH) held together by two hydrogen bonds**

How these intermolecular forces affect the physical properties of carboxylic acids is summarized in Table 19.1.

Table 19.1 **Physical Properties of Carboxylic Acids**

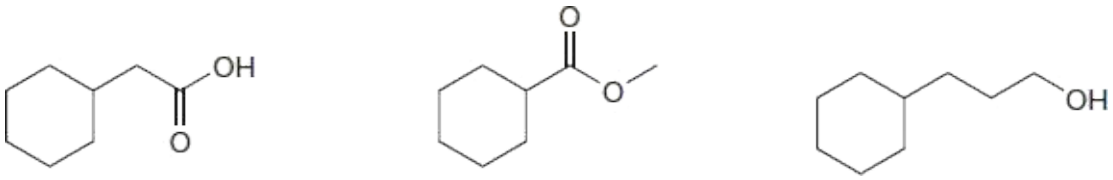
Property	Observation
Boiling point and melting point	• **Carboxylic acids have higher boiling points and melting points than other compounds of comparable molecular weight.** 
Solubility	• **Carboxylic acids are soluble in organic solvents regardless of size.** • **Carboxylic acids having ≤ 5 C's are water soluble because they can hydrogen bond with H_2O (Section 3.4C).** • **Carboxylic acids having > 5 C's are water insoluble because the nonpolar alkyl portion is too large to dissolve in the polar H_2O solvent. These "fatty" acids dissolve in a nonpolar fat-like environment but do not**

	dissolve in water.

Key: VDW = van der Waals, DD = dipole–dipole, HB = hydrogen bonding

Problem 19.7

Rank the following compounds in order of increasing boiling point. Which compound is the most water soluble? Which compound is the least water soluble?



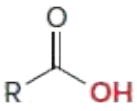
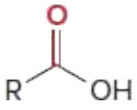
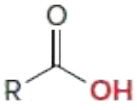
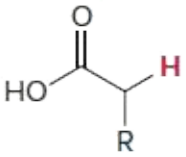
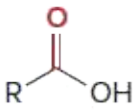
19.3B Spectroscopic Properties

Many details of the spectroscopy of carboxylic acids and nitriles have been presented in Spectroscopy Parts B and C:

- The infrared absorptions of carboxylic acids: Section B.4B and Table B.2
- The infrared absorption of nitriles: Section B.4C and Table B.2
- ^{1}H and ^{13}C NMR absorptions: Tables C.1 and C.5

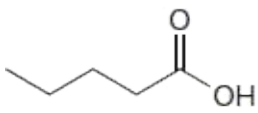
Key NMR and IR absorptions for carboxylic acids and nitriles are summarized in Table 19.2, and Figure 19.4 illustrates ^{1}H and ^{13}C NMR spectra for a simple carboxylic acid.

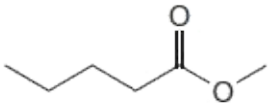
Table 19.2 Characteristic Spectroscopic Absorptions of Carboxylic Acids and Nitriles

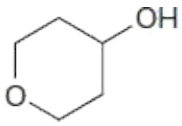
Compound	Type of spectroscopy	Type of C, H	Absorption
Carboxylic acid	IR absorptions		2500–3500 cm^{-1} (very broad, strong)
			1710 cm^{-1} (strong)
	^{1}H NMR absorptions		10–12 ppm
			2–2.5 ppm
	^{13}C NMR absorption		170–210 ppm
Nitrile	IR absorption	—C≡N	2250 cm^{-1}
	^{13}C NMR absorption	—C≡N	115–120 ppm

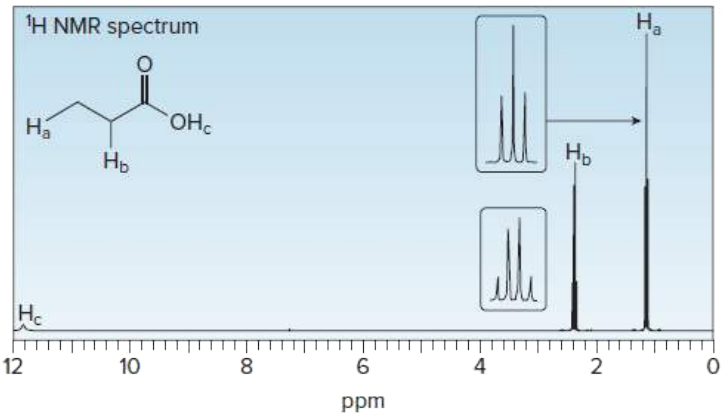
Problem 19.8

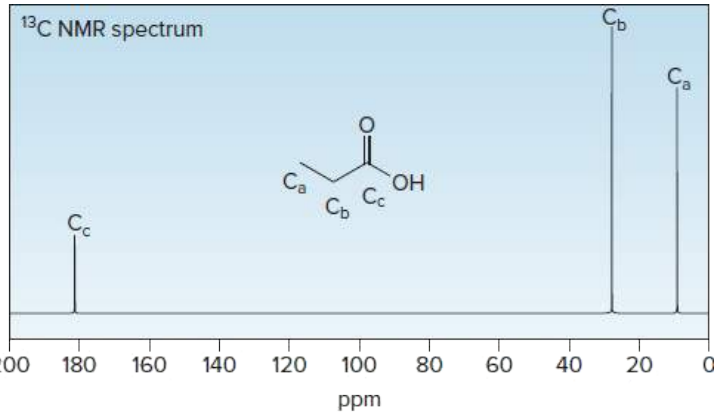
Explain how you could use IR spectroscopy to distinguish among the following three compounds.









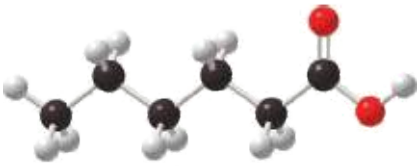


- **^{1}H NMR spectrum:** There are three signals due to three different kinds of H atoms. The H_a and H_b signals are split into a triplet and quartet, respectively. The H_c signal, a singlet, is due to the highly deshielded OH proton.
- **^{13}C NMR spectrum:** There are three signals due to three different kinds of carbon atoms. The carbonyl carbon is highly deshielded.

Figure 19.4 **The ^{1}H and ^{13}C NMR spectra of propanoic acid**

formic acid

acetic acid



hexanoic acid

Female ginkgo trees produce seeds with an unpleasant odor due to the presence of hexanoic acid. ***©Dr. Steven J. Wolf***

Although oxalic acid is toxic, you would have to eat about 9 pounds of spinach at one time to ingest a fatal dose.
©bialasiewicz/123RF

19.4 Interesting Carboxylic Acids and Nitriles

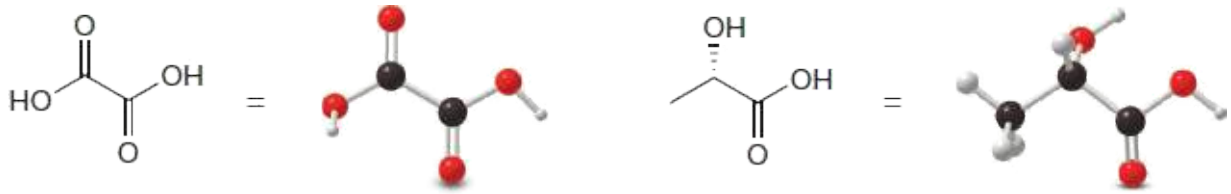
Several simple carboxylic acids have characteristic odors and flavors.

Formic acid (HCOOH), a carboxylic acid with an acrid odor and a biting taste, is responsible for the sting of some types of ants. The name is derived from the Latin word *formica*, meaning “ant.”

Acetic acid (CH_3COOH) is the sour-tasting component of vinegar. The name comes from the Latin word *acetum*, meaning "vinegar." The air oxidation of ethanol to acetic acid is the process that makes "bad" wine taste sour. Acetic acid is an industrial starting material for polymers used in paints and adhesives. Pure acetic acid is often called *glacial* acetic acid because it freezes just below room temperature (mp = 17 °C), forming white crystals reminiscent of the ice in a glacier.

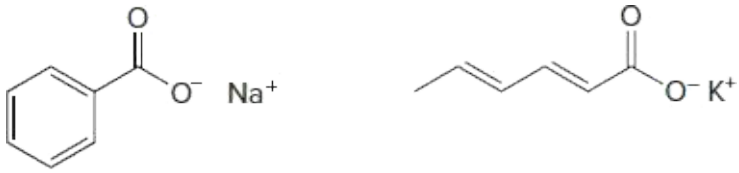
Hexanoic acid [$CH^3(CH^2)^4COOH$] is a low-molecular-weight carboxylic acid with the foul odor of dirty socks and locker rooms. Its common name, caproic acid, is derived from the Latin word *caper*, meaning "goat." The fleshy coat of seeds that are produced by female ginkgo trees contains hexanoic acid, giving the seeds an unpleasant and even repulsive odor.

Oxalic acid and lactic acid are simple carboxylic acids quite prevalent in nature. Oxalic acid occurs naturally in spinach and rhubarb. Lactic acid gives sour milk its distinctive taste.



oxalic acid lactic acid

Salts of carboxylic acids are commonly used as preservatives. Sodium benzoate, a fungal growth inhibitor, is a preservative used in soft drinks, and potassium sorbate is an additive that prolongs the shelf life of baked goods and other foods.

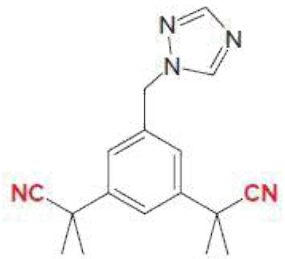


sodium benzoate potassium sorbate

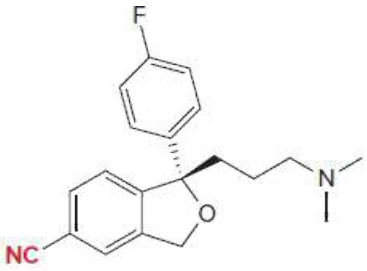
Soaps, the sodium salts of fatty acids, were discussed in Section 3.6.

Although nitriles are much less common than carboxylic acids, the naturally occurring cyanohydrin derivatives discussed in Section 18.8 constitute one group of compounds that contain a nitrile. In addition, several widely used drugs contain one or more cyano groups, including anastrozole, used to reduce the recurrence of breast cancer in women whose tumors are estrogen positive; escitalopram, used to treat depression and

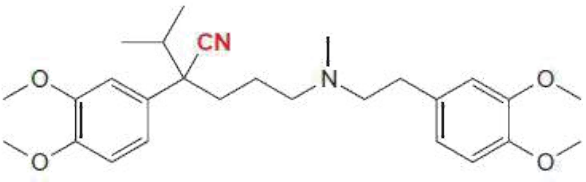
anxiety; and verapamil for high blood pressure and chest pain.



Generic name anastrozole
Trade name Arimidex



Generic name escitalopram
Trade names Cipralex, Lexapro

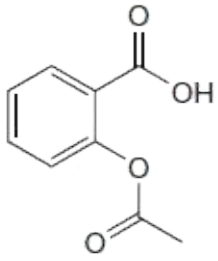


Generic name verapamil
Trade names Calan, Verelan

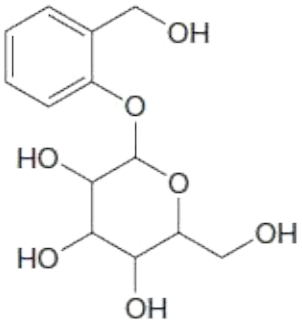
Anastrozole is called an aromatase inhibitor because it blocks the activity of the aromatase enzyme, which is responsible for estrogen synthesis. This inhibits tumor growth in those forms of breast cancer that are stimulated by estrogen.

19.5 Aspirin, Arachidonic Acid, and Prostaglandins

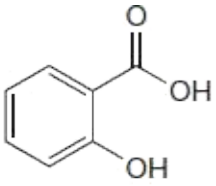
Recall from Chapter 2 that aspirin (acetylsalicylic acid) is a synthetic carboxylic acid, similar in structure to salicin, a naturally occurring compound isolated from willow bark, and salicylic acid, found in meadowsweet.



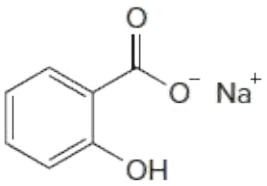
aspirin
(acetylsalicylic acid)



salicin
(isolated from
willow bark)



salicylic acid
(isolated from
meadowsweet)



sodium salicylate
(sweet carboxylate salt)

The word *aspirin* is derived from the prefix *a-* for *acetyl* + *spir* from the Latin name *spirea* for the meadowsweet plant.

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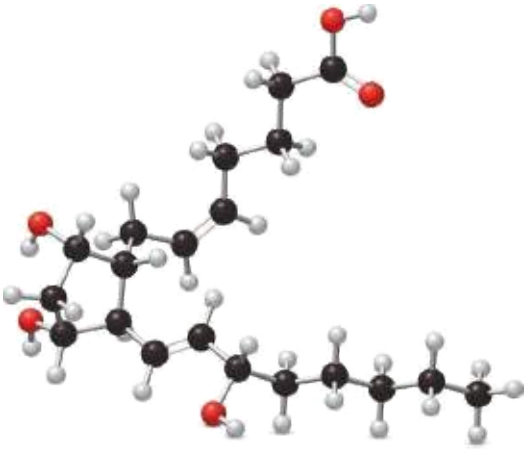
Aspirin is the most widely used pain reliever and anti-inflammatory agent in the world, yet its mechanism of action remained unknown until the 1970s. John Vane, Bengt Samuelsson, and Sune Bergstrom shared the 1982 Nobel Prize in Physiology or Medicine for unraveling the details of its mechanism.

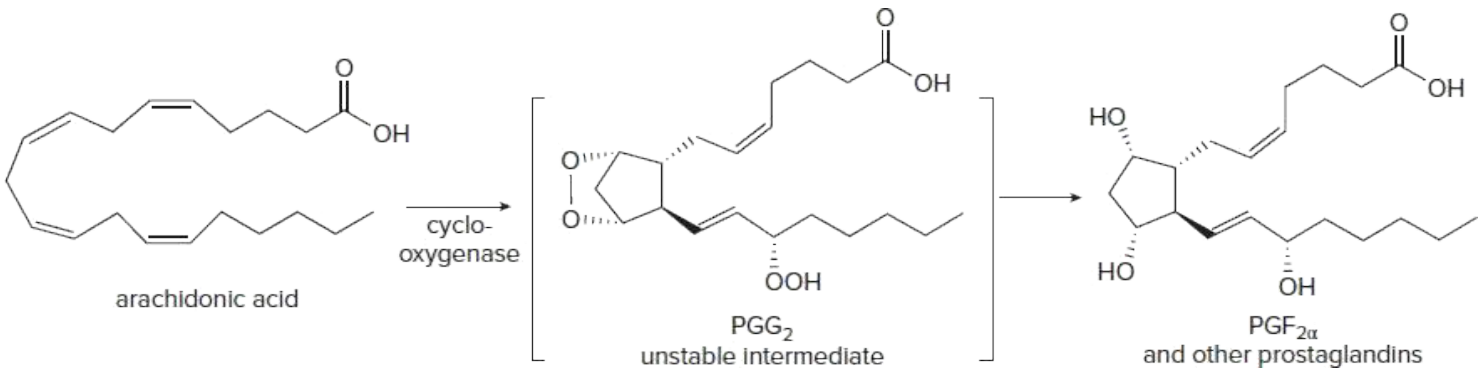
Both salicylic acid and sodium salicylate (its sodium salt) were widely used analgesics in the nineteenth century, but both had undesirable side effects. Salicylic acid irritated the mucous membranes of the mouth and stomach, and sodium salicylate was too sweet for most patients. Aspirin, a synthetic compound, was first sold in 1899 after Felix Hoffmann, a German chemist at Bayer Company, developed a feasible commercial synthesis. Hoffmann's work was motivated by personal reasons: his father suffered from rheumatoid arthritis and was unable to tolerate the sweet taste of sodium salicylate.

How does aspirin relieve pain and reduce inflammation? Aspirin blocks the synthesis of prostaglandins, 20-carbon fatty acids with a five-membered ring that are responsible for pain, inflammation, and a wide variety of other biological functions. $PGF_{2\alpha}$ contains the typical carbon skeleton of a prostaglandin.

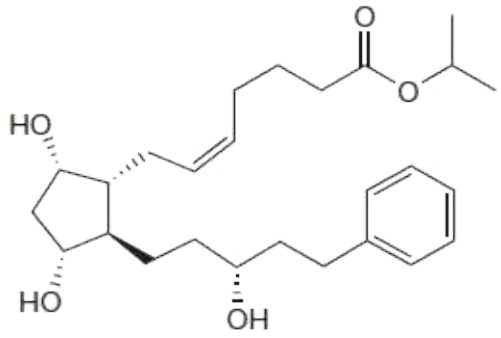


$PGF_{2\alpha}$
a prostaglandin

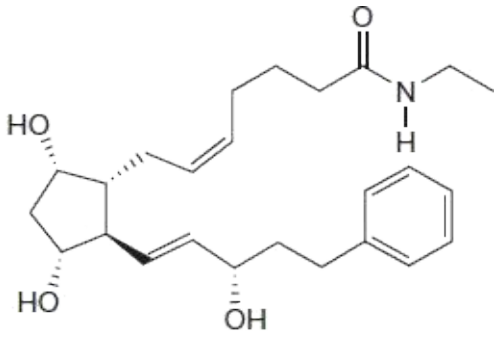
Prostaglandins are not stored in cells. Rather, they are synthesized from Page 894 arachidonic acid, a polyunsaturated fatty acid having four cis double bonds.
Unlike hormones, which are transported in the bloodstream to their sites of action, prostaglandins act where they are synthesized. Aspirin acts by blocking the synthesis of prostaglandins from arachidonic acid. Aspirin inactivates cyclooxygenase, an enzyme that converts arachidonic acid to PGG_2, an unstable precursor of $PGF_{2\alpha}$ and other prostaglandins. Aspirin lessens pain and decreases inflammation because it prevents the synthesis of prostaglandins, the compounds responsible for both of these physiological responses.



Although prostaglandins have a wide range of biological activity, their inherent instability often limits their usefulness as drugs. Consequently, more-stable analogues with useful medicinal properties have been synthesized. For example, latanoprost (trade name Xalatan) and bimatoprost (trade name Lumigan) are prostaglandin analogues used to reduce eye pressure in individuals with glaucoma.



latanoprost



bimatoprost

Problem 19.9

How many tetrahedral stereogenic centers does $PGF_{2\alpha}$ contain? Draw its enantiomer. How many of its double bonds can exhibit cis-trans isomerism? Considering both its double bonds and its tetrahedral stereogenic centers, how many stereoisomers are possible for $PGF_{2\alpha}$?

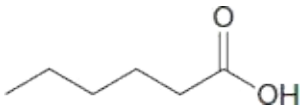
19.6 Preparation of Carboxylic Acids

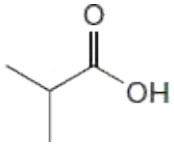
We begin our study of the reactions involving carboxylic acids and nitriles by summarizing methods that introduce a carboxy group presented in earlier chapters. In Sections 19.7–19.11, we then concentrate on the acidity of carboxylic acids, and in Section 19.12, we examine the preparation and reactions of nitriles.

Where have we encountered carboxylic acids as reaction products before? The carbonyl carbon is highly oxidized, because it has three C—O bonds, so carboxylic acids are often prepared by oxidation reactions. Four oxidation methods and one carbon–carbon bond-forming reaction are listed in Table 19.3.

Problem 19.10

What alcohol can be oxidized to each carboxylic acid?

a.


b.


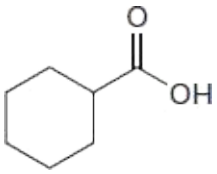
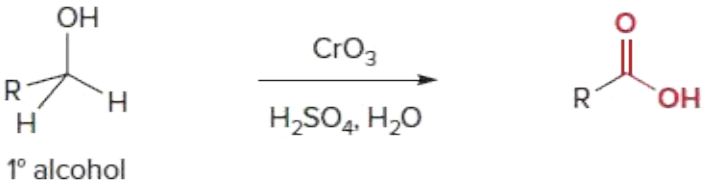
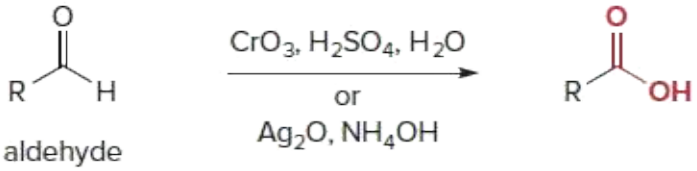
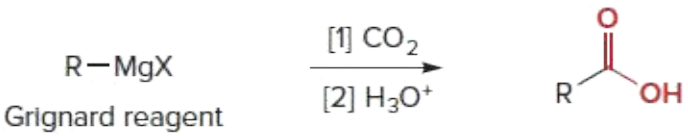
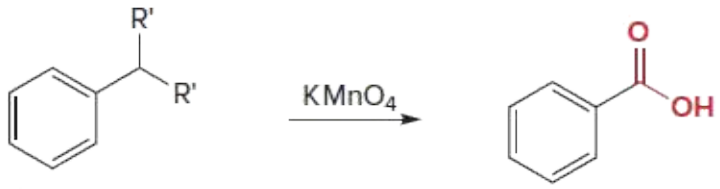
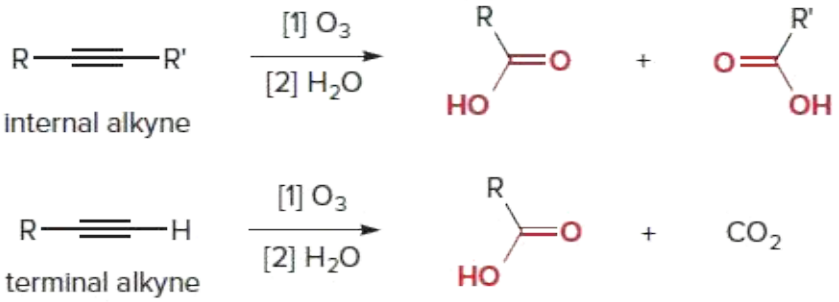
c.


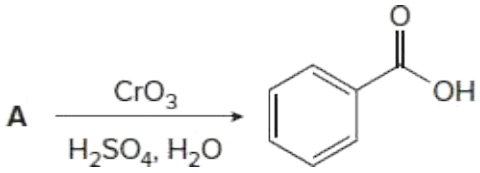
Table 19.3 Methods That Synthesize Carboxylic Acids

Method	Reaction
[1] Oxidation of 1° alcohols (Section 12.12B)	 1° alcohol
[2] Oxidation of aldehydes (Section 17.8)	 aldehyde
[3] Carboxylation of Grignard reagents (Section 17.14)	 Grignard reagent
[4] Oxidation of alkyl benzenes (Section 16.15A)	 alkyl benzene R' = H or alkyl
[5] Oxidative cleavage of alkynes (Section 12.11)	 internal alkyne terminal alkyne

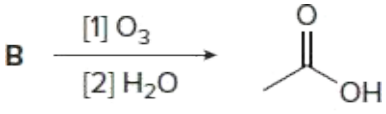
Problem 19.11

Identify A–F in the following reactions.

a.

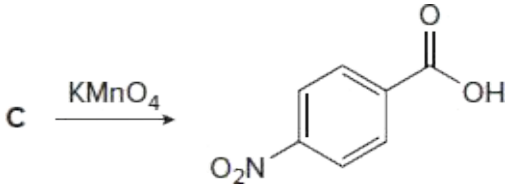


b.

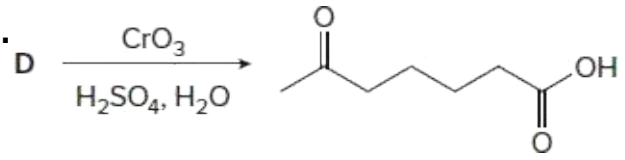


(2 equiv)

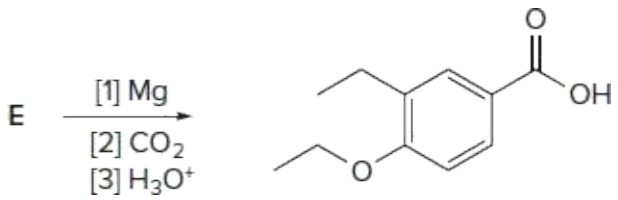
c.



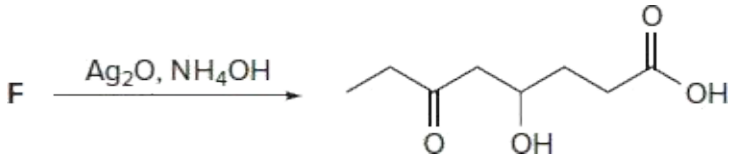
d.



e.



f.

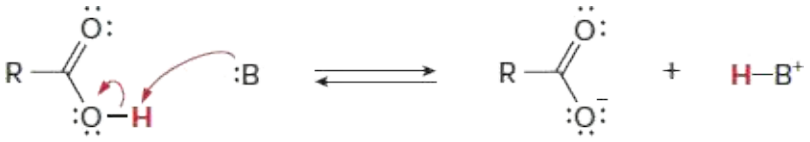


19.7 Carboxylic Acids—Strong Organic Brønsted–Lowry Acids

The polar C—O and O—H bonds, nonbonded electron pairs on oxygen, and the π bond give a carboxylic acid many reactive sites, complicating its chemistry somewhat. By far, the most important reactive feature of a carboxylic acid is its polar O—H bond, which is readily cleaved with base.

- **Carboxylic acids are strong organic acids, and as such, readily react with Brønsted–Lowry bases to form carboxylate anions.**

Recall from Section 2.3 that the lower the pK_a, the stronger the acid.



carboxylate anion

What bases are used to deprotonate a carboxylic acid? As we learned in Section 2.3, equilibrium favors the products of an acid–base reaction when the weaker base and acid are formed. Because a weaker acid has a higher pK_a, this general rule results:

- **An acid can be deprotonated by a base that has a conjugate acid with a *higher* pK_a.**

Because the pK_a values of many carboxylic acids are ~5, bases that have conjugate acids with pK_a values *higher* than 5 are strong enough to deprotonate them. Thus,

acetic acid (pK_a = 4.8) and benzoic acid (pK_a = 4.2) can be deprotonated with NaOH and $NaHCO_3$, as shown in the following equations.

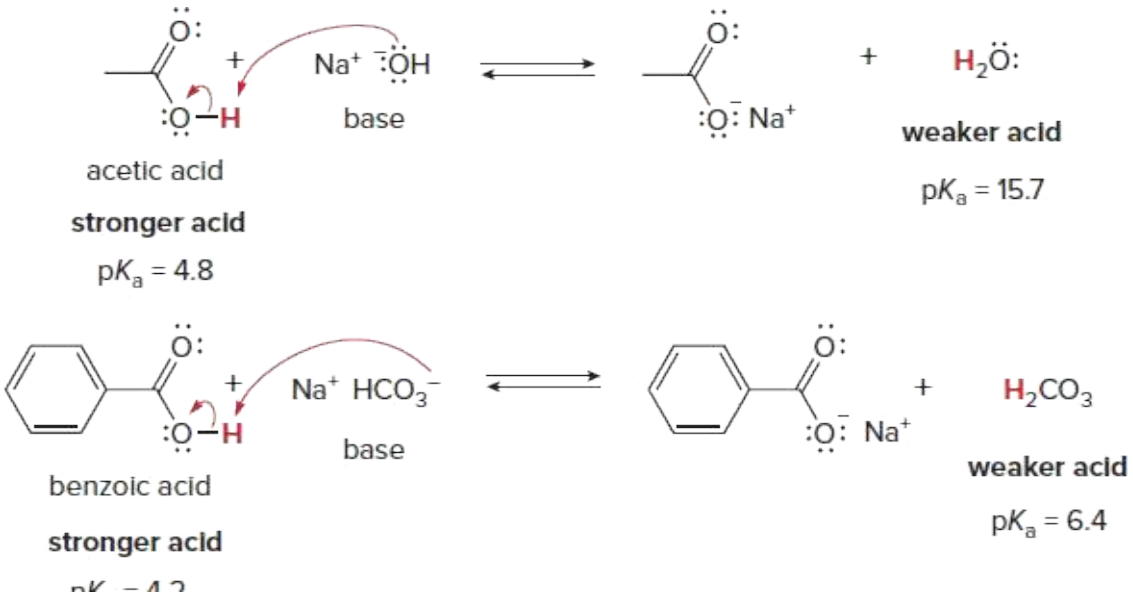
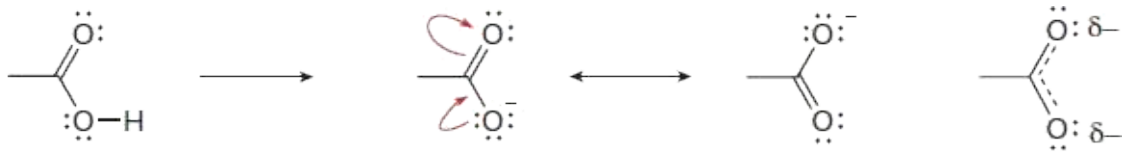


Table 19.4 lists common bases that can be used to deprotonate carboxylic acids. It is noteworthy that even a weak base like $NaHCO_3$ is strong enough to remove a proton from RCOOH.

Table 19.4 Common Bases Used to Deprotonate Carboxylic Acids

	Base	Conjugate acid (pK_a)
Increasing basicity ↓	$Na^+ HCO_3^-$	H_2CO_3 (6.4)
	NH_3	NH_4^+ (9.4)
	Na_2CO_3	HCO_3^- (10.2)
	$Na^+ {}^-OCH_3$	CH_3OH (15.5)
	$Na^+ {}^-OH$	H_2O (15.7)
	$Na^+ {}^-OCH_2CH_3$	CH_3CH_2OH (16)
	$Na^+ H^-$	H_2 (35)

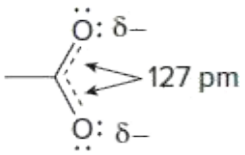
Why are carboxylic acids such strong organic acids? Remember that a strong acid has a weak, stabilized conjugate base. Deprotonation of a carboxylic acid forms a resonance-stabilized conjugate base—a carboxylate anion. Two equivalent resonance structures can be drawn for acetate (the conjugate base of acetic acid), both of which place a negative charge on an electronegative O atom. In the resonance hybrid, therefore, the negative charge is delocalized over two oxygen atoms.



acetic acid | two resonance structures for acetate, the conjugate base | hybrid

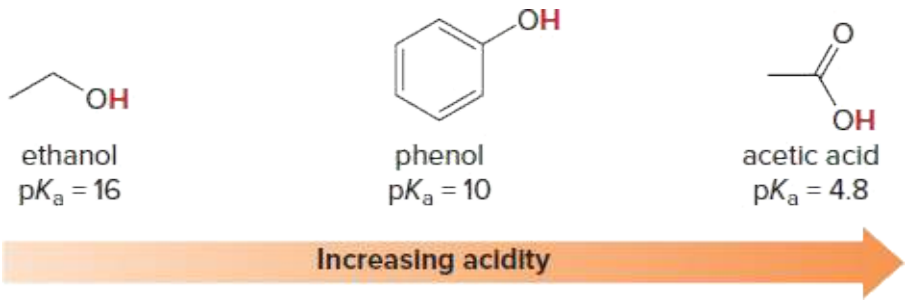
How resonance affects acidity was first discussed in Section 2.5C.

Experimental data support this resonance description of acetate. The acetate anion has two C—O bonds of equal length (127 pm) and intermediate between the length of a C—O single bond (136 pm) and C=O (121 pm).



acetate hybrid

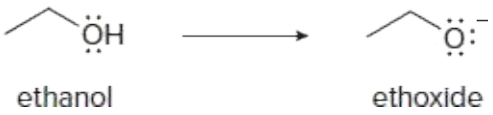
Resonance stabilization accounts for why carboxylic acids are more acidic than other compounds with O—H bonds—namely, alcohols and phenols. For example, the pK_a values of ethanol (CH_3CH_2OH) and phenol (C_6H_5OH) are 16 and 10, respectively, both higher than the pK_a of acetic acid (4.8).



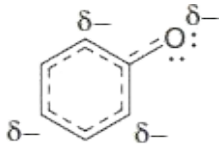
To understand the relative acidity of ethanol, phenol, and acetic acid, we must compare the stability of their conjugate bases and use this rule:

- **Anything that stabilizes a conjugate base A:$^-$ makes the starting acid H—A more acidic.**

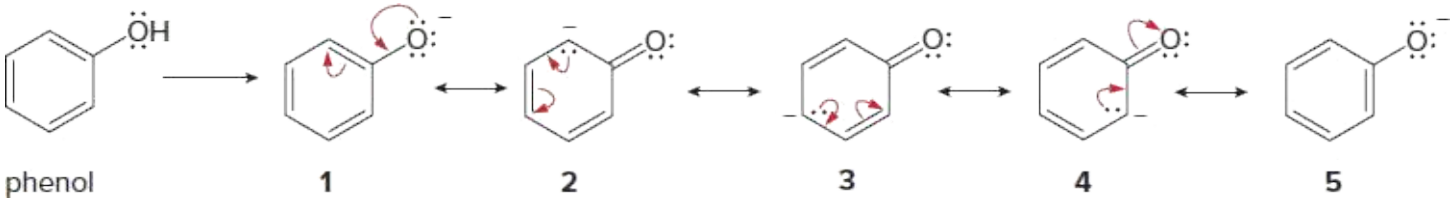
Ethoxide, the conjugate base of ethanol, bears a negative charge on an oxygen atom, but there are no additional factors to further stabilize the anion. Because ethoxide is less stable than acetate, ethanol is a weaker acid than acetic acid.



The resonance hybrid of phenoxide illustrates that its negative charge is dispersed over four atoms—three C atoms and one O atom.



Like acetate, phenoxide ($C_6H_5O^-$, the conjugate base of phenol) is also resonance stabilized. In the case of phenoxide, however, there are *five* resonance structures that disperse the negative charge over a total of *four* different atoms (three different carbons and the oxygen).



Phenoxide is more stable than ethoxide, but less stable than acetate, because acetate has two electronegative oxygen atoms upon which to delocalize the negative charge, whereas phenoxide has only one. Additionally, phenoxide resonance structures 2–4 have the negative charge on a carbon, a less electronegative element than oxygen. As a result, structures 2–4 are less stable than structures 1 and 5, which have the negative charge on oxygen.

Page 898

Moreover, resonance structures 1 and 5 have intact aromatic rings, whereas structures 2–4 do not. This, too, makes structures 2–4 less stable than 1 and 5. Figure 19.5 summarizes this information about phenoxide by displaying the approximate relative energies of its five resonance structures and its hybrid.

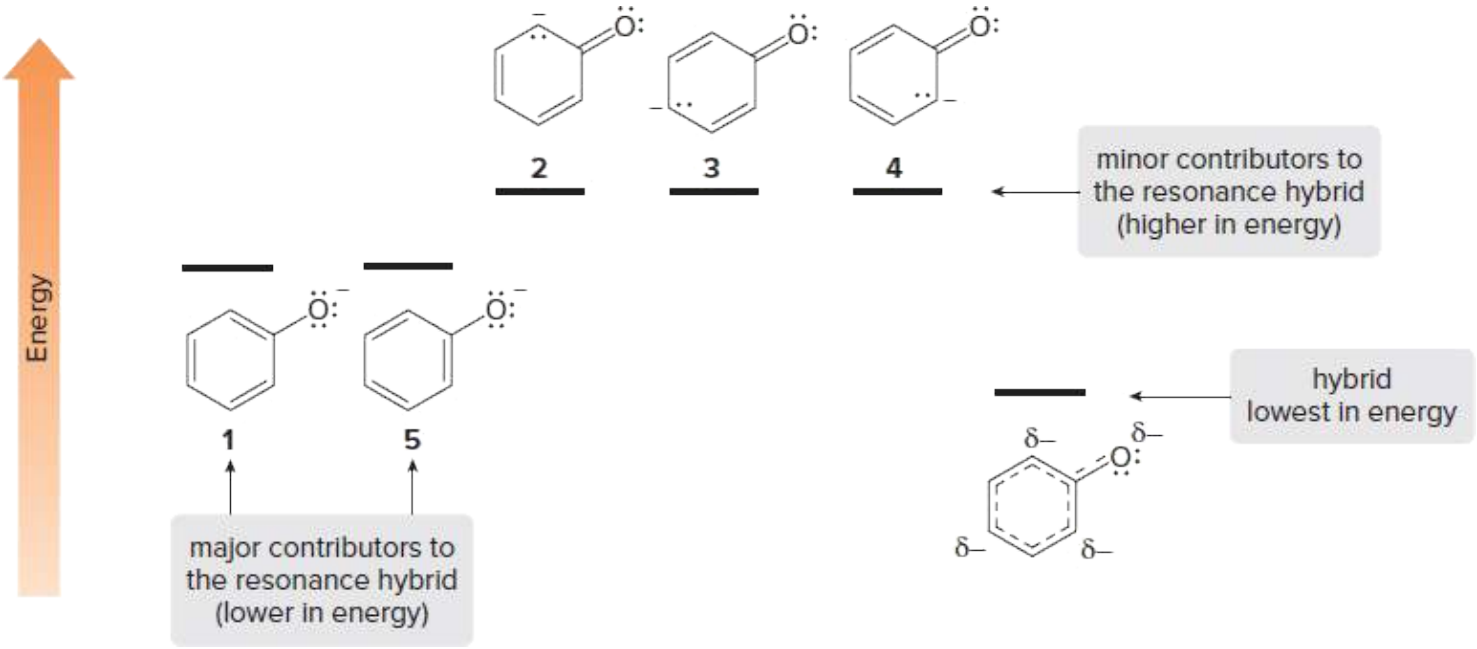


Figure 19.5 **The relative energies of the five resonance structures for phenoxide and its hybrid**

As a result, resonance stabilization of the conjugate base is important in determining acidity, but the absolute number of resonance structures alone is not what's important. We must evaluate their relative contributions to predict the relative stability of the conjugate bases.

Keep in mind that although carboxylic acids are strong organic acids, they are still *much weaker* than strong inorganic acids like HCl and H_2SO_4, which have pK_a values < 0.

- **Because of their O—H bond, RCOOH, ROH, and C_6H_5OH are *more acidic* than most organic hydrocarbons.**
- **A carboxylic acid is a *stronger* acid than an alcohol or a phenol because its conjugate base is more effectively resonance stabilized.**

The relationship between acidity and stability of the conjugate base is summarized for acetic acid, phenol, and ethanol in Figure 19.6.

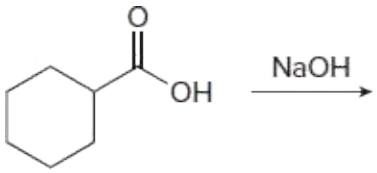
Because alcohols and phenols are weaker acids than carboxylic acids, stronger bases are needed to deprotonate them. To deprotonate C_6H_5OH (pK_a = 10), a base whose conjugate acid has a pK_a > 10 is needed. Thus, of the bases listed in Table 19.4, $NaOCH_3$, NaOH, $NaOCH_2CH_3$, and NaH are strong enough. To deprotonate

CH_3CH_2OH (pK_a = 16), only NaH is strong enough.

Problem 19.12

Draw the products of each acid–base reaction.

a.



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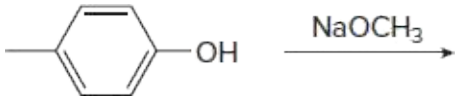

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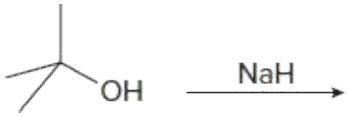
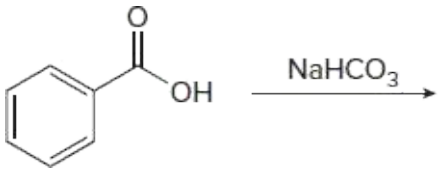
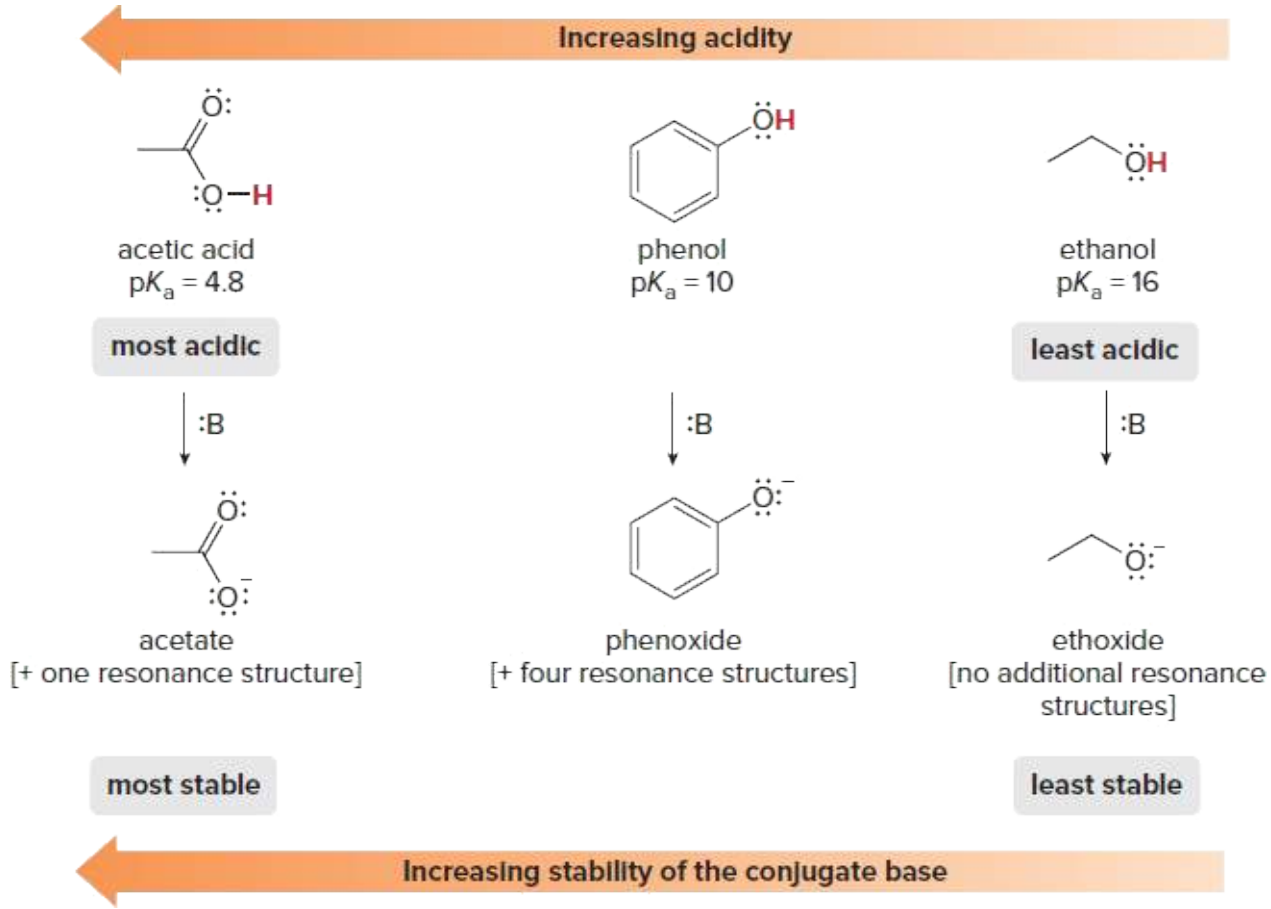


d.





- **Acetate is the *most* stable conjugate base because it has two equivalent resonance structures, both of which place a negative charge on an O atom.**
- **Phenoxide has only one O atom to accept the negative charge. The two resonance structures that contain an intact aromatic ring and place a**

negative charge on an O atom are major contributors to the hybrid. Resonance stabilizes phenoxide but not as much as resonance stabilizes acetate.

- **Ethoxide is the *least* stable conjugate base because it has no additional resonance stabilization.**

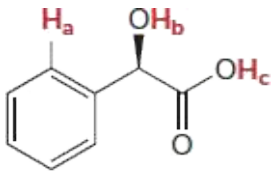
Figure 19.6 **Summary: The relationship between acidity and conjugate base stability for acetic acid, phenol, and ethanol**

Problem 19.13

Given the pK_a values in Appendix C, which of the following bases are strong enough to deprotonate CH_3COOH: (a) F^-; (b) $(CH_3)_3CO^-$; (c) CH_3^-; (d) $^-NH_2$; (e) Cl^-?

Problem 19.14

Rank the labeled protons (H_a–H_c) in mandelic acid, a naturally occurring carboxylic acid in plums and peaches, in order of increasing acidity. Explain in detail why you chose this order.



mandelic acid

19.8 Inductive Effects in Aliphatic Carboxylic Acids

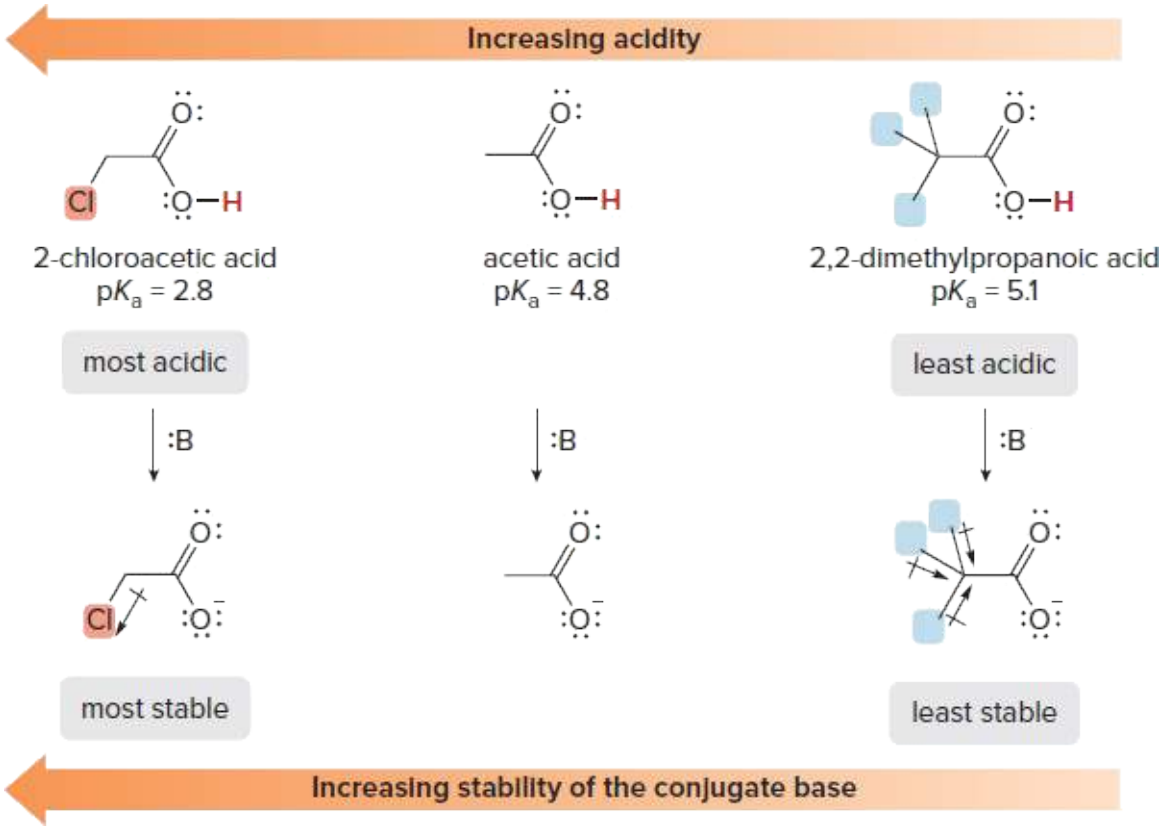
The pK_a of a carboxylic acid is affected by nearby groups that inductively donate or withdraw electron density.

- **Electron-withdrawing groups *stabilize* a conjugate base, making a carboxylic acid *more* acidic.**
- **Electron-donating groups *destabilize* the conjugate base, making a carboxylic acid *less* acidic.**

The relative acidity of CH_3COOH, $ClCH_2COOH$, and $(CH_3)_3CCOOH$ illustrates these principles in the following equations.

We first learned about inductive effects and acidity in Section

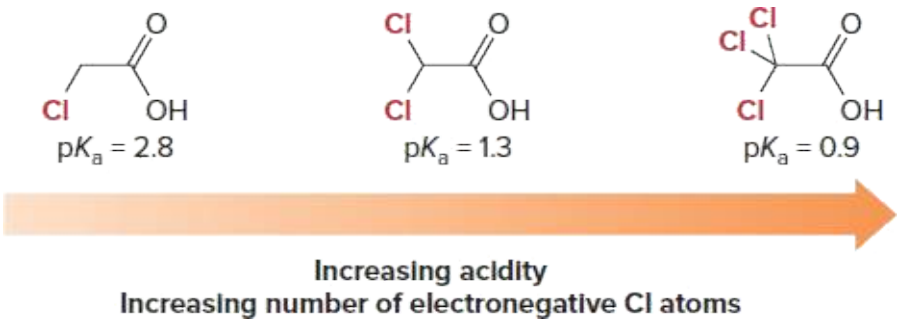
2.5B.



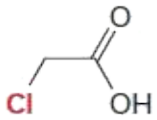
- $ClCH_2COOH$ is *more* acidic (pK_a = 2.8) than CH_3COOH (pK_a = 4.8) because its conjugate base is stabilized by the electron-withdrawing inductive effect of the electronegative Cl.
- $(CH_3)_3CCOOH$ is *less* acidic (pK_a = 5.1) than CH_3COOH because the three polarizable CH_3 groups donate electron density and destabilize the conjugate base.

The number, electronegativity, and location of substituents also affect acidity.

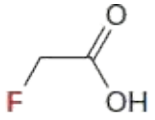
- **The larger the number of electronegative substituents, the stronger the acid.**



- **The more electronegative the substituent, the stronger the acid.**



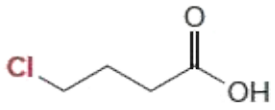
$pK_a = 2.8$



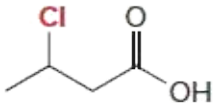
$pK_a = 2.6$

F is more electronegative than Cl. stronger acid

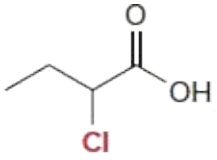
- **The closer the electron-withdrawing group to the COOH, the stronger the acid.**



4-chlorobutanoic acid
$pK_a = 4.5$



3-chlorobutanoic acid
$pK_a = 4.1$



2-chlorobutanoic acid
$pK_a = 2.9$

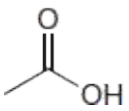
Increasing acidity
Increasing proximity of Cl to COOH

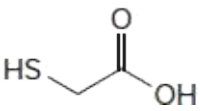
Problem 19.15

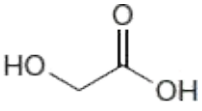
Match each of the following pK_a values (3.2, 4.9, and 0.2) to the appropriate carboxylic acid: (a) CH_3CH_2COOH; (b) CF_3COOH; (c) ICH_2COOH.

Problem 19.16

Rank the following compounds in order of increasing acidity.





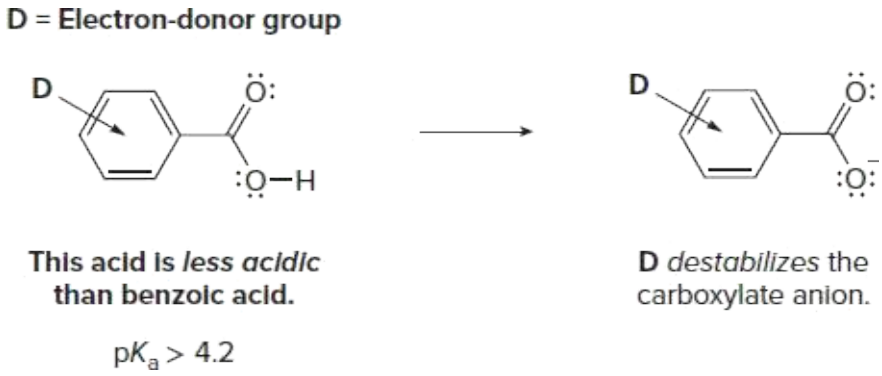


19.9 Substituted Benzoic Acids

Recall from Section 16.6 that substituents on a benzene ring either donate or withdraw electron density, depending on the balance of their inductive and resonance effects. These same effects also determine the acidity of substituted benzoic acids. There are two rules to keep in mind.

Rule [1] Electron-donor groups *destabilize* a conjugate base, making an acid *less* acidic.

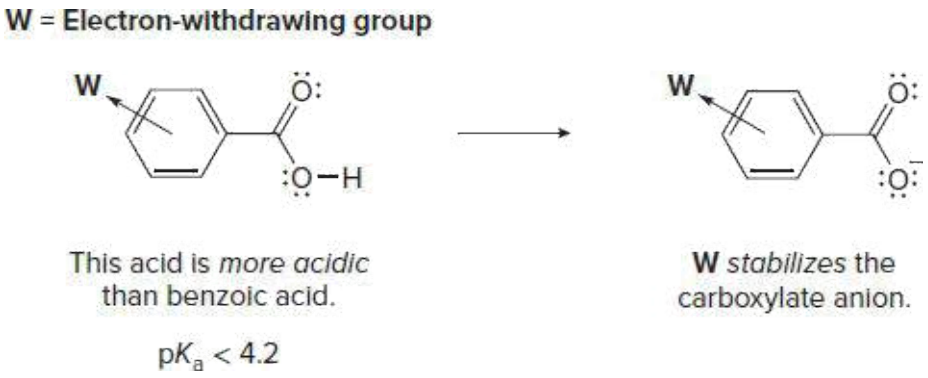
An electron-donor group destabilizes a conjugate base by donating electron density onto a negatively charged carboxylate anion. A benzoic acid substituted by an electron-donor group has a *higher* pK_a than benzoic acid (pK_a = 4.2).



The electron-donor groups that activate benzene to electrophilic attack make a benzoic acid *less* acidic.

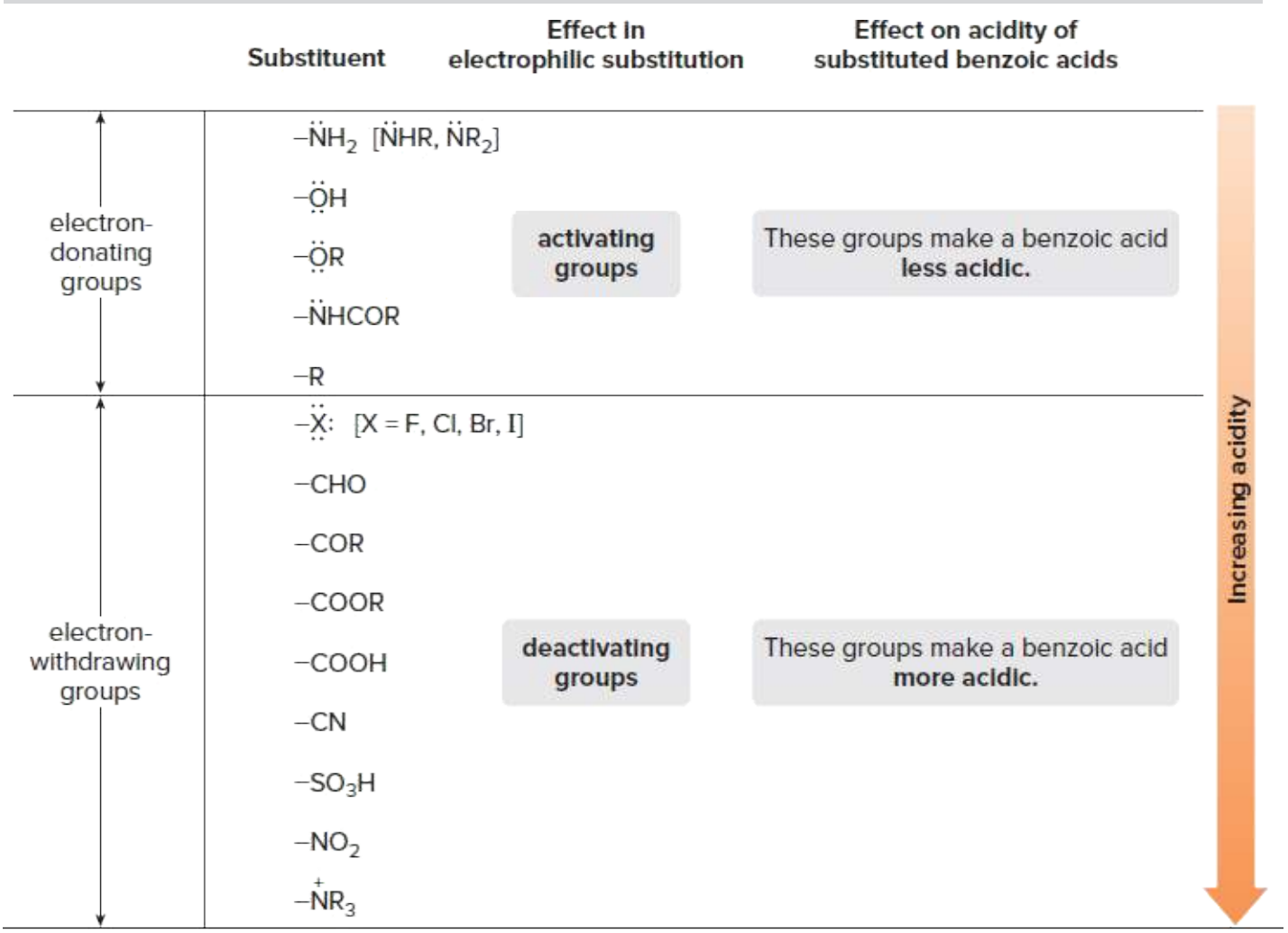
Rule [2] Electron-withdrawing groups *stabilize* a conjugate base, making an acid *more* acidic.

An electron-withdrawing group stabilizes a conjugate base by removing electron density from the negatively charged carboxylate anion. A benzoic acid substituted by an electron-withdrawing group has a *lower* pK_a than benzoic acid (pK_a = 4.2).



The electron-withdrawing groups that deactivate benzene to electrophilic attack make a benzoic acid *more* acidic.

Figure 19.7 illustrates how common electron-donating and electron-withdrawing groups affect both the rate of reaction of a benzene ring toward electrophiles and the acidity of substituted benzoic acids.

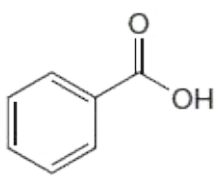


- **Groups that *donate* electron density *activate* a benzene ring toward electrophilic attack and make a benzoic acid *less* acidic.** Common electron-donating groups are R groups, or groups that have a N or O atom (with a lone pair) bonded to the benzene ring.
- **Groups that *withdraw* electron density *deactivate* a benzene ring toward electrophilic attack, and make a benzoic acid *more* acidic.** Common electron-withdrawing groups are the halogens, or groups with an atom Y (with a full or partial positive charge) bonded to the benzene ring.

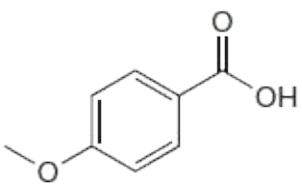
Figure 19.7 **How common substituents affect the reactivity of a benzene ring toward electrophiles and the acidity of substituted benzoic acids**

Sample Problem 19.3 Determining the Relative Acidity of Substituted Benzoic Acids

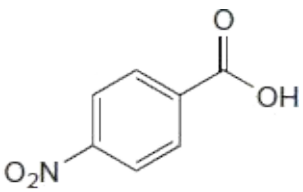
Rank the following three carboxylic acids in order of increasing acidity.



A
benzoic acid



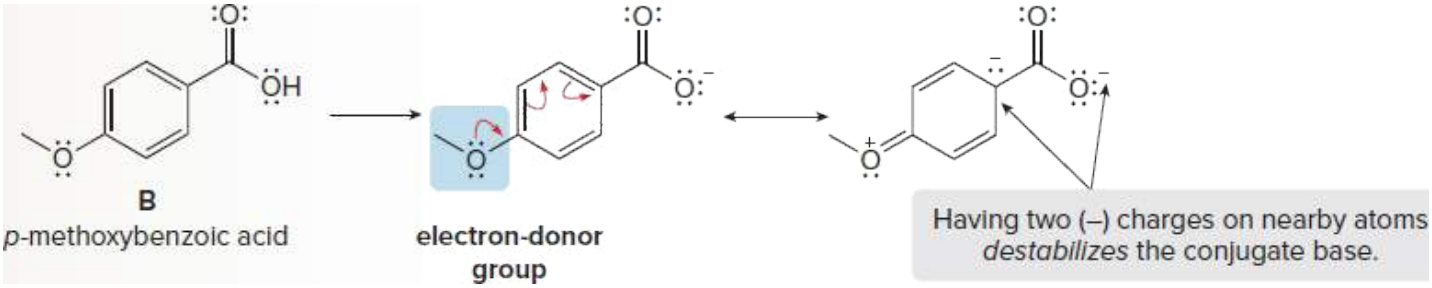
B
p-methoxybenzoic acid



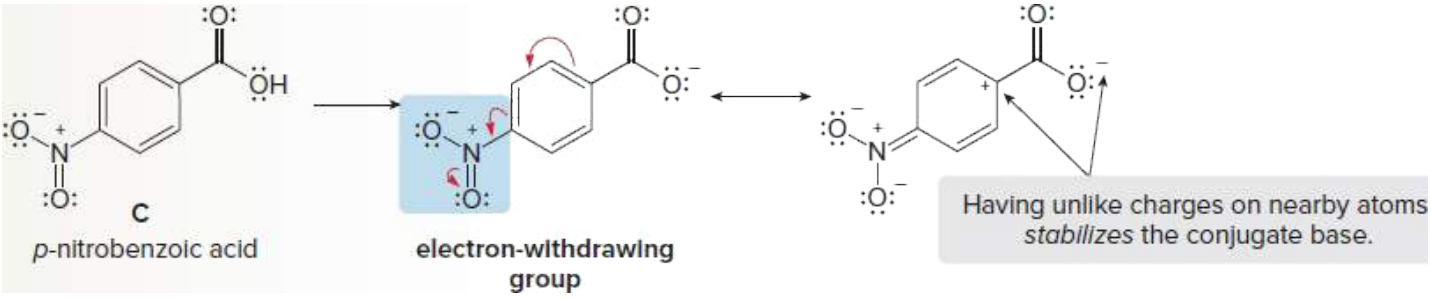
C
p-nitrobenzoic acid

Solution

***p*-Methoxybenzoic acid (B): The CH_3O group is an electron-donor group because its electron-donating resonance effect is stronger than its electron-withdrawing inductive effect (Section 16.6). This *destabilizes* the conjugate base by donating electron density to the negatively charged carboxylate anion, making B *less acidic* than benzoic acid A. Two of the possible resonance structures for B's conjugate base are drawn.**



***p*-Nitrobenzoic acid (C): The NO_2 group is an electron-withdrawing group because of both inductive effects and resonance (Section 16.6). This *stabilizes* the conjugate base by removing electron density from the negatively charged carboxylate anion, making C *more acidic* than benzoic acid A. Two of the possible resonance structures for C's conjugate base are drawn.**

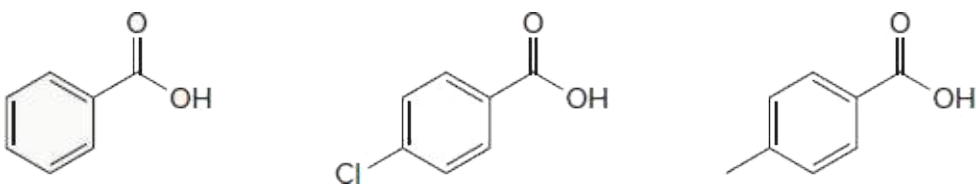


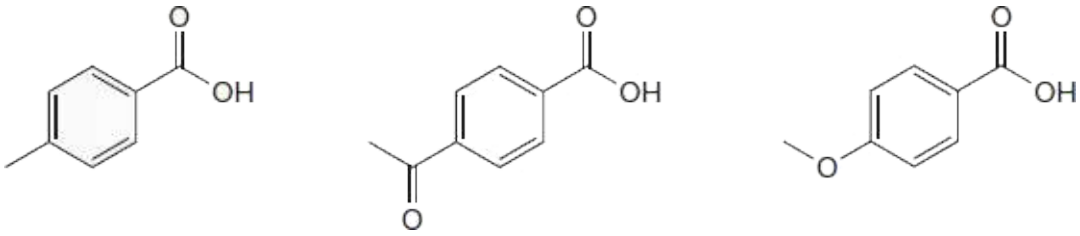
By this analysis, the order of acidity is B < A < C.

Problem 19.17

Rank the compounds in each group in order of increasing acidity.

a.



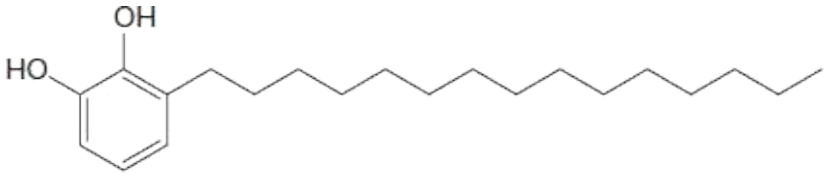
b. 

More Practice:

Try Problems 19.32, 19.39, 19.43, 19.47.

Problem 19.18

Substituted phenols show substituent effects similiar to substituted benzoic acids. Should the pK_a of phenol A, one of the naturally occurring phenols called urushiols isolated from poison ivy, be higher or lower than the pK_a of phenol (C_6H_5OH, pK_a = 10)? Explain.



A

Poison ivy contains the irritant urushiol (Problem 19.18).

©Ken Samuelsen/Getty Images

Extraction has long been and remains the first step in isolating a natural product from its source.

19.10 Extraction

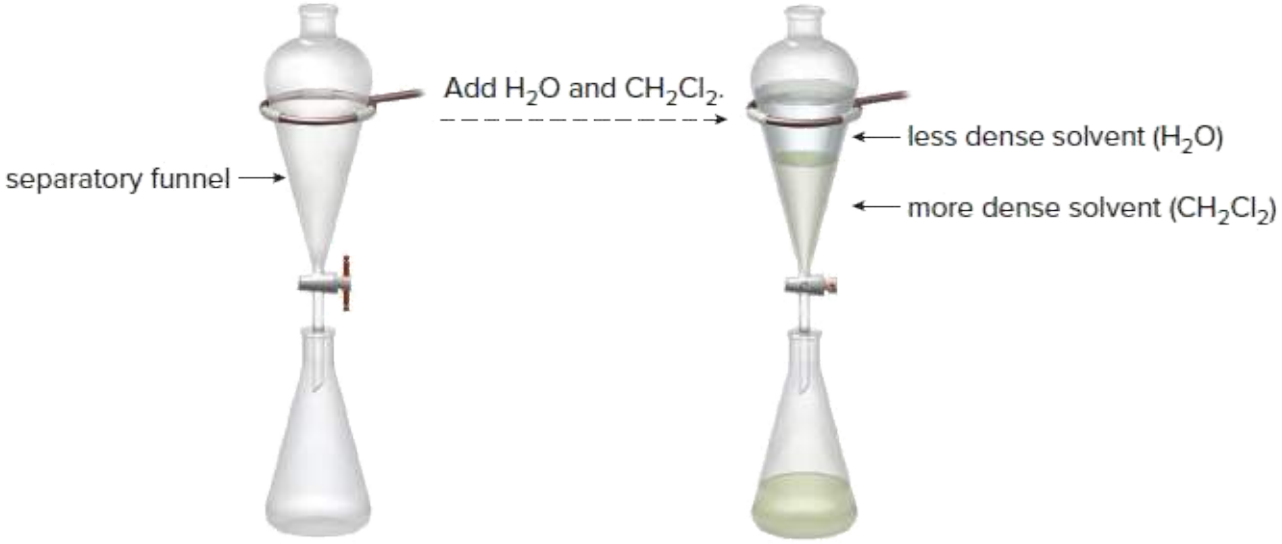
An organic chemist in the laboratory must separate and purify mixtures of compounds. One particularly useful technique is extraction, which uses solubility differences and

acid–base principles to separate and purify compounds.

Two solvents are used in extraction: water or an aqueous solution such as 10% $NaHCO_3$ or 10% NaOH; and an organic solvent such as dichloromethane (CH_2Cl_2), diethyl ether, or hexane. Compounds are separated by their solubility differences in an aqueous and organic solvent.

An item of glassware called a separatory funnel, depicted in Figure 19.8, is used for the extraction. When two insoluble liquids are added to the separatory funnel, two layers form, with the less dense liquid on top and the more dense liquid on the bottom.

Suppose a mixture of benzoic acid (C_6H_5COOH) and NaCl is added to a separatory funnel containing H_2O and CH_2Cl_2. The benzoic acid would dissolve in the organic layer, and the NaCl would dissolve in the water layer. Separating the organic and aqueous layers and placing them in different flasks separates the benzoic acid and NaCl from each other.



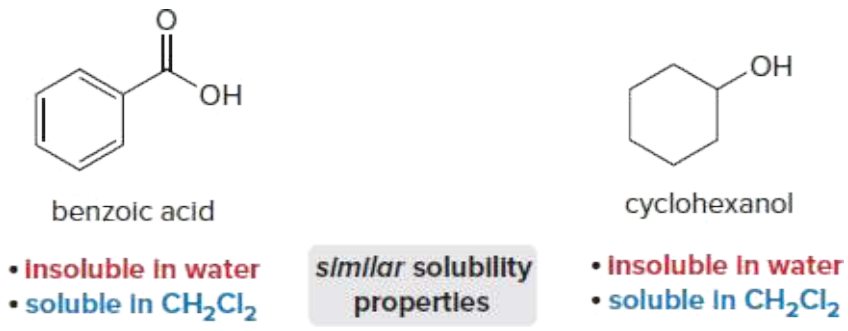
- When two insoluble liquids are added to a separatory funnel, two layers are visible, and the less dense liquid forms the upper layer.
- To separate the layers, the lower layer can be drained from the bottom of the separatory funnel by opening the stopcock. The top layer can then be poured out the top neck of the funnel.

Figure 19.8 **Using a separatory funnel for extraction**

How could we separate a mixture of benzoic acid and cyclohexanol? Both compounds are organic, and as a result, both are soluble in an organic solvent such as CH_2Cl_2 and insoluble in water. If a mixture of benzoic acid and cyclohexanol were added to a separatory funnel with CH_2Cl_2 and water, both would dissolve in the CH_2Cl_2 layer, and the two compounds would *not* be separated from each other. Is it

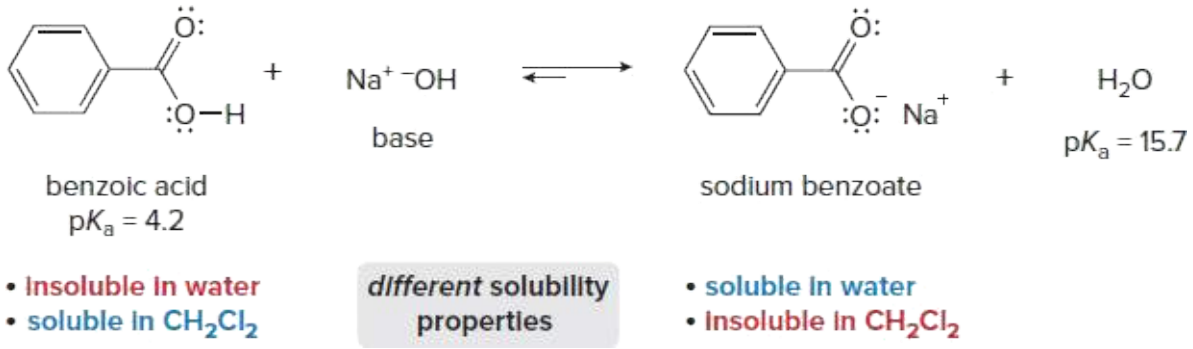
possible to use extraction to separate two compounds of this sort that have similar solubility properties?

Recall from Tables 9.1 and 19.1 that alcohols and carboxylic acids having more than five carbons are water insoluble.

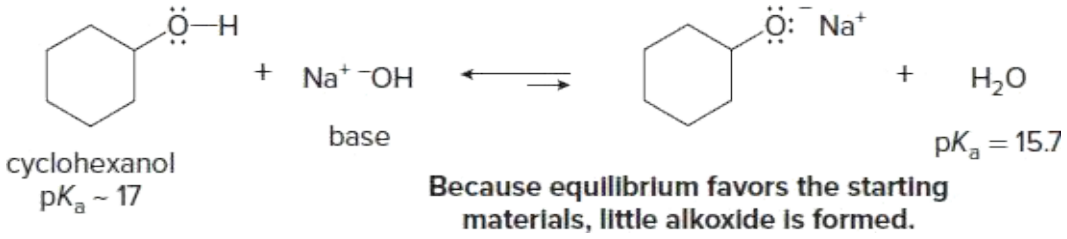


If a carboxylic acid is one of the compounds, the answer is *yes*, because we can use acid–base chemistry to change its solubility properties.

When benzoic acid (a strong organic acid) is treated with aqueous NaOH, benzoic acid is deprotonated, forming sodium benzoate. Because sodium benzoate is ionic, it is *soluble* in water, but *insoluble* in organic solvents.



A similar acid–base reaction does *not* occur when cyclohexanol is treated with NaOH because organic alcohols are much weaker organic acids, so they can be deprotonated only by a *very strong base* such as NaH. NaOH is not strong enough to form significant amounts of the sodium alkoxide.

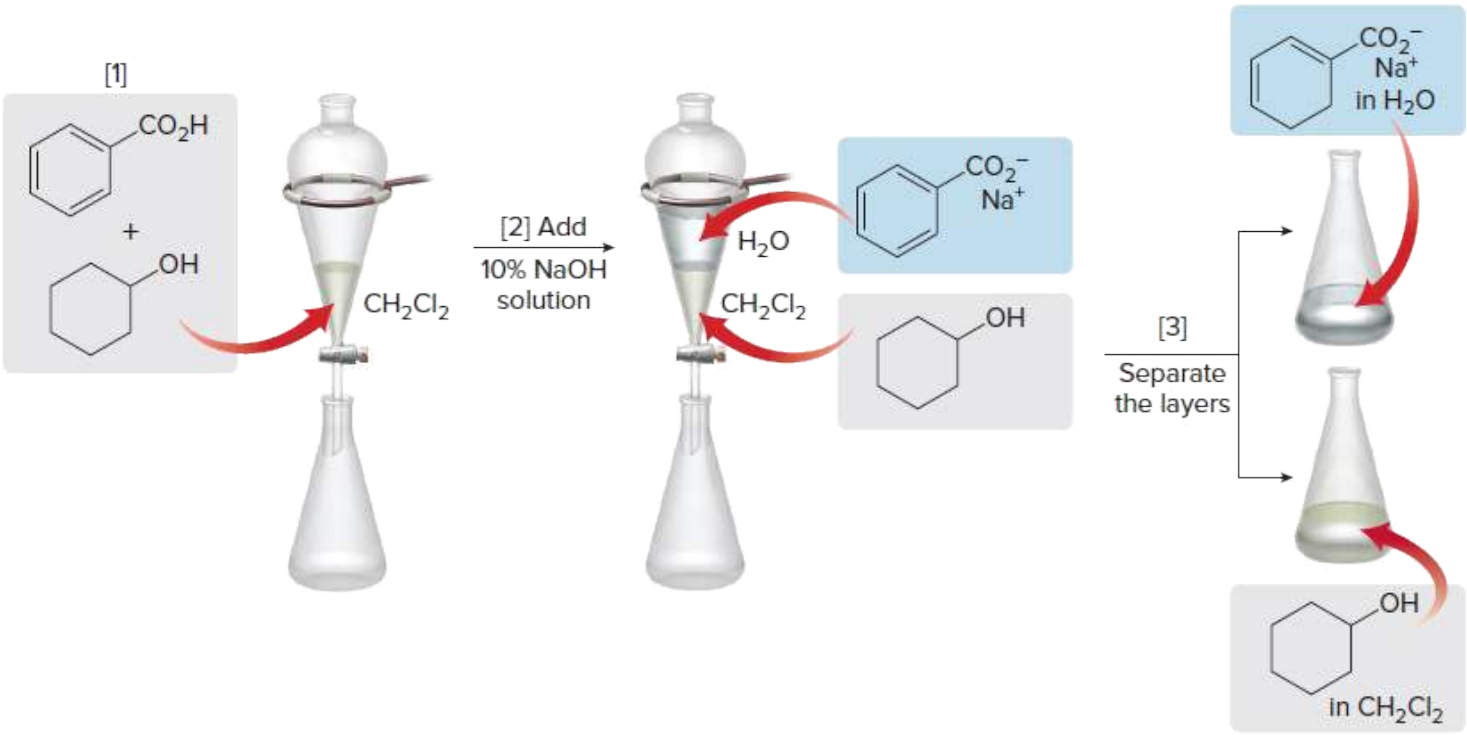


This difference in acid–base chemistry can be used to separate benzoic acid and cyclohexanol by the stepwise extraction procedure illustrated in Figure 19.9. This

extraction scheme relies on two principles:

- **Extraction can separate only compounds having different solubility properties. One compound must dissolve in the aqueous layer and one must dissolve in the organic layer.**
- **A carboxylic acid can be separated from other organic compounds by converting it to a water-soluble carboxylate anion by an acid–base reaction.**

Thus, the water-soluble salt, $C_6H_5CO_2^-Na^+$ (derived from $C_6H_5CO_2H$ by an acid–base reaction), can be separated from water-insoluble cyclohexanol by an extraction procedure.

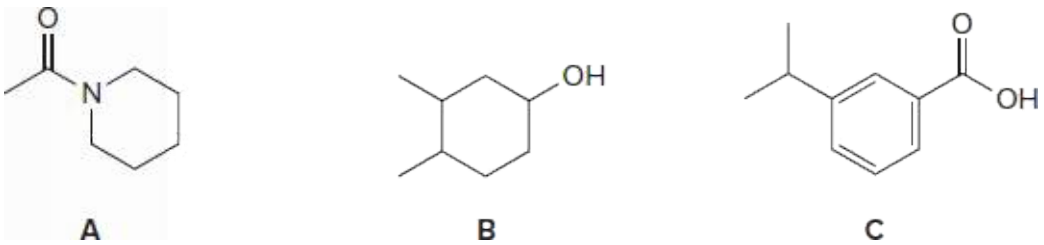


- Both compounds dissolve in the organic solvent CH_2Cl_2.
- Adding 10% aqueous NaOH solution forms two layers. When the two layers are mixed, the **NaOH deprotonates $C_6H_5CO_2H$ to form $C_6H_5CO_2^-Na^+$, which dissolves in the aqueous layer.**
- The cyclohexanol remains in the CH_2Cl_2 layer.
- Draining the lower layer out the bottom stopcock separates the two layers, and the separation process is complete.
- Cyclohexanol (dissolved in CH_2Cl_2) is in one flask. The sodium salt of benzoic acid, $C_6H_5CO_2^-Na^+$ (dissolved in water) is in another flask.

Figure 19.9 **Separation of benzoic acid and cyclohexanol by an extraction procedure**

Sample Problem 19.4 Separating Compounds by Extraction

A mixture of A, B, and C was added to a separatory funnel containing CH_2Cl_2 and 10% aqueous NaOH solution. Which compound(s) are present in the aqueous layer, and which compound(s) are present in the organic layer?



Solution

Recall the principles of solubility:

- **Organic compounds are soluble in organic solvents.**
- **Organic compounds that can hydrogen bond to H_2O are water soluble if they have ≤ 5 C's.**
- **Uncharged organic compounds with > 5 C's are not water soluble.**
- **Ionic compounds are water soluble.**

A, B, and C are uncharged organic compounds, so they are *soluble* in CH_2Cl_2, and because they each have > 5 C's, they are *insoluble* in H_2O. C, however, has a CO_2H group with an acidic H atom that can be removed with NaOH. Deprotonation forms a carboxylate anion that is now *water soluble.*

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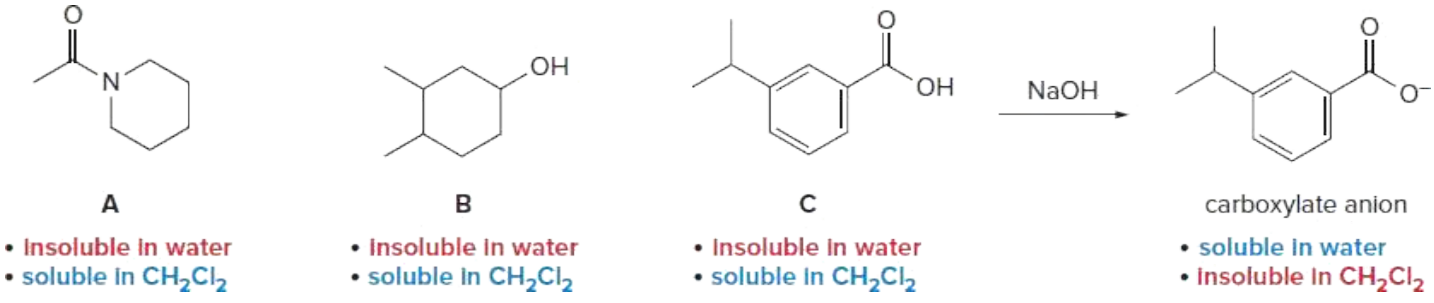
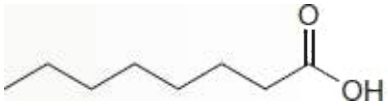
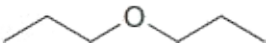


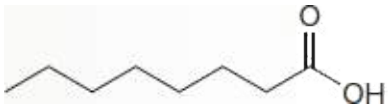
As a result, in a separatory funnel with CH_2Cl_2 and 10% aqueous NaOH solution, A and B are soluble in the CH_2Cl_2 layer, and C is deprotonated to form a carboxylate anion that is now soluble in the aqueous layer.

Problem 19.19

Which of the following pairs of compounds can be separated from each other by an extraction procedure?

a.  and

b. and 

c.  and NaCl

d. NaCl and KCl

More Practice:

Try Problems 19.56–19.58.

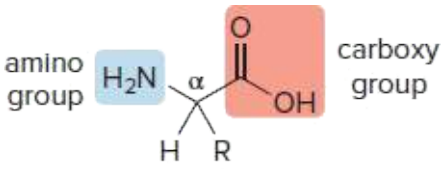
Chapter 27 discusses the synthesis of amino acids and their conversion to proteins.

19.11 Amino Acids

Amino acids, one of four kinds of small biomolecules that have important biological functions in the cell (Section 3.9), also undergo proton transfer reactions.

19.11A Introduction

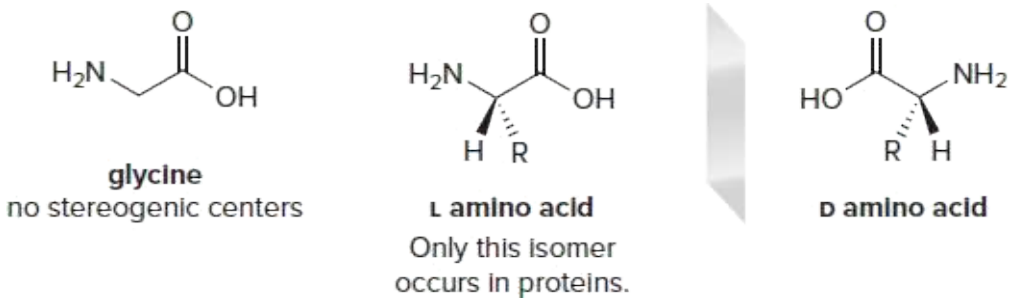
Amino acids contain two functional groups—an amino group (NH_2) and a carboxy group (COOH). In most naturally occurring amino acids, the amino group is bonded to the α carbon, so they are called α-amino acids. Amino acids are the building blocks of proteins, biomolecules that comprise muscle, hair, fingernails, and many other biological tissues.



α-amino acid

The 20 amino acids that occur naturally in proteins differ in the identity of the R group bonded to the α carbon. The simplest amino acid, called glycine, has R=H. When the R group is any other substituent, the α carbon is a stereogenic center, and there are two possible enantiomers.

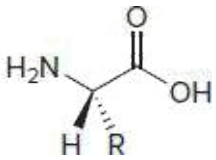
Humans can synthesize only 10 of the 20 amino acids needed for protein synthesis. The remaining 10, called essential amino acids, must be obtained from the diet and consumed on a regular, almost daily basis. Vegetarian diets must be carefully balanced to obtain all the essential amino acids. Grains—wheat, rice, and corn—are low in lysine, and legumes—beans, peas, and peanuts—are low in methionine, but a combination of these foods provides all the needed amino acids. Thus, a diet of corn tortillas and beans, or rice and tofu, provides all essential amino acids. A peanut butter sandwich on wheat bread does, too. ***©Brent Hofacker/Shutterstock***



Amino acids exist in nature as only one of these enantiomers. Except when the R group is CH_2SH, the stereogenic center on the α carbon has the *S* configuration. An older system of nomenclature names the naturally occurring enantiomer of an amino acid as the L isomer, and its unnatural enantiomer the D isomer.

The R group of an amino acid can be H, alkyl, aryl, or an alkyl chain containing a N, O, or S atom. Representative examples are listed in Table 19.5. All amino acids have common names, which are abbreviated by a three-letter or one-letter designation. For example, glycine is often written as the three-letter abbreviation Gly or the one-letter abbreviation G. These abbreviations are also given in Table 19.5. A complete list of the 20 naturally occurring amino acids is found in Figure 27.2.

Table 19.5 Representative Amino Acids

General structure: 

R group	Name	Three-letter abbreviation	One-letter abbreviation
H	glycine	Gly	G
CH_3	alanine	Ala	A
$CH_2C_6H_5$	phenylalanine	Phe	F
CH_2OH	serine	Ser	S
CH_2SH	cysteine	Cys	C
$CH_2CH_2SCH_3$	methionine	Met	M
CH_2CH_2COOH	glutamic acid	Glu	E
$(CH_2)_4NH_2$	lysine	Lys	K

Problem 19.20

Draw both enantiomers of each amino acid and label them as *R* or *S:* (a) phenylalanine; (b) methionine.

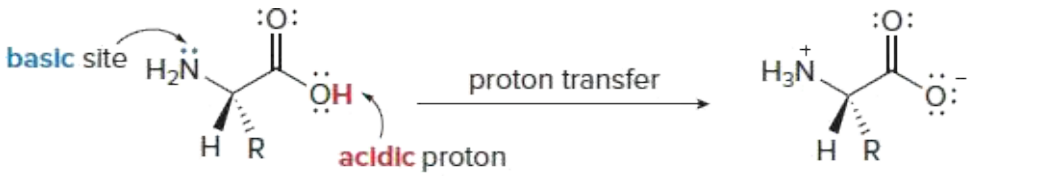
19.11B Acid–Base Properties

An amino acid is both an acid and a base.

- **The NH_2 group has a nonbonded electron pair, making it a base.**
- **The COOH group has an acidic proton, making it an acid.**

Amino acids are never uncharged neutral compounds. They exist as salts, so Page 909 they have very high melting points and are very soluble in water.

- **Proton transfer from the acidic carboxy group to the basic amino group forms a salt called a *zwitterion*, which contains both a positive and a negative charge.**



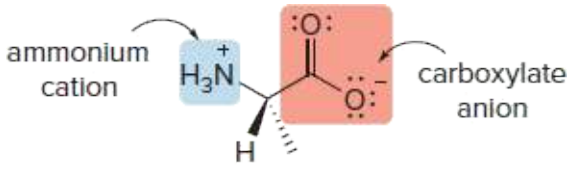
This neutral form of an amino acid does *not* exist.

zwitterion

This salt is the neutral form of an amino acid.

In actuality, an amino acid can exist in three different forms, depending on the pH of the aqueous solution in which it is dissolved.

When the pH of a solution is ~6, alanine (R = CH_3) exists in its zwitterionic form (A), having no net charge. In this form the carboxy group bears a negative charge—it is a carboxylate anion—and the amino group bears a net positive charge (an ammonium cation).



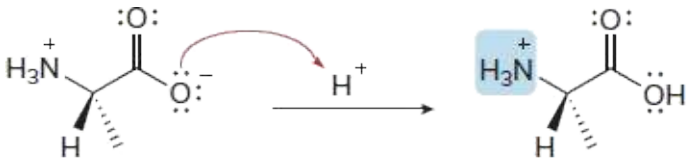
alanine

A

a neutral zwitterion

This form exists at pH ≈ 6.

When strong acid is added to lower the pH (≤ 2), the carboxylate anion is protonated and the amino acid has a net positive charge (form B)



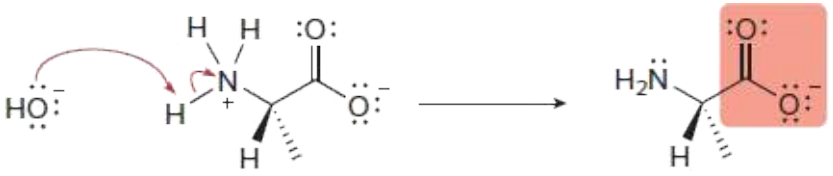
A

B

overall (+1) charge

This form exists at pH ≤ 2.

When strong base is added to A to raise the pH (≥ 10), the ammonium cation is deprotonated and the amino acid has a net negative charge (form C).



A

C

overall (–1) charge

This form exists at pH ≥ 10.

Thus, alanine exists in one of three different forms depending on the pH of the

solution in which it is dissolved. If the pH of a solution is gradually increased from 2 to 10, the following process occurs.

- **At low pH, alanine has a net (+) charge (form B).**
- **As the pH is increased to ~6, the carboxy group is deprotonated, and the amino acid exists as a zwitterion with no overall charge (form A).**
- **At high pH, the ammonium cation is deprotonated, and the amino acid has a net (−) charge (form C).**

These reactions are summarized in Figure 19.10.

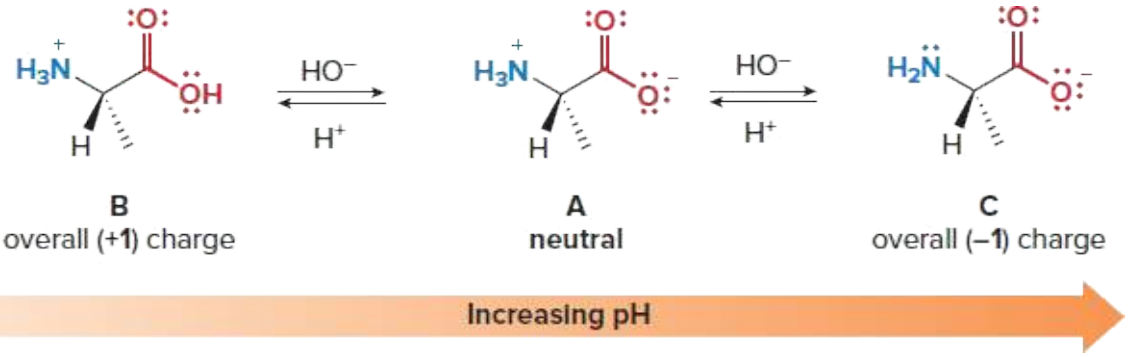


Figure 19.10 **Summary of the acid–base reactions of alanine**

Problem 19.21

Explain why amino acids, unlike most other organic compounds, are insoluble in organic solvents like diethyl ether.

Problem 19.22

Draw the positively charged, neutral, and negatively charged forms for the amino acid glycine. Which species predominates at pH 11? Which species predominates at pH 1?

19.11C Isoelectric Point

Because a protonated amino acid has at least two different protons that can be removed, a pK_a value is reported for each of these protons. For example, the pK_a of the carboxy proton of alanine is 2.35 and the pK_a of the ammonium proton is 9.87. Table 27.1 lists these values for all 20 amino acids.

- **The pH at which the amino acid exists primarily in its neutral form is called its *isoelectric point*, abbreviated as p*I*.**

More information on the isoelectric point can be found in Section 27.1.

For amino acids without other acidic or basic functional groups, the isoelectric point is the average of both pK_a values of an amino acid:

$$\text{Isoelectric point} = pI = \frac{pK_a(\text{COOH}) + pK_a(\text{NH}_3^+)}{2}$$

$$\text{For alanine:} \quad pI = \frac{2.35 + 9.87}{2} = \underset{pI \text{ (alanine)}}{6.12}$$

Problem 19.23

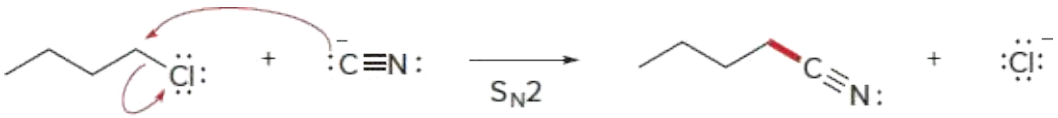
The pK_a values for the carboxy and ammonium protons of phenylalanine are 2.58 and 9.24, respectively. What is the isoelectric point of phenylalanine? Draw the structure of phenylalanine at its isoelectric point.

Problem 19.24

Explain why the pK_a of the COOH group of glycine is much lower than the pK_a of the COOH of acetic acid (2.35 compared to 4.8).

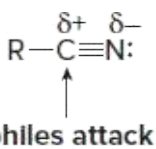
19.12 Nitriles

We end Chapter 19 with the chemistry of nitriles. Nitriles are readily prepared by S_N2 substitution reactions of unhindered methyl and 1° alkyl halides with ^-CN. This reaction adds one carbon to the alkyl halide and forms a new carbon–carbon bond.



new C–C bond in red

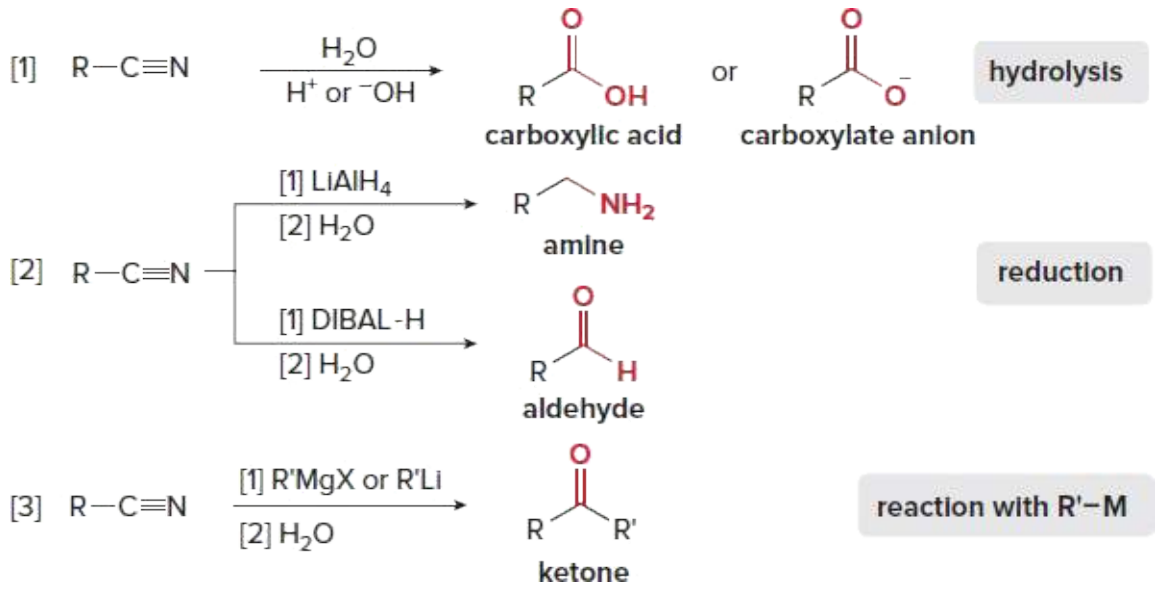
Because a nitrile contains an electrophilic carbon atom that is part of a multiple bond but no leaving group, a nitrile reacts with nucleophiles by a nucleophilic addition reaction. The nature of the nucleophile determines the structure of the product.



Nucleophiles attack here.

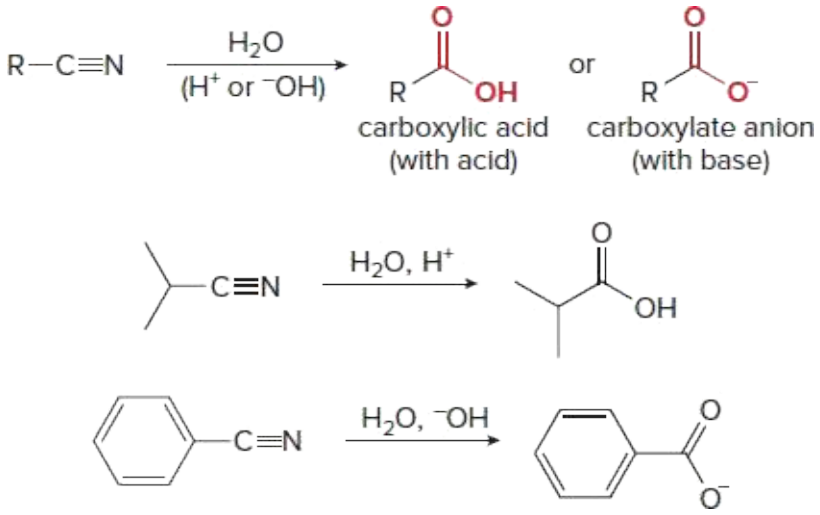
The reactions of nitriles with water, hydride, and organometallic reagents as

nucleophiles are as follows:

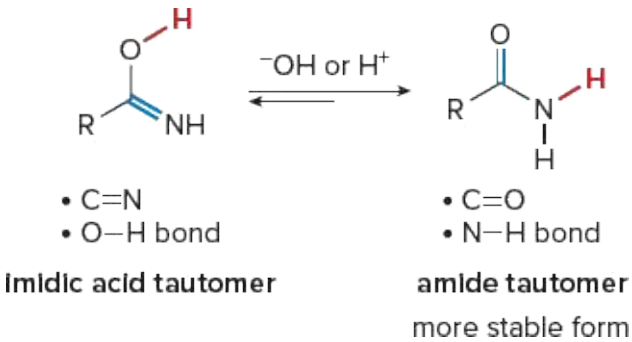


19.12A Hydrolysis of Nitriles

Nitriles are hydrolyzed with water in the presence of acid or base to yield carboxylic acids or carboxylate anions. In this reaction, the three C—N bonds are replaced by three C—O bonds.



The mechanism of this reaction involves the formation of an amide tautomer. Page 912 Two tautomers can be drawn for any carbonyl compound, and those for a 1° amide are as follows:



Recall from Chapter 11 that tautomers are constitutional isomers that differ in the location of a double bond and a proton.

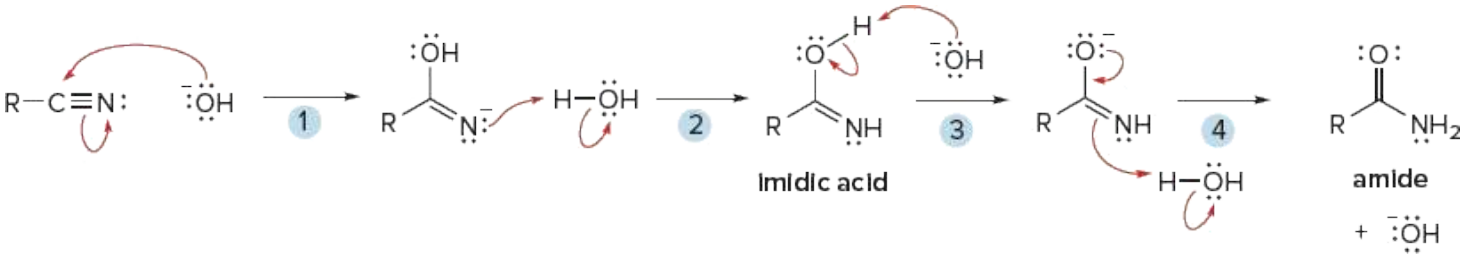
- **The amide form is the more stable tautomer, having a C=O and an N—H bond.**
- **The imidic acid tautomer is the less stable form, having a C=N and an O—H bond.**

The imidic acid and amide tautomers are interconverted by treating with acid or base, analogous to the keto–enol tautomers of other carbonyl compounds. In fact, the two amide tautomers are exactly the same as keto–enol tautomers except that a nitrogen atom replaces a carbon atom bonded to the carbonyl group.

The mechanism of nitrile hydrolysis in both acid and base consists of two parts: [1] nucleophilic addition to form the imidic acid tautomer followed by tautomerization to form the amide, and [2] hydrolysis of the amide to form RCO_2H or RCO_2^-. The mechanism is shown for the basic hydrolysis of RCN to RCO_2^- (Mechanism 19.1).

Mechanism 19.1 Hydrolysis of a Nitrile in Base

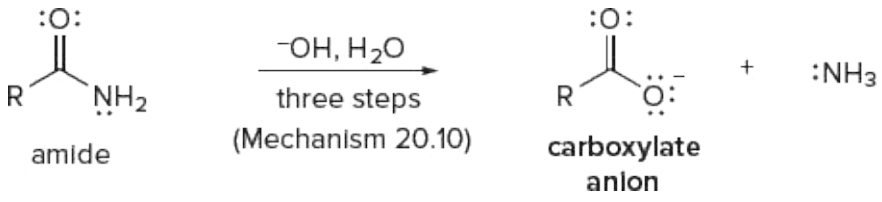
Part [1] Conversion of a nitrile to a 1° amide



1 – 2 Nucleophilic attack of $^-$OH followed by protonation forms an imidic acid.

3 – 4 Tautomerization occurs by a two-step sequence—deprotonation followed by protonation.

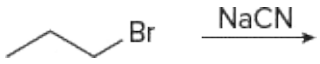
Part [2] Hydrolysis of the 1° amide to a carboxylate anion

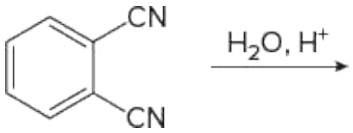


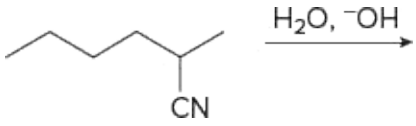
Conversion of the amide to the carboxylate occurs by a three-step sequence that will be discussed in Chapter 20 (Mechanism 20.10).

Problem 19.25

Draw the products of each reaction.

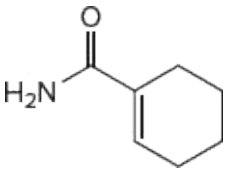
a. 

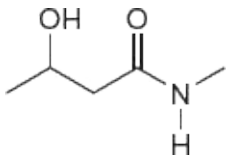
b. 

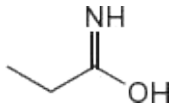
c. 

Problem 19.26

Draw a tautomer of each compound.

a. 

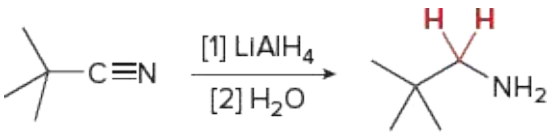
b. 

c. 

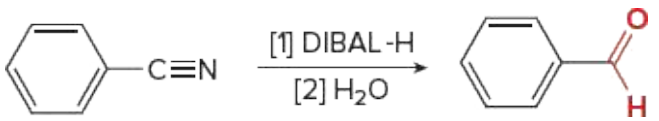
19.12B Reduction of Nitriles

Nitriles are reduced with metal hydride reagents to form either 1° amines or aldehydes, depending on the reducing agent.

- **Treatment of a nitrile with $LiAlH_4$ followed by H_2O adds two equivalents of H_2 across the triple bond, forming a 1° amine.**

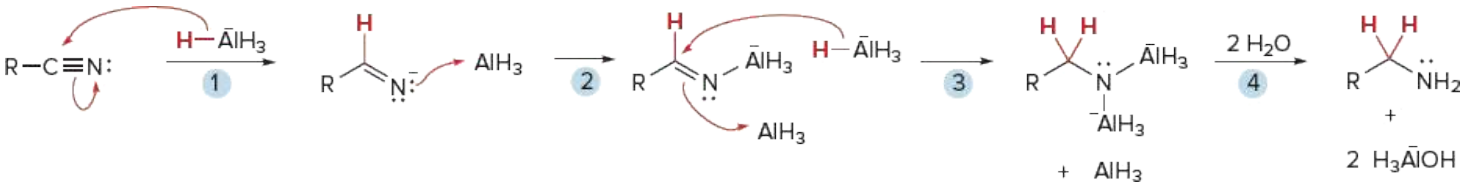


- **Treatment of a nitrile with a milder reducing agent such as DIBAL-H followed by H_2O forms an aldehyde.**



The mechanism of both reactions involves nucleophilic addition of hydride (H^-) to the polarized C—N triple bond. Mechanism 19.2 illustrates that reduction of a nitrile to an amine requires addition of two equivalents of $H:^-$ from $LiAlH_4$. It is likely that intermediate nitrogen anions complex with AlH_3 (formed in situ) to facilitate the addition. Protonation of the dianion in Step [4] forms the amine.

Mechanism 19.2 Reduction of a Nitrile with LiAlH4

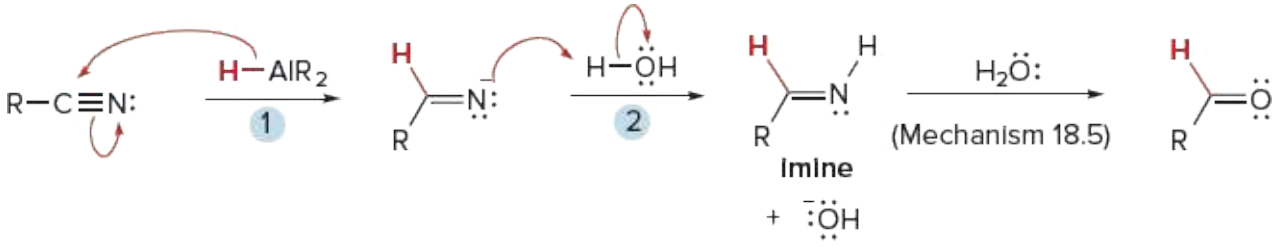


1 – 2 Addition of one equivalent of $H:^-$ from $LiAlH_4$ forms an intermediate with one new C—H bond, which complexes with AlH_3

3 – 4 Nucleophilic attack of a second equivalent of $H:^-$ and complexation with AlH_3 form a dianion, which reacts with water to form two new N—H bonds, giving the 1° amine.

With DIBAL-H, nucleophilic addition of one equivalent of hydride forms an anion (Step [1]), which is protonated with water to generate an imine, as shown in Mechanism 19.3. As described in Section 18.11, imines are hydrolyzed in water to form aldehydes. Mechanism 19.3 is written without complexation of aluminum with the anion formed in Step [1], to emphasize the identity of intermediates formed during reduction.

Mechanism 19.3 Reduction of a Nitrile with DIBAL-H



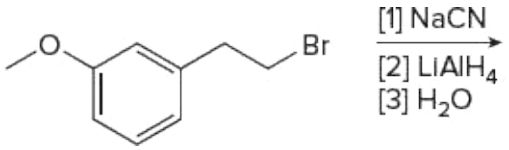
1 Addition of $H:^-$ from DIBAL-H (drawn as R_2AlH) forms the new C—H bond.

2 **Protonation forms an imine, which is hydrolyzed to an aldehyde by a stepwise sequence that is the reverse of Mechanism 18.5.**

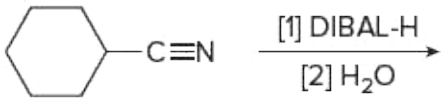
Problem 19.27

Draw the product of each reaction.

a.

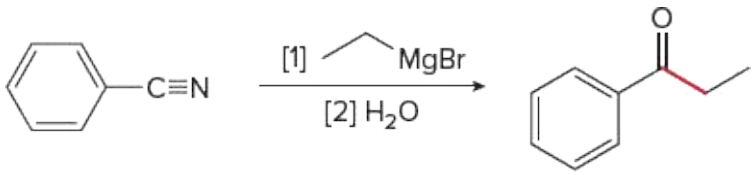


b.



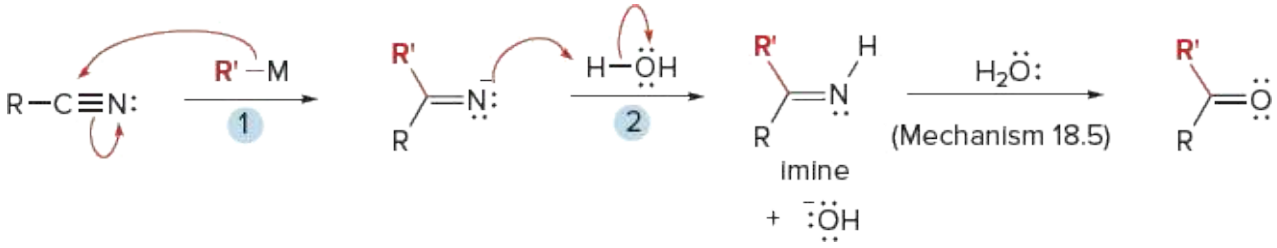
19.12C Addition of Grignard and Organolithium Reagents to Nitriles

Both Grignard and organolithium reagents react with nitriles to form ketones with a new carbon–carbon bond.



The reaction occurs by nucleophilic addition of the organometallic reagent to the polarized C—N triple bond to form an anion (Step [1]), which is protonated with water to form an imine. Water then hydrolyzes the imine, replacing the C=N by C=O as described in Section 18.11. The final product is a ketone with a new carbon–carbon bond (Mechanism 19.4).

Mechanism 19.4 Addition of Grignard and Organolithium Reagents (R—M) to Nitriles



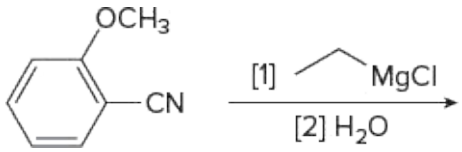
1 **Addition of $R:^-$ from R'M (M = MgX or Li) forms a new C—C bond.**

2 **Protonation forms an imine, which is hydrolyzed to a ketone by a stepwise sequence that is the reverse of Mechanism 18.5.**

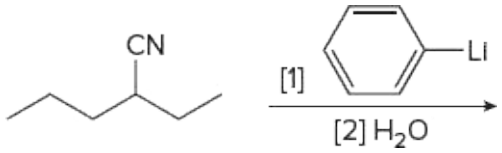
Problem 19.28

Draw the products of each reaction.

a.



b.



Problem 19.29

What reagents are needed to convert phenylacetonitrile ($C_6H_5CH_2CN$) to each compound: (a) $C_6H_5CH_2COCH_3$; (b) $C_6H_5CH_2COC(CH_3)_3$; (c) $C_6H_5CH_2CHO$; (d) $C_6H_5CH_2COOH$?

Problem 19.30

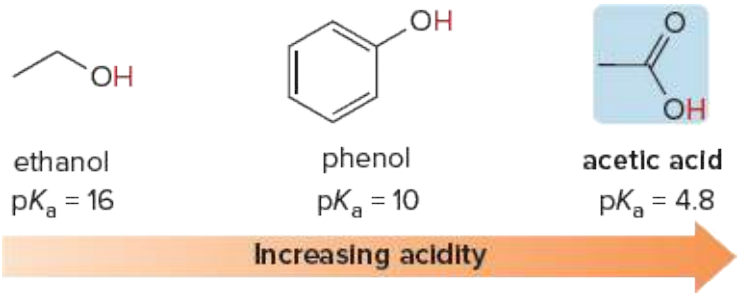
Outline two different ways that butan-2-one can be prepared from a nitrile and a Grignard reagent.

Chapter 19 REVIEW

KEY CONCEPTS

[1] Acidity and resonance effects (19.7)

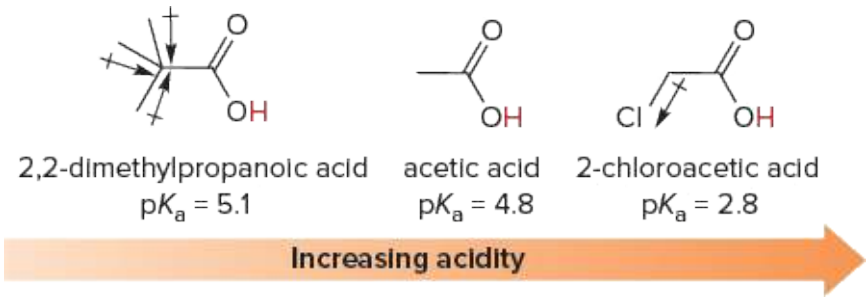
- **A carboxylic acid is more acidic than phenol and ethanol because its conjugate base is more stabilized by resonance.**



Try Problems 19.37, 19.40.

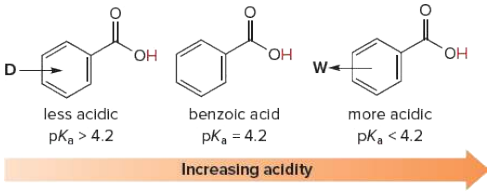
[2] Other factors that affect acidity

1 Inductive effects (19.8)



- Acidity *increases* with the presence of electron-withdrawing groups and *decreases* with the presence of electron-donating groups.

2 Substituted benzoic acids (19.9)

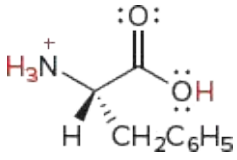


- Electron-donor groups make a substituted benzoic acid *less* acidic than benzoic acid.
- Electron-withdrawing groups make a substituted benzoic acid *more* acidic than benzoic acid.

Try Problems 19.32, 19.44, 19.47.

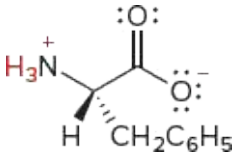
[3] Positively charged, neutral, and negatively charged forms of an amino acid (19.11); example: phenylalanine

1 Phenylalanine at pH = 1



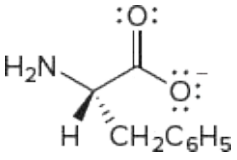
- At low pH, the amino acid has a net (+) charge.

2 Phenylalanine at pH ≈ 6



- At pH ≈ 6, the amino acid exists as a zwitterion with no overall charge.

3 Phenylalanine at pH = 11

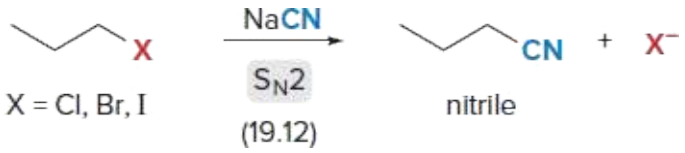


- At high pH, the amino acid has a net (–) charge.

See Figure 19.10. Try Problems 19.60, 19.61.

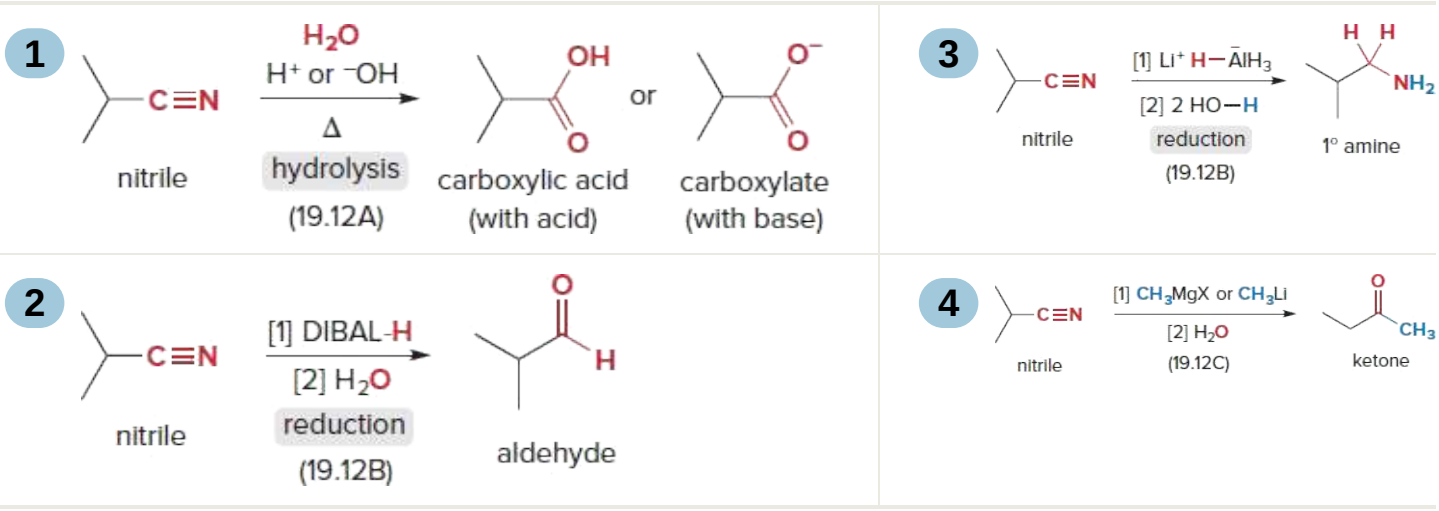
KEY REACTIONS

[1] Nitrile Synthesis



Try Problems 19.52f, 19.55a.

[2] Reactions of Nitriles

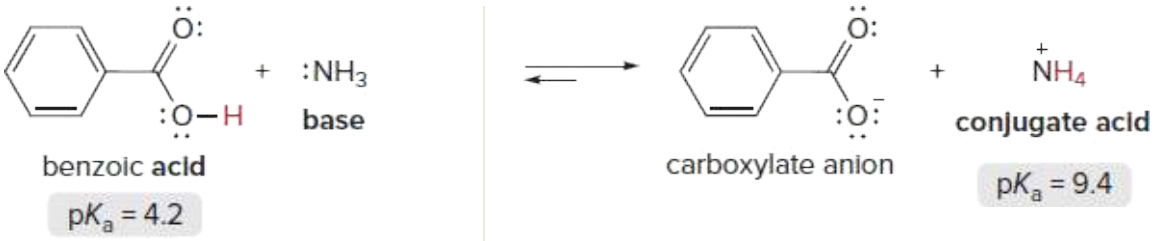


Try Problems 19.33b; 19.52e, f; 19.54; 19.55a, c, d.

KEY SKILLS

[1] Drawing the products of an acid–base reaction involving a carboxylic acid (19.7)

1 **Identify the acid and the base.**	**2** **Transfer a proton from the acid to the base.**	**3** **Dra res sta car ani**



- For equilibrium to favor the products, the base must have a conjugate acid with a pK_a > 4.2.

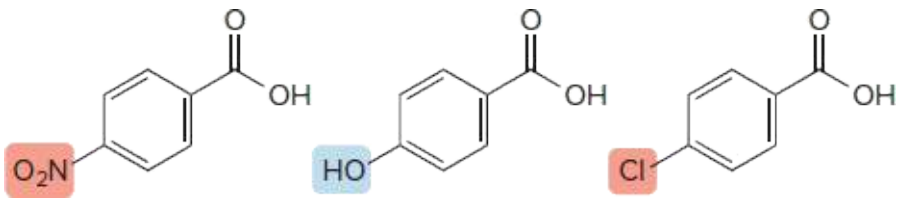
- Ca ac es ac be ca ar re st

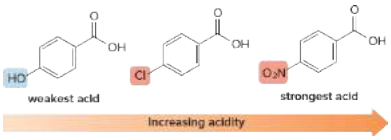
See Table 19.4. Try Problems 19.31b, 19.38c.

[2] Ranking benzoic acids in order of increasing acidity (19.9)

1 Identify electron-withdrawing or electron, donating groups.

2 Rank the compounds.





- Electron-donor groups *destabilize* the conjugate base by donating electron density to the negatively charged carboxylate anion.
- Electron-withdrawing groups *stabilize* the conjugate base by removing electron density from the negatively charged carboxylate anion.

- The strongest a has the *most* stable conjugat base.
- The weakest aci has the *least* sta conjugate base.

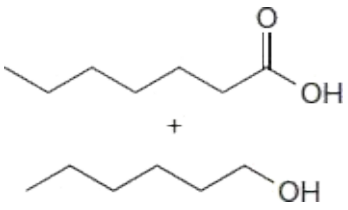
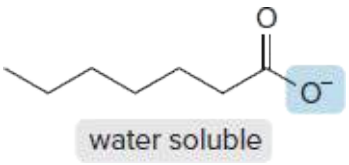
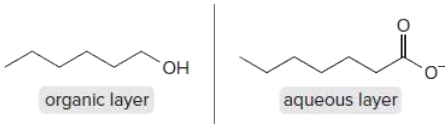
See Sample Problem 19.3. Try Problems 19.32, 19.39.

[3] Separating a carboxylic acid from an alcohol by extraction (19.10)

1 Dissolve the compounds in an

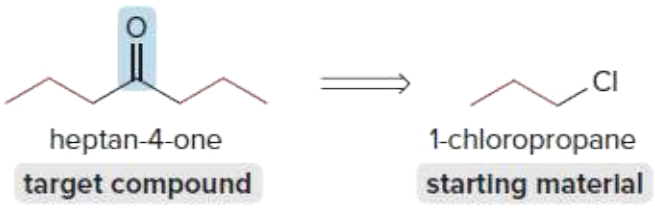
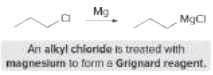
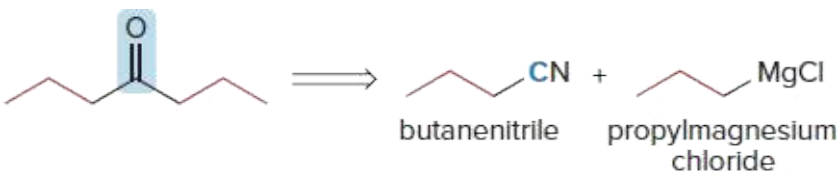
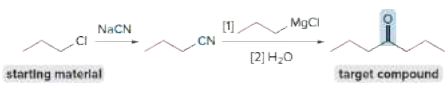
2 Add aqueous base to

3 Separate the layers.

organic solvent.	deprotonate the carboxylic acid.	
 • Both of these compounds are soluble in organic solvents.	 water soluble • When the carboxylic acid is deprotonated, it is now soluble in the H_2O layer.	 organic layer aqueous layer • The alcohol remain in the organic layer and the carboxylat in the aqueous laye

See Sample Problem 19.4, Figure 19.9. Try Problems 19.56–19.58.

[4] Devising a synthesis; example: heptan-4-one from 1-chloropropane (19.12C)

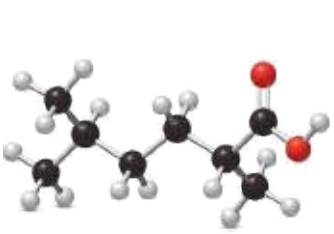
1 Compare the carbon skeletons and functional groups.	**3** Work forwards.
 heptan-4-one target compound 1-chloropropane starting material	 An alkyl chloride is treated with magnesium to form a Grignard reagent.
2 Work backwards.	**4** Complete the synthesis.
 butanenitrile propylmagnesium chloride A ketone is made from the reaction between a nitrile and a Grignard reagent.	 starting material target compound

Try Problems 19.66, 19.67.

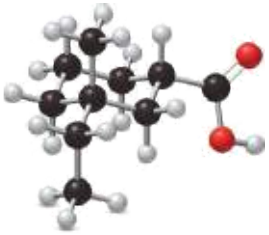
PROBLEMS

Problems Using Three-Dimensional Models

19.31 **Answer each question for A and B depicted in the ball-and-stick models.**



A



B

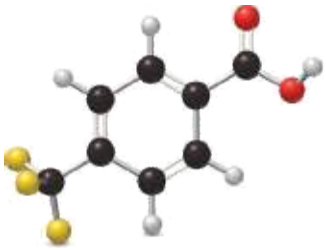
a. What is the IUPAC name for each compound?

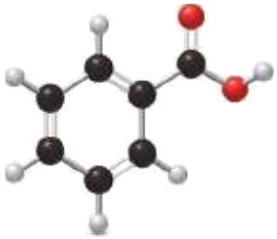
b. What product is formed when each compound is treated with NaOH?

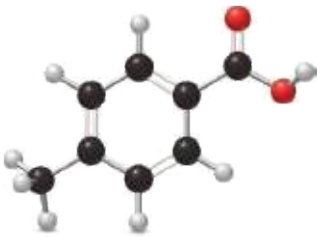
c. Name the products formed in part (b).

d. Draw the structure of an isomer that is at least 10^5 times less acidic than each compound.

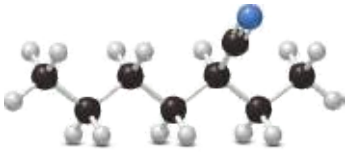
19.32 **Rank the carboxylic acids in order of increasing acidity.**







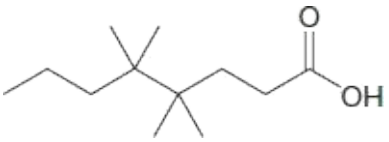
19.33 **(a) Give an acceptable name for compound C. (b) Draw the organic products formed when C is treated with each reagent: [1] H_3O^+; [2] ^-OH, H_2O; [3] $CH_3CH_2CH_2MgBr$ (excess), then H_2O; [4] $LiAlH_4$, then H_2O.**

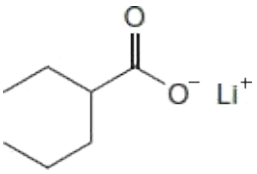


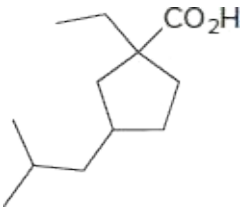
C

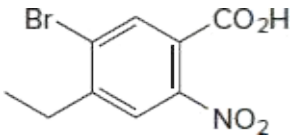
Nomenclature

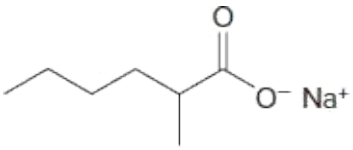
19.34 **Give the IUPAC name for each compound.**

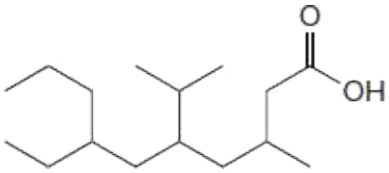
a. 

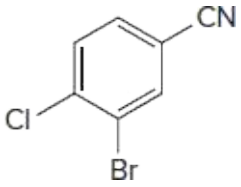
b. 

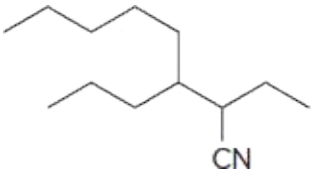
c. 

d. 

e. 

f. 

g. 

h. 

19.35 Draw the structure corresponding to each name.

a. 3,3-dimethylpentanoic acid

b. 4-chloro-3-phenylheptanoic acid

c. (*R*)-2-chloropropanoic acid

d. *m*-hydroxybenzoic acid

e. potassium acetate

f. sodium α-bromobutyrate

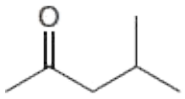
g. 2,2-dichloropentanedioic acid

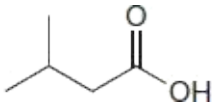
h. 4-isopropyl-2-methyloctanedioic acid

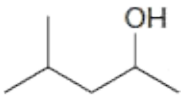
i. 3,3-dimethylpentanenitrile j. 4,5-diethyl-2-isopropylnonanenitrile

Physical Properties

19.36 **Rank the following compounds in order of increasing boiling point.**



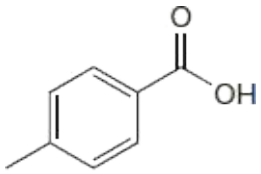




Acid–Base Reactions; General Questions on Acidity

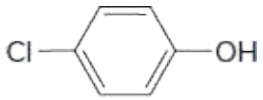
19.37 **Using the pK_a table in Appendix C, determine whether each of the following bases is strong enough to deprotonate the three compounds listed below. Bases: [1] ^-OH; [2] $CH_3CH_2^-$; [3] $^-NH_2$; [4] NH_3; [5] $HC{\equiv}C^-$.**

a.



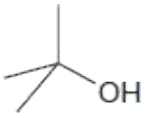
pK_a = 4.3

b.



pK_a = 9.4

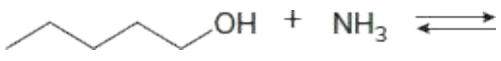
c.



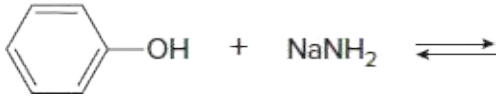
pK_a = 18

19.38 **Draw the products of each acid–base reaction, and using the pK_a table in Appendix C, determine if equilibrium favors the reactants or products.**

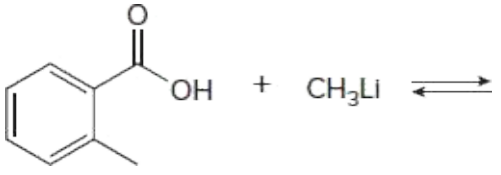
a.



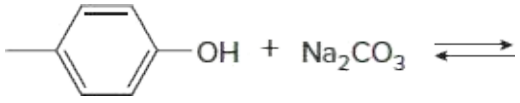
b.



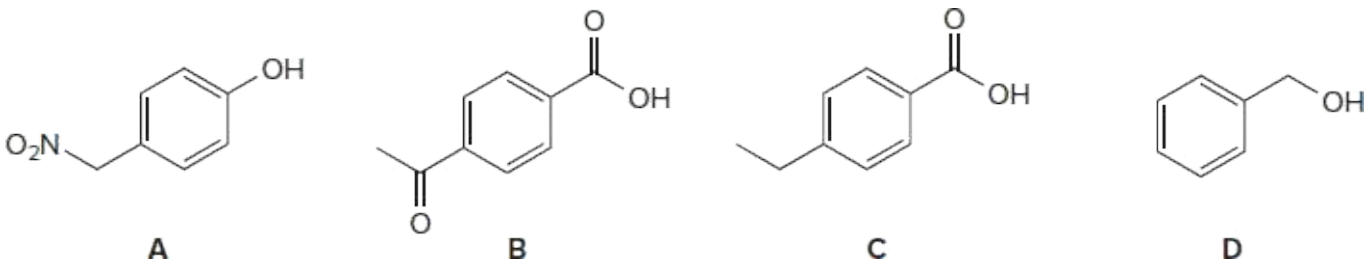
c.



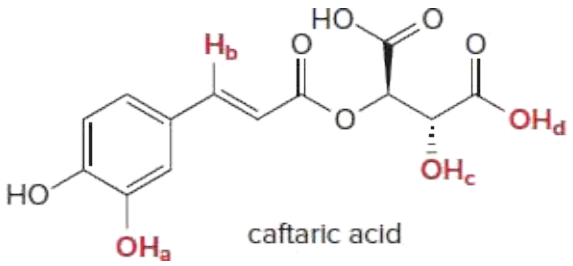
d.



19.39 **(a) Rank the following compounds in order of increasing acidity. (b) Which compound forms the strongest conjugate base?**



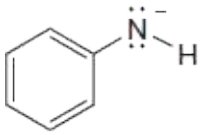
19.40 **Caftaric acid is found in grapes, wine, and raisins. Rank the labeled protons in caftaric acid in order of increasing acidity.**

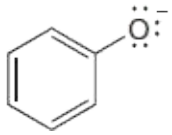


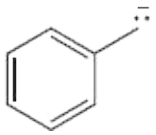
caftaric acid

19.41 **Rank the compounds in each group in order of increasing basicity.**

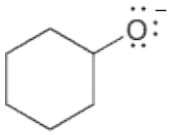
a.

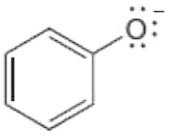


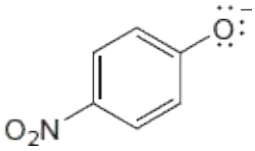




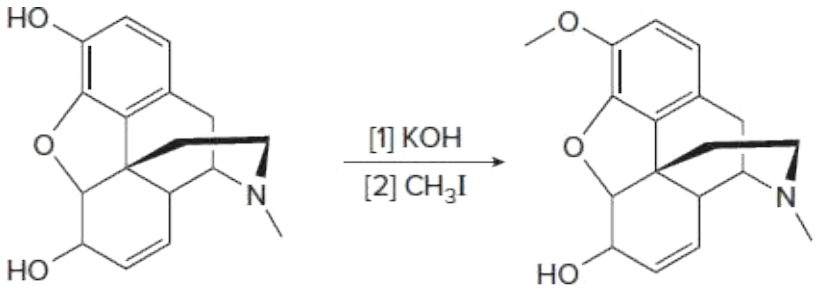
b.







19.42 **Although codeine occurs in low concentration in the opium poppy, most of the codeine used in medicine is prepared from morphine (the principal component of opium) by the following reaction. Explain why selective methylation occurs at only one OH in morphine to give codeine. Codeine is a less potent and less addictive analgesic than morphine.**



19.43 **Explain each statement.**

a. The pK_a of *p*-nitrophenol is lower than the pK_a of phenol (7.2 vs. 10).

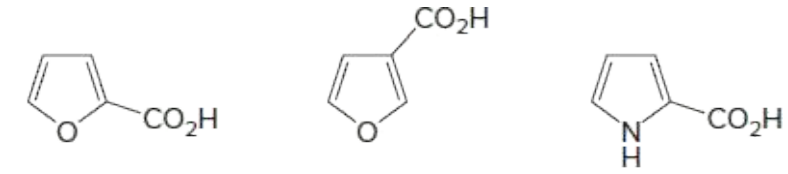
b. The pK_a of *p*-nitrophenol is lower than the pK_a of *m*-nitrophenol (7.2

vs. 8.3).

19.44 Explain this statement: Although 2-methoxyacetic acid (CH_3OCH_2COOH) is a stronger acid than acetic acid (CH_3COOH), *p*-methoxybenzoic acid ($CH_3OC_6H_4COOH$) is a weaker acid than benzoic acid (C_6H_5COOH).

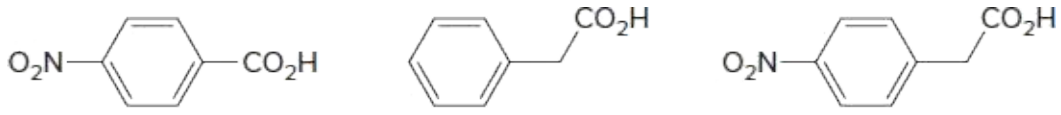
19.45 The pK_a of *p*-methylthiophenol ($CH_3SC_6H_4OH$) is 9.53. Is *p*-methylthiophenol more or less reactive in electrophilic aromatic substitution than phenol?

19.46 Explain why the pK_a of compound A is lower than the pK_a's of both compounds B and C.



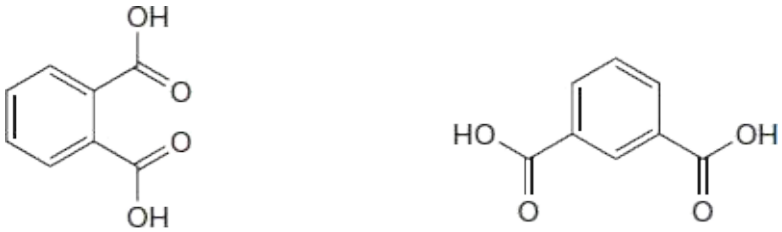
A pK_a = 3.2 **B** pK_a = 3.9 **C** pK_a = 4.4

19.47 Rank the following compounds in order of increasing acidity, and explain in detail your choice of order.



C **D** **E**

19.48 Phthalic acid and isophthalic acid have protons on two carboxy groups that can be removed with base. (a) Explain why the pK_a for loss of the first proton (pK_{a1}) is lower for phthalic acid than isophthalic acid. (b) Explain why the pK_a for loss of the second proton (pK_{a2}) is higher for phthalic acid than isophthalic acid.

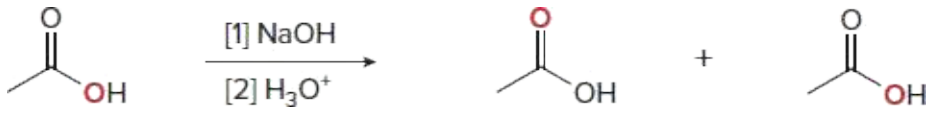


phthalic acid
pK_{a1} = 2.9
pK_{a2} = 5.4

isophthalic acid
pK_{a1} = 3.7
pK_{a2} = 4.6

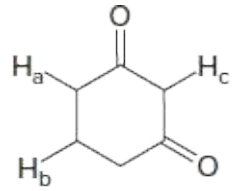
19.49 Explain this result: Acetic acid (CH_3COOH), labeled at its OH oxygen with

the uncommon ^{18}O isotope (shown in red), was treated with aqueous base, and then the solution was acidified. Two products having the ^{18}O label at different locations were formed.



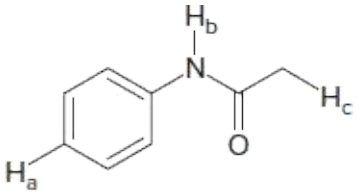
19.50 Draw all resonance structures of the conjugate bases formed by removal of the labeled protons (H_a, H_b, and H_c) in cyclohexane-1,3-dione and acetanilide. For each compound, rank these protons in order of increasing acidity and explain the order you chose.

a.



cyclohexane-1,3-dione

b.



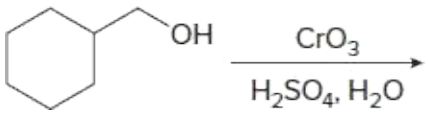
acetanilide

19.51 The pK_a of acetamide (CH_3CONH_2) is 16. Draw the structure for its conjugate base, and explain why acetamide is less acidic than CH_3COOH.

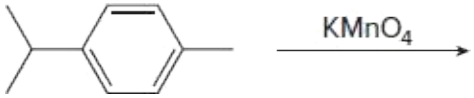
General Reactions

19.52 Draw the organic products formed in each reaction.

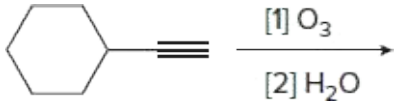
a.



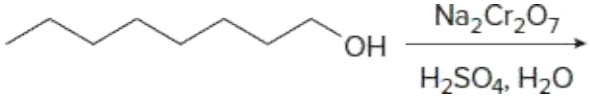
b.

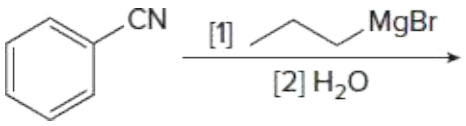


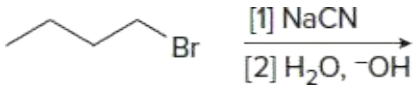
c.



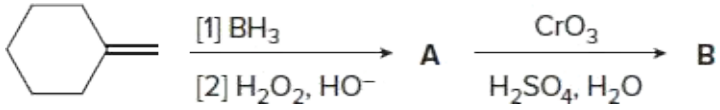
d.

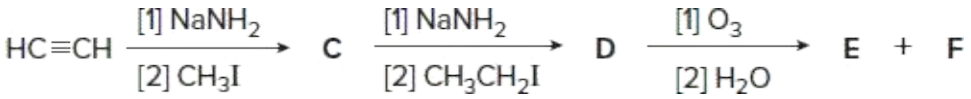


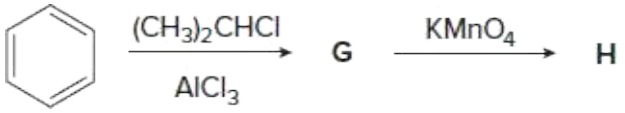
e. 

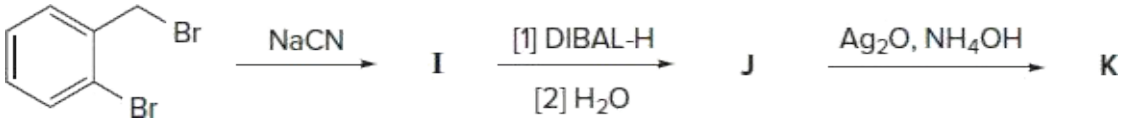
f. 

19.53 Identify the lettered compounds in each reaction sequence.

a. 

b. 

c. 

d. 

19.54 Draw the product formed when phenylacetonitrile ($C_6H_5CH_2CN$) is treated with each reagent.

a. H_3O^+

b. H_2O, ^-OH

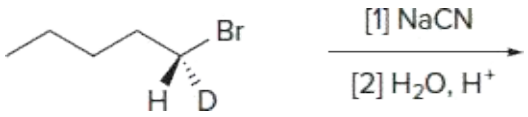
c. [1] CH_3MgBr; [2] H_2O

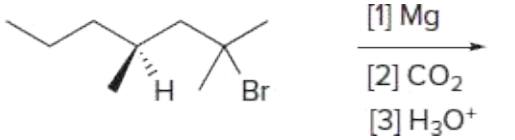
d. [1] CH_3CH_2Li; [2] H_2O

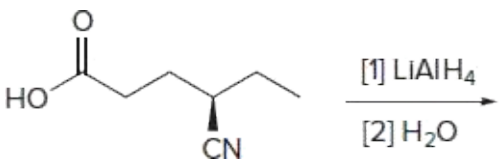
e. [1] DIBAL-H; [2] H_2O

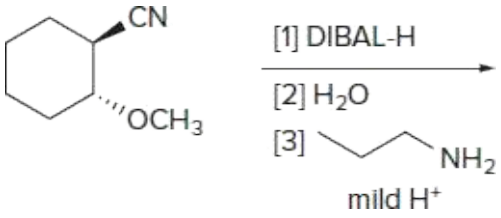
f. [1] [1] $LiAlH_4$; [2] H_2O

19.55 Draw the products of each reaction, and indicate the stereochemistry at all stereogenic centers.

a. 

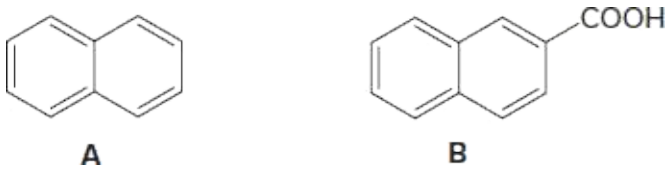
b. 

c. 

d. 

Extraction

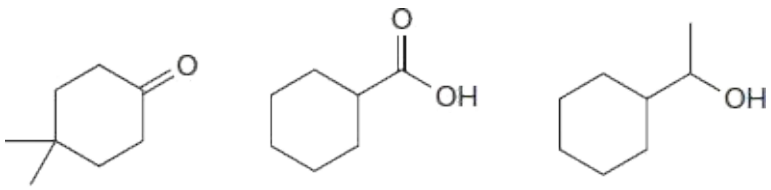
19.56 **Write out the steps needed to separate hydrocarbon A and carboxylic acid B by using an extraction procedure.**



A B

19.57 **Because phenol (C_6H_5OH) is less acidic than a carboxylic acid, it can be deprotonated by NaOH but not by the weaker base $NaHCO_3$. Using this information, write out an extraction sequence that can be used to separate C_6H_5OH, benzoic acid, and cyclohexanol. Show what compound is present in each layer at each stage of the process, and if it is present in its neutral or ionic form.**

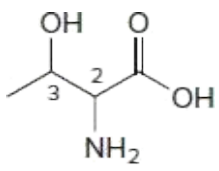
19.58 **A mixture of A, B, and C was added to a separatory funnel containing CH_2Cl_2, and an aqueous layer was added. In which layer is each compound dissolved when the aqueous layer consists of (a) pure water; (b) 10% NaOH solution; (c) 10% $NaHCO_3$ solution?**



A B C

Amino Acids

19.59 **Threonine is a naturally occurring amino acid that has two stereogenic centers.**

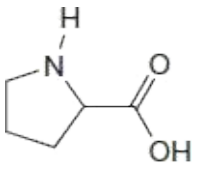


threonine

a. Draw the four possible stereoisomers using wedges and dashed wedges.

b. The naturally occurring amino acid has the 2*S*,3*R* configuration at its two stereogenic centers. Which structure does this correspond to?

19.60 Proline is an unusual amino acid because its N atom on the α carbon is part of a five-membered ring.

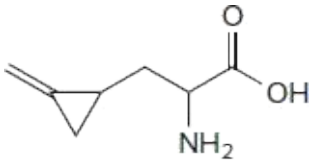


proline

a. Draw both enantiomers of proline.

b. Draw proline in its zwitterionic form.

19.61 Hypoglycin A, an amino acid derivative found in unripened lychee, is an acutely toxic compound that produces seizures, coma, and sometimes death in undernourished children when ingested on an empty stomach (Problem 5.60). (a) Draw the neutral, positively charged, and negatively charged forms of hypoglycin A. (b) Which form predominates at pH = 1, 6, and 11? (c) What is the structure of hypoclycin A at its isoelectric point?



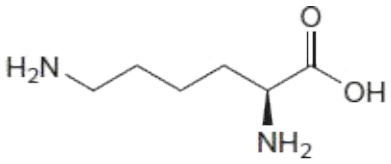
hypoglycin A

19.62 Calculate the isoelectric point for each amino acid.

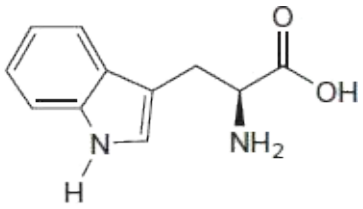
a. asparagine: pK_a (COOH) = 2.02; pK_a (α-NH_3^+) = 8.80

b. methionine: pK_a (COOH) = 2.28; pK_a (α-NH_3^+) = 9.21

19.63 Lysine and tryptophan are two amino acids that contain an additional N atom in the R group bonded to the a carbon. While lysine is classified as a basic amino acid because it contains an additional basic N atom, tryptophan is classified as a neutral amino acid. Explain why this difference in classification occurs.

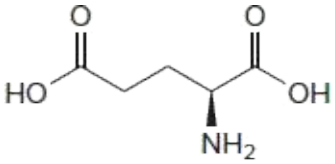


lysine



tryptophan

19.64 **Glutamic acid is a naturally occurring α-amino acid that contains a carboxy group in its R group side chain (Table 19.5). (Glutamic acid is drawn in its neutral form with no charged atoms, a form that does not actually exist at any pH.)**



glutamic acid

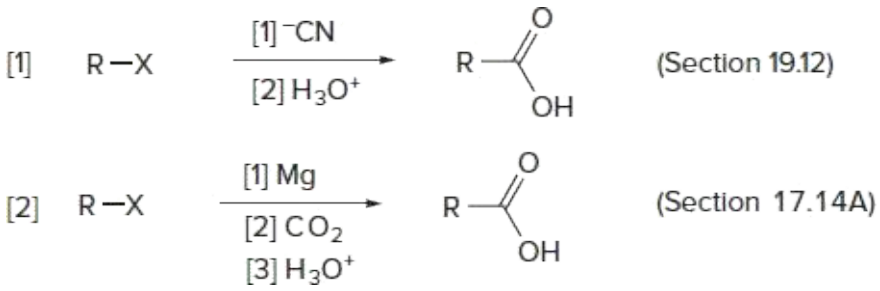
a. What form of glutamic acid exists at pH = 1?

b. I f the pH is gradually increased, what form of glutamic acid exists after one equivalent of base is added? After two equivalents? After three equivalents?

c. Propose a structure of monosodium glutamate, the common flavor enhancer known as MSG.

Synthesis

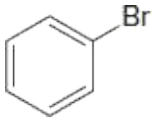
19.65 **Two methods convert an alkyl halide to a carboxylic acid having one more carbon atom.**

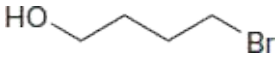


Depending on the structure of the alkyl halide, one or both of these methods may be employed. For each alkyl halide, write out a stepwise sequence that converts it to a carboxylic acid with one more carbon atom. If both methods work, draw both routes. If one method cannot be

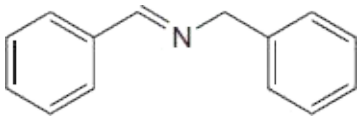
used, state why it can't.

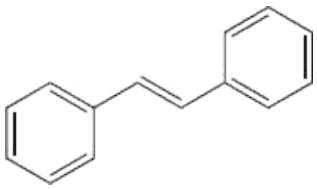
a.

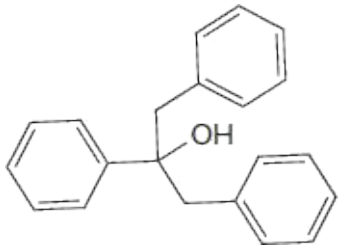
b. 

c. 

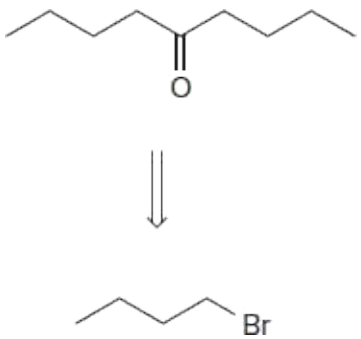
19.66 Synthesize each compound from benzonitrile (C_6H_5CN) as the only organic starting material; that is, every carbon in the product must originate in benzonitrile.

a. 

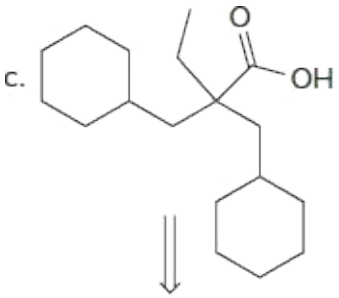
b. 

c. 

19.67 Devise a synthesis of each compound from the indicated starting material. You may also use any organic compounds with one or two carbons and any needed inorganic reagents.

a. 

b.



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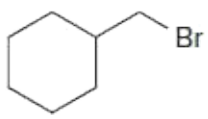

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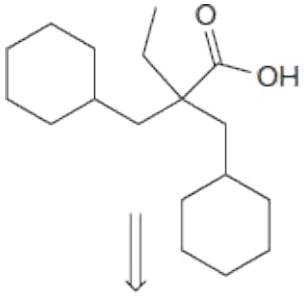
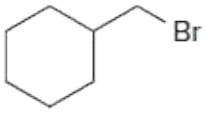




Spectroscopy

19.68 **Identify each compound from its spectral data.**

a. Molecular formula: $C_3H_5ClO_2$

IR: 3500–2500 cm^{-1}, 1714 cm^{-1}

^{1}H NMR data: 2.87 (triplet, 2 H), 3.76 (triplet, 2 H), and 11.8 (singlet, 1 H) ppm

b. Molecular formula: $C_8H_8O_3$

IR: 3500–2500 cm^{-1}, 1710 cm^{-1}

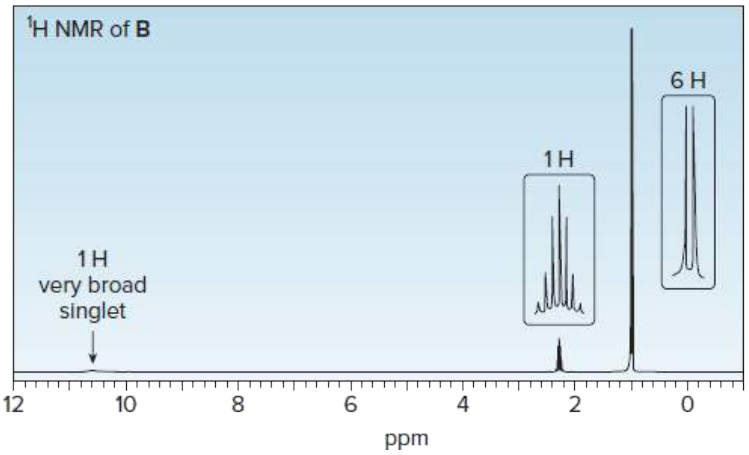
^{1}H NMR data: 4.7 (singlet, 2 H), 6.9–7.3 (multiplet, 5 H), and 11.3 (singlet, 1 H) ppm

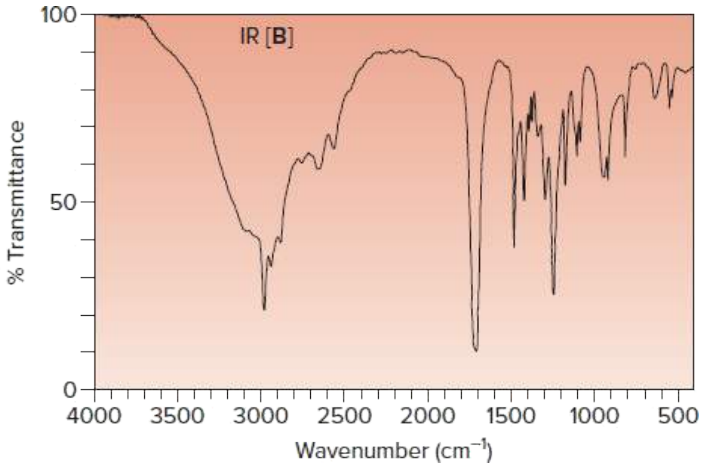
c. Molecular formula: C_4H_7N

IR: 2250 cm^{-1}

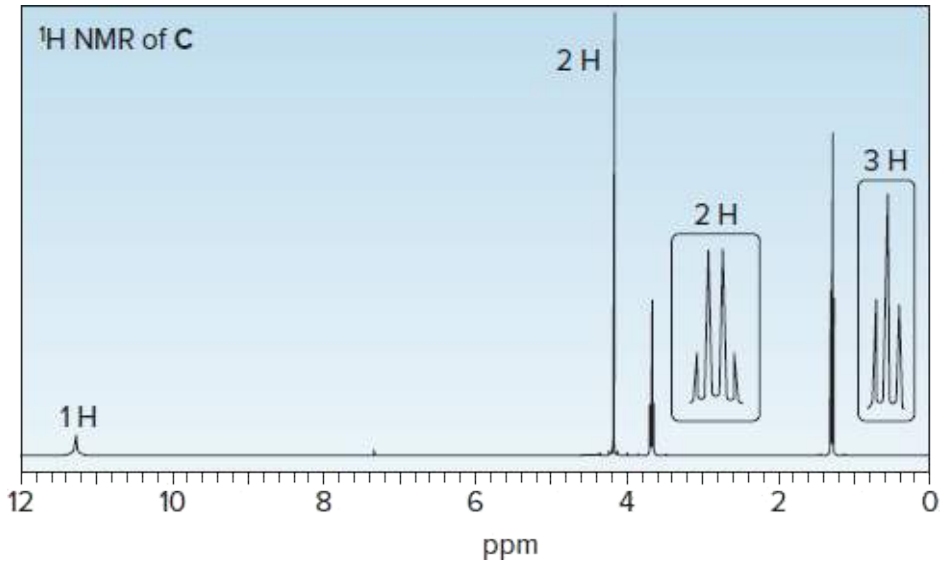
^{1}H NMR data: 1.08 (triplet, 3 H), 1.70 (multiplet, 2 H), and 2.34 (triplet, 2 H) ppm

19.69 **Use the ^{1}H NMR and IR spectra given below to identify the structure of compound B (molecular formula $C_4H_8O_2$).**

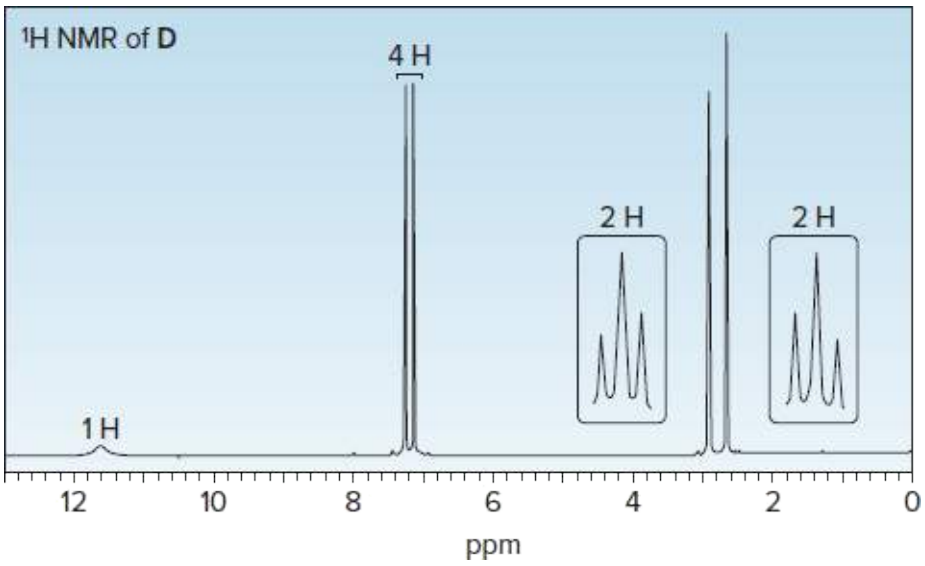




19.70 An unknown compound C (molecular formula $C_4H_8O_3$) exhibits IR absorptions at 3600–2500 and 1734 cm^{-1}, as well as the following ^1H NMR spectrum. What is the structure of C?



19.71 Propose a structure for D (molecular formula $C_9H_9ClO_2$) consistent with the given spectroscopic data. ^{13}C NMR signals at 30, 36, 128, 130, 133, 139, and 179 ppm

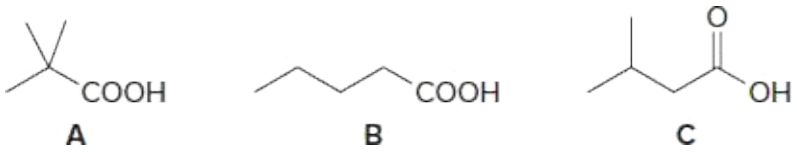


19.72 **Match the ^{13}C NMR data to the appropriate structure.**

Spectrum [1]: signals at 14, 22, 27, 34, 181 ppm

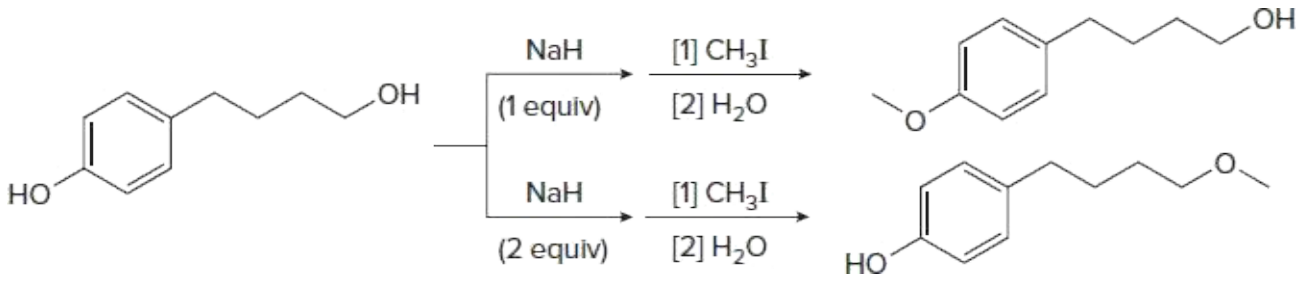
Spectrum [2]: signals at 27, 39, 186 ppm

Spectrum [3]: signals at 22, 26, 43, 180 ppm

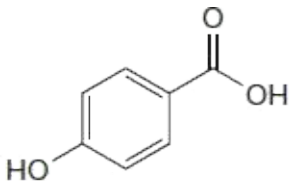


Challenge Problems

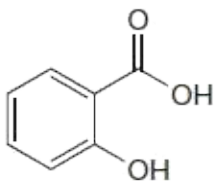
19.73 **Explain why using one or two equivalents of NaH results in different products in the following reactions.**



19.74 **Although *p*-hydroxybenzoic acid is less acidic than benzoic acid, *o*-hydroxybenzoic acid is slightly more acidic than benzoic acid. Explain this result.**

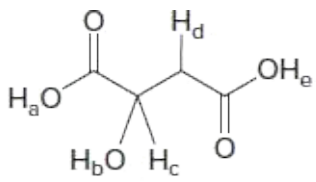


p-hydroxybenzoic acid



o-hydroxybenzoic acid

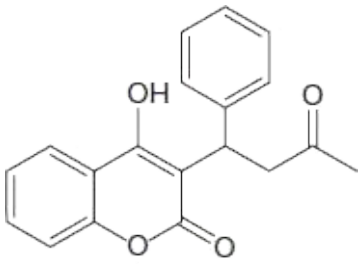
19.75 **2-Hydroxybutanedioic acid occurs naturally in apples and other fruits. Rank the labeled protons (H_a–H_e) in order of increasing acidity, and explain in detail the order you chose.**



2-hydroxybutanedioic acid

19.76 **Although it was initially sold as a rat poison, warfarin is an effective**

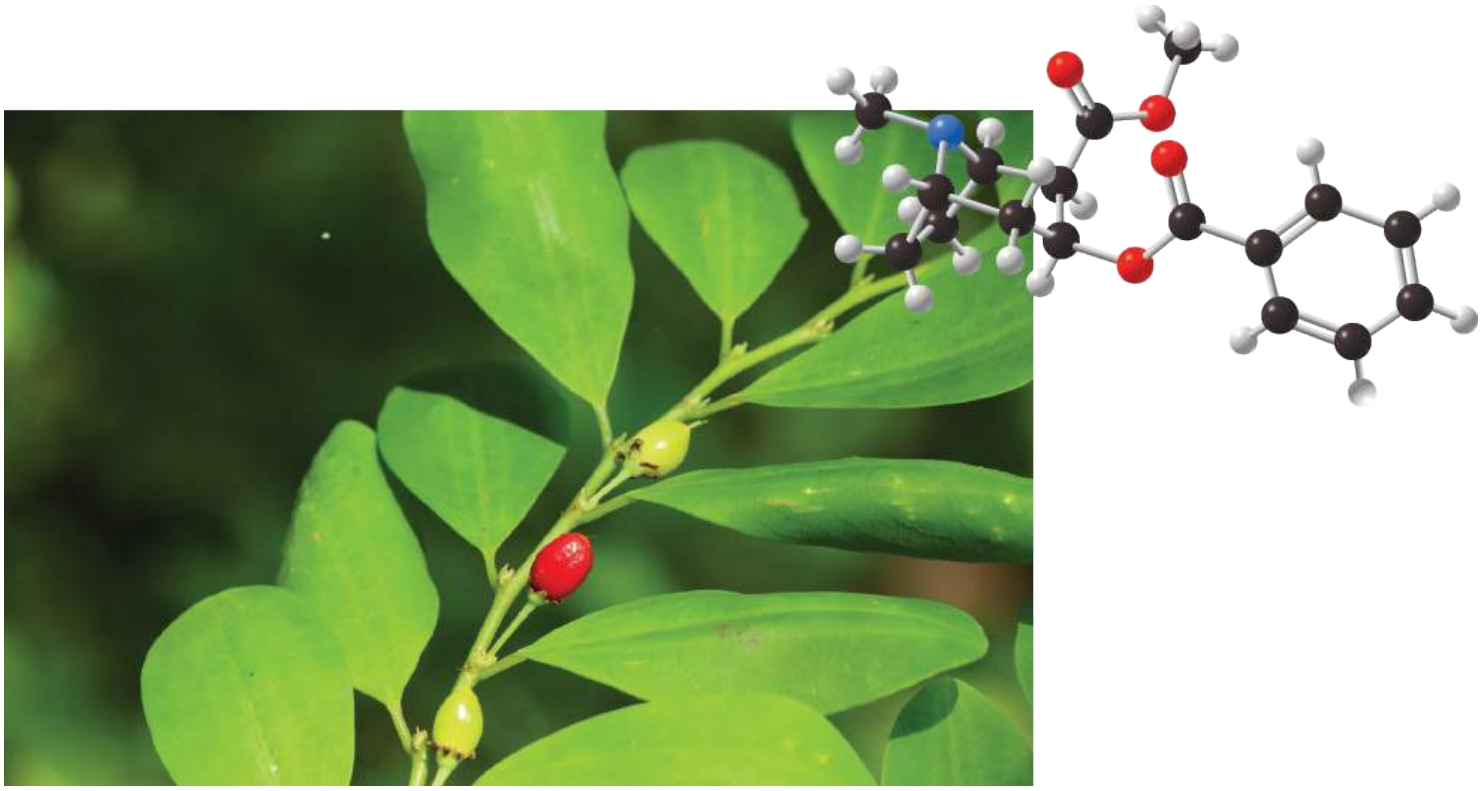
anticoagulant used to prevent blood clots. Label the most acidic proton in warfarin, and explain why its pK_a is comparable to the pK_a of a carboxylic acid.



warfarin

Carboxylic Acids and Their Derivatives—Nucleophilic Acyl Substitution

20



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20.1 Introduction

20.2 Structure and bonding

20.3 Nomenclature

20.4 Physical and spectroscopic properties

20.5 Interesting esters and amides

20.6 Introduction to nucleophilic acyl substitution

20.7 Reactions of acid chlorides

20.8 Reactions of anhydrides

20.9 Reactions of carboxylic acids

20.10 Reactions of esters
20.11 Application: Lipid hydrolysis
20.12 Reactions of amides
20.13 Application: The mechanism of action of β-lactam antibiotics
20.14 Summary of nucleophilic acyl substitution reactions
20.15 Natural and synthetic fibers
20.16 Biological acylation reactions

Cocaine is an addictive stimulant obtained from the leaves of the coca plant, *Erythroxylon coca*. Chewing coca leaves for pleasure has been practiced by the indigenous peoples of South America for over a thousand years, and coca leaves were a very minor ingredient in Coca-Cola for the first 20 years of its production. Cocaine is a widely abused recreational drug, and the possession and use of cocaine is currently illegal in most countries. Cocaine contains two esters, carboxylic acid derivatives discussed in Chapter 20.

Why Study…

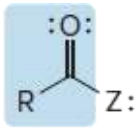
Carboxylic Acid Derivatives?

Chapter 20 continues the study of carbonyl compounds with a detailed look at nucleophilic acyl substitution, a key reaction of carboxylic acids and their derivatives. Substitution at sp^2 hybridized carbon atoms was introduced in Chapter 17 with reactions involving carbon and hydrogen nucleophiles. In Chapter 20, we learn that nucleophilic acyl substitution is a general reaction that occurs with a variety of heteroatomic nucleophiles. *Every* reaction in Chapter 20 that begins with a carbonyl compound involves nucleophilic substitution. Nucleophilic acyl substitutions are useful reactions in both the laboratory and biological systems. Penicillin is an effective antibiotic because it kills bacteria by a nucleophilic substitution mechanism.

20.1 Introduction

Chapter 20 focuses on carbonyl compounds that contain an acyl group bonded to an electronegative atom. These include the carboxylic acids, as well as carboxylic acid

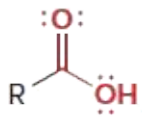
derivatives that can be prepared from them: acid chlorides, anhydrides, esters, and amides.



acyl group

Z = an atom more electronegative than carbon

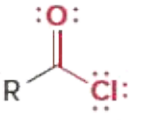
Z = OH



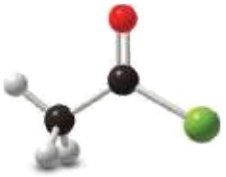
carboxylic acid

$R = CH_3$
acetic acid

Z = Cl

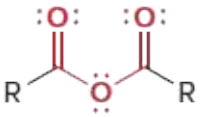


acid chloride

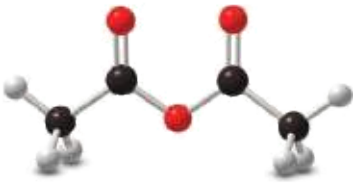


$R = CH_3$
acetyl chloride

Z = OCOR

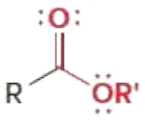


anhydride



$R = CH_3$
acetic anhydride

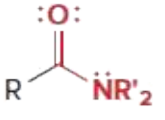
Z = OR'



ester

$R = R' = CH_3$
methyl acetate

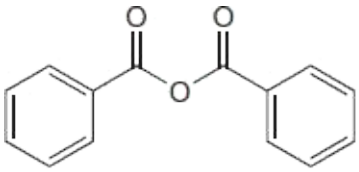
$Z = NR'_2$



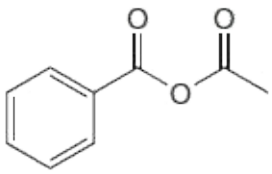
R' = H or alkyl
amide

$R = CH_3$, R' = H
acetamide

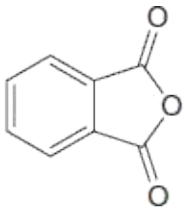
Anhydrides contain two carbonyl groups joined by a single oxygen atom. Symmetrical anhydrides have two identical alkyl groups bonded to the carbonyl carbons, and mixed anhydrides have two different alkyl groups. Cyclic anhydrides are also known.



symmetrical anhydride

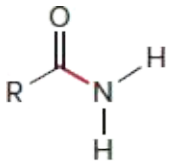


mixed anhydride

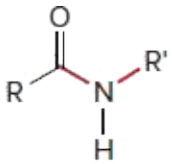


cyclic anhydride

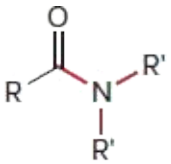
As we learned in Section 3.2, amides are classified as 1°, 2°, or 3° depending on the number of carbon atoms bonded directly to the *nitrogen* atom. Page 928



1° amide
1 C—N bond

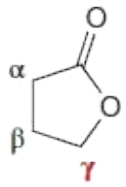


2° amide
2 C—N bonds

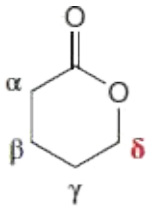


3° amide
3 C—N bonds

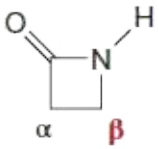
Cyclic esters and amides are called lactones and lactams, respectively. The ring size of the heterocycle is indicated by a Greek letter. An amide in a four-membered ring is called a β-lactam, because the β carbon to the carbonyl is bonded to the heteroatom. An ester in a five-membered ring is called a γ-lactone.



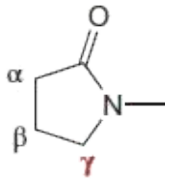
γ-lactone



δ-lactone



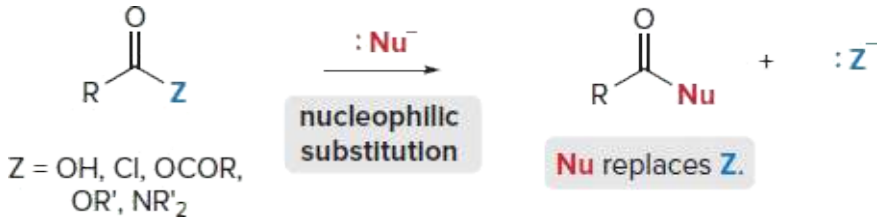
β-lactam



γ-lactam

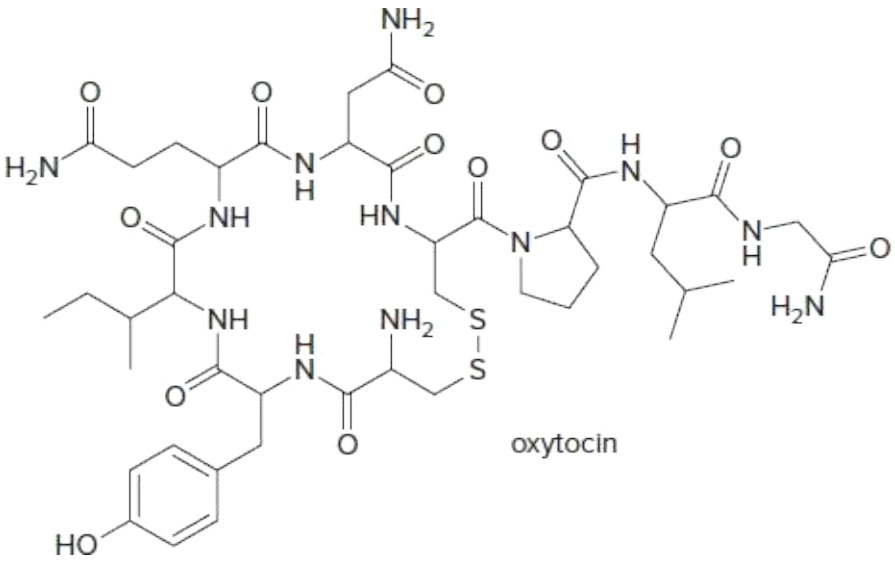
Nucleophilic acyl substitution was first discussed in Chapter 17 with R^- and H^- as the nucleophiles. This substitution reaction is general for a variety of nucleophiles, making it possible to form many different substitution products, as discussed in Sections 20.7–20.12.

All of these compounds contain an acyl group bonded to an electronegative atom Z that can serve as a leaving group. As a result, these compounds undergo nucleophilic acyl substitution. Recall from Chapters 17 and 18 that aldehydes and ketones do *not* undergo nucleophilic substitution because they have no leaving group on the carbonyl carbon.



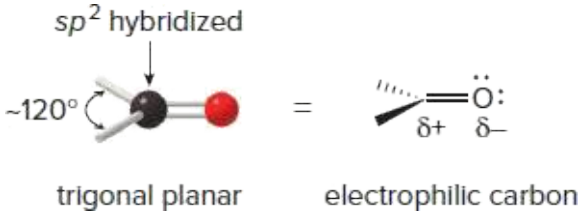
Problem 20.1

Oxytocin, sold under the trade name Pitocin, is a naturally occurring hormone used to stimulate uterine contractions and induce labor. Classify each amide in oxytocin as 1°, 2°, or 3°.



20.2 Structure and Bonding

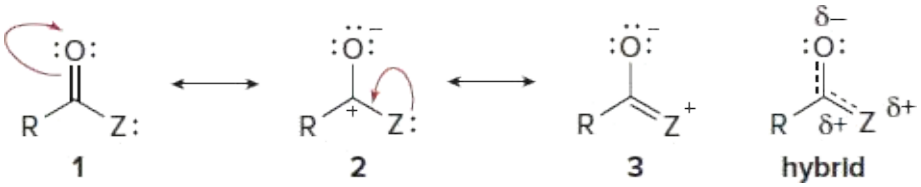
The two most important features of any carbonyl group, regardless of the other groups bonded to it, are the following:



- **The carbonyl carbon is sp^2 hybridized and trigonal planar, making it relatively *uncrowded.***
- **The electronegative oxygen atom polarizes the carbonyl group, making the carbonyl carbon *electrophilic.***

As we learned in Section B.3C, three resonance structures can be drawn for RCOZ, compared to just two for aldehydes and ketones (Section 17.1). These three resonance

structures stabilize RCOZ by delocalizing electron density. In fact, the more resonance structures 2 and 3 contribute to the resonance hybrid, the *more* stable RCOZ is.



- **The *more* basic Z is, the *more* it donates its electron pair, and the *more* resonance structure 3 contributes to the hybrid.**

To determine the relative basicity of the leaving group Z, we compare the pK_a values of the conjugate acids HZ, given in Table 20.1. The following order of basicity results:

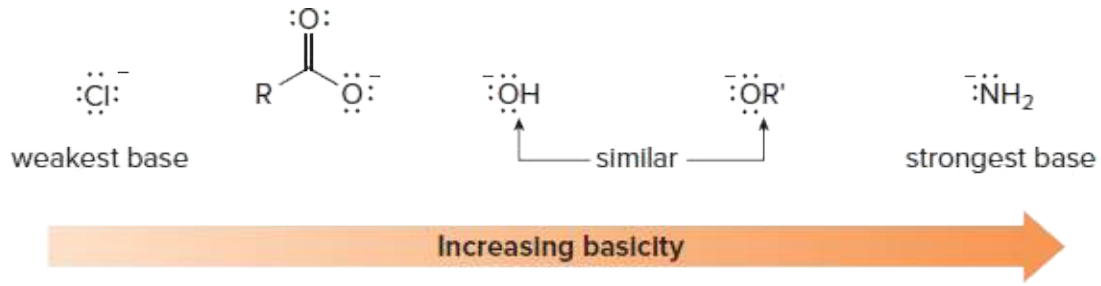


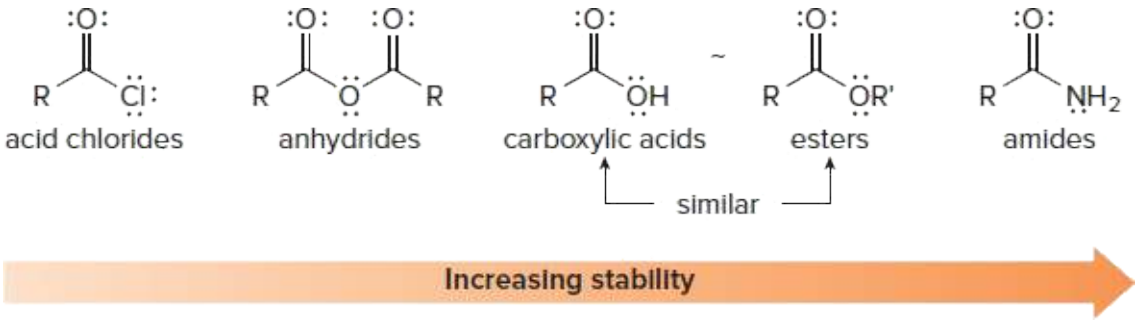
Table 20.1 pK_a Values of the Conjugate Acids (HZ) for Common Z Groups of Acyl Compounds (RCOZ)

Structure	Leaving group (Z^-)	Conjugate acid (HZ)	pK_a
RCOCl acid chloride	Cl^-	HCl	−7
$(RCO)_2O$ anhydride	RCO_2^-	RCO_2H	3–5
RCO_2H carboxylic acid	^-OH	H_2O	15.7
RCO_2R' ester	$^-OR'$	R′OH	15.5–18
$RCONR'_2$ amide	$^-NR'_2$	R'_2NH	38–40

Increasing basicity of Z ↓

↑ Increasing acidity of HZ

Because the basicity of Z determines the relative stability of the carboxylic acid derivatives, the following order of stability results:



Thus, an acid chloride is the *least* stable carboxylic acid derivative because Cl^- is the weakest base. An amide is the *most* stable carboxylic acid derivative because $^-NR'_2$ is the strongest base.

- **In summary: As the basicity of Z *increases*, the stability of RCOZ *increases* because of added resonance stabilization.**

Problem 20.2

Draw the three possible resonance structures for an acid bromide, RCOBr. Then, using the pK_a values in Appendix C, decide if RCOBr is more or less stabilized by resonance than a carboxylic acid (RCOOH).

Problem 20.3

How do the following experimental results support the resonance description of the relative stability of acid chlorides compared to amides? The C–Cl bond lengths in CH_3Cl and CH_3COCl are identical (178 pm), but the C–N bond in $HCONH_2$ is shorter than the C–N bond in CH_3NH_2 (135 pm versus 147 pm).

20.3 Nomenclature

The names of carboxylic acid derivatives are formed from the names of the parent carboxylic acids discussed in Section 19.2. Keep in mind that the common names formic acid, acetic acid, and benzoic acid are virtually always used for the parent acid, so these common parent names are used for their derivatives as well.

20.3A Naming an Acid Chloride—RCOCl

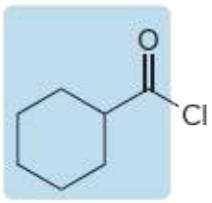
Acid chlorides are named by naming the acyl group and adding the word *chloride*. Two different methods are used.

[1] For acyclic acid chlorides: Change the suffix *-ic acid* of the parent carboxylic acid to the suffix *-yl chloride;* or

[2] **When the −COCl group is bonded to a ring: Change the suffix -*carboxylic acid* to -*carbonyl chloride.***

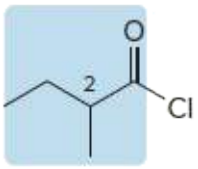
derived from
acet*ic acid*

acetyl chloride



derived from
cyclohexane*carboxylic acid*

cyclohexanecarbonyl chloride



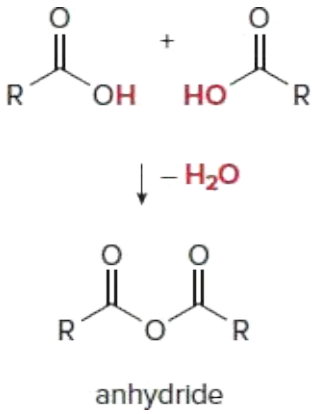
derived from
2-methylbutan*oic acid*

2-methylbutanoyl chloride

20.3B Naming an Anhydride

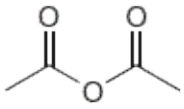
Symmetrical anhydrides are named by changing the *acid* ending of the parent carboxylic acid to the word *anhydride*. Mixed anhydrides, which are derived from two different carboxylic acids, are named by alphabetizing the names for both acids and replacing the word *acid* by the word *anhydride*.

The word *anhydride* means "without water." Removing one molecule of water from two molecules of carboxylic acid forms an anhydride.



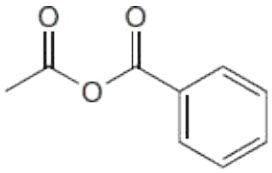
anhydride

Esters are often written as RCOOR′, where the alkyl group (R′) is written *last.* When an ester is named, however, the R′ group appears first in the name.



derived from acetic acid

acetic anhydride



derived from acetic acid and benzoic acid

acetic benzoic anhydride

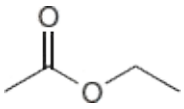
20.3C Naming an Ester—RCOOR′

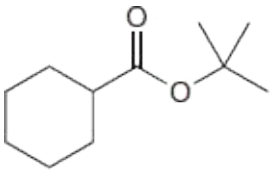
An ester has two parts to its structure, each of which must be named: an acyl group (RCO—) and an alkyl group (designated as R′) bonded to an oxygen atom.

- **In the IUPAC system, esters are identified by the suffix *-ate.***

How To Name an Ester (RCO_2R') Using the IUPAC System

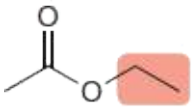
Example Give a systematic name for each ester:

a. 

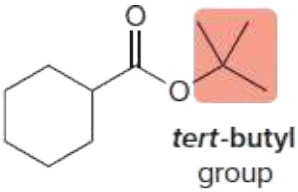
b. 

Step [1] **Name the R′ group bonded to the oxygen atom as an alkyl group.**

- **The name of the alkyl group, ending in the suffix *-yl*, becomes the *first* part of the ester name.**



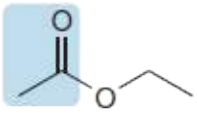
ethyl group



tert-butyl group

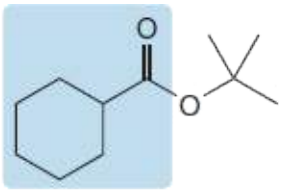
Step [2] **Name the acyl group (RCO−) by changing the *-ic acid* ending of the parent carboxylic acid to the suffix *-ate.***

- **The name of the acyl group becomes the second part of the name.**



derived from
acetic acid ----→ acetate

Answer: ethyl acetate

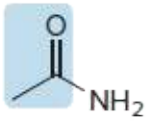


derived from
cyclohexanecarboxylic acid ----→ cyclohexanecarboxylate

Answer: *tert*-butyl cyclohexanecarboxylate

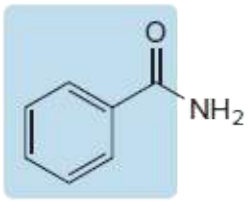
20.3D Naming an Amide

All 1° amides are named by replacing the *-ic acid, -oic acid*, or *-ylic acid* ending of the parent carboxylic acid with the suffix *amide*.



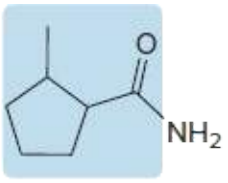
derived from
acetic acid

acetamide



derived from
benzoic acid

benzamide



derived from
2-methylcyclopentanecarboxylic acid

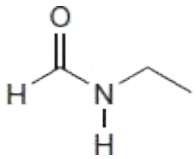
2-methylcyclopentanecarboxamide

A 2° or 3° amide has two parts to its structure: an acyl group that contains the carbonyl group (RCO–) and one or two alkyl groups bonded to the nitrogen atom.

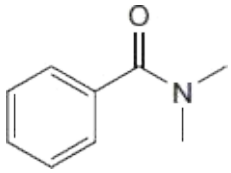
How To Name a 2° or 3° Amide

Example Give a systematic name for each amide:

a.



b.



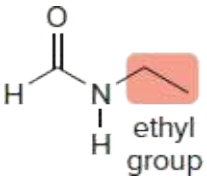
Step [1] **Name the alkyl group (or groups) bonded to the N atom of the amide. Use the prefix "N-" preceding the name of each alkyl group.**

- **The names of the alkyl groups form the *first* part of each amide name.**
- **For 3° amides, use the prefix *di-* if the two alkyl groups on N are the same. If the two alkyl groups are different, alphabetize their**

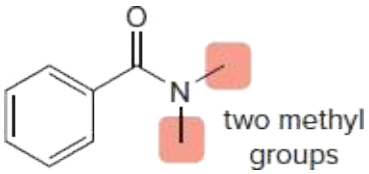
names. One "*N*-" is needed for each alkyl group, even if both R groups are identical.

- **The compound is a 2° amide with one ethyl group → *N*-ethyl.**
- **The compound is a 3° amide with two methyl groups.**
- **Use the prefix *di-* and two "*N*-" to begin the name → *N,N*-dimethyl.**

a

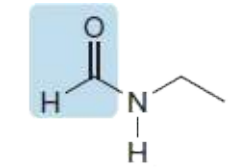


b



Step [2] Name the acyl group (RCO−) with the suffix *-amide.*

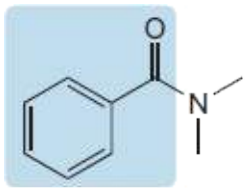
a.



derived from
formic *acid* ⟶ **form*amide***

- **Change the -ic *acid* or *-oic acid* suffix of the parent carboxylic acid to the suffix *-amide.***
- **Put the two parts of the name together.**
- **Answer: *N*-ethylformamide**

b.



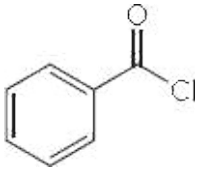
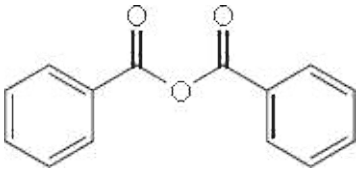
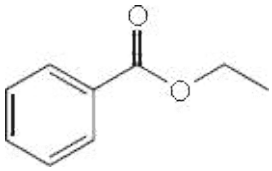
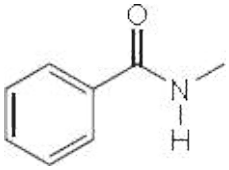
derived from
benzoic *acid* ⟶ **benz*amide***

- **Change benzoic *acid* to *benzamide.***
- **Put the two parts of the name together.**
- **Answer: *N,N*-dimethylbenzamide**

Table 20.2 summarizes the most important points about the nomenclature of carboxylic acid derivatives.

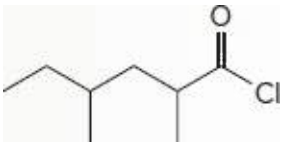
Table 20.2 Summary: Nomenclature of Carboxylic Acid

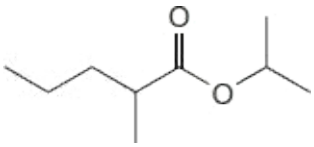
Derivatives

Compound	Name ending	Example	Name
acid chloride	-yl chloride or -carbonyl chloride		benzoyl chloride
anhydride	anhydride		benzoic anhydride
ester	-ate		ethyl benzoate
amide	-amide		*N*-methylbenzamide

Sample Problem 20.1 Naming Carboxylic Acid Derivatives

Give the IUPAC name for each compound.

a. 

b. 

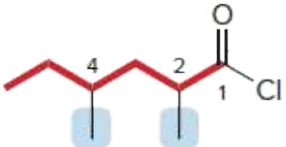
Solution

a. The functional group is an acid chloride bonded to a chain of atoms, so the name ends in *-yl chloride.*

[1] Find and name the longest chain containing the COCl:

hexanoic acid (6 C's) → hexanoyl chloride

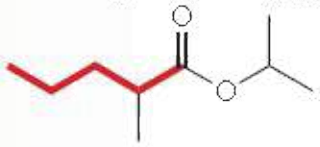
[2] Number and name the substituents:



Answer: 2,4-dimethylhexanoyl chloride

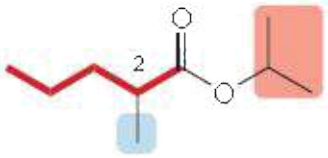
b. The functional group is an ester, so the name ends in *-ate.*

[1] Find and name the longest chain containing the carbonyl group:



pentanoic *acid* → pentano*ate*
(5 C's)

[2] Number and name the substituents:



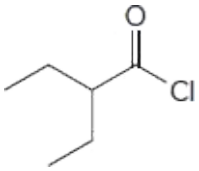
Answer: Isopropyl 2-methylpentanoate

The name of the alkyl group on the O atom goes ***first*** in the name.

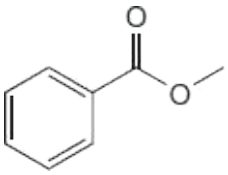
Problem 20.4

Give an IUPAC or common name for each compound.

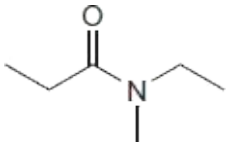
a.



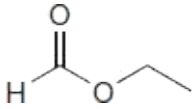
b.



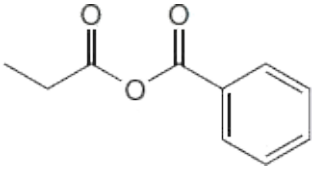
c.



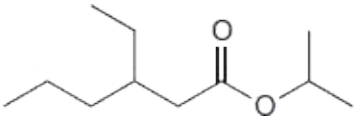
d.



e.



f.



More Practice:

Try Problems 20.32a, 20.34.

Problem 20.5

Draw the structure corresponding to each name.

a. 5-methylheptanoyl chloride

b. isopropyl propanoate

c. acetic formic anhydride

d. *N*-isobutyl-N-methylbutanamide

e. sec-butyl 2-methylhexanoate

f. *N*-ethylhexanamide

20.4 Physical and Spectroscopic Properties

20.4A Physical Properties

Because all carbonyl compounds have a polar carbonyl group, they exhibit dipole–dipole interactions. Primary (1°) and 2° amides are capable of intermolecular hydrogen bonding because they contain one or two N–H bonds. The N–H bond of one amide intermolecularly hydrogen bonds to the C=O of another amide, as shown using two acetamide molecules (CH_3CONH_2) in Figure 20.1.

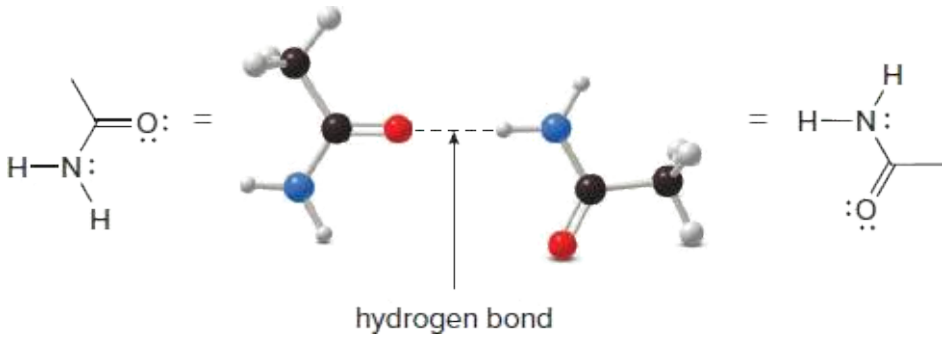


Figure 20.1 **Intermolecular hydrogen bonding between two CH_3CONH_2 molecules**

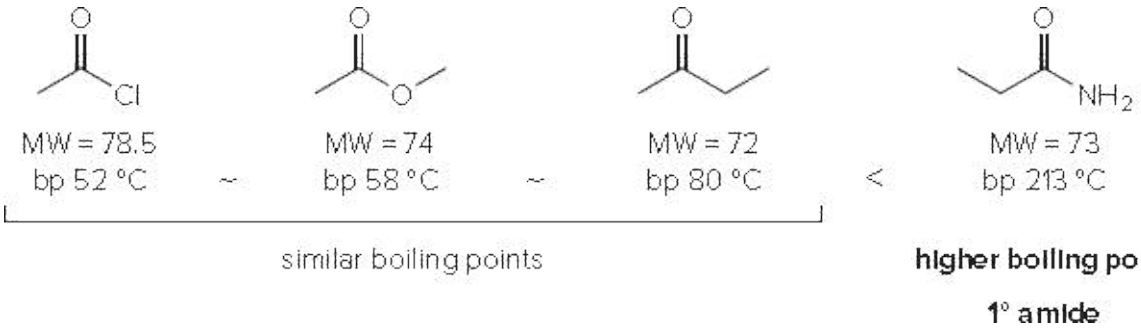
Problem 20.6

Explain why the boiling point of CH_3CONH_2 (221 °C) is significantly higher than the boiling point of CH_3CO_2H (118 °C).

How these factors affect the physical properties of carboxylic acid derivatives is summarized in Table 20.3.

Table 20.3 **Physical Properties of Carboxylic Acid Derivatives**

Property	Observation
Boiling point and melting point	• Primary (1°) and 2° amides have *higher* boiling points and melt points than compounds of comparable molecular weight. • The boiling points and melting points of other carboxylic a

	derivatives are similar to those of other polar compounds comparable size and shape. 
Solubility	• Carboxylic acid derivatives are soluble in organic solve regardless of size. • Most carboxylic acid derivatives having ≤ 5 C's are H_2O solu because they can hydrogen bond with H_2O (Section 3.4C). • Carboxylic acid derivatives having > 5 C's are H_2O insolu because the nonpolar alkyl portion is too large to dissolve in polar H_2O solvent.

Key: MW = molecular weight

20.4B Spectroscopic Properties

Many details of the spectroscopy of carboxylic acid derivatives have been presented in Spectroscopy Parts B and C.

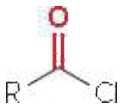
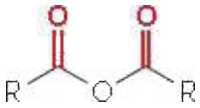
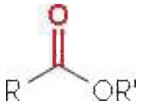
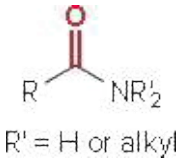
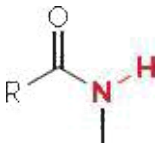
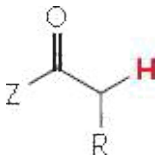
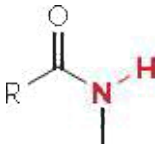
- The infrared absorption of the carbonyl group of carboxylic acid derivatives: Sections B.3C and B.4B, Sample Problem B.1, and Table B.2
- ^1H and ^{13}C NMR absorptions: Tables C.1 and C.5

Key NMR and IR absorptions for carboxylic acid derivatives are summarized in Table 20.4. Recall from Section B.3C that the location of the carbonyl absorption depends on the identity of Z in RCOZ.

- **As the basicity of Z *increases*, resonance stabilization of RCOZ *increases*, and the C=O absorption shifts to *lower* frequency.**

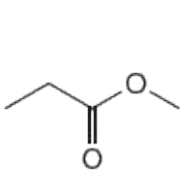
Table 20.4 Characteristic Spectroscopic Absorptions of Carboxylic Acid Derivatives

Type of	Type of C,

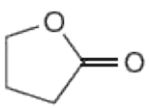
spectroscopy	Compound	H	Absorption
IR absorptions	Acid chloride		1800 cm^{-1}
	Anhydride		1820 and 1760 cm^{-1} (two peaks)
	Ester		1735–1745 cm^{-1}
	Amide		1630–1680 cm^{-1}
			3200–3400 cm^{-1} (one or two N–H stretching peaks) 1640 cm^{-1} (N–H bending)
^{1}H NMR absorptions	All acyl derivatives		2–2.5 ppm
	Amide (1° and 2°)		7.5–8.5 ppm
^{13}C NMR absorption	All acyl derivatives		160–180 ppm

Problem 20.7

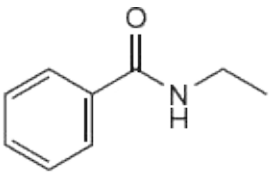
Rank the following compounds in order of increasing frequency of the C=O absorption in their IR spectra.



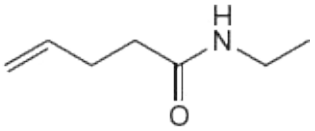
A



B



C



D

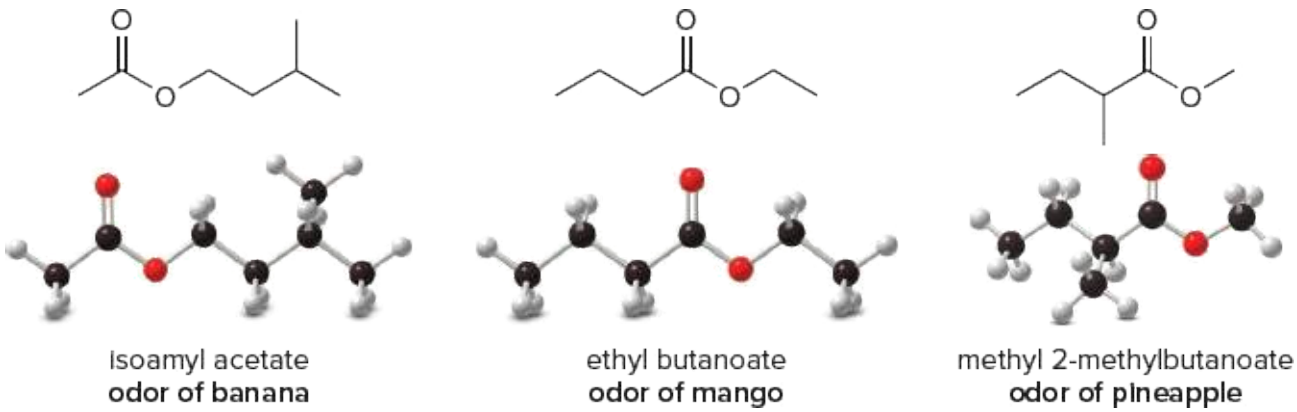
20.5 Interesting Esters and Amides

20.5A Esters

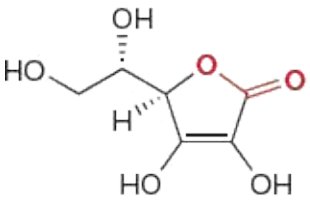
Many low-molecular-weight esters have pleasant and very characteristic odors.

The characteristic odor of many fruits is due to low-molecular-weight esters. ***©Jill Braaten***

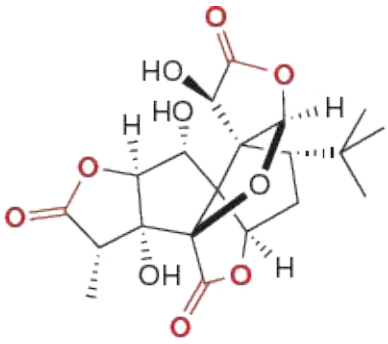
©Jill Braaten



Several esters, including vitamin C and ginkgolide B, have important biological activities.



vitamin C



ginkgolide B

Vitamin C (or ascorbic acid) is a water-soluble vitamin containing a five-membered lactone that we first discussed in Section 3.5B. Although vitamin C is synthesized in plants, humans do not have the necessary enzymes to make it, so they must obtain it from their diet.

Ginkgolide B is a major constituent of the extracts of the ginkgo tree, *Ginkgo biloba*. Ginkgo extracts are widely used herbal supplements, taken to enhance memory and treat dementia. Recent findings of the National Institutes of Health, however, have cast doubt on their efficacy in providing long-term improvement in cognition.

20.5B Amides

An important group of naturally occurring amides consists of *proteins*, polymers of amino acids joined together by amide linkages. Proteins differ in the length of the polymer chain, as well as in the identity of the R groups bonded to it. The word *protein* is usually reserved for high-molecular-weight polymers composed of 40 or more amino acid units, whereas the designation *peptide* is given to polymers of lower molecular weight.

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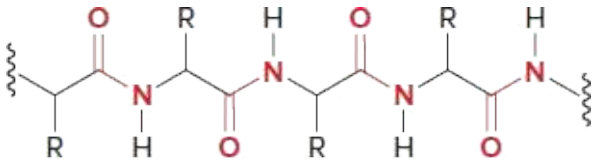
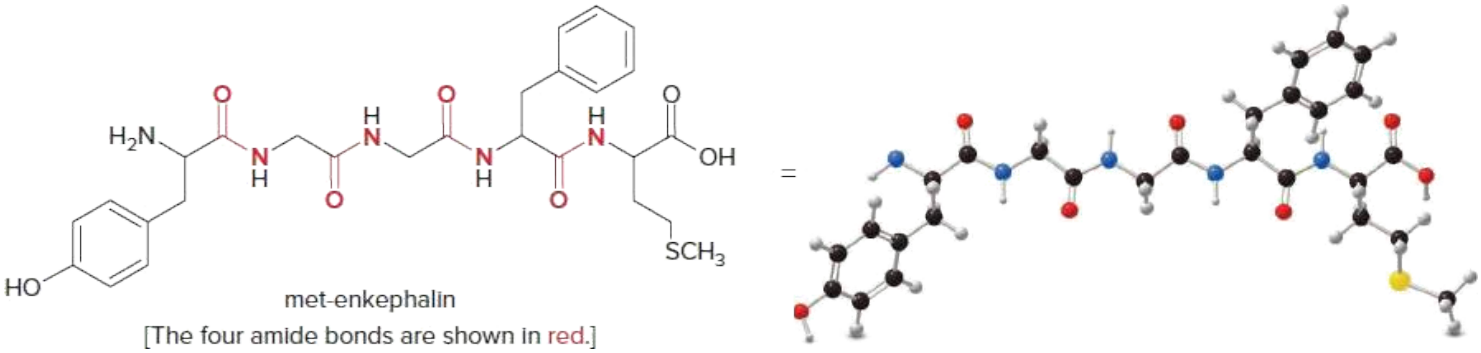


portion of a protein molecule
[Amide bonds are shown in red.]

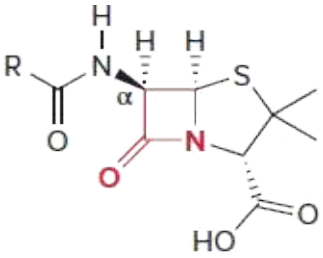
Proteins and peptides have diverse functions in the cell. They form the structural components of muscle, connective tissue, hair, and nails. They catalyze reactions and transport ions and molecules across cell membranes. Met-enkephalin, for example, a peptide with four amide bonds found predominately in nerve tissue cells, relieves pain and acts as an opiate by producing morphine-like effects.

Peptides and proteins are discussed in detail in Chapter 27.

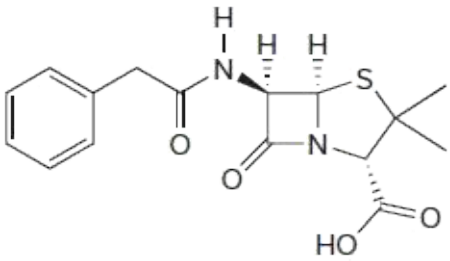


met-enkephalin
[The four amide bonds are shown in red.]

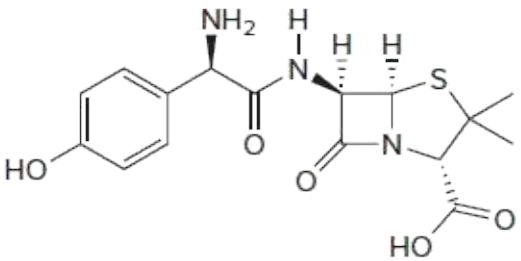
Penicillins are a group of structurally related antibiotics, known since the pioneering work of Sir Alexander Fleming led to the discovery of penicillin G in the 1920s. All penicillins contain a strained β-lactam fused to a five-membered ring, as well as a second amide located α to the β-lactam carbonyl group. Particular penicillins differ in the identity of the R group in the amide side chain.



penicillin
β-lactam shown in red

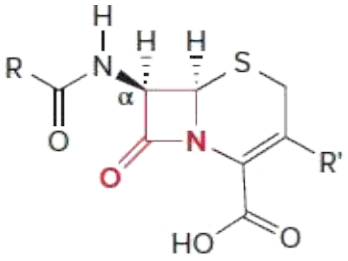


penicillin G

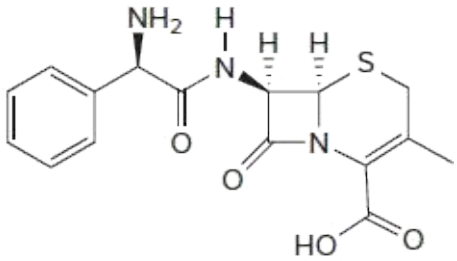


amoxicillin

Cephalosporins represent a second group of β-lactam antibiotics that contain a four-membered ring fused to a six-membered ring. Cephalosporins are generally active against a broader range of bacteria than penicillins.



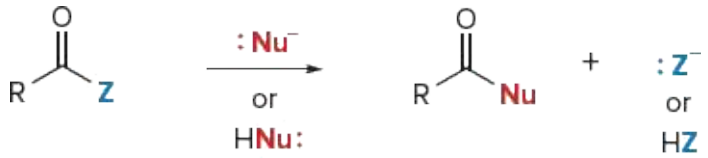
cephalosporin
β-lactam shown in red



cephalexin
Trade name Keflex

20.6 Introduction to Nucleophilic Acyl Substitution

The characteristic reaction of carboxylic acid derivatives is *nucleophilic acyl substitution*. This is a general reaction that occurs with both negatively charged nucleophiles ($Nu:^-$) and neutral nucleophiles (HNu:).



Nu replaces Z.

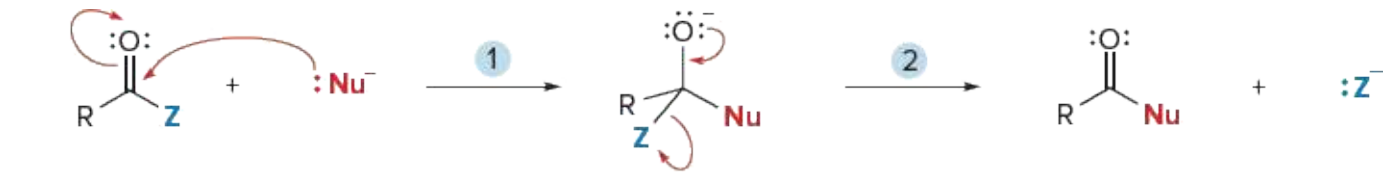
- **Carboxylic acid derivatives (RCOZ) react with nucleophiles because they contain an electrophilic, unhindered carbonyl carbon.**
- **Substitution, *not* addition, occurs because carboxylic acid derivatives (RCOZ) have a leaving group Z on the carbonyl carbon.**

The mechanism for nucleophilic acyl substitution was first presented in Section 17.2.

20.6A The Mechanism

The general mechanism for nucleophilic acyl substitution is a two-step process: nucleophilic attack followed by loss of the leaving group, as shown in Mechanism 20.1.

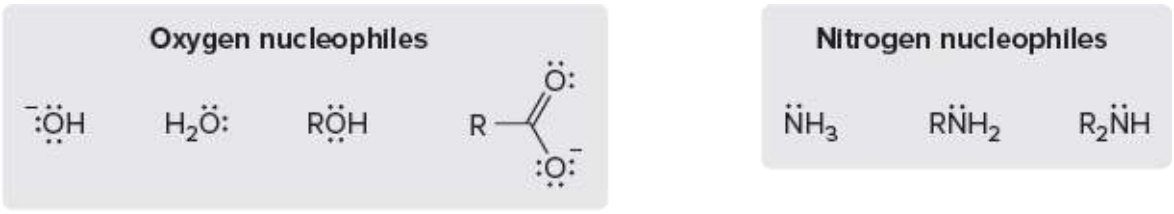
Mechanism 20.1 General Mechanism—Nucleophilic Acyl Substitution



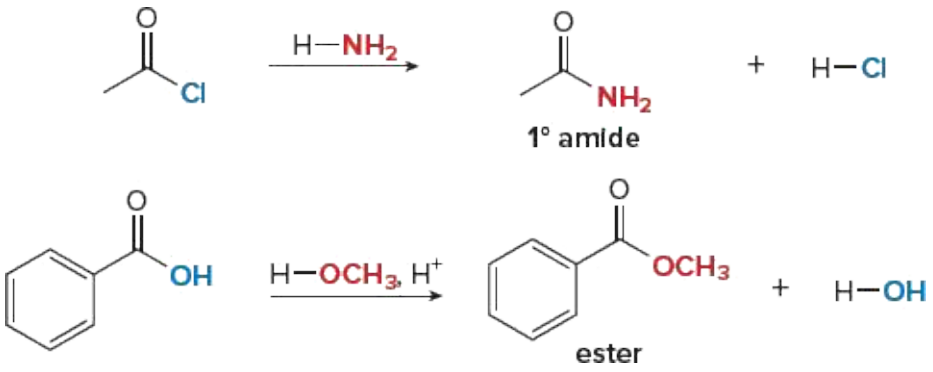
Z = OH, Cl, OCOR, OR', NH_2

1. **The nucleophile attacks the electrophilic carbonyl group. The π bond is broken, moving an electron pair out on oxygen and forming an sp^3 hybridized carbon.**
2. **An electron pair on oxygen re-forms the π bond and Z comes off as a leaving group with the electron pair in the C–Z bond.**

The overall result of addition of a nucleophile and elimination of a leaving group is *substitution* of the nucleophile for the leaving group. Recall from Chapter 17 that nucleophilic substitution occurs with carbanions (R^-) and hydride (H^-) as nucleophiles. A variety of oxygen and nitrogen nucleophiles also participate in this reaction.



Nucleophilic acyl substitution using heteroatomic nucleophiles results in the conversion of one carboxylic acid derivative another, as shown in two examples.



Each reaction results in the replacement of the leaving group by the nucleophile, regardless of the identity of or charge on the nucleophile. To draw any nucleophilic acyl substitution product:

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- **Find the sp^2 hybridized carbon with the leaving group.**
- **Identify the nucleophile.**
- **Substitute the nucleophile for the leaving group. With a neutral nucleophile, a proton must be lost to obtain a neutral substitution product.**

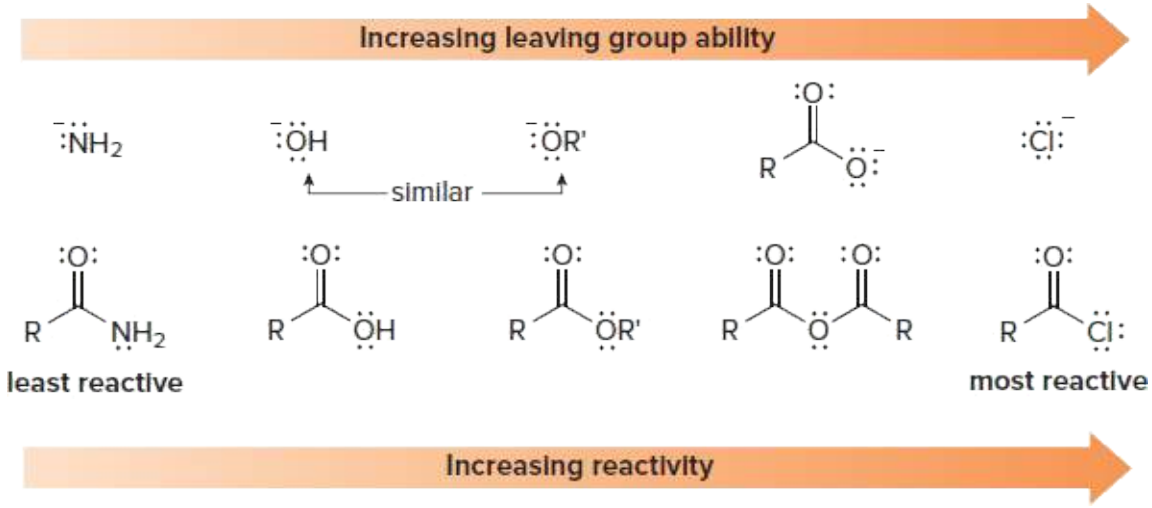
20.6B Relative Reactivity of Carboxylic Acids and Their Derivatives

As discussed in Section 17.2B, carboxylic acids and their derivatives differ greatly in reactivity toward nucleophiles. The order of reactivity parallels the leaving group ability of the group Z.

- **The better the leaving group, the more reactive RCOZ is in nucleophilic acyl substitution.**

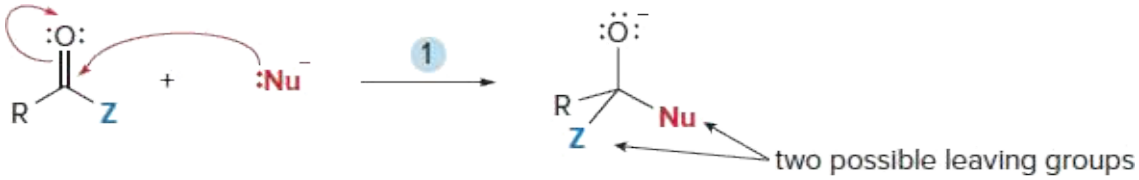
Recall that the best leaving group is the weakest base. The relative basicity of the common leaving groups, Z, is given in Table 20.1.

Thus, the following trends result:



Based on this order of reactivity, *more reactive* acyl compounds (acid chlorides and anhydrides) can be converted to *less reactive* ones (carboxylic acids, esters, and amides). The reverse is not usually true.

To see why this is so, recall that nucleophilic addition to a carbonyl group forms a tetrahedral intermediate with two possible leaving groups, Z^- or $:Nu^-$. The group that is subsequently eliminated is the *better* of the two leaving groups. For a reaction to form a substitution product, therefore, Z^- must be the better leaving group, making the starting material RCOZ a more reactive acyl compound.



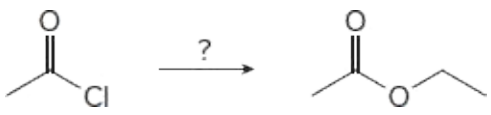
For a reaction to occur, Z must be a better leaving group than Nu.

To evaluate whether a nucleophilic substitution reaction will occur, compare the leaving group ability of the incoming nucleophile and the departing leaving group, as shown in Sample Problem 20.2.

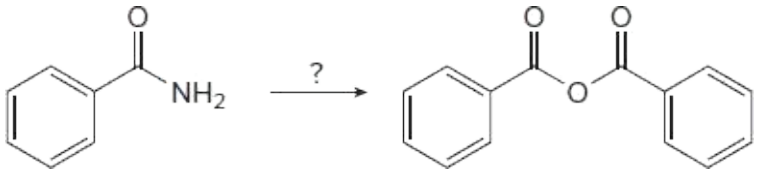
Sample Problem 20.2 Using Basicity to Determine Whether a Nucleophilic Acyl Substitution Might Occur

Determine whether each nucleophilic acyl substitution is likely to occur.

a.



b.



Solution

a. Conversion of CH_3COCl to $CH_3COOCH_2CH_3$ requires the substitution of Cl^- by $^-OCH_2CH_3$. Because Cl^- is a weaker base and therefore a better leaving group than $^-OCH_2CH_3$, this reaction occurs.

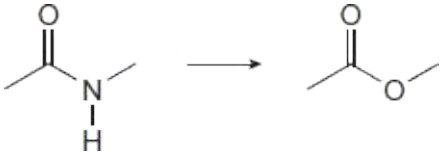
b. Conversion of $C_6H_5CONH_2$ to $(C_6H_5CO)_2O$ requires the substitution of $^-NH_2$ by $^-OCOC_6H_5$. Because $^-NH_2$ is a stronger base and therefore a poorer leaving group than $^-OCOC_6H_5$, this reaction does *not* occur.

Problem 20.8

Without reading ahead in Chapter 20, state whether it should be possible to carry out each of the following nucleophilic substitution reactions.

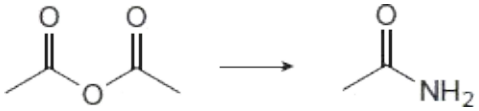
a.

b.



c.

d.



More Practice:

Try Problem 20.31.

Learn the order of reactivity of carboxylic acid derivatives. Keeping this in mind allows you to organize a very large number of reactions.

To summarize:

- **Nucleophilic substitution occurs when the leaving group Z^- is a**

weaker **base and therefore** ***better*** **leaving group than the attacking nucleophile :Nu⁻.**

- ***More*** **reactive acyl compounds can be converted to** ***less*** **reactive acyl compounds by nucleophilic substitution.**

Problem 20.9

Rank the compounds in each group in order of increasing reactivity in nucleophilic acyl substitution.

a. $C_6H_5CO_2CH_3$, C_6H_5COCl, $C_6H_5CONH_2$

b. $CH_3CH_2CO_2H$, $(CH_3CH_2CO)_2O$, $CH_3CH_2CONHCH_3$

Problem 20.10

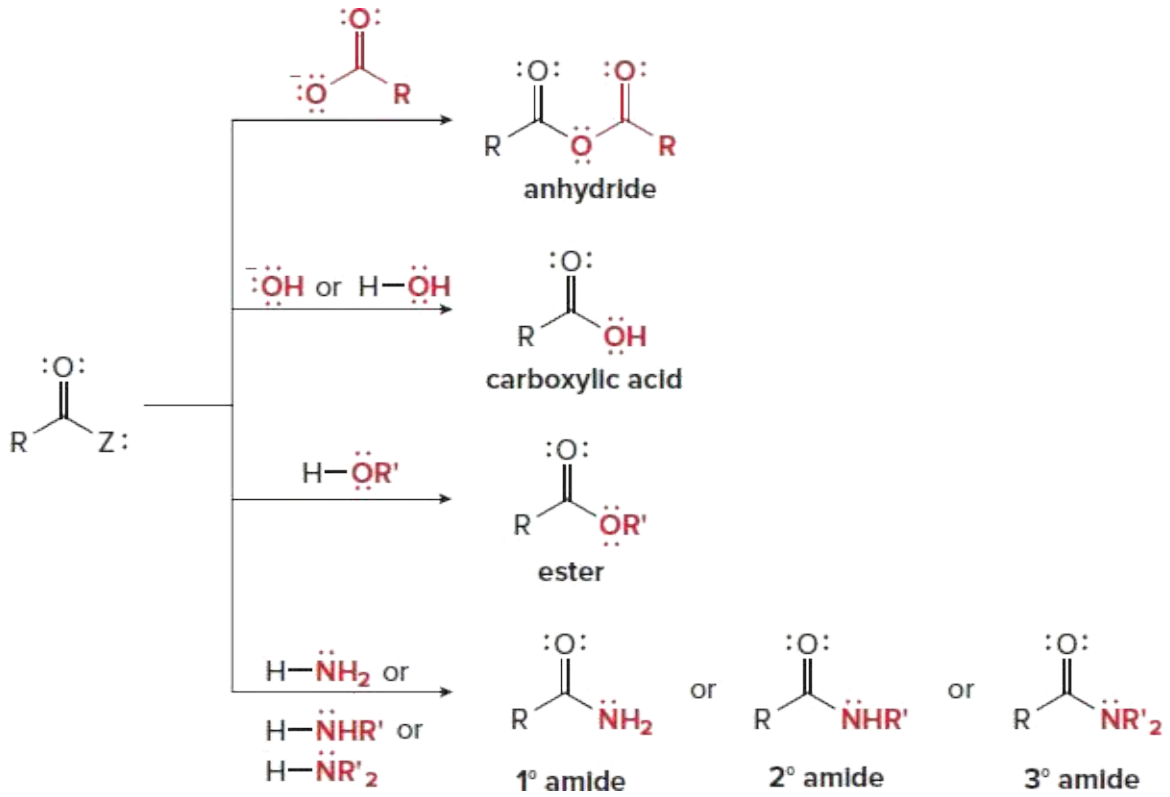
Explain why trichloroacetic anhydride [$(Cl_3CCO)_2O$] is more reactive than acetic anhydride [$(CH_3CO)_2O$] in nucleophilic acyl substitution reactions.

20.6C A Preview of Specific Reactions

Sections 20.7–20.13 are devoted to specific examples of nucleophilic acyl substitution using heteroatoms as nucleophiles. There are a great many reactions, and it is easy to confuse them unless you learn the general order of reactivity of carboxylic acid derivatives. Keep in mind that every reaction that begins with an acyl starting material involves nucleophilic substitution.

We begin with the reactions of acid chlorides, the most reactive acyl compounds, then proceed to less and less reactive carboxylic acid derivatives, ending with amides. Acid chlorides undergo many reactions, because they have the best leaving group of all acyl compounds, whereas amides undergo only one reaction, which must be carried out under harsh reaction conditions, because amides have a poor leaving group.

In general, we will examine nucleophilic acyl substitution with four different nucleophiles, as shown in the following equations.

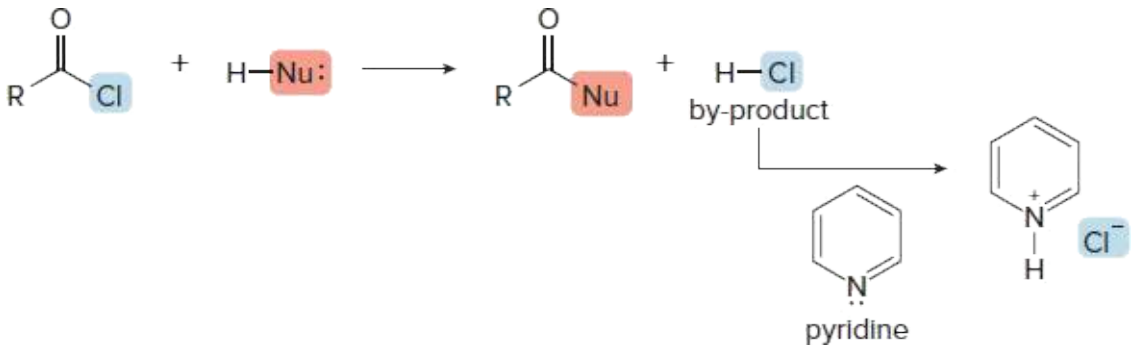


These reactions are used to make anhydrides, carboxylic acids, esters, and amides, but not acid chlorides, from other acyl compounds. Acid chlorides are the most reactive acyl compounds (they have the best leaving group), so they are not easily formed as a product of nucleophilic substitution reactions. Acid chlorides can only be prepared from carboxylic acids using special reagents, as discussed in Section 20.9A.

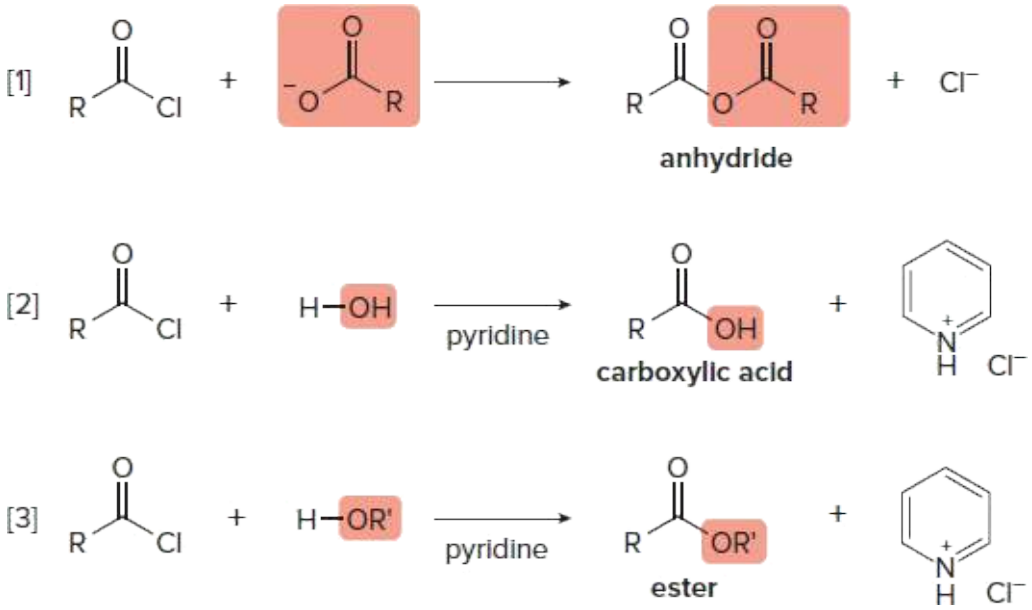
20.7 Reactions of Acid Chlorides

Acid chlorides readily react with nucleophiles to form nucleophilic substitution products, with HCl usually formed as a reaction by-product. A weak base like pyridine is added to the reaction mixture to remove this strong acid, forming an ammonium salt.

The reaction of acid chlorides with water is rapid. Exposure of an acid chloride to moist air on a humid day leads to some hydrolysis, giving the acid chloride a very acrid odor, due to the HCl formed as a by-product. ©*McGraw-Hill Education/Joe Franek, photographer*



Acid chlorides react with oxygen nucleophiles to form anhydrides, carboxylic acids, and esters.



Acid chlorides also react with ammonia and 1° and 2° amines to form 1°, 2°, and 3° amides, respectively. Two equivalents of NH_3 or amine are used. One equivalent acts as a nucleophile to replace Cl and form the substitution product, while the second equivalent reacts as a base with the HCl by-product to form an ammonium salt.

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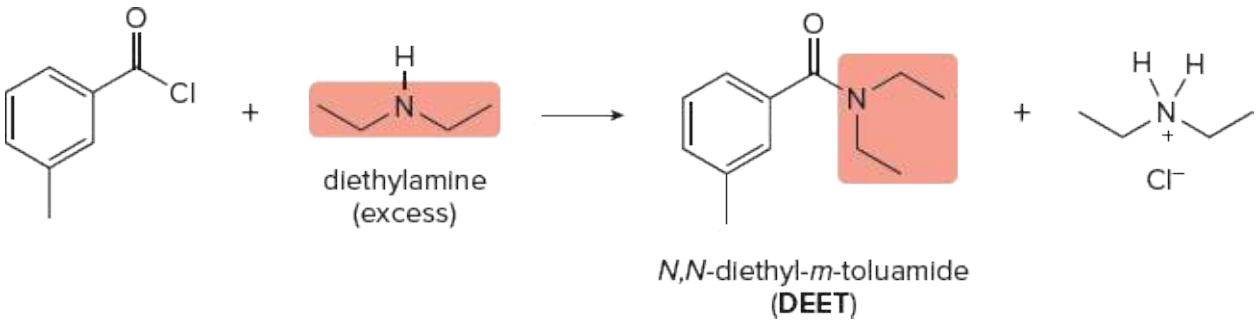
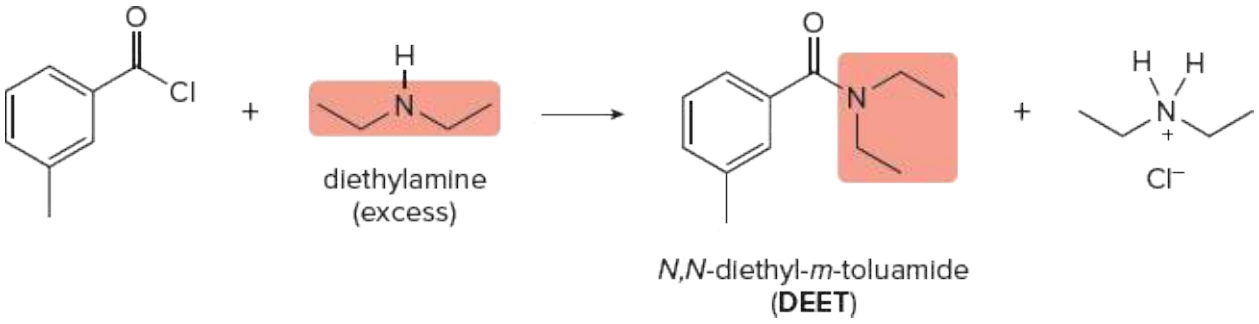
Insect repellents containing DEET have become particularly popular because of the recent spread of many insect-borne diseases such as West Nile virus and Lyme disease. DEET does not kill insects—it repels them. It is thought that DEET somehow confuses insects so that they can no longer sense the warm moist air that surrounds a human body.

Source: Scott Bauer/USDA-ARS



As an example, reaction of an acid chloride with diethylamine forms the 3° amide *N*,*N*-dietriyl-*m*-toluamide, popularly known as DEET. DEET, the active ingredient in the most widely used insect repellents, is effective against mosquitoes, fleas, and ticks.



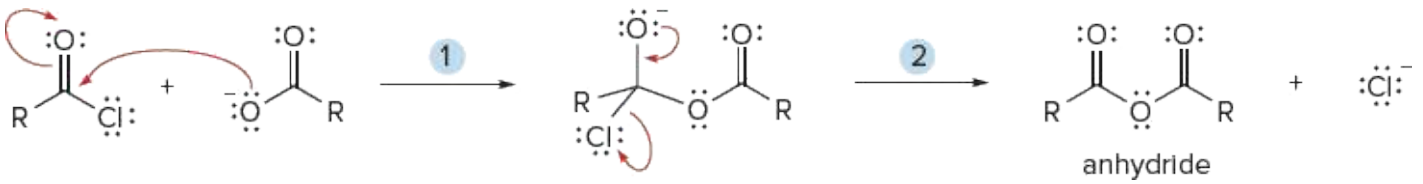
Problem 20.11

Draw the products formed when benzoyl chloride (C_6H_5COCl) is treated with each nucleophile: (a) H_2O, pyridine; (b) CH_3COO^-; (c) NH_3 (excess); (d) $(CH_3)_2NH$ (excess).

With a carboxylate nucleophile the mechanism follows the general, two-step

mechanism discussed in Section 20.6A: nucleophilic attack followed by loss of the leaving group, as shown in Mechanism 20.2.

Mechanism 20.2 Conversion of Acid Chlorides to Anhydrides

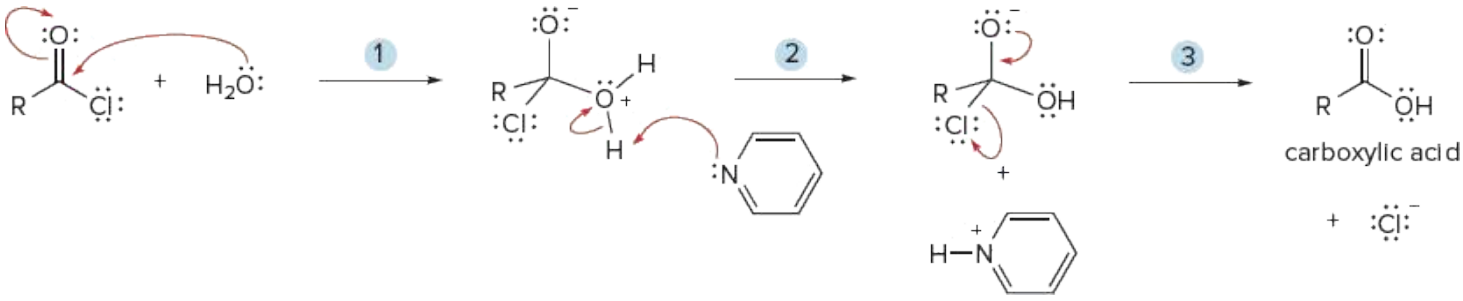


1 **The nucleophilic carboxylate anion attacks the carbonyl group, forming an *sp*^{3} hybridized carbon.**

2 **Elimination of the leaving group (Cl^-) forms the substitution product, an anhydride.**

Nucleophilic substitution with the neutral nucleophiles (H_2O, R′OH, NH_3, and so forth) requires an additional step for proton transfer. For example, the reaction of an acid chloride with H_2O as nucleophile converts an acid chloride to a carboxylic acid in three steps (Mechanism 20.3).

Mechanism 20.3 Conversion of Acid Chlorides to Carboxylic Acids



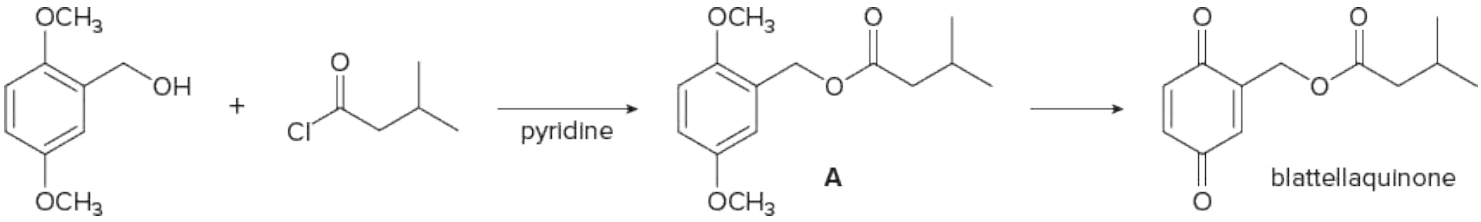
1 **The nucleophile (H_2O) attacks the carbonyl group, forming an *sp*^{3} hybridized carbon.**

2 – **3** **Loss of a proton and elimination of the leaving group (Cl^-) form the substitution product, a carboxylic acid.**

The exact same three-step process can be written for any neutral nucleophile that reacts with acid chlorides.

Problem 20.12

Draw a stepwise mechanism for the formation of A from an alcohol and acid chloride. A was converted in one step to blattellaquinone, the sex pheromone of the female German cockroach, *Blattella germanica.*



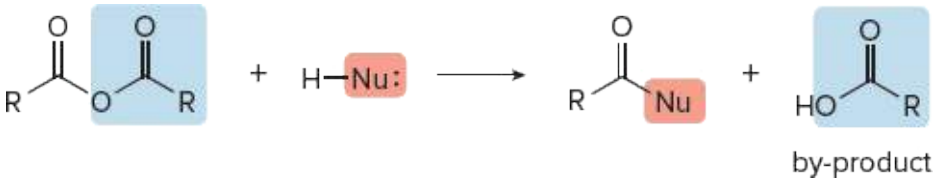
A short laboratory synthesis of blattellaquinone (Problem 20.12), the sex pheromone of the female German cockroach, opens new possibilities for cockroach population control using pheromone-baited traps.

©Coby Schal/NC State University

Nucleophilic substitution occurs only when the leaving group is a weaker base and therefore a better leaving group than the attacking nucleophile.

20.8 Reactions of Anhydrides

Although somewhat less reactive than acid chlorides, anhydrides nonetheless readily react with most nucleophiles to form substitution products. Nucleophilic substitution reactions of anhydrides are no different than the reactions of other carboxylic acid derivatives, even though anhydrides contain two carbonyl groups. Nucleophilic attack occurs at one carbonyl group, while the second carbonyl becomes part of the leaving group.



Anhydrides can't be used to make acid chlorides, because $RCOO^-$ is a stronger base

and therefore a poorer leaving group than Cl^-. Anhydrides can be used to make all other acyl derivatives, however. Reaction with water and alcohols yields carboxylic acids and esters, respectively. Reaction with two equivalents of NH_3 or amines forms 1°, 2°, and 3° amides. A molecule of carboxylic acid (or a carboxylate salt) is always formed as a by-product.

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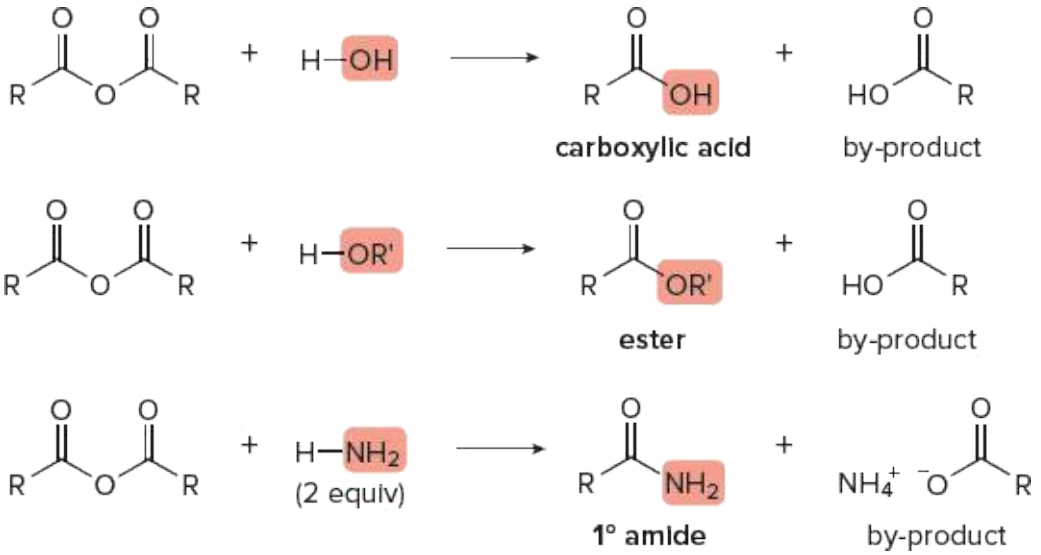
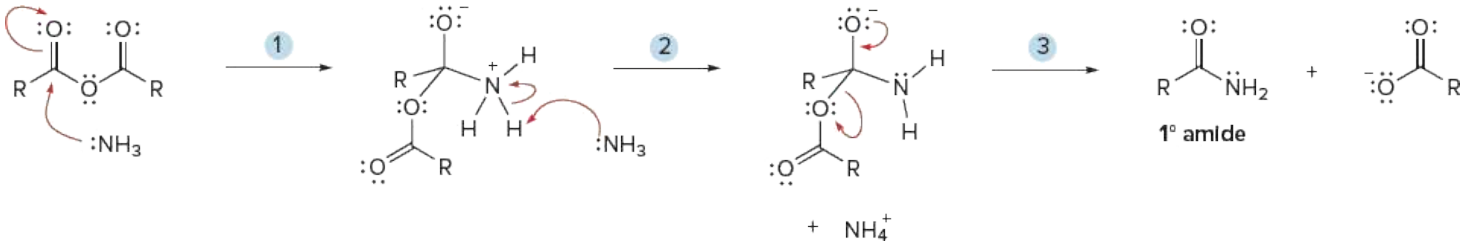


Problem 20.13

Draw the products formed when benzoic anhydride [$(C_6H_5CO)_2O$] is treated with each nucleophile: (a) H_2O; (b) CH_3OH; (c) NH_3 (excess); (d) $(CH_3)_2NH$ (excess).

The conversion of an anhydride to an amide illustrates the mechanism of nucleophilic acyl substitution with an anhydride as starting material (Mechanism 20.4). Besides the usual steps of nucleophilic addition and elimination of the leaving group, an additional proton transfer is needed.

Mechanism 20.4 Conversion of an Anhydride to an Amide

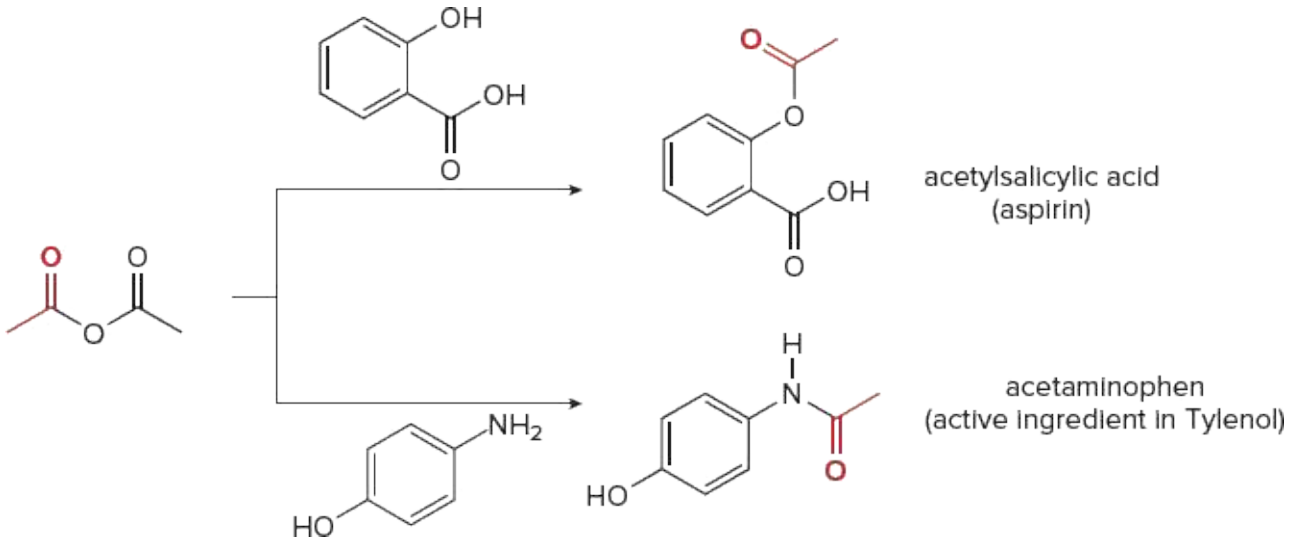


1 The nucleophile (NH_3) attacks the carbonyl, forming an sp^3 hybridized carbon.

2 – 3 Loss of a proton and elimination of the leaving group (RCO_2^-) form the substitution product, a 1° amide.

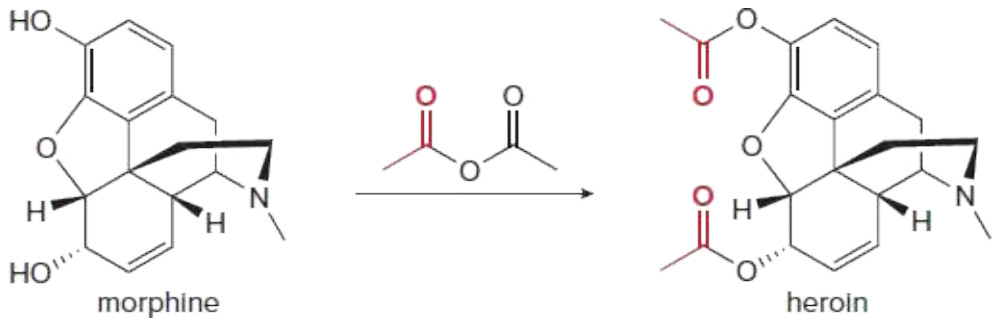
Anhydrides react with alcohols and amines with ease, so they are often used in the laboratory to prepare esters and amides. For example, acetic anhydride is used to prepare two analgesics, acetylsalicylic acid (aspirin) and acetaminophen (the active ingredient in Tylenol).

Acetaminophen reduces pain and fever, but it is not anti-inflammatory, so it is ineffective in treating conditions like arthritis, which have a significant inflammatory component. In large doses, acetaminophen causes liver damage, so dosage recommendations must be carefully followed.



These are called acetylation reactions because they result in the transfer of an Page 945 acetyl group, CH_3CO^-, from one heteroatom to another.

Heroin is prepared by the acetylation of morphine, an analgesic compound isolated from the opium poppy. Both OH groups of morphine are readily acetylated with acetic anhydride to form the diester present in heroin.



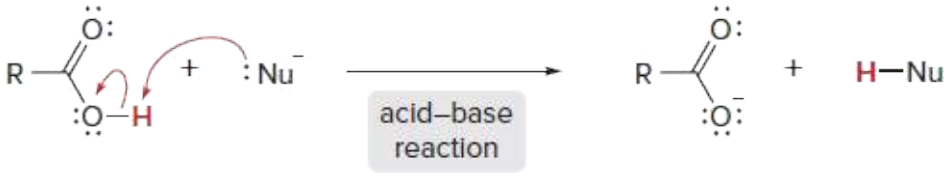
Problem 20.14

If anhydrides react like acid chlorides with the nucleophiles described in Chapter 17, draw the products formed when each of the following nucleophiles reacts with benzoic

anhydride [$(C_6H_5CO)_2O$]: (a) CH_3MgBr (2 equiv), then H_2O; (b) $LiAlH_4$, then H_2O; (c) $LiAlH[OC(CH_3)_3]_3$, then H_2O.

20.9 Reactions of Carboxylic Acids

Carboxylic acids are strong organic acids. Because acid`-base reactions proceed rapidly, any nucleophile that is also a strong base will react with a carboxylic acid by removing a proton *first*, before any nucleophilic substitution reaction can take place.



An acid–base reaction occurs with ^-OH, NH_3, and amines, all common nucleophiles used in nucleophilic acyl substitution reactions. Nonetheless, carboxylic acids do undergo nucleophilic acyl substitution and can be converted to a variety of other acyl derivatives using special reagents, with acid catalysis or, sometimes, by using rather forcing reaction conditions. These reactions are summarized in Figure 20.2 and detailed in Sections 20.9A–20.9D.

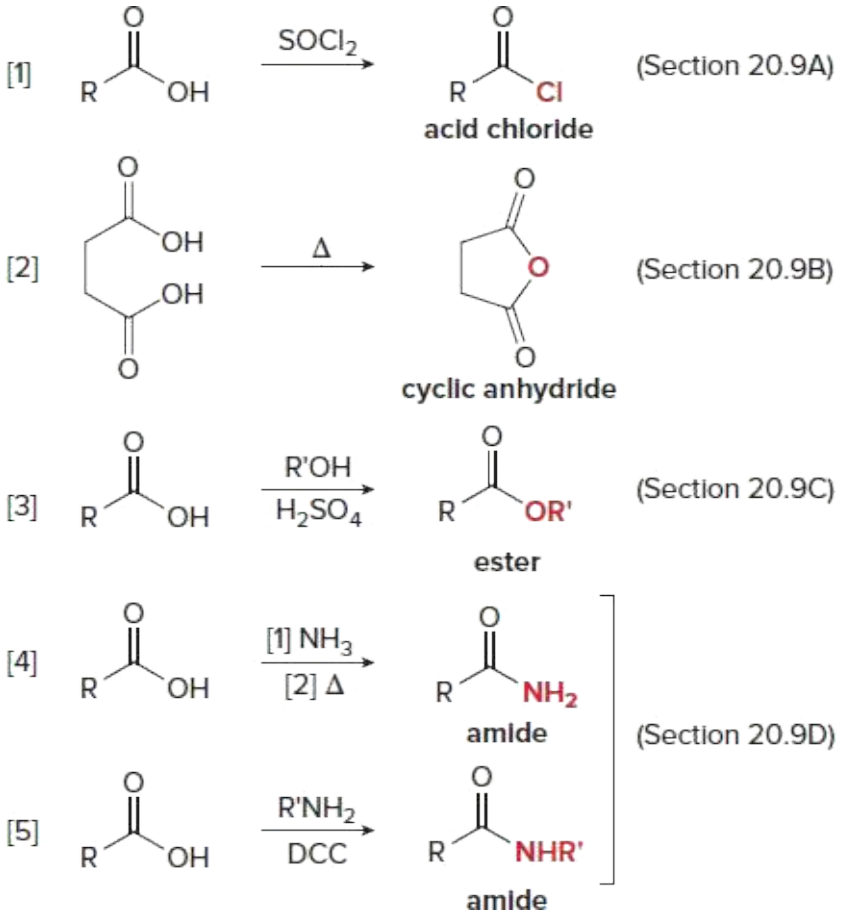
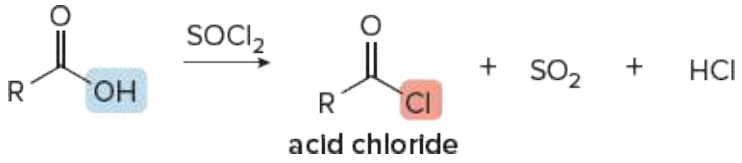


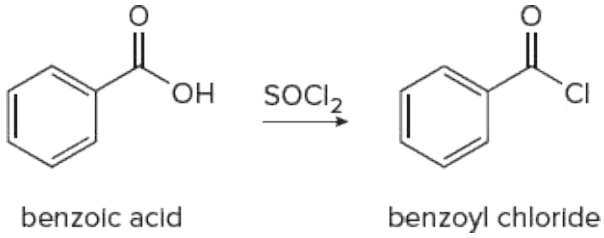
Figure 20.2 **Nucleophilic acyl substitution reactions of carboxylic acids**

20.9A Conversion of RCOOH to RCOCl

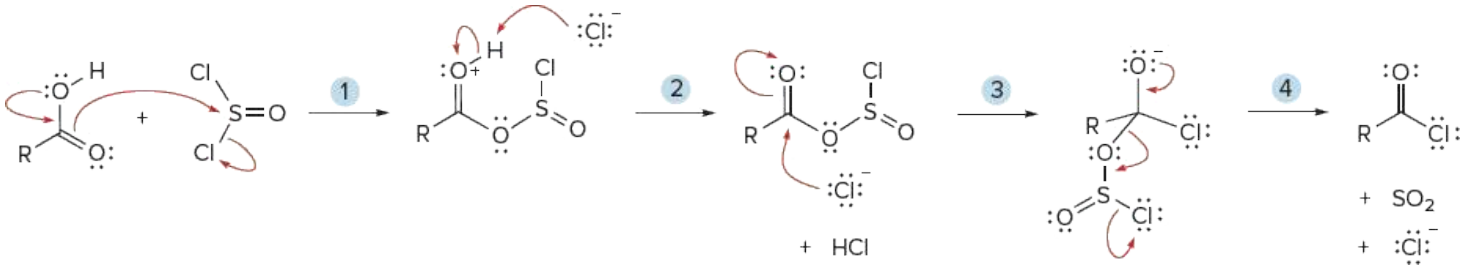
Carboxylic acids can't be converted to acid chlorides by using Cl^- as a nucleophile, because the attacking nucleophile Cl^- is a weaker base than the departing leaving group, ^-OH. But carboxylic acids *can* be converted to acid chlorides using thionyl chloride, $SOCl_2$, a reagent that was introduced in Section 9.12 to convert alcohols to alkyl chlorides.



Treatment of benzoic acid with $SOCl_2$ forms benzoyl chloride. This reaction converts a less reactive acyl derivative (a carboxylic acid) to a more reactive one (an acid chloride). This is possible because thionyl chloride converts the OH group of the acid to a better leaving group, and because it provides the nucleophile (Cl^-) to displace the leaving group. The steps in the process are illustrated in Mechanism 20.5.



Mechanism 20.5 Conversion of Carboxylic Acids to Acid Chlorides



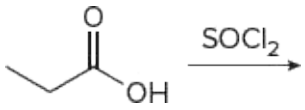
1 – 2 Reaction of the carboxylic acid with $SOCl_2$ and loss of a proton convert the OH group to OSOCl, a good leaving group.

3 – 4 Nucleophilic attack of chloride generates a tetrahedral intermediate, and loss of the leaving group (SO_2 and Cl^-) forms the acid chloride.

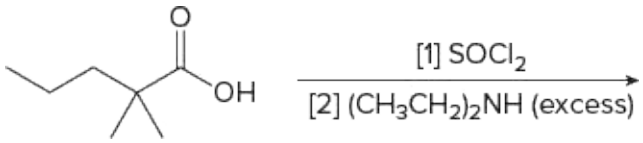
Problem 20.15

Draw the products of each reaction.

a.

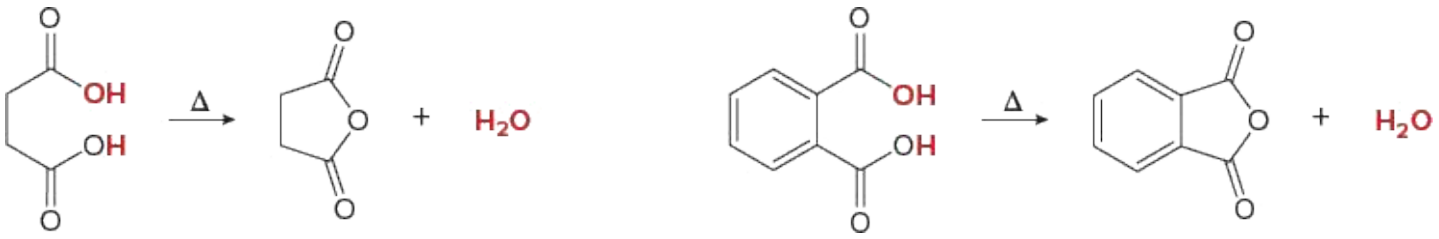


b.



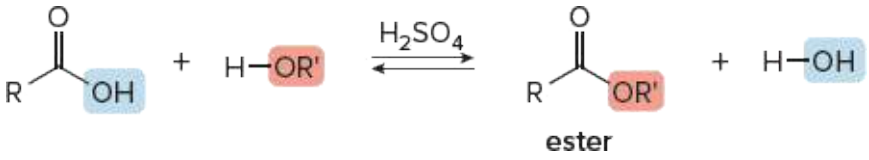
20.9B Conversion of RCOOH to $(RCO)_2O$

Carboxylic acids cannot be readily converted to anhydrides, but dicarboxylic acids can be converted to cyclic anhydrides by heating to high temperatures. This is a dehydration reaction because a water molecule is lost from the diacid.



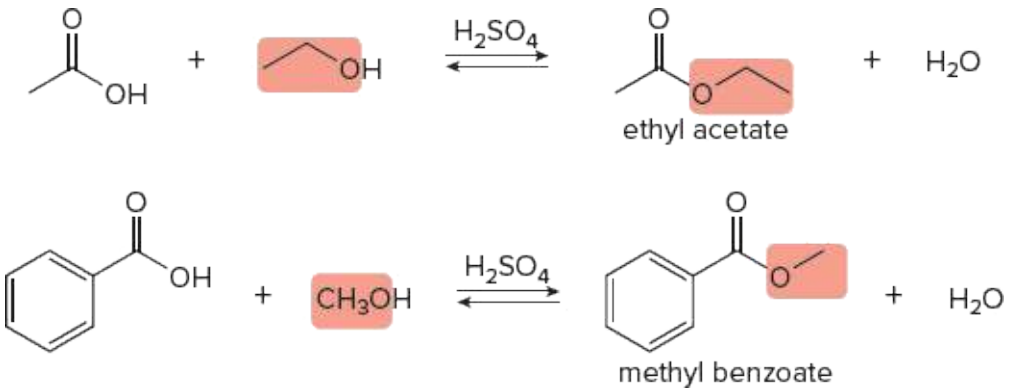
20.9C Conversion of RCOOH to RCOOR′

Treatment of a carboxylic acid with an alcohol in the presence of an acid catalyst forms an ester. This reaction is called a Fischer esterification.



This reaction is an equilibrium. According to Le Châtelier's principle (Section 9.8D), it is driven to the right by using excess alcohol or by removing the water as it is formed.

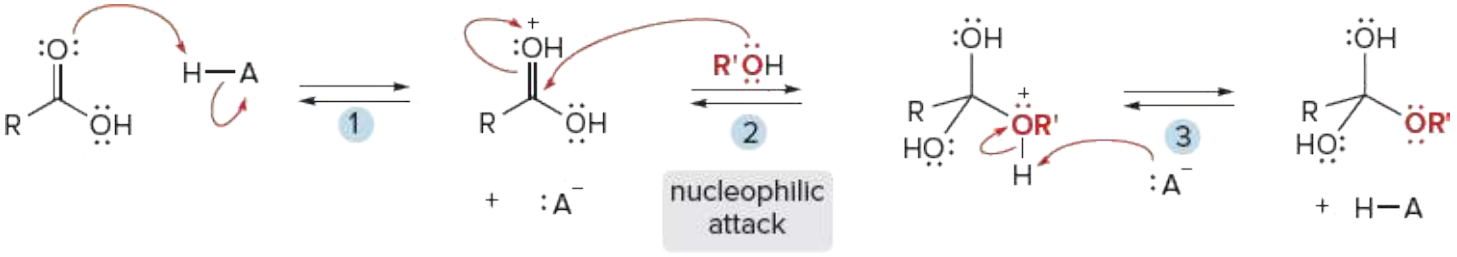
Ethyl acetate is a common organic solvent with a characteristic odor. It is used in nail polish remover and model airplane glue.



The mechanism for the Fischer esterification involves the usual two steps of nucleophilic acyl substitution—that is, addition of a nucleophile followed by elimination of a leaving group. Because the reaction is acid catalyzed, however, there are additional protonation and deprotonation steps. As always, though, the first step of any mechanism with an oxygen-containing starting material and an acid is to protonate an oxygen atom as shown with a general acid HA in Mechanism 20.6.

Mechanism 20.6 Fischer Esterification—Acid-Catalyzed Conversion of Carboxylic Acids to Esters

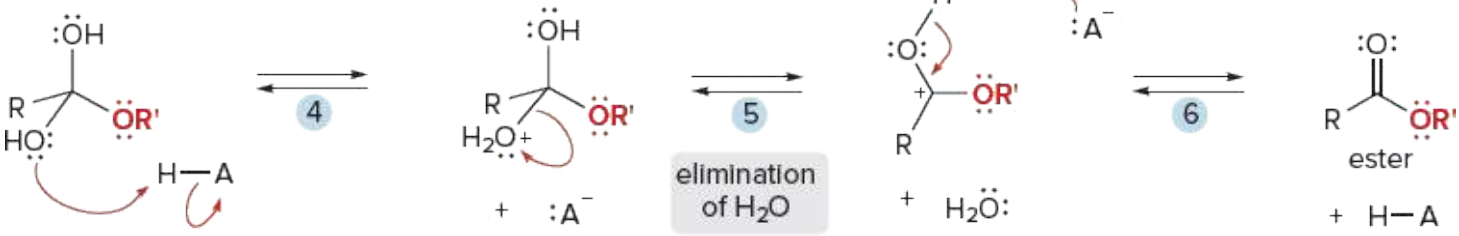
Part [1] Addition of the nucleophile R′OH



1 Protonation of the carbonyl oxygen makes the carbonyl more electrophilic.

2 – 3 Nucleophilic attack by R′OH forms a tetrahedral intermediate, and deprotonation gives the addition product.

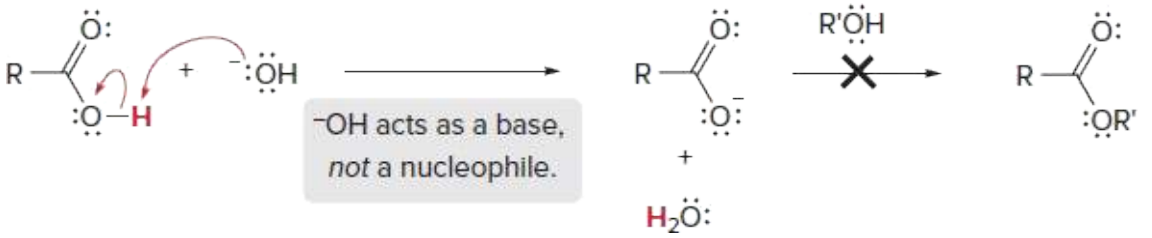
Part [2] Elimination of the leaving group H_2O



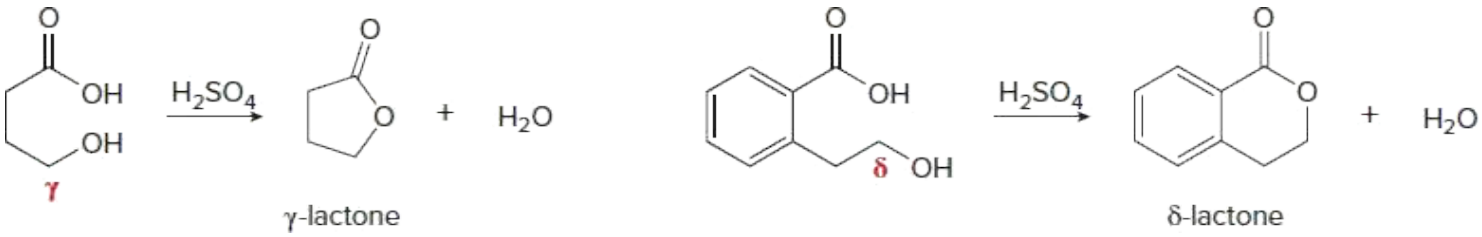
4 Protonation of the OH group forms a good leaving group.

5 – 6 Loss of H_2O and deprotonation give the ester.

Esterification of a carboxylic acid occurs in the presence of acid but not in the presence of base. Base removes a proton from the carboxylic acid, forming an electron-rich carboxylate anion, which does not react with an electron-rich nucleophile.



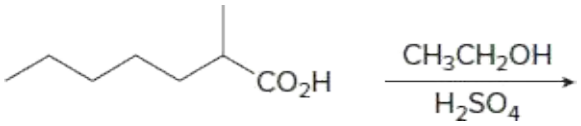
Intramolecular esterification of γ- and δ-hydroxy carboxylic acids forms five- and six-membered lactones.



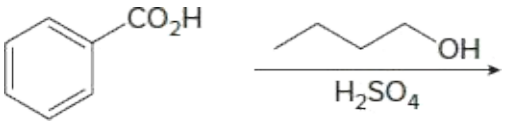
Problem 20.16

Draw the products of each reaction.

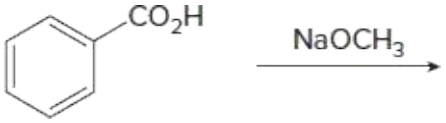
a.



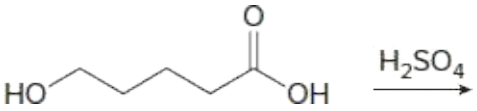
b.



c.



d.

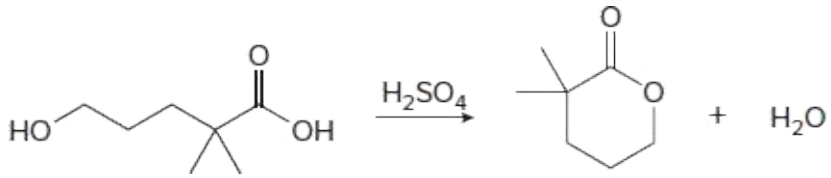


Problem 20.17

Draw the products formed when benzoic acid ($C_6H_5CO_2H$) is treated with CH_3OH having its O atom labeled with ^{18}O ($CH_3{}^{18}OH$). Indicate where the labeled oxygen atom resides in the products.

Problem 20.18

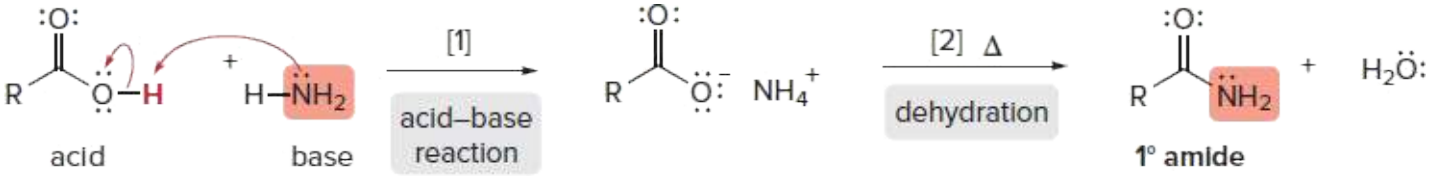
Draw a stepwise mechanism for the following reaction.



20.9D Conversion of RCOOH to RCONR′$_2$

The direct conversion of a carboxylic acid to an amide with NH_3 or an amine is very difficult, even though a more reactive acyl compound is being transformed into a less reactive one. The problem is that carboxylic acids are strong organic acids and NH_3 and amines are bases, so they undergo an acid–base reaction to form an ammonium salt before any nucleophilic substitution occurs.

Amides are much more easily prepared from acid chlorides and anhydrides, as discussed in Sections 20.7 and 20.8.



Heating at high temperature (>100 °C) dehydrates the resulting ammonium salt of the carboxylate anion to form an amide, though the yield can be low.

Therefore, the overall conversion of RCOOH to RCONH$_2$ requires two steps:

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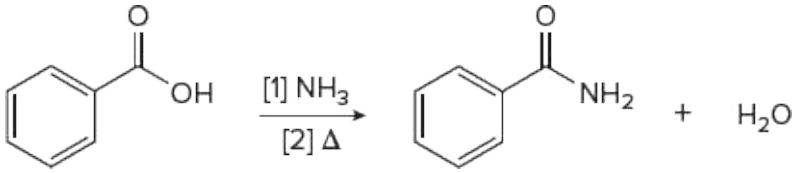
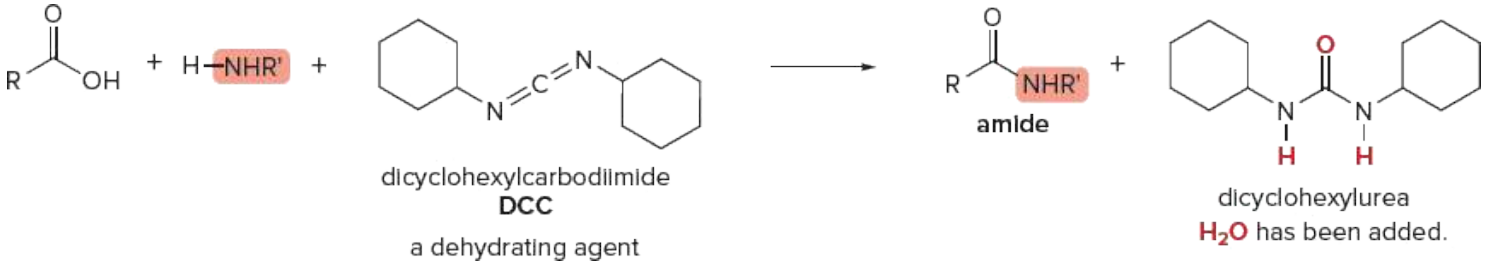
[1] Acid–base reaction of RCOOH with NH_3 to form an ammonium salt

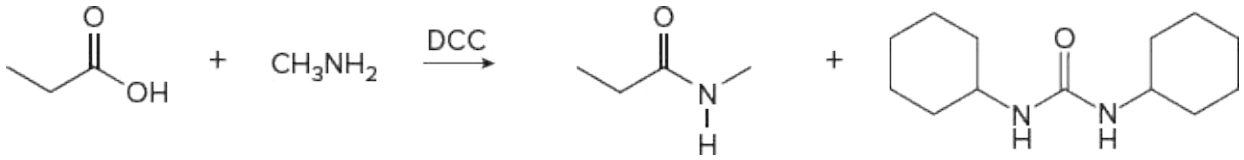
[2] Dehydration at high temperature (>100 °C)



A carboxylic acid and an amine readily react to form an amide in the presence of an additional reagent, dicyclohexylcarbodiimide (DCC), which is converted to the by-product dicyclohexylurea in the course of the reaction.



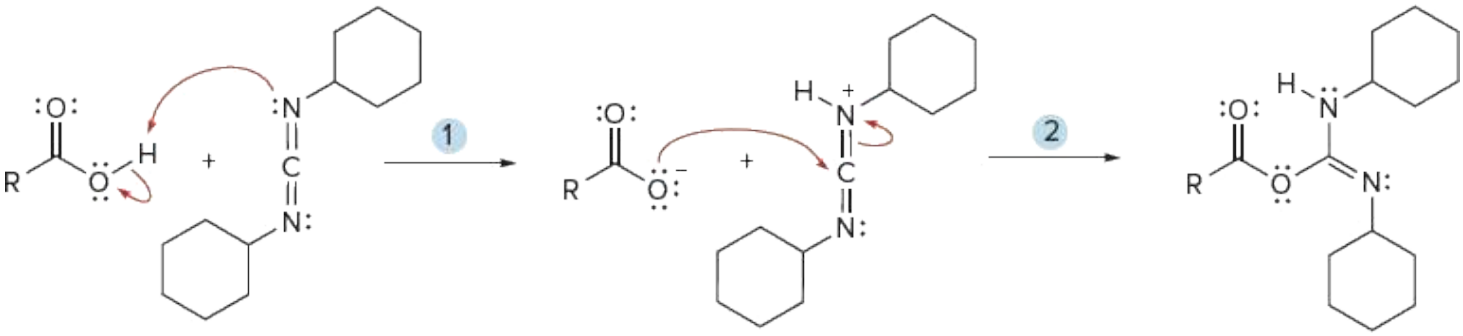
DCC is a dehydrating agent. The dicyclohexylurea by-product is formed by adding the elements of H_2O to DCC. DCC promotes amide formation by converting the carboxy OH group to a better leaving group.



The mechanism consists of two parts: [1] conversion of the OH group to a better leaving group, followed by [2] addition of the nucleophile and loss of the leaving group to form the product of nucleophilic acyl substitution (Mechanism 20.7).

Mechanism 20.7 Conversion of Carboxylic Acids to Amides with DCC

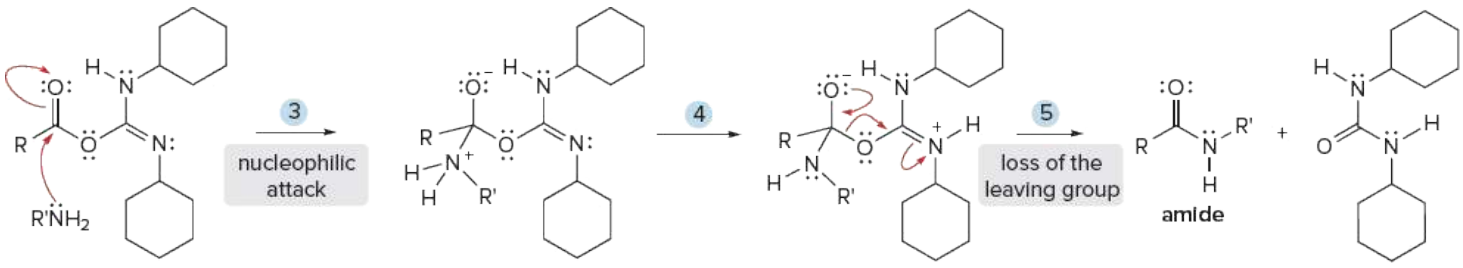
Part [1] Conversion of OH to a better leaving group



1 **Acid–base reaction results in transfer of a proton from the carboxylic acid to DCC.**

2 **Nucleophilic attack of RCO_2^- on the conjugate acid of DCC forms an addition product. The overall result of Steps [1] and [2] is conversion of OH to a better leaving group.**

Part [2] Addition of the nucleophile and loss of the leaving group



3 **Nucleophilic attack of the amine on the activated carboxy group forms a tetrahedral intermediate.**

4 – **5** **Proton transfer and elimination of dicyclohexylurea as the leaving**

group form the amide.

The reaction of an acid and an amine with DCC is often used in the laboratory to form the amide bond in peptides, as is discussed in Chapter 27.

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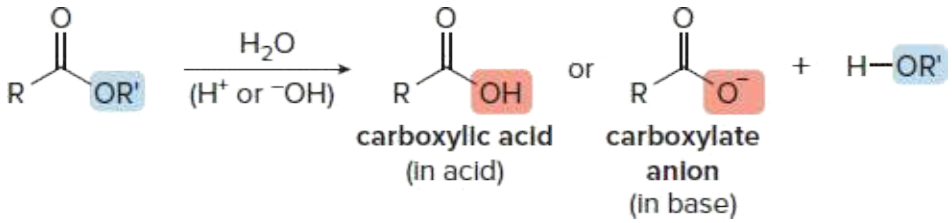
Problem 20.19

What product is formed when acetic acid is treated with each reagent: (a) CH_3NH_2; (b) CH_3NH_2, then heat; (c) CH_3NH_2 + DCC?

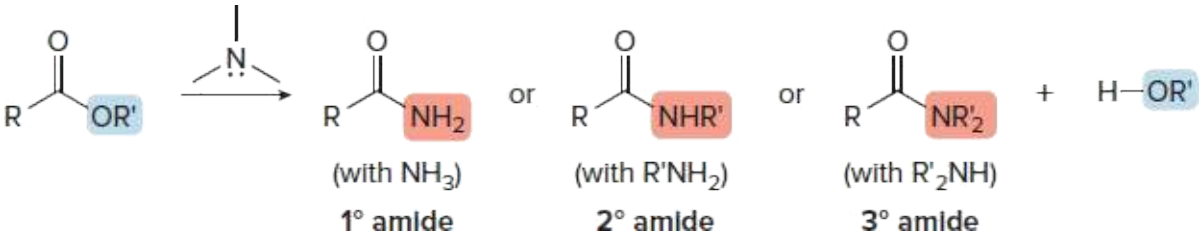
20.10 Reactions of Esters

Esters can be converted to carboxylic acids and amides.

- **Esters are hydrolyzed with water in the presence of either acid or base to form carboxylic acids or carboxylate anions.**



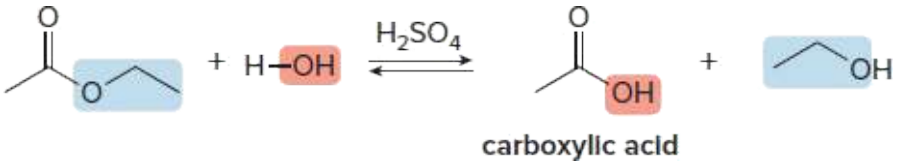
- **Esters react with NH_3 and amines to form 1°, 2°, or 3° amides.**



20.10A Ester Hydrolysis in Aqueous Acid

The hydrolysis of esters in aqueous acid is a reversible equilibrium reaction that is driven to the right by using a large excess of water.

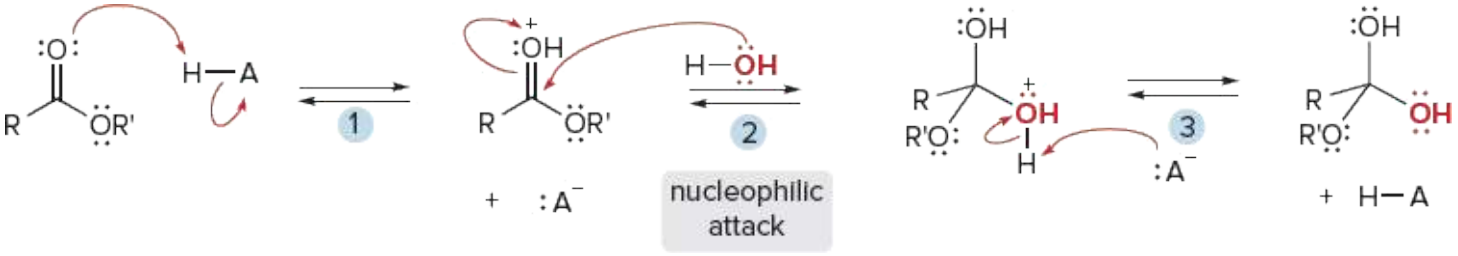
The first step in acid-catalyzed ester hydrolysis is protonation on oxygen, the same first step of any mechanism involving an oxygen-containing starting material and an acid.



The mechanism of ester hydrolysis in acid (shown in Mechanism 20.8) is the reverse of the mechanism of ester synthesis from carboxylic acids (Mechanism 20.6). Thus, the mechanism consists of the addition of the nucleophile and the elimination of the leaving group, the two steps common to all nucleophilic acyl substitutions, as well as several proton transfers, because the reaction is acid-catalyzed.

Mechanism 20.8 Acid-Catalyzed Hydrolysis of an Ester to a Carboxylic Acid

Part [1] Addition of the nucleophile H_2O



1 Protonation of the carbonyl oxygen makes the carbonyl more electrophilic.

2 – 3 Nucleophilic attack by H_2O forms a tetrahedral intermediate, and deprotonation gives the addition product.

Part [2] Elimination of the leaving group R′OH

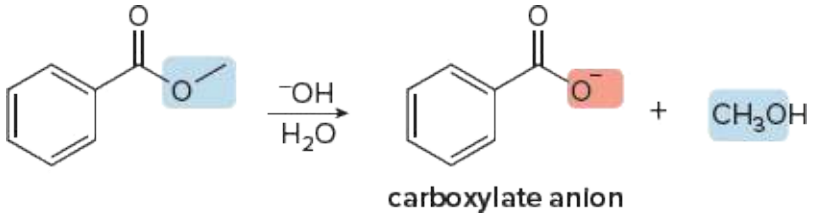
1 Protonation of the OR′ group forms a good leaving group.

2 – 3 Loss of R'OH and deprotonation give the carboxylic acid.

20.10B Ester Hydrolysis in Aqueous Base

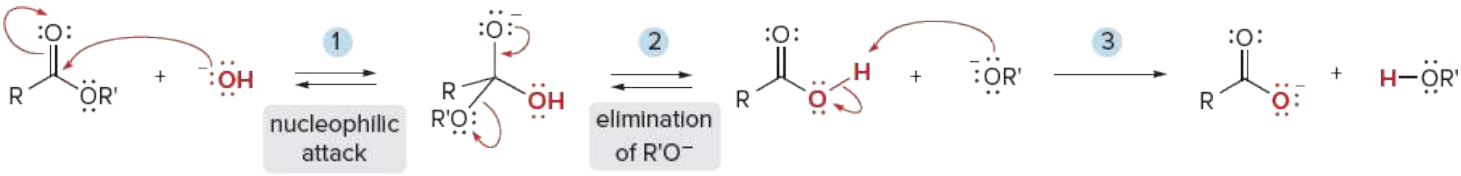
Esters are hydrolyzed in aqueous base to form carboxylate anions. Basic hydrolysis of an ester is called saponification.

The word *saponification* comes from the Latin *sapo*, meaning "soap." Soap is prepared by hydrolyzing esters in fats with aqueous base, as explained in Section 20.11B.



The mechanism for this reaction has the usual two steps of the general mechanism for nucleophilic acyl substitution presented in Section 20.6A—addition of the nucleophile followed by loss of a leaving group—plus an additional step involving proton transfer (Mechanism 20.9).

Mechanism 20.9 Base-Promoted Hydrolysis of an Ester to a Carboxylate Anion



1 – 2 **Addition of the nucleophile (⁻OH) followed by elimination of the leaving group (⁻OR′) form a carboxylic acid. These two steps are reversible**

3 **Because the carboxylic acid is a strong organic acid and the leaving group (⁻OR′) is a strong base, an acid–base reaction forms the carboxylate anion.**

The carboxylate anion is resonance stabilized, and this drives the equilibrium in its favor. Once the reaction is complete and the carboxylate anion is formed, it can be protonated with strong acid to form the neutral carboxylic acid.

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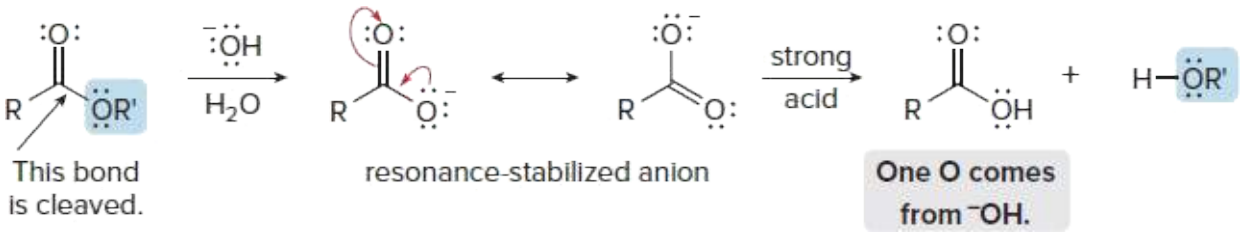
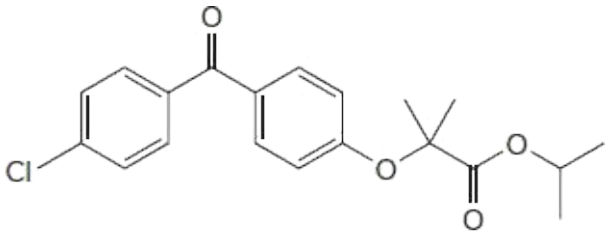
Hydrolysis is base promoted, *not* base catalyzed, because the base (⁻OH) is the nucleophile that adds to the ester and forms part of the product. It participates in the reaction and is not regenerated later.



Where do the oxygen atoms in the product come from? The C–OR′ bond in the ester is cleaved, so the OR′ group becomes the alcohol by-product (R′OH) and one of the oxygens in the carboxylate anion product comes from ⁻OH (the nucleophile).

Problem 20.20

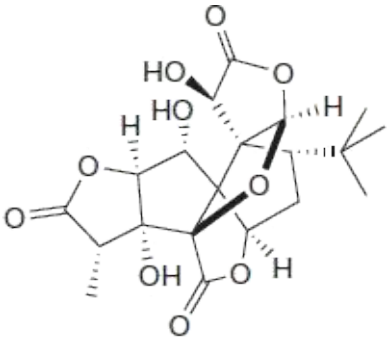
Fenofibrate is a cholesterol-lowering medication that is converted to fenofibric acid, the active drug, by hydrolysis during metabolism. What is the structure of fenofibric acid?



fenofibrate

Problem 20.21

What product is formed when the esters in ginkgolide B (Section 20.5A) are hydrolyzed in aqueous acid? Indicate the stereochemistry of all stereogenic centers.



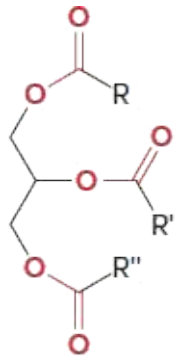
ginkgolide B

20.11 Application: Lipid Hydrolysis

20.11A Olestra—A Synthetic Fat

The most prevalent naturally occurring esters are the triacylglycerols, which were first discussed in Section 10.6. Triacylglycerols are the lipids that comprise animal fats and vegetable oils.

- **Each triacylglycerol is a triester, containing three long hydrocarbon side chains.**
- **Unsaturated triacylglycerols have one or more double bonds in their long hydrocarbon chains, whereas saturated triacylglycerols have none.**

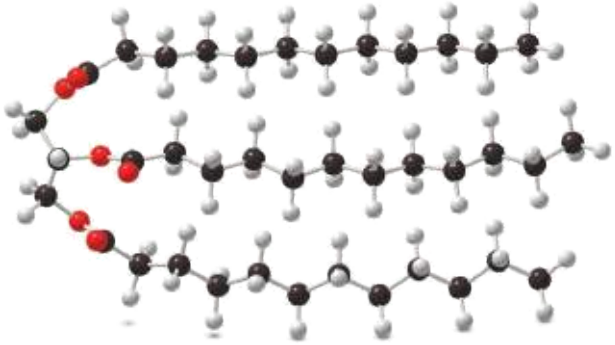


triacylglycerol

R groups have 11–19 C's.

[Three ester groups are labeled in red.]

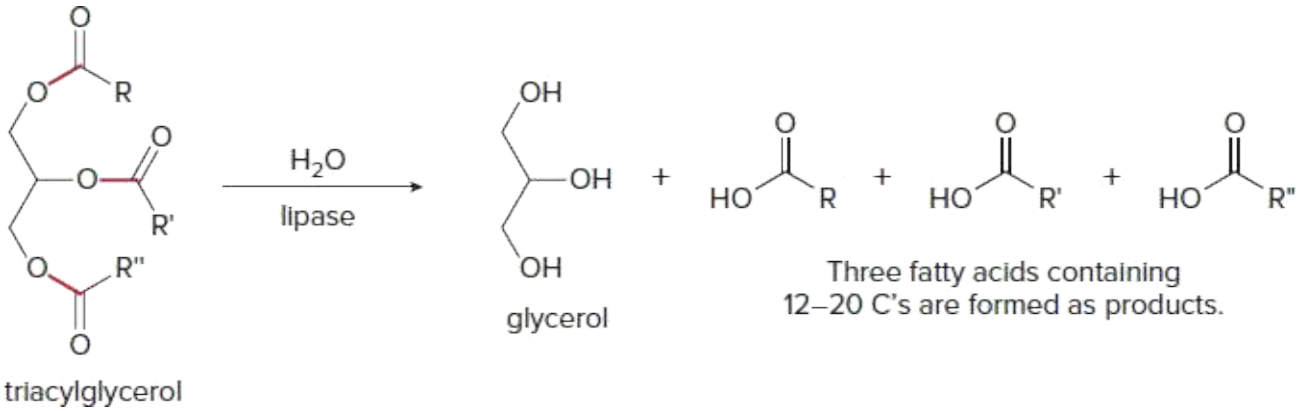
Figure 20.3 contains a ball-and-stick model of a saturated fat.



- This triacylglycerol has no double bonds in the three R groups (each with 11 C's) bonded to the ester carbonyls, making it a saturated fat.

Figure 20.3 **The three-dimensional structure of a saturated triacylglycerol**

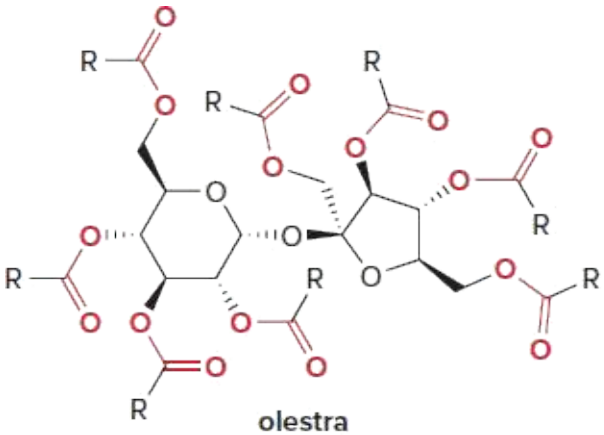
Animals store energy in the form of triacylglycerols, kept in a layer of fat cells below the surface of the skin. This fat serves to insulate the organism, as well as provide energy for its metabolic needs for long periods. The first step in the metabolism of a triacylglycerol is hydrolysis of the ester bonds to form glycerol and three fatty acids. In cells, this reaction is carried out with enzymes called lipases.



The fatty acids produced on hydrolysis are then oxidized in a stepwise fashion, ultimately yielding CO_2 and H_2O, as well as a great deal of energy. Oxidation of fats yields twice as much energy per gram as oxidation of an equivalent weight of carbohydrate.

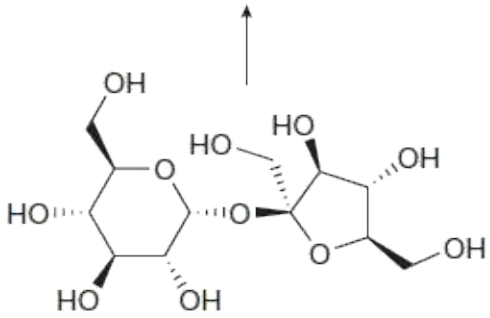
Some snack foods contain the "fake fat" olestra, giving them fewer calories than snack foods containing triacylglycerols for the calorie-conscious consumer. ©*McGraw-Hill Education/Jill Braaten, photographer*

Diets high in fat content lead to a large amount of stored fat, ultimately causing an individual to be overweight. One attempt to reduce calories in common snack foods has been to substitute "fake fats" such as olestra (trade name Olean) for triacylglycerols.

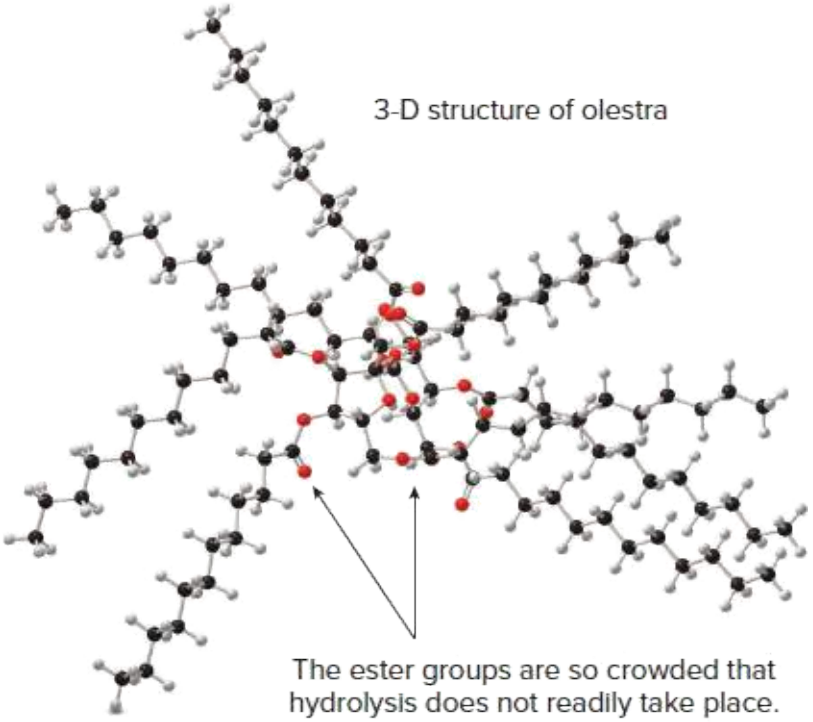


olestra

a polyester of sucrose
a synthetic fat
[R groups contain 11–19 C's.]



sucrose



Olestra is a polyester formed from long-chain fatty acids and sucrose, the Page 954 sweet-tasting carbohydrate in table sugar. Naturally occurring triacylglycerols are also polyesters formed from long-chain fatty acids, but olestra has so many ester units clustered together in close proximity that they are too hindered to be hydrolyzed, so it passes through the body unchanged, providing no calories to the consumer.

Thus, olestra's many C–C and C–H bonds make it similar in solubility to naturally occurring triacylglycerols, but its three-dimensional structure makes it inert to hydrolysis because of steric hindrance.

Problem 20.22

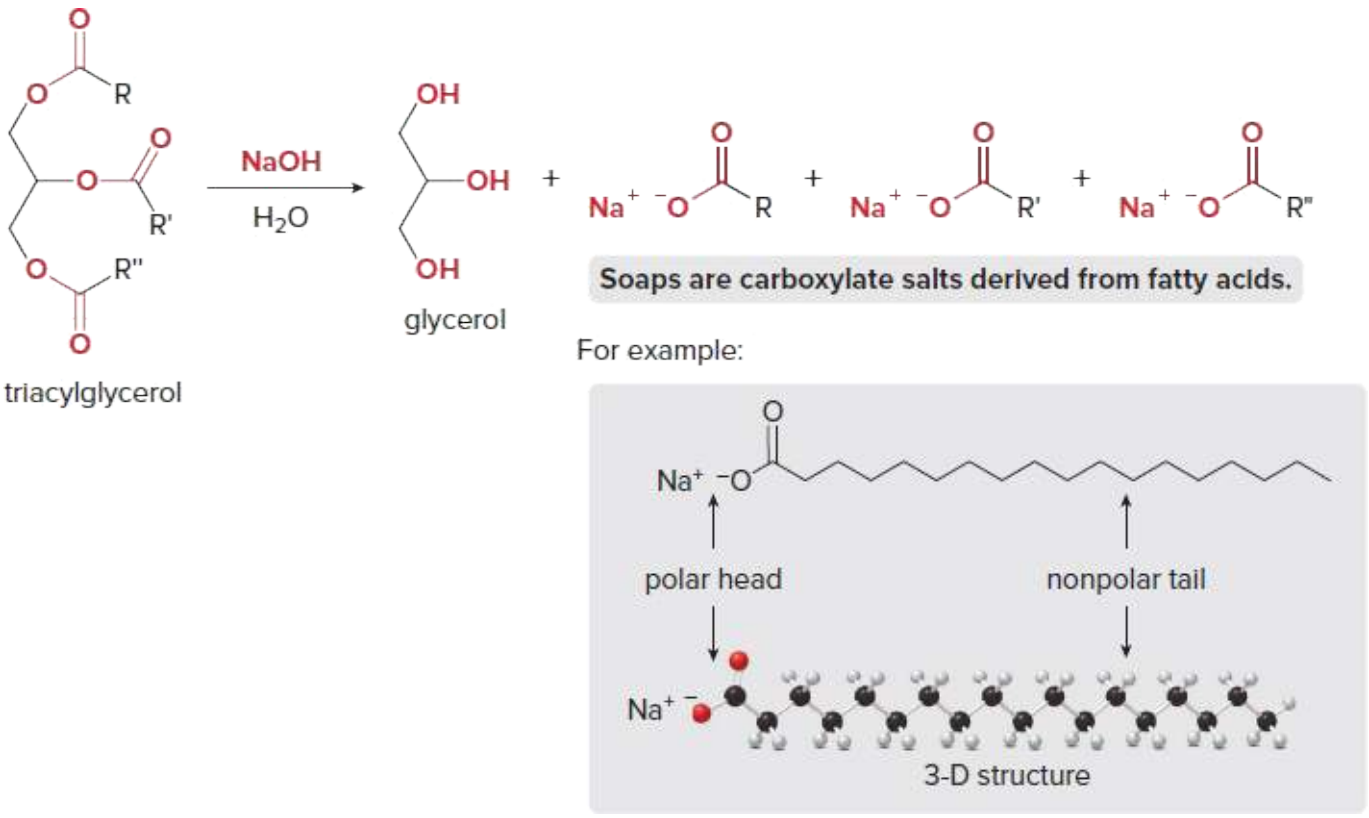
How would you synthesize olestra from sucrose?

20.11B The Synthesis of Soap

Soap is prepared by the basic hydrolysis or saponification of a triacylglycerol. Heating an animal fat or vegetable oil with aqueous base hydrolyzes the three esters to form glycerol and sodium salts of three fatty acids. These carboxylate salts are soaps, which clean away dirt because of their two structurally different regions. The nonpolar tail dissolves grease and oil and the polar head makes it soluble in water (Figure 3.4).

Soap was discussed in Section 3.6.

All soaps are salts of fatty acids. The main difference between soaps is the addition of other ingredients that do not alter their cleaning properties: dyes for color, scents for a pleasing odor, and oils for lubrication. Soaps that float are aerated, so that they are less dense than water. ©*Jill Braaten*

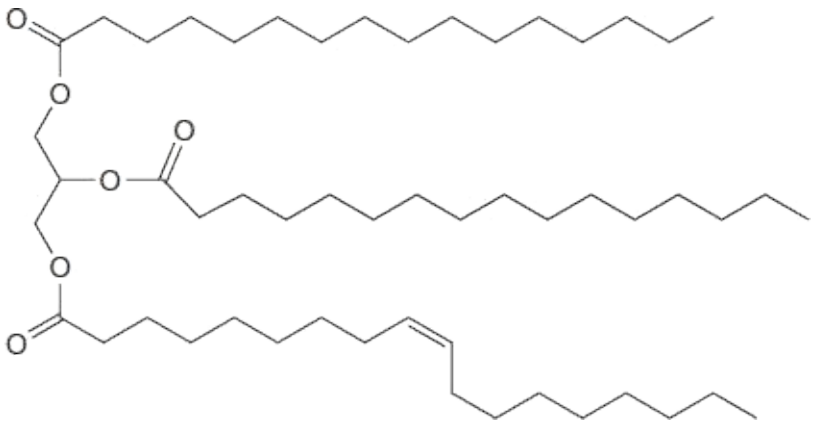


Soaps are typically made from lard (from hogs), tallow (from cattle or sheep), coconut oil, or palm oil. Most triacylglycerols have two or three different R groups in their hydrocarbon chains, so soaps are usually mixtures of two or three different carboxylate

salts.

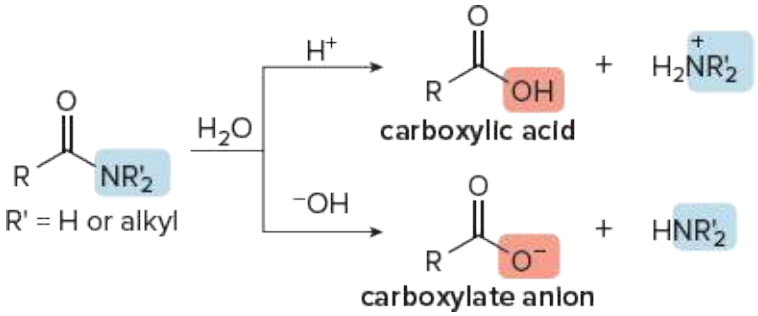
Problem 20.23

What is the composition of the soap prepared by hydrolysis of the following triacylglycerol?

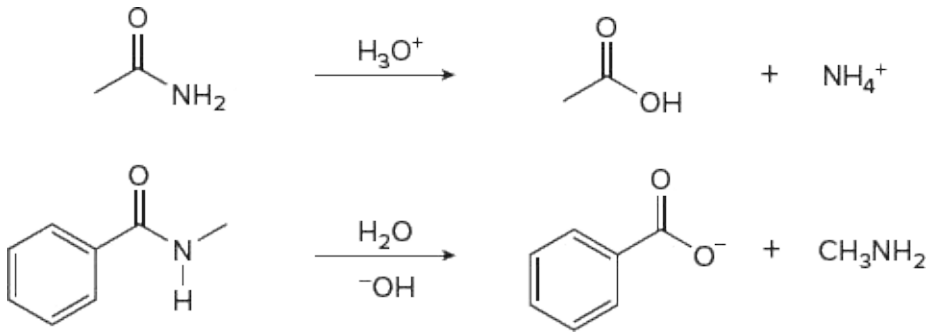


20.12 Reactions of Amides

Because amides have the poorest leaving group of all the carboxylic acid derivatives, they are the least reactive. Under strenuous reaction conditions, amides are hydrolyzed in acid or base to form carboxylic acids or carboxylate anions.



In acid, the amine by-product is protonated as an ammonium ion, whereas in base, a neutral amine is formed.



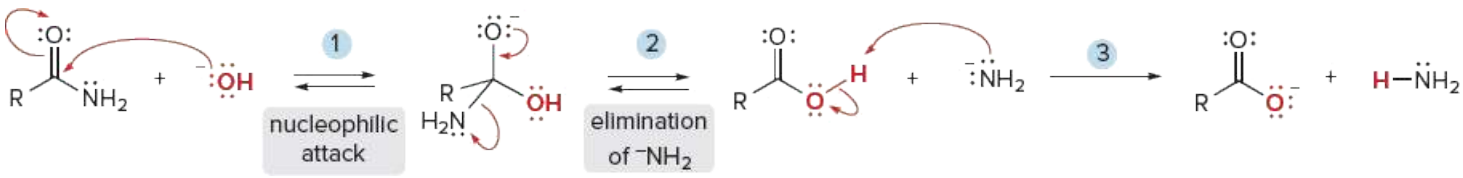
The relative lack of reactivity of the amide bond is notable in proteins, which are

polymers of amino acids connected by amide linkages (Section 20.5B). Proteins are stable in aqueous solution in the absence of acid or base, so they can perform their various functions in the aqueous cellular environment without breaking down. The hydrolysis of the amide bonds in proteins requires a variety of specific enzymes.

The mechanism of amide hydrolysis in acid is exactly the same as the mechanism of ester hydrolysis in aqueous acid (Section 20.10A) except that the leaving group is different.

The mechanism of amide hydrolysis in base has the usual two steps of the general mechanism for nucleophilic acyl substitution—addition of the nucleophile followed by loss of a leaving group—plus an additional proton transfer. The initially formed carboxylic acid reacts further under basic conditions to form the resonance-stabilized carboxylate anion, and this drives the reaction to completion. Mechanism 20.10 is written for a 1° amide.

Mechanism 20.10 Amide Hydrolysis in Base



1 – 2 **Addition of the nucleophile (^-OH) followed by elimination of the leaving group ($^-NH_2$) form a carboxylic acid. These two steps are reversible.**

3 **Because the carboxylic acid is a strong organic acid and the leaving group ($^-NH_2$) is a strong base, an acid–base reaction forms the carboxylate anion.**

Step [2] of Mechanism 20.10 deserves additional comment. For amide hydrolysis to occur, the tetrahedral intermediate must lose $^-NH_2$, a *stronger* base and therefore *poorer* leaving group than ^-OH. This means that loss of $^-NH_2$ does not often happen. Instead, ^-OH is lost as the leaving group most of the time, and the starting material is regenerated. But, when $^-NH_2$ is occasionally eliminated, the carboxylic acid product is converted to a lower-energy carboxylate anion in Step [3], and this drives the equilibrium to favor its formation.

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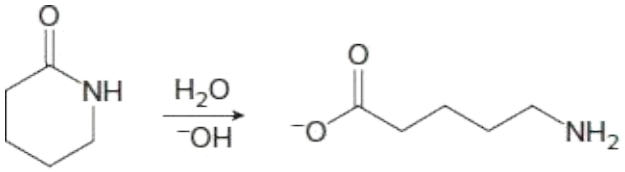
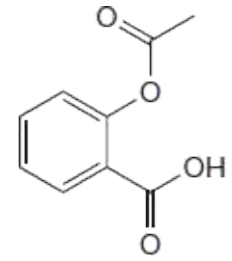
Problem 20.24

Draw a stepwise mechanism for the following reaction.

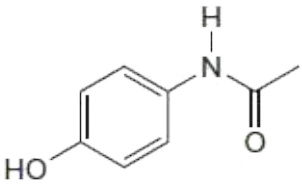


Problem 20.25

With reference to the structures of acetylsalicylic acid (aspirin) and acetaminophen (the active ingredient in Tylenol), explain why acetaminophen tablets can be stored in the medicine cabinet for years, but aspirin tablets slowly decompose over time.



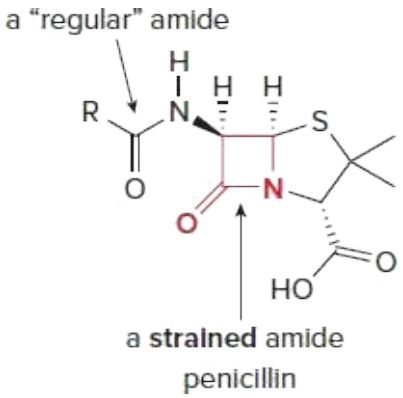
acetylsalicylic acid



acetaminophen

20.13 Application: The Mechanism of Action of β-Lactam Antibiotics

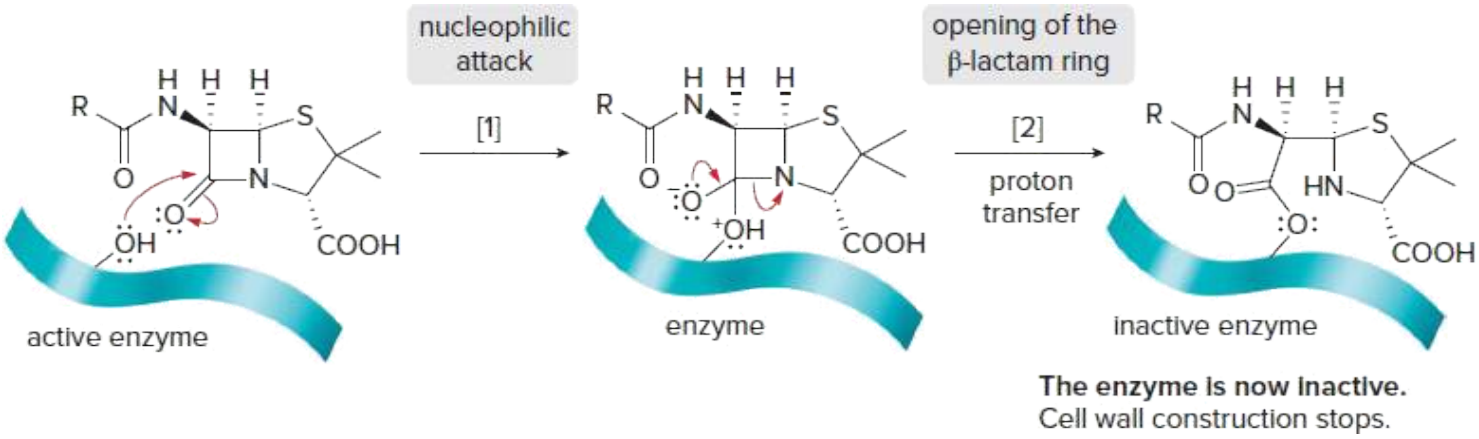
Penicillin and related β-lactams kill bacteria by a nucleophilic acyl substitution reaction. All penicillins have an unreactive amide side chain and a very reactive amide that is part of a β-lactam. The β-lactam is more reactive than other amides because it is part of a strained, four-membered ring that is readily opened with nucleophiles.



penicillin

Unlike mammalian cells, bacterial cells are surrounded by a fairly rigid cell wall, which allows the bacterium to live in many different environments. This protective cell wall is composed of carbohydrates linked together by peptide chains containing amide linkages, formed using the enzyme glycopeptide transpeptidase.

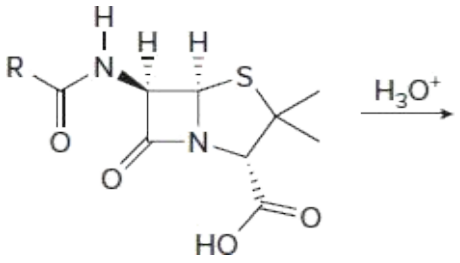
Penicillin interferes with the synthesis of the bacterial cell wall. A nucleophilic OH group of the glycopeptide transpeptidase enzyme cleaves the β-lactam ring of penicillin by a nucleophilic acyl substitution reaction. The opened ring of the penicillin molecule remains covalently bonded to the enzyme, thus deactivating the enzyme, halting cell wall construction, and killing the bacterium. Penicillin has no effect on mammalian cells because they are surrounded by a flexible membrane composed of a lipid bilayer (Chapter 3) and not a cell wall.



Thus, penicillin and other β-lactam antibiotics are biologically active precisely because they undergo a nucleophilic acyl substitution reaction with an important bacterial enzyme.

Problem 20.26

Some penicillins cannot be administered orally because their β-lactam is rapidly hydrolyzed by the acidic environment of the stomach. What product is formed in the following hydrolysis reaction?



20.14 Summary of Nucleophilic Acyl Substitution Reactions

To help you organize and remember all of the nucleophilic acyl substitution reactions that can occur at a carbonyl carbon, keep in mind these two principles:

- **The *better* the leaving group, the *more reactive* the carboxylic acid**

derivative.

- **More reactive acyl compounds can always be converted to less reactive ones. The reverse is not usually true.**

This results in the following order of reactivity:

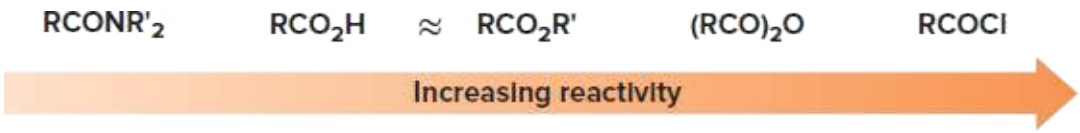


Table 20.5 summarizes the specific nucleophilic acyl substitution reactions. Use it as a quick reference to remind you which products can be formed from a given starting material.

Table 20.5 Summary of the Nucleophilic Substitution Reactions of Carboxylic Acids and Their Derivatives

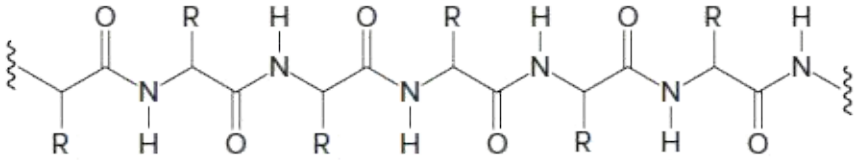
Starting material		Product: RCOCl	$(RCO)_2O$	RCO_2H	RCO_2R'	$RCONR'_2$
[1] RCOCl	→	–	✓	✓	✓	✓
[2] $(RCO)_2O$	→	✗	–	✓	✓	✓
[3] RCO_2H	→	✓	✓	–	✓	✓
[4] RCO_2R'	→	✗	✗	✓	–	✓
[5] $RCONR'_2$	→	✗	✗	✓	✗	–

Table key: ✓ = A reaction occurs.
✗ = No reaction occurs.

20.15 Natural and Synthetic Fibers

All natural and synthetic fibers are high-molecular-weight polymers. Natural fibers are obtained from either plant or animal sources, and this determines the fundamental nature of their chemical structure. Fibers like wool and silk obtained from animals are proteins, so they are formed from amino acids joined together by many amide linkages. Cotton and linen, on the other hand, are derived from plants, so they are carbohydrates having the general structure of cellulose, formed from glucose monomers. General structures for these polymers are shown in Figure 20.4.

a. Wool and silk—Proteins with many amide bonds



b. Cotton and linen—Carbohydrates like cellulose

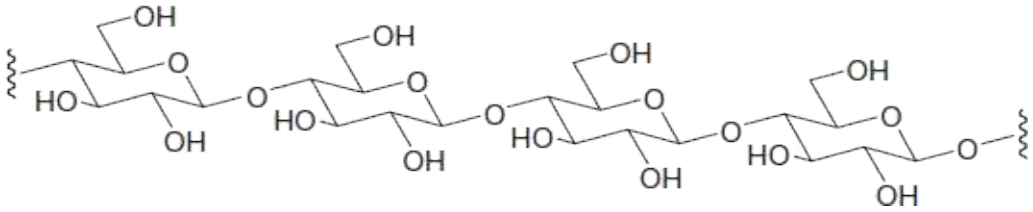


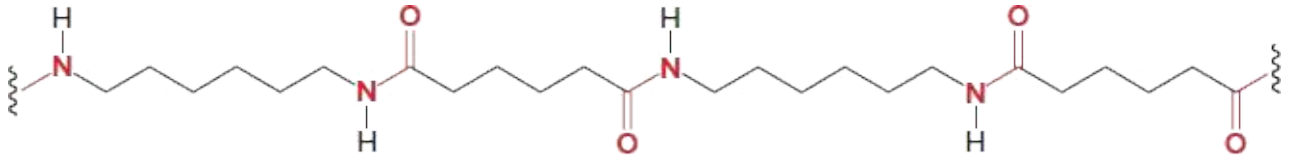
Figure 20.4 **The general structure of the common natural fibers**

An important practical application of organic chemistry has been the preparation of synthetic fibers, many of which have properties that are different from and sometimes superior to their naturally occurring counterparts. The two most common classes of synthetic polymers are based on polyamides and polyesters.

20.15A Nylon—A Polyamide

The search for a synthetic fiber led to the discovery of nylon, a polyamide that is strong and durable and resembles the silk produced by silkworms. There are several different kinds of nylon, but the most well known is called nylon 6,6.

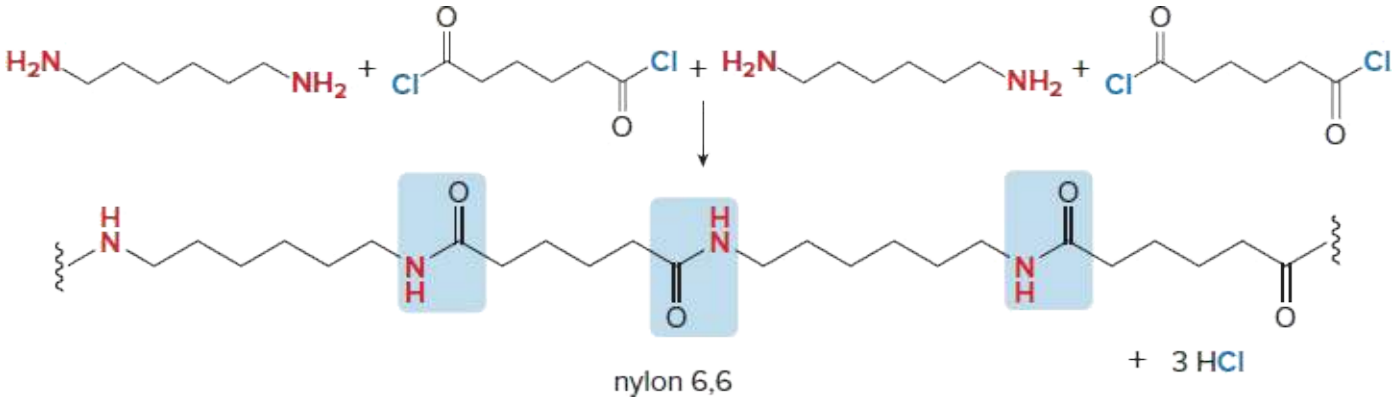
DuPont built the first commercial nylon plant in 1938. Although it was initially used by the military to make parachutes, nylon quickly replaced silk in many common products after World War II. ***©Jeff Morgan 14/Alamy Stock Photo***



[The amide bonds are labeled in red.]

nylon 6,6

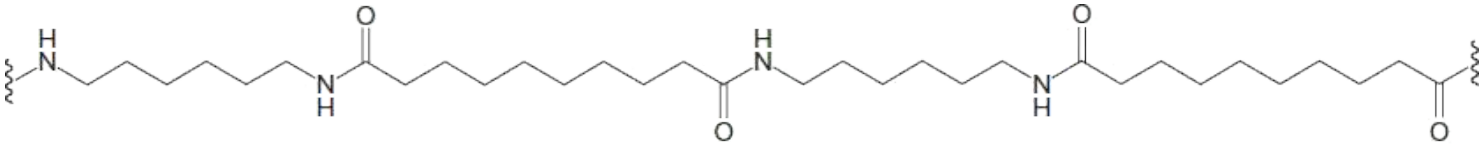
Nylon 6,6 can be synthesized from two six-carbon monomers (hence its name)—adipoyl chloride ($ClOCCH_2CH_2CH_2CH_2COCl$) and hexamethylenediamine ($H_2NCH_2CH_2CH_2CH_2CH_2CH_2NH_2$). This diacid chloride and diamine react together to form new amide bonds, yielding the polymer. Nylon is called a condensation polymer because a small molecule, in this case HCl, is eliminated during its synthesis.



nylon 6,6 + 3 HCl

Problem 20.27

What two monomers are needed to prepare nylon 6,10?

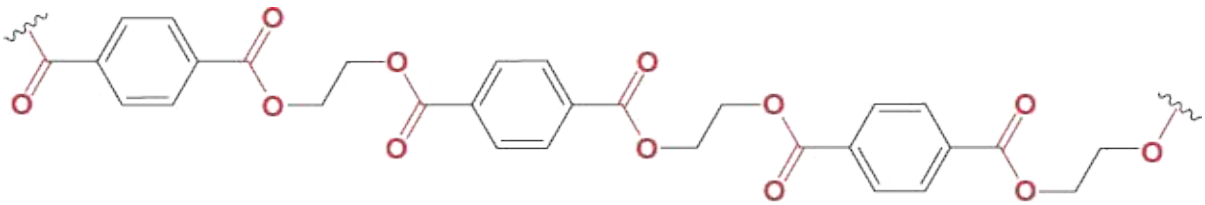


nylon 6,10

20.15B Polyesters

Polyesters constitute a second major class of condensation polymers. The most common polyester is polyethylene terephthalate (PET), which is sold under a variety of trade names (Dacron, Terylene, and Mylar) depending on its use.

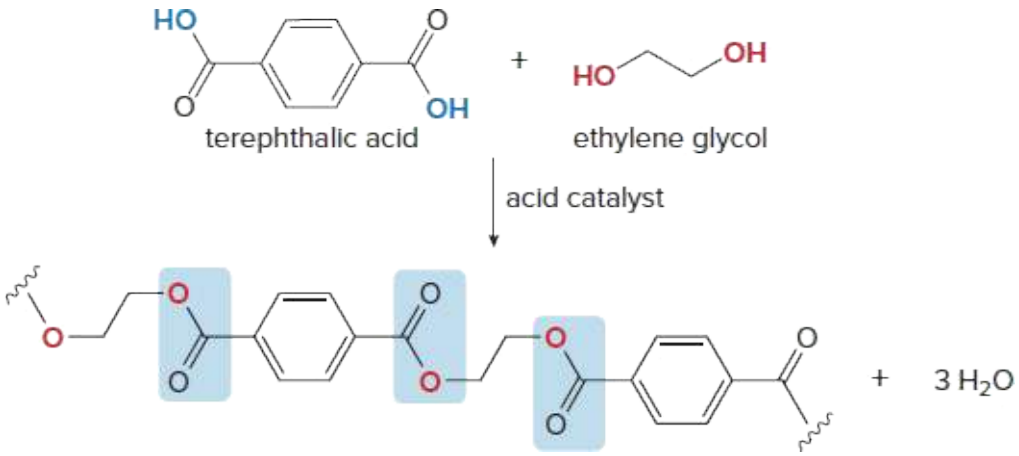
As we will learn in Section 28.9, PET is more easily recycled than other common polymers. For example, recycled PET is used to make reusable shopping bags. ©*Jill Braaten*



polyethylene terephthalate
PET
(Dacron, Terylene, and Mylar)

Ester bonds (in red) join the carbon skeleton together.

One method of synthesizing a polyester is by acid-catalyzed esterification of a diacid with a diol (Fischer esterification).



Because these polymers are easily and cheaply prepared and form strong and chemically stable materials, they have been used in clothing, films, tires, and many

other products.

Problem 20.28

Draw the structure of Kodel, a polyester formed from 1,4-dihydroxymethylcyclohexane and terephthalic acid. Explain why fabrics made from Kodel are stiff and crease resistant.

1,4-dihydroxymethylcyclohexane terephthalic acid

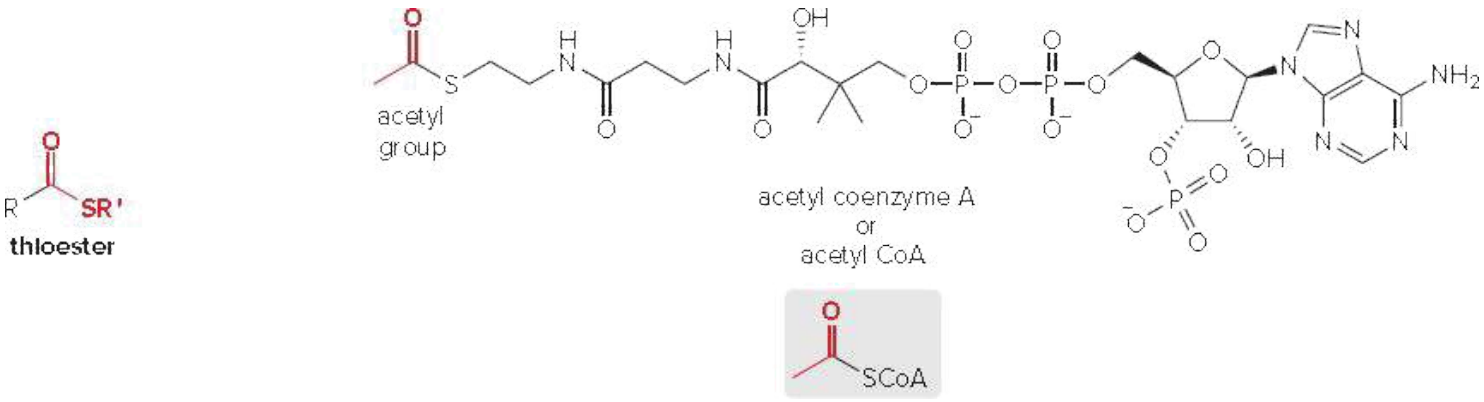
Problem 20.29

Poly(lactic acid) (PLA) has received much recent attention because the lactic acid monomer [$CH_3CH(OH)COOH$] from which it is made can be obtained from carbohydrates rather than petroleum. This makes PLA a more "environmentally friendly" polyester. (A further discussion of green polymer synthesis is presented in Chapter 28.) Draw the structure of PLA.

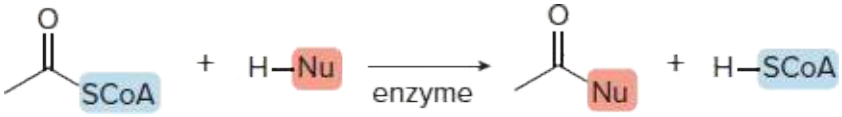
20.16 Biological Acylation Reactions

Nucleophilic acyl substitution is a common reaction in biological systems. These acylation reactions are called acyl transfer reactions because they result in the transfer of an acyl group from one atom to another (from Z to Nu in this case).

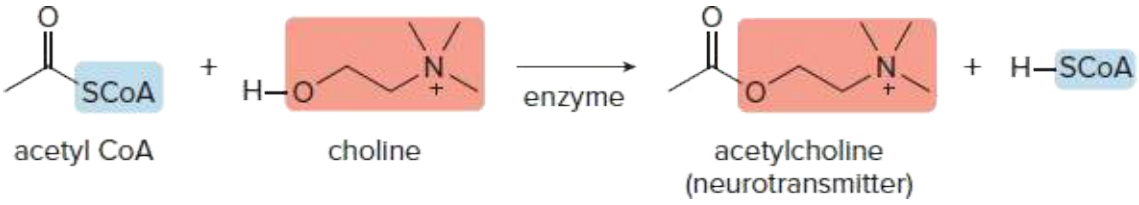
In cells, such acylations occur with the sulfur analogue of an ester, called a thioester, having the general structure RCOSR′. The most common thioester is called acetyl coenzyme A, often referred to as acetyl CoA.



- **A thioester (RCOSR′) has a good leaving group (⁻SR′), so, like other acyl compounds, it undergoes substitution reactions with other nucleophiles. With acetyl CoA, an acetyl group is transferred from SCoA to a nucleophile, :Nu⁻.**



For example, acetyl CoA undergoes enzyme-catalyzed nucleophilic acyl substitution with choline, forming acetylcholine, a charged compound that transmits nerve impulses between nerve cells.



Many other acyl transfer reactions are important cellular processes. Thioesters of fatty acids react with cholesterol, forming cholesteryl esters in an enzyme-catalyzed reaction (Figure 20.5). These esters are the principal form in which cholesterol is stored and transported in the body. Because cholesterol is a lipid, insoluble in the aqueous environment of the blood, it travels through the bloodstream in particles that also contain proteins and phospholipids. These particles are classified by their density.

- LDL particles (low-density lipoproteins) transport cholesterol from the liver to the tissues.
- HDL particles (high-density lipoproteins) transport cholesterol from the tissues back to the liver, where it is metabolized or converted to other steroids.

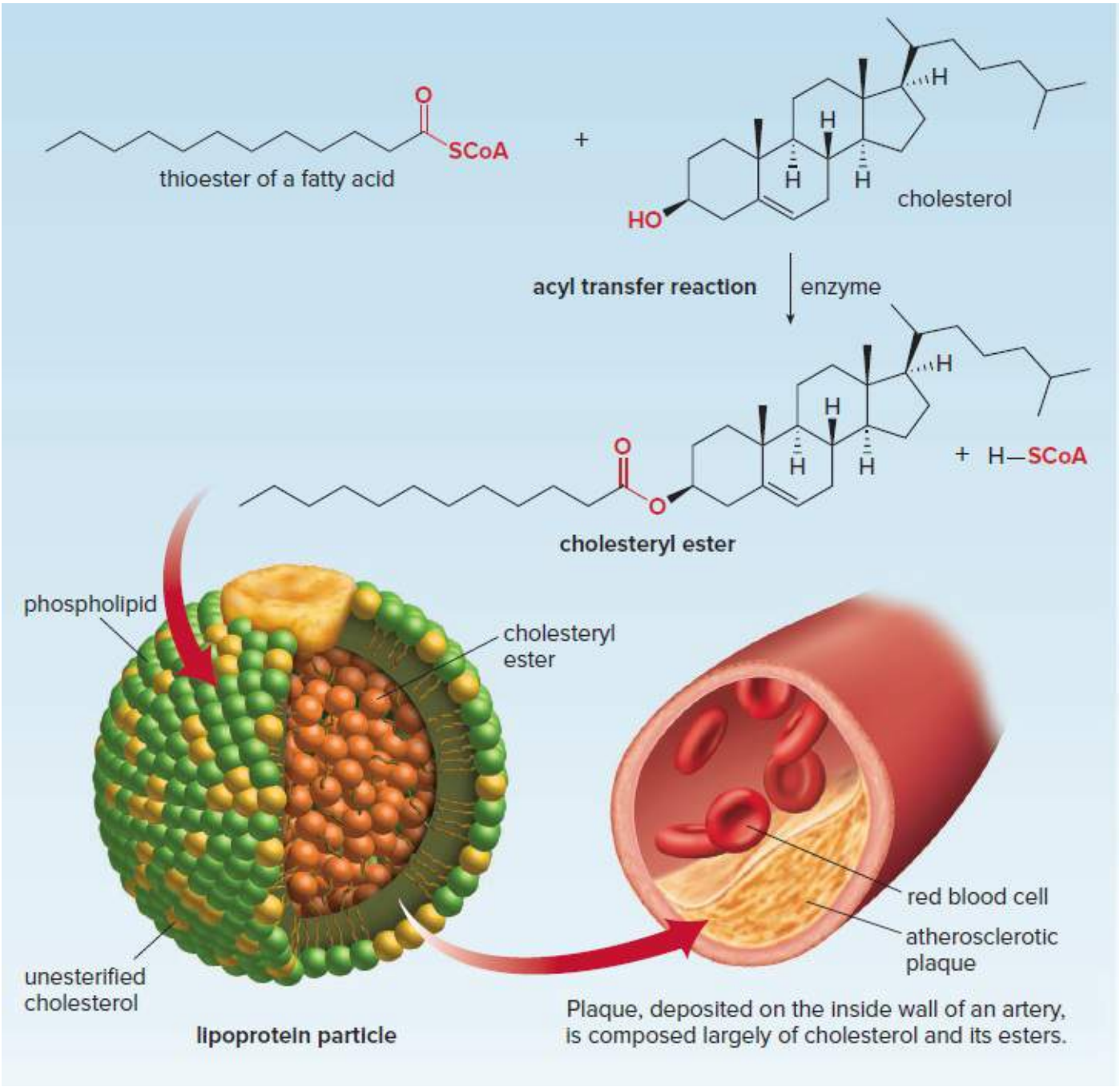


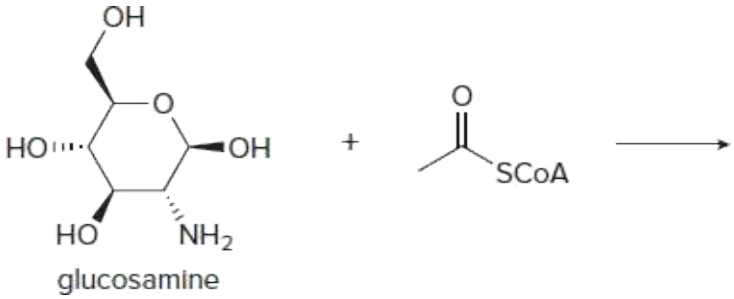
Figure 20.5 **Cholesteryl esters and lipoprotein particles**

Atherosclerosis is a disease that results from the buildup of fatty deposits on the walls of arteries, forming deposits called plaque. Plaque is composed largely of the cholesterol (esterified as an ester) of LDL particles. LDL is often referred to as "bad cholesterol" for this reason. In contrast, HDL particles are called "good cholesterol" because they reduce the amount of cholesterol in the bloodstream by transporting it back to the liver.

Problem 20.30

Glucosamine is a dietary supplement available in many over-the-counter treatments for osteoarthritis. Reaction of acetyl CoA with glucosamine forms NAG, *N*-

acetylglucosamine, the monomer used to form chitin, the carbohydrate that forms the rigid shells of lobsters and crabs. What is the structure of NAG?

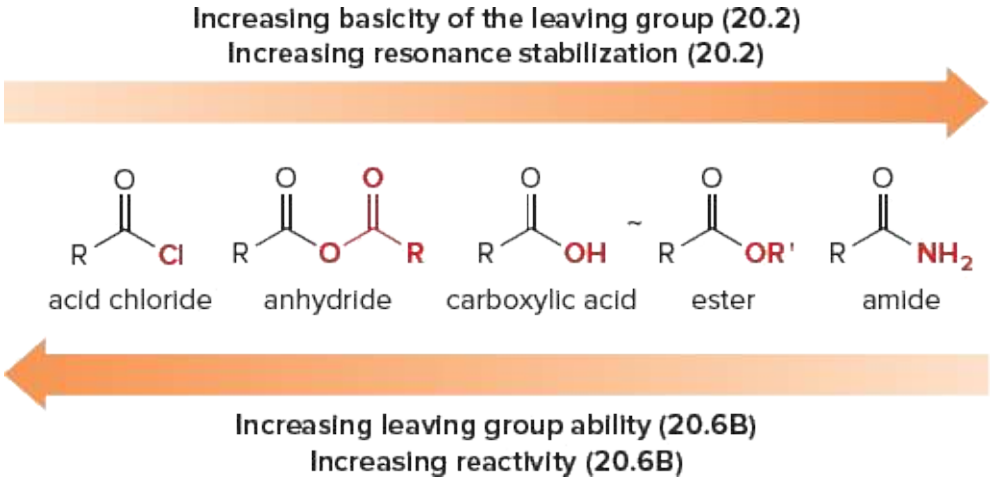


Chapter 20 REVIEW

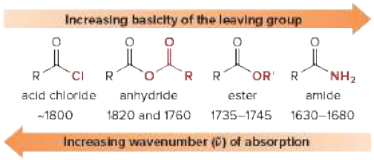
KEY CONCEPTS

The properties of RCOZ

1 The relationship between the basicity of Z^- and the properties of RCOZ



2 The effect of Z in RCOZ on IR absorption (20.4B)

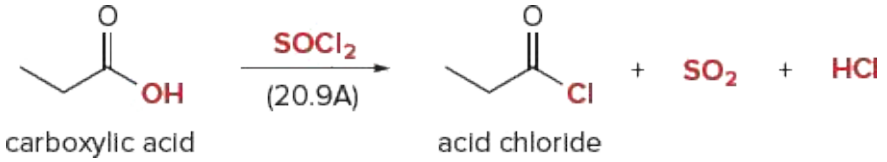


Try Problems 20.31, 20.63.

KEY REACTIONS

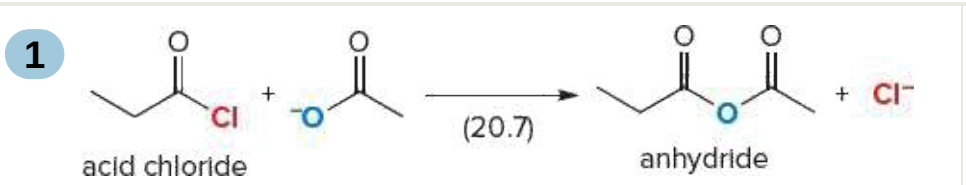
Nucleophilic Acyl Substitution Reactions

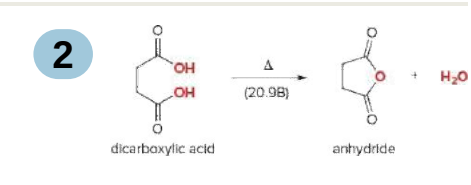
[1] Reactions that produce acid chlorides (RCOCl)



Try Problem 20.39c.

[2] Reactions that produce anhydrides [$(RCO)_2O$]





Try Problems 20.39i, 20.40g.

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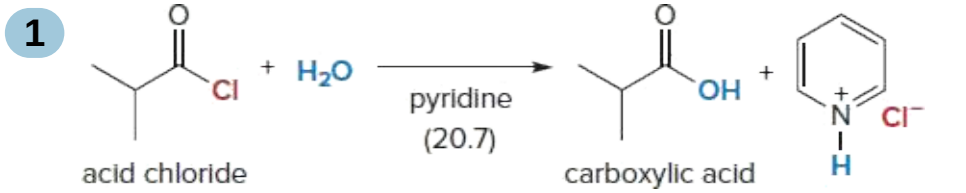
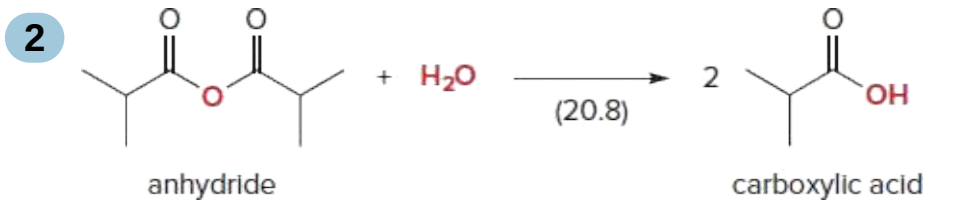
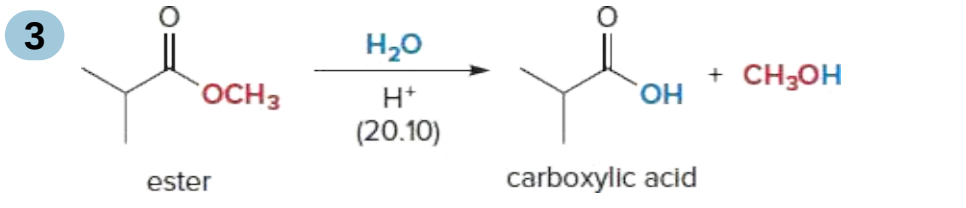
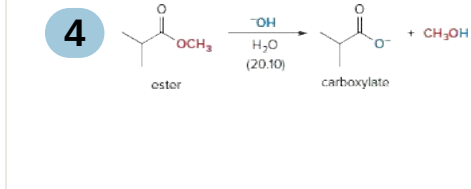
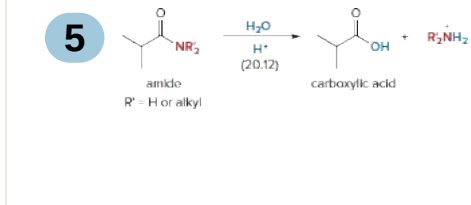
[3] Reactions that produce carboxylic acids (RCOOH) and carboxylates ($RCOO^-$)

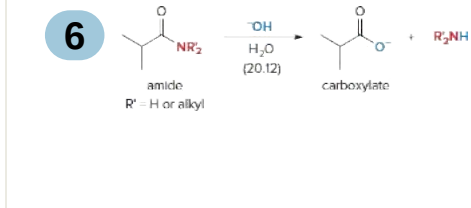






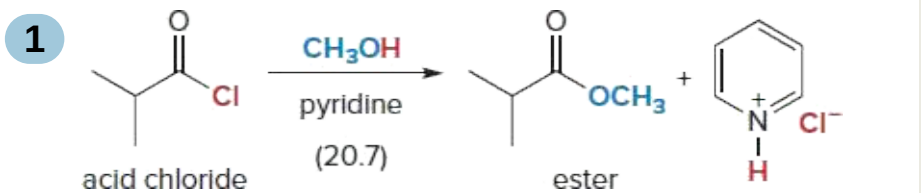


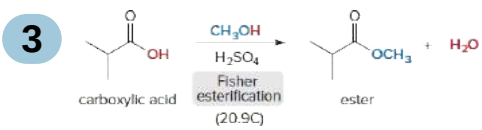


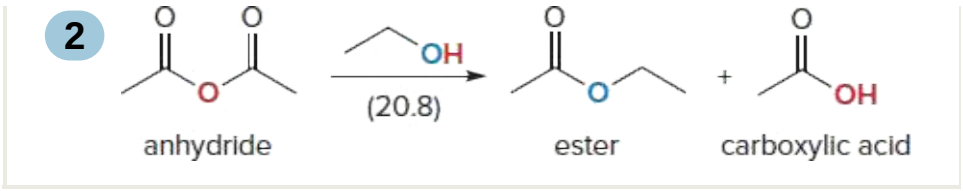


Try Problems 20.32b [1], [2]; 20.40b–d; 20.42; 20.44b; 20.45.

[4] Reactions that produce esters (RCOOR')

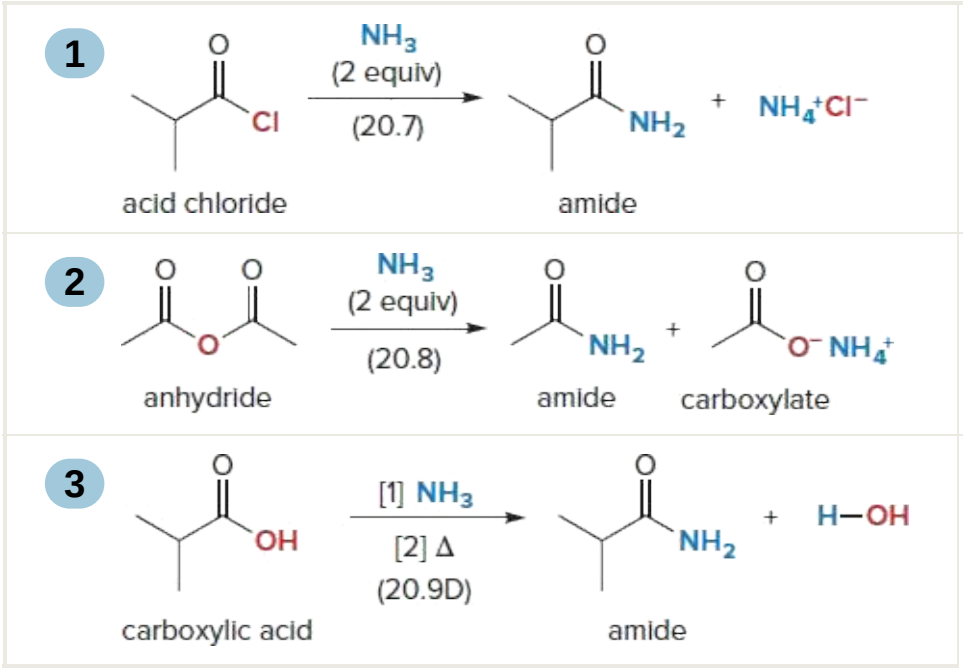


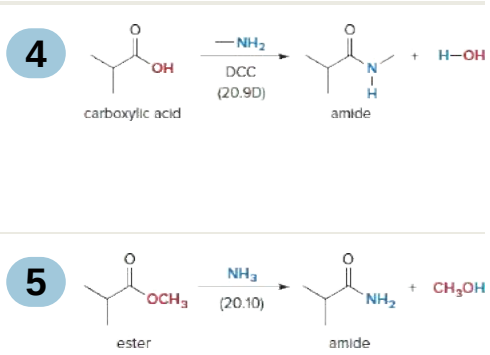




Try Problems 20.39g, l; 20.44a, c.

[5] Reactions that produce amides (RCONR′2)





Try Problems 20.39f, j, k; 20.40a, h; 20.44d.

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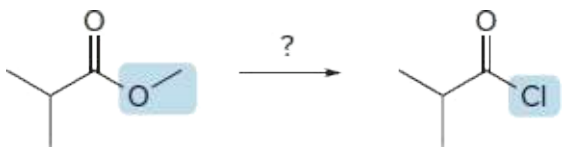
KEY SKILLS

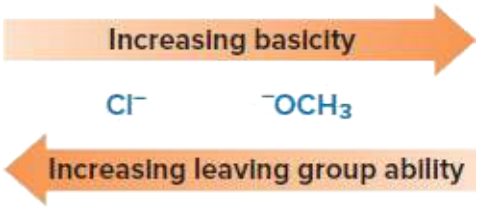
[1] Determining whether a nucleophilic acyl substitution will occur (20.6B)

1 **Identify the different groups attached to the C=O.**

2 **Compare basicity of the leaving group and nucleophile to determine if the reaction will occur.**



- **This conversion requires the substitution of $^{-}OCH_3$ by Cl^{-}.**

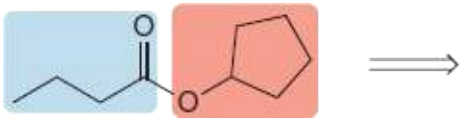
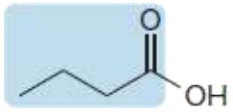
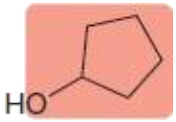


- **Because $^{-}OCH_3$ is a stronger base and therefore a poorer leaving group than Cl^{-}, this**

reaction does *not* occur.

See Sample Problem 20.2. Try Problem 20.39d.

[2] Determining the carboxylic acid and alcohol needed for a Fischer esterification (20.9C)

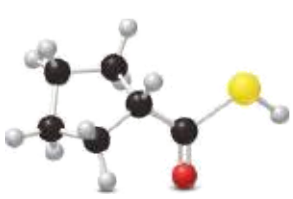
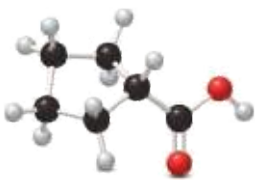
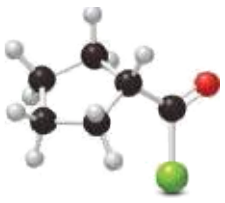
1 Cleave the carbon–oxygen single bond attached to the carbonyl.	2 Draw the RCOOH, which becomes the RC=O.	3 Draw the HOR, which becomes the OR group.
		

Try Problem 20.56.

PROBLEMS

Problems Using Three-Dimensional Models

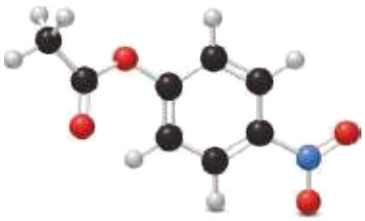
20.31 Rank the following compounds in order of increasing reactivity in nucleophilic acyl substitution.

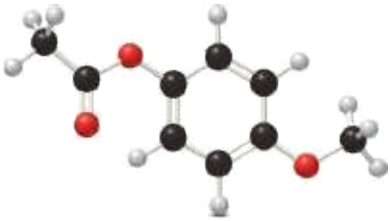
20.32 (a) Give an acceptable name for compound A. (b) Draw the organic products formed when A is treated with each reagent: [1] H_3O^+; [2] ^-OH, H_2O; [3] $CH_3CH_2CH_2MgBr$ (excess), then H_2O; [4] $LiAlH_4$, then H_2O.

A

20.33 Which ester, C or D, is more reactive in nucleophilic acyl substitution? Explain your reasoning.



C

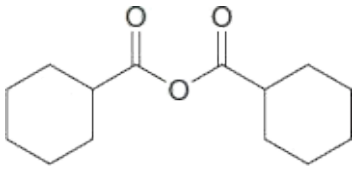


D

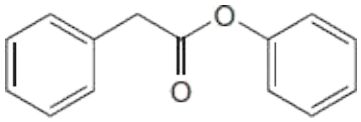
Nomenclature

20.34 Give the IUPAC or common name for each compound.

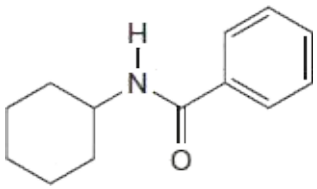
a.



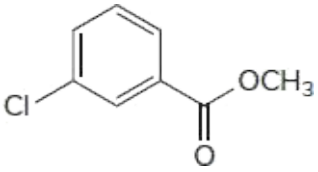
b.



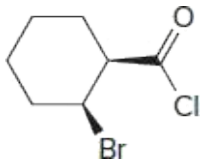
c.



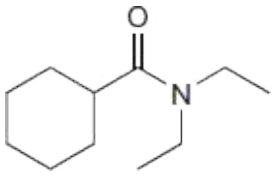
d.



e.



f.



20.35 Give the structure corresponding to each name.

a. cyclohexyl propanoate

b. cyclohexanecarboxamide

c. benzoic propanoic anhydride

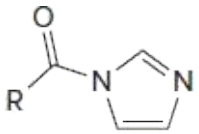
d. 3-methylhexanoyl chloride

e. octyl butanoate

f. *N,N*-dibenzylformamide

Properties of Carboxylic Acid Derivatives

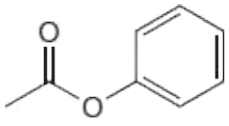
20.36 Explain why imidazolides are much more reactive than other amides in nucleophilic acyl substitution.



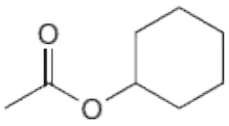
imidazolide

20.37 Explain why CH_3CONH_2 is a stronger acid and a weaker base than $CH_3CH_2NH_2$.

20.38 (a) Propose an explanation for the difference in the frequency of the carbonyl absorptions of phenyl acetate (1765 cm^{-1}) and cyclohexyl acetate (1738 cm^{-1}). (b) Which carbonyl group is more effectively stabilized by resonance? (c) Which ester reacts faster when treated with aqueous base?



phenyl acetate



cyclohexyl acetate

Reactions

20.39 Draw the product formed when phenylacetic acid ($C_6H_5CH_2COOH$) is treated with each reagent. With some reagents, no reaction occurs.

a. $NaHCO_3$

b. NaOH

c. $SOCl_2$

d. NaCl

e. NH_3 (1 equiv)

f. NH_3, Δ

g. CH_3OH, H_2SO_4

h. CH_3OH, ^-OH

i. [1] NaOH; [2] CH_3COCl

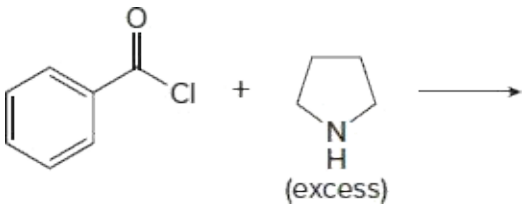
j. CH_3NH_2, DCC

k. [1] $SOCl_2$; [2] $CH_3CH_2CH_2NH_2$ (excess)

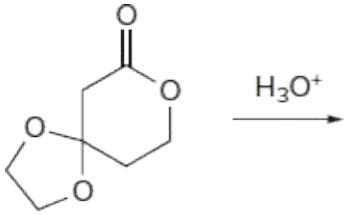
l. [1] $SOCl_2$; [2] $(CH_3)_2CHOH$

20.40 Draw the organic products formed in each reaction.

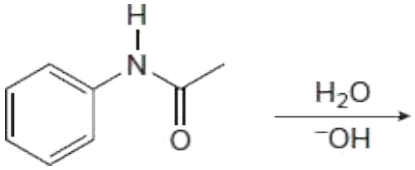
a.



b.



c.



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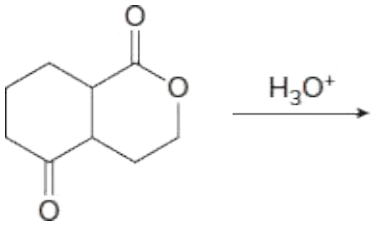

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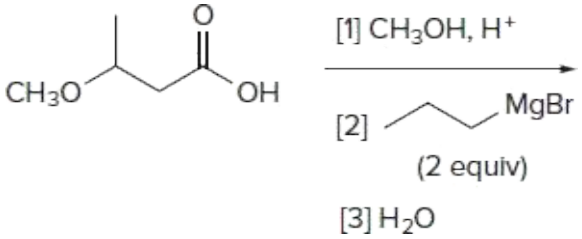

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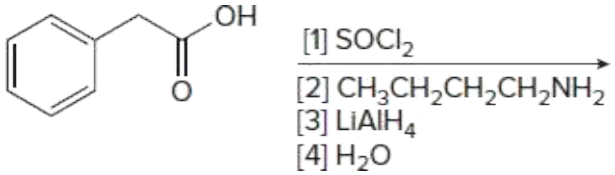
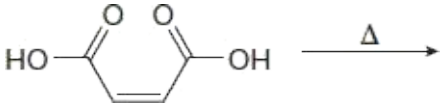
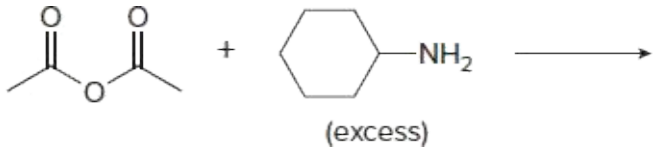


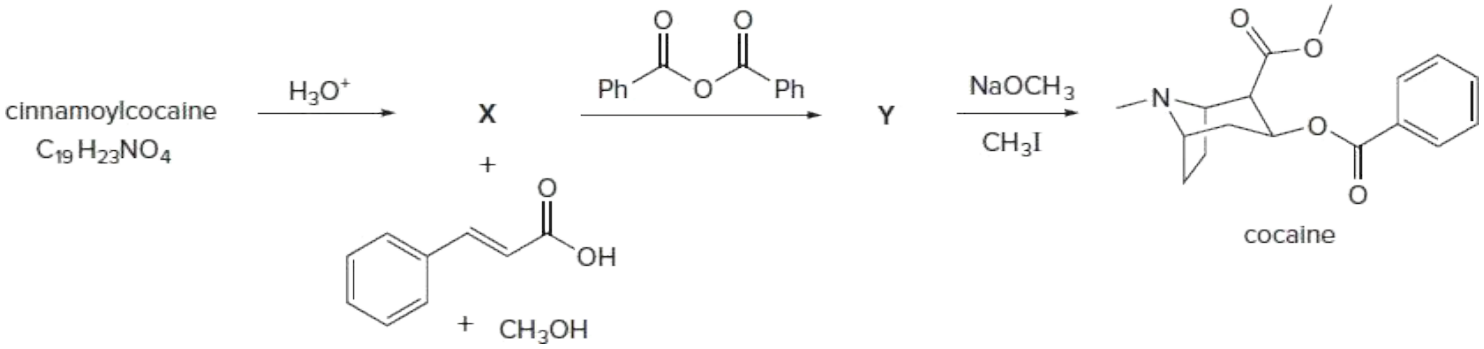
g.



h.

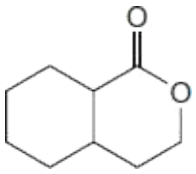


20.41 Cinnamoylcocaine, a natural product that occurs in coca leaves, can be converted to cocaine, the chapter-opening molecule, by the following reaction sequence. Identify the structure of cinnamoylcocaine, as well as intermediates X and Y.

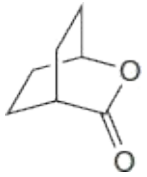


20.42 What products are formed by hydrolysis of each lactone or lactam with acid?

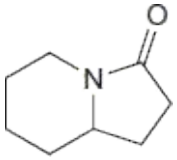
a.



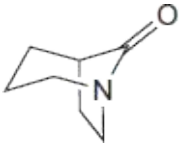
b.



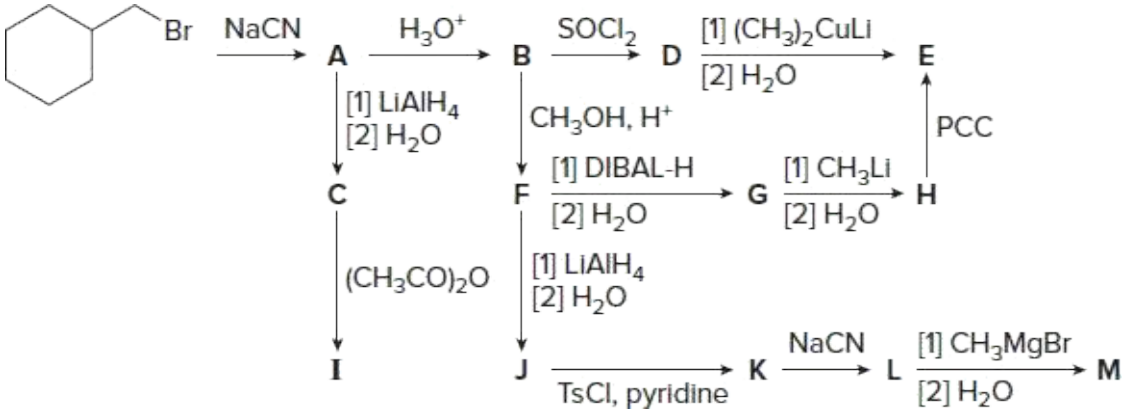
c.



d.

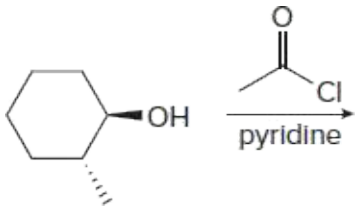


20.43 Identify compounds A-M in the following reaction sequence.

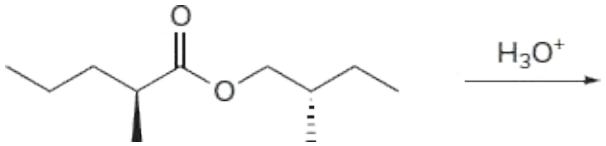


20.44 Draw the products of each reaction and indicate the stereochemistry at any stereogenic centers.

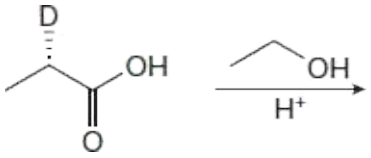
a.



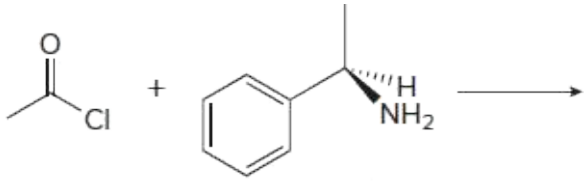
b.



c.



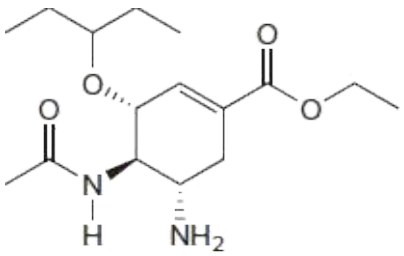
d.



(2 equiv)

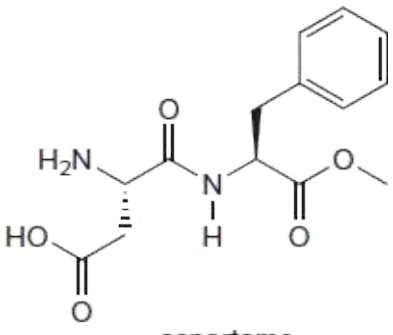
20.45 What products are formed when all of the amide and ester bonds are hydrolyzed in each of the following compounds? Tamiflu [part (a)] is the trade name of the antiviral agent oseltamivir, thought to be the most effective agent in treating influenza. Aspartame [part (b)] is the artificial sweetener used in Equal and many diet beverages. One of the products of this hydrolysis reaction is the amino acid phenylalanine. Infants afflicted with phenylketonuria cannot metabolize this amino acid, so it accumulates, causing mental retardation. When the affliction is identified early, a diet limiting the consumption of phenylalanine (and compounds like aspartame that are converted to it) can make a normal life possible.

a.



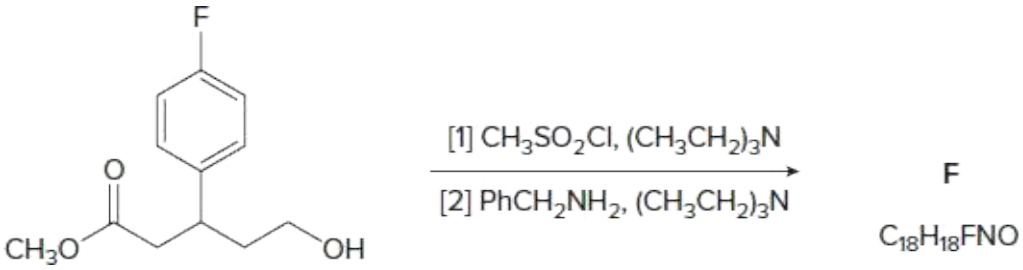
oseltamivir

b.



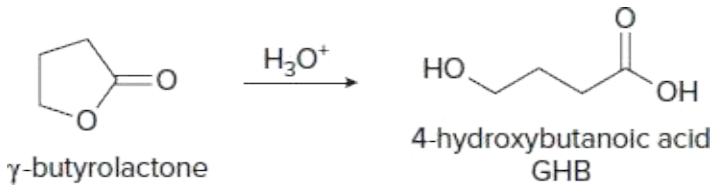
aspartame

20.46 **Identify F in the following reaction sequence. F was converted in several steps to the antidepressant paroxetine (trade name Paxil; see also Problem 9.9).**



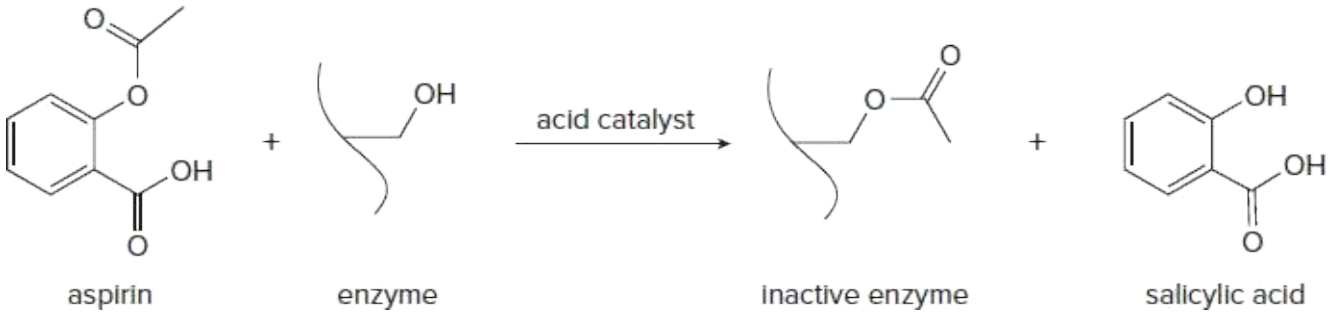
Mechanism

20.47 **Although γ-butyrolactone is a biologically inactive compound, it is converted in the body to 4-hydroxybutanoic acid (GHB), an addictive and intoxicating recreational drug. Draw a stepwise mechanism for this conversion in the presence of acid.**

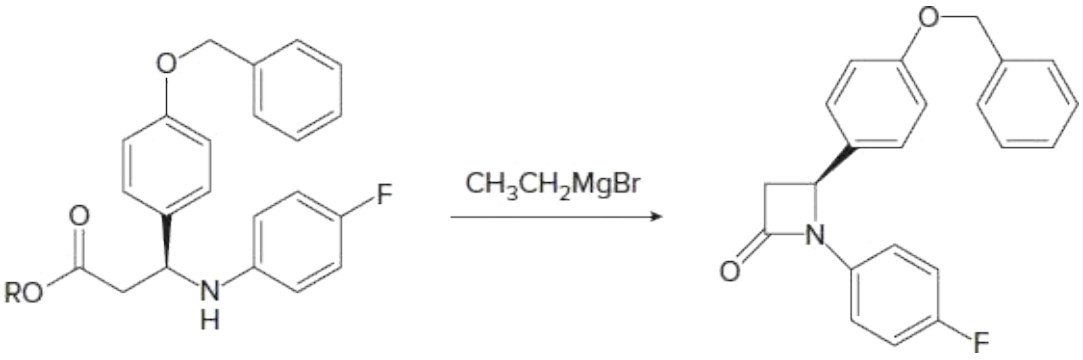


20.48 **Aspirin is an anti-inflammatory agent because it inhibits the conversion of arachidonic acid to prostaglandins by the transfer of its acetyl group (CH_3CO-) to an OH group at the active site of an enzyme (Section 19.5).**

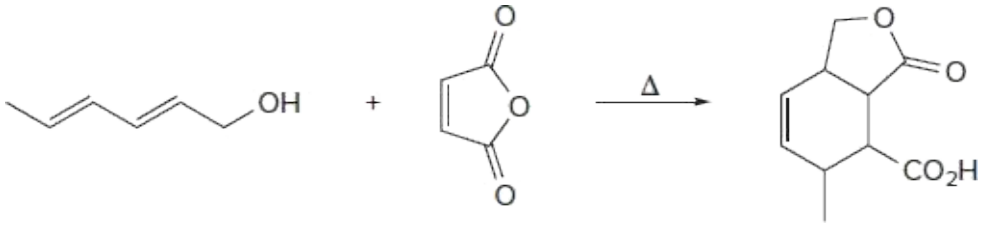
This reaction, called transesterification, results in the conversion of one ester to another by a nucleophilic acyl substitution reaction. Draw a stepwise mechanism for the given transesterification.



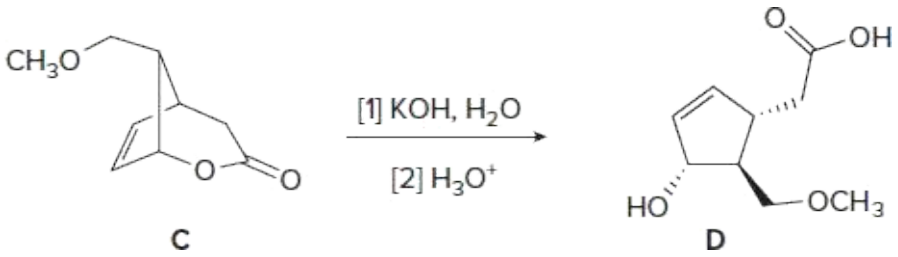
20.49 **Draw a stepwise mechanism for the following reaction, one step in the synthesis of the cholesterol-lowering drug ezetimibe (Section 17.6).**



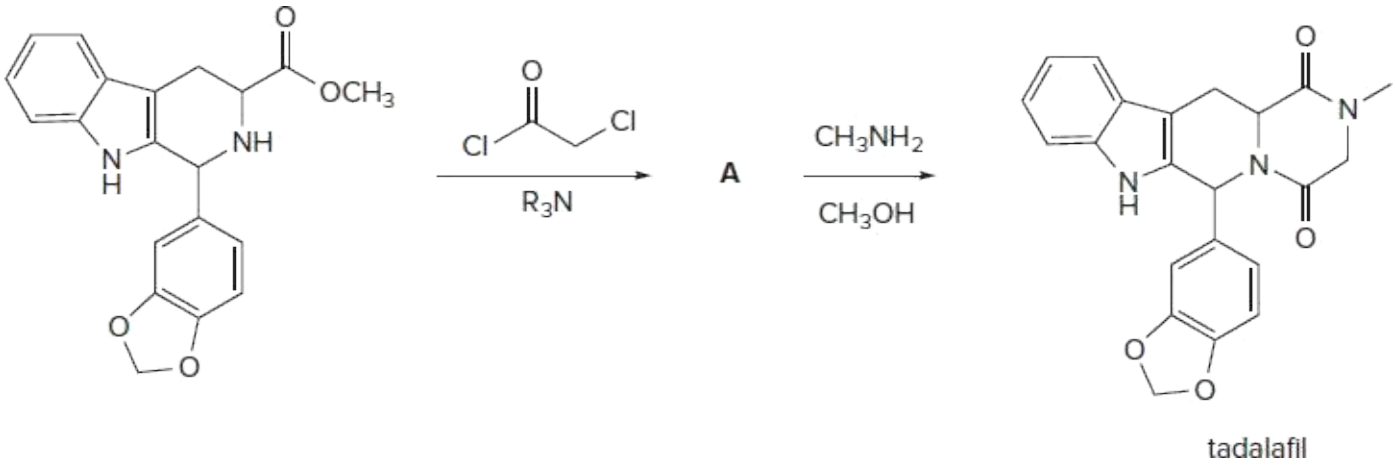
20.50 **Draw a stepwise mechanism for the following reaction, which involves both a Diels–Alder reaction and a nucleophilic acyl substitution.**



20.51 **Draw a stepwise mechanism for the conversion of lactone C to carboxylic acid D. C is a key intermediate in the synthesis of prostaglandins (Section 19.5) by Nobel Laureate E. J. Corey and co-workers at Harvard University.**



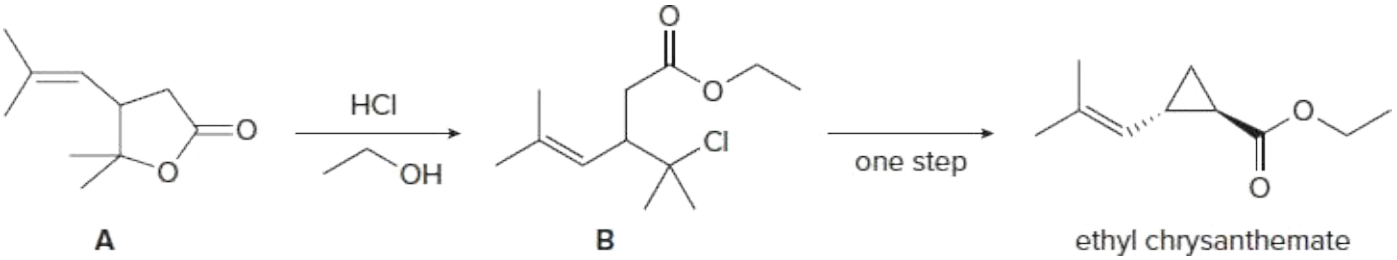
20.52 **Two steps in the synthesis of tadalafil, a drug sold under the trade name Cialis for the treatment of erectile dysfunction, are shown. Identify intermediate A, and draw a mechanism for the conversion of A to tadalafil.**



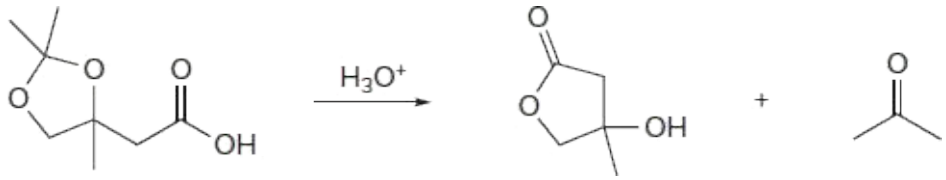
tadalafil

20.53 **Draw a stepwise mechanism for the conversion of lactone A to ester B using HCl in ethanol. B is converted in one step to ethyl chrysanthemate, a useful intermediate in the synthesis of a variety of pyrethrins, naturally**

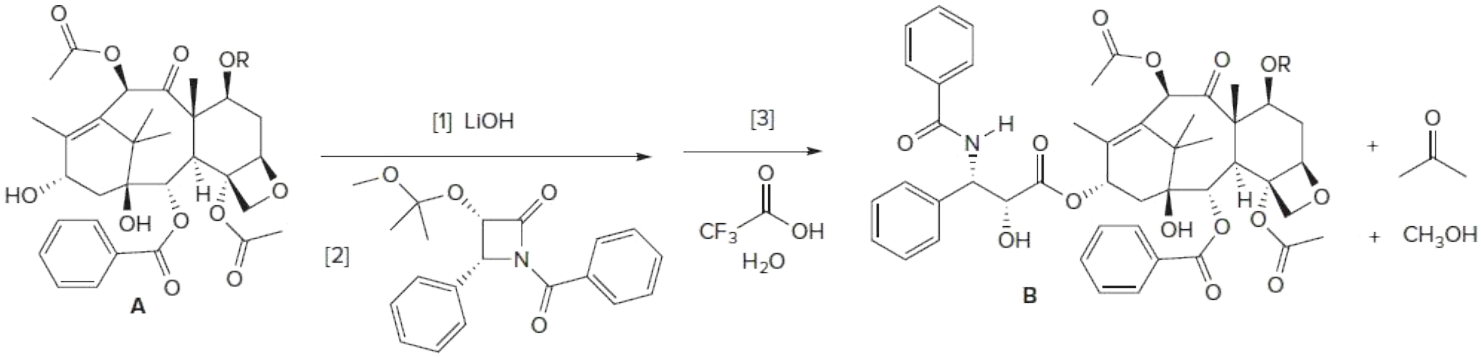
occurring insecticides with three-membered rings that are isolated from chrysanthemums (Section 24.4).



20.54 Draw a stepwise mechanism for the following reaction.



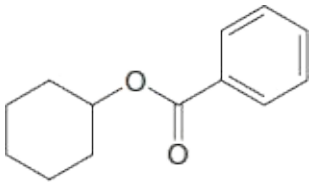
20.55 Three steps in the synthesis of the anticancer drug Taxol (paclitaxel, Chapter 5 opening molecule) involve the conversion of A to B. Draw stepwise mechanisms for Steps [2] and [3] in this reaction scheme.



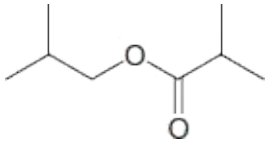
Synthesis

20.56 What carboxylic acid and alcohol are needed to prepare each ester by Fischer esterification?

a.

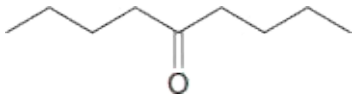


b.

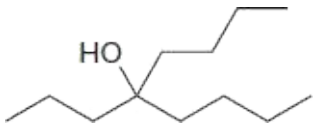


20.57 Devise a synthesis of each compound using 1-bromobutane ($CH_3CH_2CH_2CH_2Br$) as the only organic starting material. You may use any other inorganic reagents.

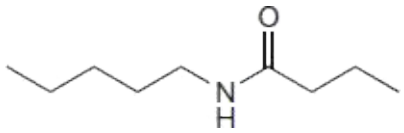
a.



b.



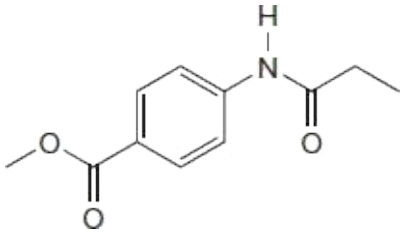
c.



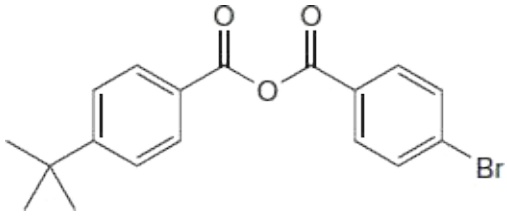
20.58 **Devise a synthesis of benzocaine, ethyl *p*-aminobenzoate ($H_2NC_6H_4CO_2CH_2CH_3$), from benzene, organic alcohols, and any needed organic or inorganic reagents. Benzocaine is the active ingredient in the topical anesthetic Orajel (Section 16.15C).**

20.59 **Devise a synthesis of each compound from benzene and organic alcohols containing four or fewer carbons. You may also use any required organic or inorganic reagents.**

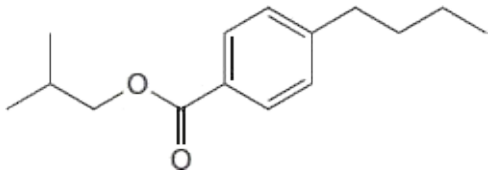
a.



b.

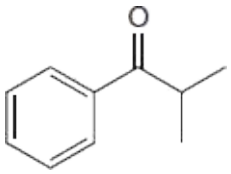


c.

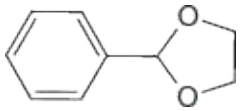


20.60 **How would you convert benzoic acid ($C_6H_5CO_2H$) to each compound?**

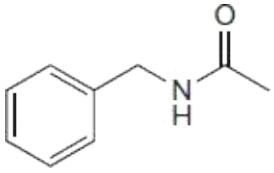
a.

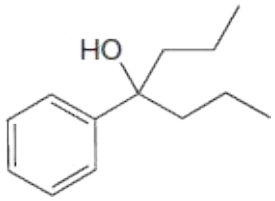


b.



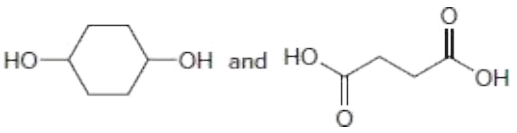
c.

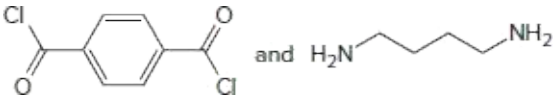


d. 

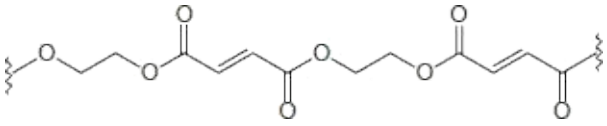
Polymers

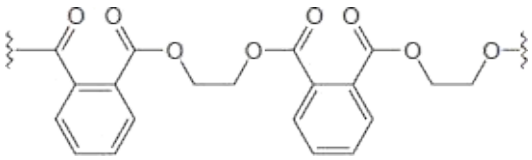
20.61 What polyester or polyamide can be prepared from each pair of monomers?

a. 

b. 

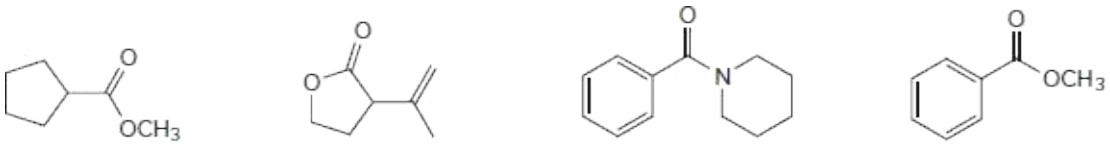
20.62 What two monomers are needed to prepare each polymer?

a. 

b. 

Spectroscopy

20.63 Rank compounds A–D in order of increasing frequency of the C=O absorption in their IR spectra.



A B C D

20.64 Identify the structures of each compound from the given data.

a. Molecular formula $C_6H_{12}O_2$

IR absorption: 1738 cm^{-1}

^{1}H NMR: 1.12 (triplet, 3 H), 1.23 (doublet, 6 H), 2.28 (quartet, 2 H), and 5.00 (septet, 1 H) ppm

b. Molecular formula C_8H_9NO

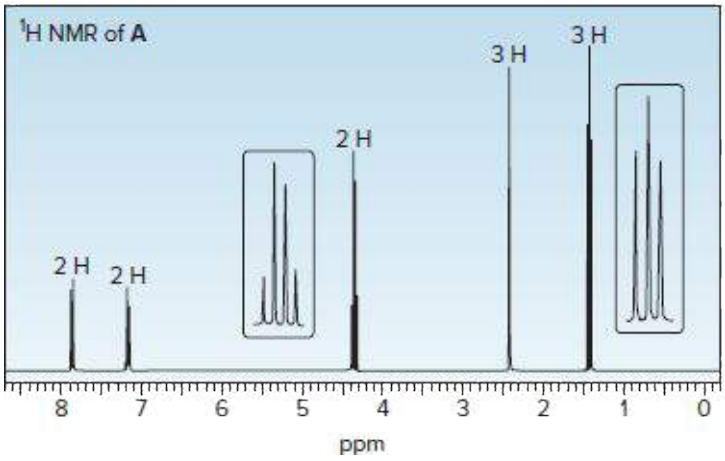
IR absorptions: 3328 and 1639 cm^{-1}

2.95 (singlet, 3 H), 6.95 (singlet, 1 H),

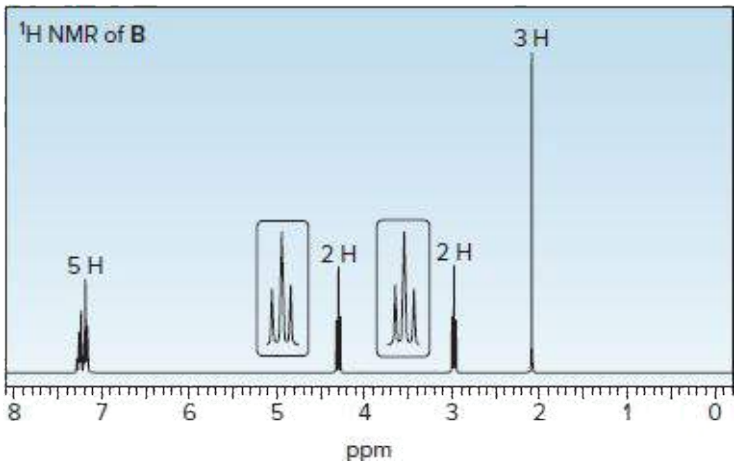
	^{1}H NMR:	**and 7.3–7.7 (multiplet, 5 H) ppm**
c.	**Molecular formula**	**$C_{10}H_{12}O_2$**
	IR absorption:	**1740 cm^{-1}**
	^{1}H NMR:	**1.2 (triplet, 3 H), 2.4 (quartet, 2 H), 5.1 (singlet, 2 H),**
		and 7.1–7.5 (multiplet, 5 H) ppm

20.65 Identify the structures of A and B, isomers of molecular formula $C_{10}H_{12}O_2$, from their IR data and ^{1}H NMR spectra.

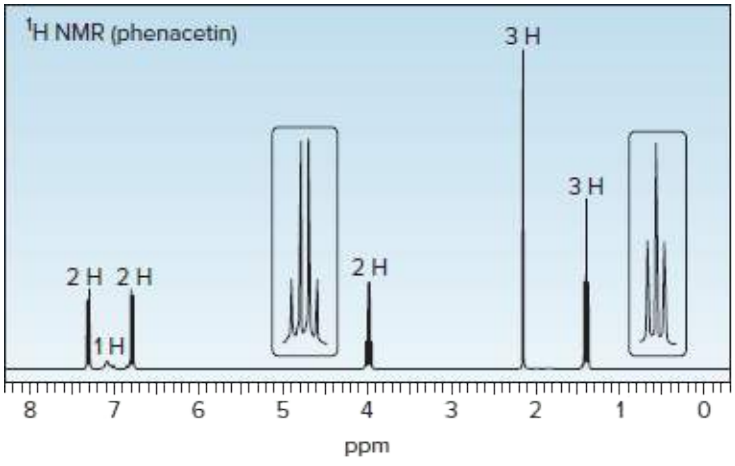
a. IR absorption for A at 1718 cm^{-1}

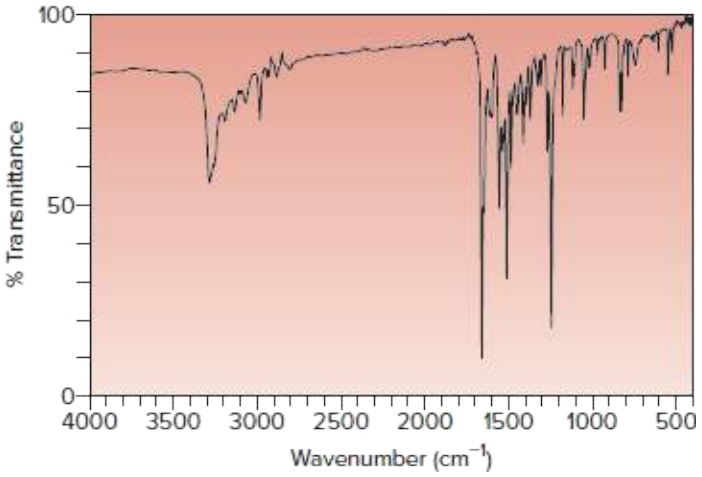


b. IR absorption for B at 1740 cm^{-1}

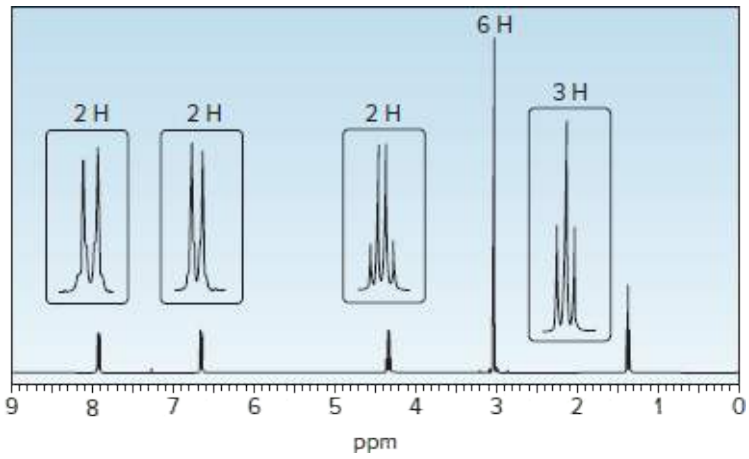


20.66 Phenacetin is an analgesic compound having molecular formula $C_{10}H_{13}NO_2$. Once a common component in over-the-counter pain relievers such as APC (aspirin, phenacetin, caffeine), phenacetin is no longer used because of its liver toxicity. Deduce the structure of phenacetin from its ^{1}H NMR and IR spectra.



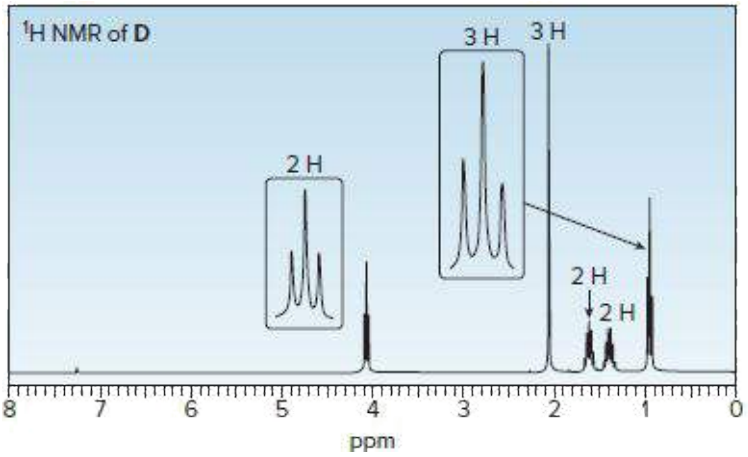


20.67 Identify the structure of compound C (molecular formula $C_{11}H_{15}NO_2$), which has an IR absorption at 1699 cm^{-1} and the ^1H NMR spectrum shown below.

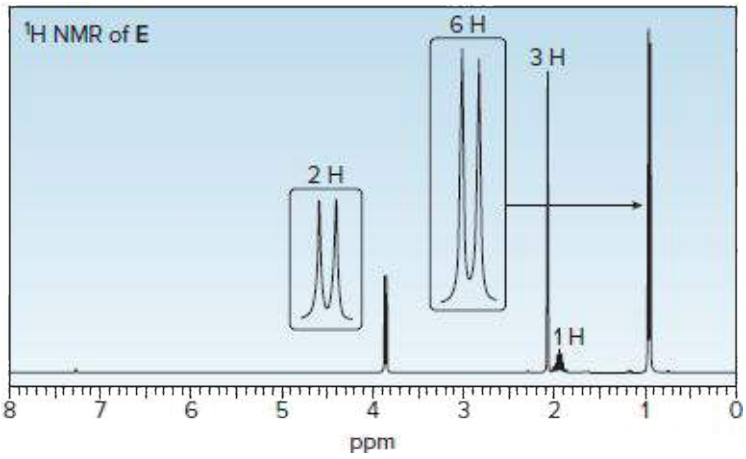


20.68 Identify the structures of D and E, isomers of molecular formula $C_6H_{12}O_2$, from their IR and ^1H NMR data. Signals at 1.35 and 1.60 ppm in the ^1H NMR spectrum of D and 1.90 ppm in the ^1H NMR spectrum of E are multiplets.

a. IR absorption for D at 1743 cm^{-1}

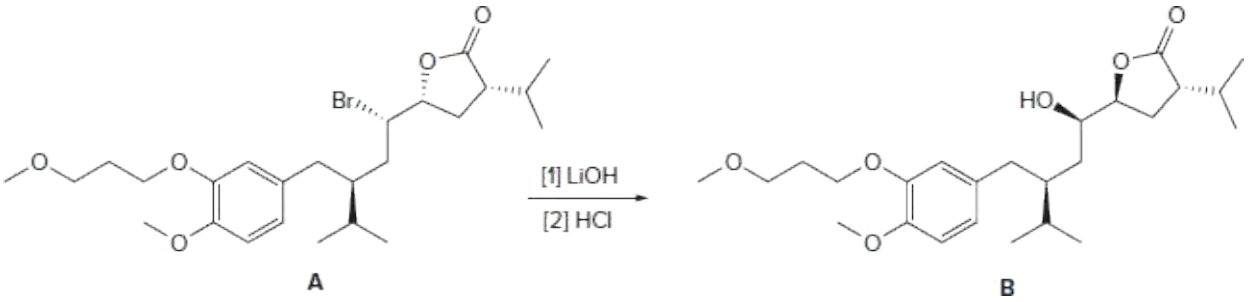


b. IR absorption for E at 1746 cm^{-1}



Challenge Problems

20.69 One step in the synthesis of aliskiren, a drug used to treat hypertension (Problems 5.7 and 12.61), involves the conversion of A to B. Draw a stepwise mechanism for this process that explains the observed stereochemistry.

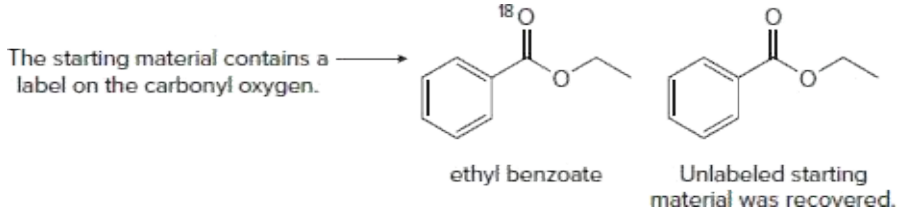


20.70 With reference to amides A and B, the carbonyl of one amide absorbs at a much higher wavenumber in its IR spectrum than the carbonyl of the other amide. Which absorbs at a higher wavenumber and why?

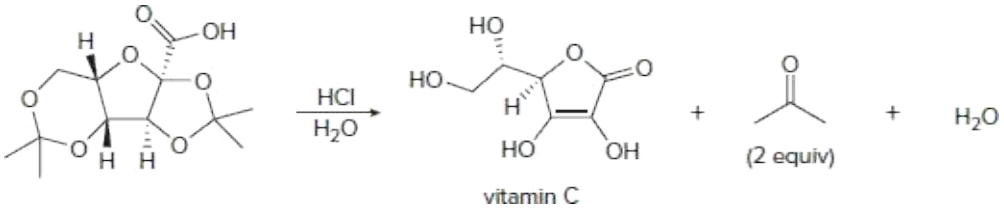
20.71 The ^{1}H NMR spectrum of 2-chloroacetamide ($ClCH_2CONH_2$) shows three signals at 4.02, 7.35, and 7.60 ppm. What protons give rise to each signal? Explain why three signals are observed.

20.72 Compelling evidence for the existence of a tetrahedral intermediate in nucleophilic acyl substitution was obtained in a series of elegant experiments carried out by Myron Bender in 1951. The key experiment was the reaction of aqueous ^{-}OH with ethyl benzoate ($C_6H_5COOCH_2CH_3$) labeled at the carbonyl oxygen with ^{18}O. Bender did not allow the hydrolysis to go to completion, and then examined the presence of a label in the *recovered starting material.* He found that some of the recovered ethyl benzoate no longer contained a label at the carbonyl oxygen. With reference to the accepted mechanism of nucleophilic acyl

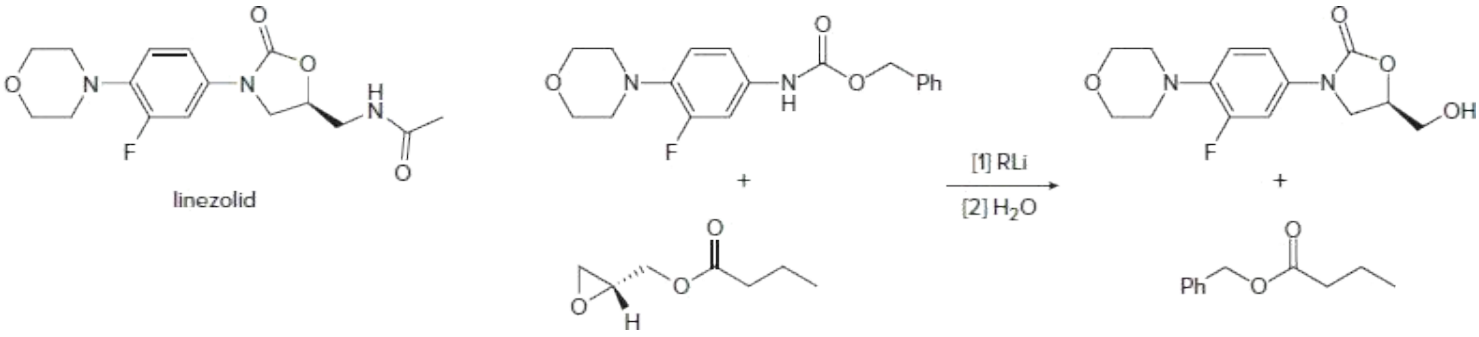
substitution, explain how this provides evidence for a tetrahedral intermediate.



20.73 Draw a stepwise mechanism for the following reaction, the last step in a five-step industrial synthesis of vitamin C that begins with the simple carbohydrate glucose.

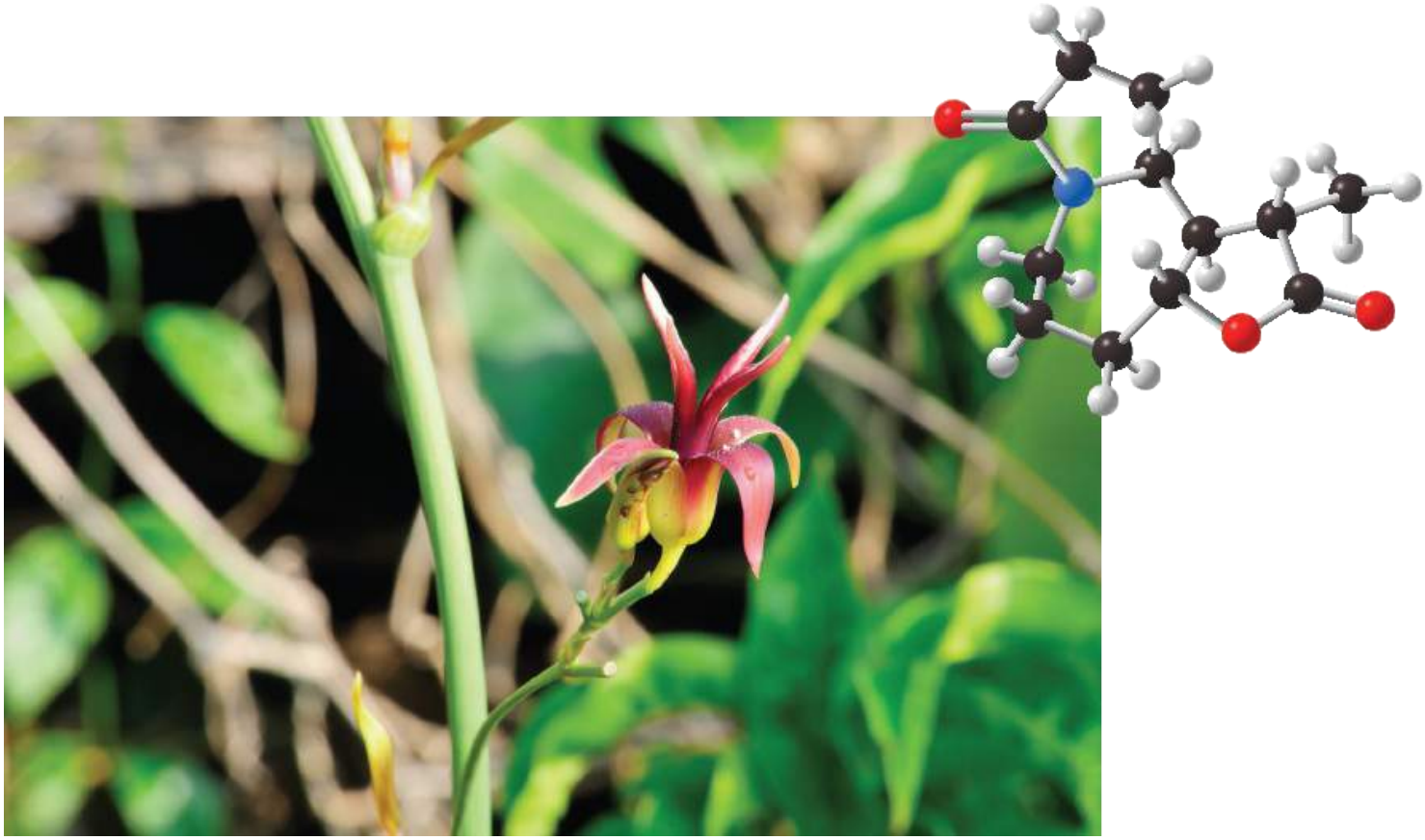


20.74 Draw a stepwise mechanism for the following reaction, a key step in the synthesis of linezolid, an antibacterial agent.



Substitution Reactions of Carbonyl Compounds at the α Carbon

21



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21.1 Introduction

21.2 Enols

21.3 Enolates

21.4 Enolates of unsymmetrical carbonyl compounds

21.5 Racemization at the α carbon

21.6 A preview of reactions at the α carbon

21.7 Halogenation at the α carbon

21.8 Direct enolate alkylation

21.9 Malonic ester synthesis

21.10 Acetoacetic ester synthesis

Stemoamide is an amide isolated from the roots of *Stemona tuberosa*, a flowering plant native to China, Southeast Asia, and New Guinea. Extracts from *Stemona tuberosa* have been used in traditional Chinese medicine for treatment of bronchitis and other respiratory illnesses. Stemoamide was isolated in 1992, and its structure was determined by NMR and IR spectroscopy. Stemoamide has been synthesized in the laboratory by several research groups. The last step in a 2011 synthesis involved enolate alkylation, a substitution reaction discussed in Chapter 21.

Why Study…

Reactions at the α Carbon of a Carbonyl Group?

Chapters 21 and 22 focus on reactions that occur at the α carbon to a carbonyl group. These reactions are different from the reactions of Chapters 17, 18, and 20, all of which involved nucleophilic attack at the electrophilic carbonyl carbon. In reactions at the α carbon, the carbonyl compound serves as a *nucleophile* that reacts with a carbon or halogen electrophile to form a new bond to the α carbon.

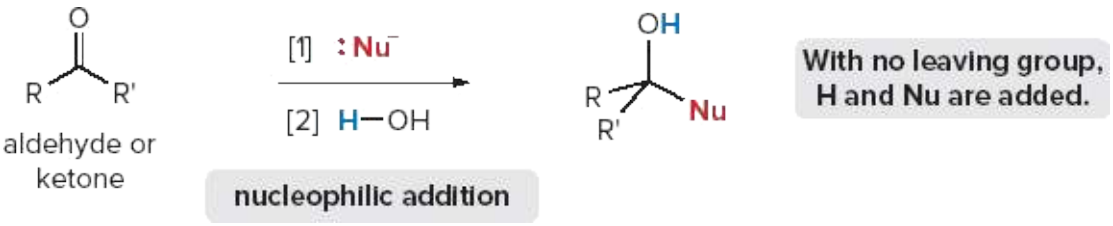
Chapter 21 concentrates on substitution reactions at the α carbon, whereas Chapter 22 concentrates on reactions between two carbonyl compounds, one of which serves as the nucleophile and one of which is the electrophile. Many of the reactions in Chapter 21 form new carbon–carbon bonds, thus adding to your repertoire of reactions that can be used to synthesize more-complex organic molecules from simple precursors. As you will see, the reactions introduced in Chapter 21 have been used to prepare a wide variety of interesting and useful compounds.

21.1 Introduction

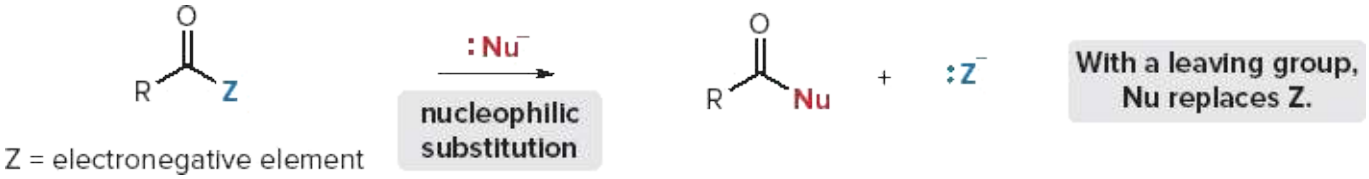
Up to now, the discussion of carbonyl compounds has centered on their reactions with nucleophiles at the electrophilic carbonyl carbon. Two general reactions are observed, depending on the structure of the carbonyl starting material.

- ***Nucleophilic addition* occurs when there is no electronegative atom Z**

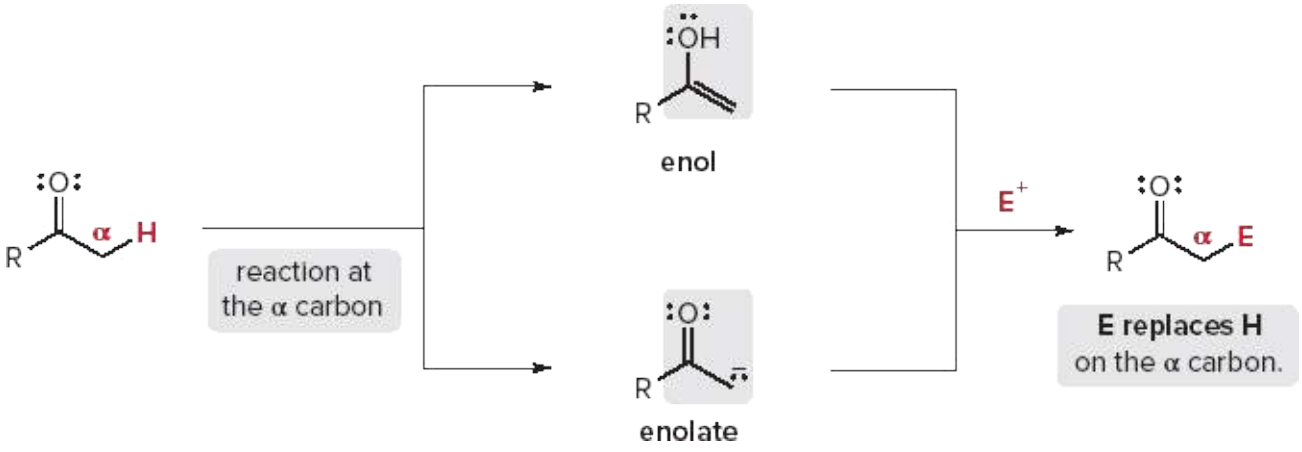
on the carbonyl carbon (as with aldehydes and ketones).



- ***Nucleophilic acyl substitution*** **occurs when there is an electronegative atom Z on the carbonyl carbon (as with carboxylic acids and their derivatives).**



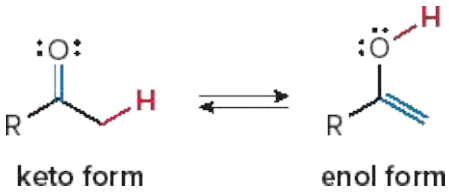
Reactions can also occur at the α carbon to the carbonyl group. These reactions proceed by way of enols or enolates, two electron-rich intermediates that react with electrophiles, forming a new bond on the α carbon. This reaction results in the substitution of the electrophile E for hydrogen.



Hydrogen atoms on the α carbon are called α hydrogens.

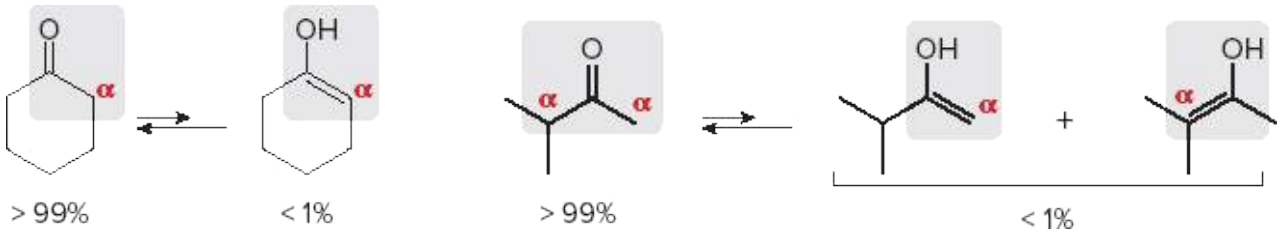
21.2 Enols

Recall from Chapter 11 that enol and keto forms are tautomers of the carbonyl group that differ in the position of a double bond and a proton. These constitutional isomers are in equilibrium with each other.

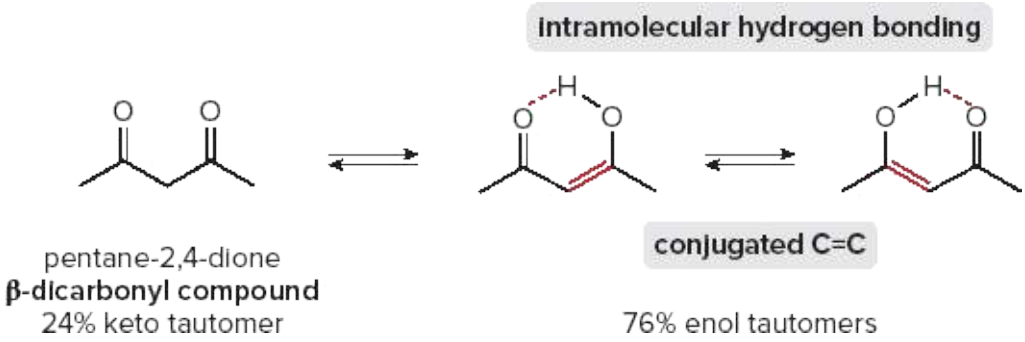


- **A keto tautomer has a C=O and an additional C–H bond.**
- **An enol tautomer has an O–H group bonded to a C=C.**

Equilibrium favors the keto form for most carbonyl compounds largely because a C=O is much stronger than a C=C. For simple carbonyl compounds, < 1% of the enol is present at equilibrium. With unsymmetrical ketones, moreover, two different enols are possible, yet they still total < 1%.



With compounds containing two carbonyl groups separated by a single carbon (called β-dicarbonyl compounds or 1,3-dicarbonyl compounds), however, the concentration of the keto form sometimes exceeds the concentration of the keto form.

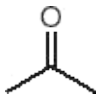


Two factors stabilize the enol of β-dicarbonyl compounds: conjugation and intramolecular hydrogen bonding. The C=C of the enol is conjugated with the carbonyl group, allowing delocalization of the electron density in the π bonds. Moreover, the OH of the enol can hydrogen bond to the oxygen of the nearby carbonyl group. Such intramolecular hydrogen bonds are especially stabilizing when they form a six-membered ring, as in this case.

Sample Problem 21.1 Interconverting Keto and Enol Tautomers

Convert each compound to its enol or keto tautomer.

a.

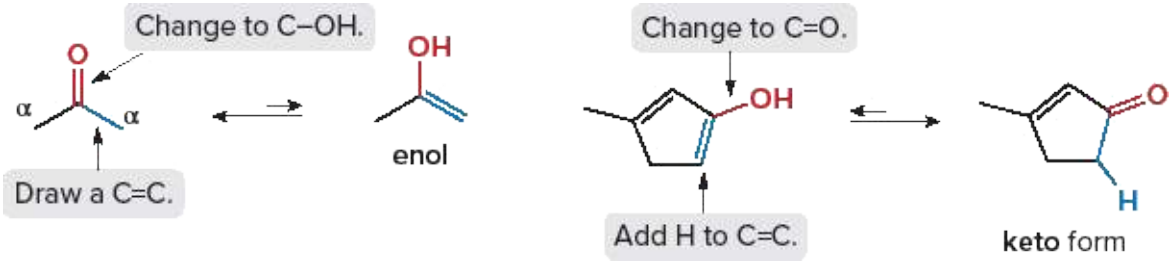


b.

Solution

a. To convert a carbonyl compound to its enol tautomer, draw a double bond between the carbonyl carbon and the α carbon, and change the C=O to C–OH. In this case, both α carbons are identical, so only one enol is possible.

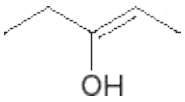
b. To convert an enol to its keto tautomer, change the C–OH to C=O and add a proton to the other end of the C=C.



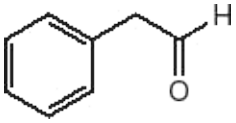
Problem 21.1

Draw the enol or keto tautomer(s) of each compound.

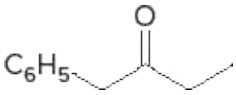
a.



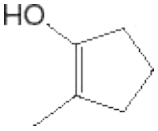
b.



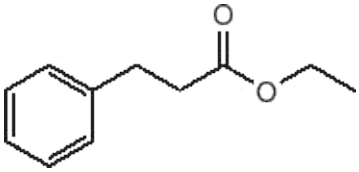
c.



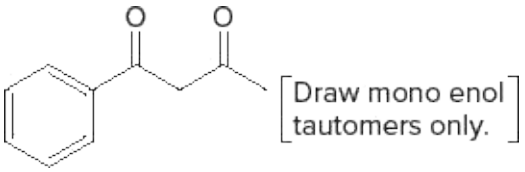
d.



e.



f.

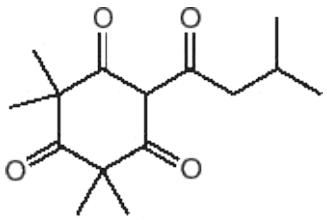


More Practice:

Try Problems 21.30, 21.32, 21.33, 21.38a, 21.40.

Problem 21.2

Leptospermone is a herbicide produced by the bottlebrush plant. Draw all possible mono enol tautomers of leptospermone, ignoring stereoisomers. Determine if all the tautomers are similar in stability, or if one tautomer is more or less stable than the others.



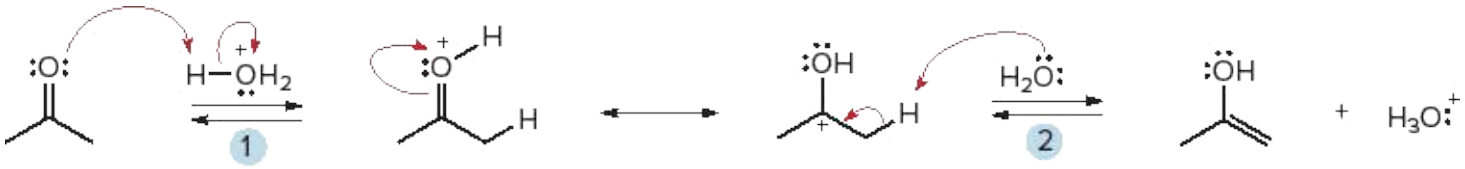
leptospermone

Callistimon citrinus*, commonly called bottlebrush, is a plant native to Australia and the source of leptospermone (Problem 21.2). ©*Rafael Santos Rodriguez/Shutterstock

21.2A The Mechanism of Tautomerization

Tautomerization, the process of converting one tautomer to another, is catalyzed by both acid and base. Tautomerization always requires two steps (protonation and deprotonation), but the order of these steps depends on whether the reaction takes place in acid or base. In Mechanisms 21.1 and 21.2 for tautomerization, the keto form is converted to the enol form. All of the steps are reversible, though, so they equally apply to the conversion of the enol form to the keto form.

Mechanism 21.1 Tautomerization in Acid



1 **With acid, protonation *precedes* deprotonation. Protonation of the carbonyl forms a resonance-stabilized carbocation.**

2 **Removal of a proton forms the enol.**

Mechanism 21.2 Tautomerization in Base

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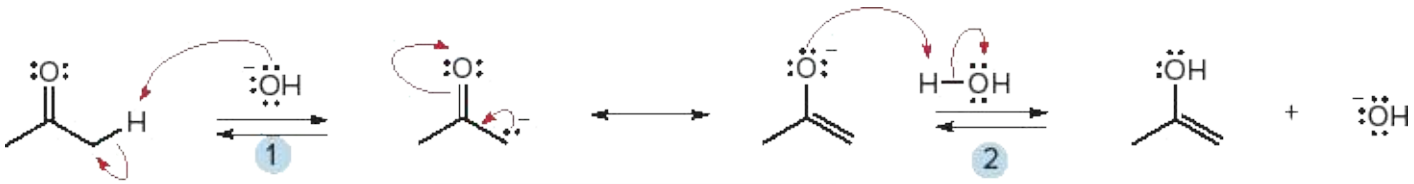
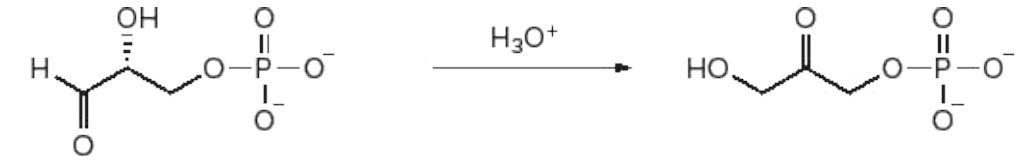


1 **With base, deprotonation *precedes* protonation. Removal of a proton on the α carbon forms a resonance-stabilized enolate.**

2 **Protonation of the enolate forms the enol.**

Problem 21.3

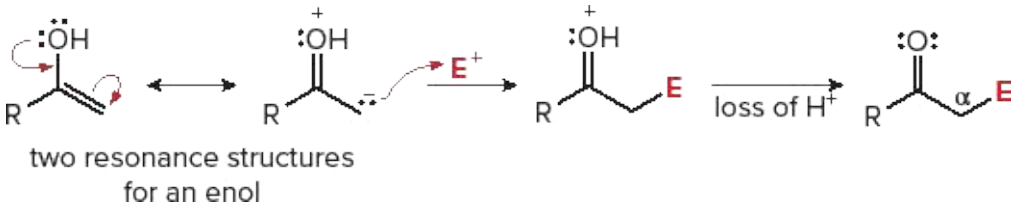
During the metabolism of glucose, glyceraldehyde 3-phosphate is converted to dihydroxyacetone phosphate by a process that involves two keto–enol tautomerizations. Draw a stepwise mechanism for this reaction in the presence of acid.



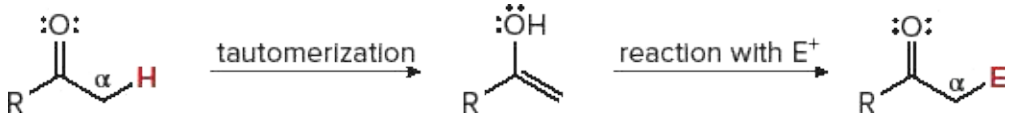
21.2B How Enols React

Like other compounds with carbon–carbon double bonds, enols are electron rich, so they react as nucleophiles. Enols are even more electron rich than alkenes, though, because the OH group has a powerful electron-donating resonance effect. A second resonance structure can be drawn for the enol that places a negative charge on one of the carbon atoms. As a result, this carbon atom is especially nucleophilic, and it can

react with an electrophile E^+ to form a new bond to carbon. Loss of a proton then forms a neutral product.



- **Reaction of an enol with an electrophile E^+ forms a new C–E bond on the α carbon. The net result is substitution of H by E on the α carbon.**



Problem 21.4

When phenylacetaldehyde ($C_6H_5CH_2CHO$) is dissolved in D_2O with added DCl, the hydrogen atoms α to the carbonyl are gradually replaced by deuterium atoms. Write a mechanism for this process that involves enols as intermediates.

21.3 Enolates

Enolates are formed when a base removes a proton on the α carbon to a carbonyl group. A C–H bond on the α carbon is more acidic than many other sp^3 hybridized C–H bonds, because the resulting enolate is resonance stabilized. Moreover, one of the resonance structures is especially stable because it places a negative charge on an electronegative oxygen atom.

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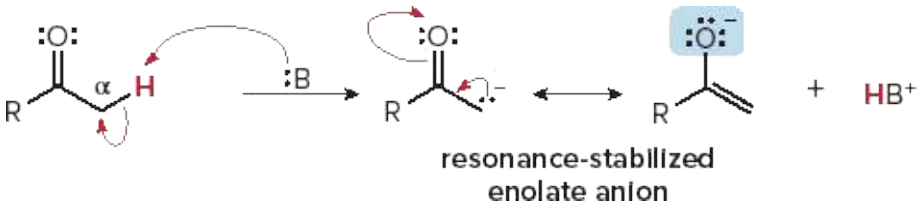
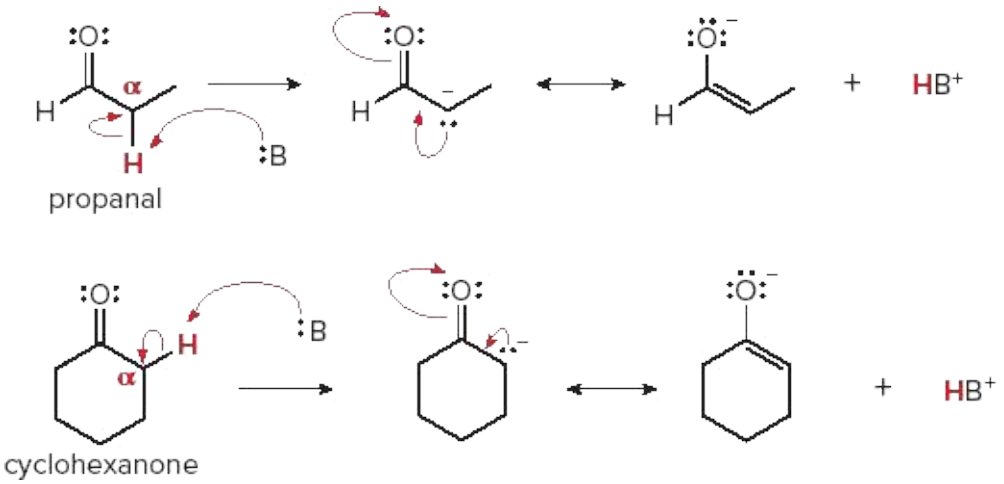
Forming enolates from carbonyl compounds was first discussed in Section 18.6.

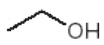
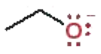
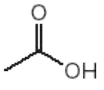


Enolates are always formed by removal of a proton on the α carbon.



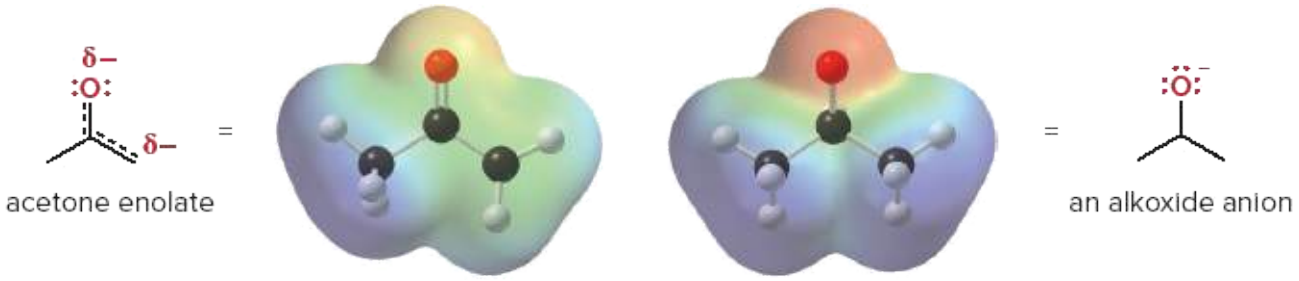
The pK_a of the α hydrogen in an aldehyde or ketone is ~20. As shown in Table 21.1, this makes it considerably more acidic than the C–H bonds in CH_3CH_3 and $CH_3CH{=}CH_2$. Although C–H bonds α to a carbonyl are *more acidic* than many other C–H bonds, they are still *less acidic* than O–H bonds that always place the negative charge of the conjugate base on an electronegative oxygen atom (c.f. CH_3CH_2OH and CH_3COOH in Table 21.1).

Table 21.1 A Comparison of pK_a Values

	Compound	pK_a	Conjugate base	Structural features of the conjugate base
Increasing acidity Increasing stability of the conjugate base	CH_3CH_3	50	$CH_3\ddot{C}H_2$	• The conjugate base has a (–) charge on C, but is not resonance stabilized.
		43		• The conjugate base has a (–) charge on C, and is resonance stabilized.
		19.2		• **The conjugate base has two resonance structures, one of which has a (–) charge on O.**
		16		• The conjugate base has a (–) charge on O, but is not resonance stabilized.
		4.8		• The conjugate base has two resonance structures, both of which have a (–) charge on O.

- **Resonance stabilization of the conjugate base *increases* acidity.**
  - $CH_2{=}CHCH_3$ is more acidic than CH_3CH_3.
  - CH_3COOH is more acidic than CH_3CH_2OH.
- **Placing a negative charge on O in the conjugate base *increases* acidity.**
  - CH_3CH_2OH is more acidic than CH_3CH_3.
  - CH_3COCH_3 is more acidic than $CH_2{=}CHCH_3$.
  - CH_3COOH (with two O atoms) is more acidic than CH_3COCH_3.

The electrostatic potential plots in Figure 21.1 compare the electron density of the acetone enolate, which is resonance stabilized and delocalized, with that of $(CH_3)_2CHO^-$, an alkoxide that is not resonance stabilized.

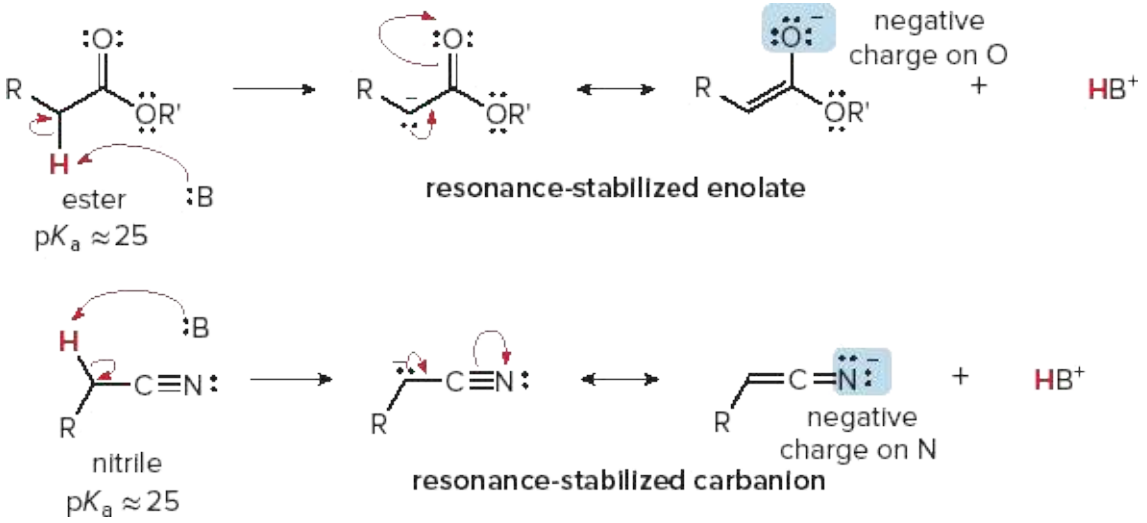


- **The acetone enolate is resonance stabilized.** The negative charge is delocalized on the oxygen atom (pale red) and the carbon atom (pale green).
- **The alkoxide anion is *not* resonance stabilized.** The negative charge is concentrated on the oxygen atom only (deep red).

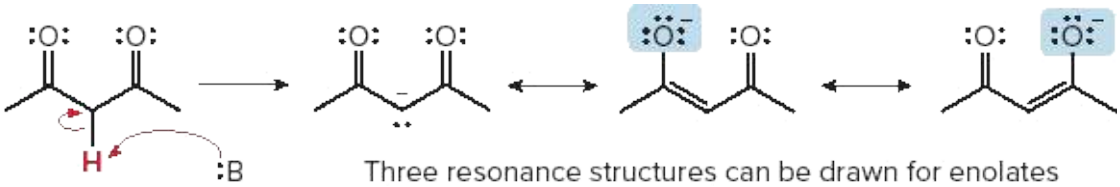
Figure 21.1 **Electron density in an enolate and an alkoxide**

21.3A Examples of Enolates and Related Anions

In addition to enolates from aldehydes and ketones, enolates from esters and 3° amides can be formed, although the α hydrogen is somewhat less acidic. Nitriles also have acidic protons on the carbon atom adjacent to the cyano group, because the negative charge of the conjugate base is stabilized by delocalization onto an electronegative nitrogen atom.



The protons on the carbon between the two carbonyl groups of a β-dicarbonyl compound are especially acidic because resonance delocalizes the negative charge on two different oxygen atoms. Table 21.2 lists pK_a values for β-dicarbonyl compounds as well as other carbonyl compounds and nitriles.



pentane-2,4-dione
$pK_a = 9$

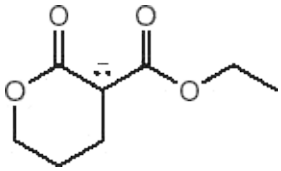
β-dicarbonyl compound

Three resonance structures can be drawn for enolates derived from β-dicarbonyl compounds.

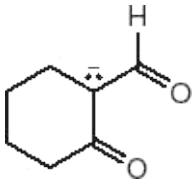
Problem 21.5

Draw additional resonance structures for each anion.

a.



b.



c.

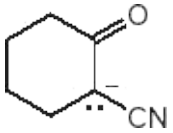


Table 21.2 pK_a Values for Some Carbonyl Compounds and Nitriles

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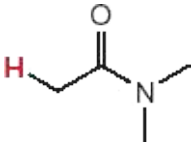
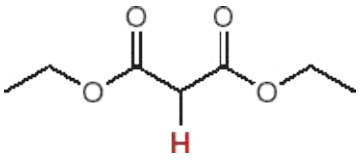
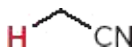
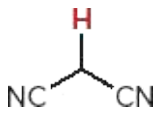
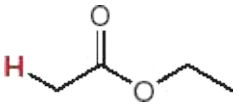
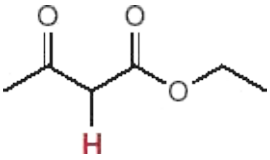
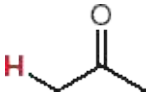
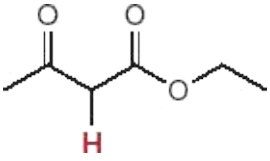
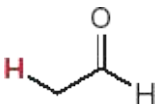
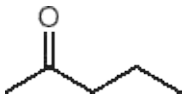
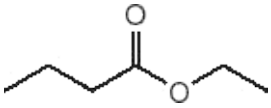
Compound type	Example	pK_a	Compound type	Example
[1] Amide		30	[6] 1,3-Diester	
[2] Nitrile		25	[7] 1,3-Dinitrile	
[3] Ester		25	[8] β-Keto ester	
[4] Ketone		19.2	[9] β-Diketone	
[5] Aldehyde		17		

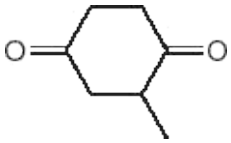
Problem 21.6

Which C–H bonds in the following molecules are acidic because the resulting conjugate base is resonance stabilized?

a. 

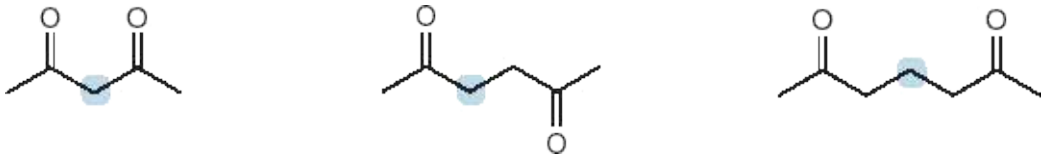
b.

c. 

d. 

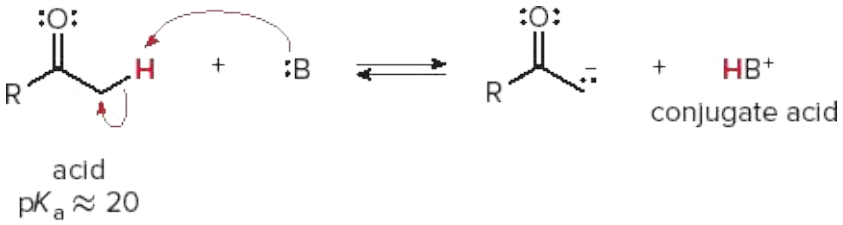
Problem 21.7

Rank the protons in the labeled CH_2 groups in order of increasing acidity, and explain why you chose this order.



21.3B The Base

The formation of an enolate is an acid–base equilibrium, so the *stronger* the base, the *more* enolate that forms.



***Stronger* bases drive the equilibrium to the *right*.**

We can predict the extent of an acid–base reaction by comparing the pK_a of the starting acid (the carbonyl compound in this case) with the pK_a of the conjugate acid formed. The equilibrium favors the side with the *weaker* acid (the acid with the *higher* pK_a value). The pK_a of many carbonyl compounds is ~20, so a significant amount of enolate will form only if the pK_a of the conjugate acid is > 20.

We have now used the term *amide* in two different ways–first

as a functional group ($RCONH_2$) and now as a base (e.g., $^-NH_2$, which can be purchased as a sodium or lithium salt, NaNH2 or LiNH2, respectively). In Chapter 21 we will use dialkylamides, $^-NR_2$, in which the two H atoms of $^-NH_2$ have been replaced by R groups.

Enolate formation with LDA is typically carried out at −78 °C, a convenient temperature to maintain in the laboratory because it is the temperature at which dry ice (solid CO_2) sublimes. Immersing a reaction flask in a cooling bath containing dry ice and acetone keeps its contents at a constant low temperature.

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The common bases used to form enolates are hydroxide (^-OH), various alkoxides (^-OR), hydride (H^-), and dialkylamides ($^-NR_2$). How much enolate is formed using each of these bases is indicated in Table 21.3.

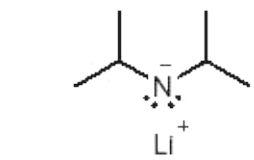
Table 21.3 Enolate Formation with Various Bases: $RCOCH_3$ ($pK_a \approx 20$) + $B: \rightarrow RCOCH_2^- + HB^+$

	Base (B:)	Conjugate acid (HB^+)	pK_a of HB^+	% Enolate
[1]	$Na^+ {}^-OH$	H_2O	15.7	< 1%
[2]	$Na^+ {}^-OCH_2CH_3$	CH_3CH_2OH	16	< 1%
[3]	$K^+ {}^-OC(CH_3)_3$	$(CH_3)_3COH$	18	1–10%
[4]	Na^+H^-	H_2	35	100%
[5]	Li^+	$HN[CH(CH_3)_2]_2$	40	100%

$^{-}N[CH(CH_3)_2]_2$

When the pK_a of the conjugate acid is < 20, as it is for $^{-}$OH and all $^{-}$OR (entries 1–3), only a small amount of enolate is formed at equilibrium. These bases are more useful in forming enolates when more acidic 1,3-dicarbonyl compounds are used as starting materials. They are also used when both the enolate and the carbonyl starting material are involved in the reaction, as is the case for reactions described in Chapter 22.

To form an enolate in essentially 100% yield, a much stronger base such as lithium diisopropylamide, $Li^+ {}^{-}N[CH(CH_3)_2]_2$, abbreviated as LDA, is used (entry 5). LDA is a strong nonnucleophilic base. Like the other nonnucleophilic bases (Sections 7.8B and 8.1), its bulky isopropyl groups make the nitrogen atom too hindered to serve as a nucleophile. It is still able, though, to remove a proton in an acid–base reaction.

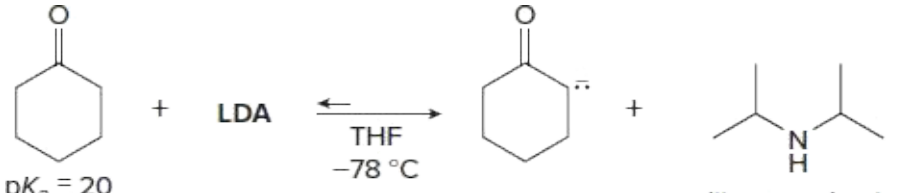


lithium diisopropylamide

LDA

The N atom is too crowded to be a nucleophile.

LDA quickly deprotonates essentially all of the carbonyl starting material, even at −78 °C, to form the enolate product. THF is the typical solvent for these reactions.

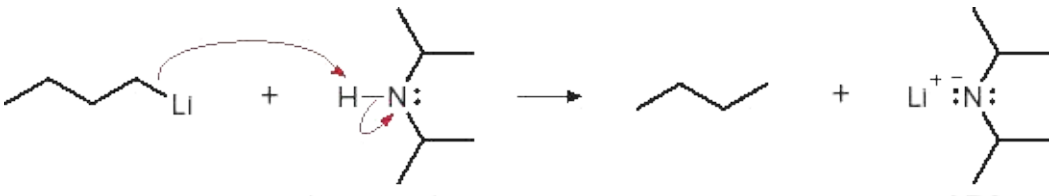


pK_a = 20

diisopropylamine
pK_a = 40

Equilibrium greatly favors the products.
Essentially all of the ketone is converted to enolate.

LDA can be prepared by deprotonating diisopropylamine with an organolithium reagent such as butyllithium, and then used immediately in a reaction.



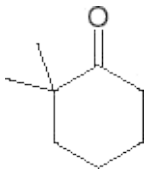
diisopropylamine

LDA

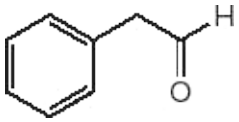
Problem 21.8

Draw the product formed when each starting material is treated with LDA in THF solution at −78 °C.

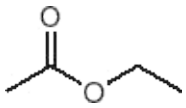
a.



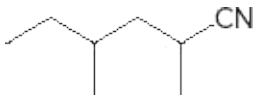
b.



c.



d.

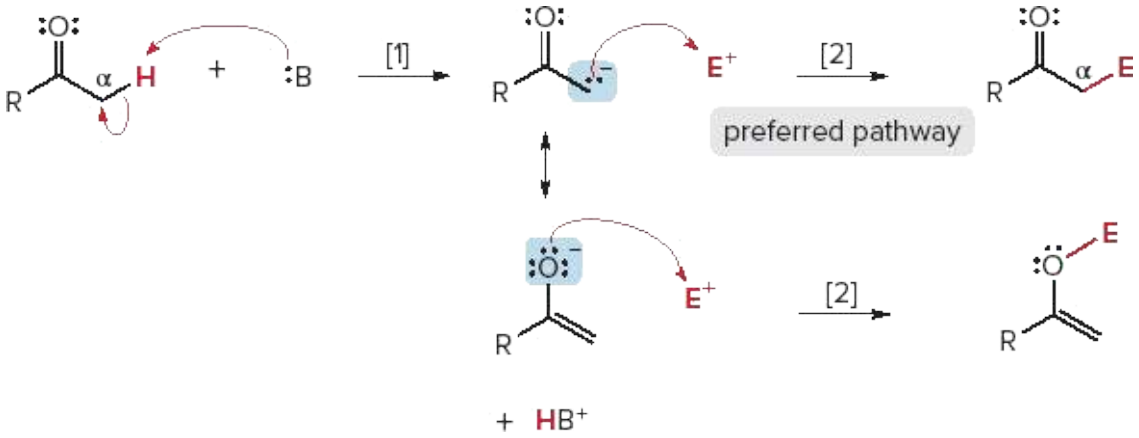


Problem 21.9

As we learned in Chapter 17, organolithium reagents (RLi) are strong bases that readily react with acidic protons. Why aren't organolithium reagents used to generate enolates?

21.3C General Reactions of Enolates

Enolates are nucleophiles, and as such they react with many electrophiles. Because an enolate is resonance stabilized, however, it has two reactive sites—the carbon and oxygen atoms that bear the negative charge. A nucleophile with two reactive sites is called an *ambident nucleophile*. In theory, each of these atoms could react with an electrophile to form two different products, one with a new bond to carbon and one with a new bond to oxygen.



Because enolates usually react at carbon instead of oxygen, the resonance structure that places the negative charge on

oxygen will often be omitted in multistep mechanisms.

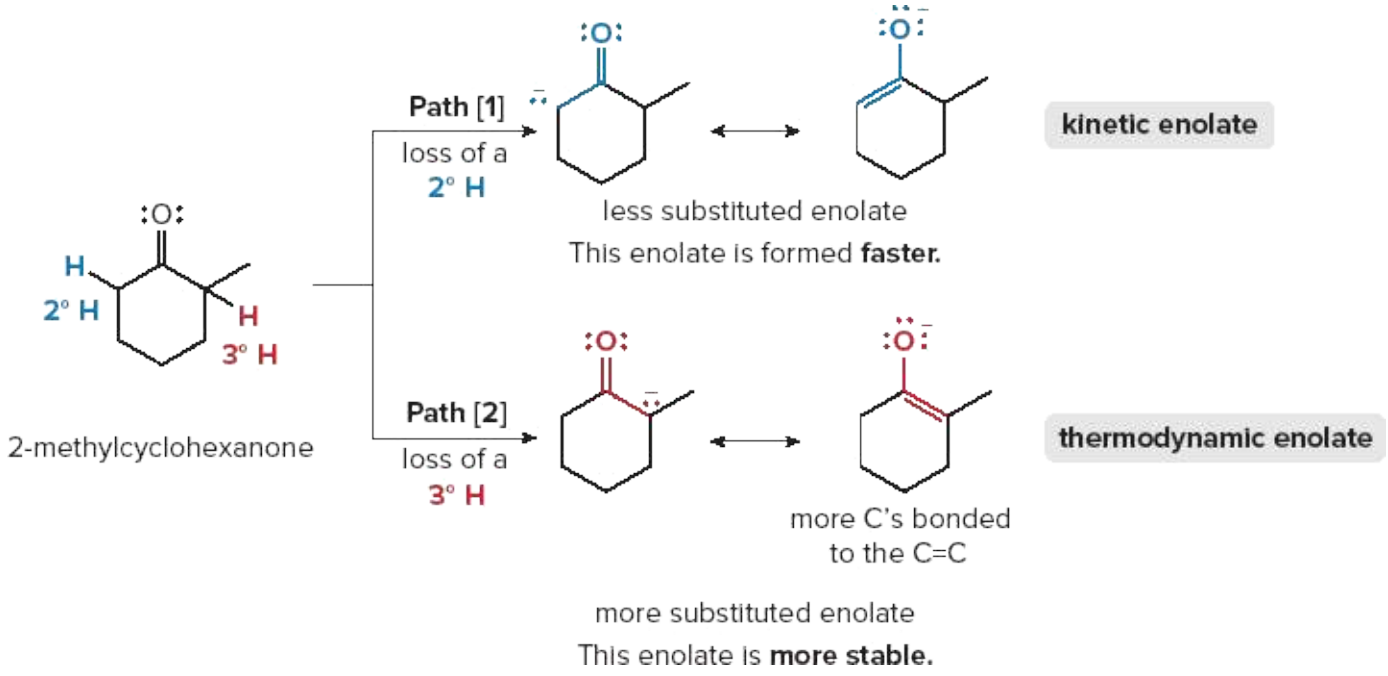
An enolate usually reacts at the carbon end, however, because this site is more nucleophilic. Thus, enolates generally react with electrophiles on the α carbon, so that many reactions in Chapter 21 follow a two-step path:

[1] Reaction of a carbonyl compound with base forms an enolate.

[2] Reaction of the enolate with an electrophile forms a new bond on the α carbon.

21.4 Enolates of Unsymmetrical Carbonyl Compounds

What happens when an unsymmetrical carbonyl compound like 2-methylcyclohexanone is treated with base? Two enolates are possible, one formed by removal of a 2° hydrogen, and one formed by removal of a 3° hydrogen.



Path [1] occurs *faster* than Path [2] because it results in removal of the less hindered 2° hydrogen, forming an enolate on the less substituted α carbon.
Path [2] results in removal of a 3° hydrogen, forming the *more stable* enolate with the more substituted double bond. This enolate predominates at equilibrium.

Page 983

- **The kinetic enolate is formed faster because it is the *less substituted* enolate.**
- **The thermodynamic enolate is lower in energy because it is the *more***

***substituted* enolate.**

It is possible to regioselectively form one or the other enolate by the proper use of reaction conditions, because the base, solvent, and reaction temperature all affect the identity of the enolate formed.

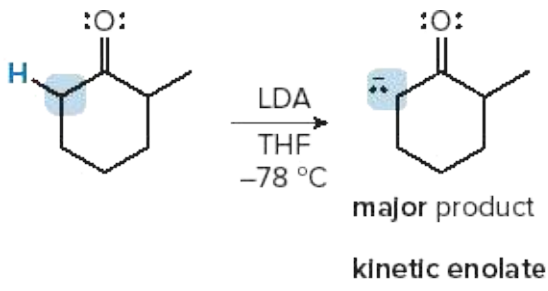
Kinetic Enolates

The kinetic enolate forms faster, so mild reaction conditions favor it over slower processes with higher energies of activation. It is the less stable enolate, so it must not be allowed to equilibrate to the more stable thermodynamic enolate. The kinetic enolate is favored by

[1] A strong nonnucleophilic base. A strong base ensures that the enolate is formed rapidly. A bulky base like LDA removes the more accessible proton on the less substituted carbon much faster than a more hindered proton.

[2] Polar aprotic solvent. The solvent must be polar to dissolve the polar starting materials and intermediates. It must be aprotic so that it does not protonate any enolate that is formed. THF is both polar and aprotic.

[3] Low temperature. The temperature must be low (−78 °C) to prevent the kinetic enolate from equilibrating to the thermodynamic enolate.



- **A kinetic enolate is formed with a strong, nonnucleophilic base (LDA) in a polar aprotic solvent (THF) at low temperature (−78 °C).**

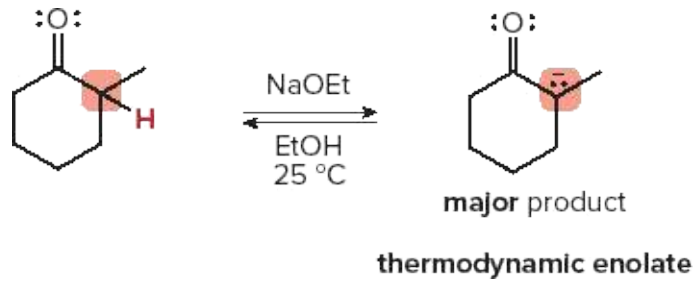
Thermodynamic Enolates

A thermodynamic enolate is favored by equilibrating conditions. This is often achieved using a strong base in a protic solvent. A strong base yields both enolates, but in a protic solvent, enolates can also be protonated to re-form the carbonyl starting material. At equilibrium, the lower-energy intermediate always wins out, so that the more stable, more substituted enolate is present in higher concentration. Thus, the thermodynamic enolate is favored by

[1] A strong base. $Na^+ {}^-OCH_2CH_3$, $K^+ {}^-OC(CH_3)_3$, or other alkoxides are common.

[2] Protic solvent. CH_3CH_2OH or other alcohols.

[3] Room temperature (25 °C).



- **A thermodynamic enolate is formed with a strong base (RO^-) in a polar protic solvent (ROH) at room temperature.**

To simplify structures, we use abbreviations:

Me = CH_3, so $NaOCH_3$ = NaOMe

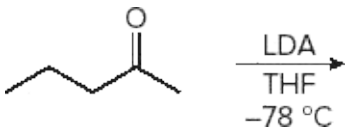
Et = CH_2CH_3, so $NaOCH_2CH_3$ = NaOEt

***t*Bu = $C(CH_3)_3$, so $KOC(CH_3)_3$ = KO*t*Bu**

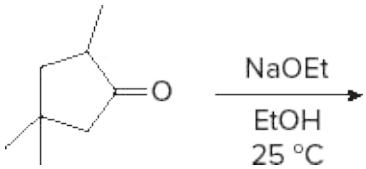
Sample Problem 21.2 Determining the Enolate Formed from an Unsymmetrical Ketone

What is the major enolate formed in each reaction?

a.

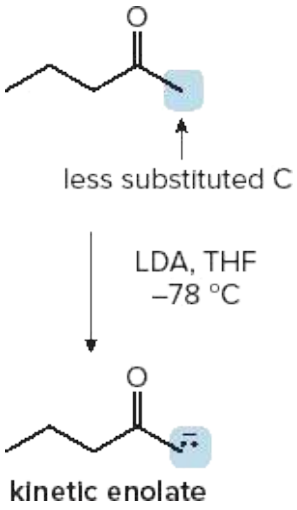


b.

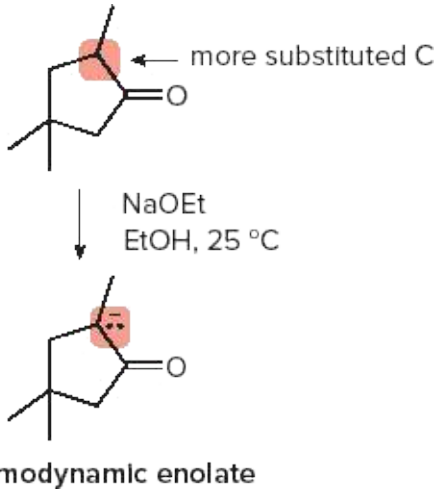


Solution

a. LDA is a strong, nonnucleophilic base that removes a proton on the less substituted α carbon to form the kinetic enolate.



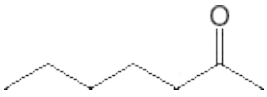
b. $NaOCH_2CH_3$ (a strong base) and CH_3CH_2OH (a protic solvent) favor removal of a proton from the more substituted α carbon to form the thermodynamic enolate.



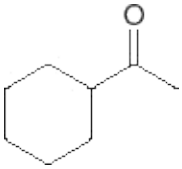
Problem 21.10

What enolate is formed when each ketone is treated with LDA in THF solution? What enolate is formed when these same ketones are treated with $NaOCH_3$ in CH_3OH solution?

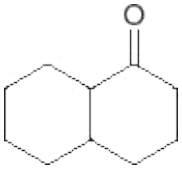
a.



b.



c.



More Practice:

Try Problem 21.36.

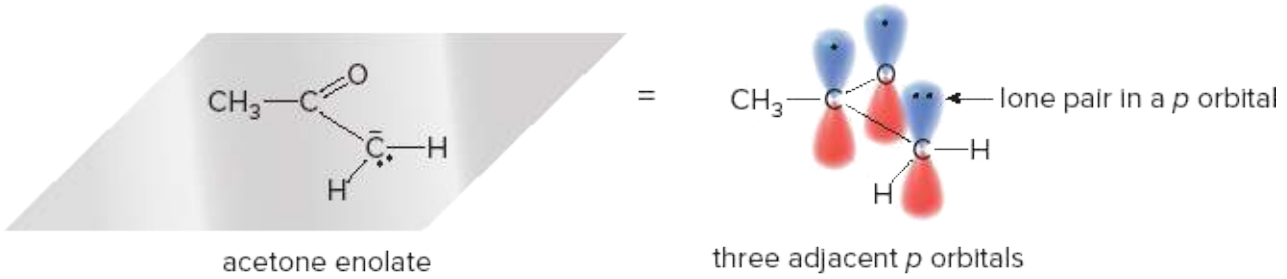
21.5 Racemization at the α Carbon

Recall from Section 14.5 that an enolate can be stabilized by the delocalization of electron density only if it possesses the proper geometry and hybridization.

- **The electron pair on the carbon adjacent to the C=O must occupy a *p* orbital that overlaps with the two other *p* orbitals of the C=O, making an enolate conjugated.**

- **Thus, all three atoms of the enolate are sp^2 hybridized and trigonal planar.**

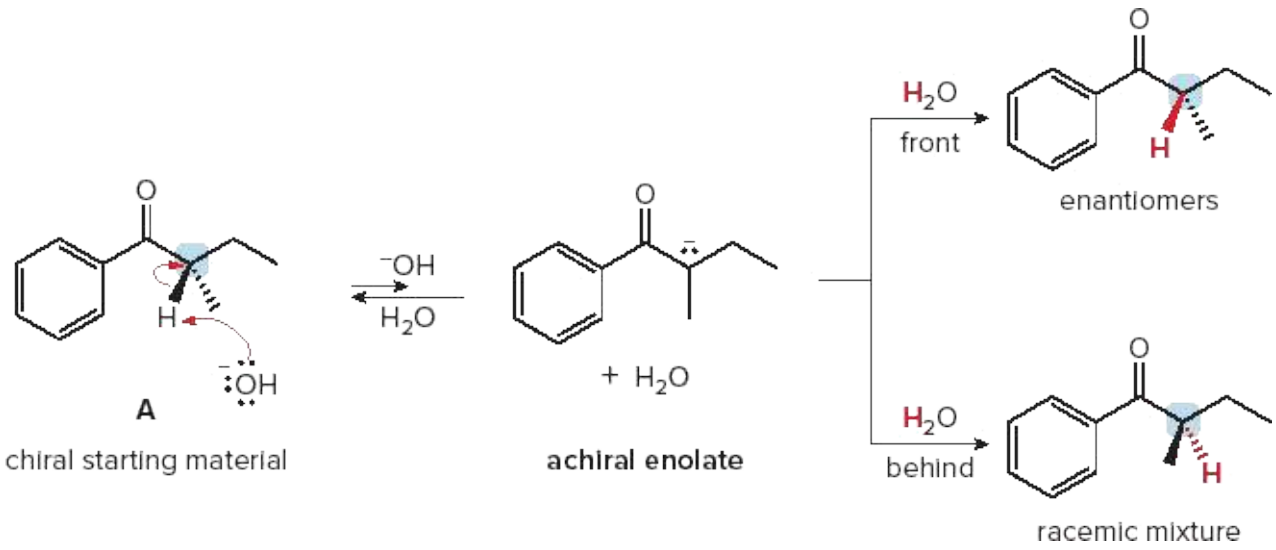
These bonding features are shown in the acetone enolate in Figure 21.2.



- The O atom and both C's of the enolate are **sp^2 hybridized** and lie in a plane.
- Each atom has a *p* orbital extending above and below the plane; these orbitals overlap to delocalize electron density.

Figure 21.2 **The hybridization and geometry of the acetone enolate $(CH_3COCH_2)^-$**

When the α carbon to the carbonyl is a stereogenic center, treatment with Page 985 aqueous base leads to racemization by a two-step process: deprotonation to form an enolate and protonation to re-form the carbonyl compound. For example, chiral ketone A reacts with aqueous ^-OH to form an achiral enolate having an sp^2 hybridized α carbon. Because the enolate is planar, it can be protonated with H2O with equal probability from both directions, yielding a racemic mixture of two ketones.



Problem 21.11

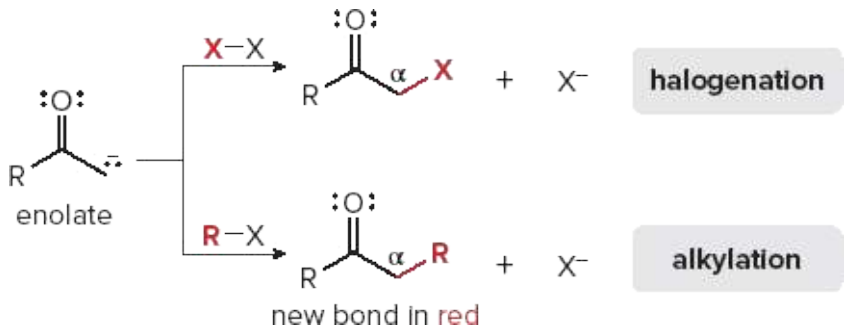
Explain each observation: (a) When (*R*)-2-methylcyclohexanone is treated with NaOH in H_2O, the optically active solution gradually loses optical activity. (b) When (*R*)-3-methylcyclohexanone is treated with NaOH in H_2O, the solution remains optically active.

21.6 A Preview of Reactions at the α Carbon

Having learned about the synthesis and properties of enolates, we can now turn our attention to their reactions. Like enols, enolates are nucleophiles, but because they are negatively charged, enolates are much more nucleophilic than neutral enols. Consequently, they undergo a wider variety of reactions.

Two general types of reactions of enolates—substitutions and reactions with other carbonyl compounds—will be discussed in the remainder of Chapter 21 and in Chapter 22. Both reactions form new bonds to the carbon α to the carbonyl.

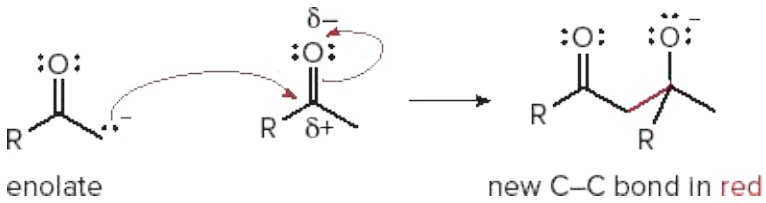
- **Enolates react with electrophiles to afford substitution products.**



Two different kinds of substitution reactions are examined: halogenation with X_2 and alkylation with alkyl halides RX. These reactions are detailed in Sections 21.7–21.10.

- **Enolates react with other carbonyl groups at the electrophilic carbonyl**

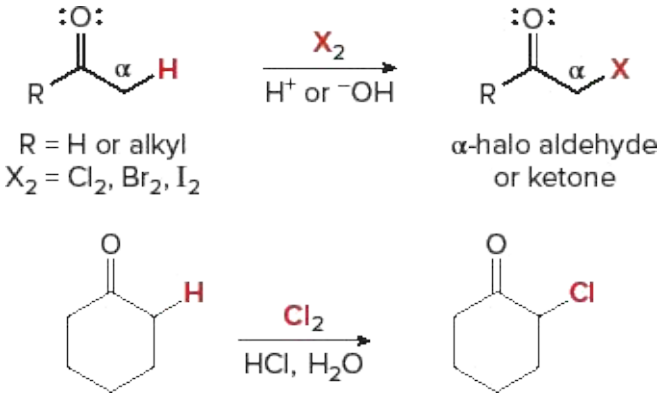
carbon.



These reactions are more complicated because the initial addition adduct goes on to form different products depending on the structure of the carbonyl group. These reactions form the subject of Chapter 22.

21.7 Halogenation at the α Carbon

The first substitution reaction we examine is halogenation. Treatment of a ketone or aldehyde with halogen and either acid or base results in substitution of X for H on the α carbon, forming an α-halo aldehyde or ketone. Halogenation readily occurs with Cl_2, Br_2, and I_2.

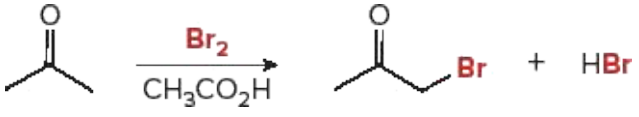


The mechanisms of halogenation in acid and base are somewhat different.

- **Reactions done in acid generally involve *enol* intermediates.**
- **Reactions done in base generally involve *enolate* intermediates.**

21.7A Halogenation in Acid

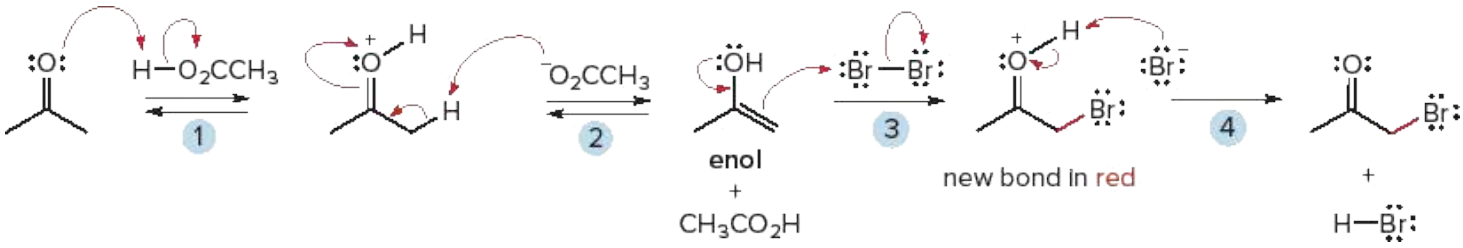
Halogenation is often carried out by treating a carbonyl compound with a halogen in acetic acid. In this way, acetic acid is both the solvent and the acid catalyst for the reaction.



The mechanism of acid–catalyzed halogenation consists of two parts: tautomerization

of the carbonyl compound to the enol form, and reaction of the enol with halogen. Mechanism 21.3 illustrates the reaction of $(CH_3)_2C{=}O$ with Br_2 in CH_3CO_2H.

Mechanism 21.3 Acid-Catalyzed Halogenation at the α Carbon

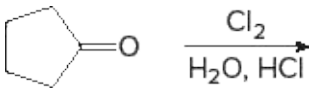


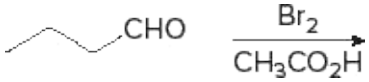
1 – 2 The ketone is converted to its enol tautomer by the two-step process of protonation followed by deprotonation.

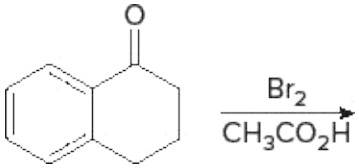
3 – 4 Addition of the halogen to the enol forms a new bond to Br on the α carbon, and deprotonation yields the substitution product.

Problem 21.12

Draw the products of each reaction.

a. 

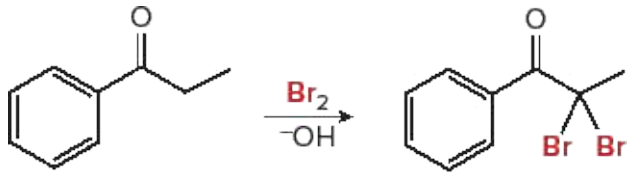
b. 

c. 

Reactions of carbonyl compounds with base invariably involve enolates because the α hydrogens of the carbonyl compound are easily removed.

21.7B Halogenation in Base

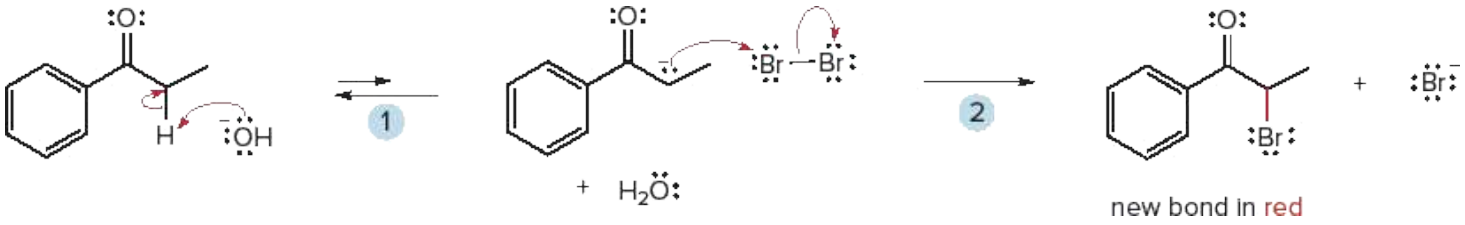
Halogenation in base is much less useful, because it is often difficult to stop the reaction after addition of just one halogen atom to the α carbon. For example, treatment of propiophenone with Br_2 and aqueous ^-OH yields a dibromo ketone.



propiophenone

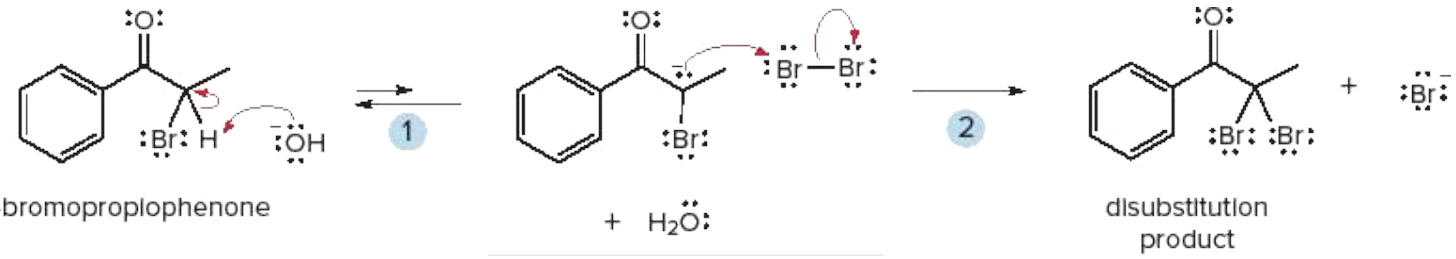
The mechanism for introduction of each Br atom involves the same two steps: deprotonation with base followed by reaction with Br_2 to form a new C–Br bond, as shown in Mechanism 21.4.

Mechanism 21.4 Halogenation at the α Carbon in Base



1. **Treatment of the ketone with base forms a nucleophilic enolate.**
2. **Reaction of the enolate with Br2 forms the substitution product in which one H is replaced by Br on the α carbon.**

Only a small amount of the enolate forms at equilibrium using ⁻OH as base, but the enolate is such a strong nucleophile that it readily reacts with Br_2, thus driving the equilibrium to the right. Then, the same two steps introduce the second Br atom on the α carbon: deprotonation followed by nucleophilic attack.

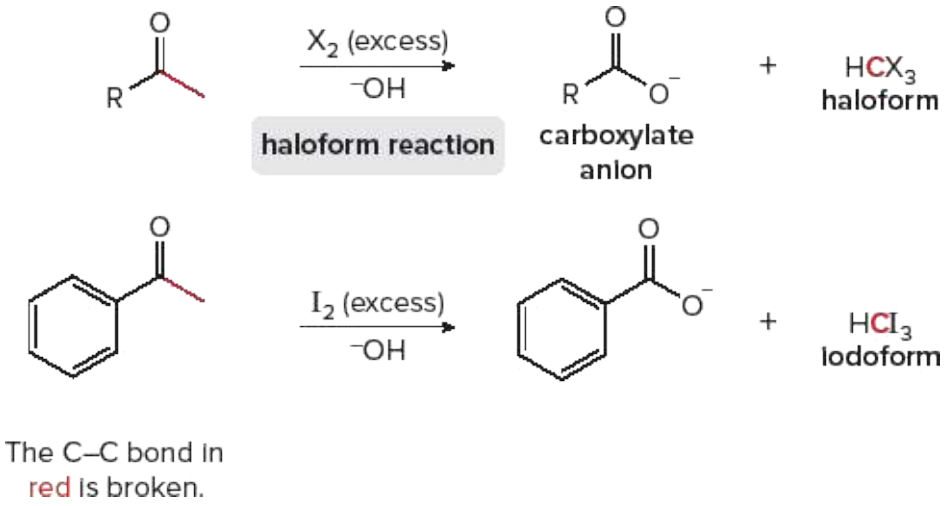


α-bromopropiophenone

disubstitution product

It is difficult to stop this reaction after the addition of one Br atom because the electron-withdrawing inductive effect of Br stabilizes the second enolate. As a result, the α H of α-bromopropiophenone is more acidic than the α H atoms of propiophenone, making it easier to remove with base.

Halogenation of a methyl ketone with excess halogen, called the haloform reaction, results in cleavage of a carbon–carbon σ bond and formation of two products, a carboxylate anion and CHX_3 (commonly called haloform).



Although all ketones with α hydrogens react with base and I_2, only methyl ketones form CHI_3 (iodoform), a pale yellow solid that precipitates from the reaction mixture. This reaction is the basis of the iodoform test, once a common chemical method to detect methyl ketones. Methyl ketones give a positive iodoform test (appearance of a yellow solid), whereas other ketones give a negative iodoform test (no change in the reaction mixture).

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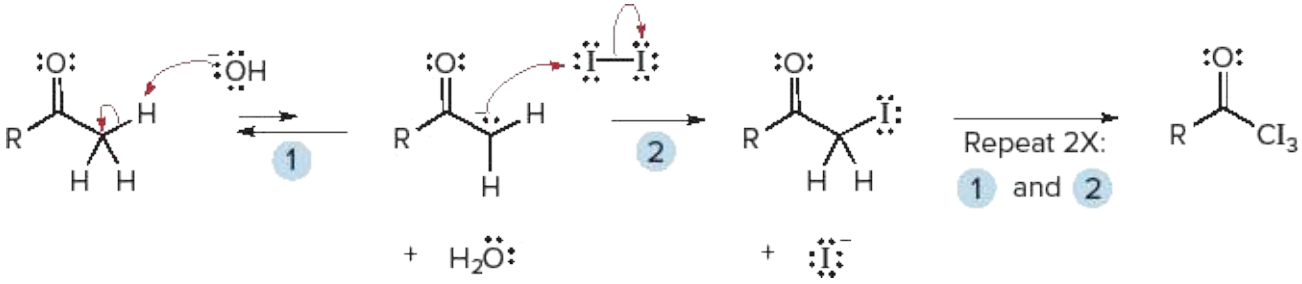
In the haloform reaction, the three H atoms of the CH_3 group are Page 988 successively replaced by X to form an intermediate that is oxidatively cleaved with base. Mechanism 21.5 is written with I_2 as halogen, forming CHI_3 (iodoform) as product.

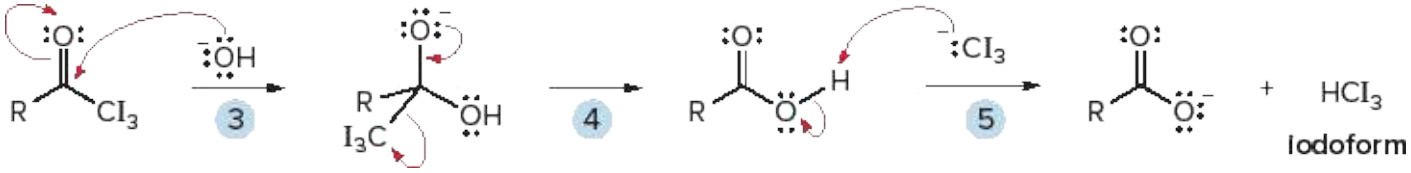
Mechanism 21.5 The Haloform Reaction

Part [1] Halogenation at the α carbon



1 – 2 Removal of a proton forms an enolate that reacts with I_2 to yield an α-iodo ketone. Steps [1] and [2] are repeated twice more to form the triiodo substitution product.

Part [2] Oxidative cleavage with ^-OH



3 Nucleophilic addition of ^-OH forms a tetrahedral intermediate.

4 Elimination of $^-CI_3$ cleaves a carbon–carbon bond, forming the substitution product.

5 Proton transfer generates the carboxylate anion and HCI_3, iodoform.

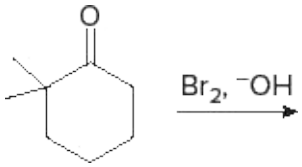
Steps [3] and [4] result in a nucleophilic *substitution* reaction of a *ketone*. Because ketones normally undergo nucleophilic *addition*, this two-step sequence makes the haloform reaction unique. Substitution occurs because the three electronegative halogen atoms make CX_3 (CI_3 in the example) a good leaving group.

Figure 21.3 summarizes the three possible outcomes of halogenation at the α carbon, depending on the substrate and chosen reaction conditions.

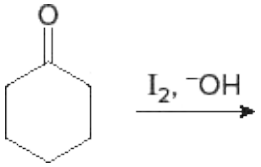
Problem 21.13

Draw the products of each reaction. Assume excess halogen is present.

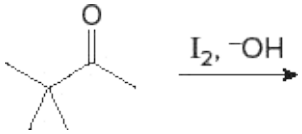
a.



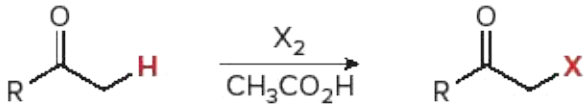
b.



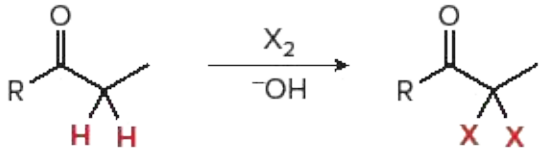
c.



a. **Halogenation in acid**—Monosubstitution on the α carbon



b. **General halogenation in base**—Polysubstitution on the α carbon



c. **Halogenation of *methyl* ketones** with excess X_2 and base—Oxidative cleavage

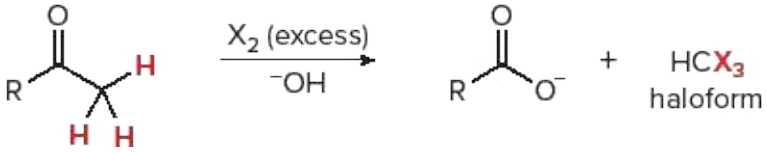
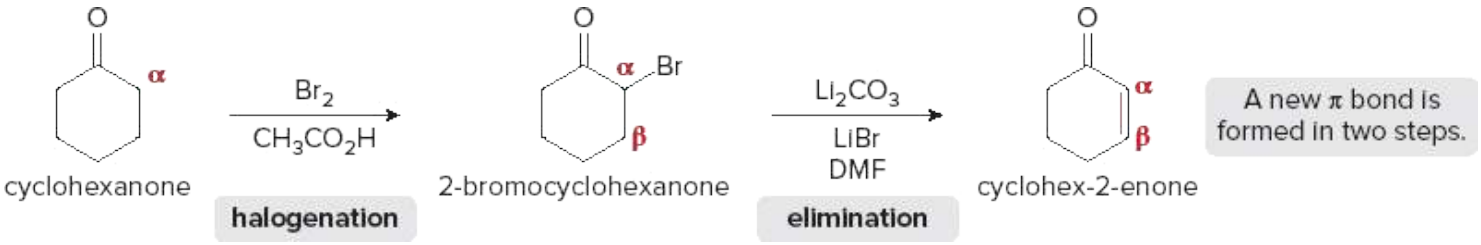


Figure 21.3 **Summary: Halogenation reactions at the α carbon to a carbonyl group**

21.7C Reactions of α-Halo Carbonyl Compounds

α-Halo carbonyl compounds undergo two useful reactions—elimination with base and substitution with nucleophiles.

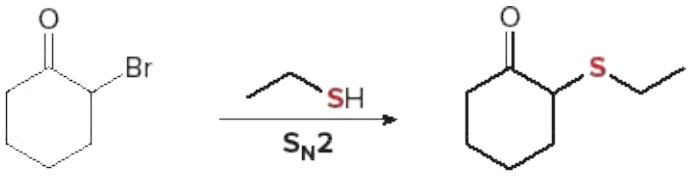
For example, treatment of 2-bromocyclohexanone with the base Li_2CO_3 in the presence of LiBr in the polar aprotic solvent DMF [$HCON(CH_3)_2$] affords cyclohex-2-enone by elimination of the elements of Br and H from the α and β carbons, respectively. Thus, a two-step method can convert a carbonyl compound such as cyclohexanone to an α,β-unsaturated carbonyl compound such as cyclohex-2-enone.



[1] Bromination at the α carbon is accomplished with Br_2 in CH_3CO_2H.

[2] Elimination of Br and H occurs with Li_2CO_3 and LiBr in DMF.

α-Halo carbonyl compounds also react with nucleophiles by S_N2 reactions. For example, reaction of 2-bromocyclohexanone with CH_3CH_2SH affords the substitution product A.

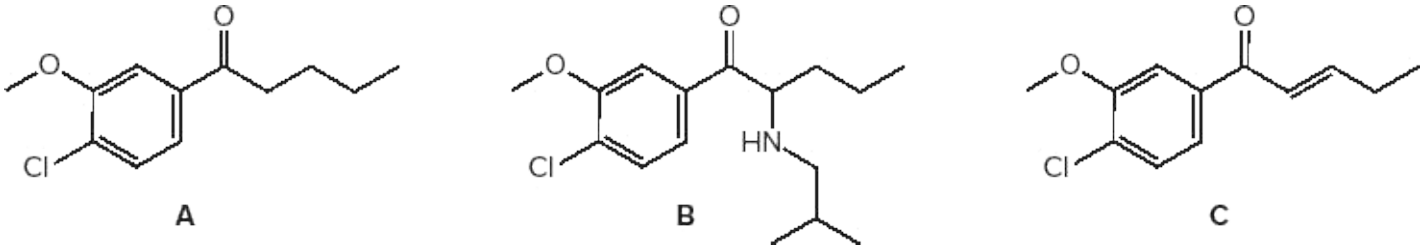


2-bromocyclohexanone A

α,β-Unsaturated carbonyl compounds undergo a variety of 1,2- and 1,4-addition reactions as discussed in Section 17.15.

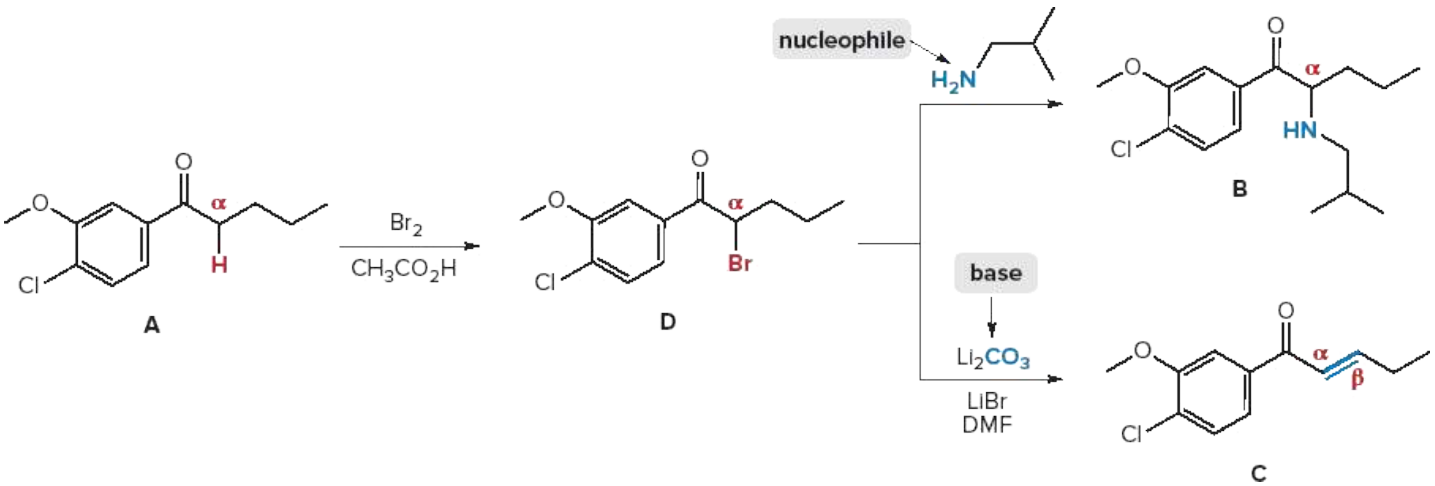
Sample Problem 21.3 Using α-Halo Carbonyl Compounds in Synthesis

What steps are needed to convert ketone A to B and C?



Solution

To introduce the N atom on the α carbon to form B or the double bond between the α and β carbons to form C, we must first convert A to an α-halo ketone, D. The halogen can then act as a leaving group in a substitution reaction to form B, or an elimination reaction to form C.



- **Reaction of D with an amine nucleophile forms the substitution product B by an S_N2 mechanism.**
- **Reaction of D with a base forms the elimination product C. The elements of Br and H are removed from the α and β carbons to form a π**

bond.

Problem 21.14

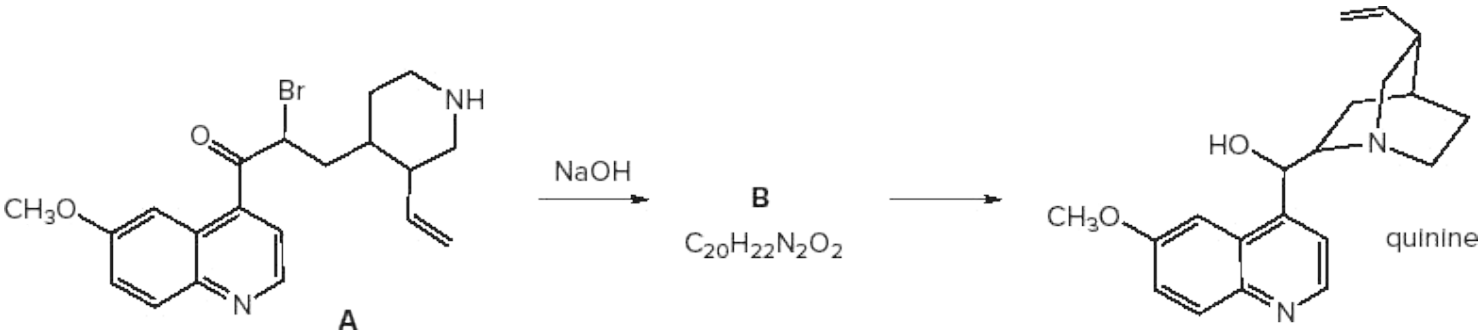
Draw the organic products formed when 2-bromopentan-3-one ($CH_3CH_2COCHBrCH_3$) is treated with each reagent: (a) Li_2CO_3, LiBr, DMF; (b) $CH_3CH_2NH_2$; (c) CH_3SH.

More Practice:

Try Problems 21.49c, e; 21.51; 21.52.

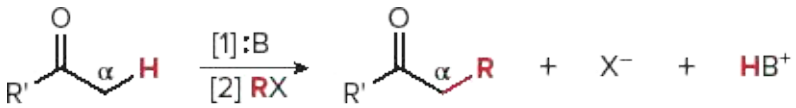
Problem 21.15

A key step in a synthesis of the antimalarial drug quinine involves an intramolecular nucleophilic substitution that converts A to B. Draw the structure of B and give the reagents needed to convert B to quinine.



21.8 Direct Enolate Alkylation

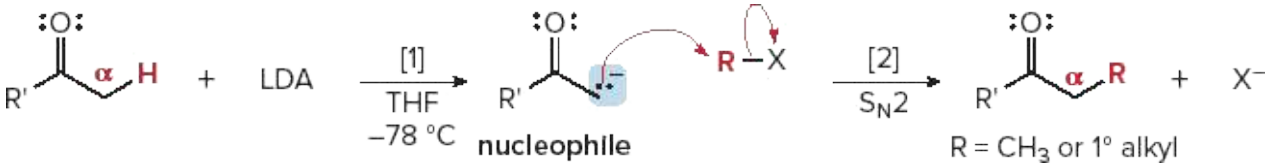
Treatment of an aldehyde or ketone with base and an alkyl halide (RX) results in *alkylation*—the substitution of R for H on the α carbon atom. Alkylation forms a new carbon–carbon bond on the α carbon.



new bond in red

21.8A General Features

We will begin with the most direct method of alkylation, and then (in Sections 21.9 and 21.10) examine two older, multistep methods that are still used today. Direct alkylation is carried out by a two-step process:

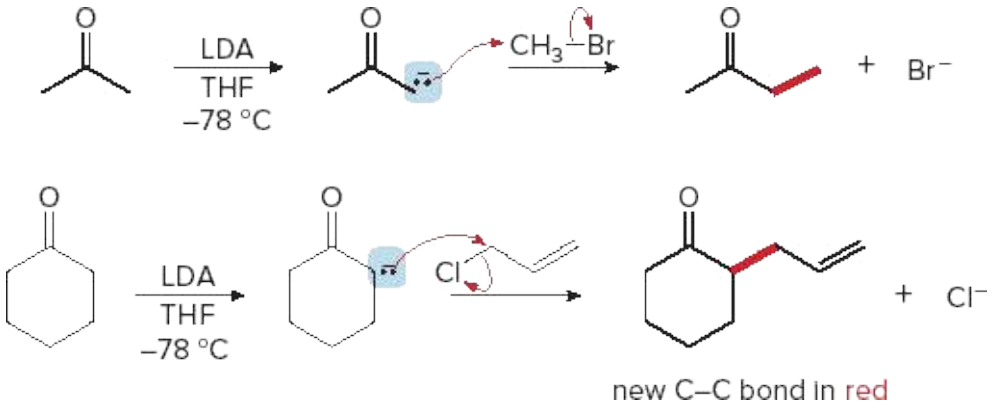


[1] Deprotonation: Base removes a proton from the α carbon to generate an enolate. The reaction works best with a strong nonnucleophilic base like LDA in THF solution at low temperature (−78 °C).

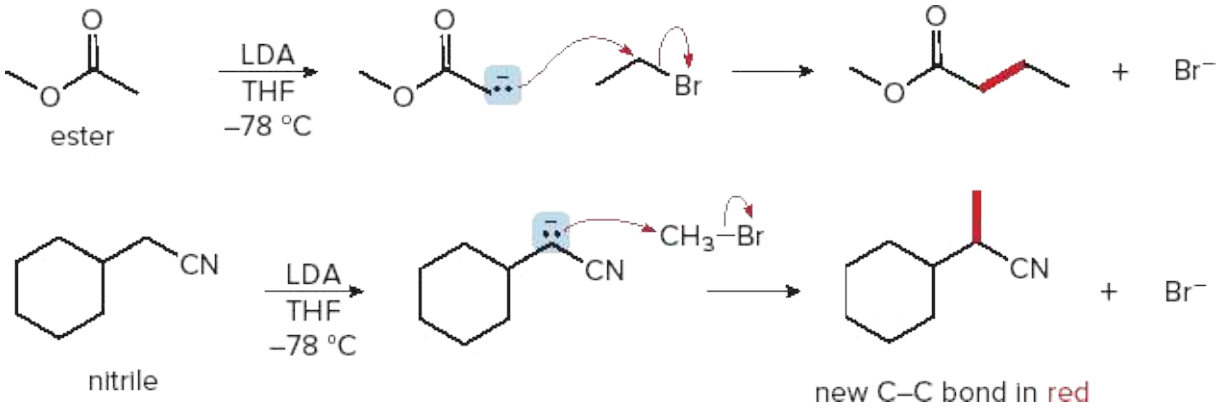
[2] Nucleophilic attack: The nucleophilic enolate attacks the alkyl halide, displacing the halide (a good leaving group) and forming the alkylation product by an S_N2 reaction.

R_3CX, CH_2=CHX, and C_6H_5X do *not* undergo alkylation reactions with enolates, because they are unreactive in S_N2 reactions.

Because Step [2] is an S_N2 reaction, it works best with unhindered methyl and 1° alkyl halides. Hindered alkyl halides and those with halogens bonded to sp^2 hybridized carbons do *not* undergo substitution.

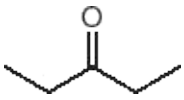


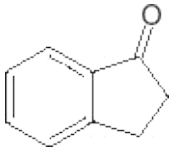
Ester enolates and carbanions derived from nitriles are also alkylated under these conditions.

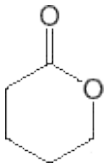


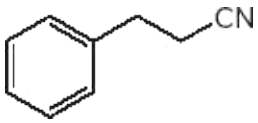
Problem 21.16

What product is formed when each compound is treated first with LDA in THF solution at low temperature, followed by CH_3CH_2I?

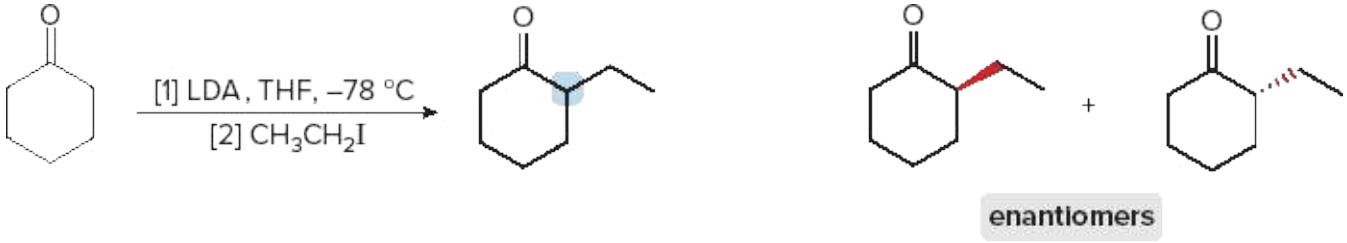
a. 

b. 

c. 

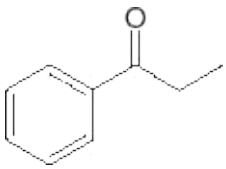
d. 

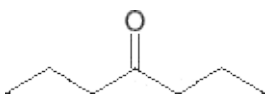
The stereochemistry of enolate alkylation follows the general rule governing the stereochemistry of reactions: an achiral starting material yields an achiral or racemic product. For example, when cyclohexanone (an achiral starting material) is converted to 2-ethylcyclohexanone by treatment with base and CH_3CH_2I, a new stereogenic center (labeled in blue) is introduced, and both enantiomers of the product are formed in equal amounts—that is, a racemic mixture.

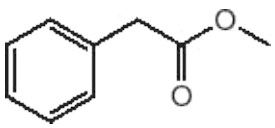


Problem 21.17

Draw the products obtained (including stereochemistry) when each compound is treated with LDA, followed by CH3I.

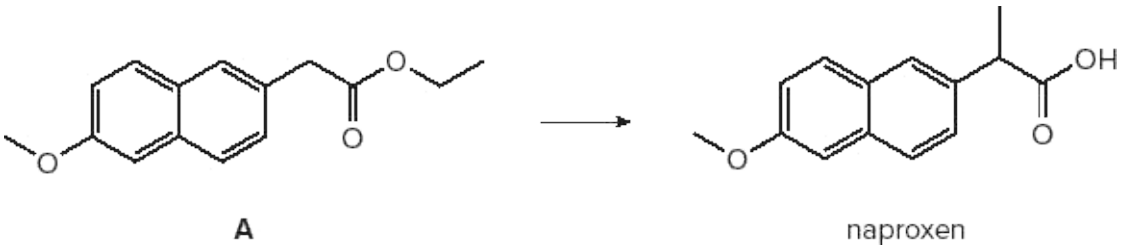
a. 

b. 

c. 

Problem 21.18

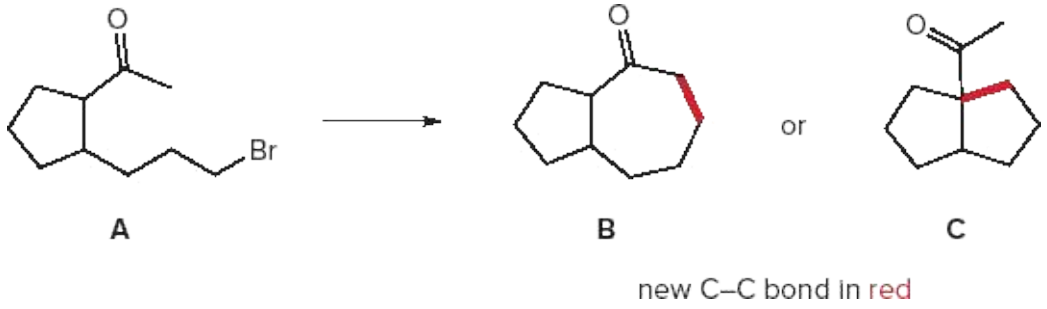
The analgesic naproxen can be prepared by a stepwise reaction sequence from ester A. Using enolate alkylation in one step, what reagents are needed to convert A to naproxen? Draw the structure of each intermediate. Explain why a racemic product is formed.



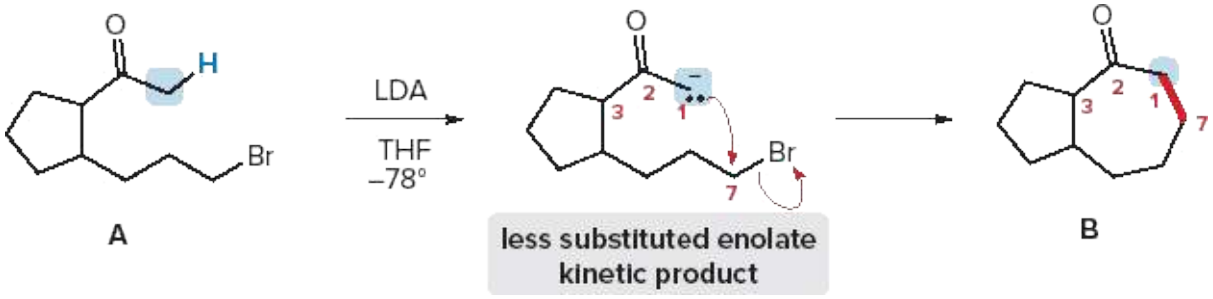
21.8B Alkylation of Unsymmetrical Ketones

An unsymmetrical ketone can be regioselectively alkylated to yield one major product. The strategy depends on the use of the appropriate base, solvent, and temperature to form the kinetic or thermodynamic enolate (Section 21.4), which is then treated with an alkyl halide to form the alkylation product.

An example of this strategy is seen in the intramolecular alkylation of bromo ketone A to form either B or C, depending on the reaction conditions.

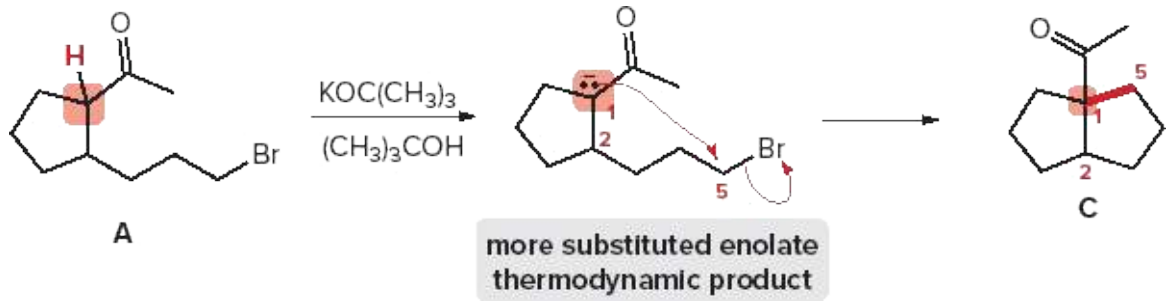


- **Treatment of A with LDA in THF at −78° gives the less substituted enolate, which undergoes an intramolecular S_N2 reaction to form the seven-membered ring in B.**



- **Treatment of A with $KOC(CH_3)_3$ in $(CH_3)_3COH$ at room temperature gives the *more* substituted enolate, which undergoes an**

intramolecular S_N2 reaction to form the five-membered ring in C.

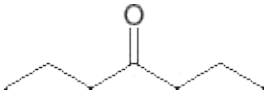


Finally, while enolate alkylation at the less substituted α carbon using LDA is a reliable regio-selective reaction, enolate alkylation at the more substituted α carbon with $KOC(CH_3)_3$ may lead to mixtures of products. Regioselectivity depends on the identity of the substrate and the experimental parameters, which sometimes must be carefully monitored to maximize the yield of the desired alkylation product.

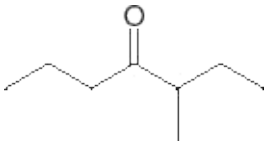
Problem 21.19

How can pentan-2-one be converted to each compound?

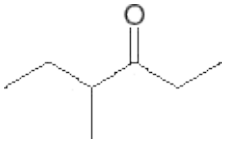
a.



b.



c.

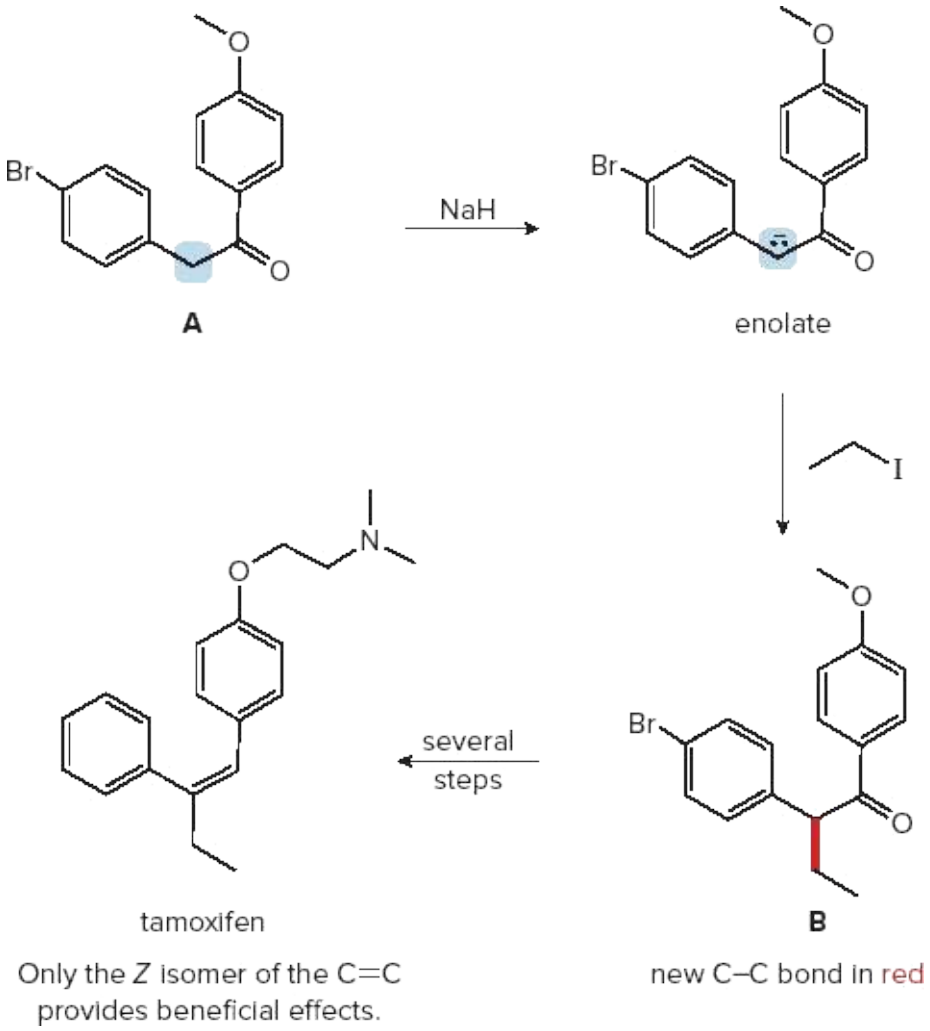


21.8C Application of Enolate Alkylation: Tamoxifen Synthesis

Tamoxifen has been commercially available since the 1970s, sold under the brand name of Nolvadex.

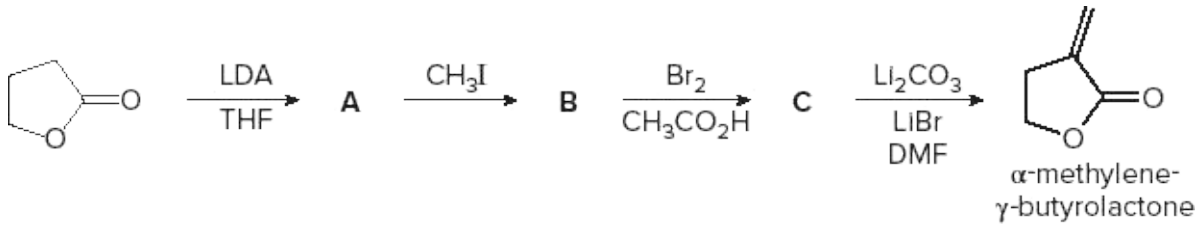
©McGraw-Hill Education/Mary Reeg, photographer

Tamoxifen is a potent anticancer drug that has been used to treat certain forms of breast cancer for many years. One step in the synthesis of tamoxifen involves the treatment of ketone A with NaH as base to form an enolate. Alkylation of this enolate with CH_3CH_2I forms B in high yield. B is converted to tamoxifen in several steps, some of which are reactions you have already learned.



Problem 21.20

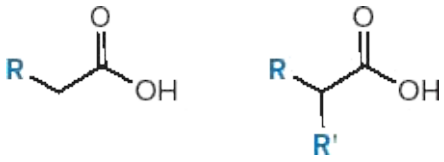
Identify A, B, and C, intermediates in the synthesis of the five-membered ring called an α-methylene-γ-butyrolactone. This heterocyclic ring system is present in some antitumor agents.



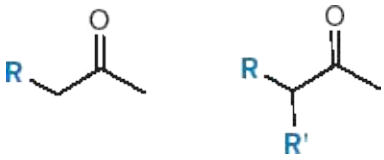
21.9 Malonic Ester Synthesis

Besides the direct method of enolate alkylation discussed in Section 21.8, a new alkyl group can also be introduced on the α carbon using the malonic ester synthesis and the acetoacetic ester synthesis.

- The malonic ester synthesis prepares carboxylic acids having two general structures:



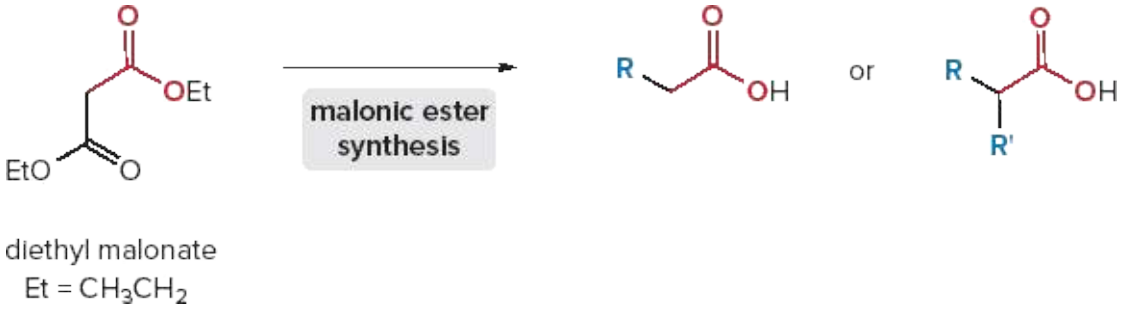
- The acetoacetic ester synthesis prepares methyl ketones having two general structures:



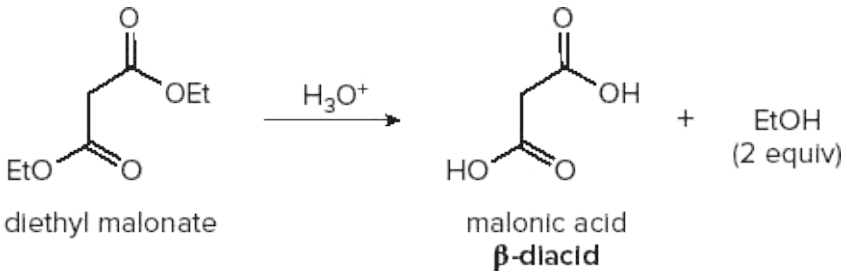
21.9A Background for the Malonic Ester Synthesis

- **The malonic ester synthesis is a stepwise method for converting diethyl malonate to a carboxylic acid having one or two alkyl groups on the α carbon.**

To simplify the structures, the CH_3CH_2 groups of the esters are abbreviated as Et.

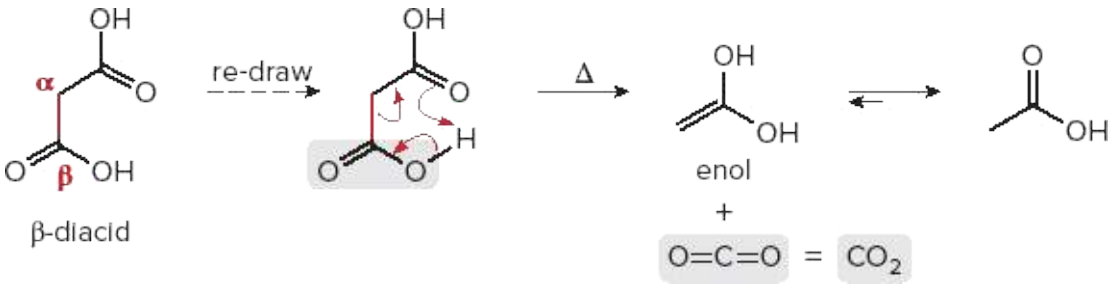


Before writing out the steps in the malonic ester synthesis, recall from Section 20.10 that esters are hydrolyzed by aqueous acid. Thus, heating diethyl malonate with acid and water hydrolyzes both esters to carboxy groups, forming a β-diacid (1,3-diacid).

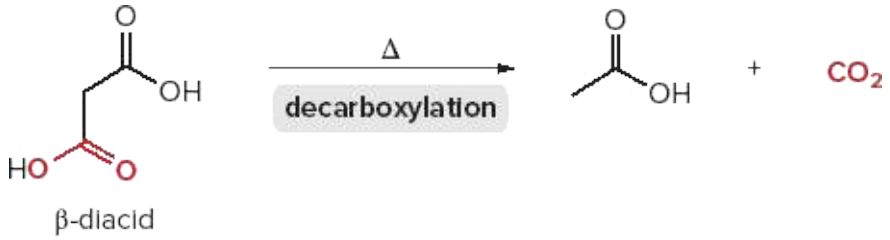


The resulting β-diacids are unstable to heat. They decarboxylate (lose CO_2), resulting in cleavage of a carbon–carbon bond and formation of a carboxylic acid. Decarboxylation is not a general reaction of all carboxylic acids. It occurs with β-diacids, however, because CO_2 can be eliminated through a cyclic, six-atom transition state. This forms an enol of a carboxylic acid, which in turn tautomerizes to the more

stable keto form.



The net result of decarboxylation is cleavage of a carbon–carbon bond on the α carbon, with loss of CO2.



Decarboxylation occurs readily whenever a carboxy group (COOH) is bonded to the α carbon of another carbonyl group. For example, β-keto acids also readily lose CO_2 on heating to form ketones.

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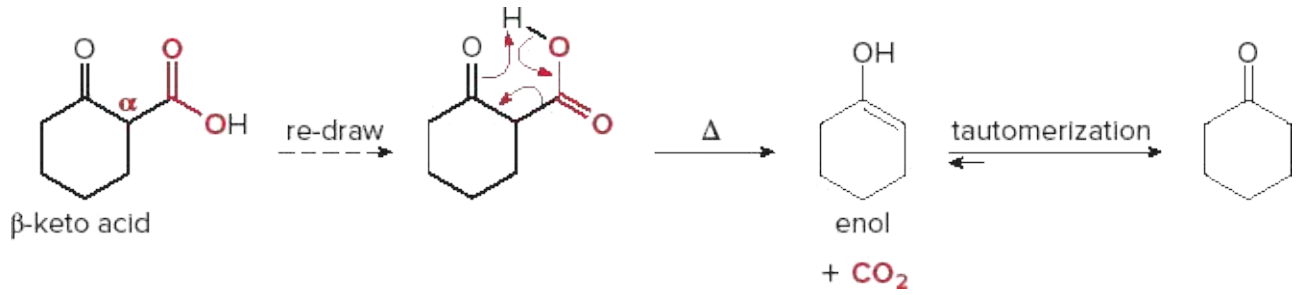
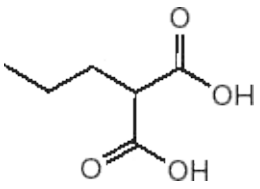


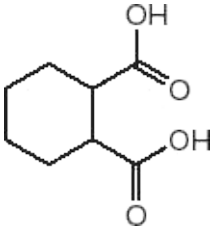
Problem 21.21

Which of the following compounds will readily lose CO_2 when heated?

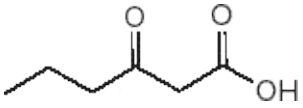
a.



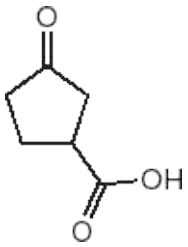
b.



c.

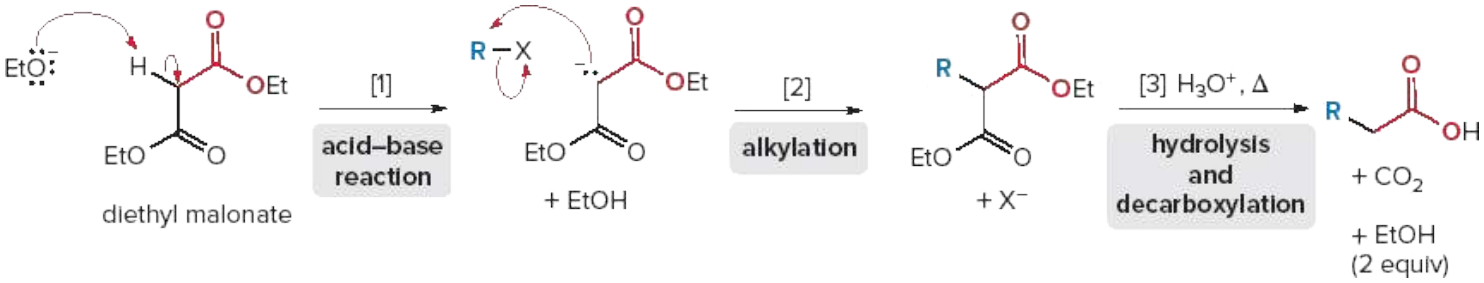


d.

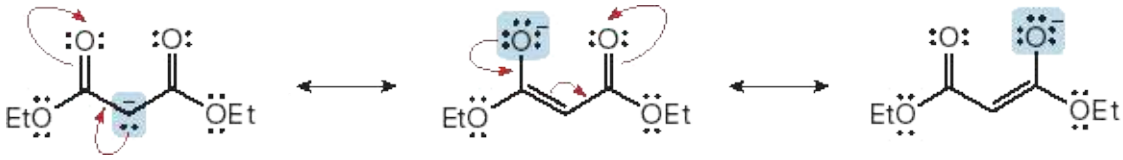


21.9B Steps in the Malonic Ester Synthesis

The malonic ester synthesis converts diethyl malonate to a carboxylic acid in three steps.



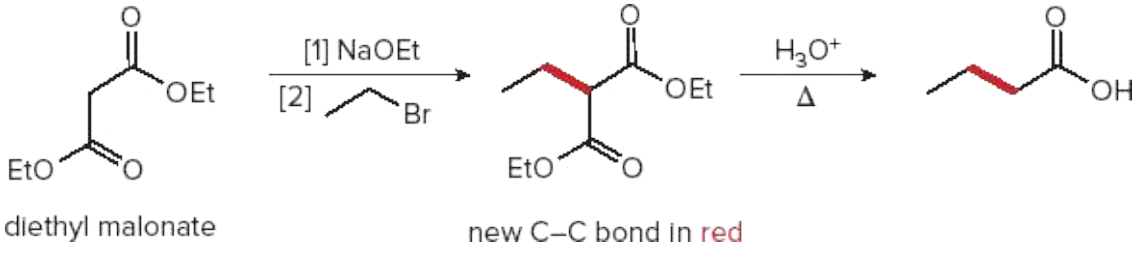
[1] Deprotonation. Treatment of diethyl malonate with $^{-}$OEt removes the acidic α proton between the two carbonyl groups. Recall from Section 21.3A that these protons are more acidic than other α protons because three resonance structures can be drawn for the enolate, instead of the usual two. Thus, $^{-}$OEt, rather than the stronger base LDA, can be used for this reaction.



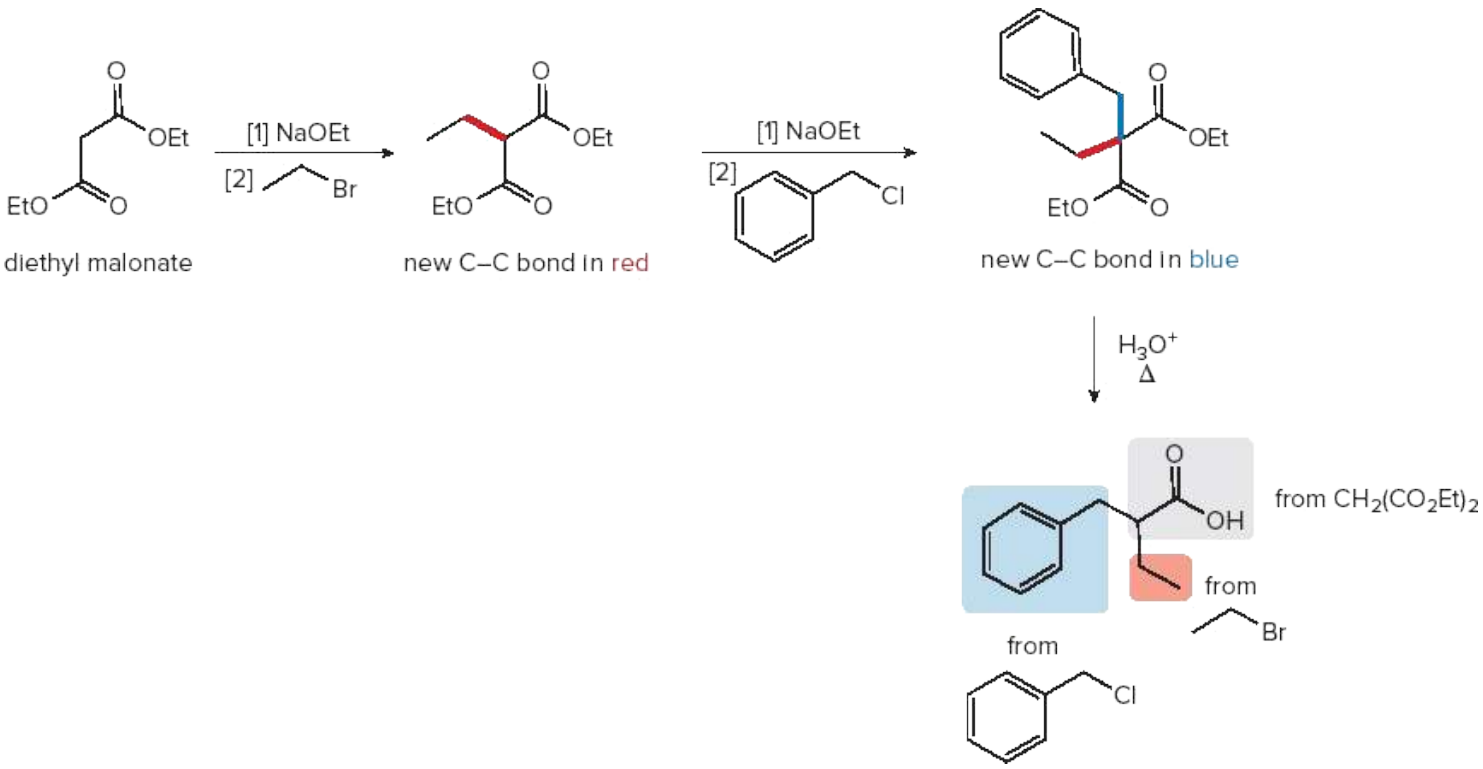
[2] Alkylation. The nucleophilic enolate reacts with an alkyl halide in an S_N2 reaction to form a substitution product. Because the mechanism is S_N2, the yields are higher when R is CH_3 or a 1° alkyl group.

[3] Hydrolysis and decarboxylation. Heating the diester with aqueous acid hydrolyzes the diester to a β-diacid, which loses CO_2 to form a carboxylic acid.

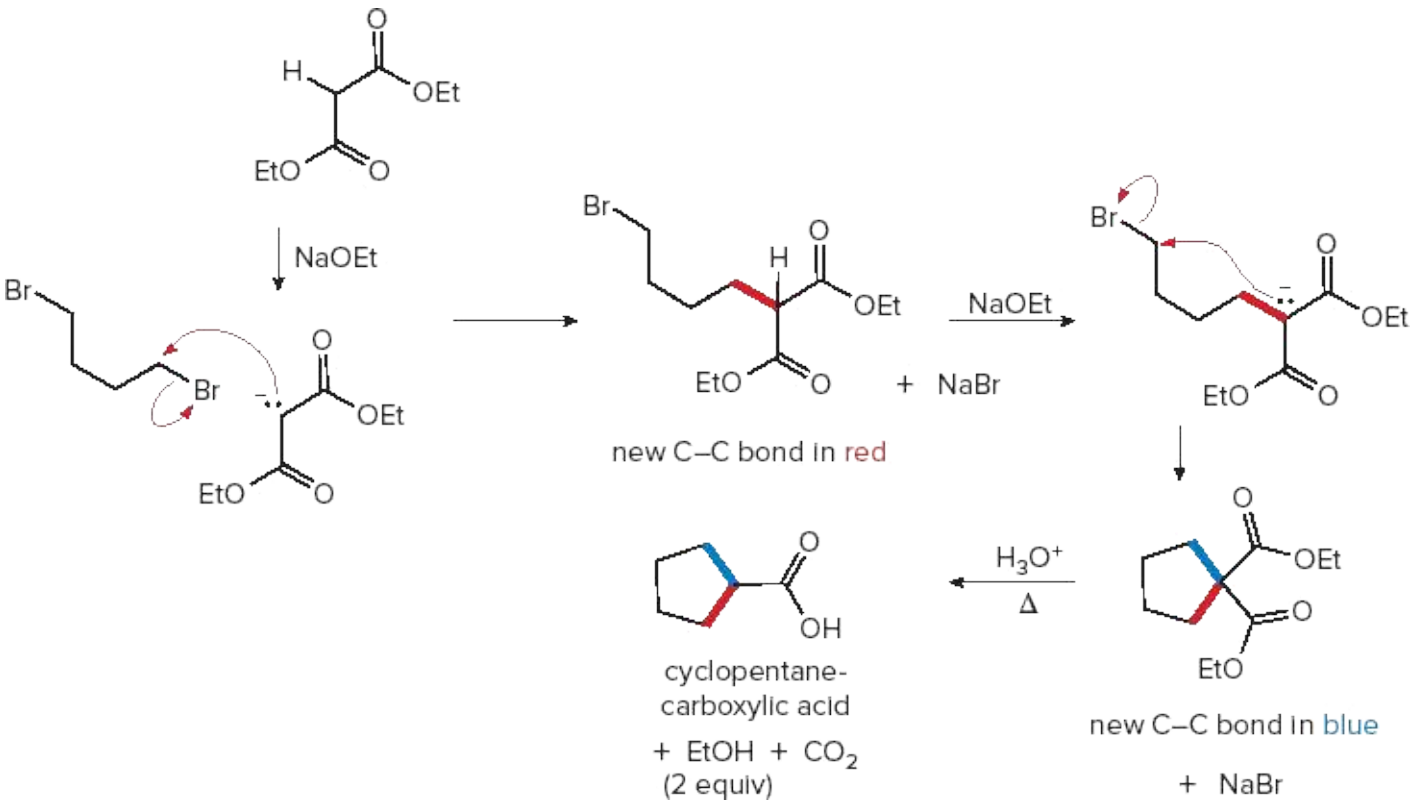
The synthesis of butanoic acid ($CH_3CH_2CH_2COOH$) from diethyl malonate illustrates the basic process:



If the first two steps of the reaction sequence are repeated *prior* to hydrolysis and decarboxylation, then a carboxylic acid having *two new alkyl groups* on the α carbon can be synthesized. This is illustrated in the synthesis of 2-benzylbutanoic acid [$CH_3CH_2CH(CH_2C_6H_5)COOH$] from diethyl malonate:

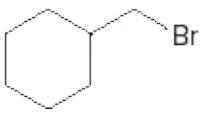


An intramolecular malonic ester synthesis can be used to form rings having three to six atoms, provided the appropriate dihalide is used as starting material. For example, cyclopentanecarboxylic acid can be prepared from diethyl malonate and 1,4-dibromobutane ($BrCH_2CH_2CH_2CH_2Br$) by this sequence of reactions:



Problem 21.22

Draw the products of each reaction.

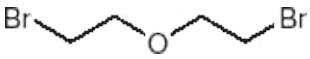
a. $CH_2(CO_2Et)_2$ → [1] NaOEt, [2]  → H_3O^+, Δ

b. $CH_2(CO_2Et)_2$ → [1] NaOEt, [2] CH_3Br → [1] NaOEt, [2] CH_3Br → H_3O^+, Δ

Problem 21.23

What cyclic product is formed from each dihalide using the malonic ester synthesis?

a.

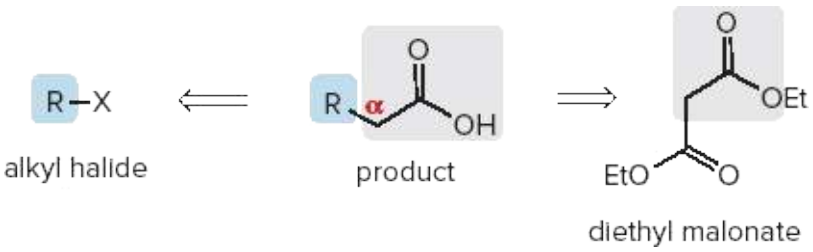
b. 

21.9C Retrosynthetic Analysis

To use the malonic ester synthesis, you must be able to determine what starting materials are needed to prepare a given compound—that is, you must work backwards in the retrosynthetic direction. This involves a two-step process:

[1] Locate the α carbon to the COOH group, and identify all alkyl groups bonded to the α carbon.

[2] Break the molecule into two (or three) components: Each alkyl group bonded to the α carbon comes from an alkyl halide. The remainder of the molecule comes from $CH_2(COOEt)_2$.

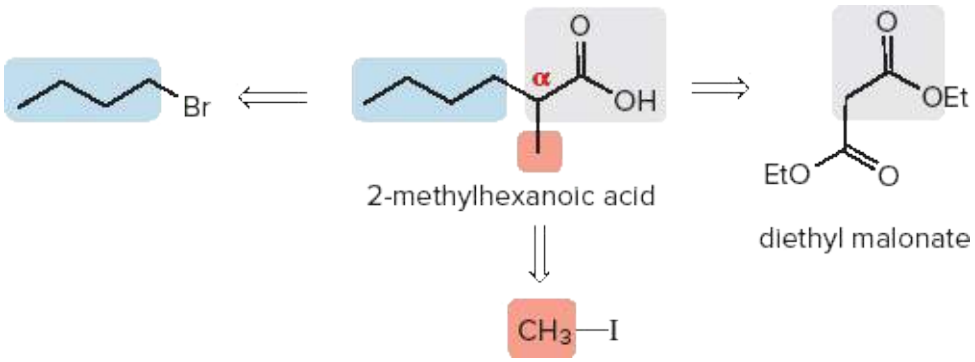


Sample Problem 21.4 Determining the Starting Materials in a Malonic Ester Synthesis

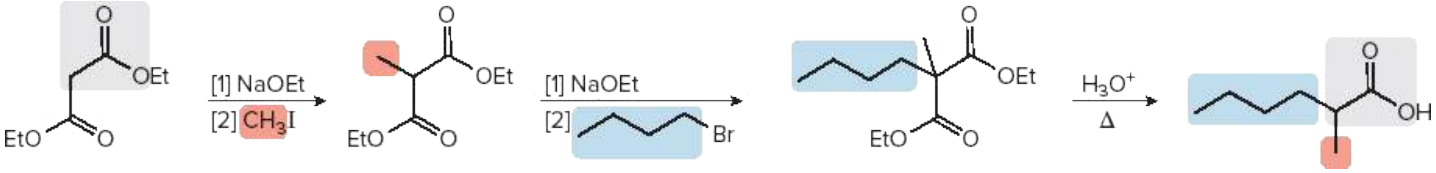
What starting materials are needed to prepare 2-methylhexanoic acid [$CH_3CH_2CH_2CH_2CH(CH_3)COOH$] using a malonic ester synthesis?

Solution

The target molecule has two different alkyl groups bonded to the α carbon, so three components are needed for the synthesis:



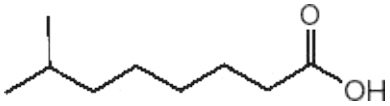
Writing the synthesis in the synthetic direction:



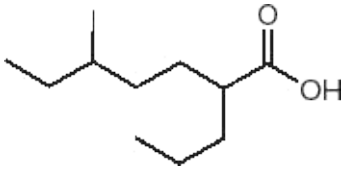
Problem 21.24

What alkyl halides are needed to prepare each carboxylic acid by the malonic ester synthesis?

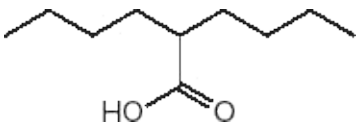
a.



b.



c.



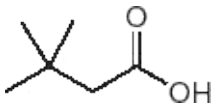
More Practice:

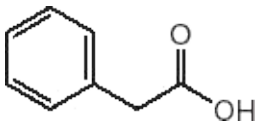
Try Problems 21.42–21.44.

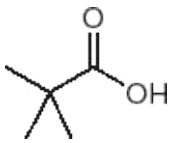
Problem 21.25

Explain why each of the following carboxylic acids cannot be prepared by a malonic ester synthesis.

a.

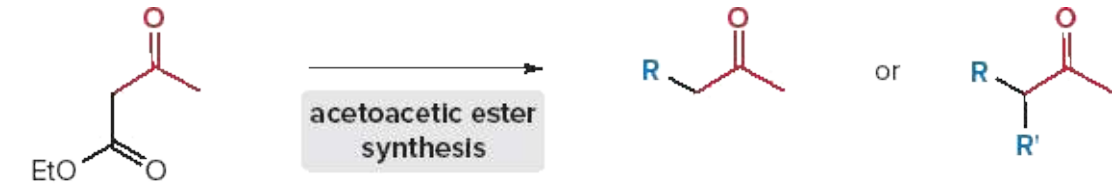


b. 

c. 

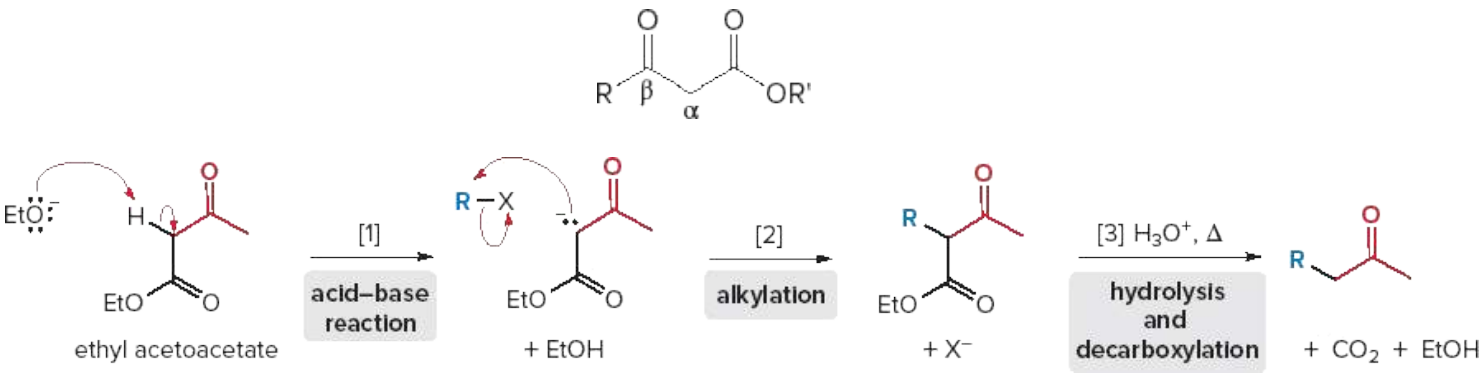
21.10 Acetoacetic Ester Synthesis

- **The acetoacetic ester synthesis is a stepwise method for converting ethyl acetoacetate to a ketone having one or two alkyl groups on the α carbon.**



21.10A Steps in the Acetoacetic Ester Synthesis

The steps in the acetoacetic ester synthesis are exactly the same as those in the malonic ester synthesis. Because the starting material, CH_3COCH_2COOEt, is a β-keto ester, the final product is a ketone, not a carboxylic acid.

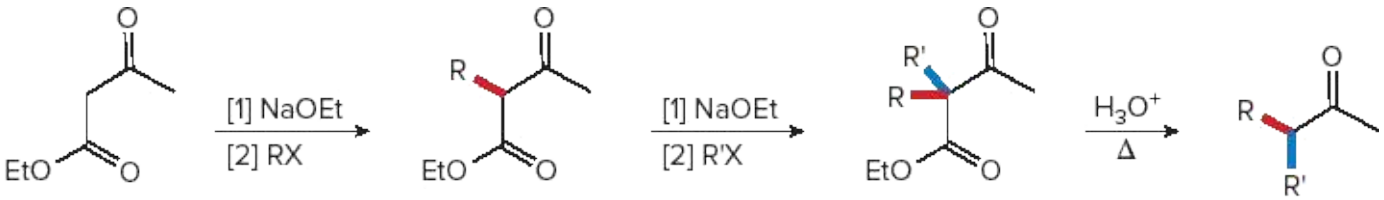


[1] Deprotonation. Treatment of ethyl acetoacetate with ^-OEt removes the acidic proton between the two carbonyl groups.

[2] Alkylation. The nucleophilic enolate reacts with an alkyl halide (RX) in an S_N2 reaction to form a substitution product. Because the mechanism is S_N2, the yields are higher when R is CH_3 or a 1° alkyl group.

[3] Hydrolysis and decarboxylation. Heating the β-keto ester with aqueous acid hydrolyzes the ester to a β-keto acid, which loses CO_2 to form a ketone.

If the first two steps of the reaction sequence are repeated *prior* to hydrolysis and decarboxylation, then a ketone having *two new alkyl groups* on the α carbon can be synthesized.

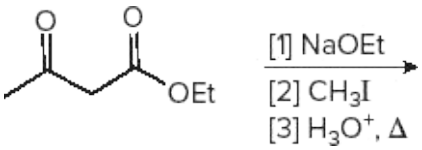


ethyl acetoacetate — new C–C bond in red — new C–C bond in blue

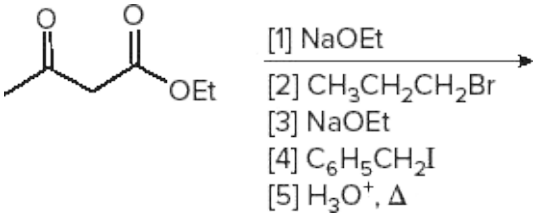
Problem 21.26

What ketones are prepared by the following reactions?

a.



b.

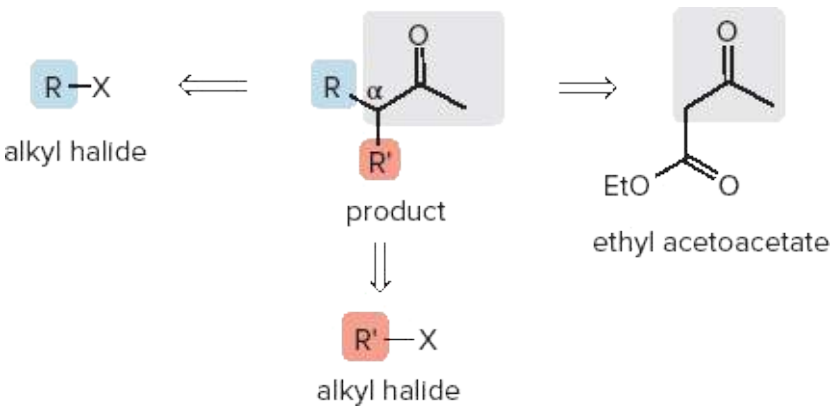


21.10B Retrosynthetic Analysis

To determine what starting materials are needed to prepare a given ketone using the acetoacetic ester synthesis, you must again work in the retrosynthetic direction. This involves a two-step process:

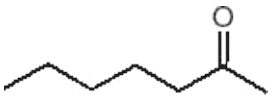
[1] Identify the alkyl groups bonded to the α carbon to the carbonyl group.

[2] Break the molecule into two (or three) components: Each alkyl group bonded to the α carbon comes from an alkyl halide. The remainder of the molecule comes from CH_3COCH_2COOEt.



For a ketone with two R groups on the α carbon, three components are needed.

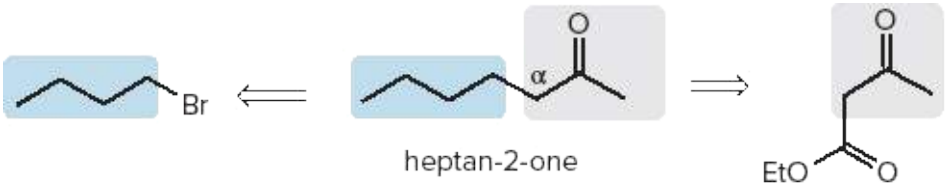
Sample Problem 21.5 **Determining the Starting Materials in an Acetoacetic Ester Synthesis What starting materials are needed to synthesize heptan-2-one using the acetoacetic ester synthesis?**



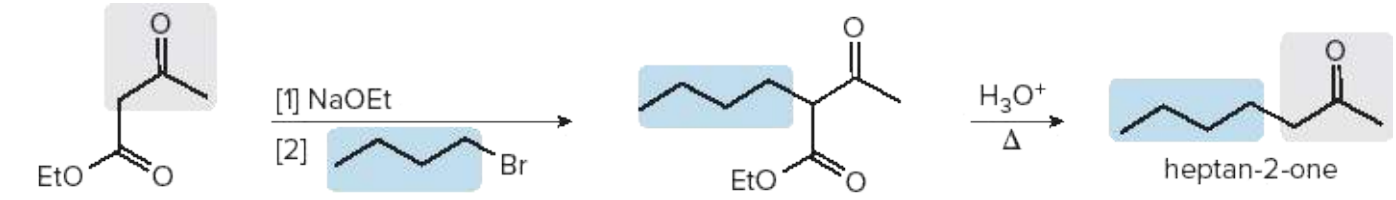
heptan-2-one

Solution

Heptan-2-one has only one alkyl group bonded to the α carbon, so only one alkyl halide is needed in the acetoacetic ester synthesis.



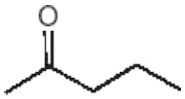
Writing the acetoacetic ester synthesis in the synthetic direction:



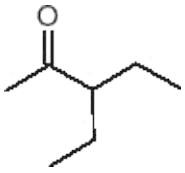
Problem 21.27

What alkyl halides are needed to prepare each ketone using the acetoacetic ester synthesis?

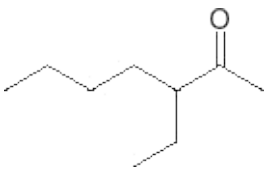
a.



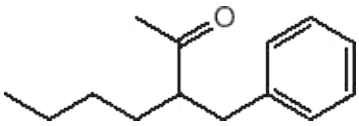
b.



c.



d.



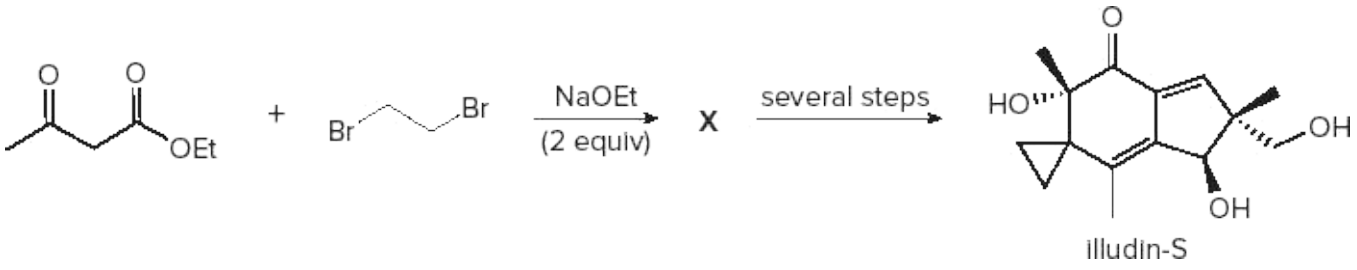
More Practice:

Try Problems 21.47, 21.48.

The jack-o'-lantern, source of the antitumor agent illudin-S (Problem 21.28) ©*iStock/Getty Images*

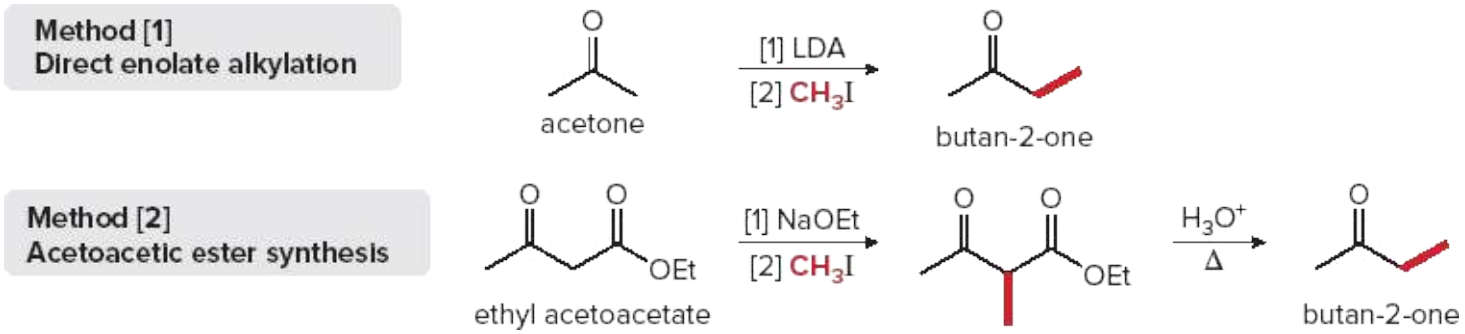
Problem 21.28

Treatment of ethyl acetoacetate with NaOEt (2 equiv) and $BrCH_2CH_2Br$ forms compound X. This reaction is the first step in the synthesis of illudin-S, an antitumor substance isolated from the jack-o'-lantern, a poisonous, saffron-colored mushroom. What is the structure of X?



illudin-S

The acetoacetic ester synthesis and direct enolate alkylation are two different methods that prepare similar ketones. Butan-2-one, for example, can be synthesized from acetone by direct enolate alkylation with CH_3I (Method [1]), or by alkylation of ethyl acetoacetate followed by hydrolysis and decarboxylation (Method [2]).



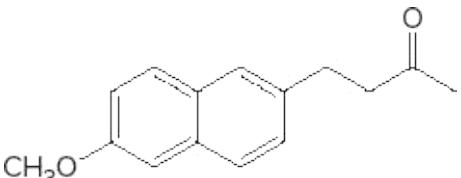
Why would you ever make butan-2-one from ethyl acetoacetate when you could make it in fewer steps from acetone? There are many factors to consider. First of all, synthetic organic chemists like to have a variety of methods to accomplish a single kind of reaction. Sometimes subtle changes in the structure of a starting material make one reaction work better than another.

In the chemical industry, moreover, cost is an important issue. Any reaction needed to make a large quantity of a useful drug or other consumer product must use cheap starting materials. Direct enolate alkylation usually requires a very strong base like LDA to be successful, whereas the acetoacetic ester synthesis utilizes NaOEt. NaOEt can be prepared from cheaper starting materials, and this makes the acetoacetic ester synthesis an attractive method, even though it involves more steps.

Thus, each method has its own advantages and disadvantages, depending on the starting material, the availability of reagents, the cost, and the occurrence of side reactions.

Problem 21.29

Nabumetone is a pain reliever and anti-inflammatory agent sold under the brand name of Relafen.



nabumetone

a. Write out a synthesis of nabumetone from ethyl acetoacetate.

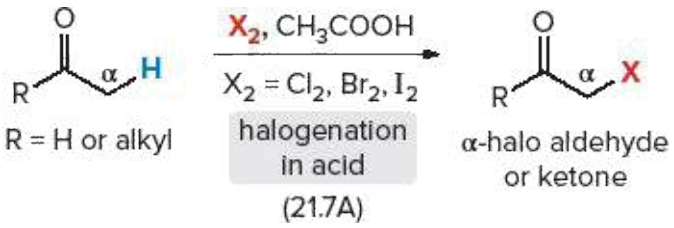
b. What ketone and alkyl halide are needed to synthesize nabumetone by direct enolate alkylation?

Chapter 21 REVIEW

KEY CONCEPTS

[1] Halogenation at the α carbon

1



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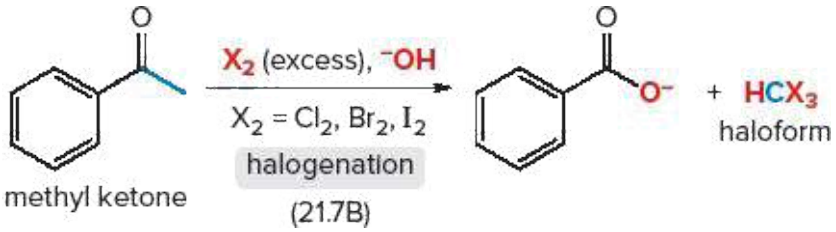
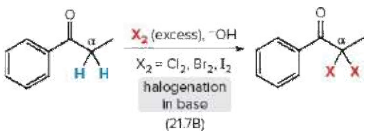


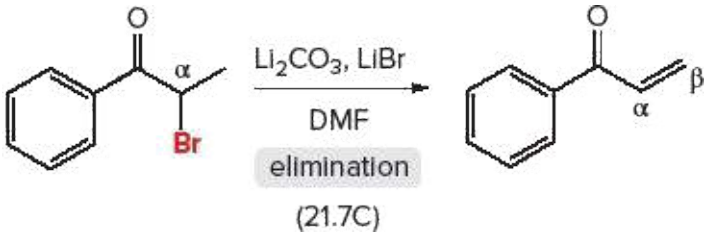
3



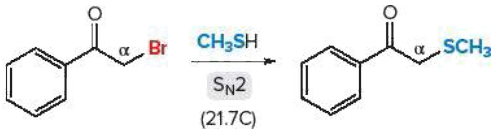
See Figure 21.3. Try Problems 21.41; 21.49e, f, h.

[2] Reactions of α-halo carbonyl compounds

1



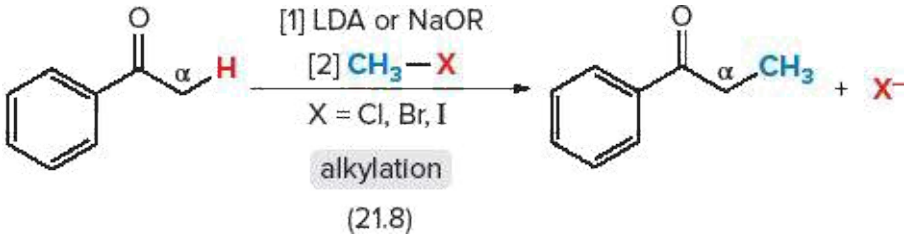
2



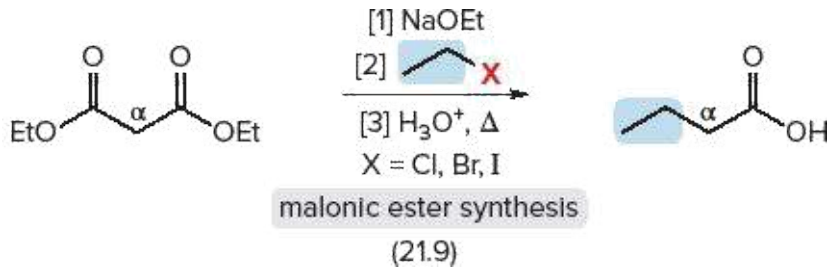
See Sample Problem 21.3. Try Problems 21.49c, e; 21.51; 21.52.

[3] Alkylation reactions at the α carbon

1



2



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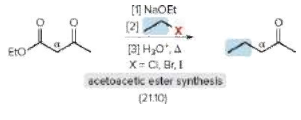

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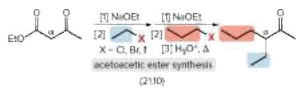
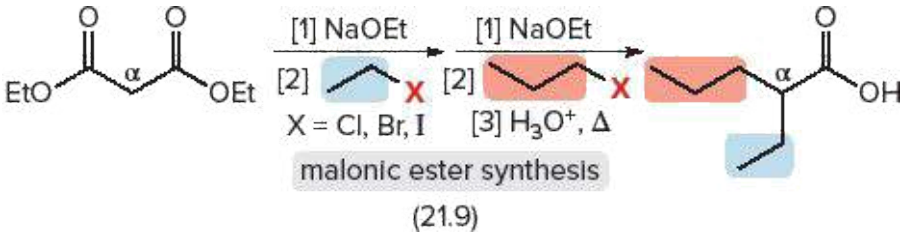


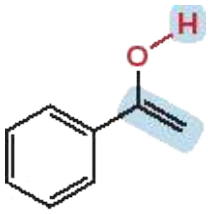
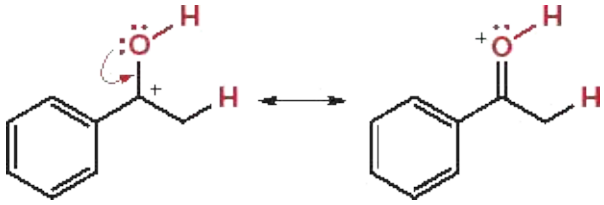
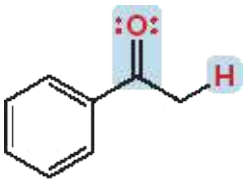
3



Try Problems 21.49b, d, g; 21.50; 21.56.

KEY SKILLS

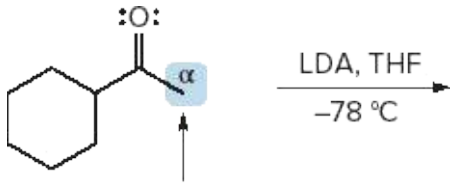
[1] Converting an enol to a keto tautomer in acid (21.2)

1 Locate the C=C and the H atom on the OH group.	**2** Add a proton to the C=C, and draw the two resonance structures.	**3** Remove a proton from the OH group.
 enol		 keto tautomer
• An enol tautomer has an OH group bonded to a C=C.	• The H adds to the C atom that is *not* attached to the OH group.	• A keto tautomer has a C=O and an additional C–H bond.

See Sample Problem 21.1. Try Problems 21.30, 21.32, 21.38a, 21.40.

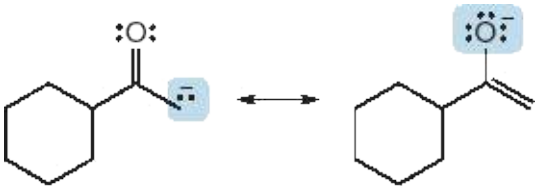
[2] Determining the major enolate formed in a reaction (21.4)

1 Identify the base and the proton to be removed.	**2** Draw the enolate.



less substituted C

- **LDA is a strong, nonnucleophilic base that removes a proton from the less substituted α carbon.**



resonance-stabilized **kinetic enolate**

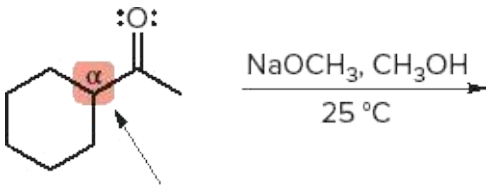
- **The kinetic enolate is less substituted and favored by strong base, polar aprotic solvent, and low temperature.**

See Sample Problem 21.2. Try Problem 21.36.

[3] Determining the major enolate formed in a reaction (21.4)

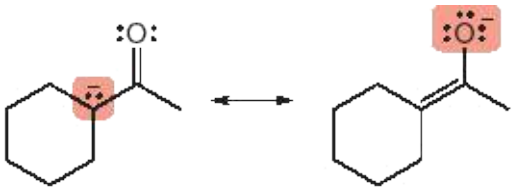
1 **Identify the base and the proton to be removed.**

2 **Draw the enolate.**



more substituted C

- **$NaOCH_3$ is a strong base that removes a proton from the more substituted α carbon.**



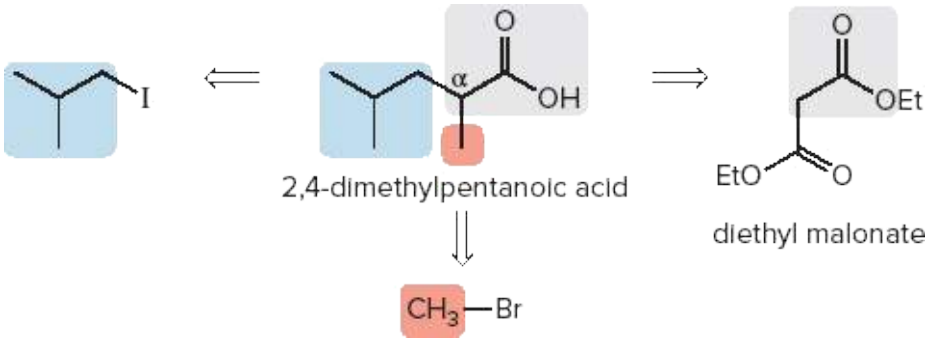
resonance-stabilized **thermodynamic enolate**

- **The thermodynamic enolate is more substituted and favored by strong base, polar protic solvent, and higher temperature.**

See Sample Problem 21.2.

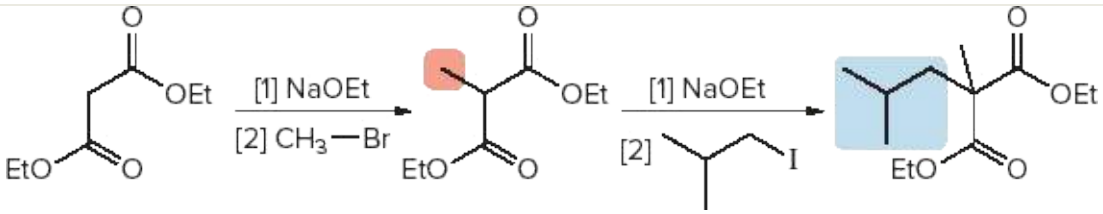
[4] Preparing a carboxylic acid using a malonic ester synthesis (21.9B); example: 2,4-dimethylpentanoic acid

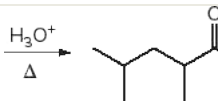
1 **Break the molecule into three components.**



2 **Deprotonate and alkylate the α carbon twice.**

3 **Hydrolyze esters and decarboxy**



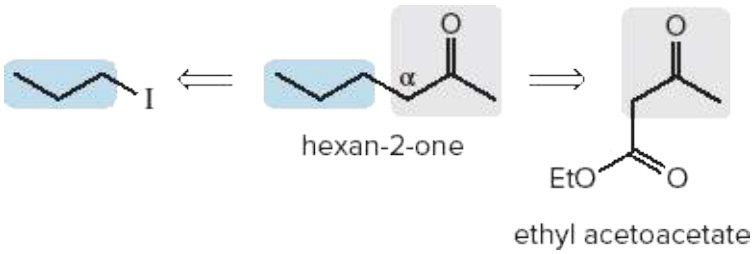


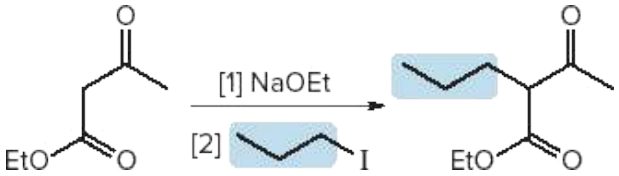
See Sample Problem 21.4. Try Problems 21.42-21.44.

[5] Preparing a ketone using the acetoacetic ester synthesis (21.10B); example: hexan-2-one

1 **Break the molecule into two components.**

2 **Deprotonate and alkylate the α carbon.**





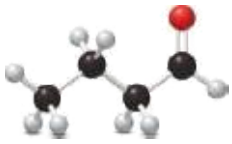
See Sample Problem 21.5. Try Problems 21.47, 21.48.

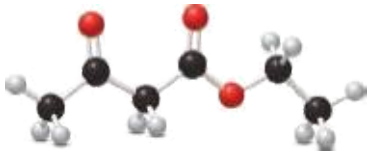
PROBLEMS

Problems Using Three-Dimensional Models

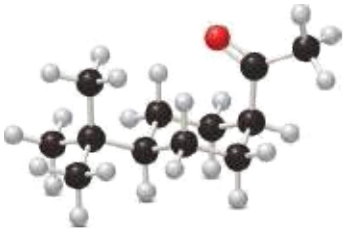
21.30 **Draw enol tautomer(s) for each compound. Ignore stereoisomers.**

a.



b. 

21.31 **The cis ketone A is isomerized to a trans ketone B with aqueous NaOH. A similar isomerization does not occur with ketone C. (a) Draw the structure of B using a chair cyclohexane. (b) Label the substituents in C as cis or trans, and explain the difference in reactivity.**

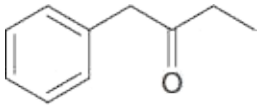


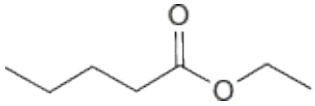
A

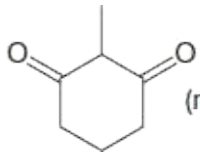
C

Enols, Enolates, and Acidic Protons

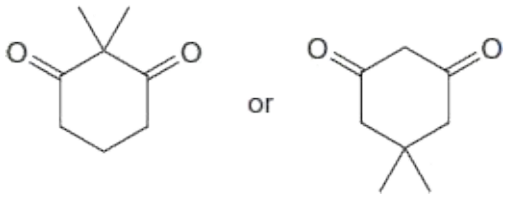
21.32 **Draw enol tautomer(s) for each compound.**

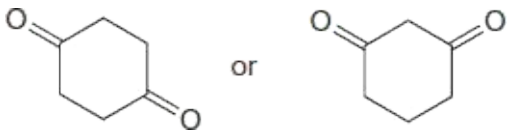
a. 

b. 

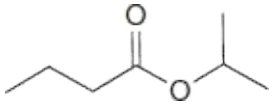
c. 
(mono enol form)

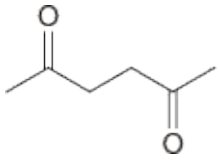
21.33 **Which carbonyl compound in each pair exhibits the higher percentage of the enol tautomer?**

a. 

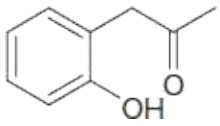
b. 

21.34 **What hydrogen atoms in each compound have a pK_a ≤ 25?**

a. 

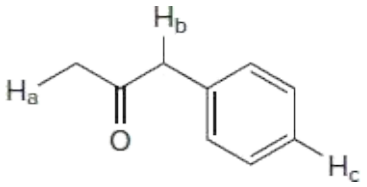
b. 

c.

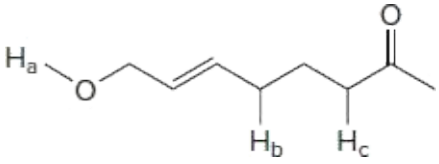


21.35 Rank the labeled protons in each compound in order of increasing acidity.

a.

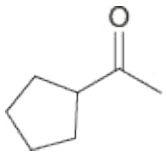


b.

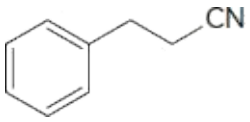


21.36 What is the major enolate (or carbanion) formed when each compound is treated with LDA?

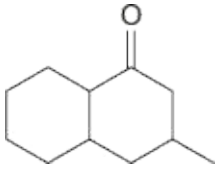
a.



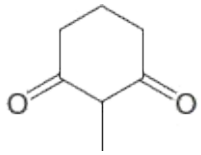
b.



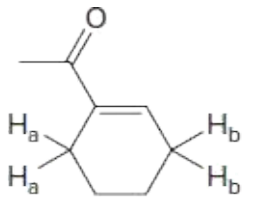
c.



d.

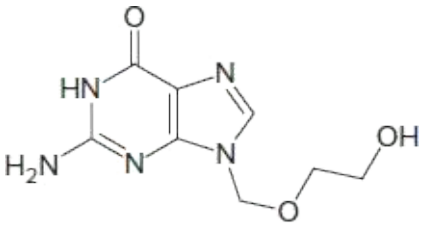


21.37 Why is the pK_a of the H_a protons in 1-acetylcyclohexene higher than the pK_a of the H_b protons?



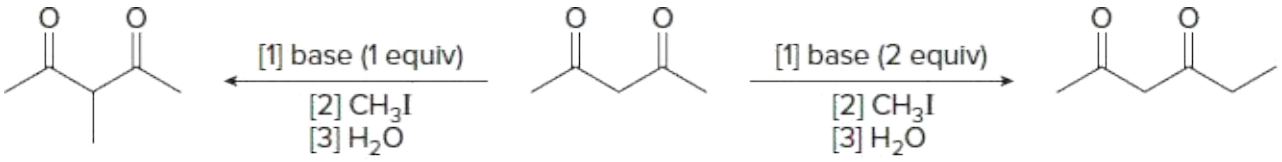
1-acetylcyclohexene

21.38 Acyclovir is an effective antiviral agent used to treat the herpes simplex virus. (a) Draw the enol form of acyclovir, and explain why it is aromatic. (b) Why is acyclovir typically drawn in its keto form, despite the fact that its enol is aromatic?



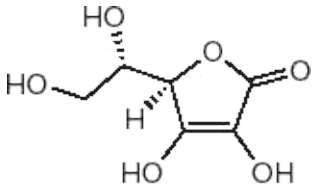
acyclovir

21.39 **Explain why pentane-2,4-dione forms two different alkylation products (A or B) when the number of equivalents of base is increased from one to two.**



A pentane-2,4-dione B

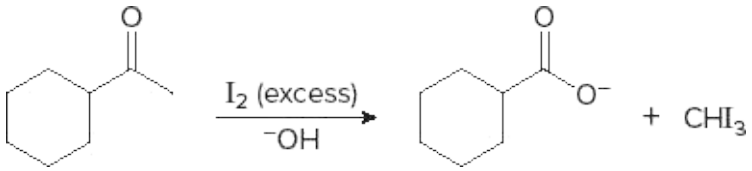
21.40 **Vitamin C is a stable enediol. Draw the structure of the two keto tautomers in equilibrium with the enediol, and explain why the enediol is more stable than the other tautomers.**



vitamin C
an enediol

Halogenation

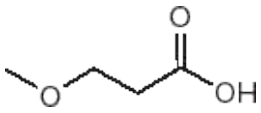
21.41 **Draw a stepwise mechanism for the following reaction.**



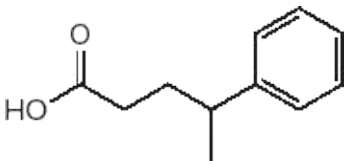
Malonic Ester Synthesis

21.42 **What alkyl halides are needed to prepare each carboxylic acid using the malonic ester synthesis?**

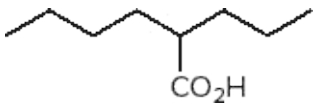
a.



b.

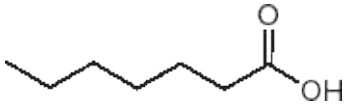


c.

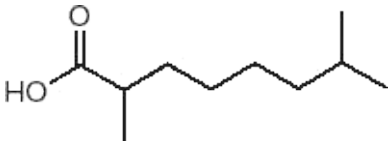


21.43 **Use the malonic ester synthesis to prepare each carboxylic acid.**

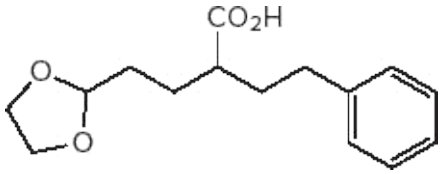
a.



b.

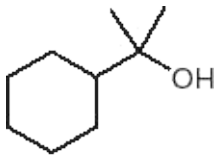


c.



21.44 **Devise a synthesis of valproic acid [$(CH_3CH_2CH_2)_2CHCO_2H$], a medicine used to treat epileptic seizures, using the malonic ester synthesis.**

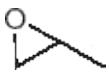
21.45 **Synthesize A from diethyl malonate and any needed organic compounds and inorganic reagents.**



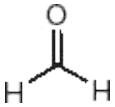
A

21.46 **The enolate derived from diethyl malonate reacts with a variety of electrophiles (not just alkyl halides) to form new carbon–carbon bonds. With this in mind, draw the products formed when $Na^+ {}^-CH(CO_2Et)_2$ reacts with each electrophile, followed by treatment with H_2O.**

a.



b.



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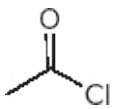
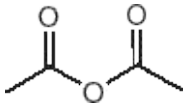


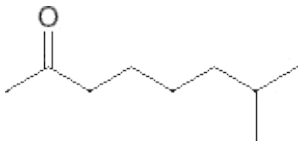
d.



Acetoacetic Ester Synthesis

21.47 **What alkyl halides are needed to prepare each ketone using the acetoacetic ester synthesis?**

a.



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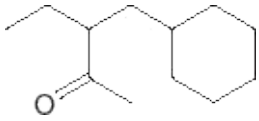
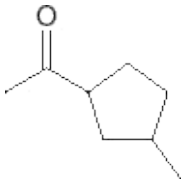
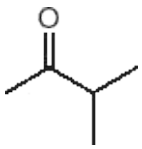


c.



21.48 **Synthesize each compound from ethyl acetoacetate. You may use any other organic compounds or inorganic reagents.**

a.



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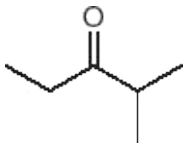

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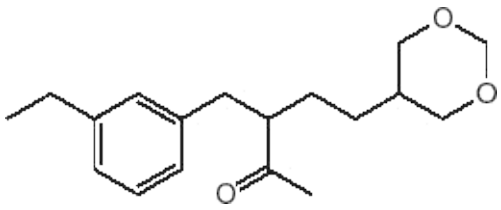
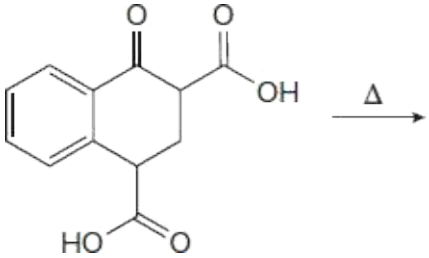


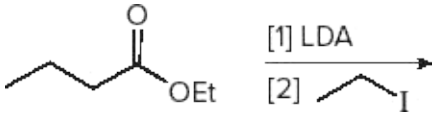
Reactions

21.49 **Draw the organic products formed in each reaction.**

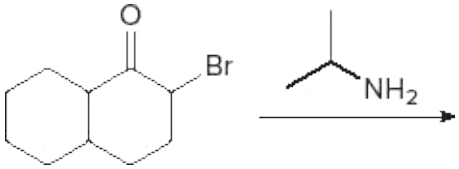
a.



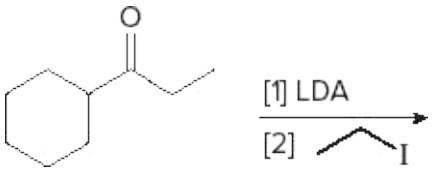
b.



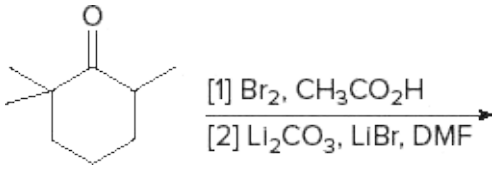
c.



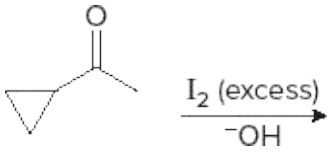
d.



e.

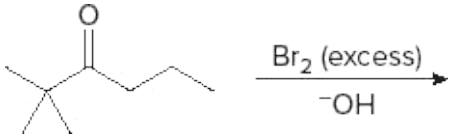


f.



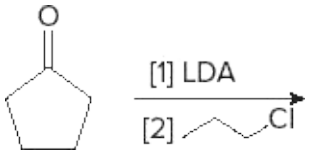
g.

h.

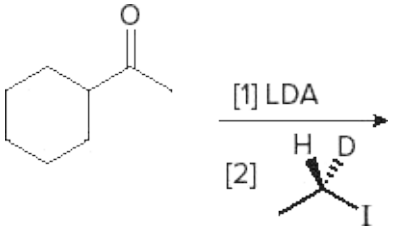


21.50 Draw the products formed (including stereoisomers) in each reaction.

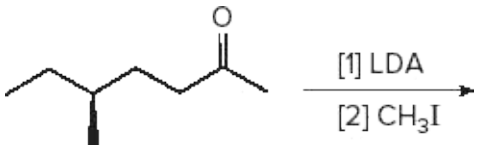
a.



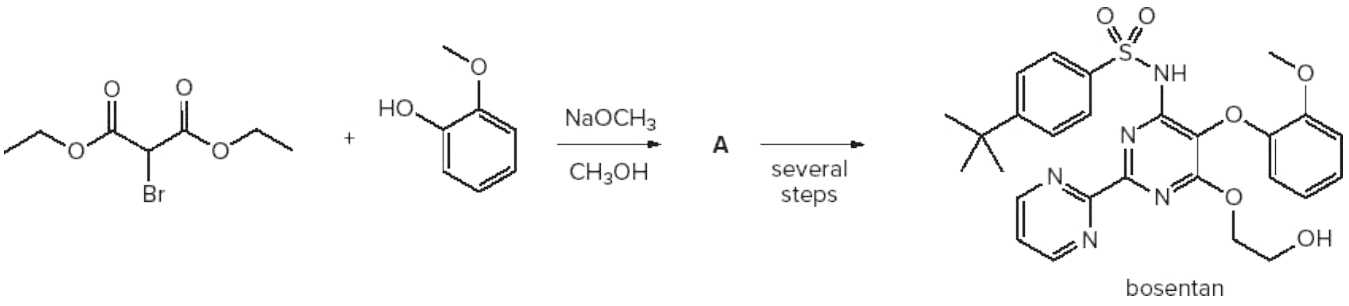
b.



c.



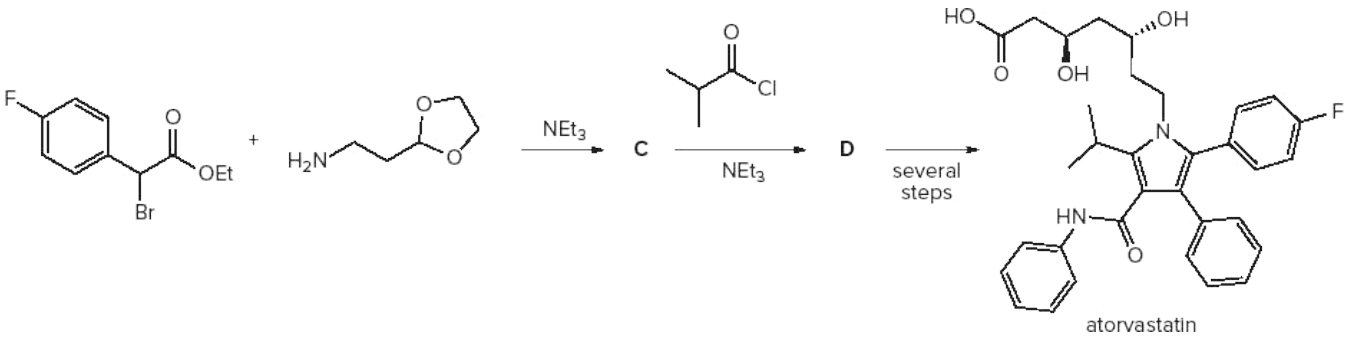
21.51 Identify A in the following reaction, one step in the synthesis of bosentan, a drug used to treat a chronic connective tissue disorder that can cause pulmonary hypertension and open wounds on the fingertips (digital ulcers). Identify the atoms in bosentan that originate in A.



bosentan

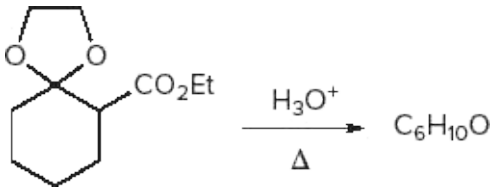
21.52 Identify C and D in the following reaction scheme, two steps in the synthesis of the cholesterol-lowering drug atorvastatin (trade name

Lipitor, Section 29.8).

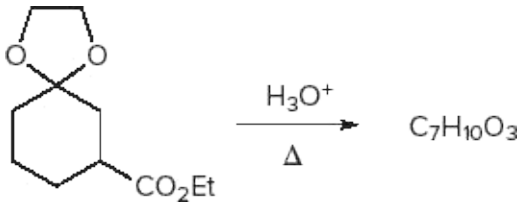


21.53 Identify the product in each reaction, and explain why starting materials with identical functional groups give different products.

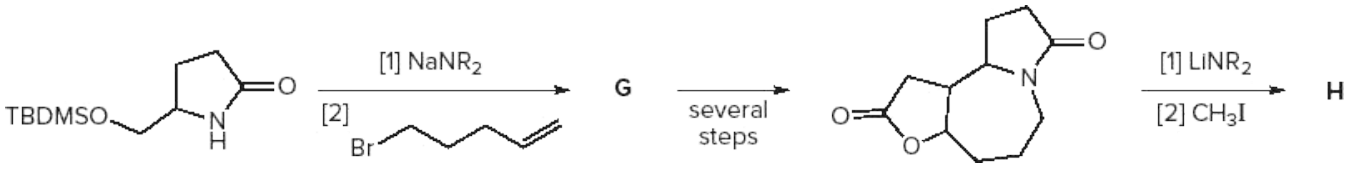
a.



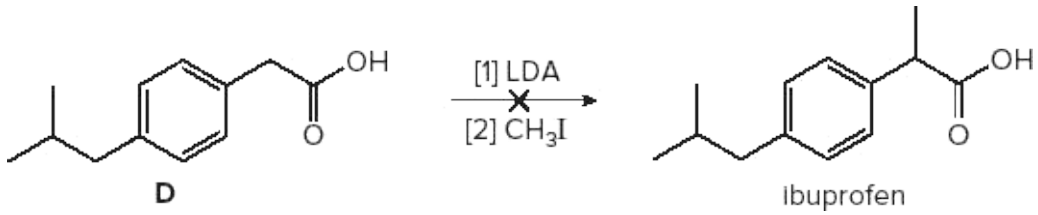
b.



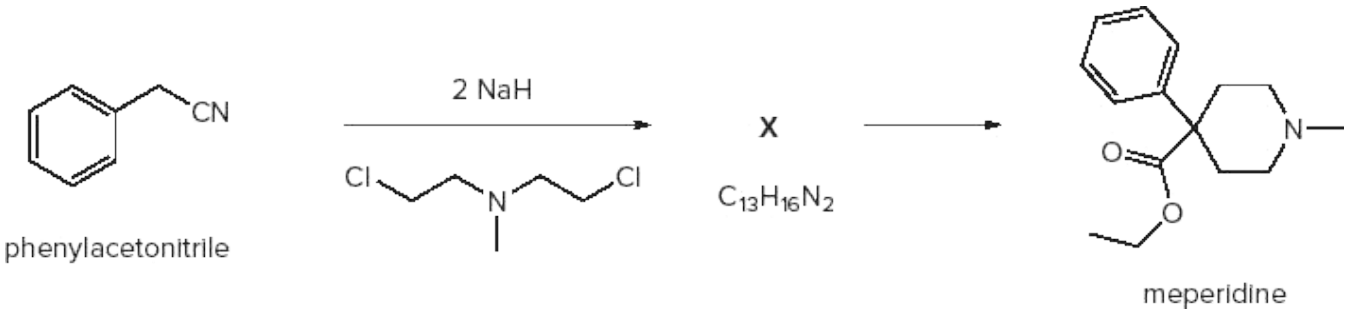
21.54 Identify compounds G and H in the following reaction scheme. H represents the structure of stemoamide, the chapter-opening molecule.



21.55 Direct alkylation of D by treatment with one equivalent of LDA and CH_3I does not form ibuprofen. Identify the product of this reaction and explain how it is formed.



21.56 A key step in the synthesis of the narcotic analgesic meperidine (trade name Demerol) is the conversion of phenylacetonitrile to X. (a) What is the structure of X? (b) What reactions convert X to meperidine?

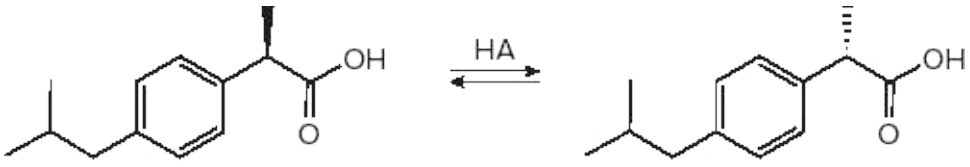


phenylacetonitrile

meperidine

Mechanism

21.57 Although ibuprofen is sold as a racemic mixture, only the *S* enantiomer acts as an analgesic. In the body, however, some of the *R* enantiomer is converted to the *S* isomer by tautomerization to an enol and then protonation to regenerate the carbonyl compound. Write a stepwise mechanism for this isomerization.



R isomer
inactive enantiomer

S isomer
active enantiomer

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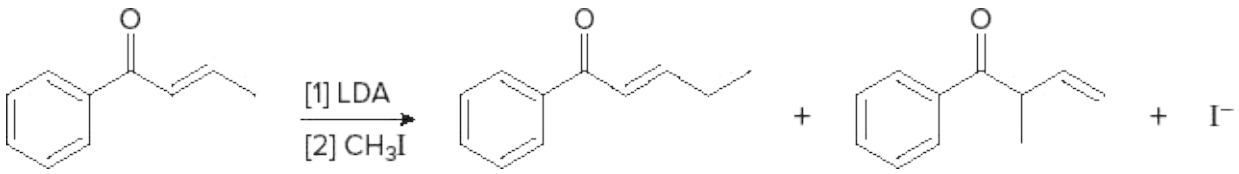
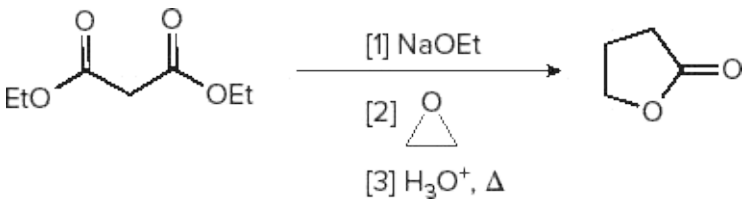
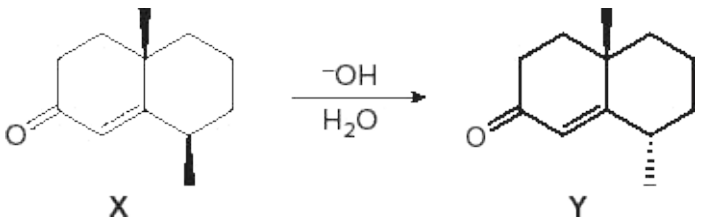
21.58 Draw a stepwise mechanism showing how two alkylation products are formed in the following reaction.



21.59 Draw a stepwise mechanism for the following reaction.

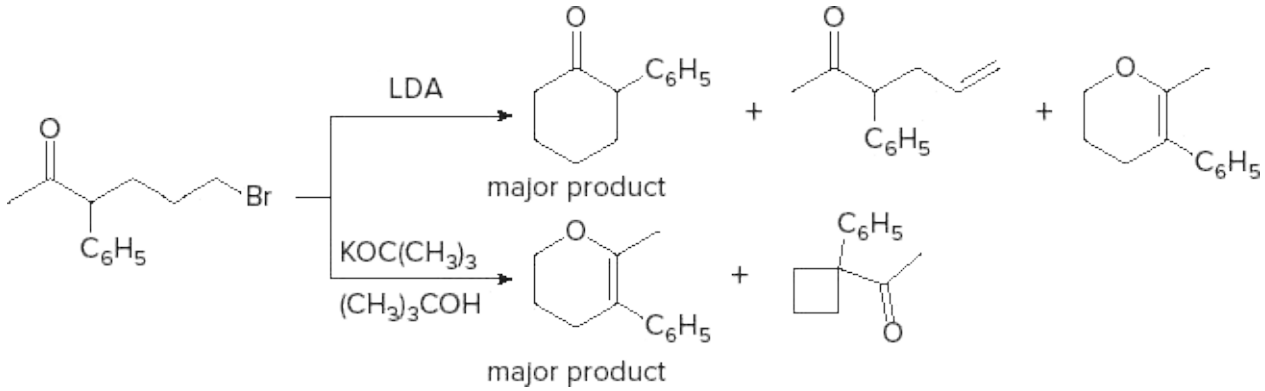


21.60 Treatment of α,β-unsaturated carbonyl compound X with base forms the diastereomer Y. Write a stepwise mechanism for this reaction. Explain why one stereogenic center changes configuration but the other does not.



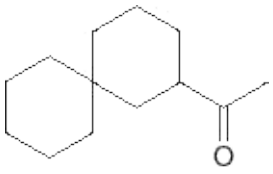
X Y

21.61 Draw stepwise mechanisms illustrating how each product is formed.



Synthesis

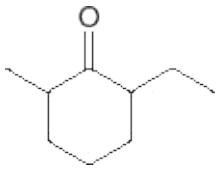
21.62 (a) Draw two different halo ketones that can form A by an intramolecular alkylation reaction. (b) How can A be synthesized by an acetoacetic ester synthesis?



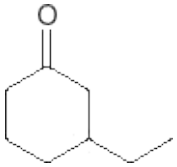
A

21.63 Synthesize each compound from cyclohexanone and organic halides having ≤ 4 C's. You may use any other inorganic reagents.

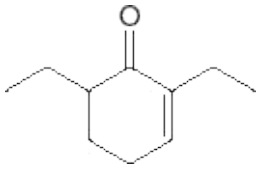
a.



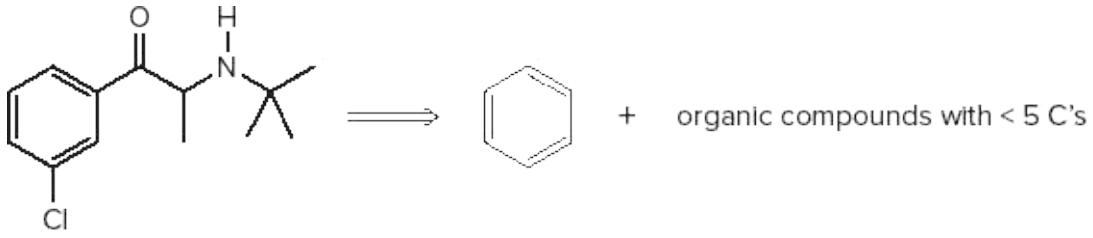
b.



c.

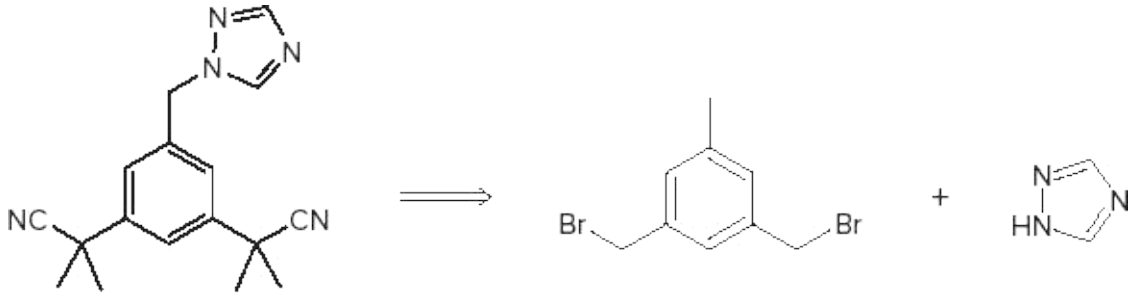


21.64 Bupropion, sold under the trade name of Zyban, is an antidepressant that was approved to aid smoking cessation in 1997. Devise a synthesis of bupropion from benzene, organic compounds that have fewer than five carbons, and any required inorganic reagents.



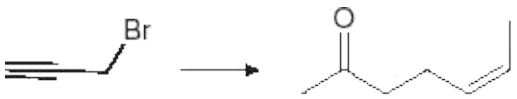
bupropion

21.65 **Devise a synthesis of anastrozole, a drug used to reduce the recurrence of breast cancer (Section 19.4), from the given compounds. You may use any other needed organic compounds or inorganic reagents.**



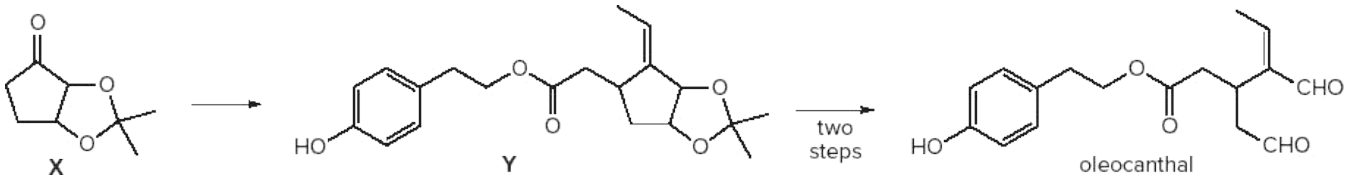
anastrozole

21.66 **Synthesize (*Z*)-hept-5-en-2-one from ethyl acetoacetate ($CH_3COCH_2CO_2Et$) and the given starting material. You may also use any other organic compounds or required inorganic reagents.**



(*Z*)-hept-5-en-2-one

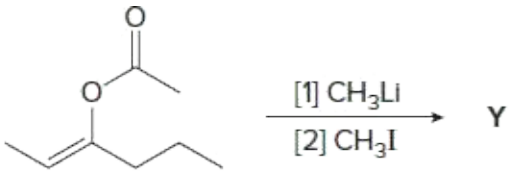
21.67 **Oleocanthal is a naturally occurring antioxidant isolated from olive oil. A published synthesis involved the conversion of ketone X to ester Y, which was converted in two steps to oleocanthal. Devise a synthesis of Y from X, phenol (C_6H_5OH), organic compounds with four or fewer carbons, and any needed organic and inorganic reagents.**



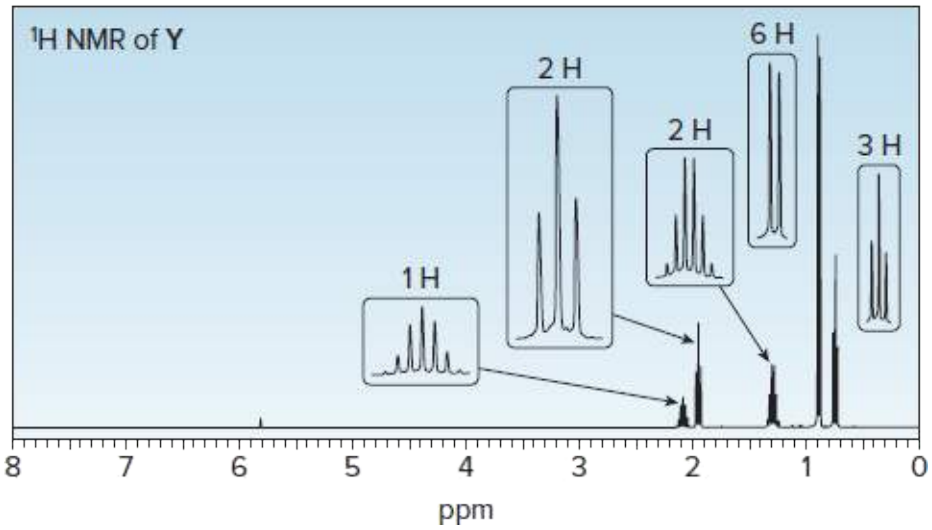
X Y oleocanthal

Spectroscopy

21.68 **Treatment of W with CH_3Li, followed by CH_3I, affords compound Y ($C_7H_{14}O$) as the major product. Y shows a strong absorption in its IR spectrum at 1713 cm^{-1}, and its ^1H NMR spectrum is given below. (a) Propose a structure for Y. (b) Draw a stepwise mechanism for the conversion of W to Y.**

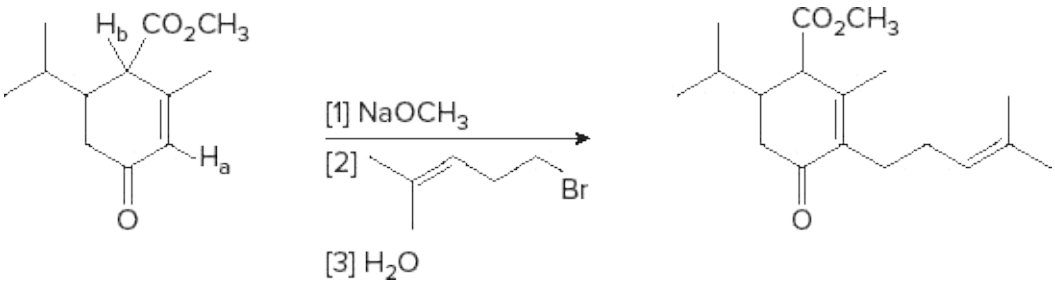


W

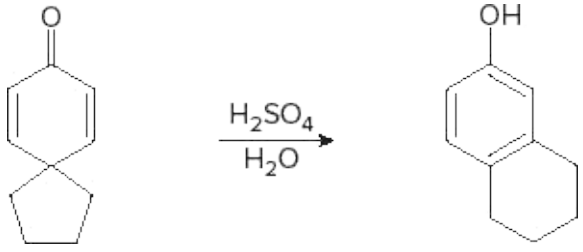


Challenge Problems

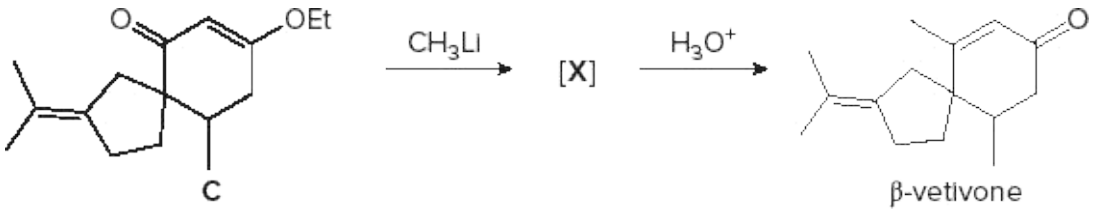
21.69 **Explain why H_a is much less acidic than H_b. Then draw a mechanism for the following reaction.**



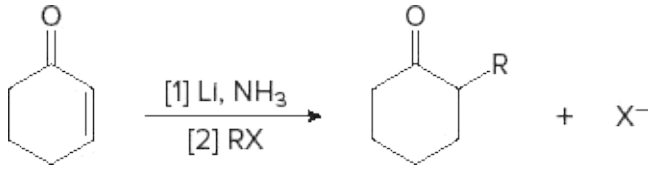
21.70 **Devise a stepwise mechanism for the following reaction.**



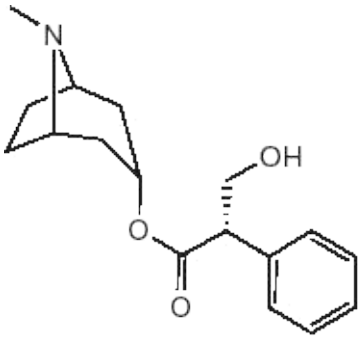
21.71 **The last step in the synthesis of β-vetivone, a major constituent of vetiver, a perennial grass found in tropical and subtropical regions of the world, involves treatment of C with CH_3Li to form an intermediate X, which forms β-vetivone with aqueous acid. Identify the structure of X and draw a mechanism for converting X to β-vetivone.**



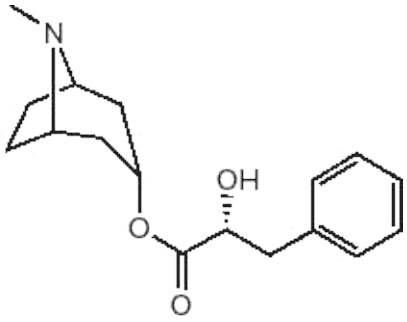
21.72 **Keeping in mind the mechanism for the dissolving metal reduction of alkynes to trans alkenes in Chapter 12, write a stepwise mechanism for the following reaction, which involves the conversion of an α,β-unsaturated carbonyl compound to a carbonyl compound with a new alkyl group on the α carbon.**



21.73 **(−)-Hyoscyamine, an optically active drug used to treat gastrointestinal disorders, is isolated from *Atropa belladonna*, the deadly nightshade plant, by a basic aqueous extraction procedure. If too much base is used during isolation, optically inactive material is isolated. (a) Explain this result by drawing a stepwise mechanism. (b) Explain why littorine, an isomer isolated from the tailflower plant in Australia, can be obtained optically pure regardless of the amount of base used during isolation.**



(–)-hyoscyamine



(–)-littorine

Carbonyl Condensation Reactions

22

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22.1 The aldol reaction

22.2 Crossed aldol reactions

22.3 Directed aldol reactions

22.4 Intramolecular aldol reactions

22.5 The Claisen reaction

22.6 The crossed Claisen and related reactions
22.7 The Dieckmann reaction
22.8 The Michael reaction
22.9 The Robinson annulation

Ibuprofen is the generic name for the pain reliever known by the trade names of Motrin and Advil. Like aspirin, ibuprofen acts as an anti-inflammatory agent by blocking the synthesis of prostaglandins from arachidonic acid. One step in a commercial synthesis of ibuprofen involves the reaction of a nucleophilic enolate with an electrophilic carbonyl group. In Chapter 22, we learn about the carbon–carbon bond-forming reactions of enolates with carbonyl electrophiles.

Why Study …

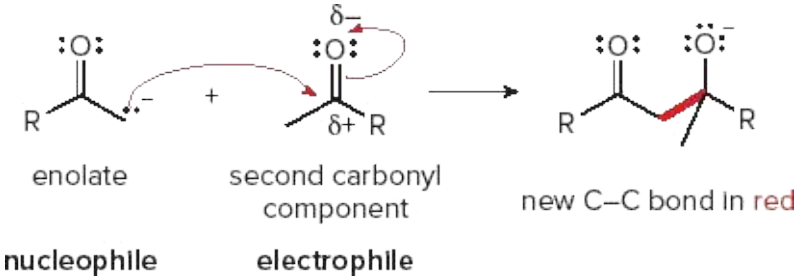
Carbonyl Condensation Reactions?

In Chapter 22, we examine carbonyl condensations—that is, reactions between two carbonyl compounds—a second type of reaction that occurs at the α carbon of a carbonyl group. Much of what is presented in Chapter 22 applies principles you have already learned. Many of the reactions may look more complicated than those in previous chapters, but they are fundamentally the same. Nucleophiles attack electrophilic carbonyl groups to form the products of nucleophilic addition or substitution, depending on the structure of the carbonyl starting material.

Every reaction in Chapter 22 forms a new carbon–carbon bond at the α carbon to a carbonyl group, so these reactions are extremely useful in the synthesis of complex natural products.

22.1 The Aldol Reaction

Chapter 22 concentrates on the second general reaction of enolates—reaction with other carbonyl compounds. In these reactions, one carbonyl component serves as the nucleophile and one serves as the electrophile, and a new carbon–carbon bond is formed.



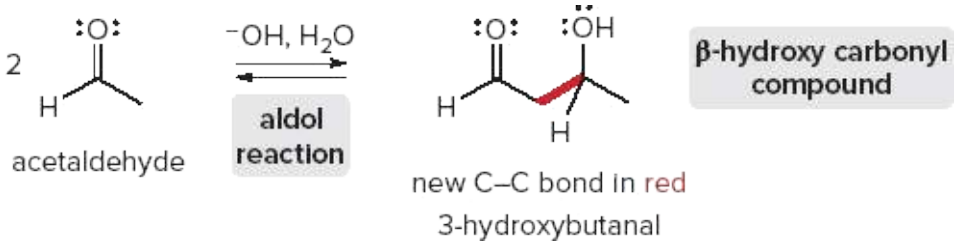
The presence or absence of a leaving group on the electrophilic carbonyl carbon determines the structure of the product. Even though they appear somewhat more complicated, these reactions are often reminiscent of the nucleophilic addition and nucleophilic acyl substitution reactions of Chapters 18 and 20. Four types of reactions are examined:

- Aldol reaction (Sections 22.1–22.4)
- Claisen reaction (Sections 22.5–22.7)
- Michael reaction (Section 22.8)
- Robinson annulation (Section 22.9)

22.1A General Features of the Aldol Reaction

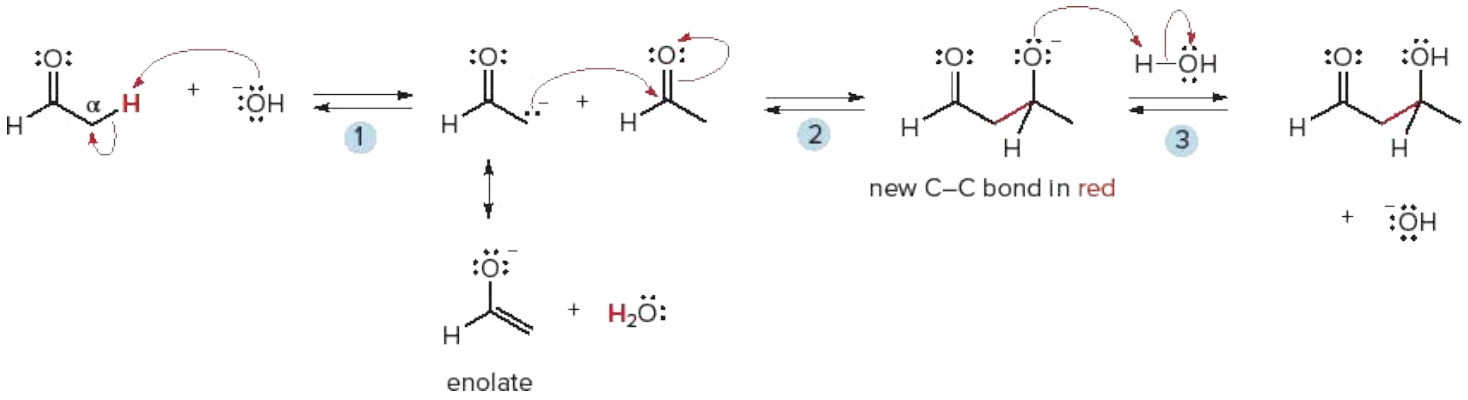
Many aldol products contain an *aldehyde* and an alcoh*ol*—hence the name *aldol*.

In the aldol reaction, two molecules of an aldehyde or ketone react with each other in the presence of base to form a β-hydroxy carbonyl compound. For example, treatment of acetaldehyde with aqueous $^-$OH forms 3-hydroxybutanal, a β-hydroxy aldehyde.



The mechanism of the aldol reaction has three steps, as shown in Mechanism 22.1. Carbon–carbon bond formation occurs in Step [2], when the nucleophilic enolate reacts with the electrophilic carbonyl carbon.

Mechanism 22.1 The Aldol Reaction

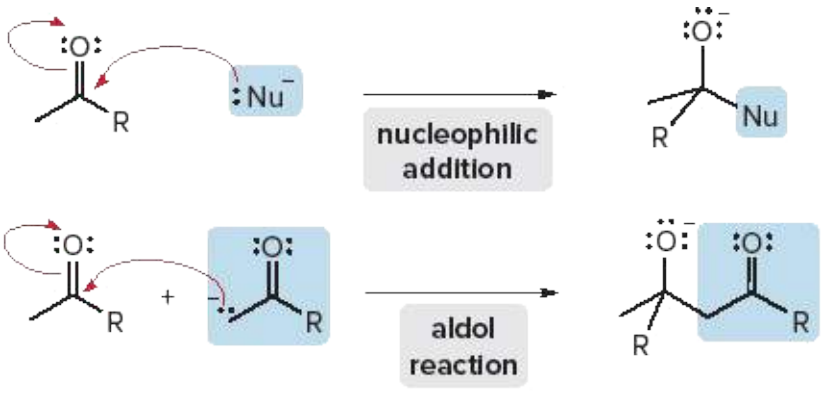


1. **The base removes a proton on the α carbon to form a resonance-stabilized enolate.**
2. **Nucleophilic attack of the enolate on an electrophilic carbonyl in another molecule of aldehyde forms a new C—C bond.**
3. **Protonation of the alkoxide forms the β-hydroxy aldehyde.**

The aldol reaction is a reversible equilibrium, so the position of the equilibrium depends on the base and the carbonyl compound. $^-$OH is the base typically used in an aldol reaction. Recall from Section 21.3B that only a small amount of enolate forms with $^-$OH. In this case, that's appropriate because the starting aldehyde is needed to react with the enolate in the second step of the mechanism.

Aldol reactions can be carried out with either aldehydes or ketones. With aldehydes, the equilibrium usually favors the products, but with ketones the equilibrium favors the starting materials. There are ways of driving this equilibrium to the right, however, so we will write aldol products whether the substrate is an aldehyde or a ketone.

- **The characteristic reaction of aldehydes and ketones is *nucleophilic addition* (Section 18.7). An aldol reaction is a nucleophilic addition in which an enolate is the nucleophile. See the comparison in Figure 22.1.**



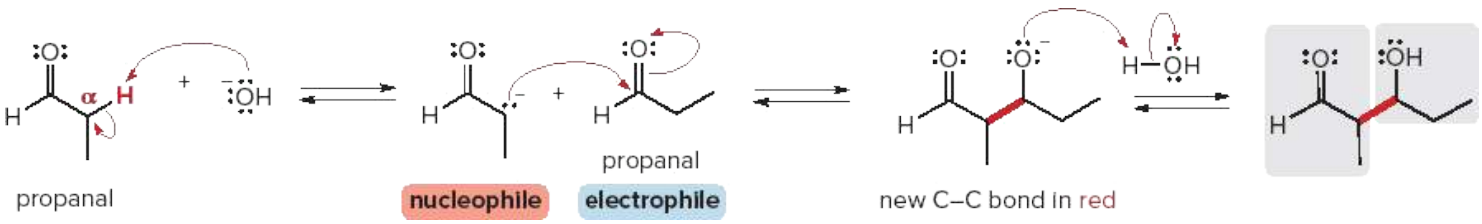
- Aldehydes and ketones react by nucleophilic addition. In an aldol reaction, **an enolate is the nucleophile** that adds to the carbonyl group.

Figure 22.1 The aldol reaction—An example of nucleophilic addition

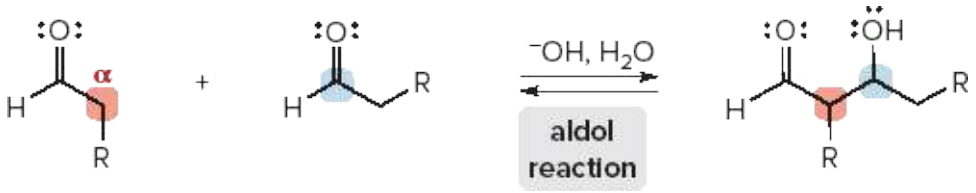
- Aldehydes and ketones react by nucleophilic addition. In an aldol reaction, an enolate is the nucleophile that adds to the carbonyl group.

A second example of an aldol reaction is shown with propanal as starting material. The two molecules of the aldehyde that participate in the aldol reaction react in opposite ways:

- **One molecule of propanal becomes an enolate—an electron-rich *nucleophile.***
- **One molecule of propanal serves as the *electrophile* because its carbonyl carbon is electron deficient.**



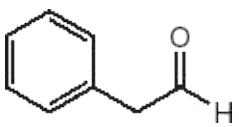
These two examples illustrate the general features of the aldol reaction. The α carbon of one carbonyl component becomes bonded to the carbonyl carbon of the other component.



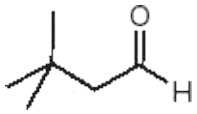
Problem 22.1

Draw the aldol product formed from each compound.

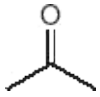
a.

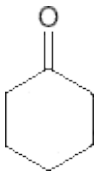


b.



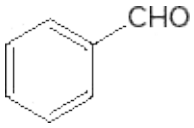
c.

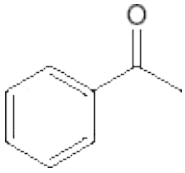


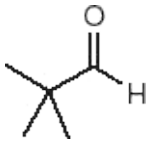
d. 

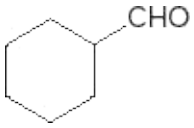
Problem 22.2

Which carbonyl compounds do not undergo an aldol reaction when treated with OH in H_2O?

a. 

b. 

c. 

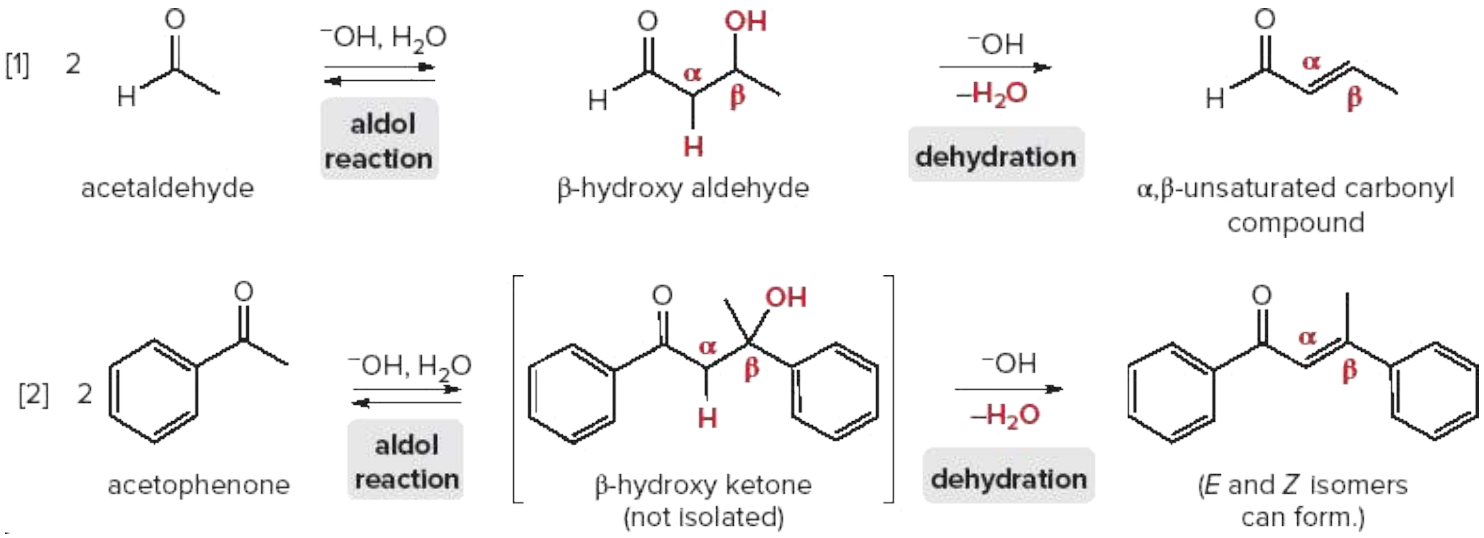
d. 

22.1B Dehydration of the Aldol Product

All alcohols—including β-hydroxy carbonyl compounds—dehydrate in the presence of *acid.* Only β-hydroxy carbonyl compounds dehydrate in the presence of base.

An aldol reaction is often called an aldol condensation, because the β-hydroxy carbonyl compound that is initially formed loses H_2O by dehydration. A *condensation reaction* is one in which a small molecule, in this case H_2O, is eliminated during a reaction.

The β-hydroxy carbonyl compounds formed in the aldol reaction dehydrate more readily than other alcohols. In fact, under the basic reaction conditions, the initial aldol product is often not isolated. Instead, it loses the elements of H_2O from the α and β carbons to form an α,β-unsaturated carbonyl compound, a conjugated product.

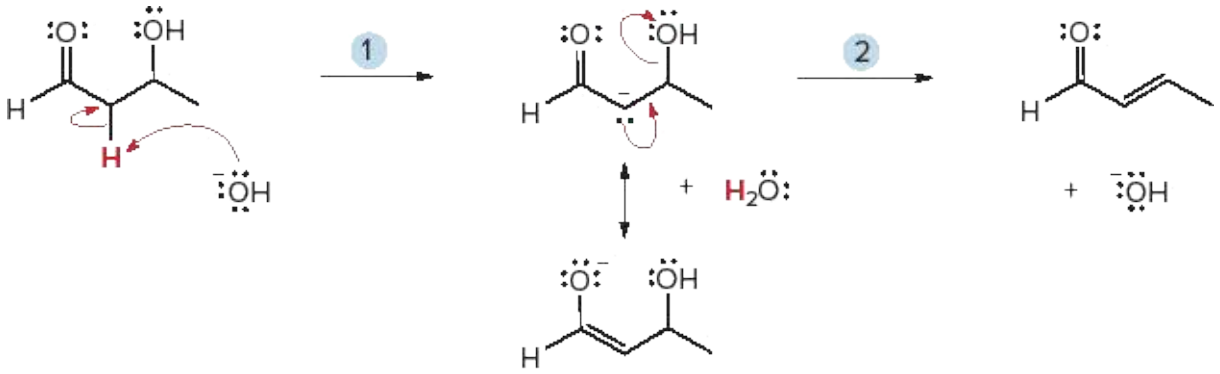


It may or may not be possible to isolate the β-hydroxy carbonyl compound under the conditions of the aldol reaction.

- **When the α,β-unsaturated carbonyl compound is *also conjugated* with a carbon–carbon double bond or a benzene ring, as in the case of Reaction [2], elimination of H_2O is spontaneous and the β-hydroxy carbonyl compound cannot be isolated.**

The mechanism of dehydration consists of two steps: deprotonation Page 1015 followed by loss of ⁻OH, as shown in Mechanism 22.2.

Mechanism 22.2 Dehydration of β-Hydroxy Carbonyl Compounds with Bases



1. **The base removes a proton on the α carbon to form a resonance-stabilized enolate.**
2. **⁻OH is eliminated as the electron pair of the enolate forms the new π bond.**

Like E1 elimination, E1cB requires two steps. Unlike E1, though, the intermediate in E1cB is a *carbanion*, not a carbocation. E1cB stands for Elimination, unimolecular, conjugate base.

This elimination mechanism, called the E1cB mechanism, differs from the two more general mechanisms of elimination, E1 and E2, which were discussed in Chapter 8. The E1cB mechanism involves two steps and proceeds by way of an anionic intermediate.

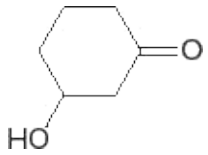
Regular alcohols dehydrate only in the presence of acid but not base, because hydroxide is a poor leaving group. When the hydroxy group is β to a carbonyl group, however, loss of H and OH from the α and β carbons forms a conjugated double bond, and the stability of the conjugated system makes up for having such a poor leaving group.

Dehydration of the initial β-hydroxy carbonyl compound drives the equilibrium of an aldol reaction to the right, thus favoring product formation. Once the conjugated α,β-unsaturated carbonyl compound forms, it is *not* re-converted to the β-hydroxy carbonyl compound.

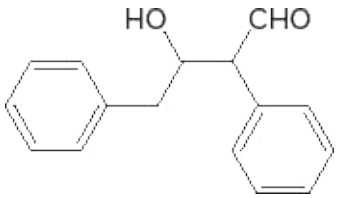
Problem 22.3

What unsaturated carbonyl compound is formed by dehydration of each β-hydroxy carbonyl compound?

a.



b.



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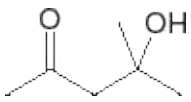
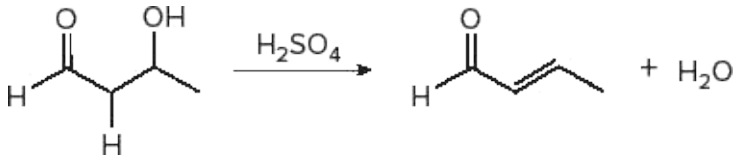


Problem 22.4

Acid-catalyzed dehydration of β-hydroxy carbonyl compounds occurs by the mechanism discussed in Section 9.8. With this in mind, draw a stepwise mechanism for the following reaction.



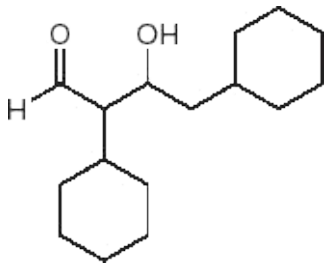
22.1C Retrosynthetic Analysis

To utilize the aldol reaction in synthesis, you must be able to determine which aldehyde or ketone is needed to prepare a particular β-hydroxy carbonyl compound or α,β-unsaturated carbonyl compound—that is, you must be able to work backwards, in the retrosynthetic direction.

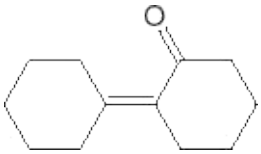
How To Synthesize a Compound Using the Aldol Reaction

Example What starting material is needed to prepare each compound by an aldol reaction?

a.



b.



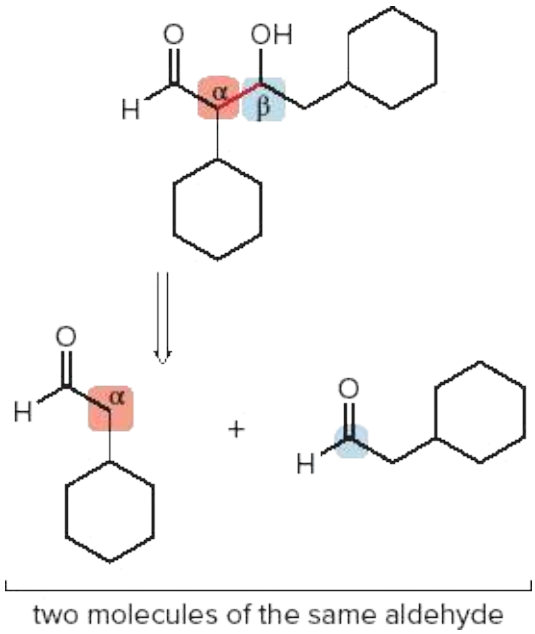
Step [1] **Locate the α and β carbons of the carbonyl group.**

- **When a carbonyl group has two different α carbons, choose the side that contains the OH group (in a β-hydroxy carbonyl compound) or is part of the C=C (in an α,β-unsaturated carbonyl compound).**

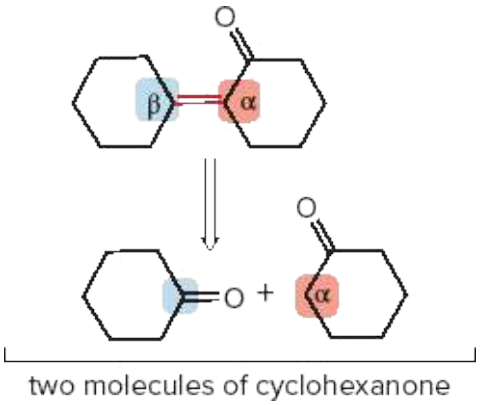
Step [2] **Break the molecule into two components between the α and β carbons.**

- **The α carbon and all remaining atoms bonded to it belong to one carbonyl component. The β carbon and all remaining atoms bonded to it belong to the other carbonyl component. Both components are identical in all aldols we have thus far examined.**

  a. **Break the molecule into two halves at the labeled bond.**



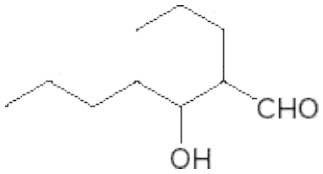
b. Break the molecule into two halves at the labeled bond.



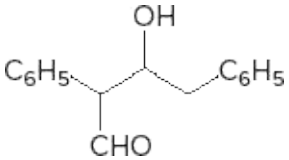
Problem 22.5

What aldehyde or ketone is needed to prepare each compound by an aldol reaction?

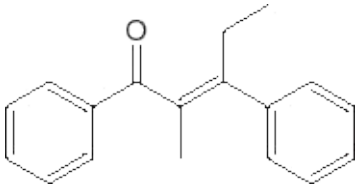
a.



b.



c.



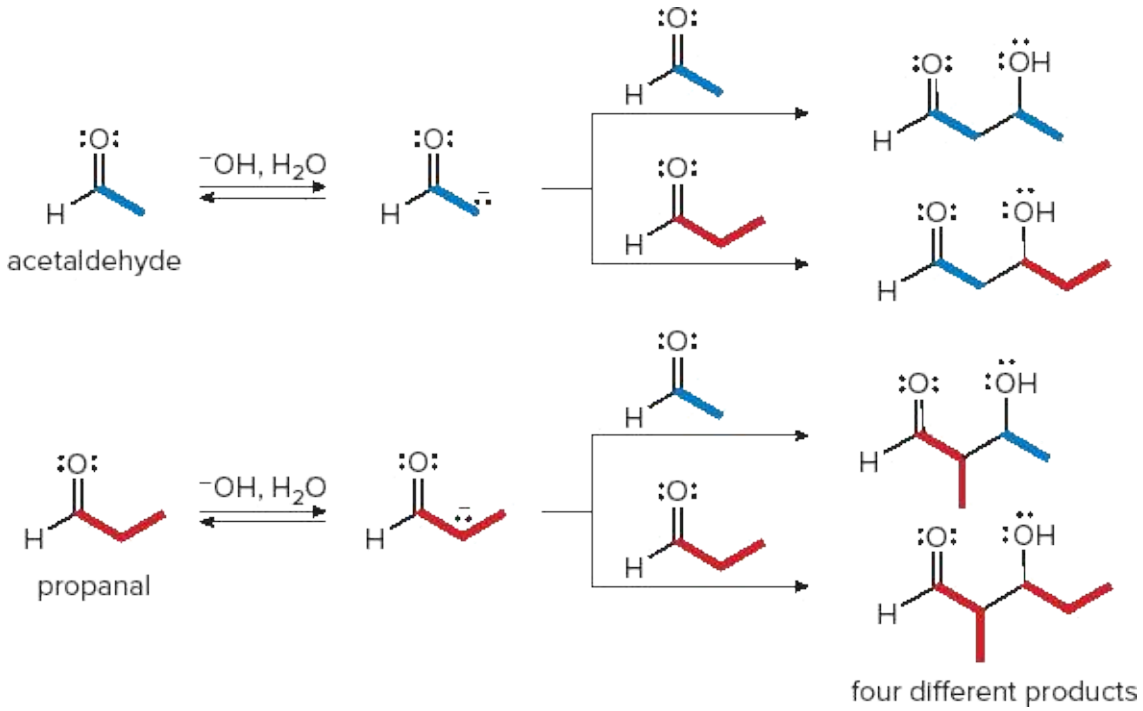
22.2 Crossed Aldol Reactions

In all of the aldol reactions discussed so far, the electrophilic carbonyl and the nucleophilic enolate have originated from the *same* aldehyde or ketone. Sometimes, though, it is possible to carry out an aldol reaction between two *different* carbonyl compounds.

- **An aldol reaction between two different carbonyl compounds is called a *crossed aldol* or *mixed aldol reaction*.**

22.2A A Crossed Aldol Reaction with Two Different Aldehydes, Both Having α H Atoms

When two different aldehydes, both having α H atoms, are combined in an aldol reaction, *four* different β-hydroxy carbonyl compounds are formed. Four products form, not one, because *both* aldehydes can lose an acidic α hydrogen atom and form an enolate in the presence of base. *Both* enolates can then react with *both* carbonyl compounds, as shown for acetaldehyde and propanal in the following reaction scheme.



- **Conclusion: When two different aldehydes have α hydrogens, a crossed aldol reaction is *not* synthetically useful.**

22.2B Synthetically Useful Crossed Aldol Reactions

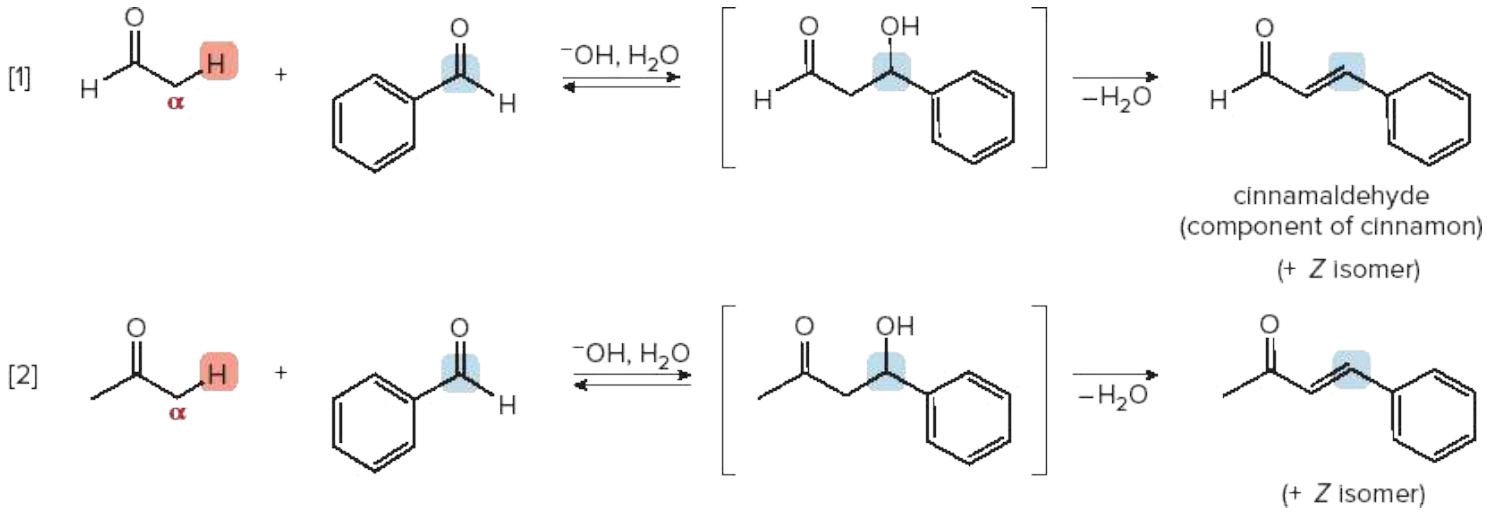
Crossed aldols are synthetically useful in two different situations.

- **A crossed aldol occurs when only *one* carbonyl component has α H**

atoms.

When one carbonyl compound has no α hydrogens, a crossed aldol reaction often leads to one product. Two common carbonyl compounds with no α hydrogens used for this purpose are formaldehyde (CH_2=O) and benzaldehyde (C_6H_5CHO).

For example, reaction of C_6H_5CHO (as the electrophile) with either acetaldehyde (CH_3CHO) or acetone [$(CH_3)_2C$=O] in the presence of base forms a single α,β-unsaturated carbonyl compound after dehydration.



The yield of a single crossed aldol product is increased further if the electrophilic carbonyl component is relatively unhindered (as is the case with most aldehydes) and if it is used in excess.

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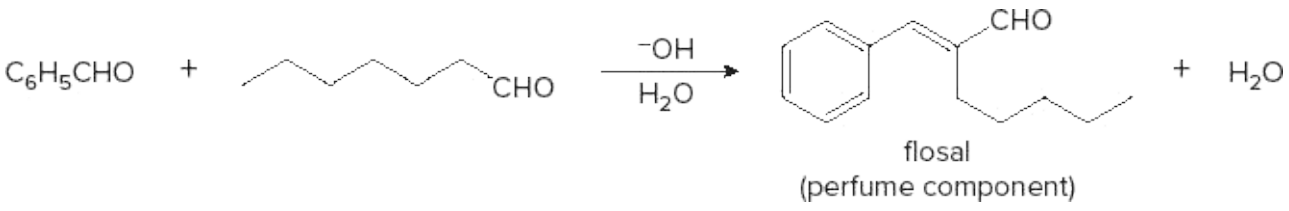
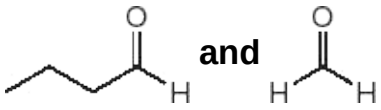
Problem 22.6

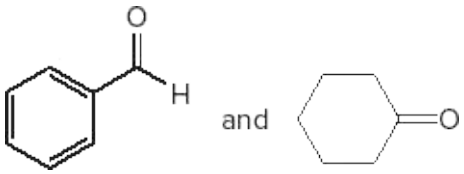
2-Pentylcinnamaldehyde, commonly called flosal, is a perfume ingredient with a jasmine-like odor. Flosal is an α,β-unsaturated aldehyde made by a crossed aldol reaction between benzaldehyde (C_6H_5CHO) and heptanal ($CH_3CH_2CH_2CH_2CH_2CH_2CHO$), followed by dehydration. Draw a stepwise mechanism for the following reaction that prepares flosal.



Problem 22.7

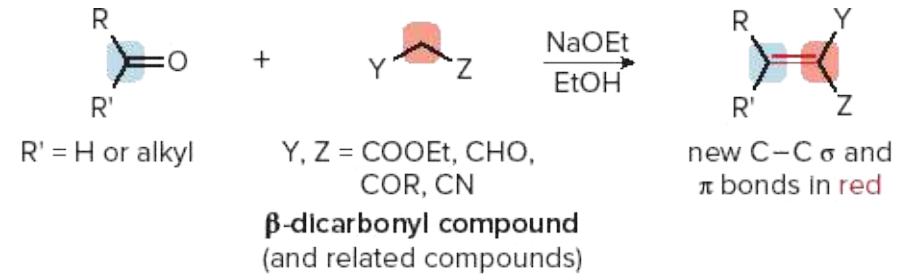
Draw the products formed in each crossed aldol reaction.

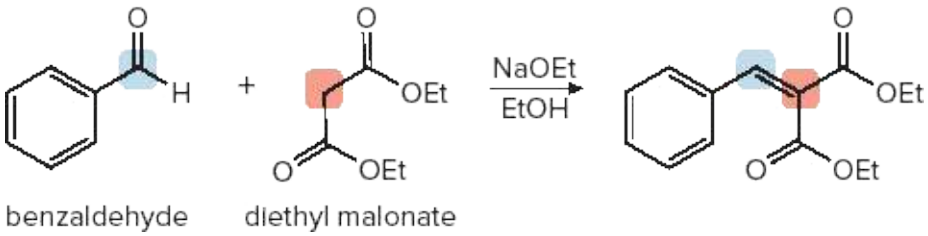
a.  **and**

b. 

- **A crossed aldol occurs when one carbonyl component has especially acidic α H atoms.**

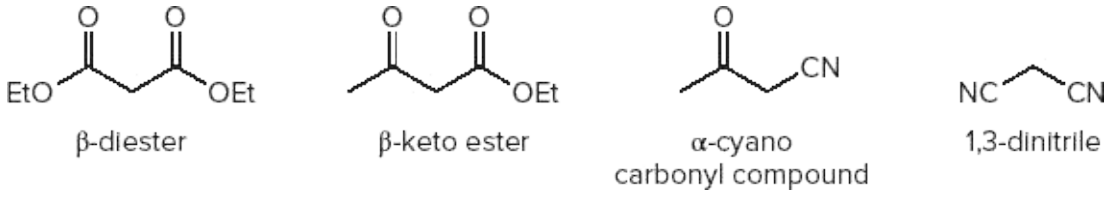
A useful crossed aldol reaction takes place between an aldehyde or ketone and a β-dicarbonyl (or similar) compound.





As we learned in Section 21.3, the α hydrogens between two carbonyl groups are especially acidic, so they are more readily removed than other α H atoms. As a result, the β-dicarbonyl compound always becomes the enolate component of the aldol reaction. Figure 22.2 shows the steps for the crossed aldol reaction between diethyl malonate and benzaldehyde. In this type of crossed aldol reaction, the initial β-hydroxy carbonyl compound *always* loses water to form the highly conjugated product.

β-Dicarbonyl compounds are sometimes called active methylene compounds because they are more reactive toward base than other carbonyl compounds. 1,3-Dinitriles and α-cyano carbonyl compounds are also active methylene compounds.



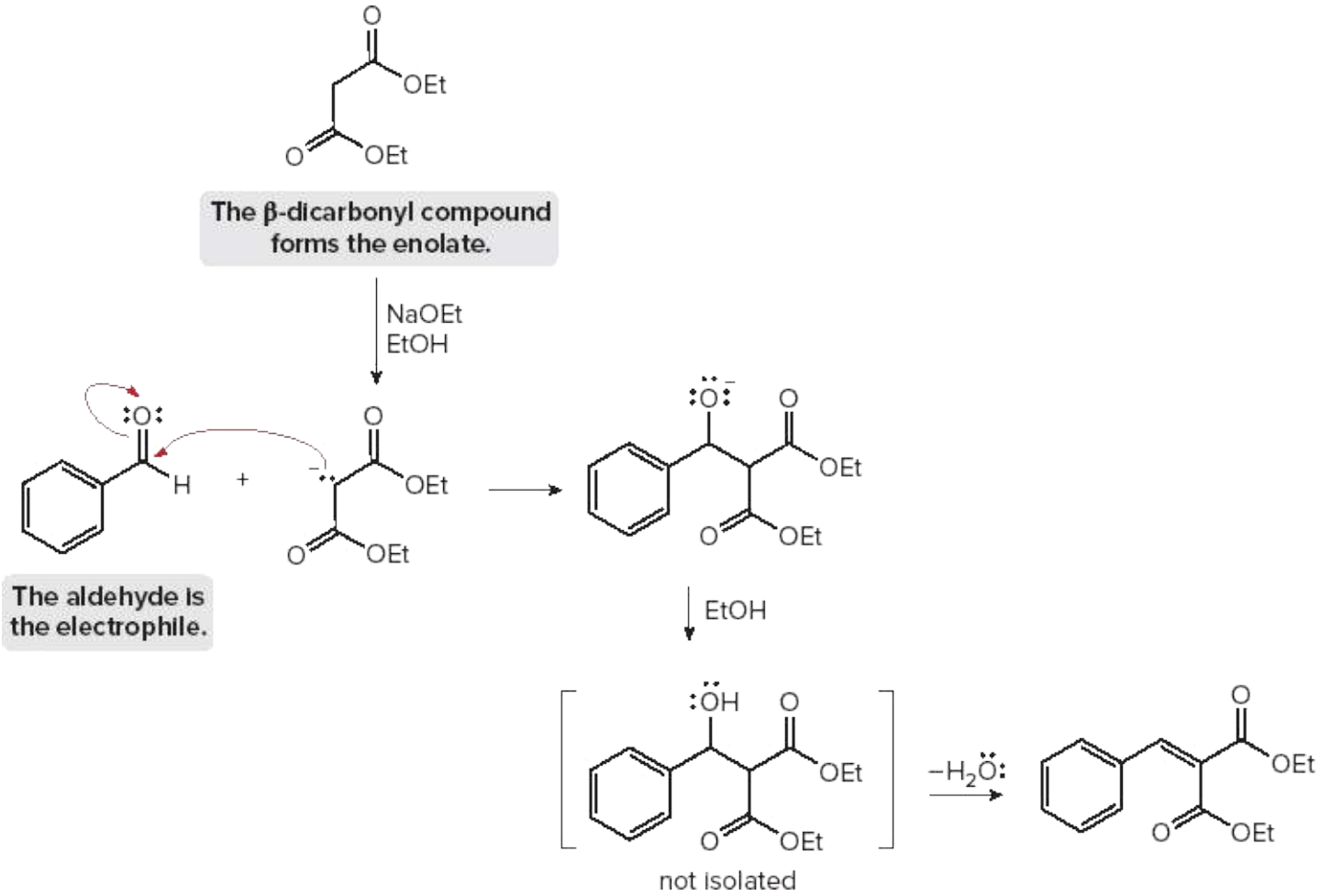


Figure 22.2 **Crossed aldol reaction between benzaldehyde and $CH_2(COOEt)_2$**

Problem 22.8

Draw the products formed in the crossed aldol reaction of phenylacetaldehyde ($C_6H_5CH_2CHO$) with each compound: (a) $CH_2(COOEt)_2$; (b) $CH_2(COCH_3)_2$; (c) CH_3COCH_2CN.

Problem 22.9

The first steps in the synthesis of azelnidipine, a calcium channel blocker (Problem 9.63), involves the reaction of β-keto ester A with aldehyde B in the presence of base. What crossed aldol product is formed in this reaction?

A B

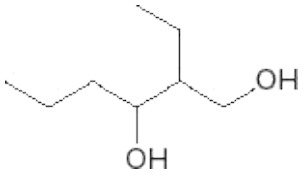
22.2C Useful Transformations of Aldol Products

The aldol reaction is synthetically useful because it forms new carbon–carbon bonds, generating products with two functional groups. Moreover, the β-hydroxy carbonyl compounds formed in aldol reactions are readily transformed into a variety of other compounds. Figure 22.3 illustrates how the crossed aldol product obtained from cyclohexanone and formaldehyde (CH_2=O) can be converted to other compounds by reactions learned in earlier chapters.

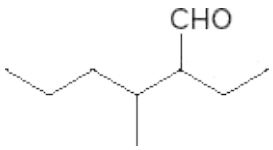
Problem 22.10

What aldol product is formed when two molecules of butanal react together in the presence of base? What reagents are needed to convert this product to each of the following compounds?

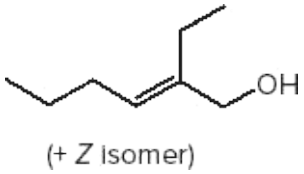
a.



b.

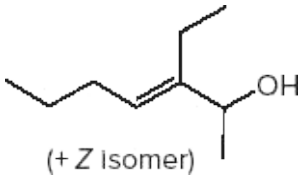


c.

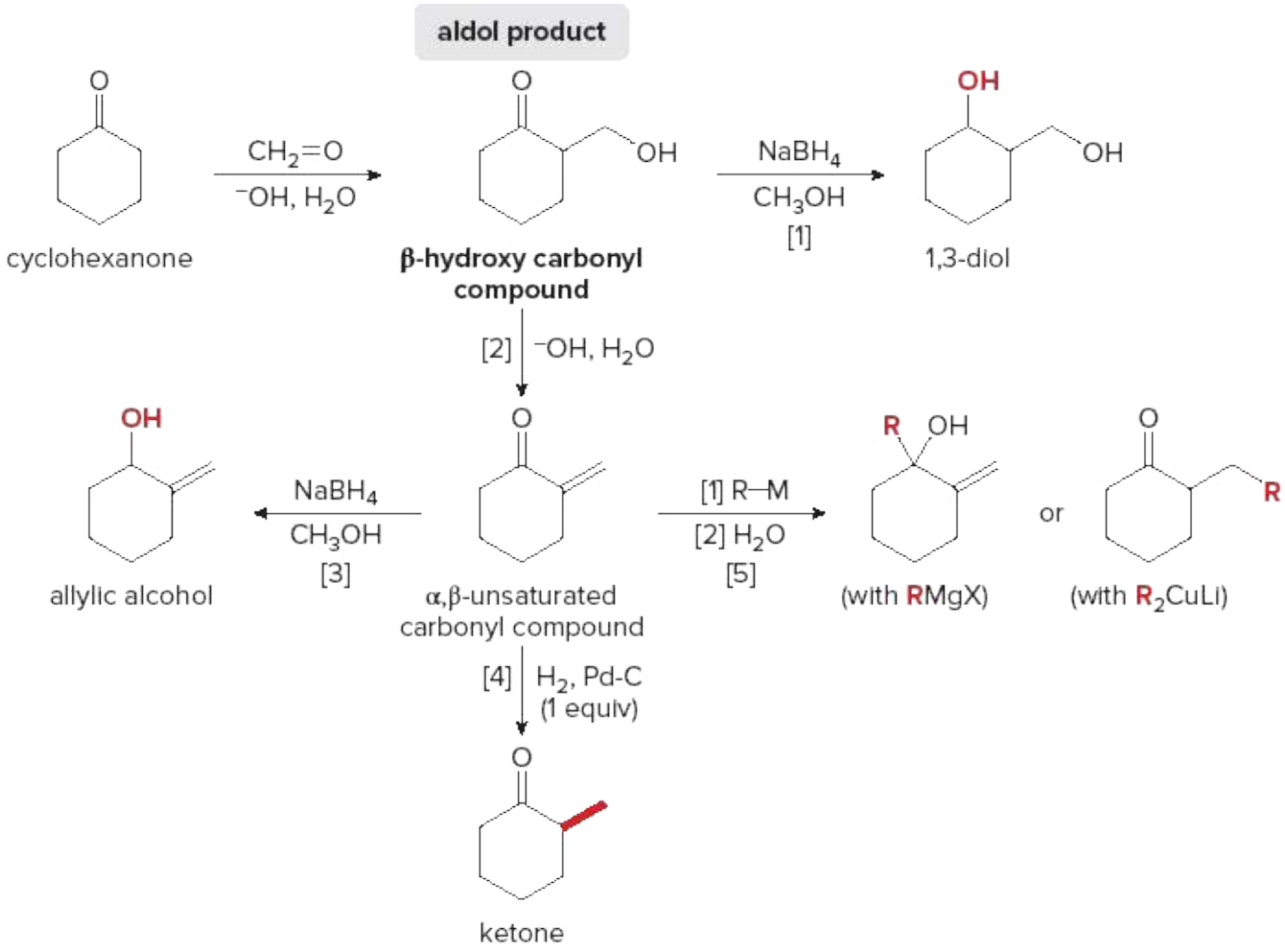


(+ *Z* isomer)

d.



(+ *Z* isomer)



- The β-hydroxy carbonyl compound formed from the crossed aldol reaction can be reduced with $NaBH_4$, CH_3OH (Section 17.4A) to form a 1,3-diol (Reaction [1]) or dehydrated to form an α,β-unsaturated carbonyl compound (Reaction [2]).
- Reduction of the α,β-unsaturated carbonyl compound forms an allylic alcohol with $NaBH_4$ (Reaction [3]), or a ketone with H_2 and Pd-C (Reaction [4]); see Section 17.4C.
- Reaction of the α,β-unsaturated carbonyl compound with an organometallic reagent forms two different products depending on the choice of RM (Reaction [5]); see Section 17.15.

Figure 22.3 **Conversion of a β-hydroxy carbonyl compound to other compounds**

22.3 Directed Aldol Reactions

A directed aldol reaction is a variation of the crossed aldol reaction that clearly defines which carbonyl compound becomes the nucleophilic enolate and which reacts at the electrophilic carbonyl carbon. The strategy of a directed aldol reaction is as follows:

[1] Prepare the enolate of one carbonyl component with LDA.

[2] Add the second carbonyl compound (the electrophile) to this enolate.

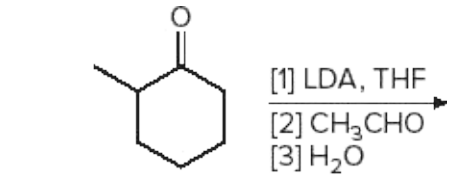
Because the steps are done sequentially and a strong nonnucleophilic base is used to form the enolate of only one carbonyl component, a variety of carbonyl substrates can be used in the reaction. Both carbonyl components can have α hydrogens because only

one enolate is prepared with LDA. Also, when an unsymmetrical ketone is used, LDA selectively forms the less substituted, kinetic enolate.

Sample Problem 22.1 illustrates the steps of a directed aldol reaction between a ketone and an aldehyde, both of which have α hydrogens.

Sample Problem 22.1 Determining the Product of a Directed Aldol Reaction

Draw the product of the following directed aldol reaction.



2-methylcyclohexanone

Solution

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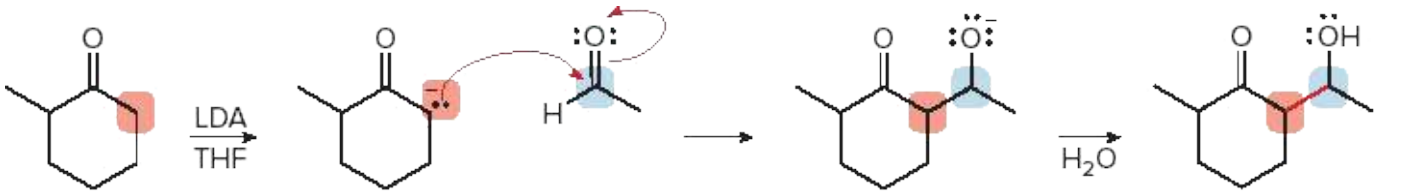
2-Methylcyclohexanone forms an enolate on the less substituted carbon, which then reacts with the electrophile, CH_3CHO.



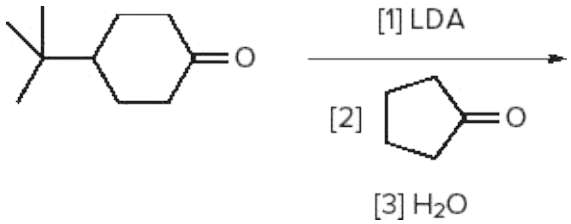
less substituted kinetic enolate

new C–C bond in red

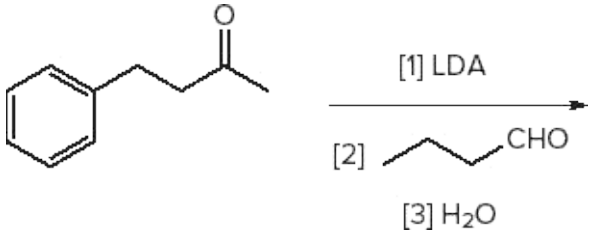
Problem 22.11

Draw the product of each directed aldol reaction.

a.



b.



More Practice:

Try Problems 22.32, 22.48c.

Figure 22.4 illustrates how a directed aldol reaction was used in the synthesis of periplanone B, the sex pheromone of the female American cockroach.

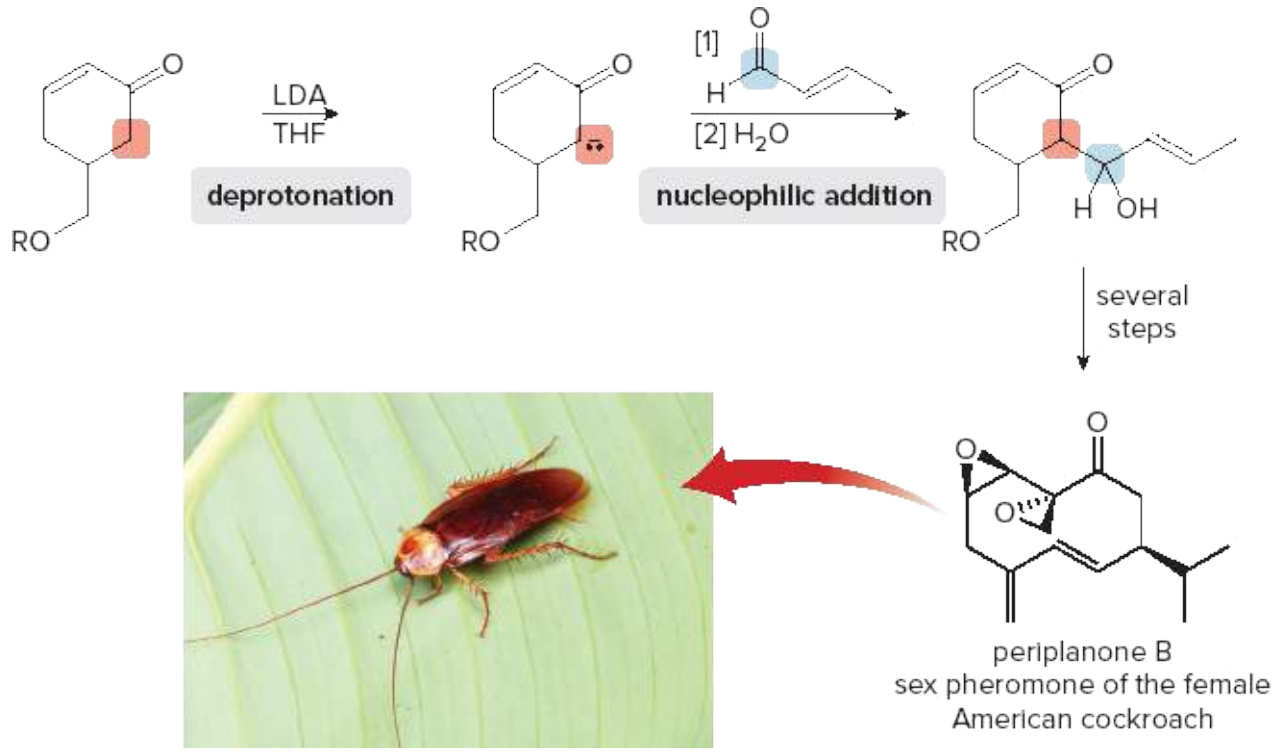


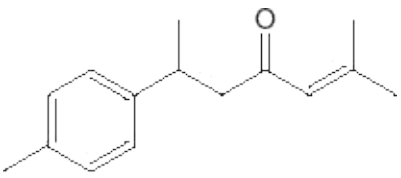
Figure 22.4 **A directed aldol reaction in the synthesis of periplanone B**

©National Geographic Creative/Alamy Stock Photo

To determine the needed carbonyl components for a directed aldol, follow the same strategy used for a regular aldol reaction in Section 22.1C, as shown in Sample Problem 22.2.

Sample Problem 22.2 Determining the Starting Materials of a Directed Aldol Reaction

What starting materials are needed to prepare *ar*-turmerone using a directed aldol reaction? *ar*-Turmerone is a principal component of the essential oil derived from turmeric root.



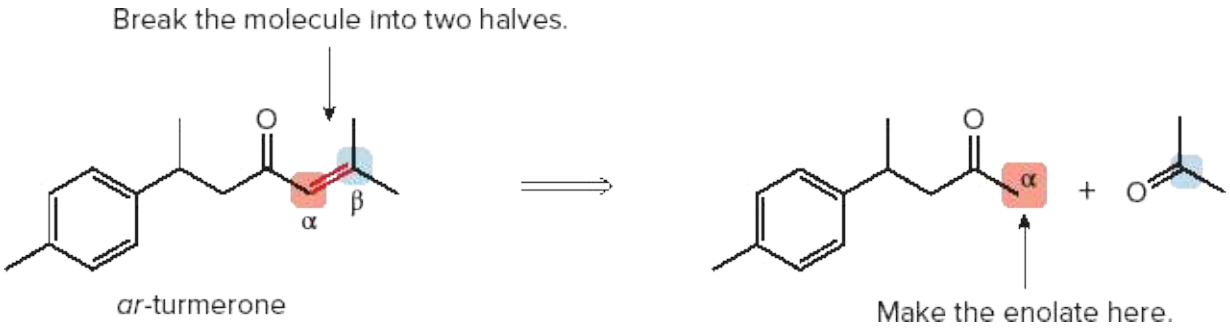
ar-turmerone

The dried and ground root of the turmeric plant (Sample Problem 22.2), a tropical perennial in the ginger family, is an essential ingredient in curry powder. ***©Jill Braaten***

Donepezil (trade name Aricept, Problem 22.13) is a drug used to improve cognitive function in patients suffering from Alzheimer's disease and other types of dementia. ***©Jill Braaten***

Solution

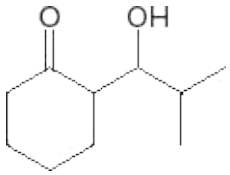
When the desired product is an α,β-unsaturated carbonyl compound, identify the α and β carbons that are part of the C=C, and break the molecule into two components between these carbons.



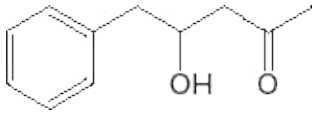
Problem 22.12

What carbonyl starting materials are needed to prepare each compound using a directed aldol reaction?

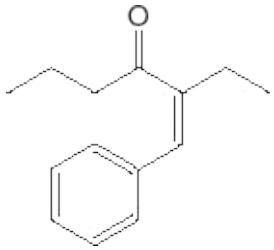
a.



b.



c.

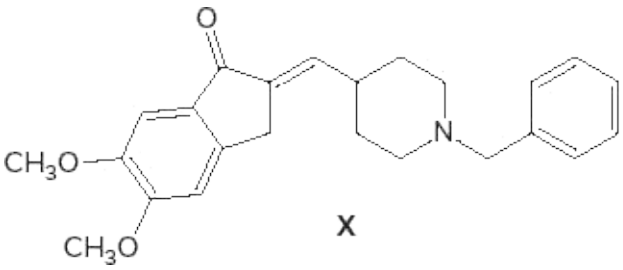


More Practice:

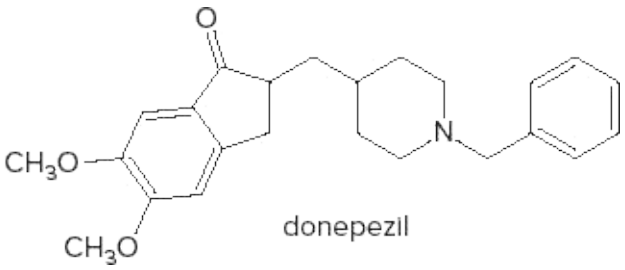
Try Problem 22.34.

Problem 22.13

A key step in the synthesis of donepezil is a directed aldol reaction that forms α,β-unsaturated carbonyl compound X. What carbonyl starting materials are needed to prepare X using a directed aldol reaction? What reagents are needed to convert X to donepezil?



X

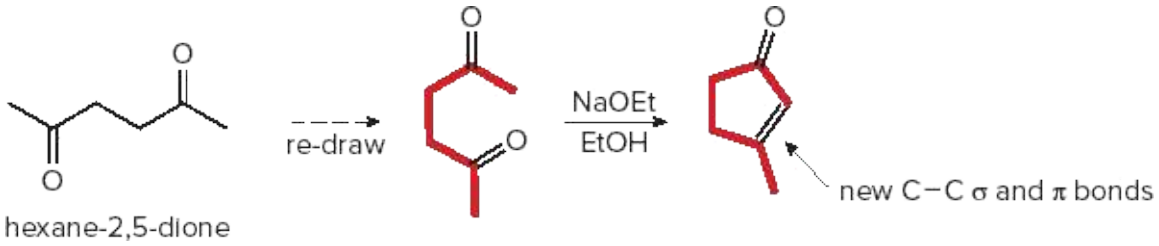


donepezil

22.4 Intramolecular Aldol Reactions

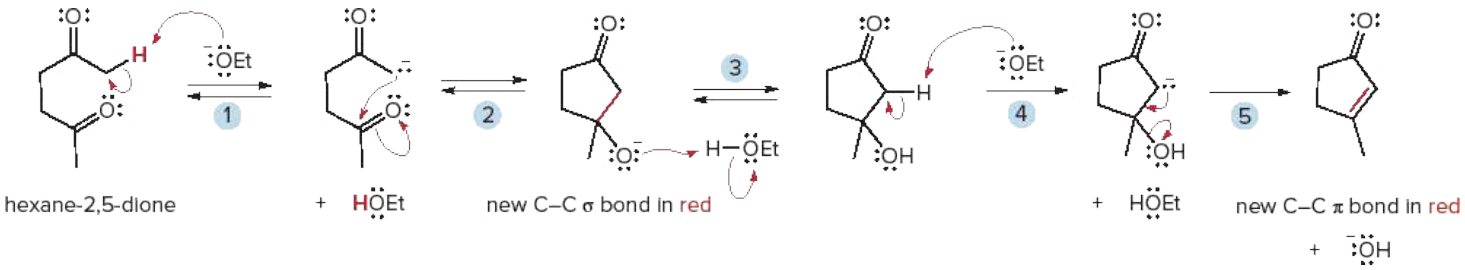
Hexane-2,5-dione is called a 1,4-dicarbonyl compound to emphasize the relative position of its carbonyl groups. 1,4-Dicarbonyl compounds are starting materials for synthesizing five-membered rings.

Aldol reactions with dicarbonyl compounds can be used to make five- and six-membered rings. The enolate formed from one carbonyl group is the nucleophile, and the carbonyl carbon of the other carbonyl group is the electrophile. For example, treatment of hexane-2,5-dione with base forms a five-membered ring.



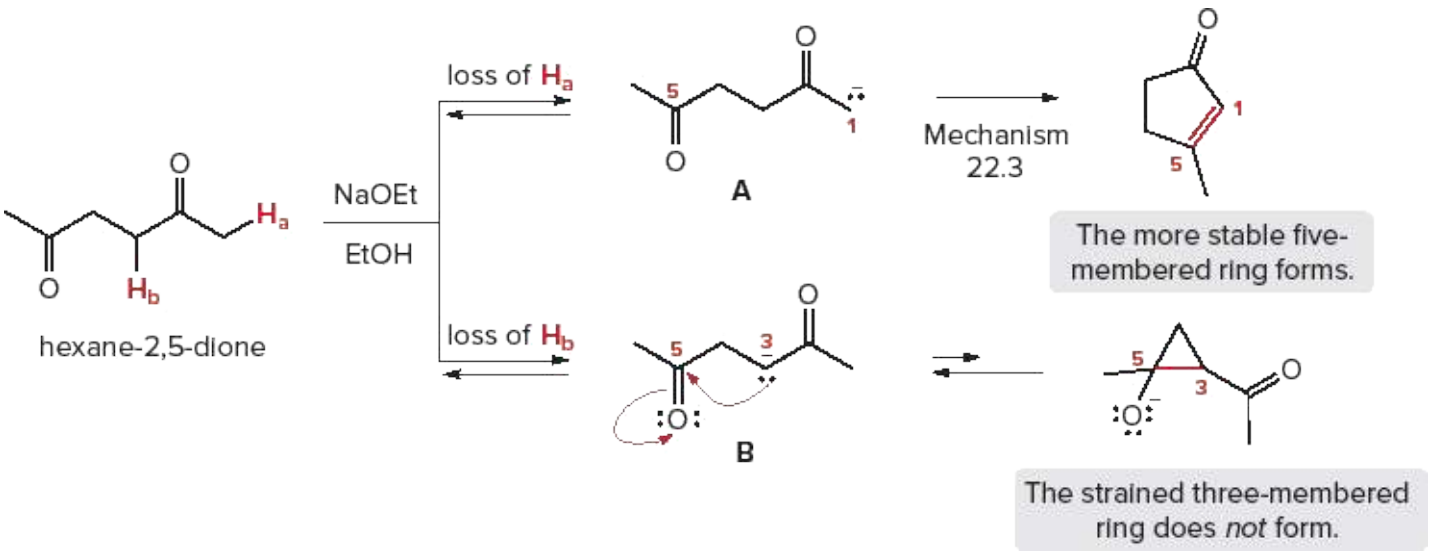
The steps in this process, shown in Mechanism 22.3, are no different from the general mechanisms of the aldol reaction and dehydration described in Section 22.1.

Mechanism 22.3 The Intramolecular Aldol Reaction



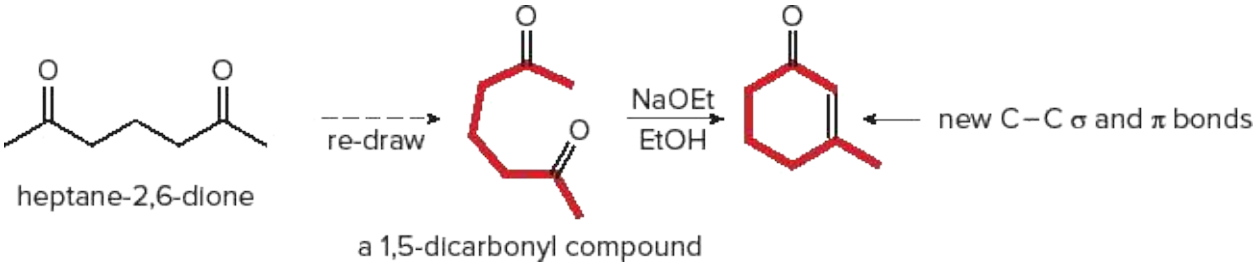
1. **The base removes a proton on the α carbon to form a resonance-stabilized enolate.**
2. **Nucleophilic attack of the enolate on the electrophilic carbonyl *in the same molecule* forms a new C—C σ bond, generating the five-membered ring.**
3. **Protonation of the alkoxide forms the β-hydroxy carbonyl compound.**
4. – 5. **Dehydration occurs by the two-step E1cB mechanism—loss of a proton to form an enolate and elimination of $^-$OH to form a π bond.**

When hexane-2,5-dione is treated with base in Step [1], two different enolates are possible—enolates A and B, formed by removal of H_a and H_b, respectively. Although enolate A goes on to form the five-membered ring, intramolecular cyclization using enolate B would lead to a strained three-membered ring.



Because the three-membered ring is much higher in energy than the enolate starting material, equilibrium greatly favors the starting materials and the three-membered ring does not form. Under the reaction conditions, enolate B is re-protonated to form hexane-2,5-dione, because all steps except dehydration are equilibria. Thus, equilibrium favors formation of the more stable five-membered ring over the much less stable three-membered ring.

In a similar fashion, six-membered rings can be formed from the intramolecular aldol reaction of 1,5-dicarbonyl compounds.



The synthesis of the female sex hormone progesterone by W. S. Johnson and co-workers at Stanford University is considered one of the classics in total synthesis. The last six-membered ring needed in the steroid skeleton was prepared by a two-step sequence using an intramolecular aldol reaction, as shown in Figure 22.5.

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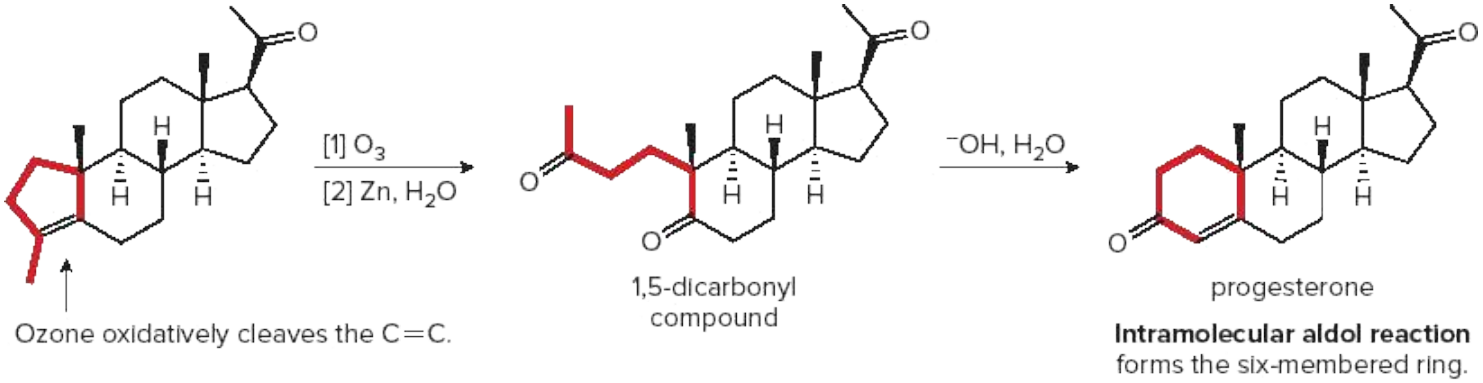


- Oxidative cleavage of the alkene with O_3, followed by Zn, H_2O (Section 12.10), gives the 1,5-dicarbonyl compound.
- Intramolecular aldol reaction of the 1,5-dicarbonyl compound with dilute ^-OH in H_2O solution forms progesterone.
- **This two-step reaction sequence converts a five-membered ring to a six-membered ring.** Reactions that synthesize larger rings from smaller ones are called **ring expansion reactions.**

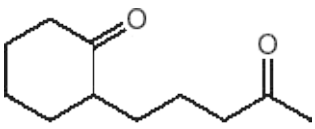
Figure 22.5 The synthesis of progesterone using an intramolecular aldol reaction

Problem 22.14

Draw a stepwise mechanism for the conversion of heptane-2,6-dione to 3-methylcyclohex-2-enone with NaOEt, EtOH.

Sample Problem 22.3 Drawing the Major Product of an Intramolecular Aldol Reaction

What is the major intramolecular aldol product formed when dicarbonyl compound A is treated with base?



A

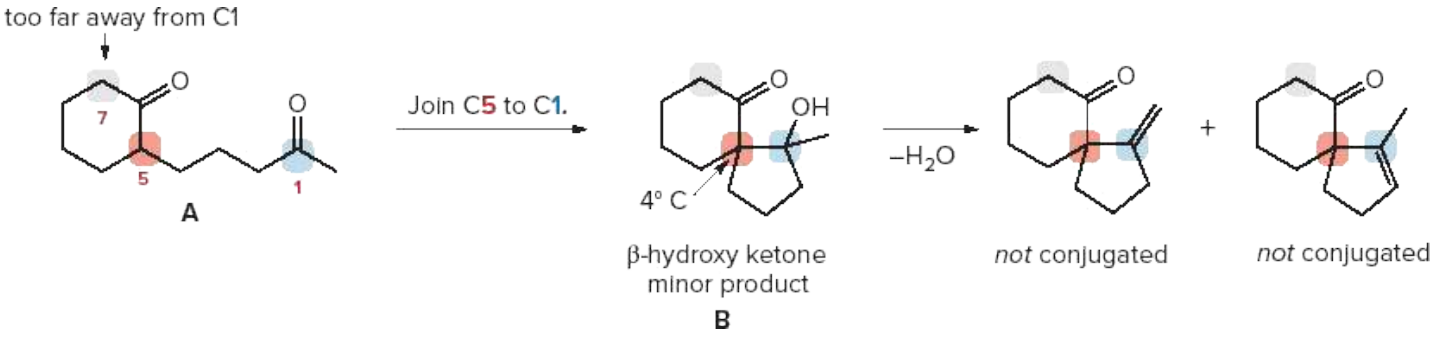
Solution

To draw the products of an intramolecular aldol reaction:

- **Identify all the α carbons that are bonded to H's.**
- **Determine how far each α carbon is from the other carbonyl carbon. Reactions that yield five- or six-membered rings are favored.**
- **α,β-Unsaturated carbonyl systems are favored over β-hydroxy carbonyl compounds that cannot dehydrate to a conjugated product.**

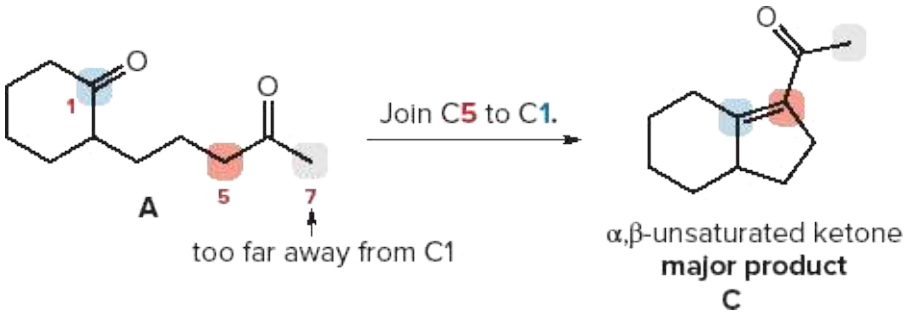
A contains four α carbons that can form enolates. First, consider enolates

from the cyclohexanone (at C5 and C7 below) reacting with the acyclic carbonyl (C1). Only the enolate at C5 forms a five-membered ring by intramolecular aldol, but the β-hydroxy ketone B can*not* dehydrate to a conjugated system because the α carbon has no H for dehydration. Thus, this path is not favored.



Then, consider enolates from the acyclic ketone (at C5 and C7 below) reacting with the cyclohexanone carbonyl (C1). Only the enolate at C5 forms a five-membered ring by intramolecular aldol, and dehydration forms an α,β-unsaturated carbonyl compound C, so C is the major product.

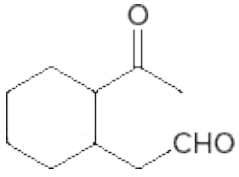
Page 1025



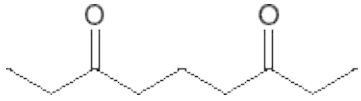
Problem 22.15

What cyclic product is formed when each 1,5-dicarbonyl compound is treated with aqueous OH?

a.



b.

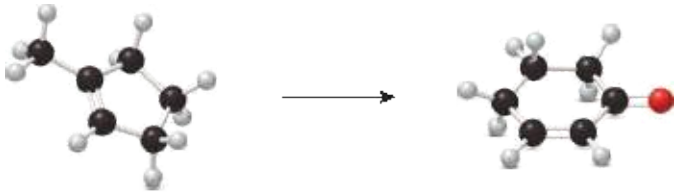


More Practice:

Try Problem 22.32.

Problem 22.16

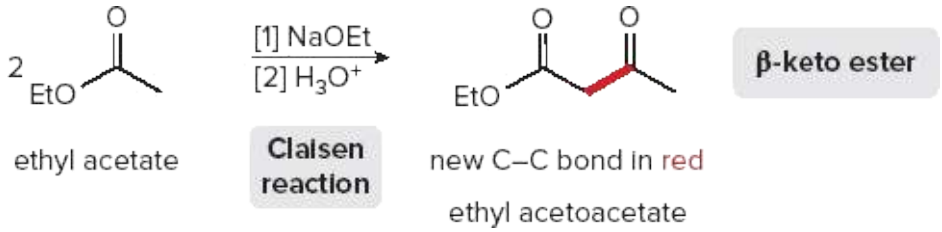
Following the two-step reaction sequence depicted in Figure 22.5, write out the steps needed to convert A to B.



22.5 The Claisen Reaction

Unlike the aldol reaction, which is base-catalyzed, a full equivalent of base is needed to deprotonate the β-keto ester formed in Step [3] of the Claisen reaction.

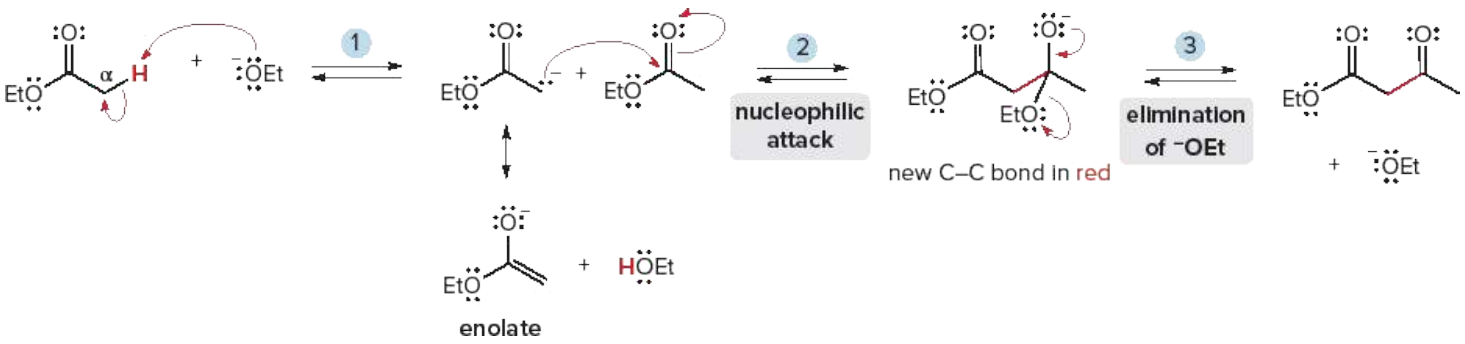
The Claisen reaction is the second general reaction of enolates with other carbonyl compounds. In the Claisen reaction, two molecules of an ester react with each other in the presence of an alkoxide base to form a β-keto ester. For example, treatment of ethyl acetate with NaOEt forms ethyl acetoacetate after protonation with aqueous acid.



The mechanism for the Claisen reaction (Mechanism 22.4) resembles the mechanism of an aldol reaction in that it involves nucleophilic addition of an enolate to an electrophilic carbonyl group. Because esters have a leaving group on the carbonyl carbon, however, loss of a leaving group occurs to form the product of substitution, *not* addition.

Mechanism 22.4 The Claisen Reaction

Part [1] Formation of the β-keto ester

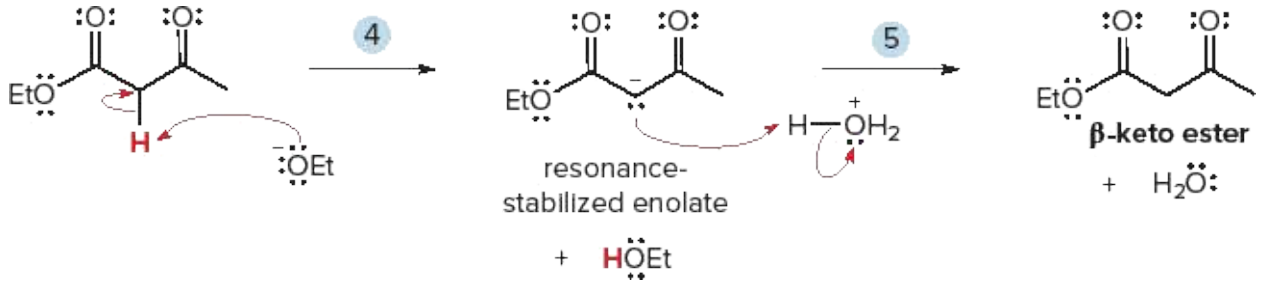


1 **The base removes a proton on the α carbon to form a resonance-stabilized enolate.**

2 **Nucleophilic attack of the enolate on an electrophilic carbonyl in another molecule of ester forms a new C—C bond.**

3 **Loss of the leaving group (⁻OEt) forms a β-keto ester.**

Part [2] Deprotonation and protonation



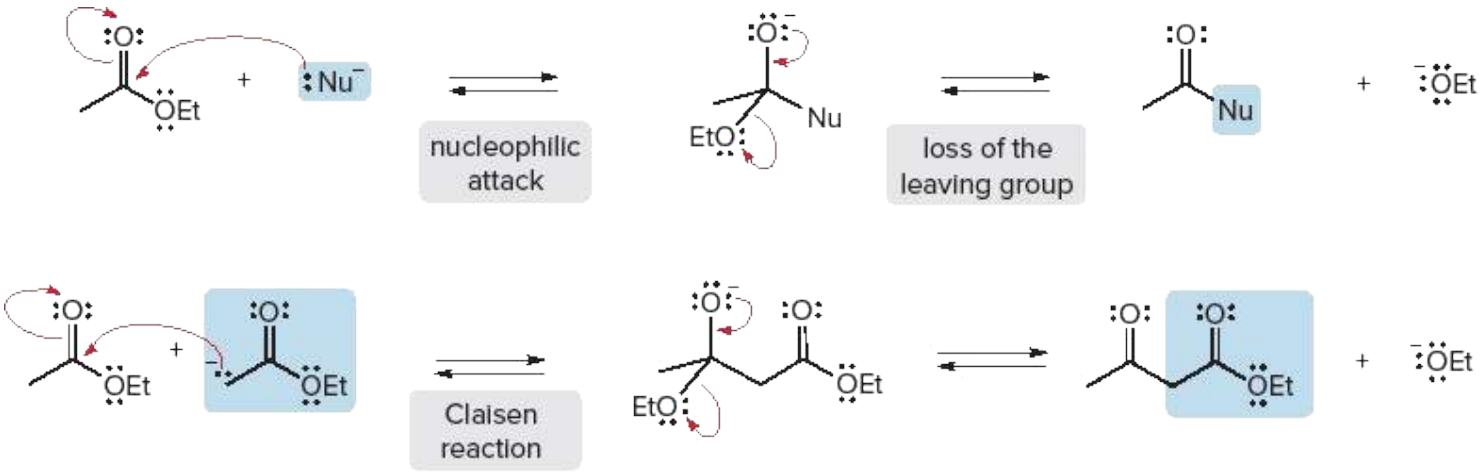
4 **Because the β-keto ester formed in Step [3] has especially acidic protons between its two carbonyl groups, the base removes a proton to form a resonance-stabilized enolate.**

5 **Protonation of the enolate with strong acid re-forms the β-keto ester.**

Because the generation of a resonance-stabilized enolate from the product β-keto ester drives the Claisen reaction (Step [4] of Mechanism 22.4), only esters with two or three hydrogens on the α carbon undergo this reaction; that is, esters must have the general structure CH_3CO_2R' or RCH_2CO_2R'.

- **Keep in mind: The characteristic reaction of esters is nucleophilic substitution. A Claisen reaction is a nucleophilic substitution in which an enolate is the nucleophile.**

Figure 22.6 compares the general reaction for nucleophilic substitution of an ester with the Claisen reaction. Sample Problem 22.4 reinforces the basic features of the Claisen reaction.



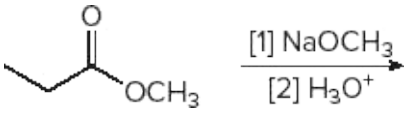
- Esters react by **nucleophilic substitution.** In a Claisen reaction, an **enolate is the nucleophile** that adds to the carbonyl group.

Figure 22.6 **The Claisen reaction—An example of nucleophilic substitution**

- Esters react by nucleophilic substitution. In a Claisen reaction, an enolate is the nucleophile that adds to the carbonyl group.

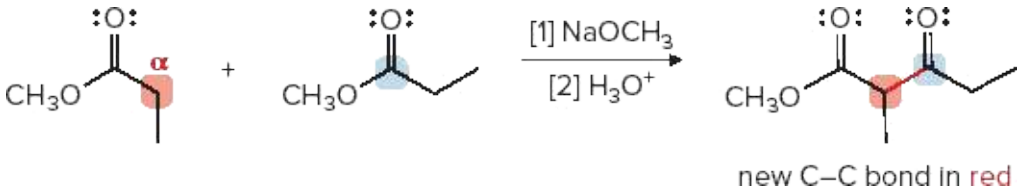
Sample Problem 22.4 Determining the Product of a Claisen Reaction

Draw the product of the following Claisen reaction.

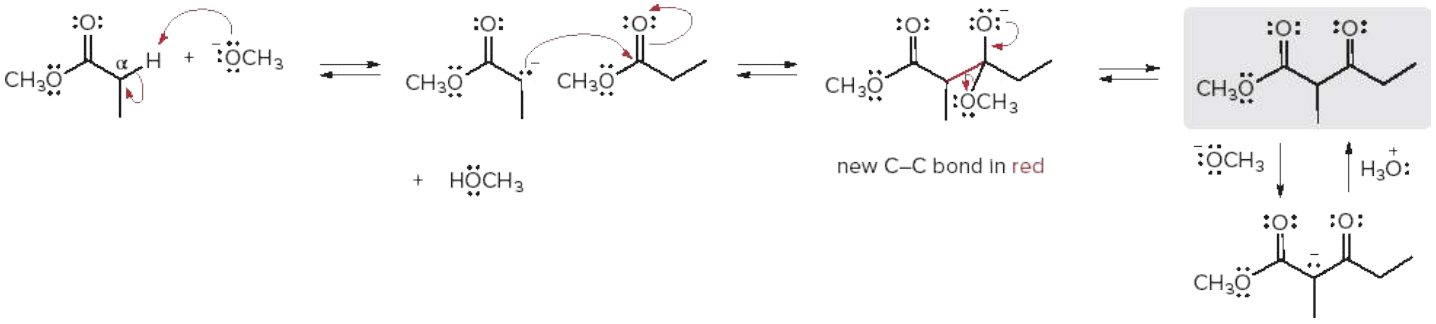


Solution

To draw the product of any Claisen reaction, form a new carbon–carbon bond between the α carbon of one ester and the carbonyl carbon of another ester, with elimination of the leaving group ($^-OCH_3$ in this case).



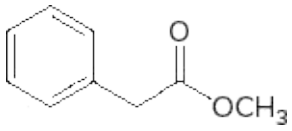
Next, write out the steps of the reaction to verify this product.



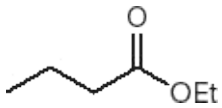
Problem 22.17

What β-keto ester is formed when each ester is used in a Claisen reaction?

a.



b.



More Practice:

Try Problem 22.39.

22.6 The Crossed Claisen and Related Reactions

Like the aldol reaction, it is sometimes possible to carry out a Claisen reaction with two different carbonyl components as starting materials.

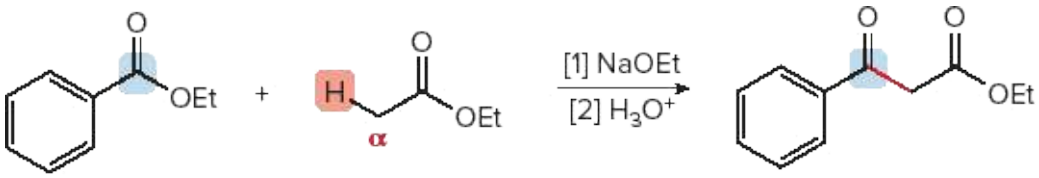
- **A Claisen reaction between two different carbonyl compounds is called a *crossed Claisen reaction*.**

22.6A Two Useful Crossed Claisen Reactions

A crossed Claisen reaction is synthetically useful in two different instances.

- **A crossed Claisen occurs between two different esters when only one has α hydrogens.**

When one ester has no α hydrogens, a crossed Claisen reaction often leads Page 1028 to one product. Common esters with no α H atoms include ethyl formate (HCO_2Et) and ethyl benzoate ($C_6H_5CO_2Et$). For example, the reaction of ethyl benzoate (as the electrophile) with ethyl acetate (which forms the enolate) in the presence of base forms predominately one β-keto ester.



ethyl benzoate ethyl acetate

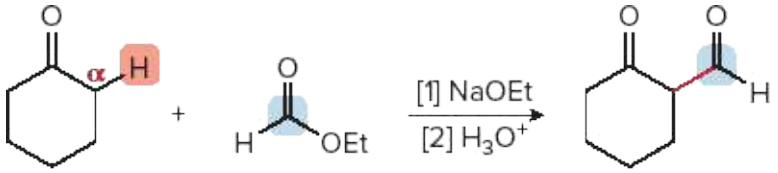
Only this ester can form an enolate.

new C–C bond in red

β-keto ester

- **A crossed Claisen occurs between a ketone and an ester.**

The reaction of a ketone and an ester in the presence of base also forms the product of a crossed Claisen reaction. The enolate is generally formed from the ketone component, and the reaction works best when the ester has no α hydrogens. The product of this crossed Claisen reaction is a β-dicarbonyl compound, but *not* a β-keto ester.



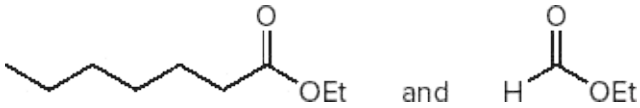
new C–C bond in red

β-dicarbonyl compound

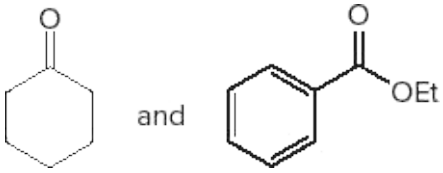
Problem 22.18

What crossed Claisen product is formed from each pair of compounds?

a.



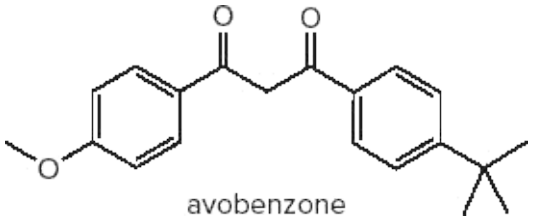
b.



Sunscreen ingredients (Problem 22.19) ©*McGraw-Hill*

Problem 22.19

Avobenzone is a conjugated compound that absorbs ultraviolet light with wavelengths in the 320–400 nm region, so it is a common ingredient in commercial sunscreens. Write out two different crossed Claisen reactions that form avobenzone.



avobenzone

22.6B Other Useful Variations of the Crossed Claisen Reaction

β-Dicarbonyl compounds are also prepared by reacting an enolate with ethyl chloroformate and diethyl carbonate.

ethyl chloroformate diethyl carbonate

These reactions resemble a Claisen reaction because they involve the same three steps:

[1] Formation of an enolate

[2] Nucleophilic addition to a carbonyl group

[3] Elimination of a leaving group

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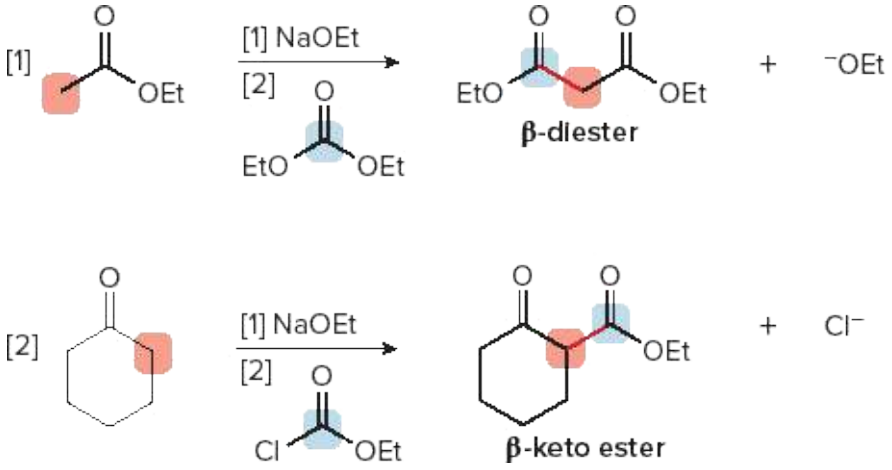
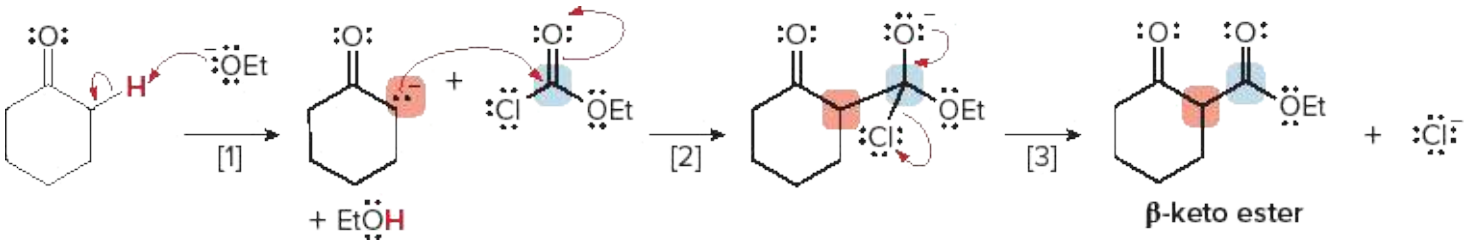
For example, reaction of an ester enolate with diethyl carbonate yields a β-diester (Reaction [1]), whereas reaction of a ketone enolate with ethyl chloroformate forms a β-keto ester (Reaction [2]). New carbon–carbon bonds are shown in red.



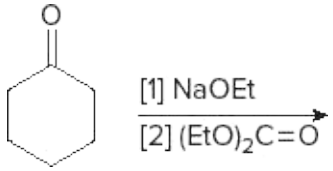
Reaction [2] is noteworthy because it provides easy access to β-keto esters, which are useful starting materials in the acetoacetic ester synthesis (Section 21.10). In this reaction, Cl^- is eliminated rather than ^-OEt in Step [3], because Cl^- is a better leaving group, as shown in the following steps.



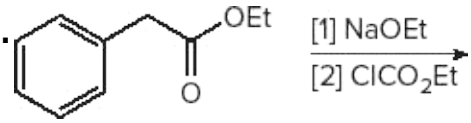
Problem 22.20

Draw the products of each reaction.

a.

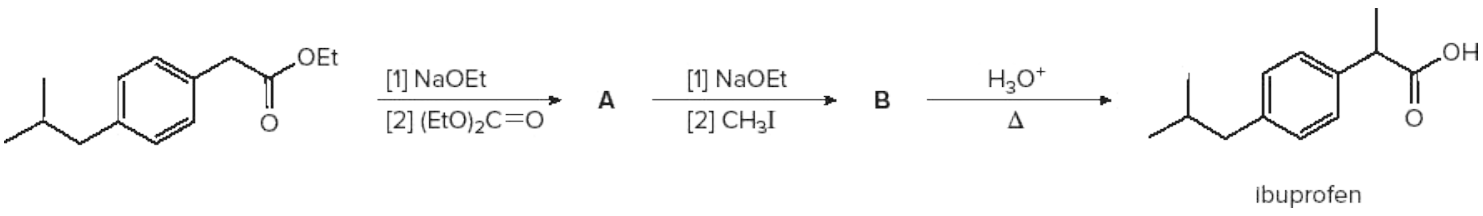


b.



Problem 22.21

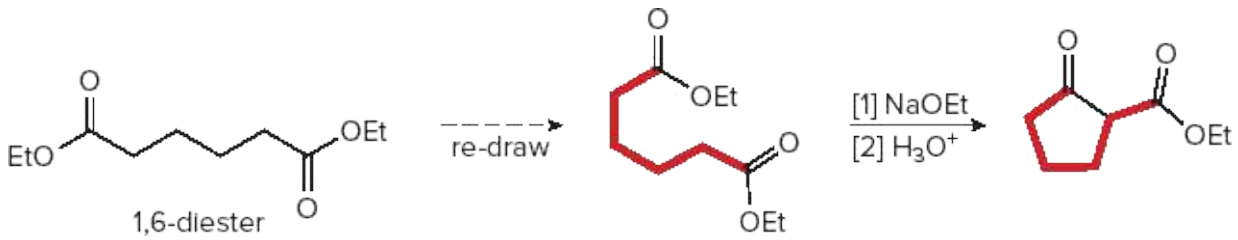
Two steps in a synthesis of the analgesic ibuprofen, the chapter-opening molecule, include a carbonyl condensation reaction, followed by an alkylation reaction. Identify intermediates A and B in the synthesis of ibuprofen.



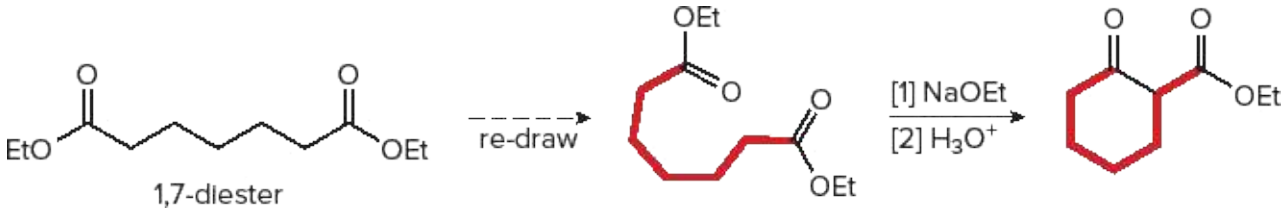
22.7 The Dieckmann Reaction

Intramolecular Claisen reactions of diesters form five- and six-membered rings. The enolate of one ester is the nucleophile, and the carbonyl carbon of the other is the electrophile. An intramolecular Claisen reaction is called a Dieckmann reaction. Two types of diesters give good yields of cyclic products.

- **1,6-Diesters yield five-membered rings by the Dieckmann reaction.**

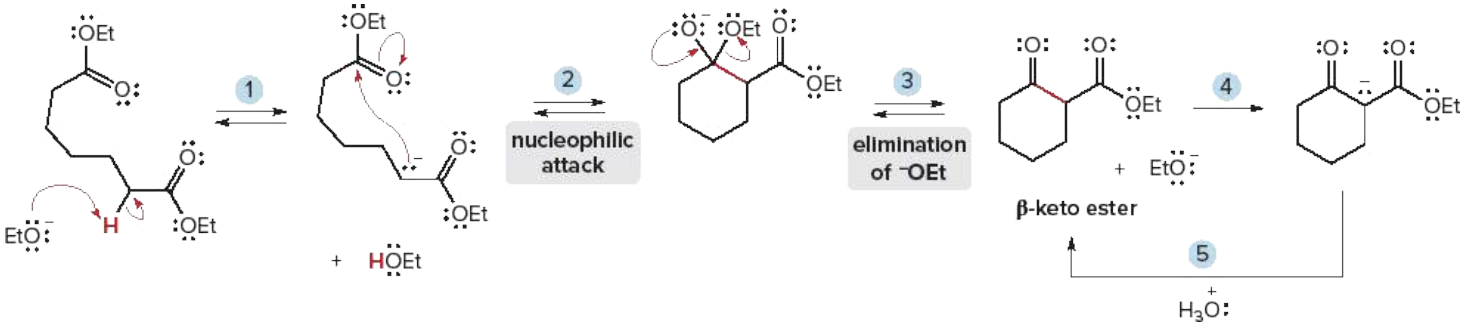


- **1,7-Diesters yield six-membered rings by the Dieckmann reaction.**



The mechanism of the Dieckmann reaction is exactly the same as the mechanism of an intermolecular Claisen reaction. It is illustrated in Mechanism 22.5 for the formation of a six-membered ring.

Mechanism 22.5 The Dieckmann Reaction



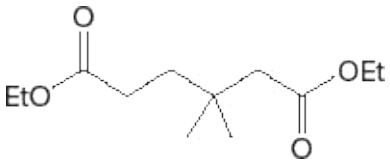
1 – 2 The base removes a proton on the α carbon to form an enolate, which attacks the electrophilic carbonyl of the other ester to form a new C—C bond.

3 Elimination of ⁻OEt forms the β-keto ester.

4 – 5 Under the basic reaction conditions, the proton between the two carbonyls is removed with base to form an enolate, which is protonated with acid to re-form the β-keto ester.

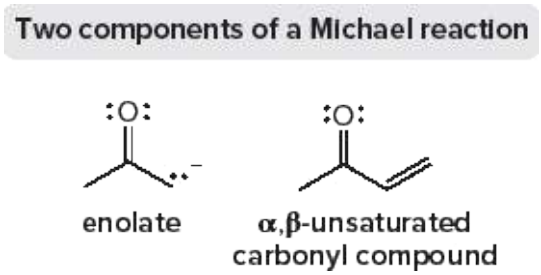
Problem 22.22

What two β-keto esters are formed in the Dieckmann reaction of the following diester?

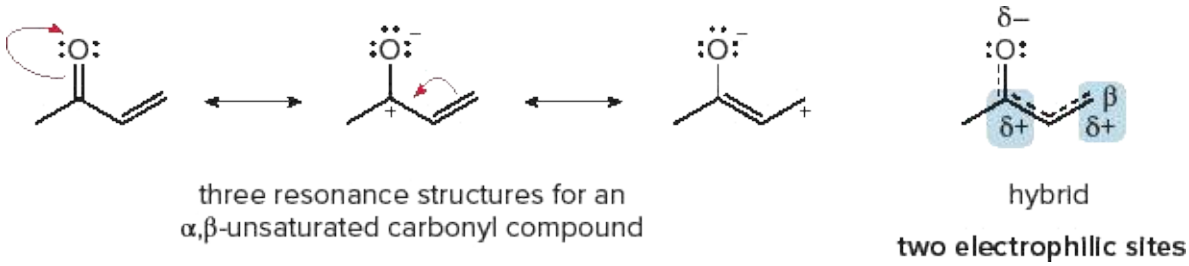


22.8 The Michael Reaction

Like the aldol and Claisen reactions, the Michael reaction involves two carbonyl components—the enolate of one carbonyl compound and an α,β-unsaturated carbonyl compound.

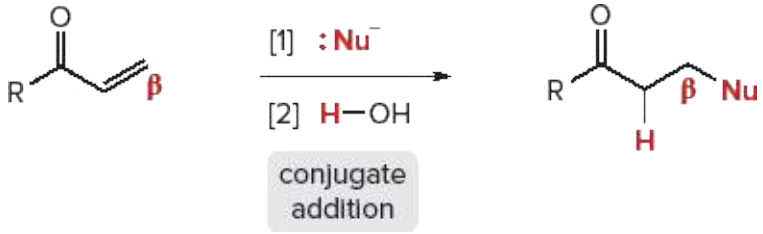


Recall from Section 17.15 that α,β-unsaturated carbonyl compounds are resonance stabilized and have two electrophilic sites—the carbonyl carbon and the β carbon.

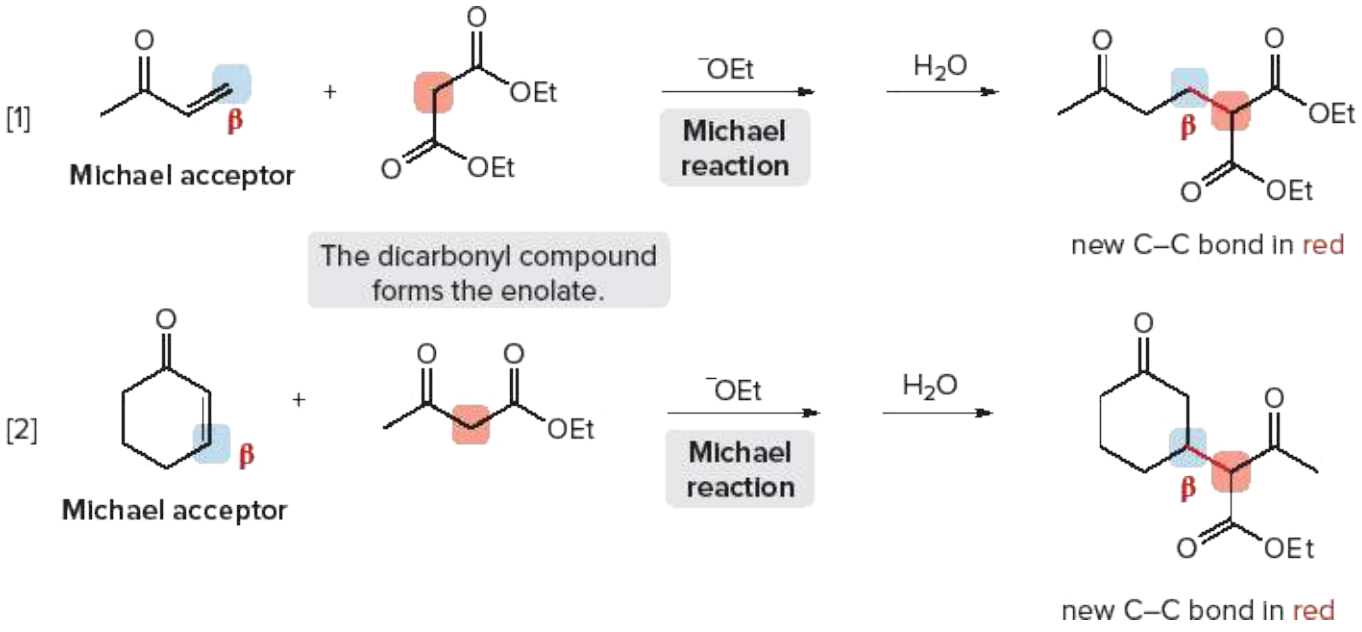


- **The Michael reaction involves the conjugate addition (1,4-addition) of a resonance-stabilized enolate to the β carbon of an α,β-unsaturated carbonyl system.**

All conjugate additions add the elements of H and Nu across the α and β carbons.



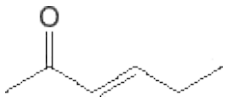
In the Michael reaction, the nucleophile is an enolate. Enolates of active methylene compounds are particularly common. The α,β-unsaturated carbonyl component is often called a Michael acceptor.



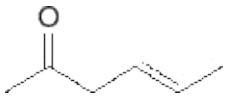
Problem 22.23

Which of the following compounds can serve as Michael acceptors?

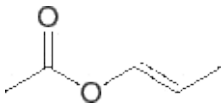
a.



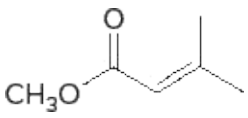
b.



c.

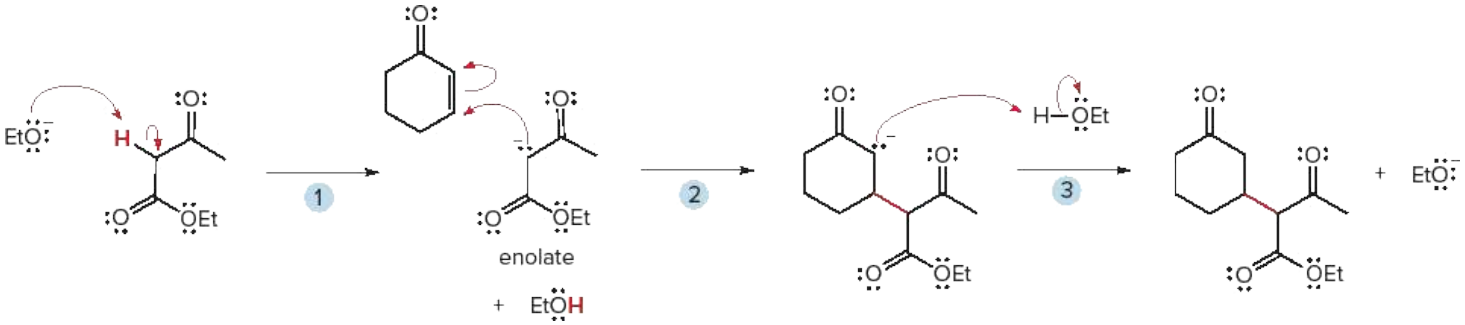


d.



The Michael reaction always forms a new carbon–carbon bond on the β carbon of the Michael acceptor. Reaction [2] is used to illustrate the mechanism of the Michael reaction in Mechanism 22.6. The key step is nucleophilic addition of the enolate to the β carbon of the Michael acceptor in Step [2].

Mechanism 22.6 The Michael Reaction



1 **The base removes a proton on the carbon between the two carbonyl**

groups to form an enolate.

2. Nucleophilic addition of the enolate to the β carbon of the α,β-unsaturated carbonyl compound forms a new carbon–carbon bond and another enolate.

3. Protonation of the enolate forms the 1,4-addition product.

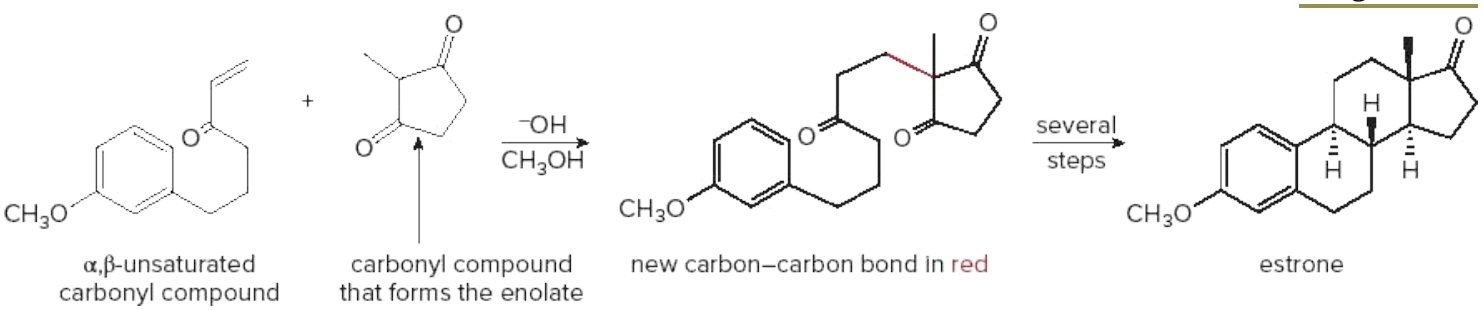
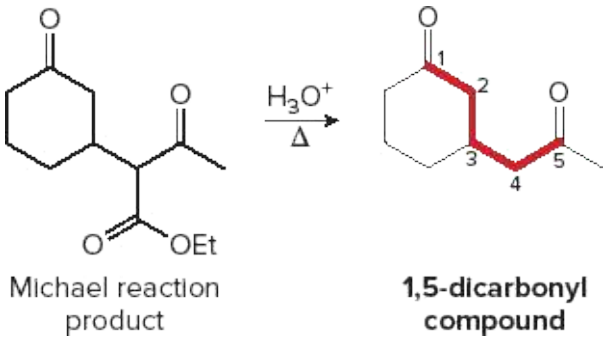


Figure 22.7 **Using a Michael reaction in the synthesis of the steroid estrone**

1,5-Dicarbonyl compounds are starting materials for intramolecular aldol reactions, as described in Section 22.4.

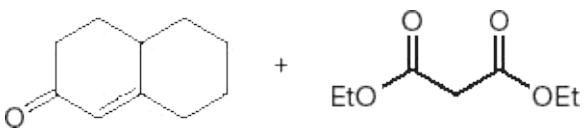
When the product of a Michael reaction is also a β-keto ester, it can be hydrolyzed and decarboxylated by heating in aqueous acid, as discussed in Section 21.9. This forms a 1,5-dicarbonyl compound. Figure 22.7 shows a Michael reaction that was a key step in the synthesis of estrone, a female sex hormone.



Problem 22.24

What product is formed when each pair of compounds is treated with NaOEt in ethanol?

a.

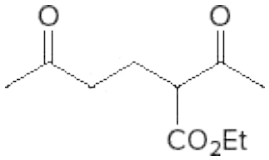


b.

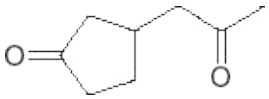
Problem 22.25

What starting materials are needed to prepare each compound by the Michael reaction?

a.



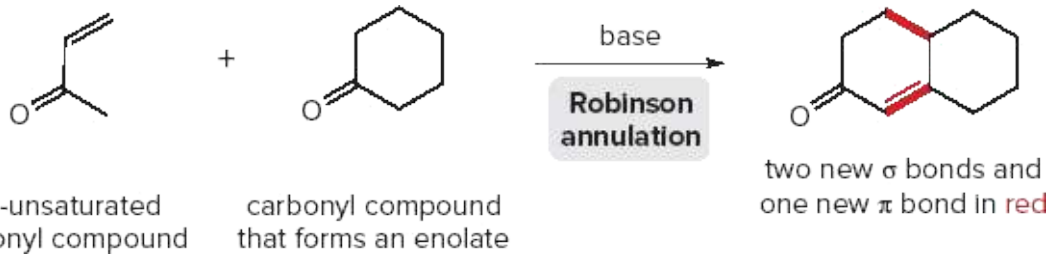
b.



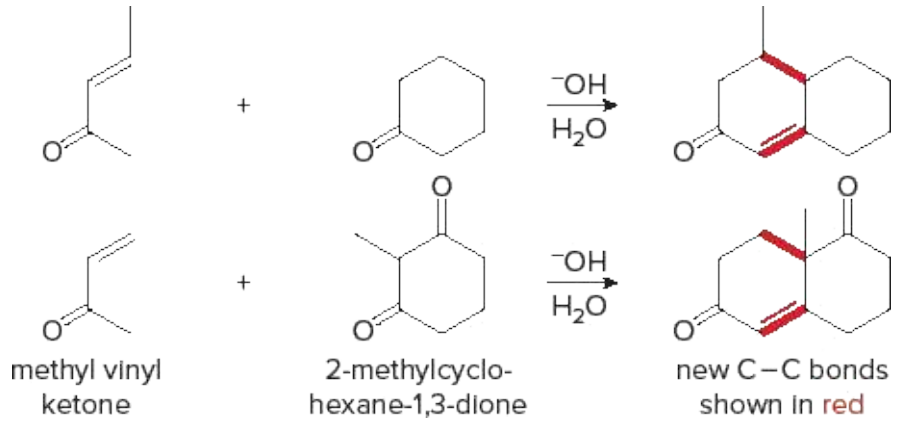
22.9 The Robinson Annulation

The word *annulation* comes from the Greek word *annulus* for "ring." The Robinson annulation is named for English chemist Sir Robert Robinson, who was awarded the 1947 Nobel Prize in Chemistry.

The Robinson annulation is a ring-forming reaction that combines a Michael reaction with an intramolecular aldol reaction. Like the other reactions in Chapter 22, it involves enolates and it forms carbon–carbon bonds. The two starting materials for a Robinson annulation are an α,β-unsaturated carbonyl compound and an enolate.



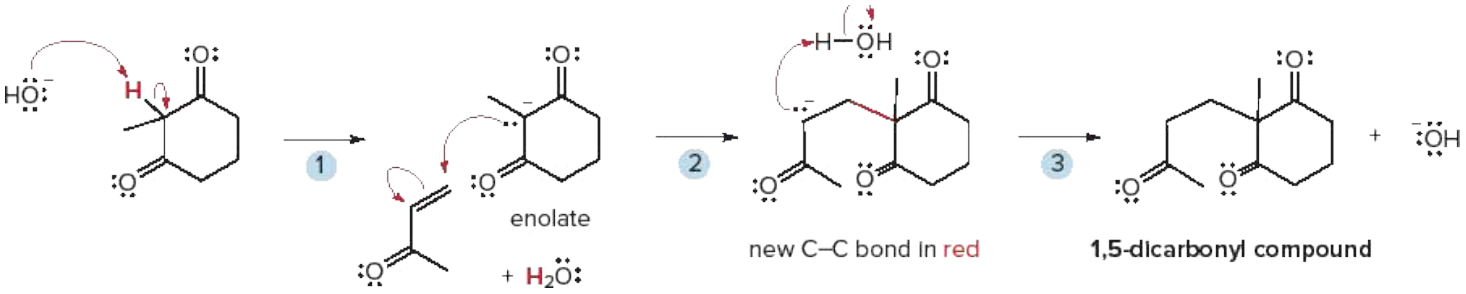
The Robinson annulation forms a six-membered ring and three new carbon–carbon bonds—two σ bonds and one π bond. The product contains an α,β-unsaturated ketone in a cyclohexane ring—that is, a cyclohex-2-enone ring. To generate the enolate component of the Robinson annulation, $^-$OH in H_2O and $^-$OEt in EtOH are typically used.



The mechanism of the Robinson annulation consists of a Michael addition to the α,β-unsaturated carbonyl compound to form a 1,5-dicarbonyl compound, followed by an intramolecular aldol reaction to form the six-membered ring. The mechanism is written out in three parts in Mechanism 22.7 for the reaction between methyl vinyl ketone and 2-methylcyclohexane-1,3-dione.

Mechanism 22.7 The Robinson Annulation

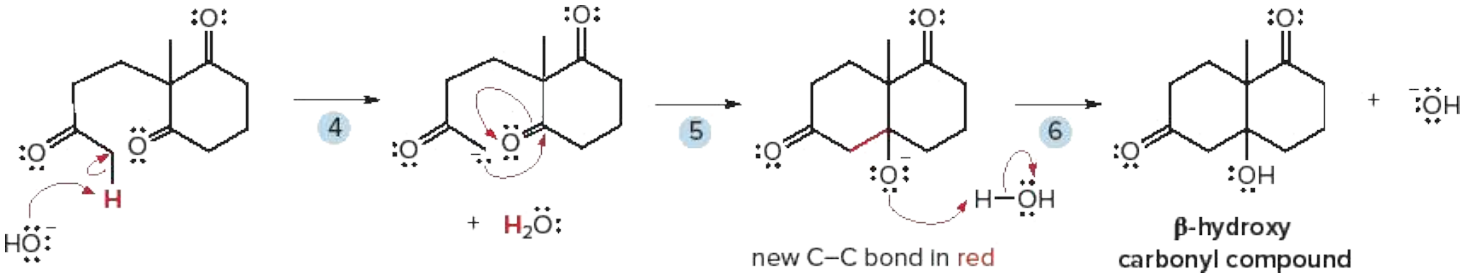
Part [1] Michael addition



1 – 2 **Base removes the most acidic proton—the proton between the two carbonyl groups—to form an enolate. Conjugate addition of the enolate to the α,β-unsaturated carbonyl compound forms a new carbon–carbon bond, generating an enolate.**

3 **Protonation of the enolate forms a 1,5-dicarbonyl compound.**

Part [2] Intramolecular aldol reaction

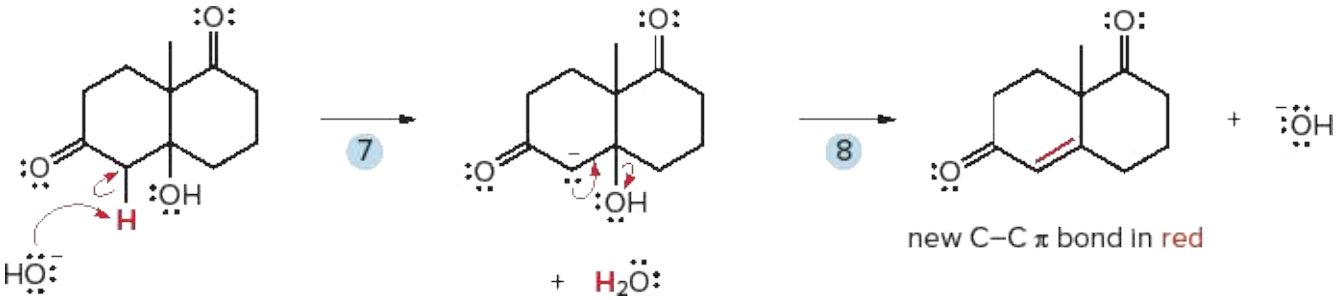


4 – 5 **The base removes a proton to form an enolate, which attacks a carbonyl group to form a new C—C σ bond, generating the six-**

membered ring.

6 Protonation of the alkoxide forms the β-hydroxy carbonyl compound.

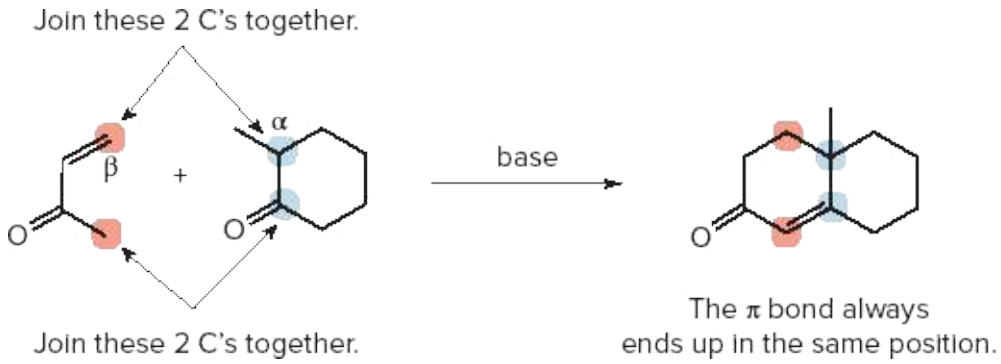
Part [3] Dehydration of the β-hydroxy carbonyl compound



7 – 8 Dehydration occurs by the two-step E1cB mechanism—loss of a proton to form an enolate and elimination of ⁻OH to form a π bond.

The mechanism begins with the three-step Michael addition that forms the Page 1034 first carbon–carbon a bond, generating the 1,5-dicarbonyl compound (Part [1]). An intramolecular aldol reaction (Part [2]) forms the second carbon–carbon σ bond, and dehydration of the β-hydroxy ketone (Part [3]) forms the π bond. All of the parts of this mechanism have been discussed in previous sections of Chapter 22. However, the end result of the Robinson annulation—the formation of a cyclohex-2-enone ring—is new.

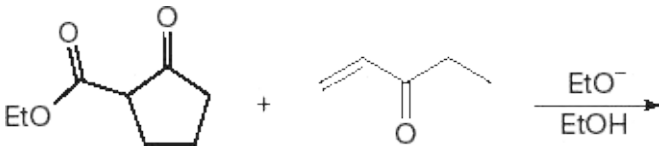
To draw the product of Robinson annulation without writing out the mechanism each time, place the α carbon of the compound that becomes the enolate next to the β carbon of the α,β-unsaturated carbonyl compound. Then, join the appropriate carbons together as shown. If you follow this method of drawing the starting materials, the double bond in the product always ends up in the same position in the six-membered ring.



Sample Problem 22.5 Drawing the Product of a Robinson Annulation

Draw the Robinson annulation product formed from the following starting

materials.

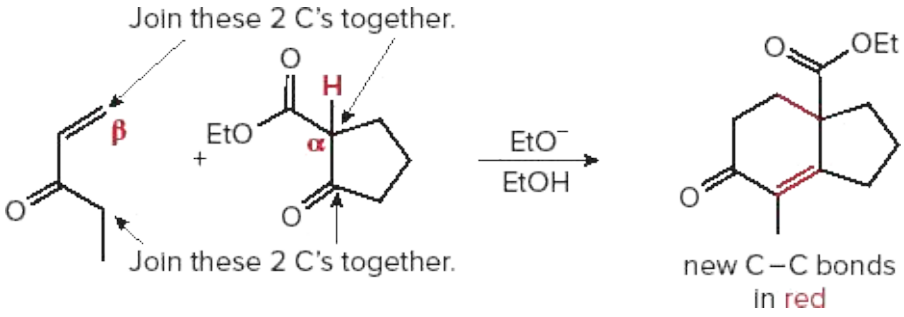


Solution

Arrange the starting materials to put the reactive atoms next to each other. For example:

- **Place the α,β-unsaturated carbonyl compound *to the left* of the carbonyl compound.**
- **Determine which α carbon will become the enolate. The most acidic H is always removed with base first, which in this case is the H (in red) on the α carbon between the two carbonyl groups. This α carbon is drawn adjacent to the β carbon of the α,β-unsaturated carbonyl compound.**

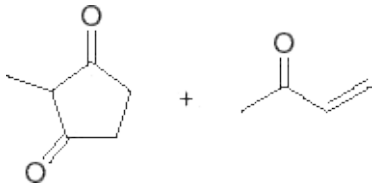
Then draw the bonds to form the new six-membered ring.



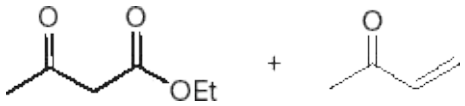
Problem 22.26

Draw the products when each pair of compounds is treated with $CH_3CH_2O^-$, CH_3CH_2OH in a Robinson annulation reaction.

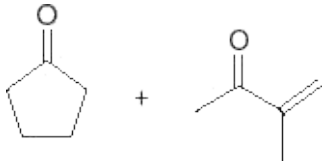
a.



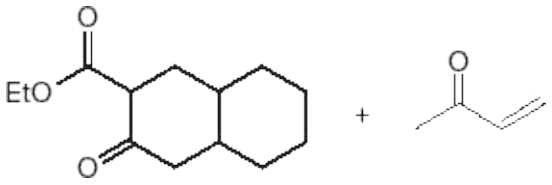
b.



c.



d.



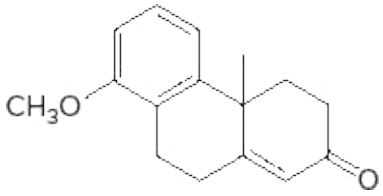
More Practice:

Try Problems 22.46, 22.66d.

To use the Robinson annulation in synthesis, you must be able to determine what starting materials are needed to prepare a given compound, by working in the retrosynthetic direction. Page 1035

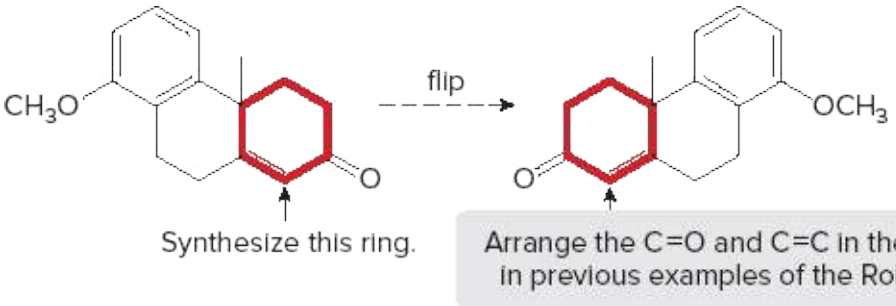
How To Synthesize a Compound Using the Robinson Annulation

Example What starting materials are needed to synthesize the following compound using a Robinson annulation?



Step [1] Locate the cyclohex-2-enone ring and re-draw the target molecule if necessary.

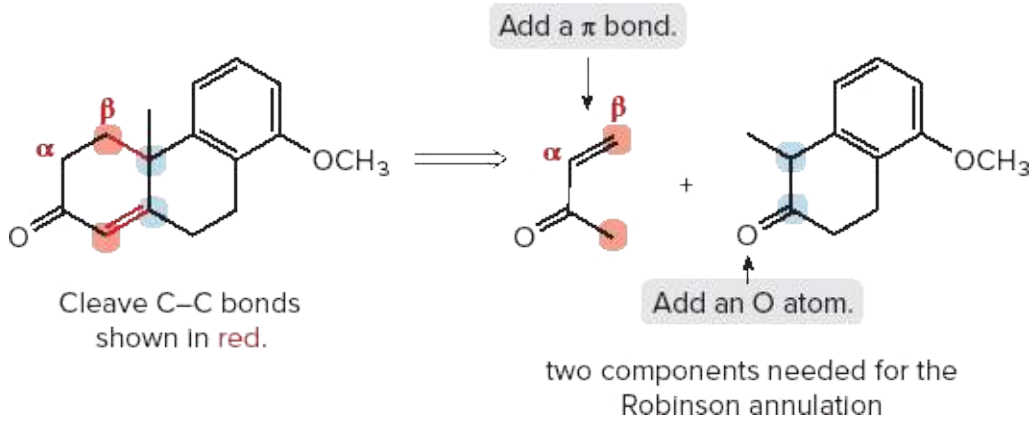
- **To most easily determine the starting materials, always arrange the α,β-unsaturated carbonyl system in the same location. The target compound may have to be flipped or rotated, and you must be careful not to move any bonds to the wrong location during this process.**



Step [2] Break the cyclohex-2-enone ring into two components.

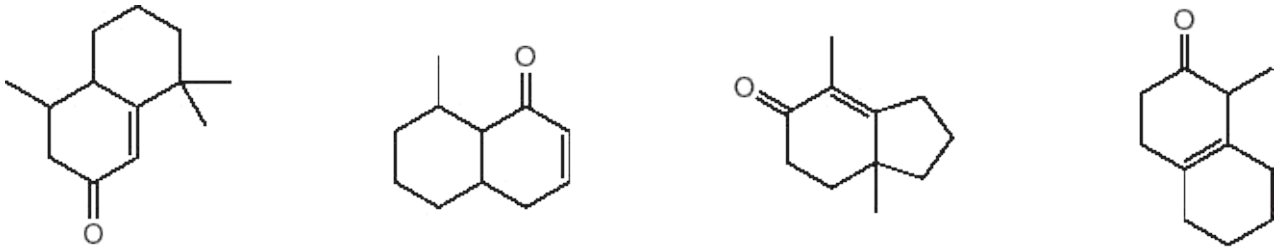
- **Break the C=C. One half becomes the carbonyl group of the enolate component.**
- **Break the bond between the β carbon and the carbon to which it**

is bonded.



Problem 22.27

Which of the following bicyclic ring systems can be prepared by an intermolecular Robinson annulation?

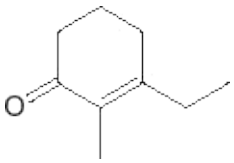


A B C D

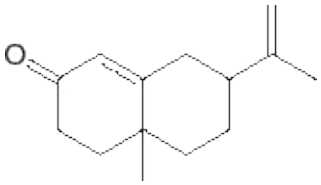
Problem 22.28

What starting materials are needed to synthesize each compound by a Robinson annulation?

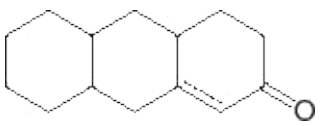
a.



b.



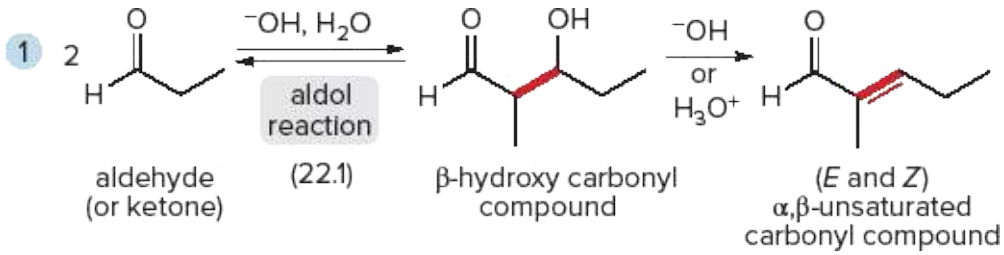
c.

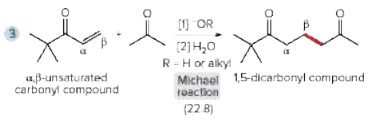


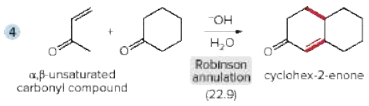
Chapter 22 REVIEW

KEY REACTIONS

[1] The four major carbonyl condensation reactions

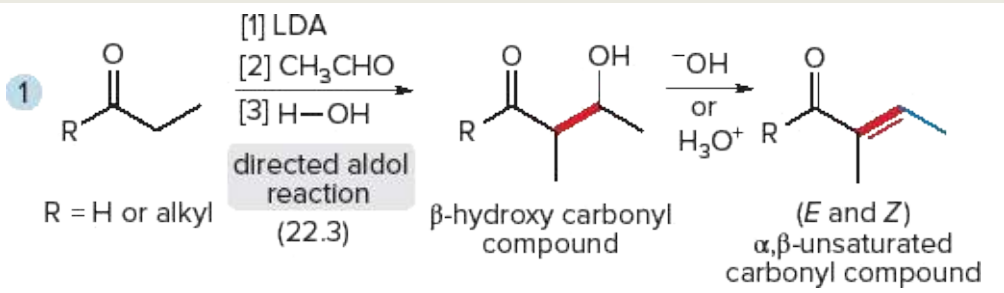


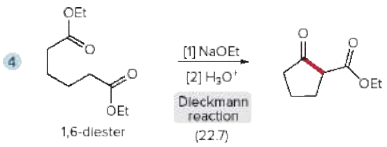


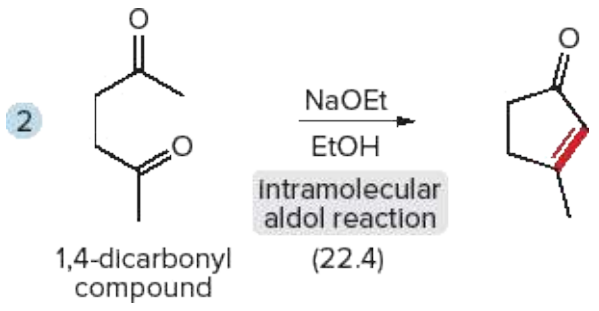


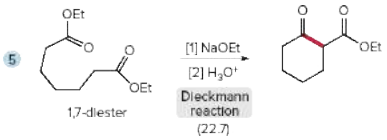
Try Problems 22.29; 22.31; 22.39; 22.43; 22.46; 22.48a, b, d, e.

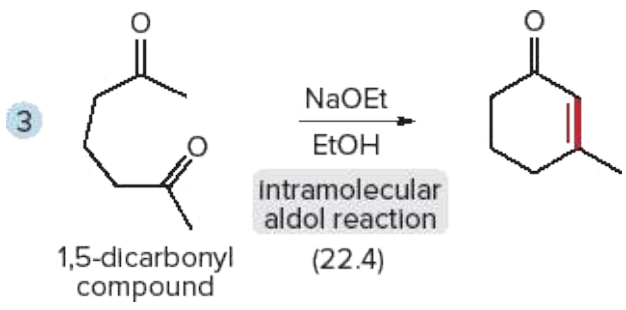
[2] Useful variations





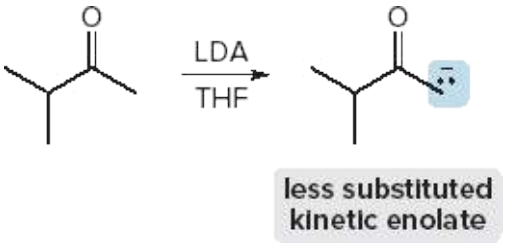
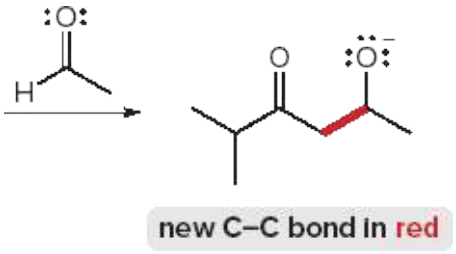
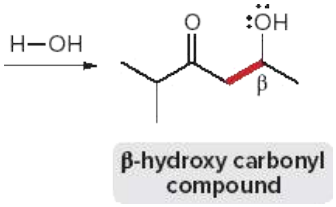






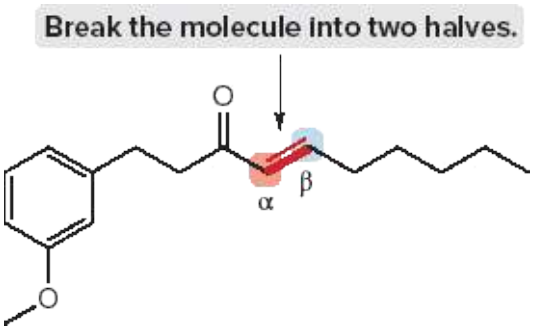
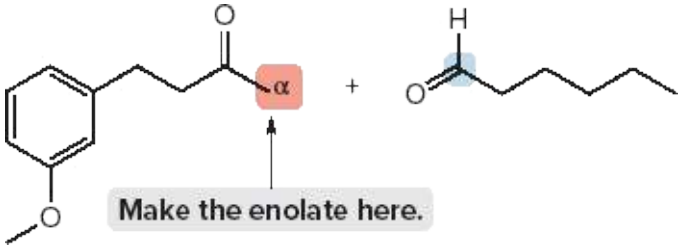
KEY SKILLS

[1] Drawing the product of a directed aldol reaction (22.3)

1 Prepare the enolate of one carbonyl component with LDA.	2 Add the second carbonyl compound to this enolate.	3 Add H_2O, and draw the product.
		

See Sample Problem 22.1. Try Problem 22.32.

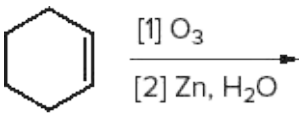
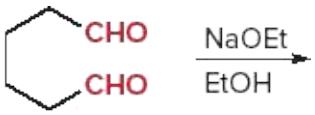
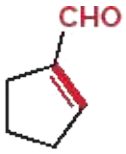
[2] Identifying the starting materials to synthesize an α,β-unsaturated carbonyl compound using a directed aldol reaction (22.3)

1 Identify the α and β carbons that are part of the C=C.	2 Break the molecule into two components between these carbons, and add a double bond to oxygen at the β carbon.
	

See Sample Problem 22.2. Try Problem 22.34.

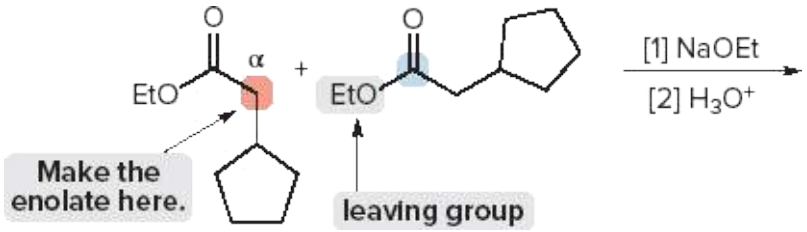
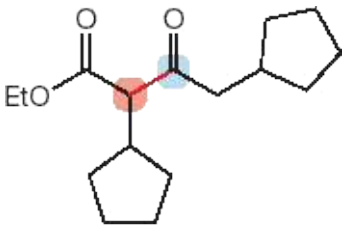
[3] Converting a six-membered ring to a five-membered ring using an intramolecular aldol reaction (22.4)

1 Treat the alkene	2 React the 1,6-	3 Draw the product.

with O_3, followed by Zn and H_2O.	dicarbonyl compound with base.	
 Ozone oxidatively cleaves the C=C.	 1,6-dicarbonyl compound	 Intramolecular aldol reaction forms the five-membered ring.

See Figure 22.5. Try Problems 22.30, 22.37.

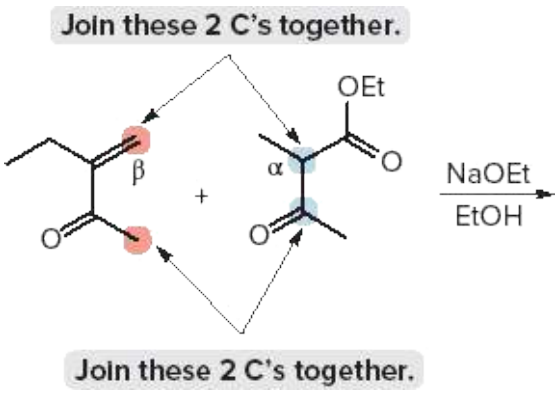
[4] Drawing the product of a Claisen reaction (22.5)

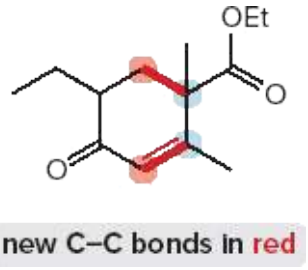
1 Identify the α carbon of one ester and the carbonyl carbon of the other.	2 Draw the product.
	 new C–C bond in red • A Claisen reaction is a nucleophilic substitution in which an enolate is the nucleophile.

See Sample Problem 22.4. Try Problems 22.39, 22.40.

[5] Drawing the product of a Robinson annulation (22.9)

1 Arrange the starting materials to put the reactive atoms next to each other.	2 Draw the product.

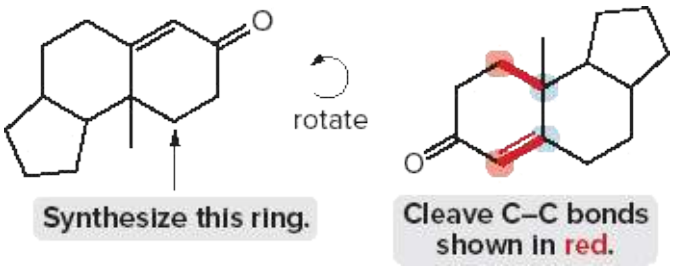




See Sample Problem 22.5. Try Problems 22.46, 22.66d.

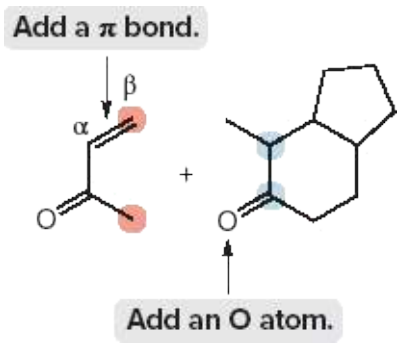
[6] Identifying the starting materials to synthesize a compound using the Robinson annulation (22.9)

1 **Locate the cyclohex-2-enone ring, and re-draw the target molecule, if necessary.**



- **Arrange the C=O and C=C in the same positions as in previous examples of the Robinson annulation.**

2 **Break the cyclohex-2-enone ring into two components.**



See *How To*, p. 1035. Try Problem 22.47.

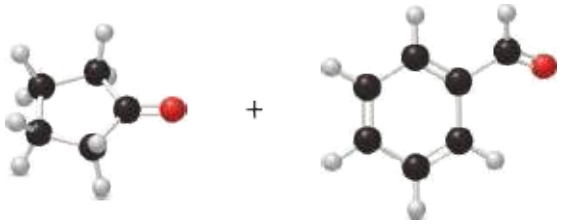
PROBLEMS

Problems Using Three-Dimensional Models

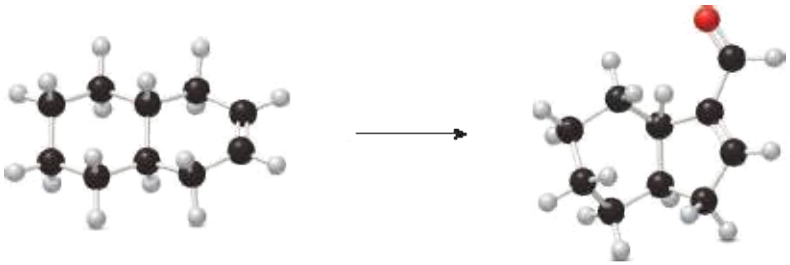
22.29 Draw the aldol product formed from each pair of starting materials using ^{-}OH, H_2O.

a.

b.



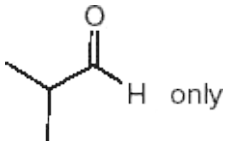
22.30 What steps are needed to convert A to B?



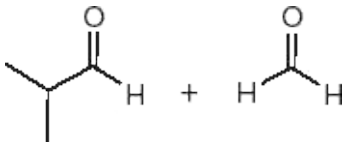
The Aldol Reaction

22.31 Draw the product formed from an aldol reaction with the given starting material(s) using ^{-}OH, H_2O.

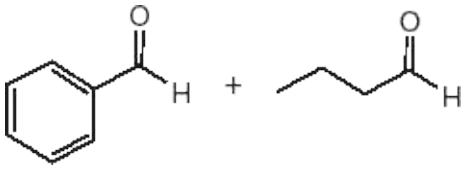
a.



b.

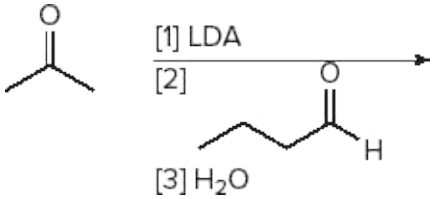


c.

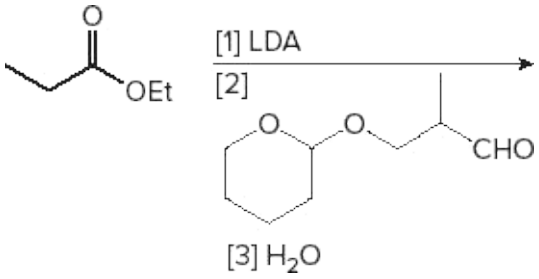


22.32 Draw the product formed in each directed aldol reaction.

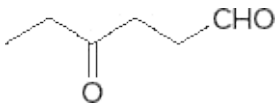
a.



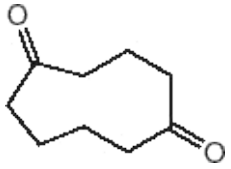
b.

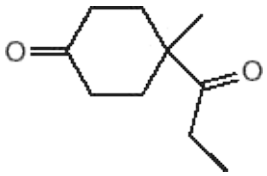


22.33 Draw the product formed when each dicarbonyl compound undergoes an intramolecular aldol reaction followed by dehydration, when possible.

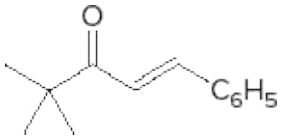
a. 

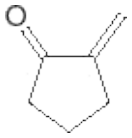
b.

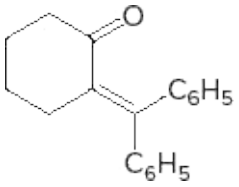
c. 

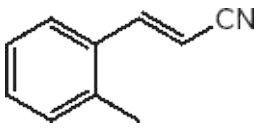
d. 

22.34 What starting materials are needed to synthesize each compound using an aldol or similar reaction?

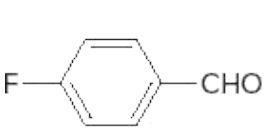
a. 

b. 

c. 

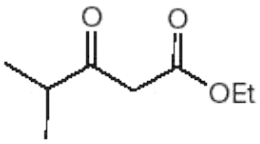
d. 

22.35 What product is formed when a solution of A and B is treated with mild base? This reaction is the first step in the synthesis of rosuvastatin (sold as a calcium salt under the trade name Crestor), a drug used to treat patients with high cholesterol.

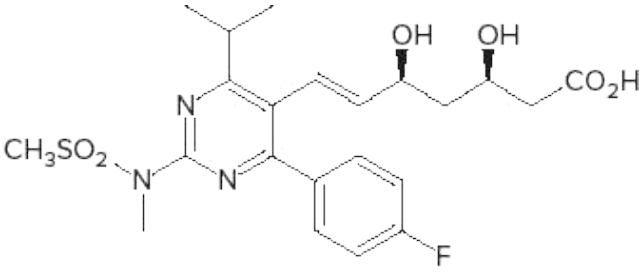


A

+

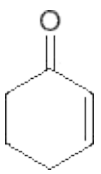


B

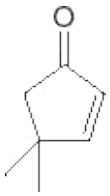


rosuvastatin

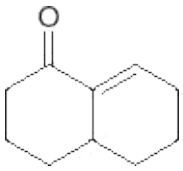
22.36 What dicarbonyl compound is needed to prepare each compound by an intramolecular aldol reaction?

a. 

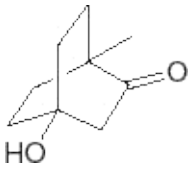
b.



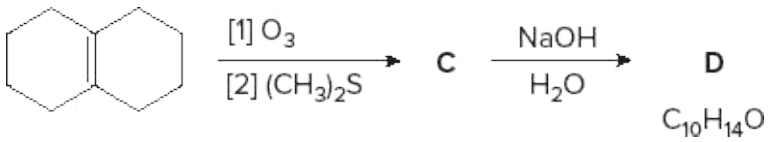
c.



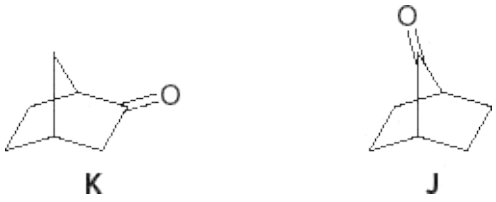
d.



22.37 Identify the structures of C and D in the following reaction sequence.



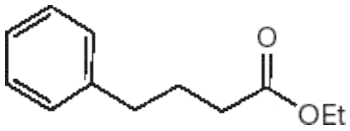
22.38 Explain why ketone K undergoes aldol reactions but ketone J does not.



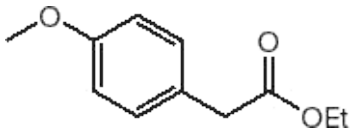
The Claisen and Dieckmann Reactions

22.39 Draw the Claisen product formed from each ester.

a.

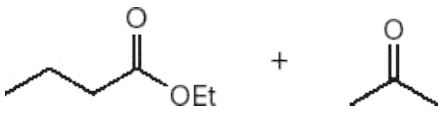


b.

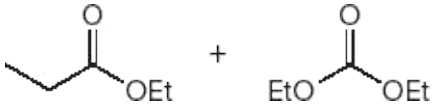


22.40 Draw the product formed from a Claisen reaction with the given starting materials using $^{-}$OEt, EtOH.

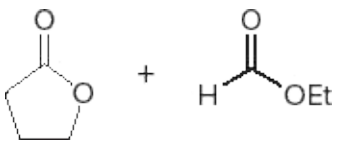
a.

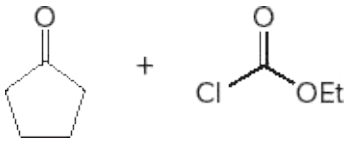


b.

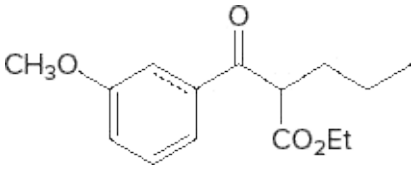


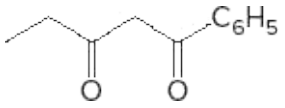
c.

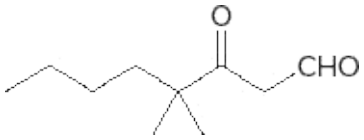


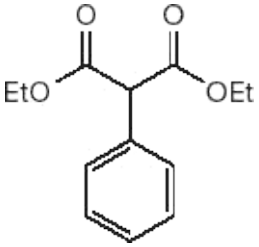
d. 

22.41 What starting materials are needed to synthesize each compound by a crossed Claisen reaction?

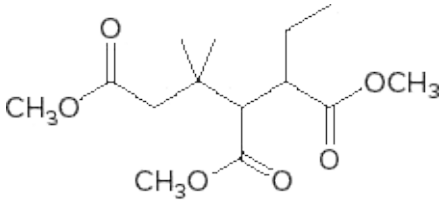
a. 

b. 

c. 

d. 

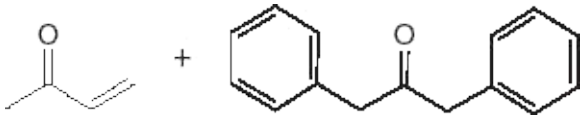
22.42 Even though B contains three ester groups, a single Dieckmann product results when B is treated with $NaOCH_3$ in CH_3OH, followed by H_3O^+. Draw the structure and explain why it is the only product formed.

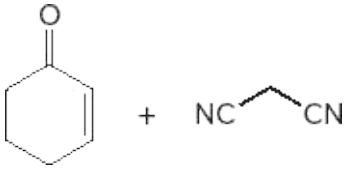


B

Michael Reaction

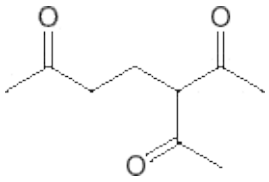
22.43 Draw the product formed from a Michael reaction with the given starting materials using ^-OEt, EtOH.

a. 

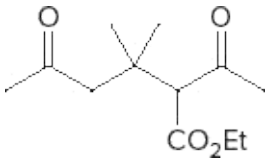
b. 

22.44 What starting materials are needed to prepare each compound using a Michael reaction?

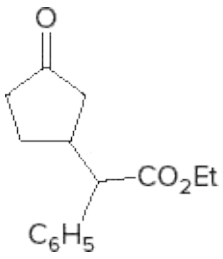
a.



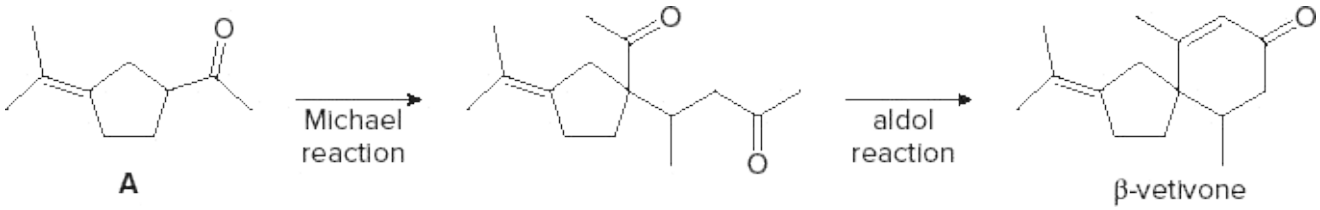
b.



c.



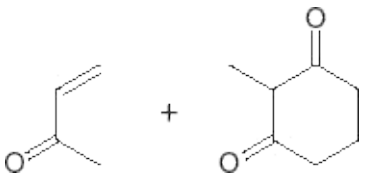
22.45 β-Vetivone is isolated from vetiver, a perennial grass that yields a variety of compounds used in traditional eastern medicine, pest control, and fragrance. In one synthesis, ketone A is converted to β-vetivone by a two-step process: Michael reaction, followed by intramolecular aldol reaction. (a) What Michael acceptor is needed for the conjugate addition? (b) Draw a stepwise mechanism for the aldol reaction, which forms the six-membered ring.



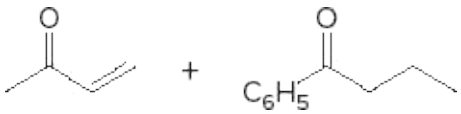
Robinson Annulation

22.46 Draw the product of each Robinson annulation from the given starting materials using ^{-}OH in H_2O solution.

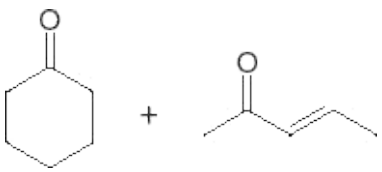
a.



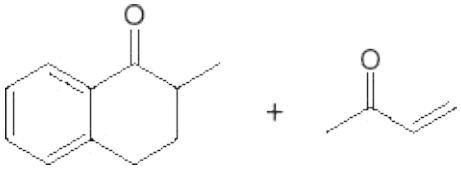
b.



c.

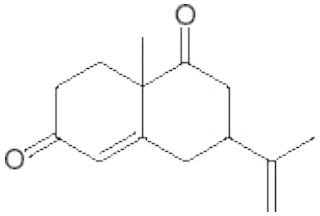


d.

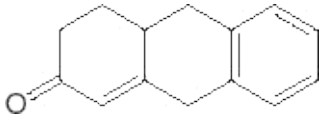


22.47 What starting materials are needed to synthesize each compound using a Robinson annulation?

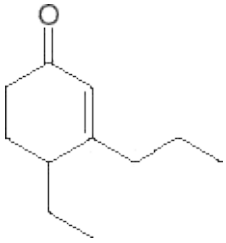
a.



b.



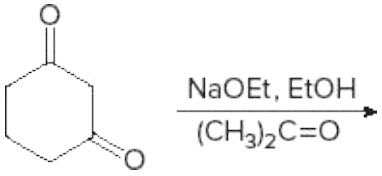
c.



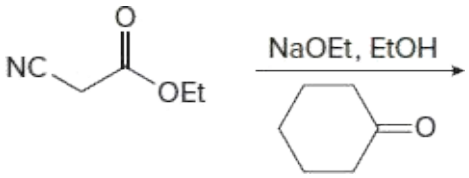
Reactions

22.48 Draw the organic products formed in each reaction.

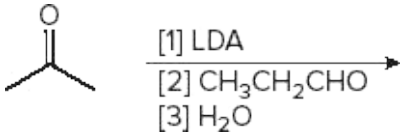
a.



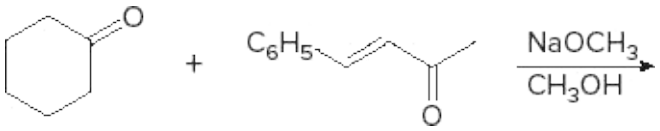
b.



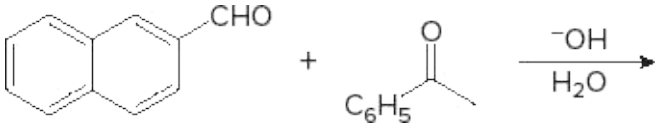
c.



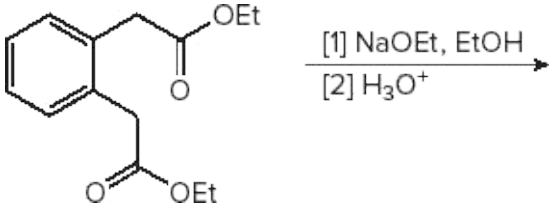
d.



e.

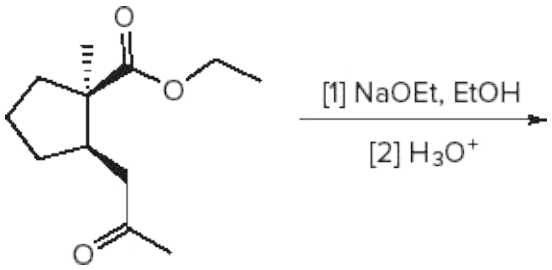


f.

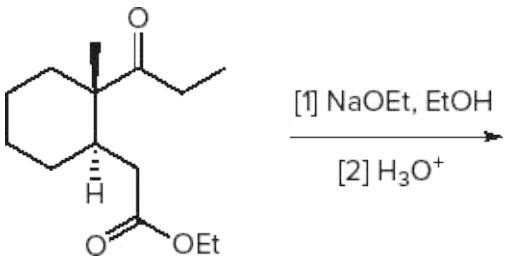


22.49 What product (including stereochemistry) is formed in each of the following intramolecular reactions?

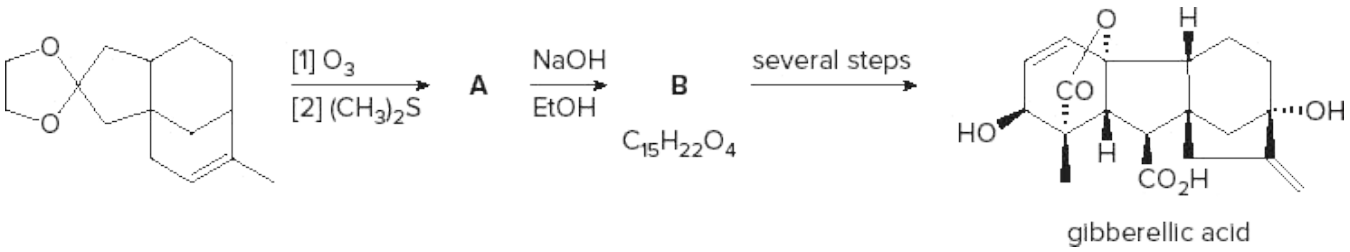
a.



b.

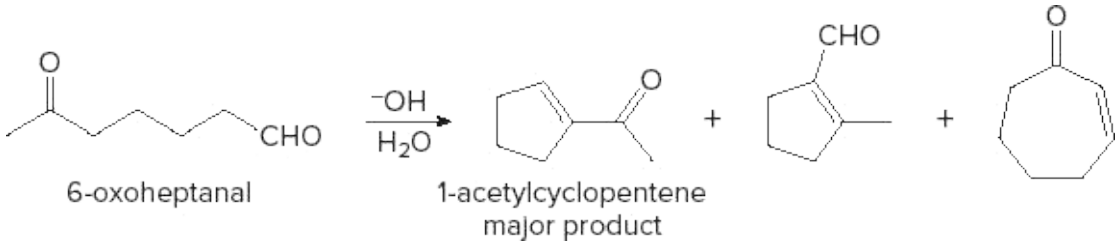


22.50 Identify compounds A and B, two synthetic intermediates in the 1979 synthesis of the plant growth hormone gibberellic acid by Corey and Smith. Gibberellic acid induces cell division and elongation, thus making plants tall and leaves large.

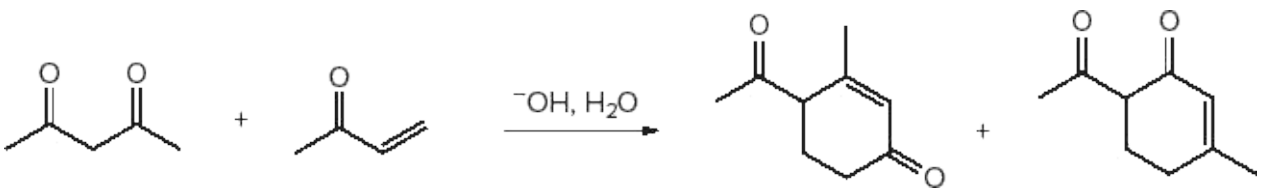


Mechanisms

22.51 In theory, the intramolecular aldol reaction of 6-oxoheptanal could yield the three compounds shown. It turns out, though, that 1-acetylcyclopentene is by far the major product. Why are the other two compounds formed in only minor amounts? Draw a stepwise mechanism to show how all three products are formed.

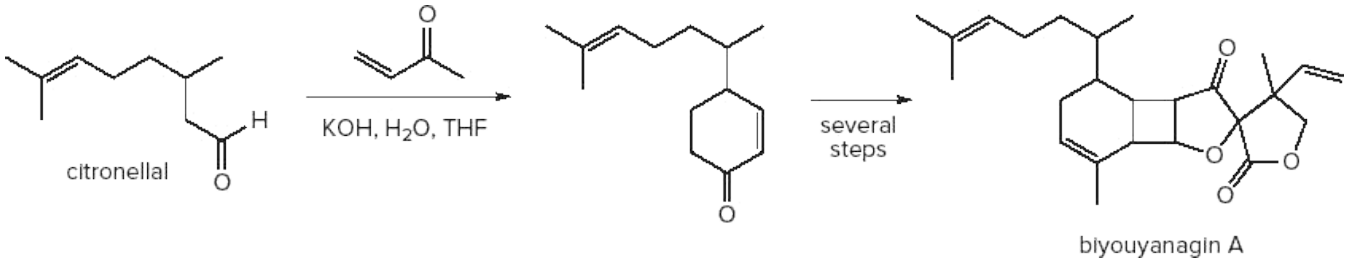


22.52 Draw a stepwise mechanism that illustrates how both products are formed in the following reaction.

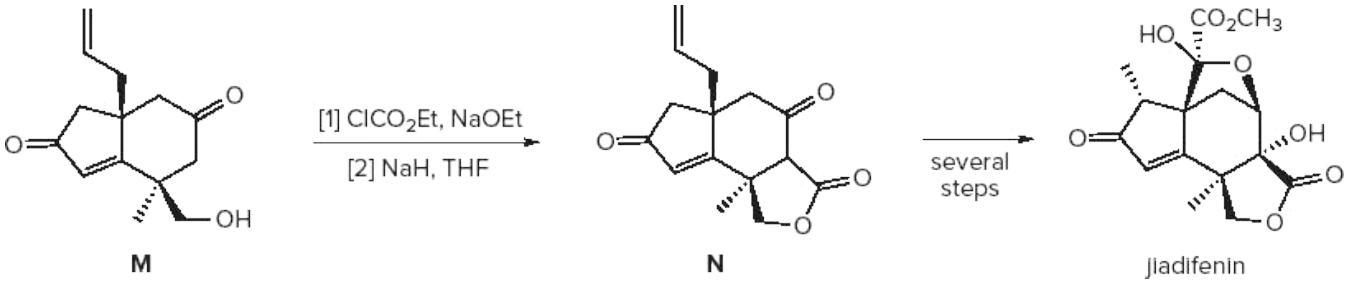


22.53 Biyouyanagin A is an anti-HIV agent isolated from the leaves of a plant of the genus ***Hypericum*** that is used in traditional Japanese medicine. The six-membered ring in

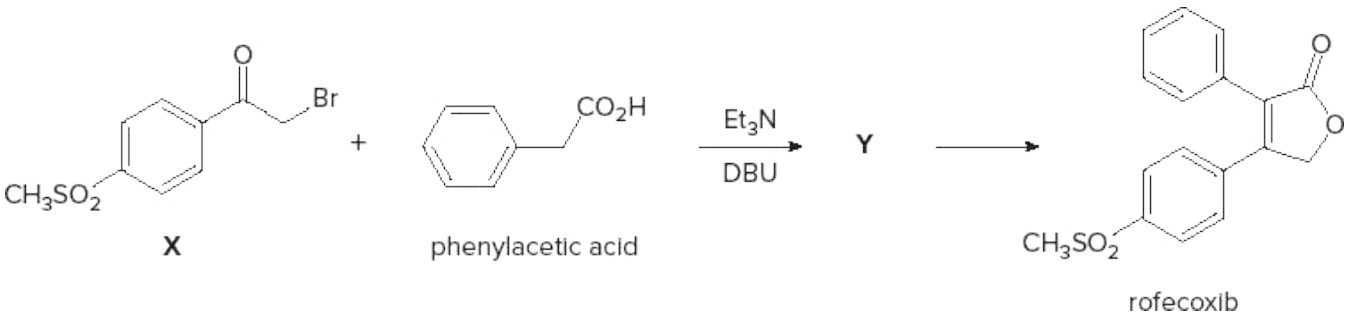
biyouyanagin A was formed in the given reaction. Draw a stepwise mechanism for this process.



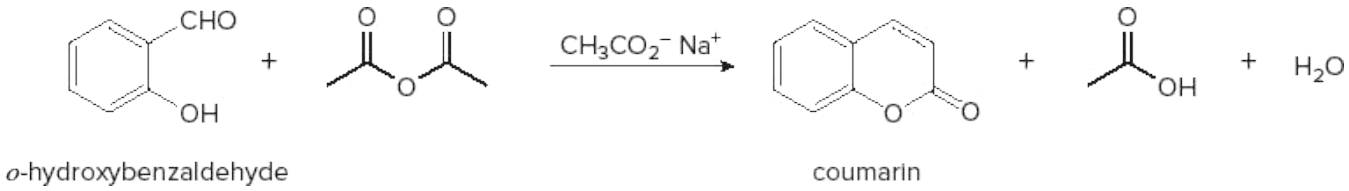
22.54 Jiadifenin is a natural product isolated from the fruit of the Chinese plant ***Illicium jiadifengpi***, which has potential for use in treating neurodegenerative disease. The lactone in jiadifenin is formed in the following two-step reaction. Write a stepwise mechanism for the conversion of M to N.



22.55 Reaction of X and phenylacetic acid forms an intermediate Y, which undergoes an intramolecular reaction to yield rofecoxib. Rofecoxib is a nonsteroidal anti-inflammatory agent once marketed under the trade name Vioxx, now withdrawn from the market because of increased risk of heart attacks from long-term use in some patients. Identify Y and draw a stepwise mechanism for its conversion to rofecoxib.

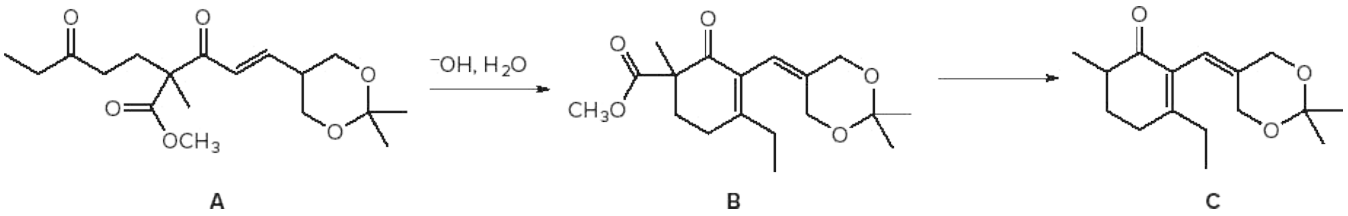


22.56 Coumarin, a naturally occurring compound isolated from lavender, sweet clover, and tonka bean, is made in the laboratory from ***o***-hydroxybenzaldehyde by the reaction depicted below. Draw a stepwise mechanism for this reaction. Coumarin derivatives are useful synthetic anticoagulants.



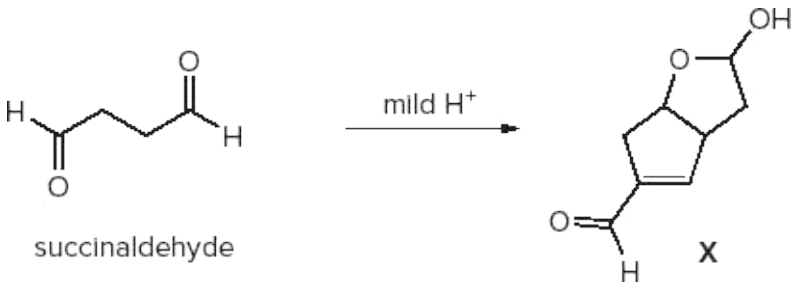
22.57 When A is treated with aqueous ^-OH, the major product is compound B, which undergoes ester hydrolysis and decarboxylation to form C. Draw a stepwise

mechanism for the conversion of A to B.



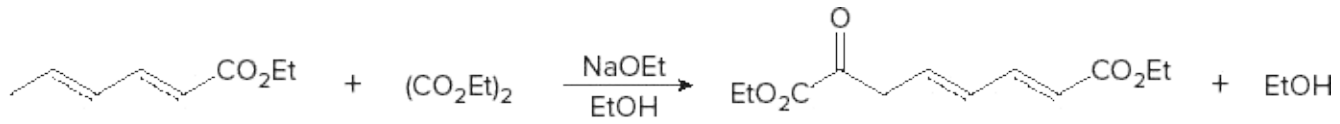
A B C

22.58 One step in a recent short synthesis of a prostaglandin (Section 19.5) involves the conversion of succinaldehyde to the bicyclic hemiacetal X. Draw a stepwise mechanism for this process. (Hint: The mechanism begins with an intermolecular aldol reaction.)



succinaldehyde X

22.59 (a) Draw a stepwise mechanism for the reaction of ethyl hexa-2,4-dienoate with diethyl oxalate in the presence of base. (b) How does your mechanism explain why a new carbon–carbon bond forms on C6? (c) Why is this reaction an example of a crossed Claisen reaction?

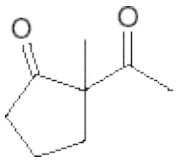


ethyl hexa-2,4-dienoate diethyl oxalate

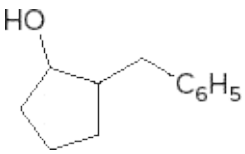
Synthesis

22.60 Devise a synthesis of each compound from cyclopentanone, benzene, and organic alcohols having ≤ 3 C's. You may also use any required organic or inorganic reagents.

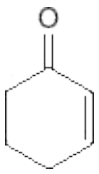
a.



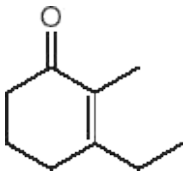
b.



c.

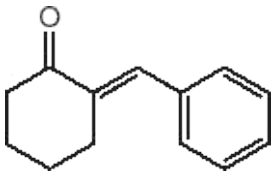


d.



22.61 How would you convert cyclohexanone to each of the following compounds?

a.



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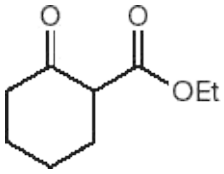
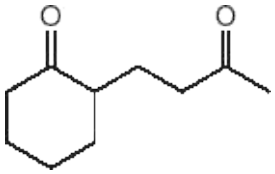
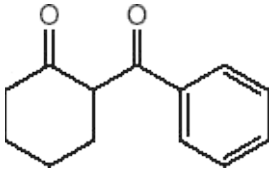


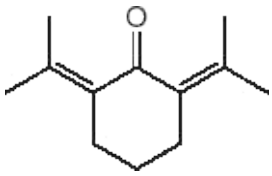
c.



d.

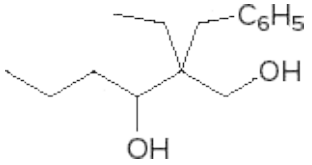


e.

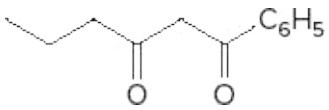


22.62 Devise a synthesis of each compound from $CH_3CH_2CH_2CO_2Et$, benzene, and alcohols having ≤ 2 C's. You may also use any required organic or inorganic reagents.

a.



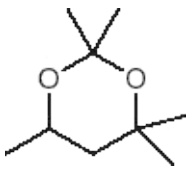
b.



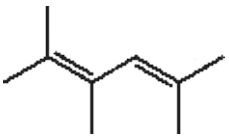
22.63 Devise a synthesis of 2-methylcyclopentanone from cyclohexene. You may also use any required reagents.

22.64 Devise a synthesis of each compound using acetone [$(CH_3)_2C=O$] as the only source of carbon atoms. You may use any needed organic or inorganic reagents.

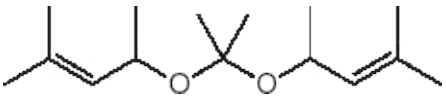
a.



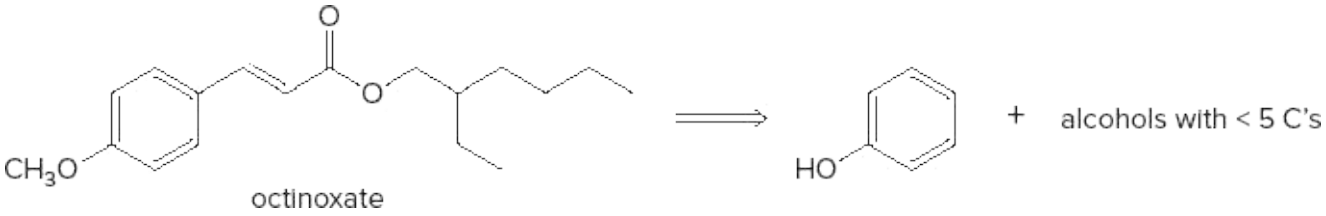
b.



c.



22.65 Octinoxate is an unsaturated ester used as an active ingredient in sunscreens. (a) What carbonyl compounds are needed to synthesize this compound using a condensation reaction? (b) Devise a synthesis of octinoxate from the given organic starting materials and any other needed reagents.



General Problem

22.66 Answer the following questions about 2-acetylcyclopentanone.

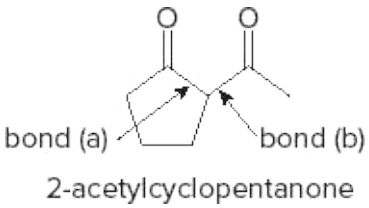
a. What starting materials are needed to form 2-acetylcyclopentanone by a Claisen reaction that forms bond (a)?

b. What starting materials are needed to form 2-acetylcyclopentanone by a Claisen reaction that forms bond (b)?

c. What product is formed when 2-acetylcyclopentanone is treated with $NaOCH_2CH_3$, followed by CH_3I?

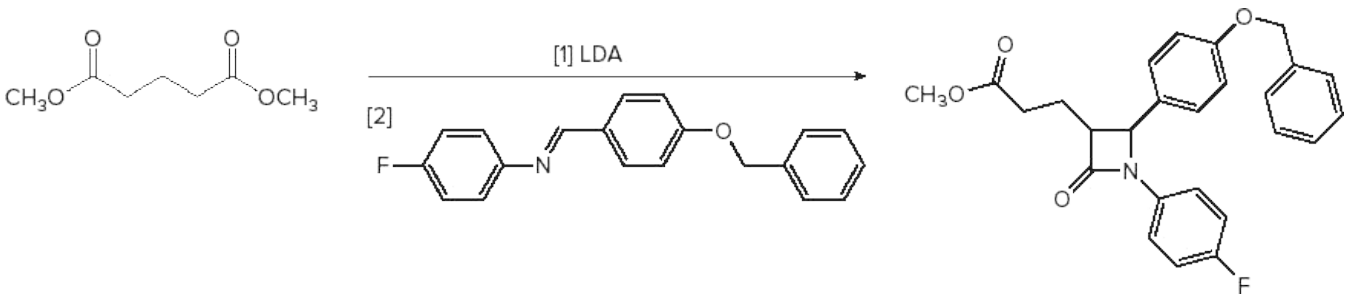
d. Draw the Robinson annulation product(s) formed by reaction of 2-acetylcyclopentanone with methyl vinyl ketone (CH_2=$CHCOCH_3$).

e. Draw the structure of the most stable enol tautomer(s).

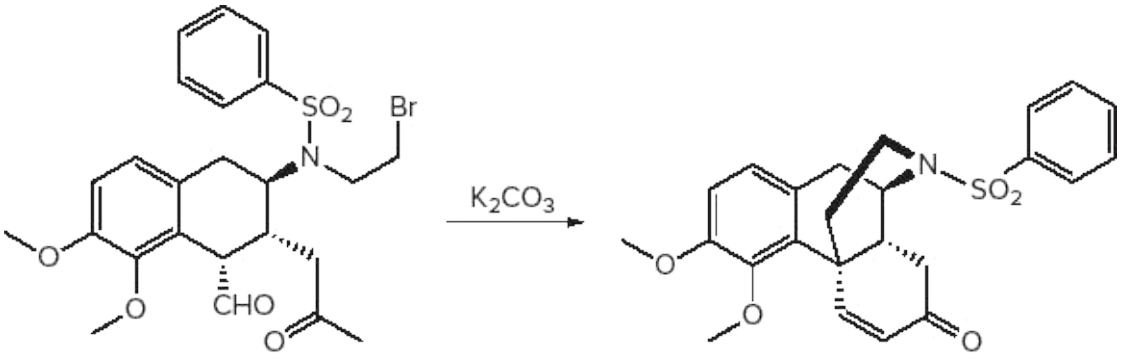


Challenge Problems

22.67 Draw a stepwise mechanism for the following reaction, which was used in the synthesis of ezetimibe (Section 17.6), a drug used to treat patients with high cholesterol.

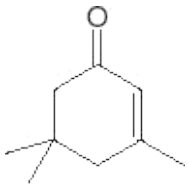


22.68 A key step in a reported synthesis of morphine (Section 2.2), the addictive opiate used to treat severe pain, involves the conversion of A to B. Draw a stepwise mechanism for this process, which involves both an intramolecular alkylation and an intramolecular aldol reaction.



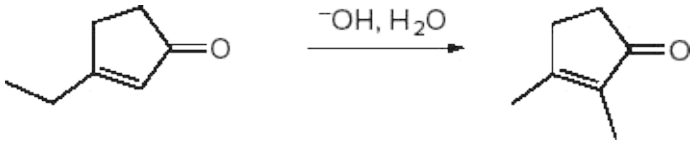
A B

22.69 Isophorone is formed from three molecules of acetone [$(CH_3)_2C{=}O$] in the presence of base. Draw a mechanism for this process.

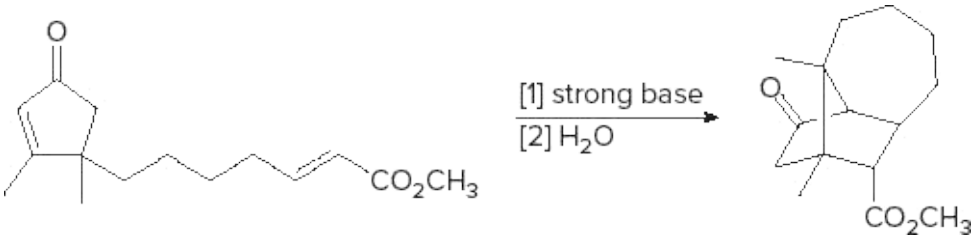


Isophorone

22.70 Devise a stepwise mechanism for the following reaction. (Hint: The mechanism begins with the conjugate addition of ^-OH.)

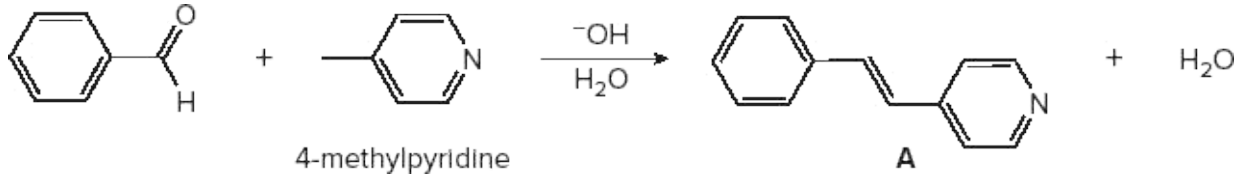


22.71 Draw a stepwise mechanism for the following reaction. (Hint: Two Michael reactions are needed.)

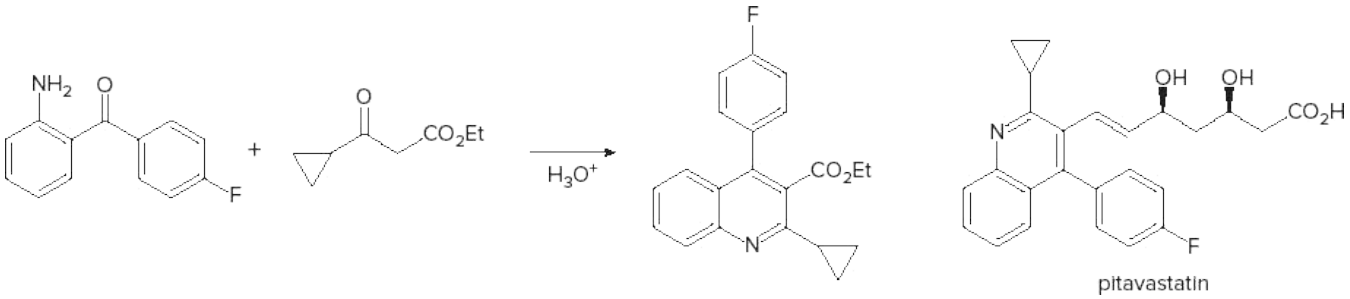


22.72 4-Methylpyridine reacts with benzaldehyde (C_6H_5CHO) in the presence of base to

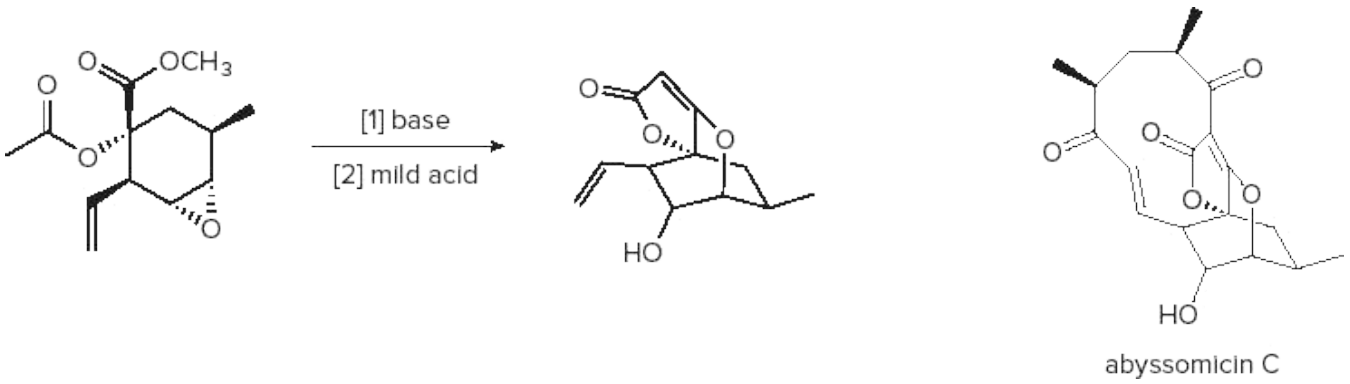
form A. (a) Draw a stepwise mechanism for this reaction. (b) Would you expect 2-methylpyridine or 3-methylpyridine to undergo a similar type of condensation reaction? Explain why or why not.



22.73 Draw a stepwise mechanism for the following reaction, one step in the synthesis of the cholesterol-lowering drug pitavastatin, marketed in Japan as a calcium salt under the name Livalo.

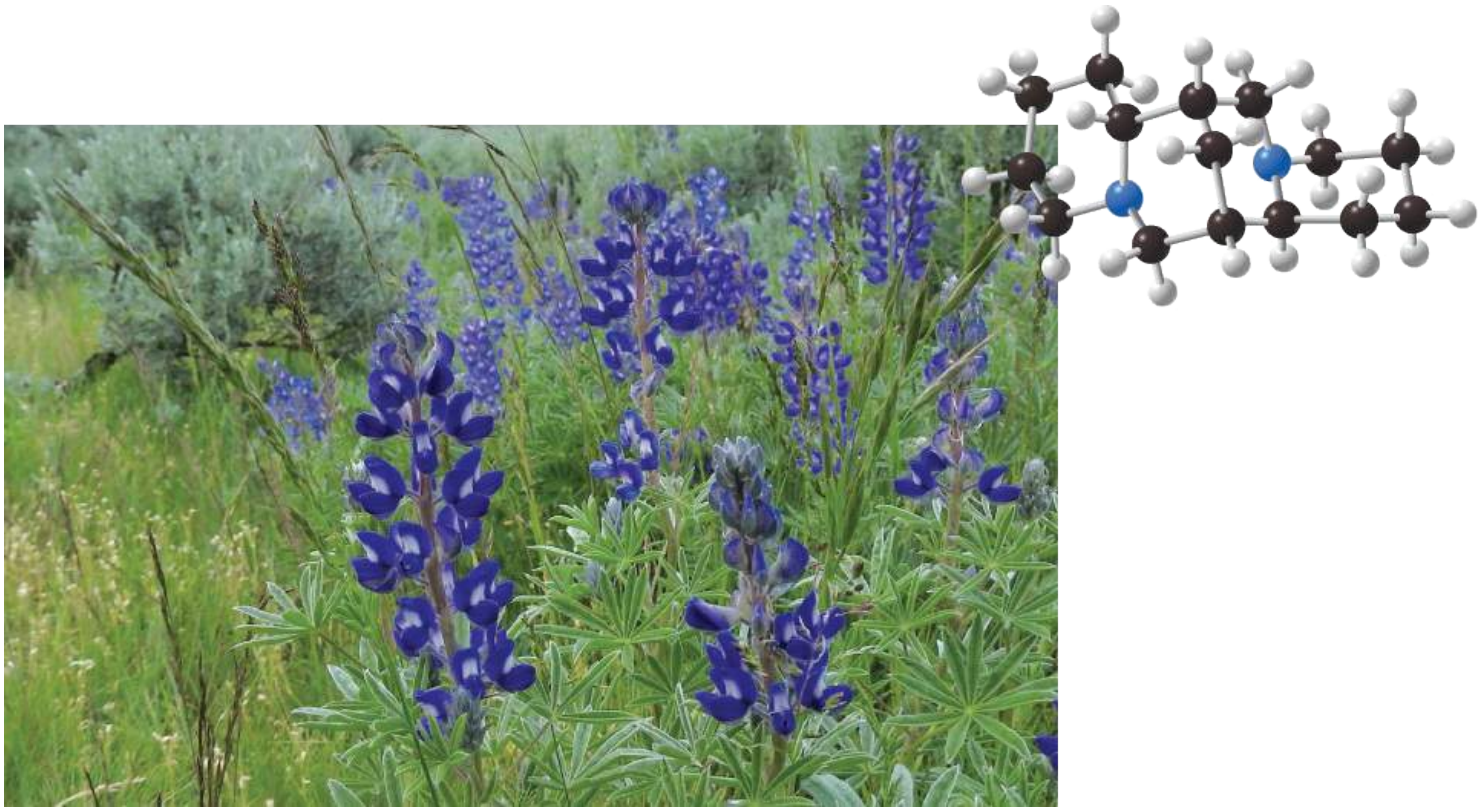


22.74 Devise a stepwise mechanism for the following reaction, a key step in the synthesis of the antibiotic abyssomicin C. Abyssomicin C was isolated from sediment collected from almost 1000 ft below the surface in the Sea of Japan. (Hint: The mechanism begins with a Dieckmann reaction.)



23

Amines



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23.1 Introduction

23.2 Structure and bonding

23.3 Nomenclature

23.4 Physical and spectroscopic properties

23.5 Interesting and useful amines

23.6 Preparation of amines

23.7 Reactions of amines—General features

23.8 Amines as bases

23.9 Relative basicity of amines and other compounds

23.10 Amines as nucleophiles
23.11 Hofmann elimination
23.12 Reaction of amines with nitrous acid
23.13 Substitution reactions of aryl diazonium salts
23.14 Coupling reactions of aryl diazonium salts
23.15 Application: Synthetic dyes and sulfa drugs

Sparteine is an alkaloid isolated from lupin, a flowering plant in the bean family that is abundant in the Andes of Peru and along roadsides in Alaska. Sparteine is an anti-arrhythmic agent—that is, a drug that suppresses abnormal heart rhythms—but it is not approved for human use by the U.S. Food and Drug Administration. Sparteine is one of the many naturally occurring amines isolated from a plant source. In Chapter 23, we learn about the properties and reactions of amines.

Why Study…

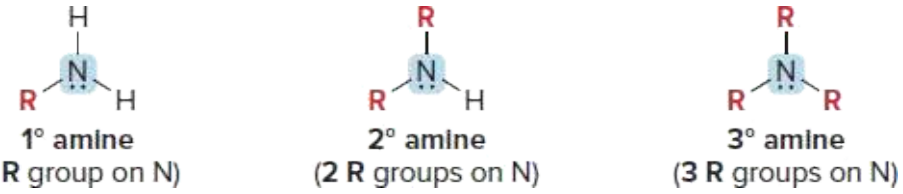
Amines?

We now leave the chemistry of carbonyl compounds to concentrate on amines, organic derivatives of ammonia (NH_3), formed by replacing one or more hydrogen atoms by alkyl or aryl groups. Amines are stronger bases and better nucleophiles than other neutral organic compounds, so much of Chapter 23 focuses on these properties.

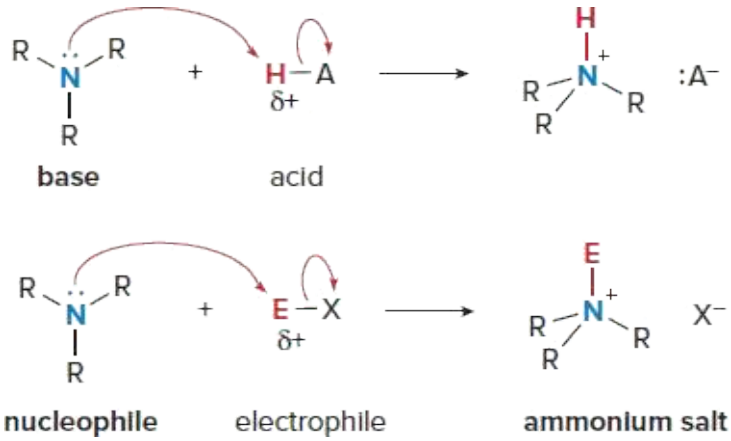
Like that of alcohols, the chemistry of amines does not fit neatly into one reaction class, and this can make learning the reactions of amines challenging. Many interesting natural products and widely used drugs are amines, so you also need to know how to introduce this functional group into organic molecules.

23.1 Introduction

Amines are organic nitrogen compounds, formed by replacing one or more hydrogen atoms of ammonia (NH_3) with alkyl groups. As discussed in Section 3.2, amines are classified as 1°, 2°, or 3° by the number of alkyl groups bonded to the *nitrogen* atom.



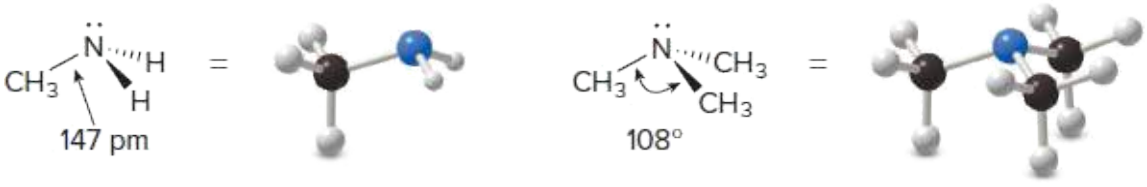
Like ammonia, the amine nitrogen atom has a nonbonded electron pair, making it both a base and a nucleophile. As a result, amines react with electrophiles to form ammonium salts—compounds with a positively charged ammonium ion and an anionic counterion.



- **The chemistry of amines is dominated by the nonbonded electron pair on the nitrogen atom.**

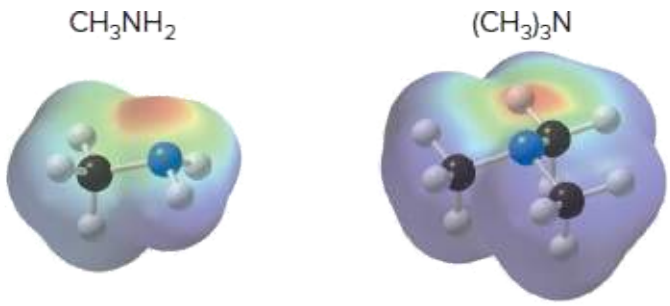
23.2 Structure and Bonding

An amine nitrogen atom is surrounded by three atoms and one nonbonded electron pair, making the N atom sp^3 hybridized and trigonal pyramidal, with bond angles of approximately 109.5°.



Because nitrogen is much more electronegative than carbon or hydrogen, the C—N and N—H bonds are all polar, with the N atom electron rich and the C and H atoms electron poor. The electrostatic potential maps in Figure 23.1 show the polar C—N and N—H bonds in CH_3NH_2 (methylamine) and $(CH_3)_3N$ (trimethylamine).

Figure 23.1 **Electrostatic potential plots of CH_3NH_2 and $(CH_3)_3N$**

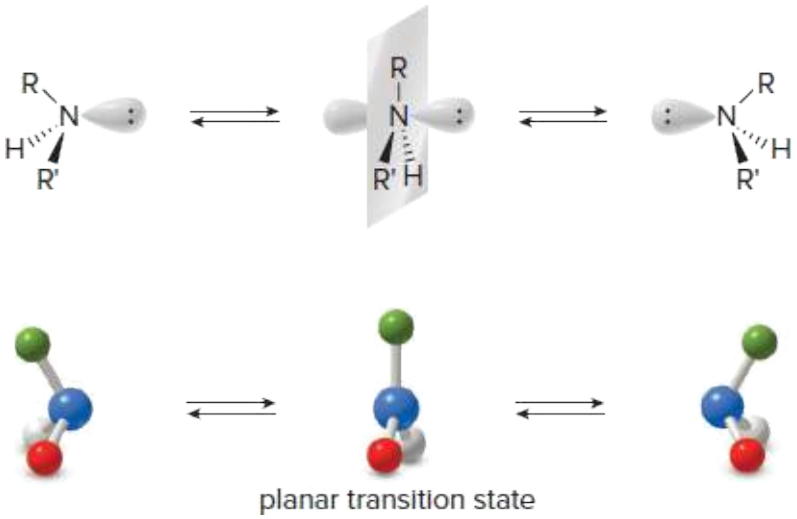


- Both amines clearly show the electron-rich region (in red) at the N atom.

An amine nitrogen atom bonded to an electron pair and three different alkyl groups is technically a stereogenic center, so two nonsuperimposable trigonal pyramids can be drawn.

nonsuperimposable mirror images

This does not mean, however, that such an amine exists as two different enantiomers, because one is rapidly converted to the other at room temperature. The amine flips inside out, passing through a trigonal planar (achiral) transition state. Because the two enantiomers interconvert, we can ignore the chirality of the amine nitrogen.



planar transition state

In contrast, the chirality of an ammonium ion with four different groups on N *cannot* be ignored. Because there is no nonbonded electron pair on the nitrogen atom, interconversion cannot occur, and the N atom is just like a carbon atom with four different groups around it.

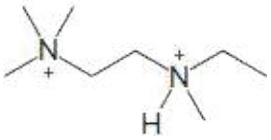
chiral ammonium ion

- **The N atom of an ammonium ion is a stereogenic center when N is surrounded by four different groups.**

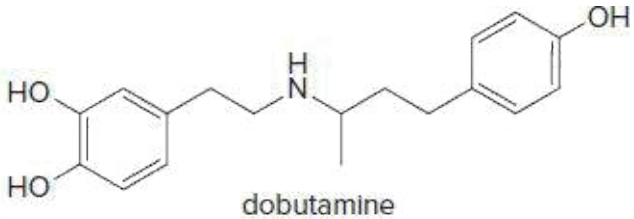
Problem 23.1

Label the stereogenic centers in each compound.

a.



b.



dobutamine
(heart stimulant used in stress tests to measure cardiac fitness)

23.3 Nomenclature

23.3A Primary Amines

Primary amines are named using either systematic or common names.

- **To assign the systematic name, find the longest continuous carbon chain bonded to the amine nitrogen, and change the *-e* ending of the parent alkane to the suffix *-amine*.**

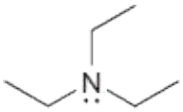
  Then use the usual rules of nomenclature to number the chain and name the substituents.
- **To assign a common name, name the alkyl group bonded to the nitrogen atom and add the suffix *-amine*, forming a single word.**

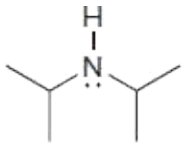
Systematic name: **methanamine**
Common name: **methylamine**

Systematic name: **cyclohexanamine**
Common name: **cyclohexylamine**

23.3B Secondary and Tertiary Amines

Secondary and tertiary amines having identical alkyl groups are named by using the prefix *di-* or *tri-* with the name of the primary amine.


triethylamine

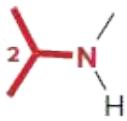

diisopropylamine

Secondary and tertiary amines having more than one kind of alkyl group are named as *N*-substituted primary amines, using the following procedure.

How To Name 2° and 3° Amines with Different Alkyl Groups

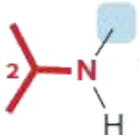
Example Name the following 2° amine: $(CH_3)_2CHNHCH_3$.

Step [1] **Designate the longest alkyl chain (or largest ring) bonded to the N atom as the parent amine and assign a systematic name.**



3 C's in the longest chain ----→ propan-2-amine

Step [2] **Name the other groups on the N atom as alkyl groups, alphabetize the names, and put the prefix *N-* before the name.**

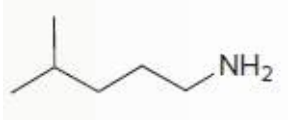

methyl substituent

Answer: *N*-methylpropan-2-amine

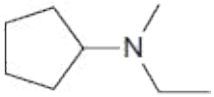
Sample Problem 23.1 Naming an Amine

Name each amine.

a.



b.

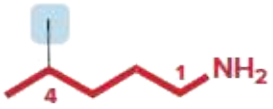


Solution

a. [1] A 1° amine: Find and name the longest chain containing the amine nitrogen.

pentane ----→ pentan*amine*
(5 C's)

[2] Number and name the substituents.

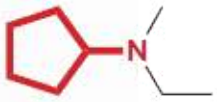


You must use a number to show the location of the NH_2 group.

Answer: 4-methylpentan-1-amine

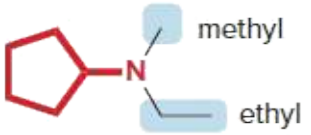
b. For a 3° amine, one alkyl group on N is the principal R group and the others are substituents.

[1] Name the ring bonded to the N.



cyclopentanamine

[2] Name the substituents.



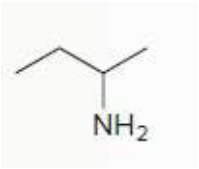
Two N's are needed, one for each alkyl group.

Answer: *N*-ethyl-*N*-methylcyclopentanamine

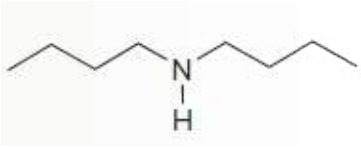
Problem 23.2

Name each amine.

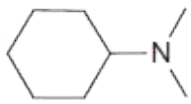
a.



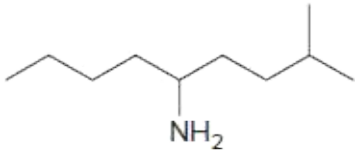
b.



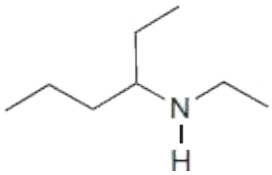
c.



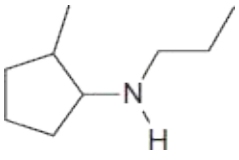
d.



e.



f.



More Practice:

Try Problems 23.35, 23.37.

23.3C Aromatic Amines

Aromatic amines are named as derivatives of aniline.

aniline *N*-ethylaniline *o*-bromoaniline

23.3D Miscellaneous Nomenclature Facts

An NH_2 group named as a substituent is called an amino group.

There are many different nitrogen heterocycles, and each ring type is named differently depending on the number of N atoms in the ring, the ring size, and whether it is aromatic or not. The structures and names of common nitrogen heterocycles are shown in Figure 23.2.

Problem 23.3

Draw a structure corresponding to each name.

a. 2,4-dimethylhexan-3-amine

b. *N*-methylpentan-1-amine

c. *N*-isopropyl-*p*-nitroaniline

d. *N*-methylpiperidine

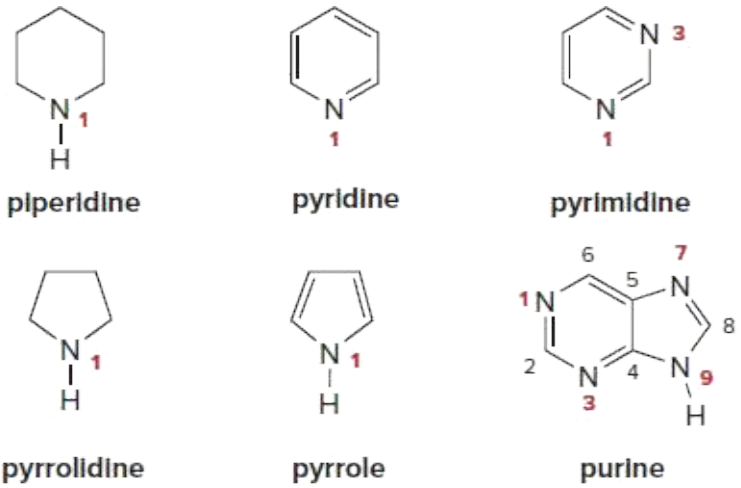
e. *N,N*-dimethylethanamine

f. 2-aminocyclohexanone

g. *N*-methylaniline

h. *m*-ethylaniline

Figure 23.2 **Common nitrogen heterocycles**



- Heterocycles with one N atom are numbered to place the N atom at the "1" position.
- Heterocycles with two N atoms are numbered to place one N atom at the "1" position and give the second N atom the lower number.

23.4 Physical and Spectroscopic Properties

23.4A Physical Properties

Amines exhibit dipole–dipole interactions because of the polar C—N and N—H bonds. Primary and secondary amines are also capable of intermolecular hydrogen bonding, because they contain N–H bonds. Because nitrogen is less electronegative than oxygen, however, intermolecular hydrogen bonds between N and H are *weaker* than those between O and H. How these factors affect the physical properties of amines is summarized in Table 23.1.

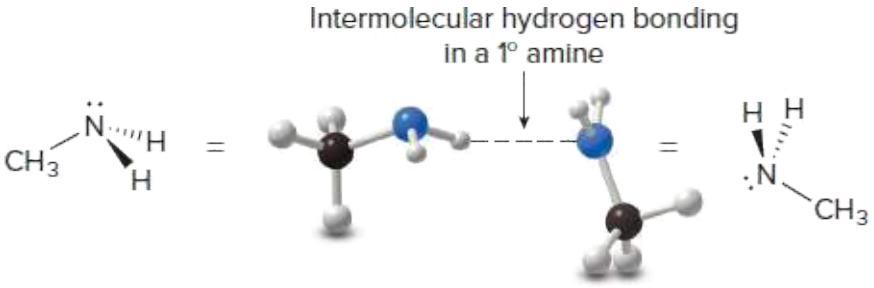
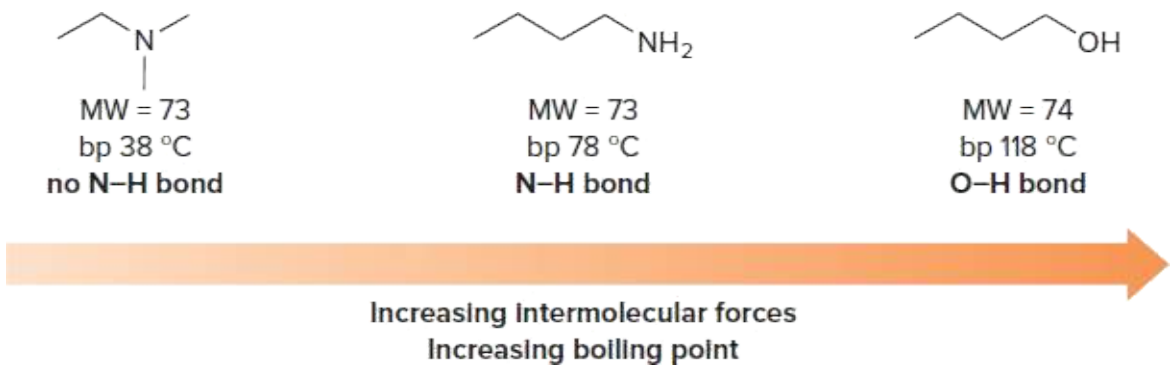


Table 23.1 Physical Properties of Amines

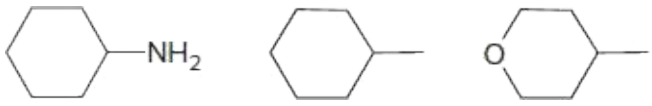
Property	Observation
Boiling point and melting point	• Primary (1°) and 2° amines have higher bp's than simi compounds (like ethers) incapable of hydrogen bonding, but lov bp's than alcohols that have stronger intermolecular hydrog bonds. • Tertiary (3°) amines have lower boiling points than 1° and amines of comparable molecular weight, because they have no I

	H bonds and are incapable of hydrogen bonding. 
Solubility	• Amines are soluble in organic solvents regardless of size. • All amines having ≤ 5 C's are H_2O soluble because they c hydrogen bond with H_2O (Section 3.4C). • Amines having > 5 C's are H_2O insoluble because the nonpolar al portion is too large to dissolve in the polar H_2O solvent.

MW = molecular weight

Problem 23.4

Arrange the compounds in order of increasing boiling point.



The general molecular formula for an amine with one N atom is $C_nH_{2n+3}N$.

23.4B Spectroscopic Properties

The spectroscopic properties of amines have been detailed in Spectroscopy Parts A, B, and C.

- Mass spectra: The odd molecular ion in Section A.1B and fragmentation patterns in Section A.4C
- Infrared absorptions: Section B.4C and Table B.2
- ^1H and ^{13}C NMR absorptions: Section C.9A and Tables C.1 and C.5

Key NMR and IR absorptions for amines are summarized in Table 23.2. Figure 23.3 illustrates that the number of N—H peaks in an IR spectrum can be used to distinguish

1°, 2°, and 3° amines.

- **1° Amines show *two* N—H absorptions at 3300–3500 cm^{-1}.**
- **2° Amines show *one* N—H absorption at 3300–3500 cm^{-1}.**
- **3° Amines do *not* absorb at 3300–3500 cm^{-1} because 3° amines have no N—H bonds.**

Table 23.2 Characteristic Spectroscopic Absorptions of Amines

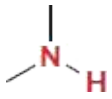
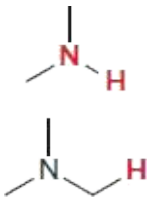
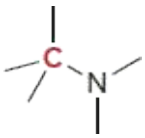
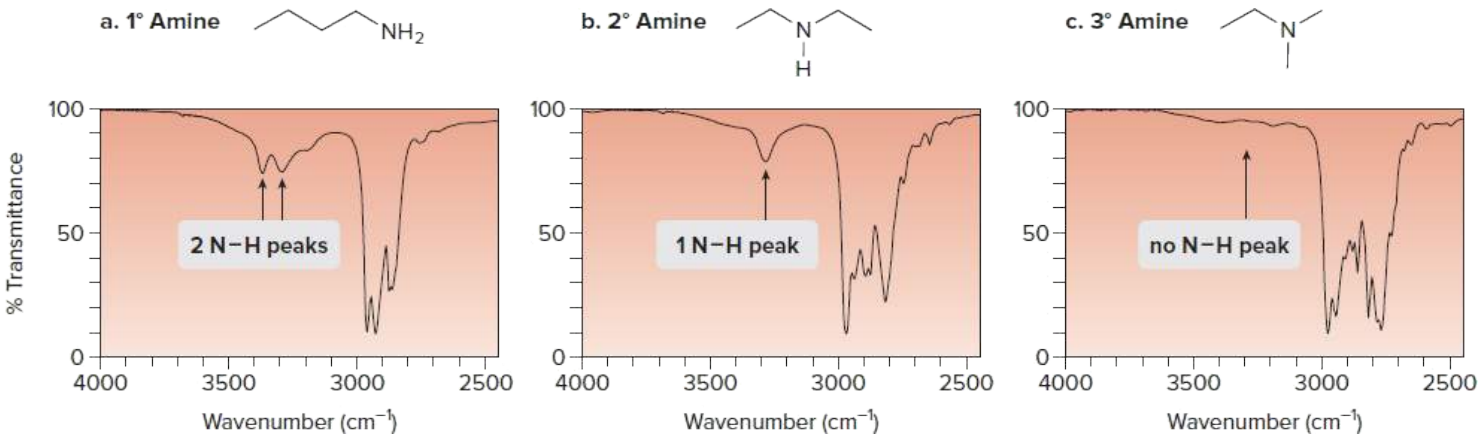
Type of spectroscopy	Type of C, H	Absorption
IR absorption		3300–3500 cm^{-1} (one or two peaks)
^{1}H NMR absorptions		0.5–5.0 ppm 2.3–3.0 ppm
^{13}C NMR absorption		30–50 ppm

Figure 23.3 The single bond region of the IR spectra for a 1°, 2°, and 3° amine



23.5 Interesting and Useful Amines

A great many simple and complex amines occur in nature, and others with biological activity have been synthesized in the lab.

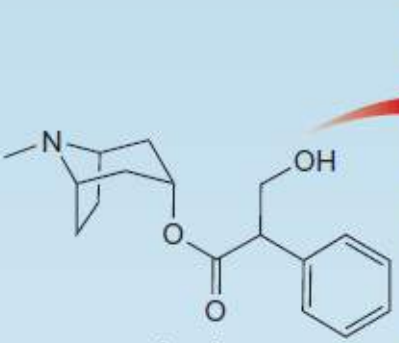
23.5A Simple Amines and Alkaloids

Many low-molecular-weight amines have *very* foul odors. Trimethylamine [$(CH_3)_3N$], formed when enzymes break down certain fish proteins, has the characteristic odor of rotting fish. Putrescine ($NH_2CH_2CH_2CH_2CH_2NH_2$) and cadaverine ($NH_2CH_2CH_2CH_2CH_2CH_2NH_2$) are both poisonous diamines with putrid odors. They, too, are present in rotting fish and are partly responsible for the odors of semen, urine, and bad breath.

The word *alkaloid* is derived from the word *alkali*, because aqueous solutions of alkaloids are slightly basic.

Naturally occurring amines derived from plant sources are called alkaloids. Alkaloids previously encountered in the text include quinine (Problem 21.15), morphine (Section 20.8), and cocaine (Chapter 20 opener). Three other common alkaloids are atropine, nicotine, and scopolamine, illustrated in Figure 23.4.

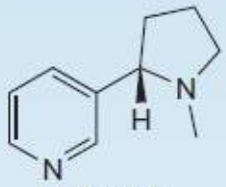
Figure 23.4 **Three common alkaloids—Atropine, nicotine, and scopolamine**



atropine

nightshade

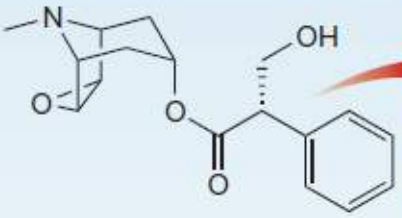
- **Atropine** is an alkaloid isolated from *Atropa belladonna*, the deadly nightshade plant. In the Renaissance, women used the juice of the berries of the nightshade to enlarge the pupils of their eyes for cosmetic reasons. Atropine causes an increase in heart rate, relaxes smooth muscles, and interferes with nerve impulses transmitted by acetylcholine. In higher doses atropine is poisonous, leading to convulsions, coma, and death.



nicotine

tobacco

- **Nicotine** is an addictive and highly toxic compound isolated from tobacco. In small doses it acts as a stimulant, but in large doses it causes depression, nausea, and even death. Nicotine is synthesized in plants as a defense against insect predators, and is used commercially as an insecticide.



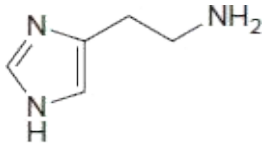
scopolamine

angel's trumpet

- **Scopolamine** is a complex amine that occurs in angel's trumpets, ornamental plants with large trumpet-shaped flowers native to South America. Transdermal patches that release a minute dose of scopolamine are used to treat the nausea and vomiting associated with motion sickness.

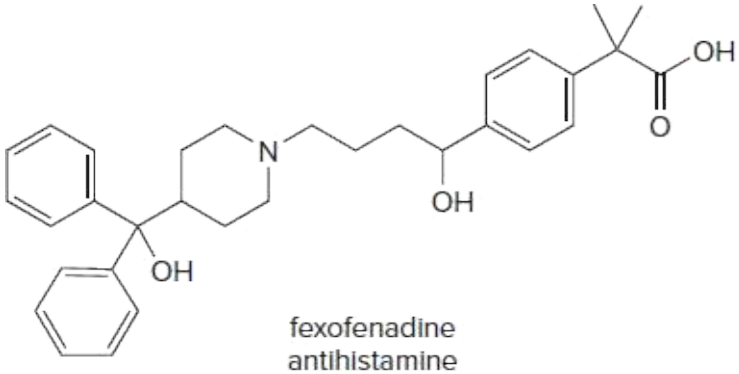
23.5B Histamine and Antihistamines

Histamine, a simple triamine first discussed in Section 15.8, is responsible for a wide variety of physiological effects. Histamine is a vasodilator (it dilates capillaries), so it is released at the site of an injury or infection to increase blood flow. It is also responsible for the symptoms of allergies, including a runny nose and watery eyes. In the stomach, histamine stimulates the secretion of acid.

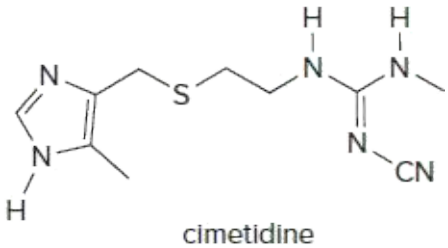


histamine

Understanding the central role of histamine in these biochemical processes has helped chemists design drugs to counteract some of its undesirable effects.



fexofenadine
antihistamine

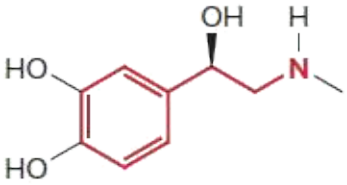


cimetidine
(Tagamet)
antiulcer drug

Antihistamines bind to the same active site of the enzyme that binds histamine in the cell, but they evoke a different response. An antihistamine like fexofenadine (trade name Allegra), for example, inhibits vasodilation, so it is used to treat the symptoms of the common cold and allergies. Unlike many antihistamines, fexofenadine does not cause drowsiness because it binds to histamine receptors but does not cross the blood–brain barrier, so it does not affect the central nervous system. Cimetidine (trade name Tagamet) is a histamine mimic that blocks the secretion of hydrochloric acid in the stomach, so it is used to treat individuals with ulcers.

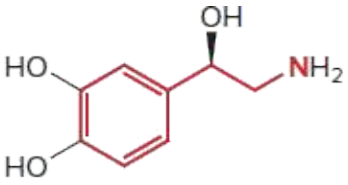
23.5C Derivatives of 2-Phenylethanamine

A large number of physiologically active compounds are derived from 2-phenylethanamine, $C_6H_5CH_2CH_2NH_2$. Some of these compounds are synthesized in cells and needed to maintain healthy mental function. Others are isolated from plant sources or are synthesized in the laboratory and have a profound effect on the brain because they interfere with normal neurochemistry. These compounds include adrenaline, noradrenaline, methamphetamine, and mescaline. Each contains a benzene ring bonded to a two-carbon unit with a nitrogen atom (shown in red).



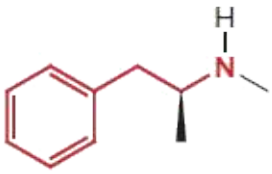
adrenaline
(epinephrine)

a hormone secreted in response to stress
(Figure 7.19)



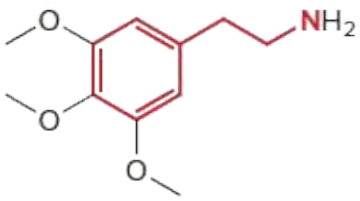
noradrenaline
(norepinephrine)

a neurotransmitter that increases heart rate
and dilates air passages



methamphetamine

an addictive stimulant sold as
speed, meth, or crystal meth



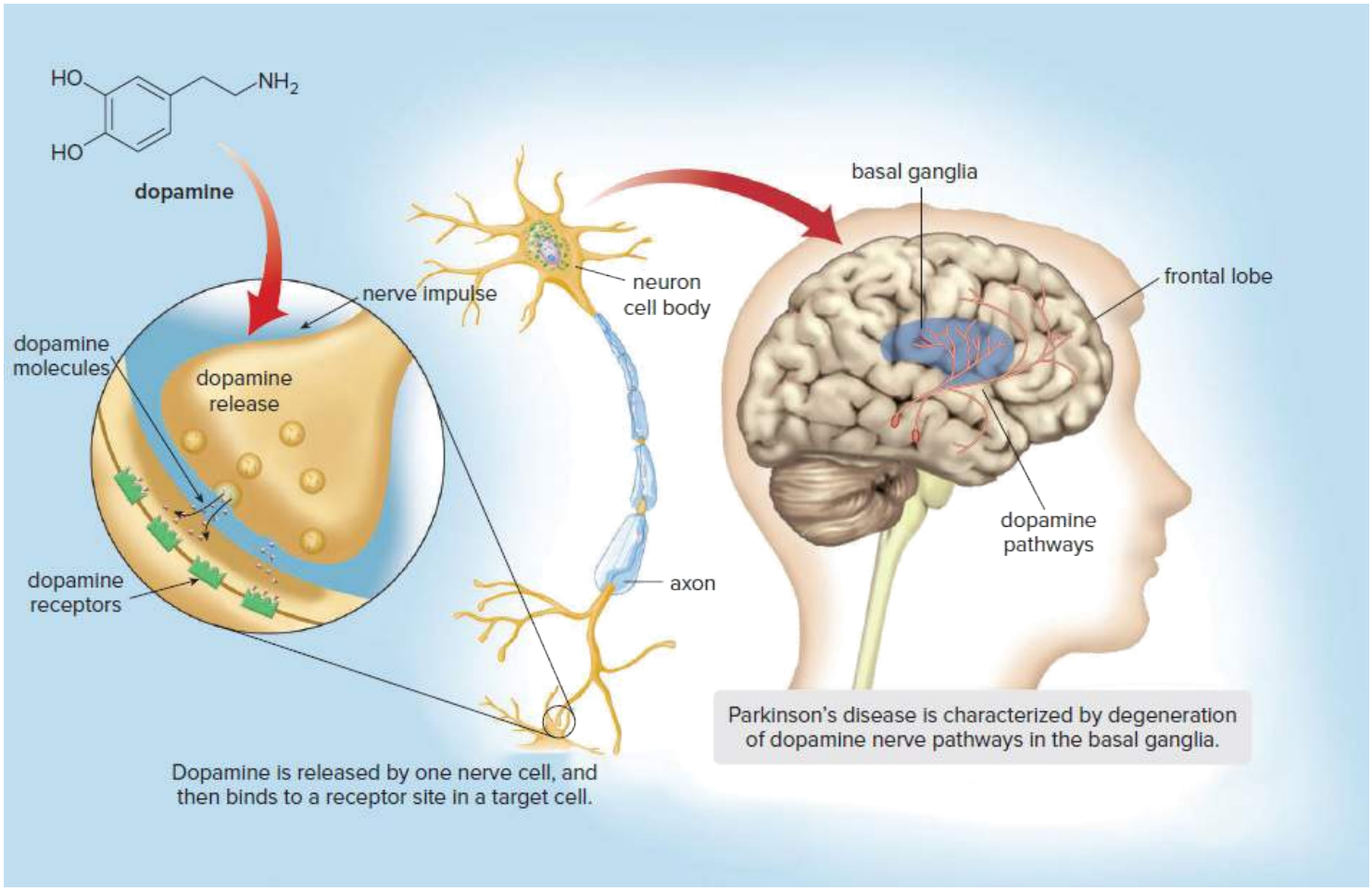
mescaline

a hallucinogen isolated from peyote, a cactus native
to the southwestern United States and Mexico

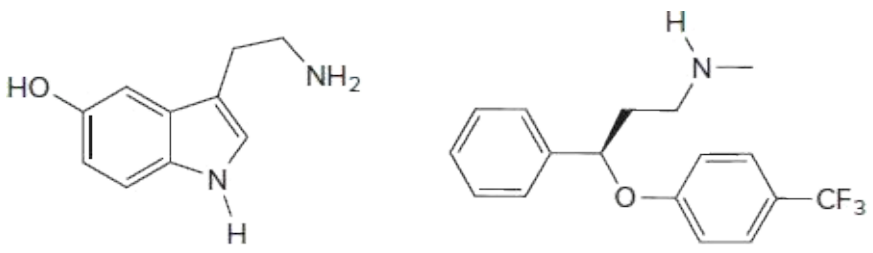
Another example, dopamine, is a neurotransmitter, a chemical messenger released by one nerve cell (neuron), which then binds to a receptor in a neighboring target cell (Figure 23.5). Dopamine affects brain processes that control movement and emotions, so proper dopamine levels are necessary to maintain an individual's mental and physical health. For example, when dopamine-producing neurons die, the level of dopamine drops, resulting in the loss of motor control symptomatic of Parkinson's disease.

Cocaine, amphetamines, and several other addictive drugs increase the level of dopamine in the brain, which results in a pleasurable "high." With time, the brain adapts to increased dopamine levels, so more drug is required for the same sensation.

Figure 23.5 **Dopamine—A neurotransmitter**

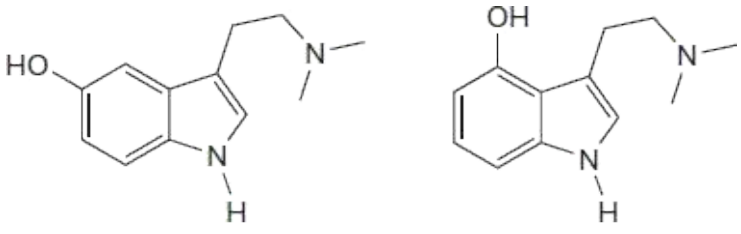


Serotonin is a neurotransmitter that plays an important role in mood, sleep, perception, and temperature regulation. A deficiency of serotonin causes depression. Understanding the central role of serotonin in determining one's mood has led to the development of a variety of drugs for the treatment of depression. The most widely used antidepressants today are selective serotonin reuptake inhibitors (SSRIs). These drugs act by inhibiting the reuptake of serotonin by the neurons that produce it, thus effectively increasing its concentration. Fluoxetine (trade name Prozac) is a common antidepressant that acts in this way.



serotonin fluoxetine

Drugs that interfere with the metabolism of serotonin have a profound effect on mental state. For example, bufotenin, isolated from *Bufo* toads from the Amazon jungle, and psilocin, isolated from *Psilocybe* mushrooms, are very similar in structure to serotonin and both cause intense hallucinations.



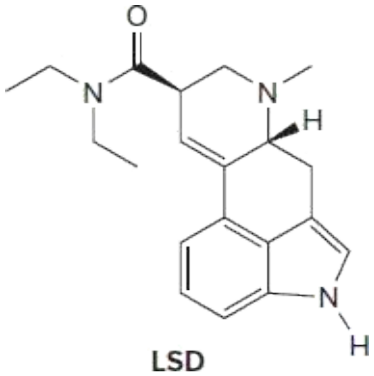
Bufo toads from the Amazon jungle are the source of the hallucinogen bufotenin.

©Daniel C. Smith

Problem 23.5

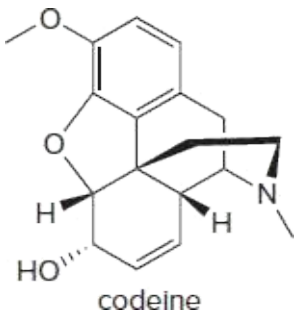
LSD (a hallucinogen) and codeine (a narcotic) are structurally more complex derivatives of 2-phenylethanamine. Identify the atoms of 2-phenylethanamine in each of the following compounds.

a.



LSD
lysergic acid diethylamide

b.



codeine

23.6 Preparation of Amines

In the preparations of a given functional group, many different starting materials form a common product (amines, in this case).

Three types of reactions are used to prepare an amine:

[1] Nucleophilic substitution using nitrogen nucleophiles

[2] Reduction of other nitrogen-containing functional groups

[3] Reductive amination of aldehydes and ketones

23.6A Nucleophilic Substitution Routes to Amines

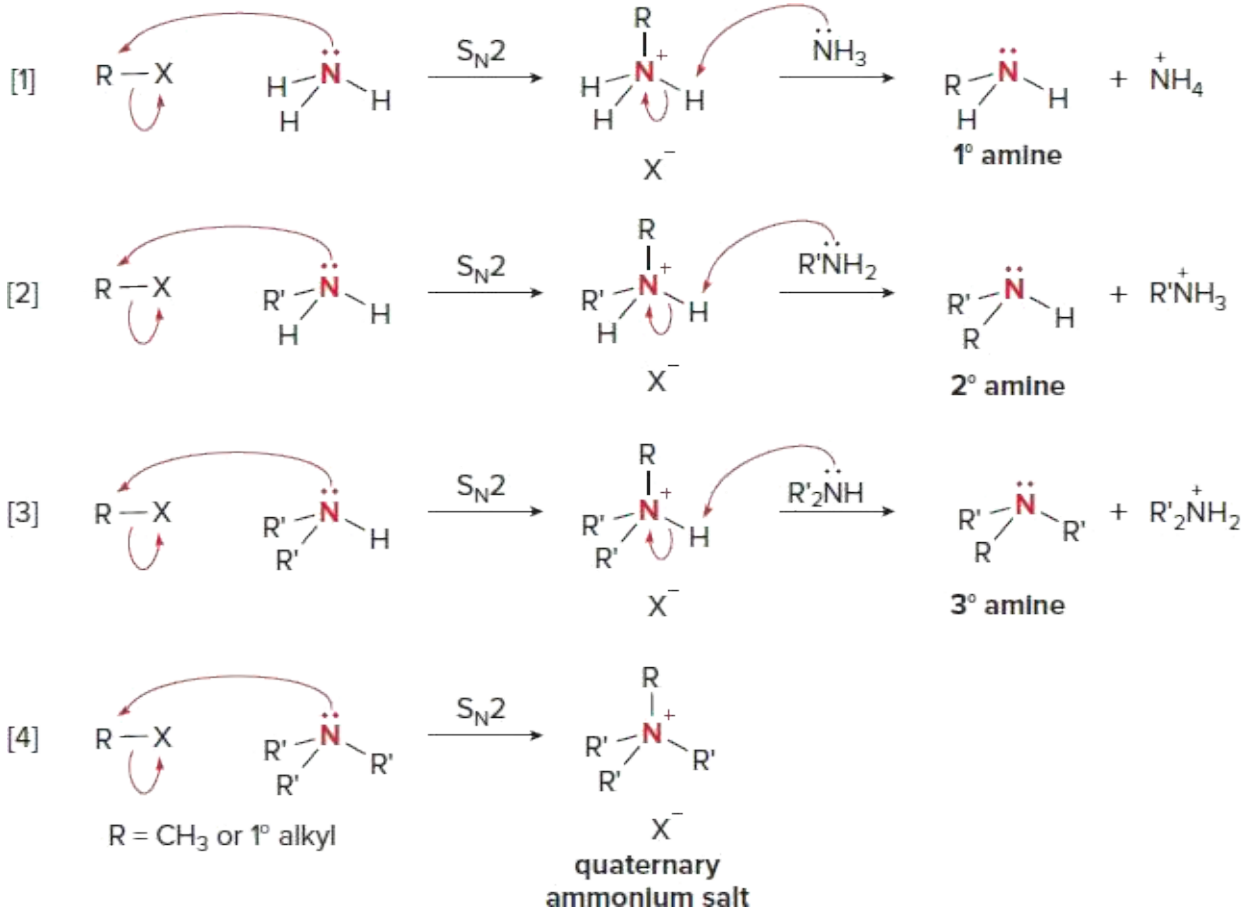
Nucleophilic substitution is the key step in two different methods for synthesizing amines: direct nucleophilic substitution and the Gabriel synthesis of 1° amines.

Direct Nucleophilic Substitution

Conceptually, the simplest method to synthesize an amine is by SN2 reaction of an alkyl halide with NH_3 or an amine. The method requires two steps:

[1] Nucleophilic attack of the nitrogen nucleophile forms an ammonium salt.

[2] Removal of a proton on N forms the amine.

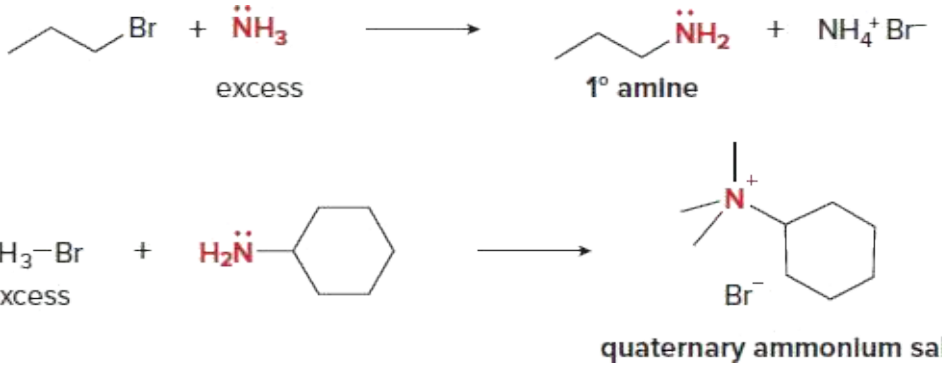


The identity of the nitrogen nucleophile determines the type of amine or

ammonium salt formed as product. One new carbon–nitrogen bond is formed in each reaction. Because the reaction follows an S_N2 mechanism, the alkyl halide must be unhindered—that is, CH_3X or RCH_2X.

Although this process seems straightforward, polyalkylation of the nitrogen nucleophile limits its usefulness. Any amine formed by nucleophilic substitution still has a nonbonded electron pair, making it a nucleophile as well. It will react with remaining alkyl halide to form a more substituted amine. Because of this, a mixture of 1°, 2°, and 3° amines often results. Only the final product—called a quaternary ammonium salt because it has four alkyl groups on N—cannot react further, and so the reaction stops.

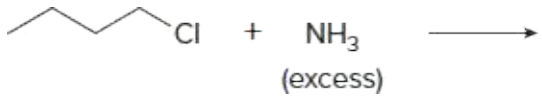
As a result, this reaction is most useful for preparing 1° amines by using a very large excess of NH3 (a relatively inexpensive starting material) and for preparing quaternary ammonium salts by alkylating any nitrogen nucleophile with one or more equivalents of alkyl halide.



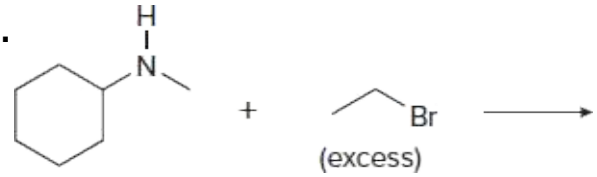
Problem 23.6

Draw the product of each reaction.

a.



b.

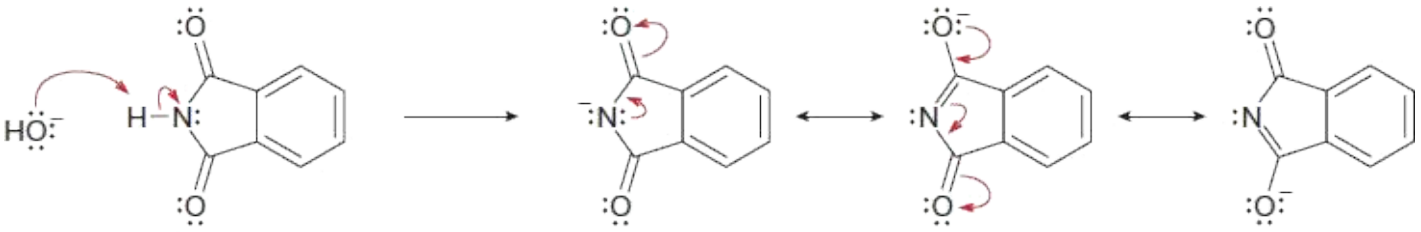


The Gabriel Synthesis of 1° Amines

To avoid polyalkylation, a nitrogen nucleophile can be used that reacts in a single nucleophilic substitution reaction—that is, the reaction forms a product that does *not* contain a nucleophilic nitrogen atom capable of reacting further.

The Gabriel synthesis consists of two steps and uses a resonance-stabilized nitrogen

nucleophile to synthesize 1° amines via nucleophilic substitution. The Gabriel synthesis begins with phthalimide, one of a group of compounds called imides. The N—H bond of an imide is especially acidic because the resulting anion is resonance stabilized by the two flanking carbonyl groups.



phthalimide
$pK_a = 10$

resonance-stabilized anion

In the Gabriel synthesis, treatment of phthalimide with ^-OH forms a nucleophilic anion that can react with an unhindered alkyl halide—that is, CH_3X or RCH_2X—in an S_N2 reaction to form a substitution product. This alkylated imide is then hydrolyzed with aqueous base to give a 1° amine and a dicarboxylate. This reaction is similar to the hydrolysis of amides to afford carboxylate anions and amines, as discussed in Section 20.12. The overall result of this two-step sequence is nucleophilic substitution of X by NH_2, so the Gabriel synthesis can be used to prepare 1° amines only.

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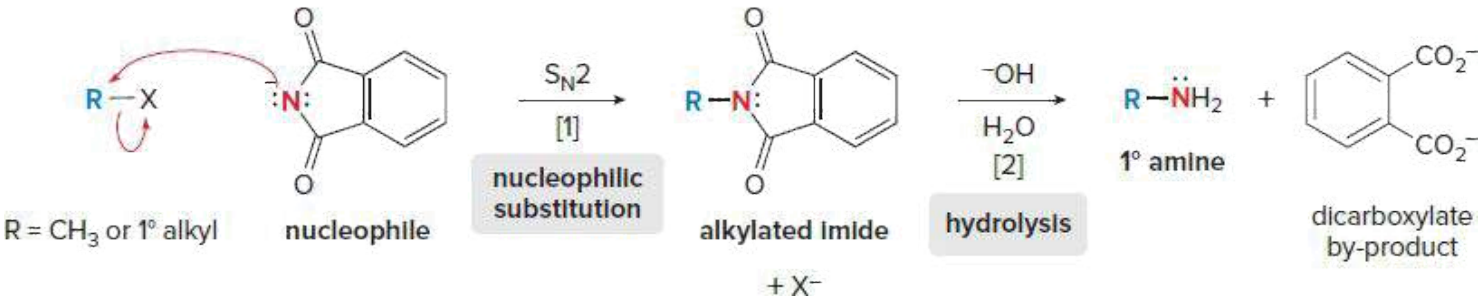
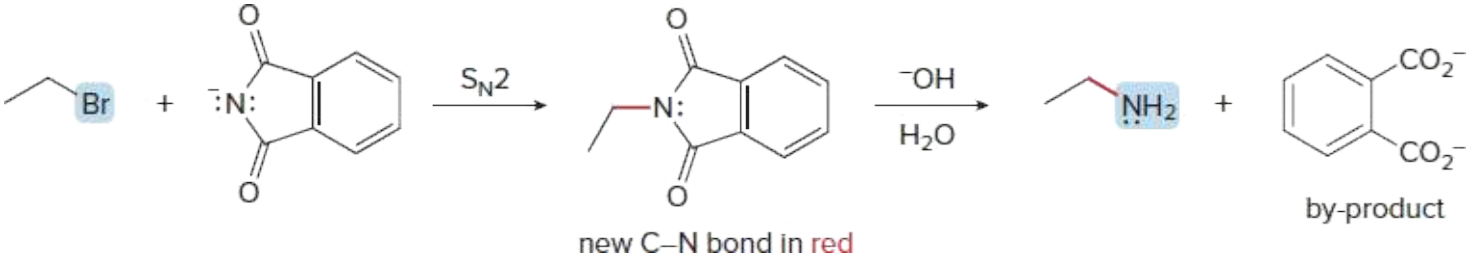
Steps in the Gabriel synthesis



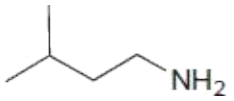
- **The Gabriel synthesis converts an alkyl halide to a 1° amine by a two-step process: nucleophilic substitution followed by hydrolysis.**

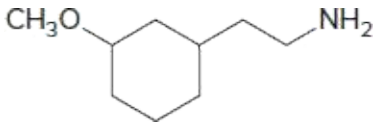


Problem 23.7

What alkyl halide is needed to prepare each 1° amine by the Gabriel synthesis?

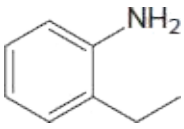
a.

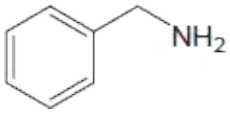
b. 

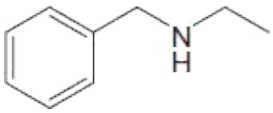
c. 

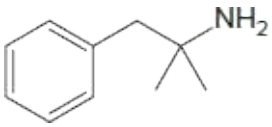
Problem 23.8

Which amines cannot be prepared by the Gabriel synthesis? Explain your choices.

a. 

b. 

c. 

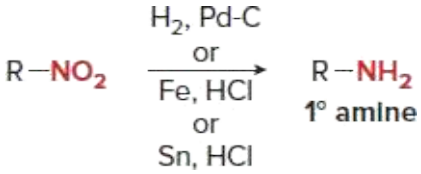
d. 

23.6B Reduction of Other Functional Groups That Contain Nitrogen

Amines can be prepared by reduction of nitro compounds, nitriles, and amides. Because the details of these reactions have been discussed previously, they are presented here in summary form only.

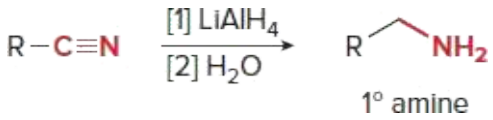
[1] From nitro compounds (Section 16.15C)

Nitro groups are reduced to 1° amines using a variety of reducing agents.

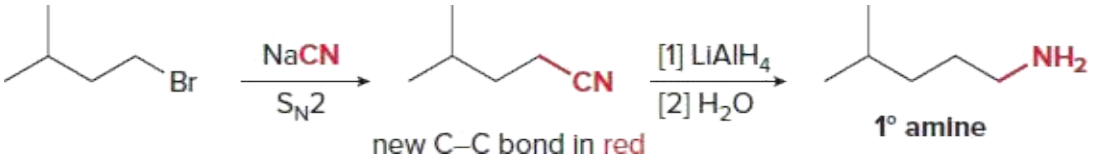


[2] From nitriles (Section 19.12B)

Nitriles are reduced to 1° amines with $LiAlH_4$.

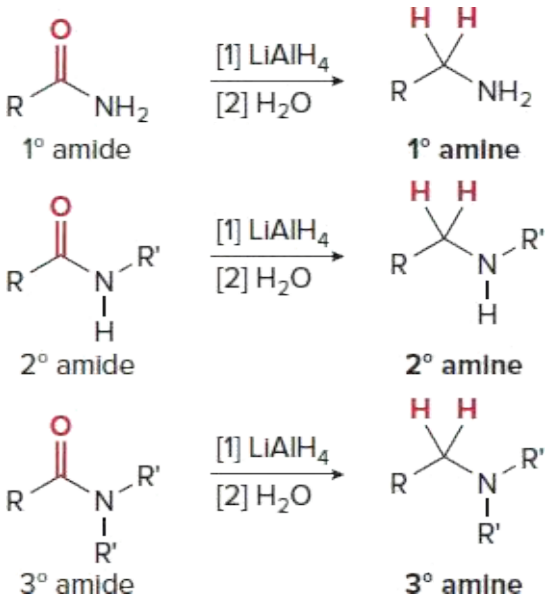


Because a cyano group is readily introduced by S_N2 substitution of alkyl halides with ^-CN, this provides a two-step method to convert an alkyl halide to a 1° amine with one more carbon atom. The conversion of $(CH_3)_2CHCH_2CH_2Br$ to $(CH_3)_2CHCH_2CH_2CH_2NH_2$ illustrates this two-step sequence.



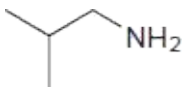
[3] From amides (Section 17.7B)

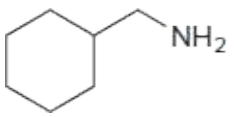
Primary (1°), 2°, and 3° amides are reduced to 1°, 2°, and 3° amines, respectively, by using $LiAlH_4$.

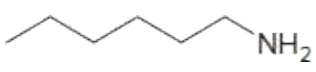


Problem 23.9

What nitro compound, nitrile, and amide are reduced to each compound?

a. 

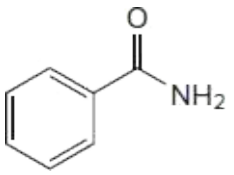
b. 

c. 

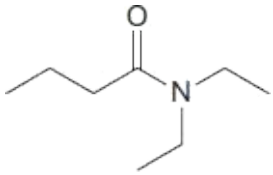
Problem 23.10

What amine is formed by reduction of each amide?

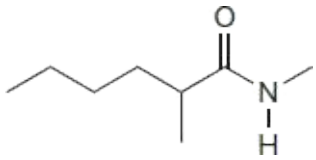
a.



b.



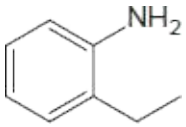
c.



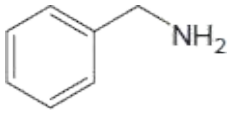
Problem 23.11

Which amines cannot be prepared by reduction of an amide?

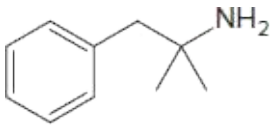
a.



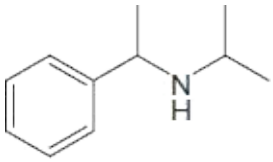
b.



c.



d.

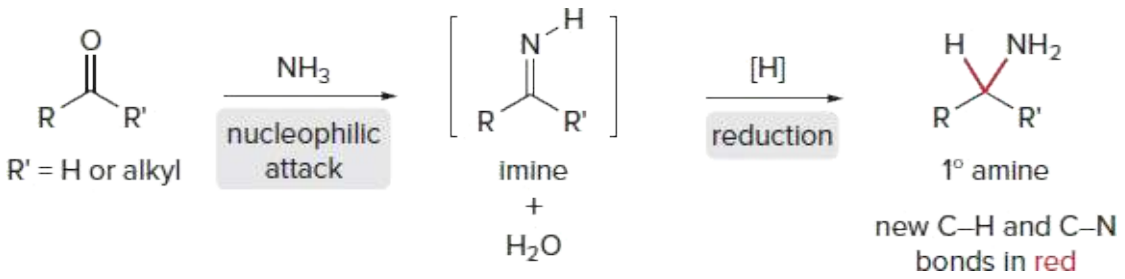


23.6C Reductive Amination of Aldehydes and Ketones

Reductive amination is a two-step method that converts aldehydes and ketones to 1°, 2°, and 3° amines. Let's first examine this method using NH_3 to prepare 1° amines. There are two distinct parts in reductive amination:

[1] Nucleophilic attack of NH_3 on the carbonyl group forms an imine (Section 18.10A), which is not isolated; then,

[2] Reduction of the imine forms an amine (Section 17.7B).

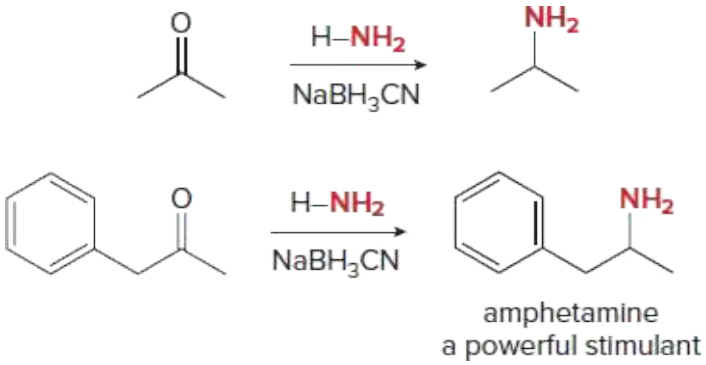


- **Reductive amination replaces a C=O by a C—H and C—N bond.**

The most effective reducing agent for this reaction is sodium cyanoborohydride (NaBH3CN). This hydride reagent is a derivative of sodium borohydride ($NaBH_4$), formed by replacing one H atom by CN.

$NaBH_3CN$
sodium cyanoborohydride

Reductive amination combines two reactions we have already learned in a different way. Two examples are shown. The second reaction is noteworthy because the product is amphetamine, a potent central nervous system stimulant.



With a 1° or 2° amine as starting material, reductive amination is used to prepare 2° and 3° amines, respectively. Note the result: Reductive amination uses an aldehyde or ketone to replace one H atom on a nitrogen atom by an alkyl group, making a more substituted amine.

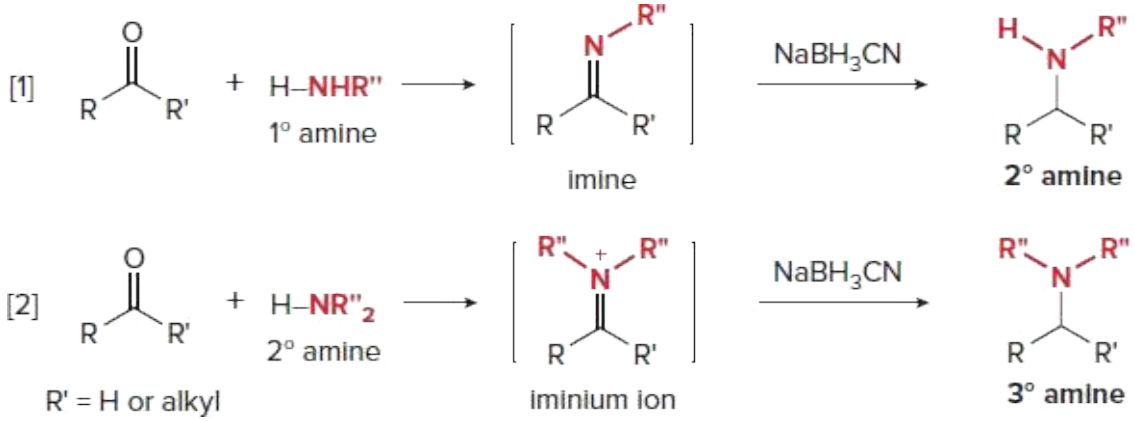
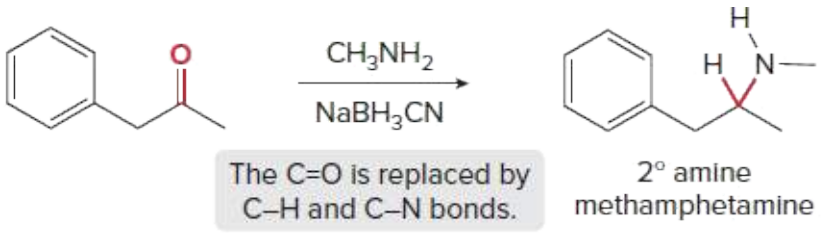


Figure 23.6 Synthesis of methamphetamine by reductive amination



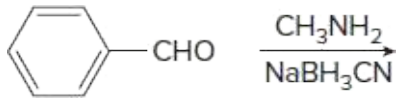
- In reductive amination, one of the H atoms bonded to N is replaced by an alkyl group. As a result, a 1° amine is converted to a 2° amine and a 2° amine is converted to a 3° amine. In this reaction, CH_3NH_2 (a 1° amine) is converted to methamphetamine (a 2° amine).

The synthesis of methamphetamine (Section 23.5C) by reductive amination is illustrated in Figure 23.6.

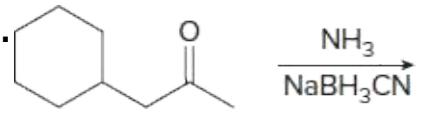
Problem 23.12

Draw the product of each reaction.

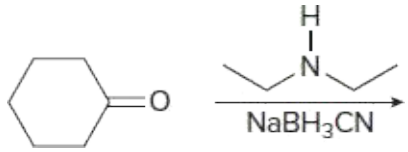
a.



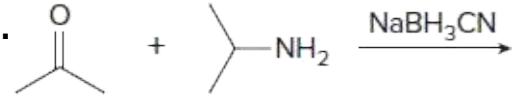
b.



c.

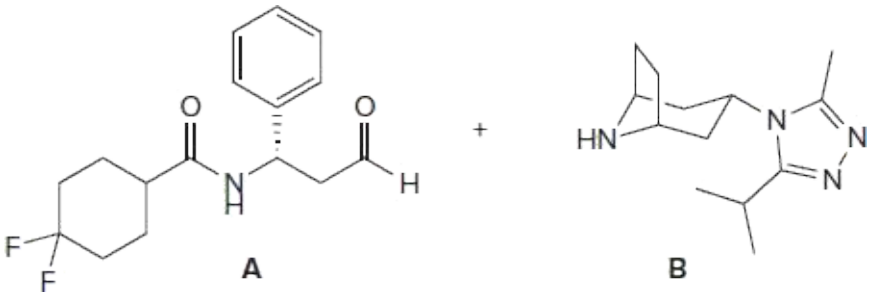


d.



Problem 23.13

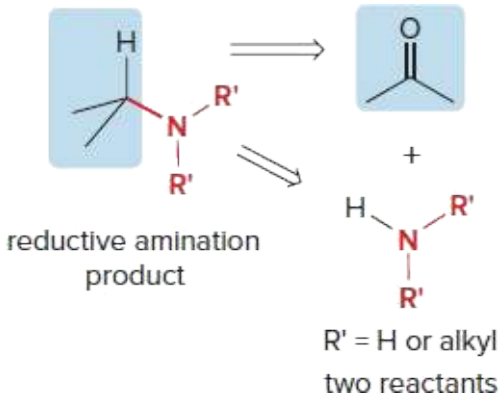
Maraviroc, a drug used to treat HIV, is prepared by reductive amination of aldehyde A with amine B. What is the structure of maraviroc, if the most basic N atom of amine B is used in reductive amination?



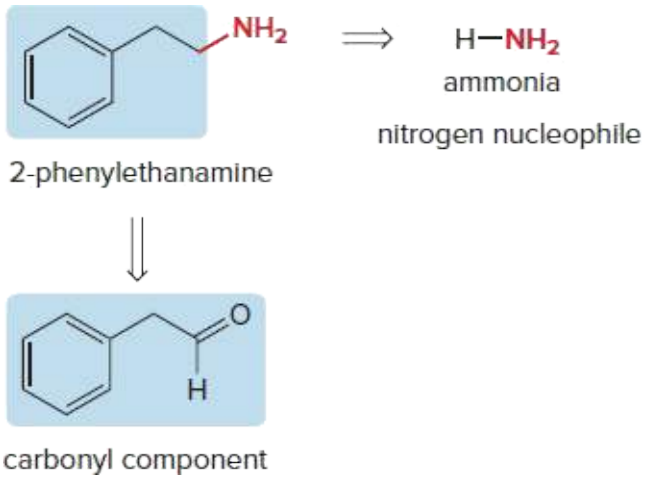
To use reductive amination in synthesis, you must be able to determine what aldehyde

or ketone and nitrogen compound are needed to prepare a given amine—that is, you must work backwards in the retrosynthetic direction. Keep in mind these two points:

- **One alkyl group on N comes from the carbonyl compound.**
- **The remainder of the molecule comes from NH_3 or an amine.**



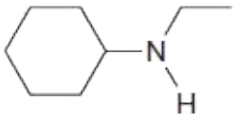
For example, 2-phenylethanamine is a 1° amine, so it has only one alkyl group bonded to N. This alkyl group must come from the carbonyl compound, and the rest of the molecule then comes from the nitrogen component. For a 1° amine, the nitrogen component must be NH_3.



There is usually more than one way to use reductive amination to synthesize 2° and 3° amines, as shown in Sample Problem 23.2 for a 2° amine.

Sample Problem 23.2 Determining the Starting Materials in a Reductive Amination

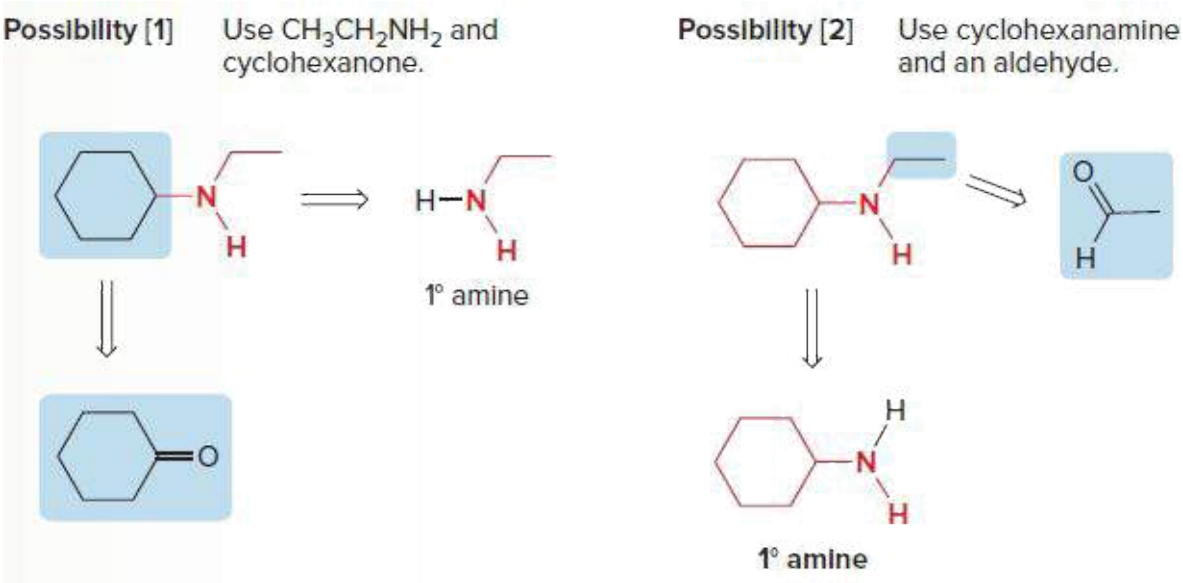
What aldehyde or ketone and nitrogen component are needed to synthesize *N*-ethylcyclohexanamine by a reductive amination reaction?



N-ethylcyclohexanamine

Solution

Because *N*-ethylcyclohexanamine has two different alkyl groups bonded to the N atom, either R group can come from the carbonyl component and there are two different ways to form a C—N bond by reductive amination.

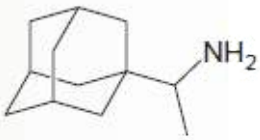


Because reductive amination adds one R group to a nitrogen atom, both routes to form the 2° amine begin with a 1° amine.

Problem 23.14

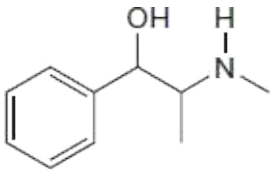
What starting materials are needed to prepare each drug using reductive amination? Give all possible pairs of compounds when more than one route is possible.

a.



rimantadine
antiviral used to treat influenza

b.



pseudoephedrine
nasal decongestant

More Practice:

Try Problems 23.48, 23.54b, 23.55b.

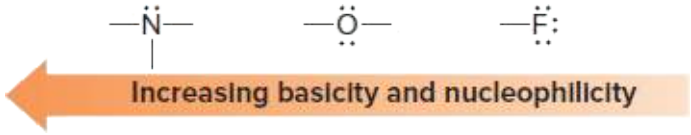
Problem 23.15

(a) Explain why phentermine [$PhCH_2C(CH_3)_2NH_2$] can't be made by a reductive amination reaction. (b) Give a systematic name for phentermine, one of the components of the banned diet drug fen–phen.

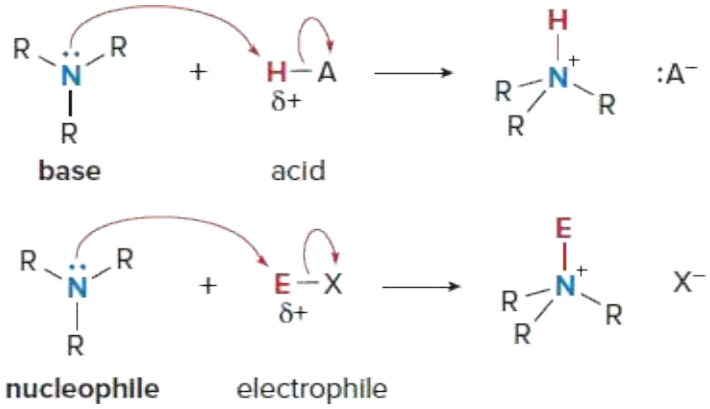
23.7 Reactions of Amines—General Features

- **The chemistry of amines is dominated by the lone pair of electrons on nitrogen.**

Only three elements in the second row of the periodic table have nonbonded electron pairs in neutral organic compounds: nitrogen, oxygen, and fluorine. Because basicity and nucleophilicity decrease across the row, nitrogen is the most basic and most nucleophilic of these elements.



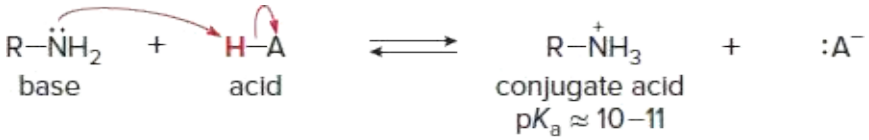
- **Amines are stronger bases and nucleophiles than other neutral organic compounds.**



- **Amines react as *bases* with compounds that contain acidic protons.**
- **Amines react as *nucleophiles* with compounds that contain electrophilic carbons.**

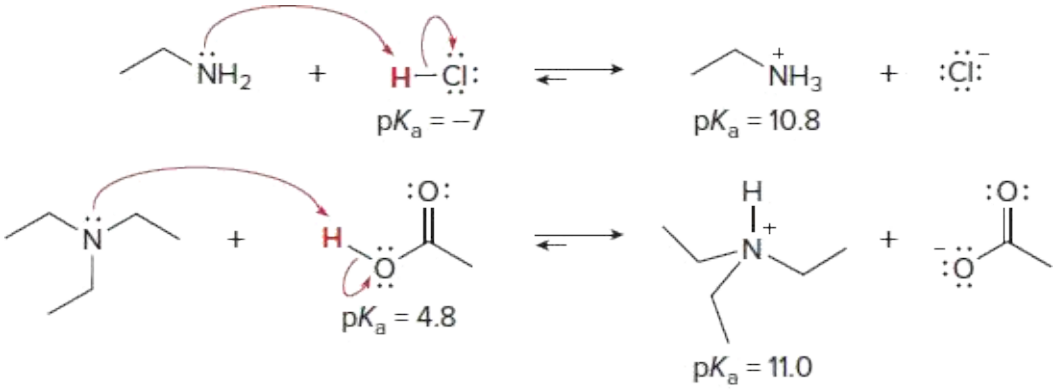
23.8 Amines as Bases

Amines react as bases with a variety of organic and inorganic acids.



To favor the products, the **pK_a of HA must be < 10.**

What acids can be used to protonate an amine? Equilibrium favors the products of an acid–base reaction when the weaker acid and base are formed. Because the pK_a of many protonated amines is 10–11, the pK_a of the starting acid must be less than 10 for equilibrium to favor the products. Amines are thus readily protonated by strong inorganic acids like HCl and H_2SO_4, and by carboxylic acids as well.



Equilibrium favors the products.

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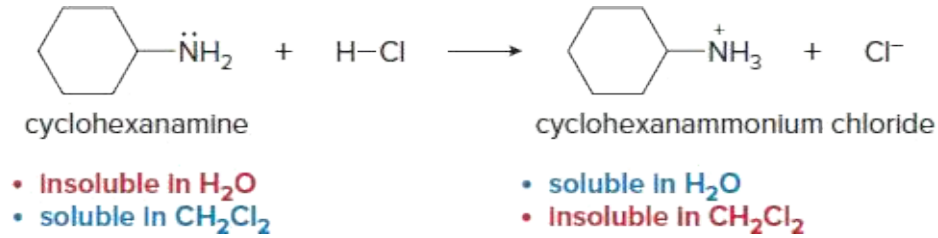
The principles used in an extraction procedure were detailed in Section 19.10.

Because amines are protonated by aqueous acid, they can be separated from other organic compounds by extraction using a separatory funnel. Extraction separates compounds based on solubility differences. When an amine is protonated by aqueous acid, its solubility properties change.

For example, when cyclohexanamine is treated with aqueous HCl, it is protonated, forming an ammonium salt. Because the ammonium salt is ionic, it is soluble in water, but insoluble in organic solvents. A similar acid–base reaction does not occur with other organic compounds like alcohols, which are much less basic.



cyclohexanamine

- Insoluble in H_2O
- soluble in CH_2Cl_2

cyclohexanammonium chloride

- soluble in H_2O
- Insoluble in CH_2Cl_2

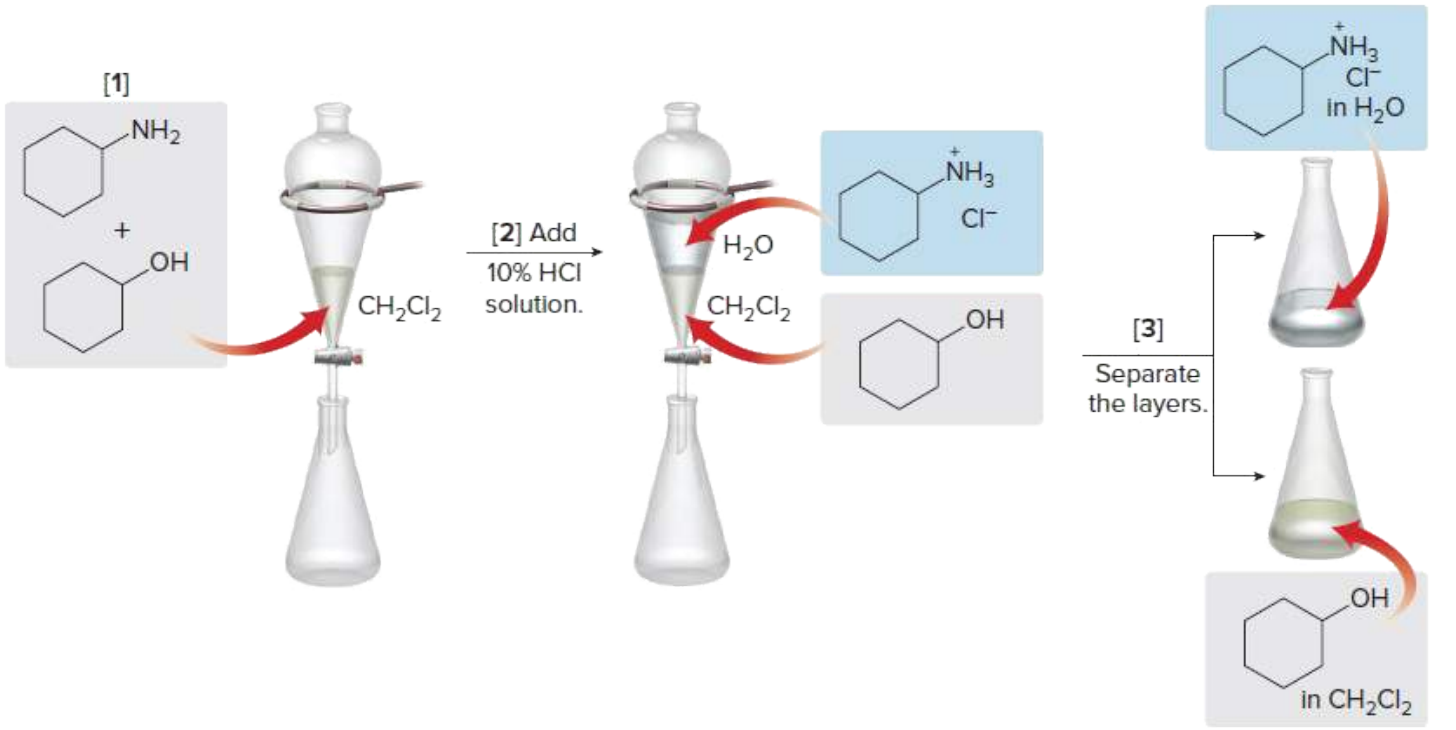
This difference in acid–base chemistry can be used to separate cyclohexanamine and cyclohexanol by the stepwise extraction procedure illustrated in Figure 23.7.

Figure 23.7 **Separation of cyclohexanamine and cyclohexanol by an extraction procedure**

Step [1] Dissolve cyclohexanamine and cyclohexanol in CH_2Cl_2.

Step [2] Add 10% HCl solution to form two layers.

Step [3] Separate the layers.



- Both compounds dissolve in the organic solvent CH_2Cl_2.

- Adding 10% aqueous HCl solution forms two layers. When the two layers are mixed, the **HCl protonates the amine (RNH_2) to form $RNH_3^+Cl^-$**, which dissolves in the aqueous layer.
- The cyclohexanol remains in the CH_2Cl_2 layer.

- Draining the lower layer out the bottom stopcock separates the two layers.
- Cyclohexanol (dissolved in CH_2Cl_2) is in one flask. The ammonium salt, $RNH_3^+Cl^-$ (dissolved in water), is in another flask.

- **An amine can be separated from other organic compounds by converting it to a water-soluble ammonium salt by an acid–base reaction.**

Thus, the water-soluble salt $C_6H_{11}NH_3^+Cl^-$ (obtained by protonation of $C_6H_{11}NH_2$)

can be separated from water-insoluble cyclohexanol by an aqueous extraction procedure.

Many antihistamines and decongestants are sold as their ammonium salts.

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Problem 23.16

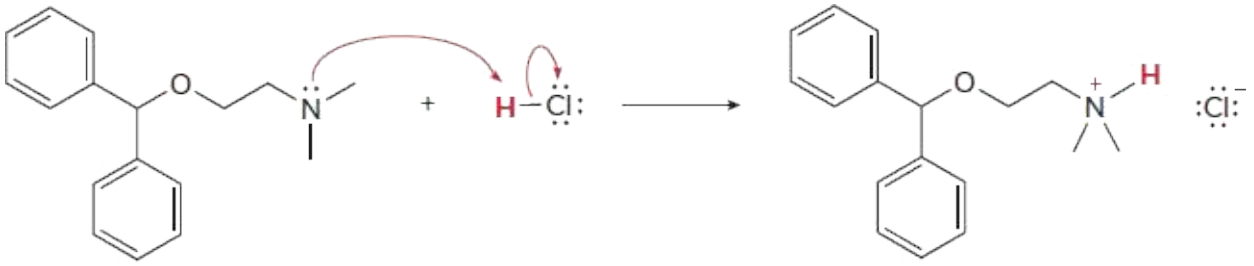
Draw the products of each acid–base reaction. Indicate whether equilibrium favors the reactants or products.

a. NH_2 + HCl ⇌

b. OH + N H ⇌

c. N H + H_2O ⇌

Many water-insoluble amines with useful medicinal properties are sold as their water-soluble ammonium salts, which are more easily transported through the body in the aqueous medium of the blood. Benadryl, formed by treating diphenhydramine with HCl, is an over-the-counter antihistamine that is used to relieve the itch and irritation of skin rashes and hives.

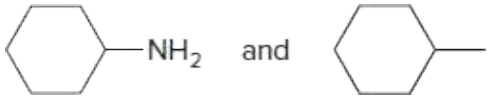


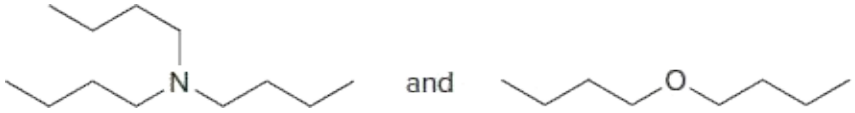
diphenhydramine
water insoluble

ammonium salt
Benadryl
(diphenhydramine hydrochloride)
water soluble

Problem 23.17

Write out steps to show how each of the following pairs of compounds can be separated by an extraction procedure.

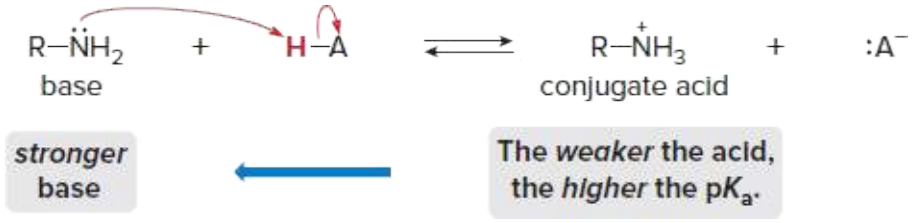
a. 

b. 

23.9 Relative Basicity of Amines and Other Compounds

The relative acidity of different compounds can be compared using their pK_a values. The relative *basicity* of different compounds (such as amines) can be compared using the pK_a values of their *conjugate acids*.

- **The *weaker* the conjugate acid, the *higher* its pK_a and the *stronger* the base.**



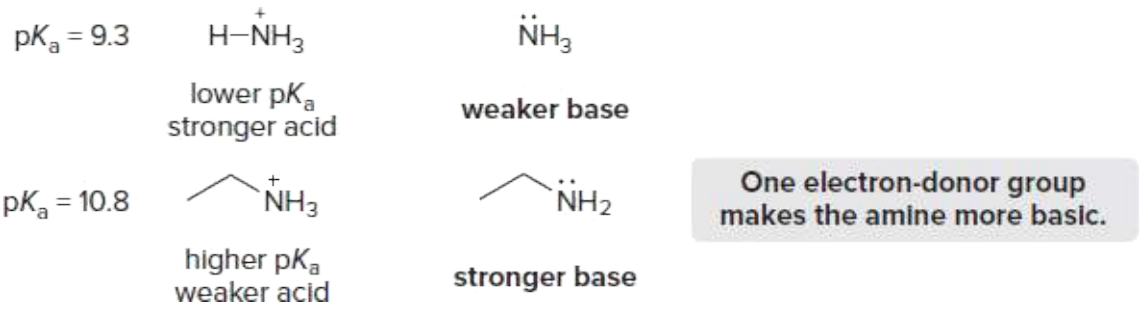
To compare the basicity of two compounds, keep in mind the following:

- **Any factor that *increases* the electron density on the N atom *increases* an amine's basicity.**
- **Any factor that *decreases* the electron density on N *decreases* an amine's basicity.**

The relative basicity of 1°, 2°, and 3° amines depends on additional factors, and will not be considered in this text.

23.9A Comparing an Amine and NH_3

Because alkyl groups are electron donating, they increase the electron density on nitrogen, which makes an amine like $CH_3CH_2NH_2$ more basic than NH_3. In fact, the pK_a of $CH_3CH_2NH_3^+$ is *higher* than the pK_a of NH_4^+, so $CH_3CH_2NH_2$ is a *stronger* base than NH_3.



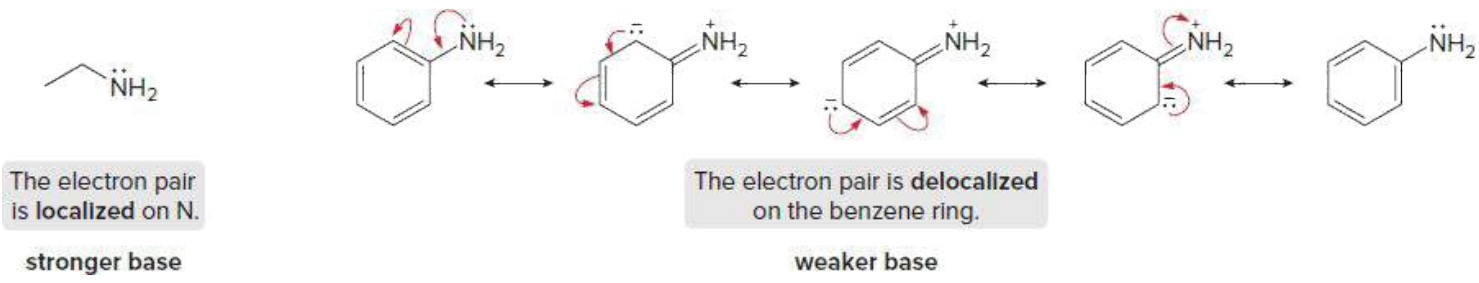
- **Primary (1°), 2°, and 3° alkylamines are *more basic* than NH_3 because of the electron-donating inductive effect of the R groups.**

Problem 23.18

Which compound in each pair is more basic: (a) $(CH_3)_2NH$ and NH_3; (b) $CH_3CH_2NH_2$ and $ClCH_2CH_2NH_2$?

23.9B Comparing an Alkylamine and an Arylamine

To compare an alkylamine ($CH_3CH_2NH_2$) and an arylamine ($C_6H_5NH_2$, aniline), we must look at the availability of the nonbonded electron pair on N. With $CH_3CH_2NH_2$, the electron pair is localized on the N atom. With an arylamine, however, the electron pair is now delocalized on the benzene ring. This *decreases* the electron density on N and makes $C_6H_5NH_2$ less basic than $CH_3CH_2NH_2$.



The pK_a values support this reasoning. Because the pK_a of $CH_3CH_2NH_3^+$ is *higher*

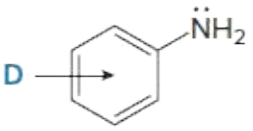
than the pK_a of $C_6H_5NH_3^+$ (10.8 vs. 4.6), $CH_3CH_2NH_2$ is a *stronger* base than $C_6H_5NH_2$.

- **Arylamines are *less basic* than alkylamines because the electron pair on N is delocalized.**

Substituted anilines are more or less basic than aniline depending on the nature of the substituent.

- **Electron-donor groups *add* electron density to the benzene ring, making the arylamine *more basic* than aniline.**

D = electron-donor group

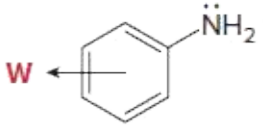


D makes the amine *more basic* than aniline.

D
$-NH_2$
$-OH$
$-OR$
$-NHCOR$
$-R$

- **Electron-withdrawing groups *remove* electron density from the benzene ring, making the arylamine *less basic* than aniline.**

W = electron-withdrawing group



W makes the amine **less basic** than aniline.

W	
$-X$	$-CN$
$-CHO$	$-SO_3H$
$-COR$	$-NO_2$
$-COOH$	$-NR_3^+$

The effect of electron-donating and electron-withdrawing groups on the acidity of substituted benzoic acids was discussed in Section 19.9.

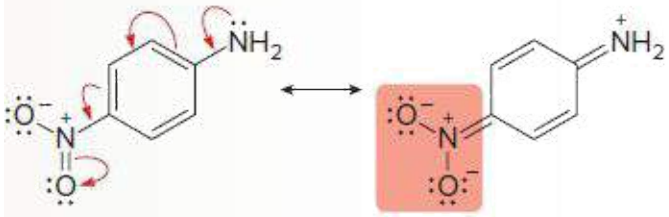
Whether a substituent donates or withdraws electron density depends on the balance of its inductive and resonance effects (Section 16.6 and Figure 16.8).

Sample Problem 23.3 Determining the Relative Basicity of Anilines

Rank the following compounds in order of increasing basicity.

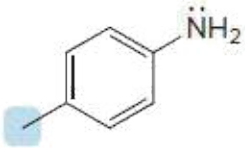
Solution

p-Nitroaniline: NO_2 is an electron-withdrawing group, making the amine *less basic* than aniline.

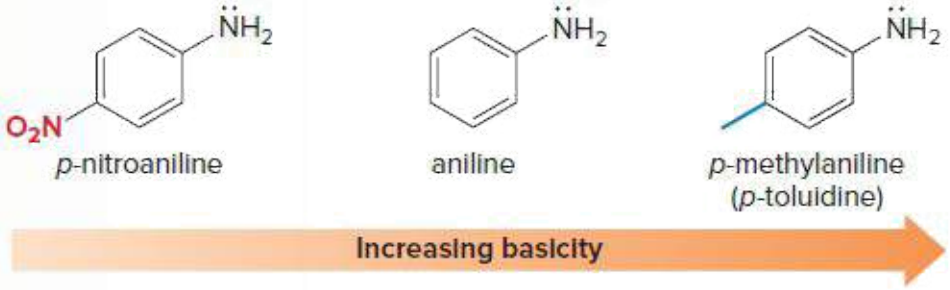


The lone pair on N is **delocalized** on the O atom, *decreasing* the basicity of the amine.

p-Methylaniline: CH_3 has an electron-donating inductive effect, making the amine *more basic* than aniline.



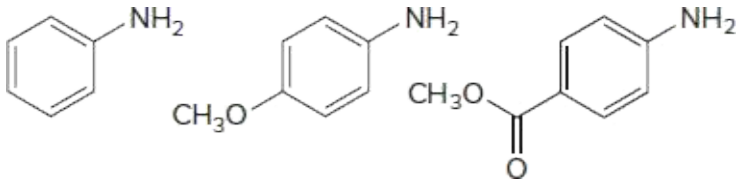
CH_3 inductively **donates** electron density, *increasing* the basicity of the amine.



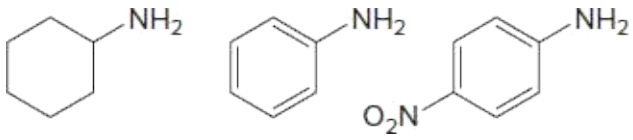
Problem 23.19

Rank the compounds in each group in order of increasing basicity.

a.



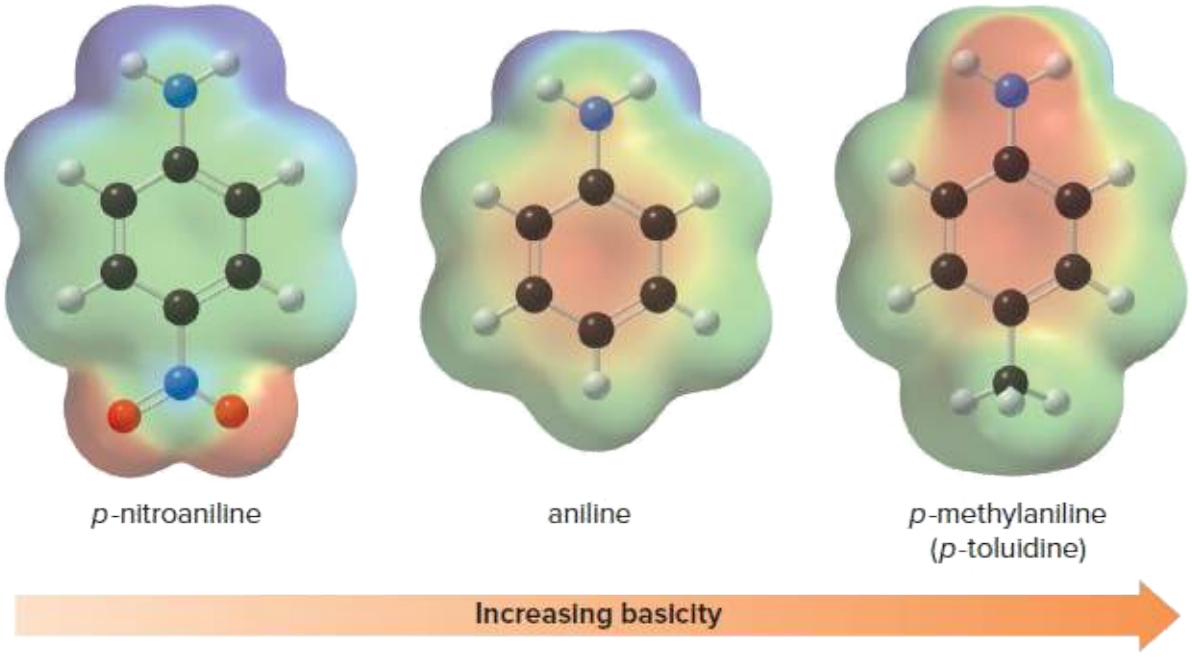
b.



More Practice:

Try Problems 23.40b, 23.45.

Figure 23.8 **Electrostatic potential plots of substituted anilines**



- The NH_2 group gets more electron rich as the para substituent changes from $NO_2 \rightarrow H \rightarrow CH_3$. This is indicated by the color change around NH_2 (from green to yellow to red) in the electrostatic potential plot.

The electrostatic potential plots in Figure 23.8 illustrate how the basicity of an aniline is related to the presence of an electron-donating or an electron-withdrawing group.

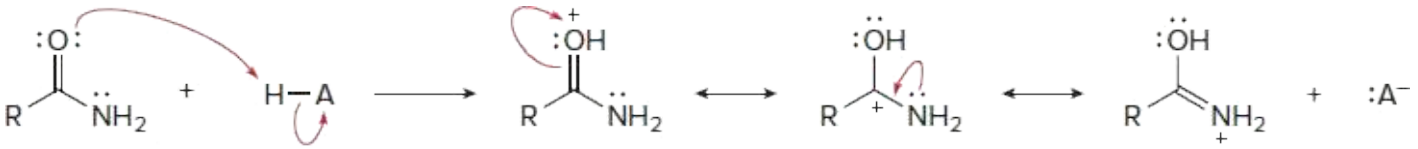
23.9C Comparing an Alkylamine and an Amide

To compare the basicity of an alkylamine (RNH_2) and an amide ($RCONH_2$), we must once again compare the availability of the nonbonded electron pair on nitrogen. With RNH_2, the electron pair is localized on the N atom. With an amide, however, the electron pair is *delocalized* on the carbonyl oxygen by resonance. This *decreases* the electron density on N, making an amide much *less basic* than an alkylamine.

The electron pair on N is **delocalized** on O by resonance.

- **Amides are much less basic than amines because the electron pair on N is delocalized.**

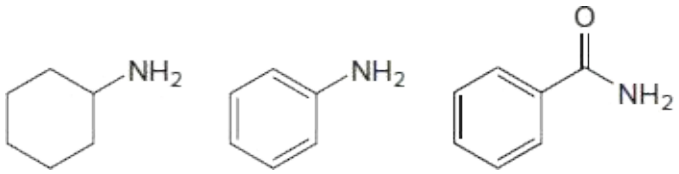
Amides are not much more basic than any carbonyl compound. When an amide is treated with acid, protonation occurs at the carbonyl oxygen, *not* the nitrogen, because the resulting cation is resonance stabilized.



three resonance structures for the conjugate acid

Problem 23.20

Rank the following compounds in order of increasing basicity.



23.9D Heterocyclic Aromatic Amines

To determine the relative basicity of nitrogen heterocycles that are also aromatic, you must know whether the nitrogen lone pair is part of the aromatic π system.

For example, pyridine and pyrrole are both aromatic, but the nonbonded electron pair on the N atom in these compounds is located in different orbitals. Recall from Section 15.8C that the lone pair of electrons in pyridine occupies an sp^2 hybridized orbital, perpendicular to the π bonds of the molecule, so it is *not* part of the aromatic system, whereas that of pyrrole resides in a *p* orbital, making it part of the aromatic system. The lone pair on pyrrole, therefore, is delocalized on all of the atoms of the five-membered ring, making pyrrole a much *weaker base* than pyridine.

pyridine

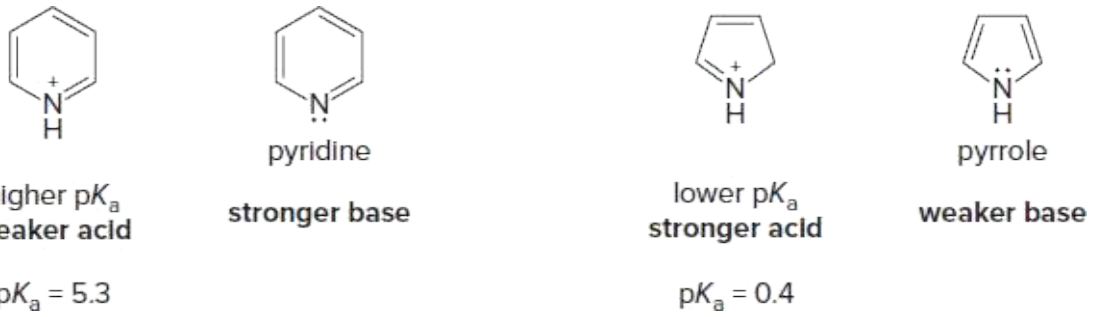
pyrrole

The lone pair resides in an sp^2 hybrid orbital.

The lone pair resides in a *p* orbital and is *delocalized* in the ring.

Protonation of pyrrole occurs at a ring *carbon*, not the N atom, as noted in Problem 15.47.

As a result, the pK_a of the conjugate acid of pyrrole is much less than that of the conjugate acid of pyridine.

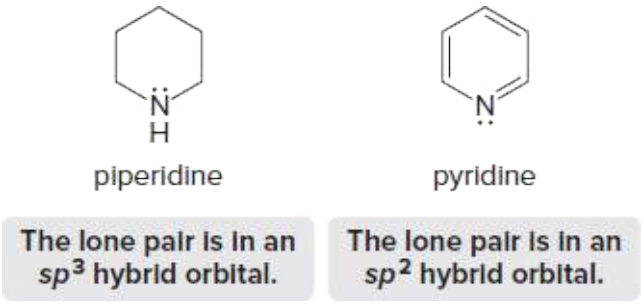


- **Pyrrole is much *less basic* than pyridine because its lone pair of electrons is part of the aromatic π system.**

The effect of hybridization on the acidity of an H—A bond was first discussed in Section 2.5D.

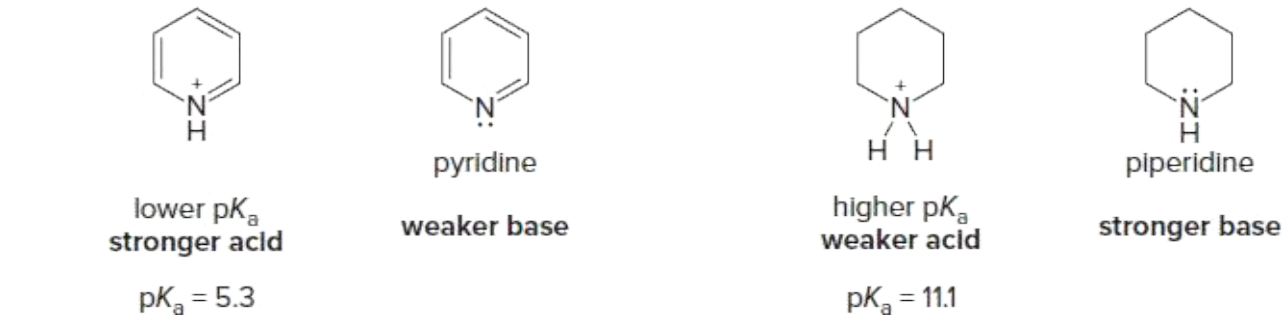
23.9E Hybridization Effects

The hybridization of the orbital that contains an amine's lone pair also affects its basicity. This is illustrated by comparing the basicity of piperidine and pyridine, two nitrogen heterocycles. The lone pair in piperidine resides in an sp^3 hybrid orbital that has 25% *s*-character. The lone pair in pyridine resides in an sp^2 hybrid orbital that has 33% *s*-character.



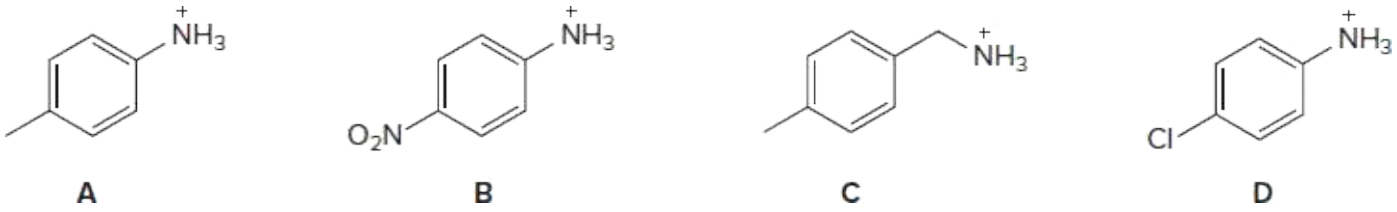
- **The *higher* the percent *s*-character of the orbital containing the lone pair, the more tightly the lone pair is held and the *weaker* the base.**

Pyridine is a weaker base than piperidine because its nonbonded pair of electrons resides in an sp^2 hybrid orbital. Although pyridine is an aromatic amine, its lone pair is *not* part of the delocalized π system, so its basicity is determined by the hybridization of its N atom. As a result, the pK_a value of the conjugate acid of pyridine is much *lower* than that of the conjugate acid of piperidine, making pyridine the *weaker* base.



Problem 23.21

Rank the following ammonium ions in order of increasing pK_a.

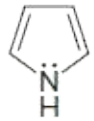


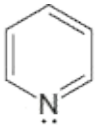
23.9F Summary of the Factors That Determine Amine Basicity

Acid–base chemistry is central to many processes in organic chemistry, so it has been a constant theme throughout this text. Tables 23.3 and 23.4 organize and summarize the acid–base principles discussed in Section 23.9. The principles in these tables can be used to determine the most basic site in a molecule that has more than one nitrogen atom, as shown in Sample Problem 23.4.

Table 23.3 Factors That Determine Amine Basicity

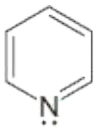
Factor	Example
[1] Inductive effects: Electron-donating groups bonded to N *increase* basicity.	• RNH_2, R_2NH, and R_3N are more basic than NH_3.
[2] Resonance effects: Delocalizing the lone pair on N *decreases* basicity.	• Arylamines ($C_6H_5NH_2$) are less basic than alkylamines (RNH2). • Amides ($RCONH_2$) are much less basic than amines (RNH_2).
[3] Aromaticity: Having the lone pair on N as part of the aromatic π system *decreases* basicity.	• Pyrrole is less basic than pyridine.


less basic


more basic

[4] Hybridization effects: Increasing the percent *s*-character in the orbital with the lone pair *decreases* basicity.

- Pyridine is less basic than piperidine.


less basic

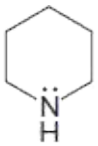
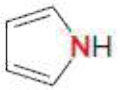

more basic

Table 23.4 Table of pK_a Values of Some Representative Organic Nitrogen Compounds

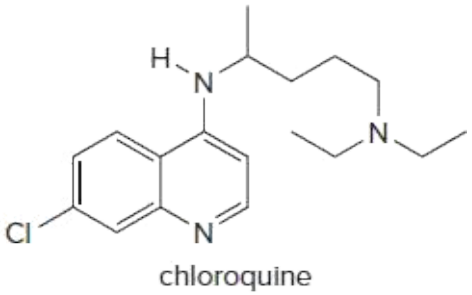
	Compound	pK_a of the conjugate acid
Ammonia	NH_3	9.3
Alkylamines[a]		11.1
	$(CH_3CH_2)_2NH$	11.1
	$(CH_3CH_2)_3N$	11.0
	$CH_3CH_2NH_2$	10.8
Arylamines[b]	*p*-$CH_3OC_6H_4NH_2$	5.3
	p-$CH_3C_6H_4NH_2$	5.1
	$C_6H_5NH_2$	4.6
	p-$NO_2C_6H_4NH_2$	1.0
Heterocyclic aromatic amines[c]		5.3
		0.4
Amides	$RCONH_2$	–1

[a] Alkylamines have pK_a values of ~10–11.
[b] The pK_a *decreases* as the electron density of the benzene ring *decreases*.
[c] The pK_a depends on whether the lone pair of N is *localized* or *delocalized*.

Sample Problem 23.4 Determining Which Nitrogen Atom Is the

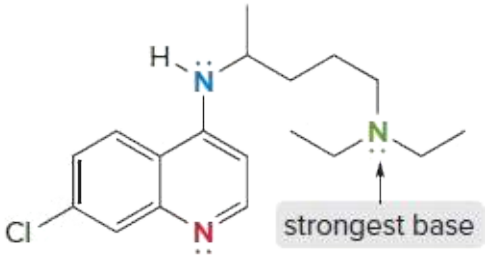
Since 1945 chloroquine has been used to treat malaria, an infectious disease caused by a protozoan parasite that is spread by the *Anopheles* mosquito. *Source: James Gathany/CDC*

Which N atom in chloroquine is the strongest base?



Solution

Examine the nitrogen atoms in chloroquine, labeled in red, blue, and green, and recall that decreasing the electron density on N decreases basicity.

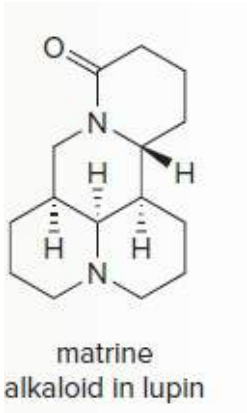


- **N is bonded to an aromatic ring, so its lone pair is delocalized in the ring like aniline, *decreasing* basicity.**
- **The lone pair is localized on N, but N is sp^2 hybridized. *Increasing* percent *s*-character *decreases* basicity.**
- **N has a localized lone pair and is sp^3 hybridized, making it the *most basic* site in the molecule.**

Problem 23.22

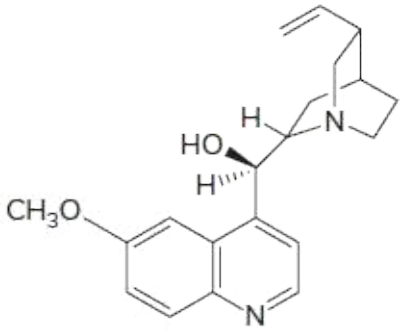
Which N atom in each compound is more basic? What product is formed when each compound is treated with HCl? Like sparteine, the chapter-opening molecule, matrine is an alkaloid isolated from lupin. Quinine, the Chapter 8 opening molecule, is an antimalarial drug obtained from the bark of the cinchona tree.

a.



matrine
alkaloid in lupin

b.



quinine
antimalarial drug

More Practice:

Try Problems 23.36a, 23.41, 23.42, 23.44.

23.10 Amines as Nucleophiles

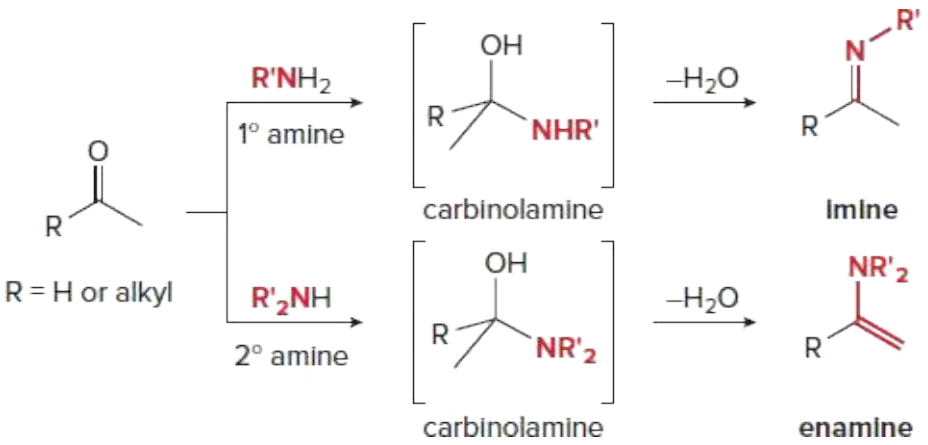
Amines react as nucleophiles with electrophilic carbon atoms. The details of these reactions have been described in Chapters 18 and 20, so they are summarized here only to emphasize the similar role that the amine nitrogen plays.

- **Amines attack carbonyl groups to form products of nucleophilic addition or substitution.**

The nature of the product depends on the carbonyl electrophile. These reactions are limited to 1° and 2° amines, because only these compounds yield neutral organic products.

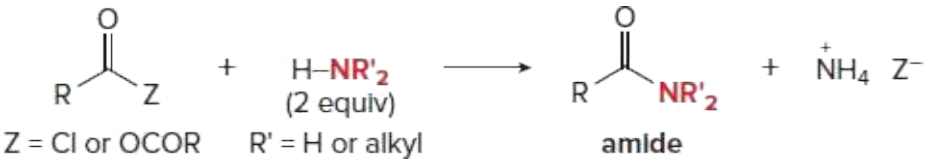
[1] Reaction of 1° and 2° amines with aldehydes and ketones (Sections 18.10–18.11)

Aldehydes and ketones react with 1° amines to form imines and with 2° amines to form enamines. Both reactions involve nucleophilic addition of the amine to the carbonyl group to form a carbinolamine, which then loses water to form the final product.



[2] Reaction of NH_3 and 1° and 2° amines with acid chlorides and anhydrides (Sections 20.7–20.8)

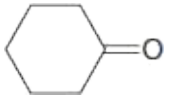
Acid chlorides and anhydrides react with NH3, 1° amines, and 2° amines to form 1°, 2°, and 3° amides, respectively. These reactions involve attack of the nitrogen nucleophile on the carbonyl group followed by elimination of a leaving group (Cl^- or RCO_2^-). The overall result of this reaction is substitution of the leaving group by the nitrogen nucleophile.



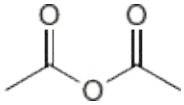
Problem 23.23

Draw the products formed when each carbonyl compound reacts with the following amines: [1] $CH_3CH_2CH_2NH_2$; [2] $(CH_3CH_2)_2NH$.

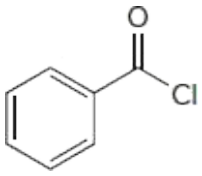
a.



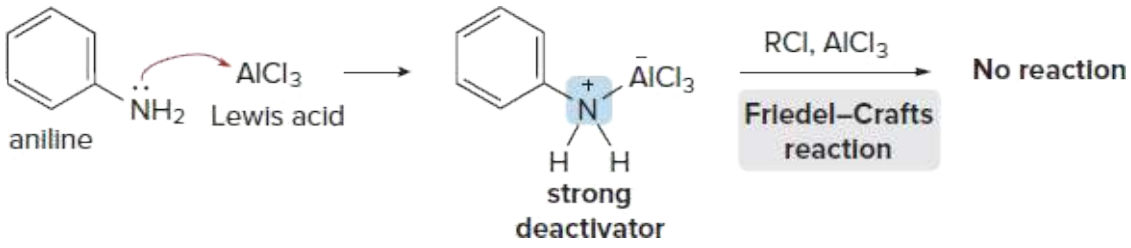
b.



c.



The conversion of amines to amides is useful in the synthesis of substituted anilines. For example, aniline itself does not undergo Friedel–Crafts reactions (Section 16.10B). Instead, its basic lone pair on N reacts with the Lewis acid ($AlCl_3$) to form a deactivated complex that does not undergo further reaction.



The N atom of an amide, however, is much less basic than the N atom of an amine, so it does not undergo a similar Lewis acid–base reaction with $AlCl_3$. A three-step reaction sequence involving an intermediate amide can thus be used to form the products of the Friedel–Crafts reaction.

[1] Convert the amine (aniline) into an amide (acetanilide).

[2] Carry out the Friedel–Crafts reaction.

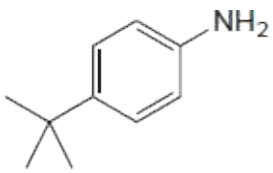
[3] Hydrolyze the amide to generate the free amino group.

This three-step procedure is illustrated in Figure 23.9. In this way, the amide serves as a protecting group for the NH_2 group, in much the same way that *tert*-butyldimethylsilyl ethers and acetals are used to protect alcohols and carbonyls, respectively (Sections 17.12 and 18.14).

Problem 23.24

Devise a synthesis of each compound from aniline ($C_6H_5NH_2$).

a.



b.

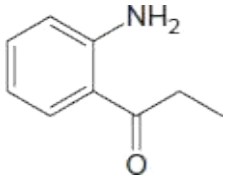
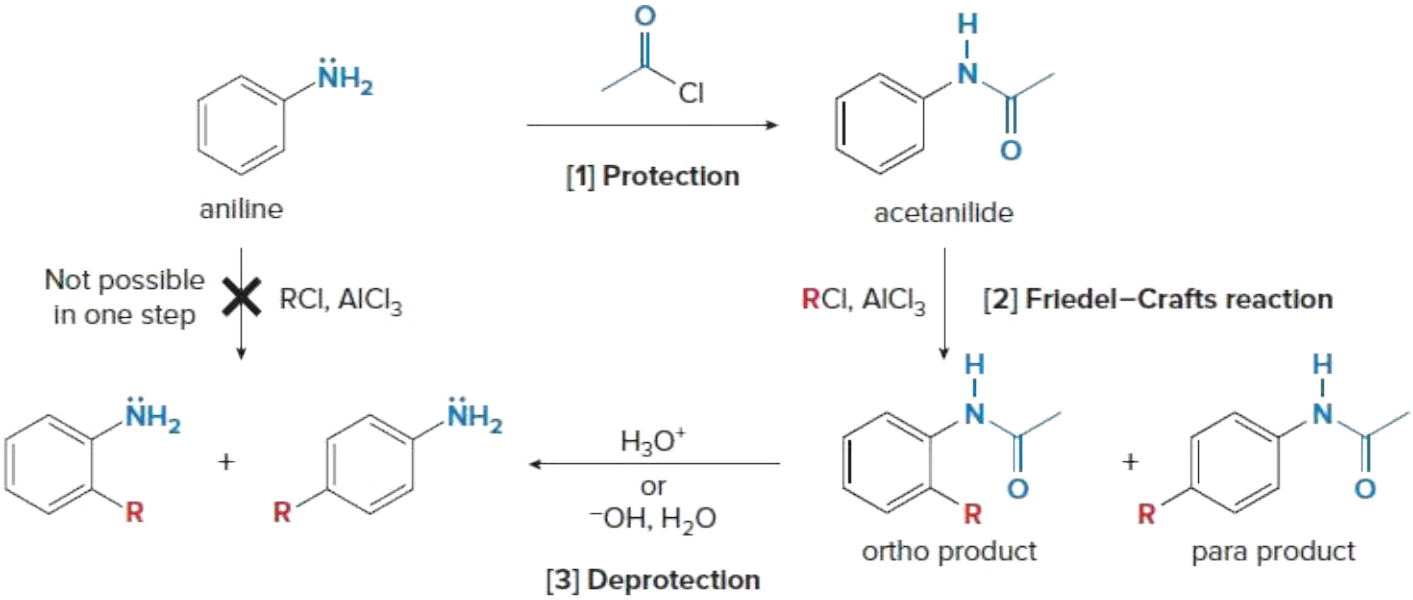


Figure 23.9 **An amide as a protecting group for an amine**



A three-step sequence uses an amide as a protecting group.
[1] Treatment of aniline with acetyl chloride (CH_3COCl) forms an **amide** (acetanilide).
[2] Acetanilide, having a much less basic N atom compared to aniline, undergoes **electrophilic aromatic substitution** under Friedel–Crafts conditions, forming a mixture of ortho and para products.
[3] **Hydrolysis of the amide** forms the Friedel–Crafts substitution products.

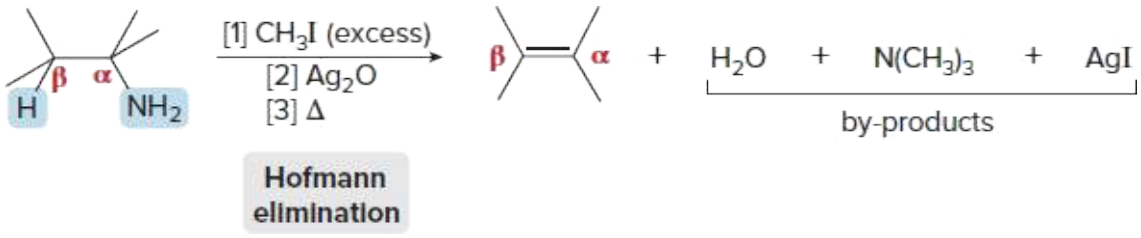
23.11 Hofmann Elimination

Amines, like alcohols, contain a poor leaving group. To undergo a β elimination reaction, for example, a 1° amine would need to lose the elements of NH_3 across two adjacent atoms. The leaving group, $^-NH_2$, is such a strong base, however, that this reaction does *not* occur.

The only way around this obstacle is to convert $^-NH_2$ to a better leaving group. The most common method to accomplish this is called a Hofmann elimination, which converts an amine to a quaternary ammonium salt prior to β elimination.

23.11A Details of the Hofmann Elimination

The Hofmann elimination converts an amine to an alkene.



The Hofmann elimination consists of three steps, as shown for the conversion of propan-1-amine to propene.

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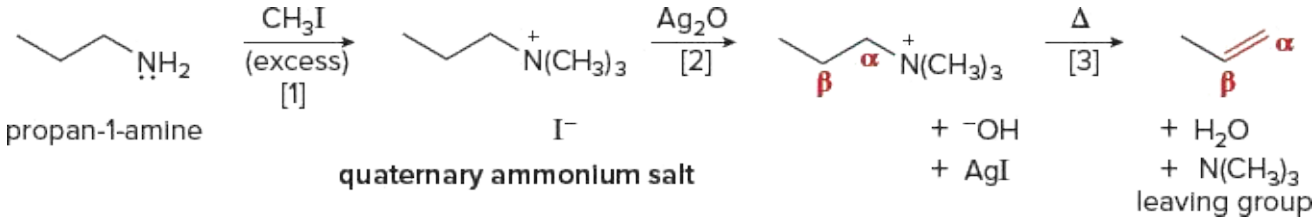
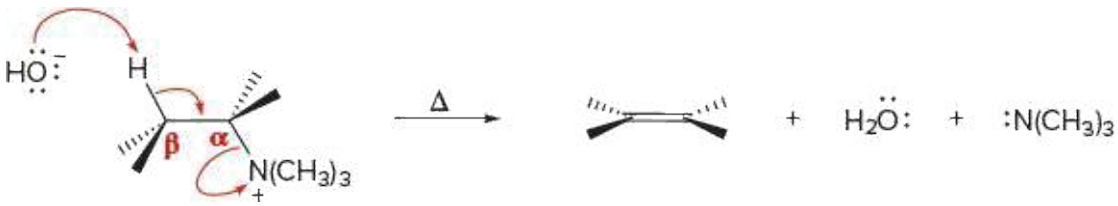


- In Step [1], the amine reacts as a nucleophile in an S_N2 reaction with excess CH_3I to form a quaternary ammonium salt. The $N(CH_3)_3$ group thus formed is a much better leaving group than $^-NH_2$.
- Step [2] converts one ammonium salt to another one with a different anion. The silver(I) oxide, Ag_2O, replaces the I^- anion with ^-OH, a strong base.
- When the ammonium salt is heated in Step [3], ^-OH removes a proton from the β carbon atom, forming the new π bond of the alkene. The mechanism of elimination is E2, so

- **All bonds are broken and formed in a single step.**
- **Elimination occurs through an anti periplanar geometry—that is, H and $N(CH_3)_3$ are oriented on opposite sides of the molecule.**

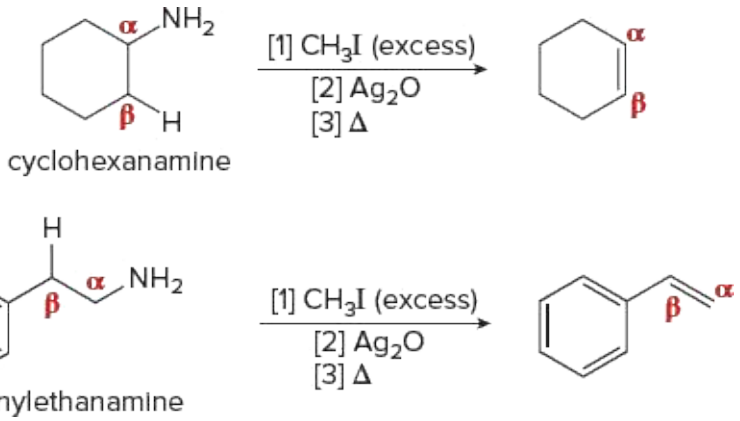
The general E2 mechanism for the Hofmann elimination is shown in Mechanism 23.1.

Mechanism 23.1 The E2 Mechanism for the Hofmann Elimination



Elimination occurs with an anti periplanar arrangement of H and $N(CH_3)_3$. Base removes a proton on the β carbon, the electron pair in the C—H bond forms the π bond, and $N(CH_3)_3$ comes off as the leaving group.

All Hofmann elimination reactions result in the formation of a new π bond between the α and β carbon atoms, as shown for cyclohexanamine and 2-phenylethanamine.

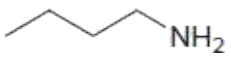


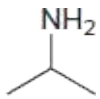
To help remember the reagents needed for the steps of the Hofmann elimination, keep in mind what happens in each step.

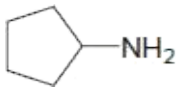
- Step [1] makes a good leaving group by forming a quaternary ammonium salt.
- Step [2] provides the strong base, ^{-}OH, needed for elimination.
- Step [3] is the E2 elimination that forms the new π bond.

Problem 23.25

Draw the product formed by treating each compound with excess CH_3I, followed by Ag_2O, and then heat.

a. 

b. 

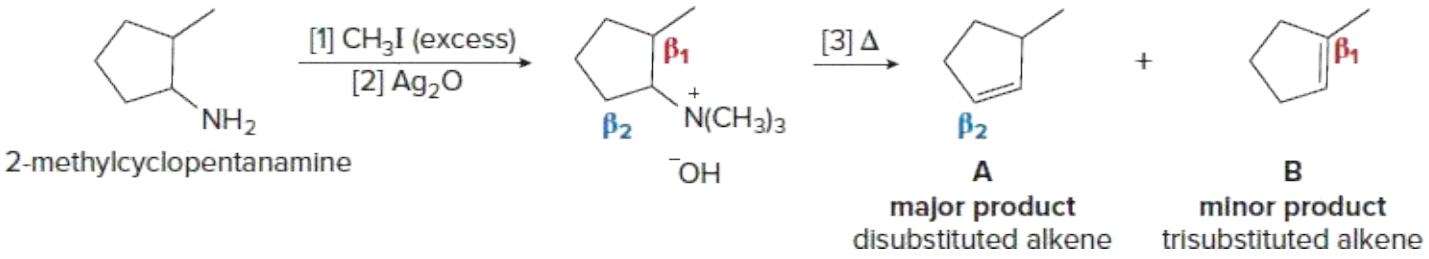
c. 

23.11B Regioselectivity of the Hofmann Elimination

There is one major difference between a Hofmann elimination and other E2 eliminations.

- **When constitutional isomers are possible, the major alkene has the *less* substituted double bond in a Hofmann elimination.**

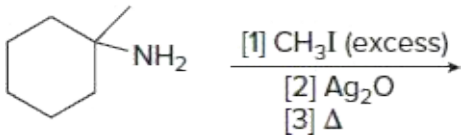
For example, Hofmann elimination of the elements of H and $N(CH_3)_3$ from 2-methylcyclopen-tanamine, which has two different β carbons (labeled β_1 and β_2), yields two constitutional isomers: the disubstituted alkene A (the major product) and the trisubstituted alkene B (the minor product).



This regioselectivity distinguishes a Hofmann elimination from other E2 eliminations, which form the *more* substituted double bond by the Zaitsev rule (Section 8.5). This result is sometimes explained by the size of the leaving group, $N(CH_3)_3$. In a Hofmann elimination, the base removes a proton from the *less* substituted, more accessible β carbon atom, because of the bulky leaving group on the nearby α carbon.

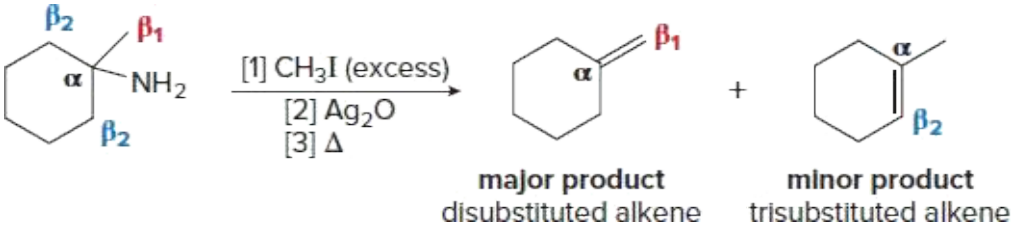
Sample Problem 23.5 Drawing the Major Product of a Hofmann Elimination

Draw the major product formed from Hofmann elimination of the following amine.



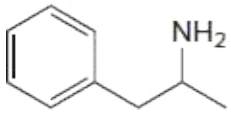
Solution

The amine has three β carbons but two of them are identical, so two alkenes are possible. Draw elimination products by forming alkenes having a C=C between the α and β carbons. The major product has the less substituted double bond—that is, the alkene with the C=C between the α and β_1 carbons in this example.

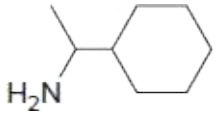


Problem 23.26

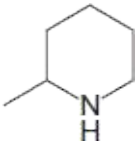
Draw the major product formed by treating each amine with excess CH_3I, followed by Ag_2O, and then heat.

a. 

b.



c.



More Practice:

Try Problems 23.53, 23.54c, 23.55c, 23.56j, 23.57.

Figure 23.10 **A comparison of E2 elimination reactions using alkyl halides and amines**

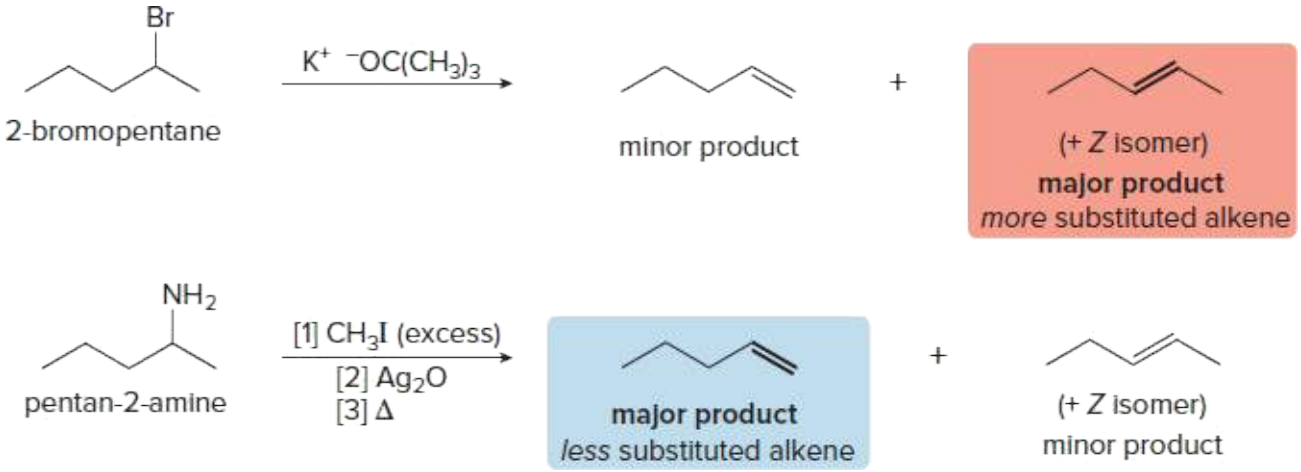
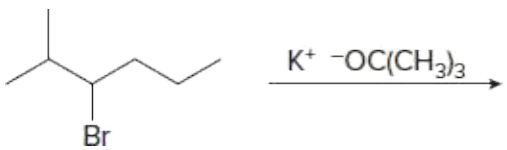


Figure 23.10 contrasts the products formed by E2 elimination reactions using an alkyl halide and an amine as starting materials. Treatment of the alkyl halide (2-bromopentane) with base forms the *more* substituted alkene as the major product, following the Zaitsev rule. In contrast, the three-step Hofmann sequence of an amine (pentan-2-amine) forms the *less* substituted alkene as major product.

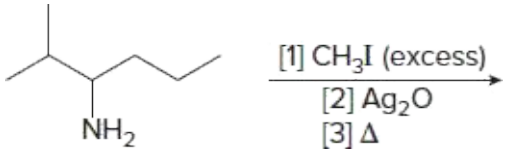
Problem 23.27

Draw the major product formed in each reaction.

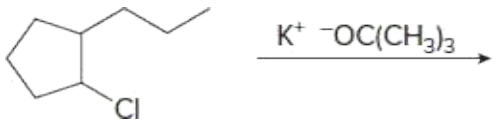
a.

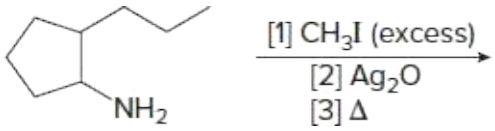


c.



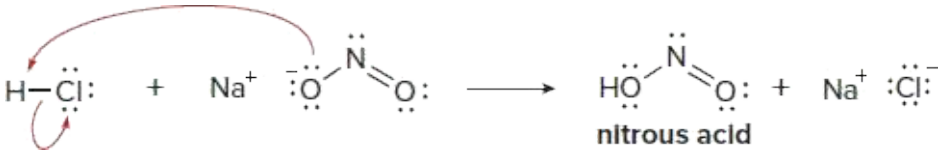
b.



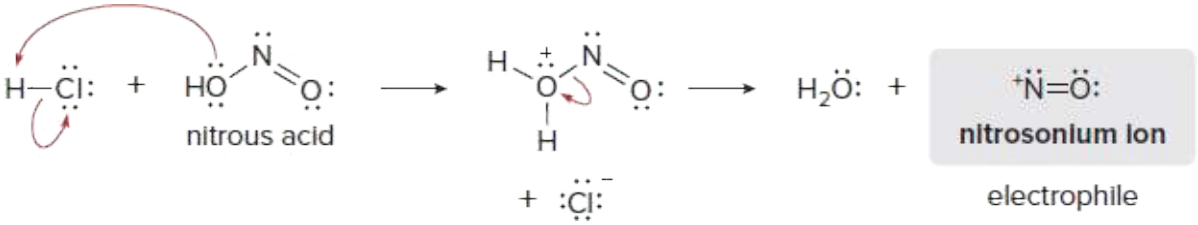
d. 

23.12 Reaction of Amines with Nitrous Acid

Nitrous acid, HNO_2, is a weak, unstable acid formed from $NaNO_2$ and a strong acid like HCl.

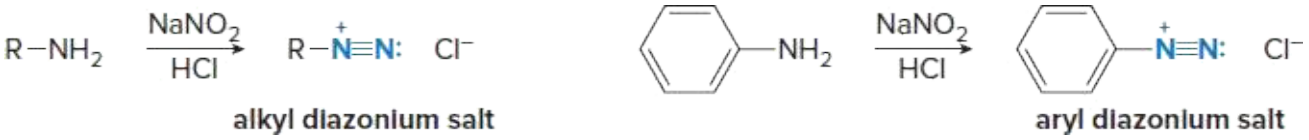


In the presence of acid, nitrous acid decomposes to ^+NO, the nitrosonium ion. This electrophile then goes on to react with the nucleophilic nitrogen atom of amines to form diazonium salts ($RN_2^+Cl^-$) from 1° amines and *N*-nitrosamines ($R_2NN{=}O$) from 2° amines.



23.12A Reaction of ^+NO with 1° Amines

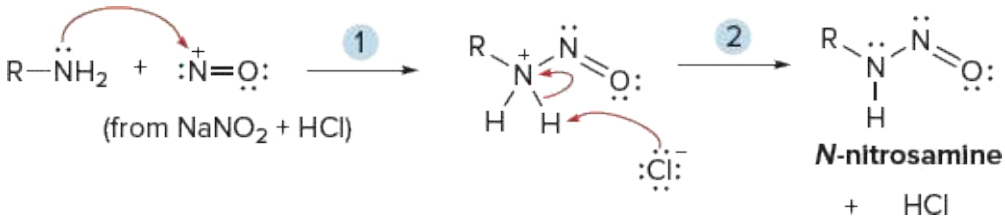
Nitrous acid reacts with 1° alkylamines and arylamines to form diazonium salts. This reaction is called diazotization.



The mechanism for this reaction begins with nucleophilic attack of the amine on the nitrosonium ion, and it can conceptually be divided into two parts: formation of an *N*-nitrosamine, followed by loss of H_2O, as shown in Mechanism 23.2.

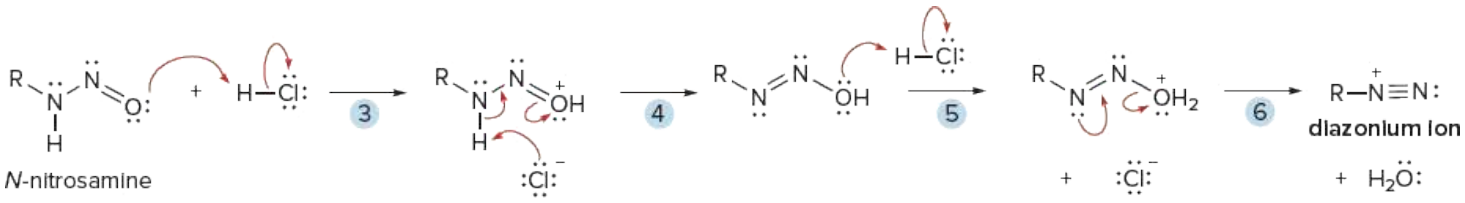
Mechanism 23.2 Formation of a Diazonium Salt from a 1° Amine

Part [1] Formation of an *N*-nitrosamine



1 – 2 Nucleophilic attack of the amine on the nitrosonium ion (^+NO), followed by loss of a proton, forms an *N*-nitrosamine.

Part [2] Formation of a diazonium salt

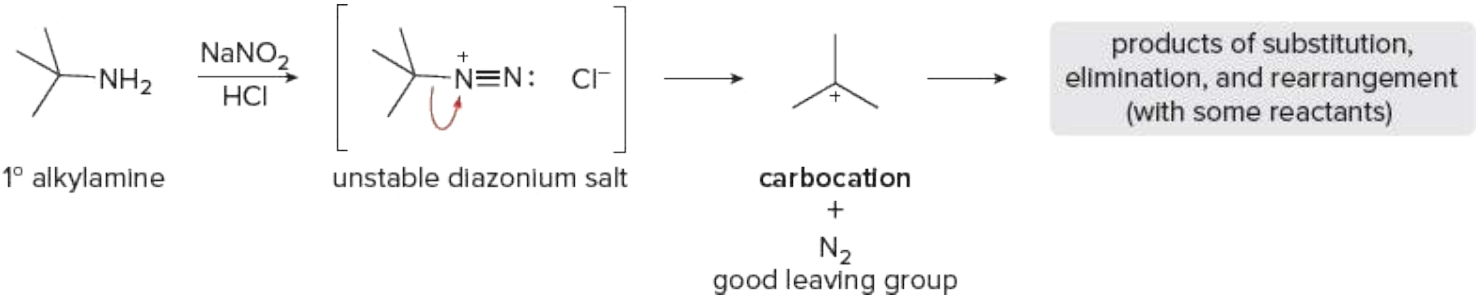


3 – 5 Three proton transfers form an intermediate with a good leaving group (H_2O).

6 Loss of water forms a diazonium ion (RN_2^+). The diazonium salt formed in this reaction consists of the diazonium ion (RN_2^+) and a chloride anion (Cl^-).

Care must be exercised in handling diazonium salts, because they can explode if allowed to dry.

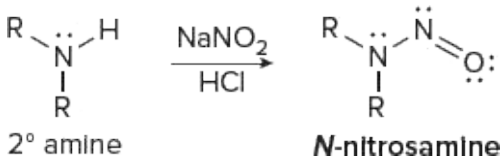
Alkyl diazonium salts are generally not useful compounds. They readily decompose below room temperature to form carbocations with loss of N2, a very good leaving group. These carbocations usually form a complex mixture of substitution, elimination, and rearrangement products.



On the other hand, aryl diazonium salts are very useful synthetic intermediates. Although they are rarely isolated and are generally unstable above 0 °C, they are useful starting materials in two general kinds of reactions described in Section 23.13.

23.12B Reaction of ^{+}NO with 2° Amines

Secondary alkylamines and arylamines react with nitrous acid to form *N*-nitrosamines.



Many *N*-nitrosamines are potent carcinogens found in some food and tobacco smoke. Nitrosamines in food can be formed in the same way they are formed in the laboratory: reaction of a 2° amine with the nitrosonium ion, formed from nitrous acid (HNO_2). Mechanism 23.3 is shown for the conversion of dimethylamine [$(CH_3)_2NH$] to *N*-nitrosodimethylamine [$(CH_3)_2NN{=}O$].

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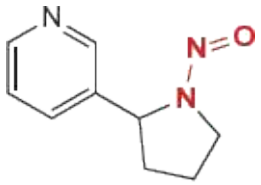
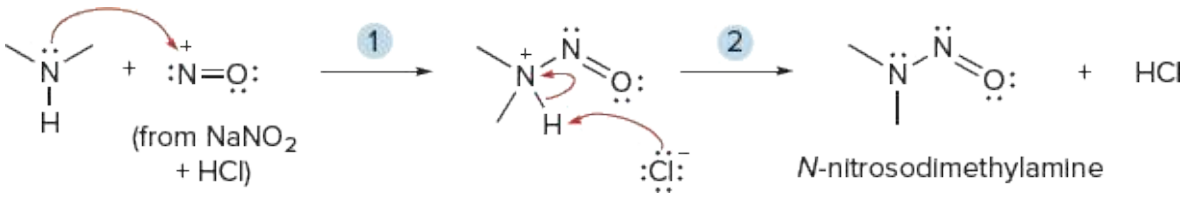


N-nitrosamine in tobacco smoke

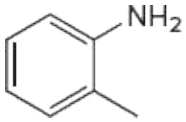
Mechanism 23.3 Formation of an *N*-Nitrosamine from a 2° Amine

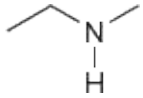


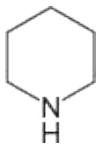
1 – 2 Nucleophilic attack of the amine on ^{+}NO, followed by loss of a proton, forms the *N*-nitrosamine.

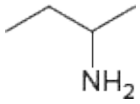
Problem 23.28

Draw the product formed when each compound is treated with $NaNO_2$ and HCl.

a. 

b. 

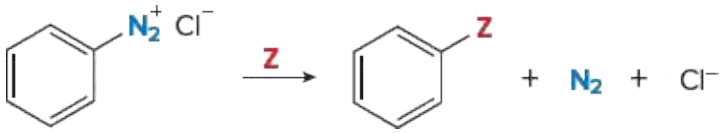
c. 

d. 

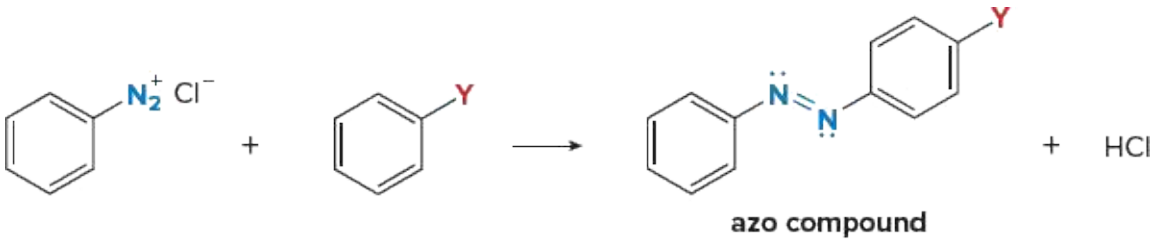
23.13 Substitution Reactions of Aryl Diazonium Salts

Aryl diazonium salts undergo two general reactions.

- **Substitution of N_2 by an atom or a group of atoms Z forms a variety of substituted benzenes.**



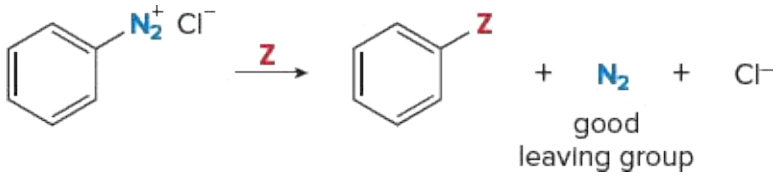
- **Coupling of a diazonium salt with another benzene derivative forms an azo compound, a compound containing a nitrogen–nitrogen double bond.**



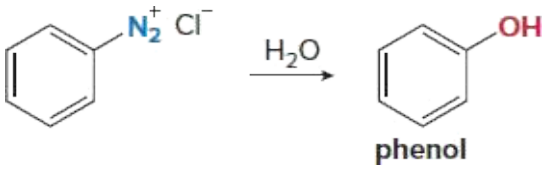
Y = NH_2, NHR, NR_2, OH (a strong electron-donor group)

23.13A Specific Substitution Reactions

Aryl diazonium salts react with a variety of reagents to form products in which Z (an atom or group of atoms) replaces N2, a very good leaving group. The mechanism of these reactions varies with the identity of Z, so we will concentrate on the products of the reactions, not the mechanisms.

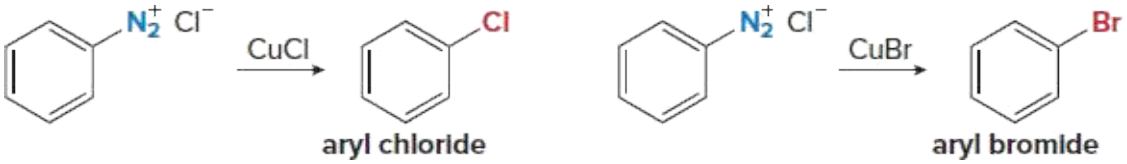


[1] Substitution by OH—Synthesis of phenols



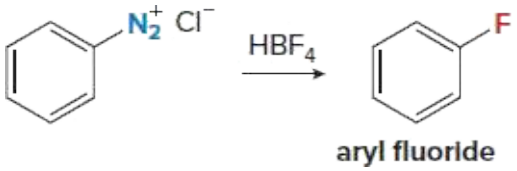
A diazonium salt reacts with H2O to form a phenol.

[2] Substitution by Cl or Br—Synthesis of aryl chlorides and bromides



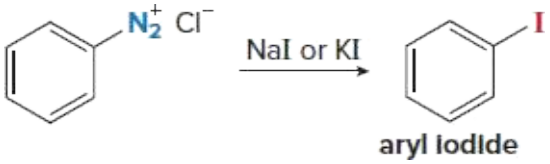
A diazonium salt reacts with copper(I) chloride or copper(I) bromide to form an aryl chloride or aryl bromide, respectively. This is called the Sandmeyer reaction. It provides an alternative to direct chlorination and bromination of an aromatic ring using Cl_2 or Br_2 and a Lewis acid catalyst.

[3] Substitution by F—Synthesis of aryl fluorides



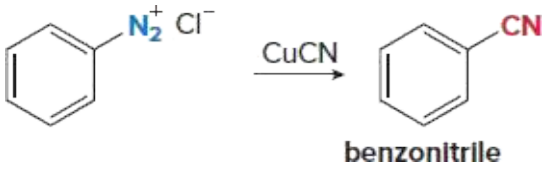
A diazonium salt reacts with fluoroboric acid (HBF4) to form an aryl fluoride. This is a useful reaction because aryl fluorides cannot be produced by direct fluorination with F_2 and a Lewis acid catalyst, because F_2 reacts too violently (Section 16.3).

[4] Substitution by I—Synthesis of aryl iodides



A diazonium salt reacts with sodium or potassium iodide to form an aryl iodide. This, too, is a useful reaction because aryl iodides cannot be produced by direct iodination with I_2 and a Lewis acid catalyst, because I2 reacts too slowly (Section 16.3).

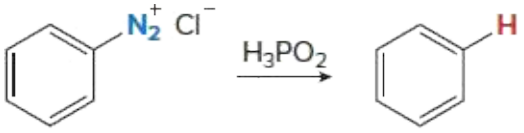
[5] Substitution by CN—Synthesis of benzonitriles



benzonitrile

A diazonium salt reacts with copper(I) cyanide to form a benzonitrile. Because a cyano group can be hydrolyzed to a carboxylic acid, reduced to an amine or aldehyde, or converted to a ketone with organometallic reagents, this reaction provides easy access to a wide variety of benzene derivatives using chemistry described in Section 19.12.

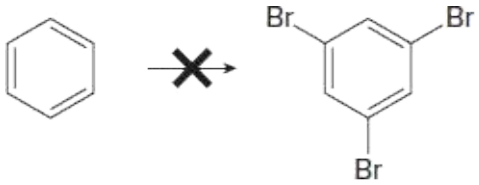
[6] Substitution by H—Synthesis of benzene



benzene

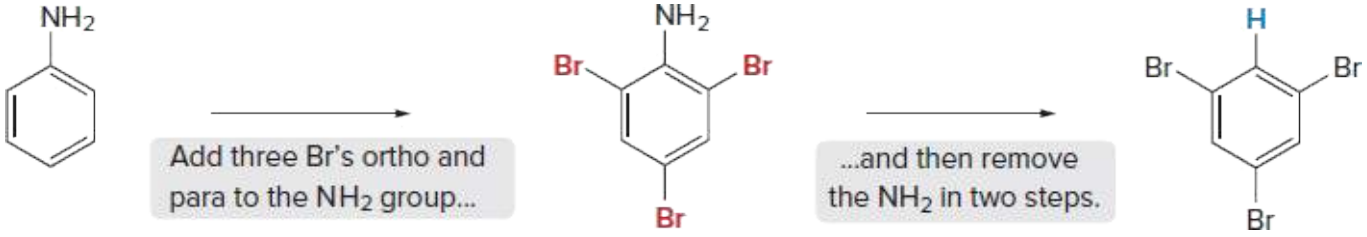
A diazonium salt reacts with hypophosphorus acid (H_3PO_2) to form benzene. This reaction has limited utility because it reduces the functionality of the benzene ring by replacing N_2 with a hydrogen atom. Nonetheless, this reaction *is* useful in synthesizing compounds that have substitution patterns that are not available by other means.

For example, it is not possible to synthesize 1,3,5-tribromobenzene from benzene by direct bromination. Because Br is an ortho, para director, bromination with Br2 and FeBr3 will not add Br substituents meta to each other on the ring.



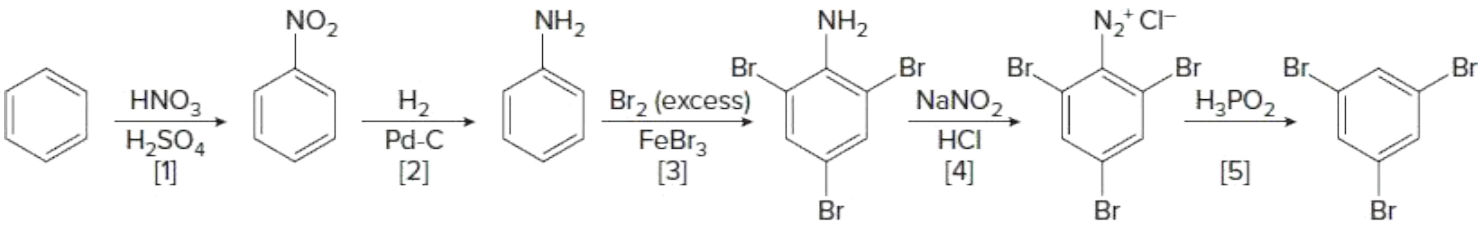
1,3,5-tribromobenzene

It is possible, however, to add three Br atoms meta to each other when aniline is the starting material. Because an NH2 group is a very powerful ortho, para director, three Br atoms are introduced in a single step on halogenation (Section 16.10A). Then, the NH_2 group can be removed by diazotization and reaction with H3PO2.



The complete synthesis of 1,3,5-tribromobenzene from benzene is outlined in Figure 23.11.

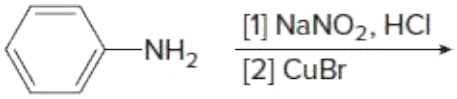
Figure 23.11 **The synthesis of 1,3,5-tribromobenzene from benzene**

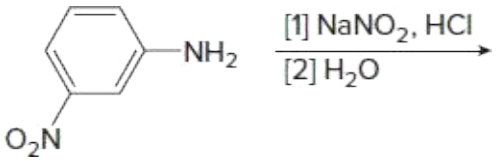


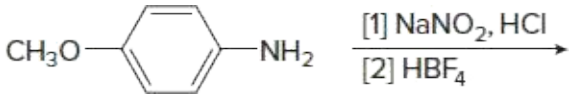
- Nitration followed by reduction forms aniline ($C_6H_5NH_2$) from benzene (Steps [1] and [2]).
- Bromination of aniline yields the tribromo derivative in Step [3].
- The NH_2 group is removed by a two-step process: diazotization with $NaNO_2$ and HCl (Step [4]), followed by substitution of the diazonium ion by H with H_3PO_2.

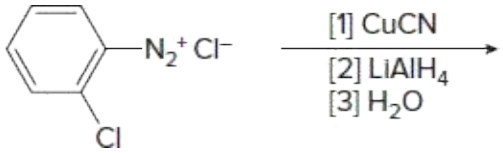
Problem 23.29

Draw the product formed in each reaction.

a. 

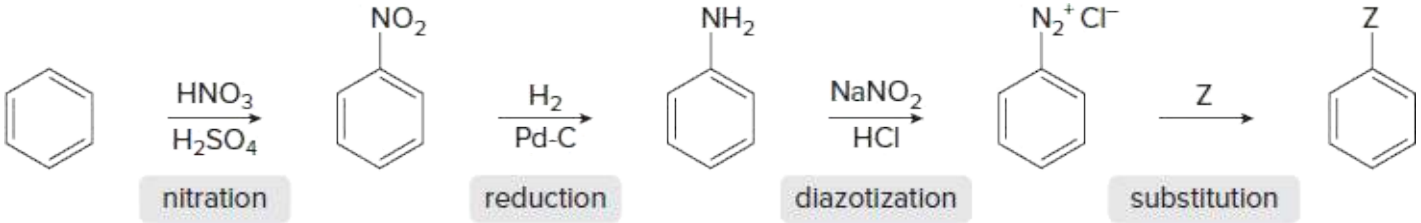
b. 

c. 

d. 

23.13B Using Diazonium Salts in Synthesis

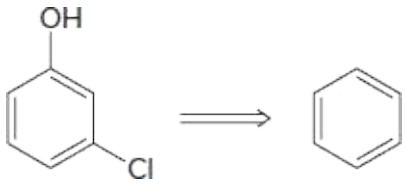
Diazonium salts provide easy access to many different benzene derivatives. Keep in mind the following four-step sequence, because it will be used to synthesize many substituted benzenes.



Sample Problems 23.6 and 23.7 apply these principles to two different multistep syntheses.

Sample Problem 23.6 Using Diazonium Salts in Synthesis

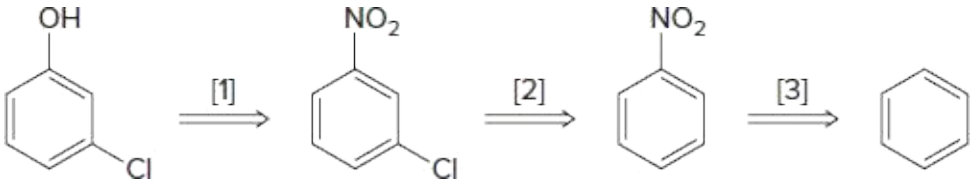
Synthesize *m*-chlorophenol from benzene.



Solution

Both OH and Cl are ortho, para directors, but they are located *meta* to each other. The OH group must be formed from a diazonium salt, which can be made from an NO2 group (a meta director) by a stepwise method.

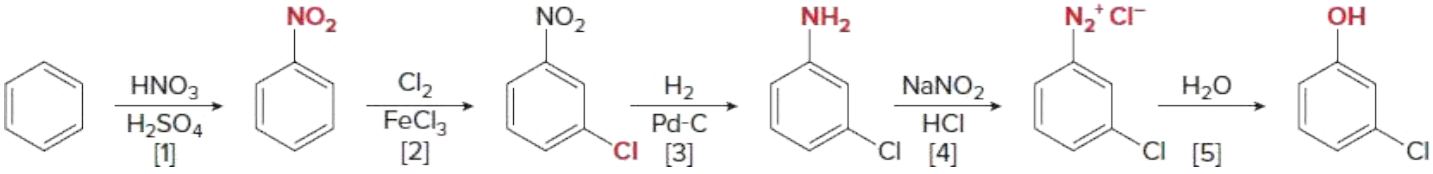
Retrosynthetic Analysis



Working backwards:

- **[1] Form the OH group from NO_2 by a three-step procedure using a diazonium salt.**
- **[2] Introduce Cl meta to NO_2 by halogenation.**
- **[3] Add the NO2 group by nitration.**

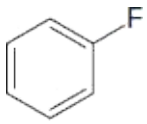
Synthesis

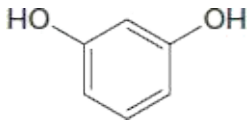


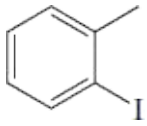
- **Nitration followed by chlorination meta to the NO_2 group forms the meta disubstituted benzene (Steps [1]–[2]).**
- **Reduction of the nitro group (Step [3]) followed by diazotization forms the diazonium salt in Step [4], which is then converted to the desired phenol by treatment with H_2O (Step [5]).**

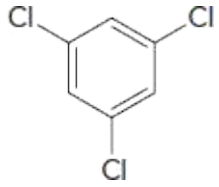
Problem 23.30

Devise a synthesis of each compound from benzene.

a. 

b. 

c. 

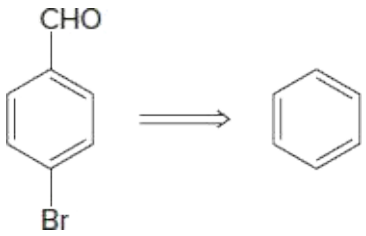
d. 

More Practice:

Try Problems 23.66a, b; 23.67a, b; 23.68; 23.69.

Sample Problem 23.7 Devising a Synthesis with Diazonium Salts

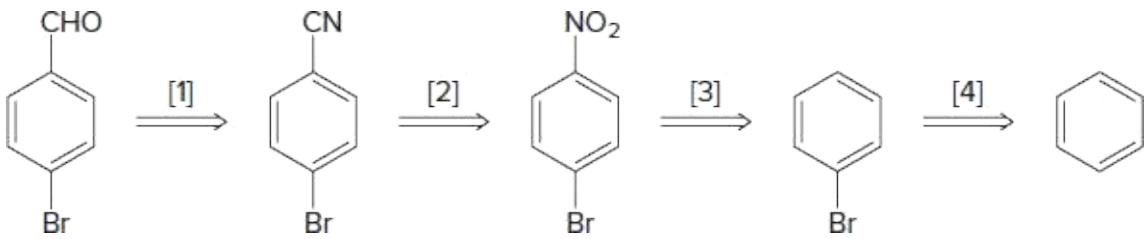
Synthesize *p*-bromobenzaldehyde from benzene.



Solution

Because the two groups are located para to each other and Br is an ortho, para director, Br should be added to the ring *first*. To add the CHO group, recall that it can be formed from CN by reduction.

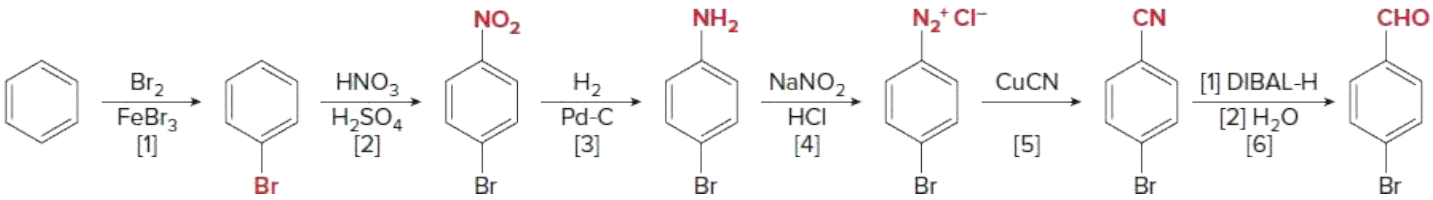
Retrosynthetic Analysis



Working backwards:

- **[1] Form the CHO group by reduction of CN.**
- **[2] Prepare the CN group from an NO2 group by a three-step sequence using a diazonium salt.**
- **[3] Introduce the NO2 group by nitration, para to the Br atom.**
- **[4] Introduce Br by bromination with Br2 and FeBr3.**

Synthesis

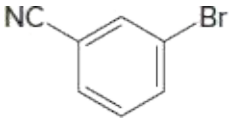


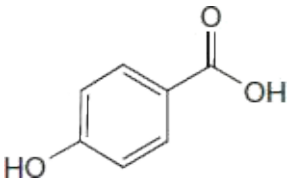
- **Bromination followed by nitration forms a disubstituted benzene with two para substituents (Steps [1]–[2]), which can be separated from its undesired ortho isomer.**
- **Reduction of the NO2 group (Step [3]) followed by diazotization forms the diazonium salt in Step [4], which is converted to a nitrile by reaction with CuCN (Step [5]).**
- **Reduction of the CN group with DIBAL-H (a mild reducing agent) forms the CHO group and completes the synthesis.**

Problem 23.31

Devise a synthesis of each compound from benzene. You may use any other organic or in organic reagents.

a.

b. 

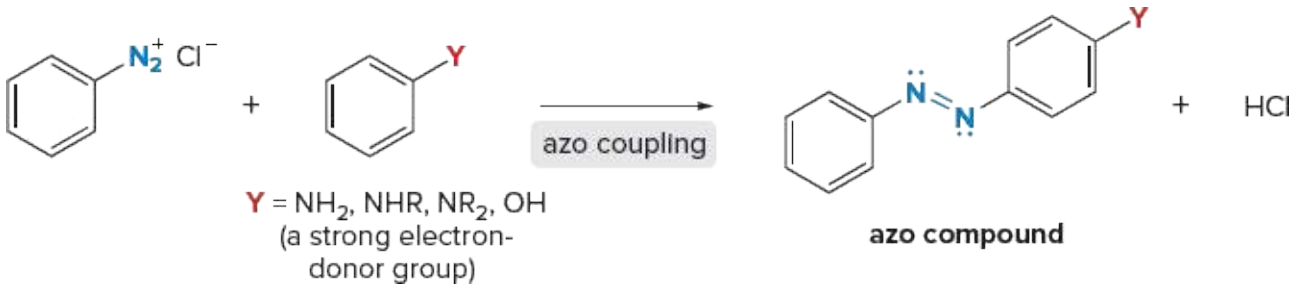
c. 

More Practice:

Try Problems 20.70a, b; 23.71; 23.72.

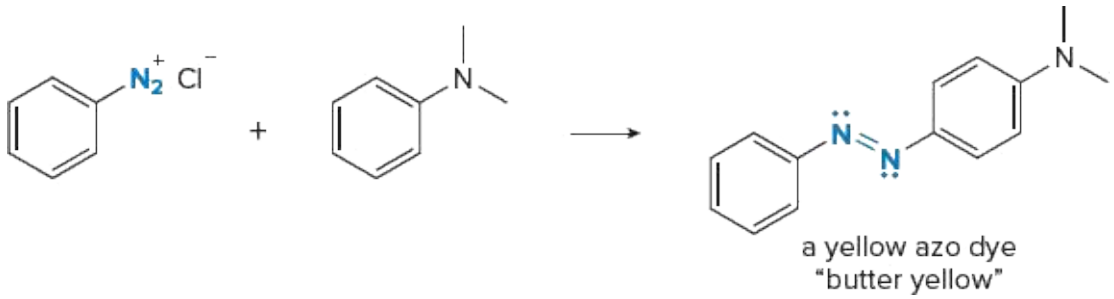
23.14 Coupling Reactions of Aryl Diazonium Salts

The second general reaction of diazonium salts is coupling. When a diazonium salt is treated with an aromatic compound that contains a strong electron-donor group, the two rings join together to form an azo compound, a compound with a nitrogen–nitrogen double bond.



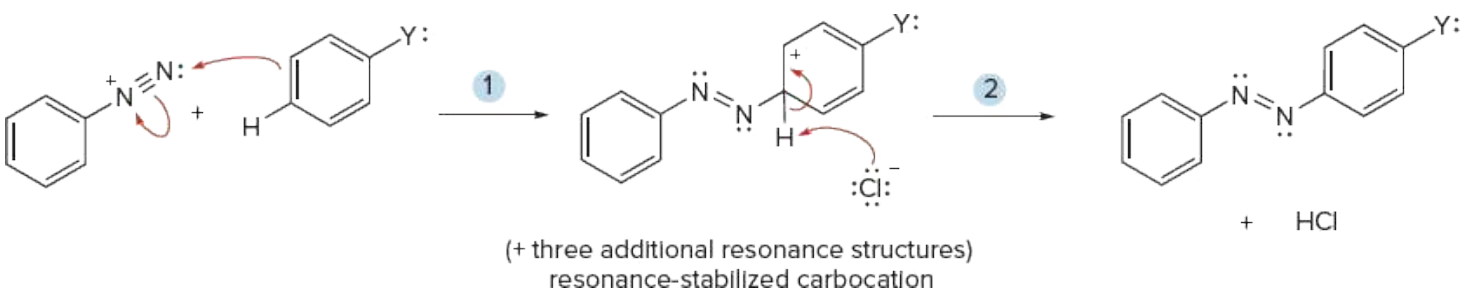
Synthetic dyes are described in more detail in Section 23.15A.

Azo compounds are highly conjugated, rendering them colored (Section 14.15). Many of these compounds, such as the azo compound "butter yellow," are synthetic dyes. Butter yellow was once used to color margarine.



This reaction is another example of electrophilic aromatic substitution, with the diazonium salt acting as the electrophile. Like all electrophilic substitutions (Section 16.2), the mechanism has two steps: addition of the electrophile (the diazonium ion) to form a resonance-stabilized carbocation, followed by deprotonation, as shown in Mechanism 23.4.

Mechanism 23.4 Azo Coupling

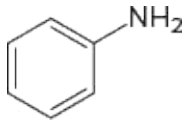


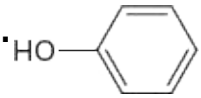
1. **The diazonium ion reacts with the benzene ring to form a resonance-stabilized carbocation.**
2. **Loss of a proton regenerates the aromatic ring.**

Because a diazonium salt is weakly electrophilic, the reaction occurs only when the benzene ring has a strong electron-donor group Y, where Y = NH2, NHR, NR2, or OH. Although these groups activate both the ortho and para positions, para substitution occurs unless the para position already has another substituent present.

Problem 23.32

Draw the product formed when $C_6H_5N_2^+Cl^-$ reacts with each compound.

a. 

b. 

c.

To determine what starting materials are needed to synthesize a particular azo compound, always divide the molecule into two components: one has a benzene ring with a diazonium ion, and one has a benzene ring with a very strong electron-donor group.

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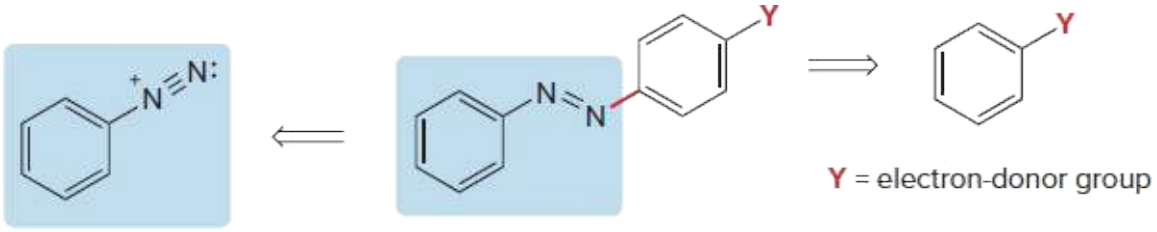
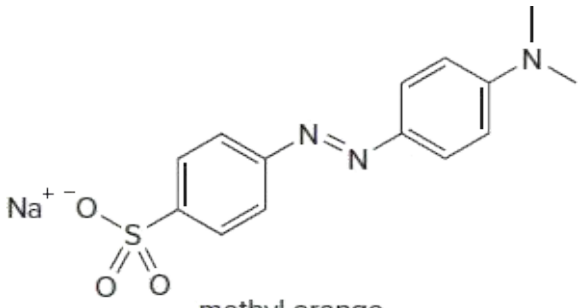


Sample Problem 23.8 Synthesizing an Azo Compound

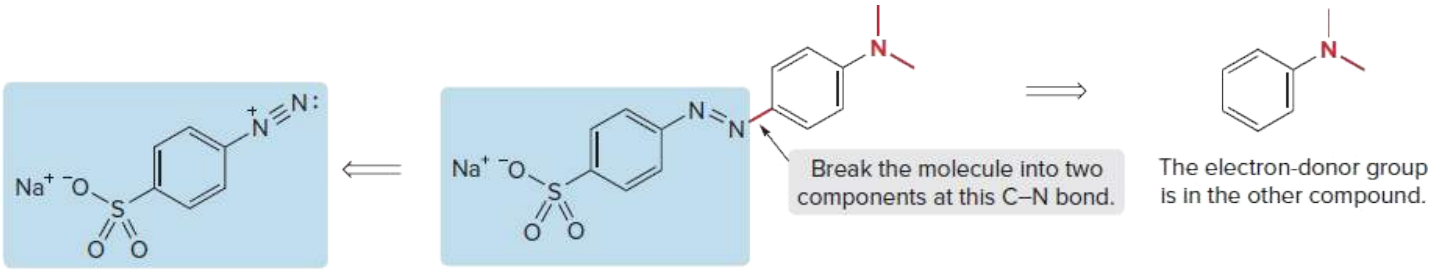
What starting materials are needed to synthesize the following azo compound?



methyl orange
an orange dye

Solution

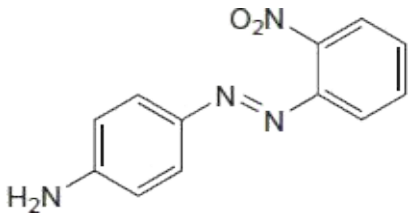
Both benzene rings in methyl orange have a substituent, but only one group, $N(CH_3)_2$, is a strong electron donor. In determining the two starting materials, the diazonium ion must be bonded to the ring that is *not* bonded to $N(CH_3)_2$.



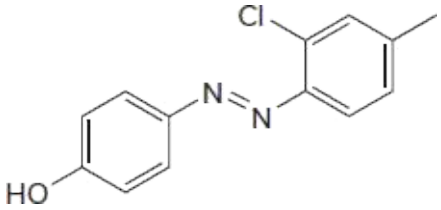
Problem 23.33

What starting materials are needed to synthesize each azo compound?

a.



b.



More Practice:

Try Problems 23.66c, 23.67c, 23.70c.

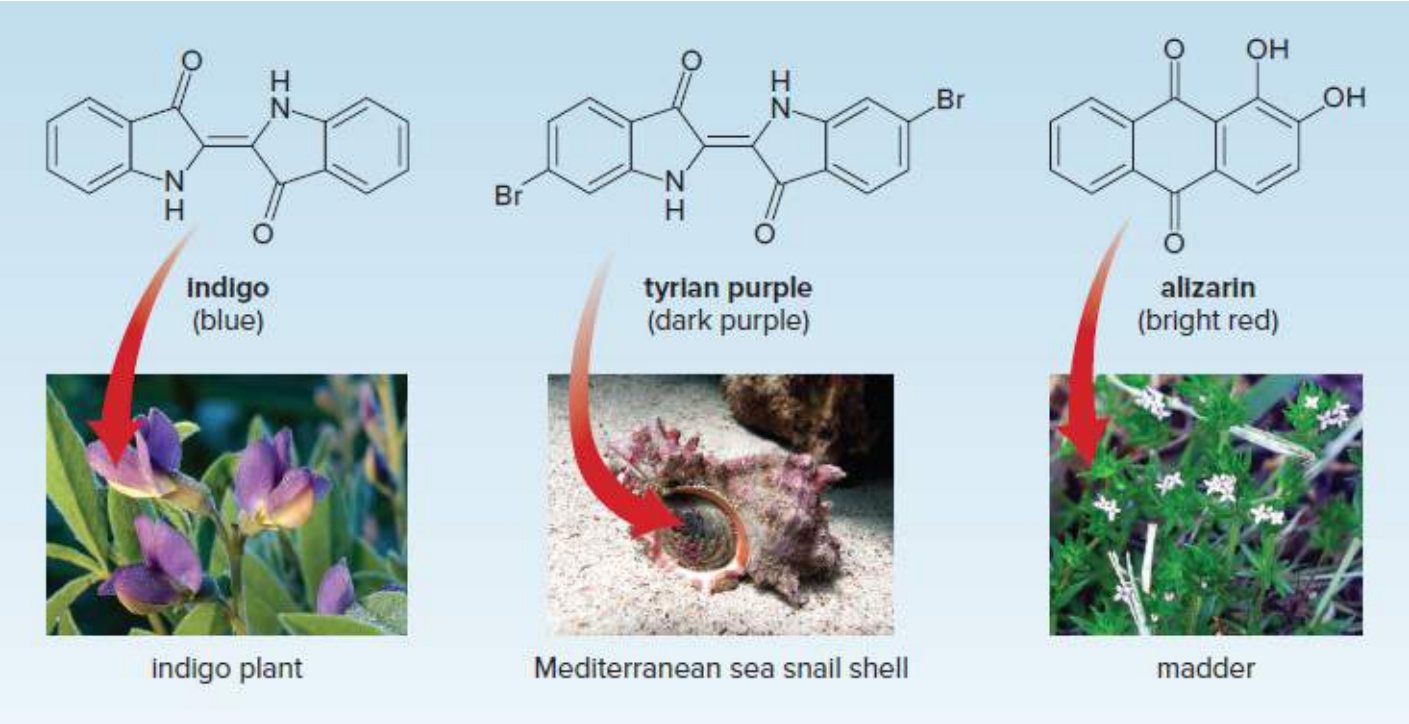
23.15 Application: Synthetic Dyes and Sulfa Drugs

Azo compounds have two important applications: as dyes and as sulfa drugs, the first

synthetic antibiotics.

23.15A Natural and Synthetic Dyes

Until 1856, all dyes were natural in origin, obtained from plants, animals, or minerals. Three natural dyes known for centuries are indigo, tyrian purple, and alizarin.

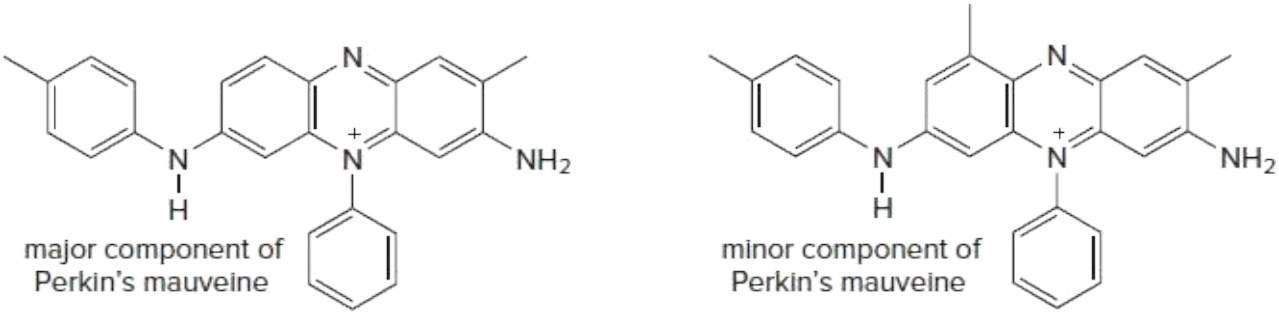


©Gail Jankus/Science Source; ©Kristina Vackova/Shutterstock; ©Bob Gibbons/Alamy Stock Photo

The blue dye indigo, derived from the plant *Indigofera tinctoria*, has been used in India for thousands of years. Traders introduced it to the Mediterranean area and then to Europe. Tyrian purple, a natural dark purple dye obtained from the mucous gland of a Mediterranean snail of the genus *Murex*, was a symbol of royalty before the collapse of the Roman Empire. Alizarin, a bright red dye obtained from madder root (*Rubia tinctorum*), a plant native to India and northeastern Asia, has been found in cloth entombed with Egyptian mummies.

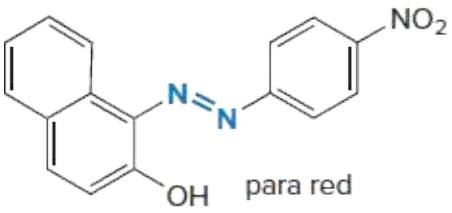
Because all three of these dyes were derived from natural sources, they were difficult to obtain, making them expensive and available only to the privileged. This all changed in 1856 when William Henry Perkin, an 18-year-old student with a makeshift home laboratory, serendipitously prepared a purple dye, which would later be called mauveine, during his failed attempt to synthesize the antimalarial drug quinine. Mauveine is a mixture of two compounds that differ in the presence of only one methyl group on one of the aromatic rings.

A purple shawl dyed with Perkin's mauveine ©*SSPL/Getty Images*

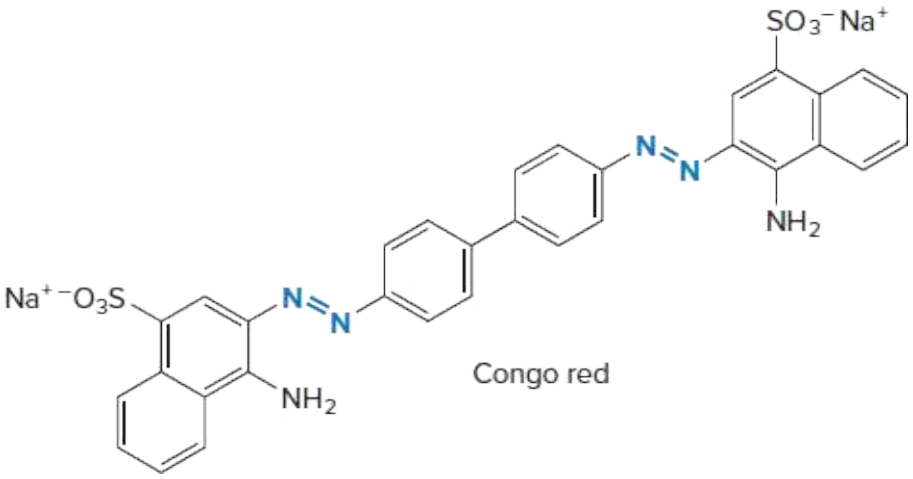


Perkin's discovery marked the beginning of the chemical industry. He patented the dye and went on to build a factory to commercially produce it on a large scale. This event began the surge of research in organic chemistry, not just in the synthesis of dyes, but in the production of perfumes, anesthetics, inks, and drugs as well. Perkin was a wealthy man when he retired at the age of 36 to devote the rest of his life to basic chemical research. The most prestigious award given by the American Chemical Society is named the Perkin Medal in his honor.

Many common synthetic dyes, such as para red and Congo red, are azo compounds, prepared by the diazonium coupling reaction described in Section 23.14.



para red



Congo red

Although natural and synthetic dyes are quite varied in structure, all of them are colored because they are highly conjugated. A molecule with eight or more π bonds in conjugation absorbs light in the visible region of the electromagnetic spectrum (Section 14.15A), taking on the color from the visible spectrum that it does *not* absorb.

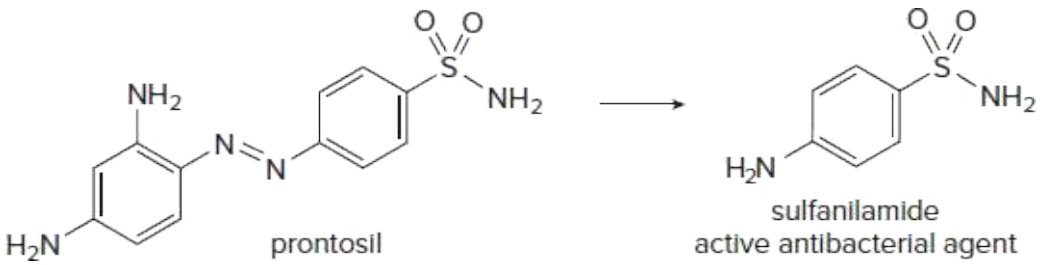
Problem 23.34

What two components are needed to prepare para red by azo coupling?

23.15B Sulfa Drugs

Although they may seem quite unrelated, the synthesis of colored dyes led to the development of the first synthetic antibiotics. Much of the early effort in this field was done by the German chemist Paul Ehrlich, who worked with synthetic dyes and used them to stain tissues. This led him on a search for dyes that were lethal to bacteria without affecting other tissue cells, hoping that these dyes could treat bacterial infections. For many years this effort was unsuccessful.

Then, in 1935, Gerhard Domagk, a German physician working for a dye manufacturer, first used a synthetic dye as a drug to kill bacteria. His daughter had contracted a streptococcal infection, and as she neared death, he gave her prontosil, an azo dye that inhibited the growth of certain bacteria in mice. His daughter recovered, and the modern era of synthetic antibiotics was initiated. For his pioneering work, Domagk was awarded the Nobel Prize in Physiology or Medicine in 1939.

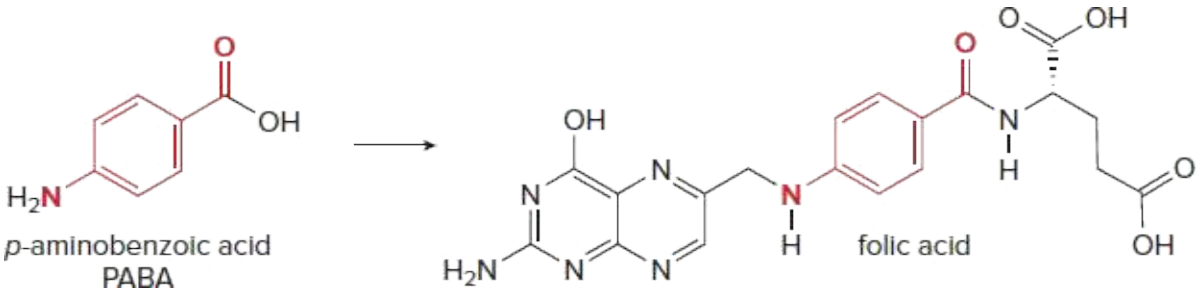


prontosil

sulfanilamide
active antibacterial agent

Prontosil and other sulfur-containing antibiotics are collectively called sulfa drugs.

Prontosil is not the active agent itself. In cells, it is metabolized to sulfanilamide, the active drug. To understand how sulfanilamide functions as an antibacterial agent we must examine folic acid, which microorganisms synthesize from *p*-aminobenzoic acid.



Sulfanilamide and *p*-aminobenzoic acid are similar in size and shape and have related functional groups. Thus, when sulfanilamide is administered, bacteria attempt to use it in place of *p*-aminobenzoic acid to prepare folic acid, and this derails folic acid synthesis, so bacteria cannot grow and reproduce. Sulfanilamide affects only bacterial cells, though, because humans do not synthesize folic acid and must obtain it from their diets.

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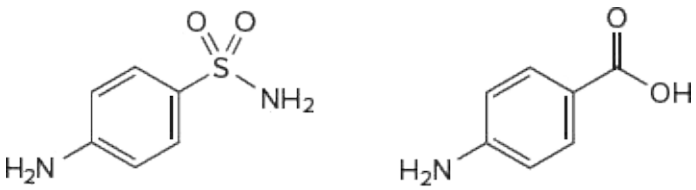
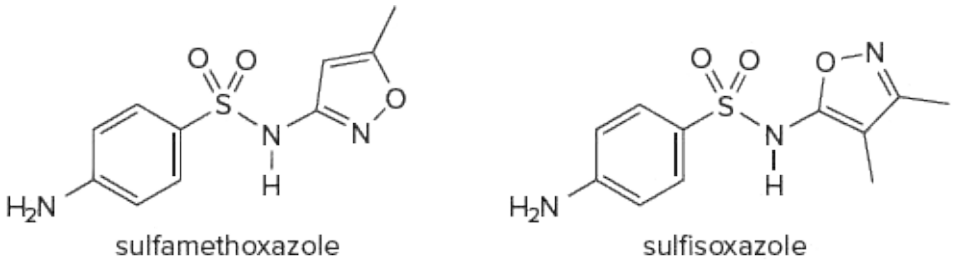


Many other compounds of similar structure have been prepared and are still widely used as antibiotics. The structures of two other sulfa drugs are shown in Figure 23.12.

Figure 23.12

Two common sulfa drugs

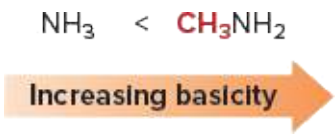


- Sulfamethoxazole is the sulfa drug in Bactrim, and sulfisoxazole is sold as Gantrisin. Both drugs are commonly used in the treatment of ear and urinary tract infections.

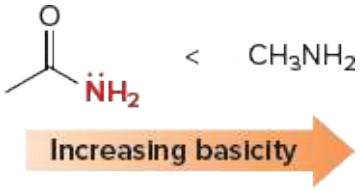
Chapter 23 REVIEW

KEY CONCEPTS

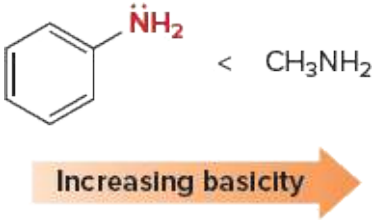
The basicity of amines (23.10)



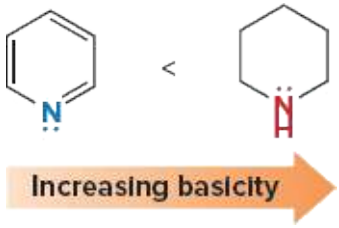
- **Alkylamines are more basic than NH_3 because of the electron-donating R groups.**



- **Alkylamines are more basic than amides, which have a delocalized lone pair from the N atom.**



- **Alkylamines are more basic than arylamines, which have a delocalized lone pair from the N atom.**



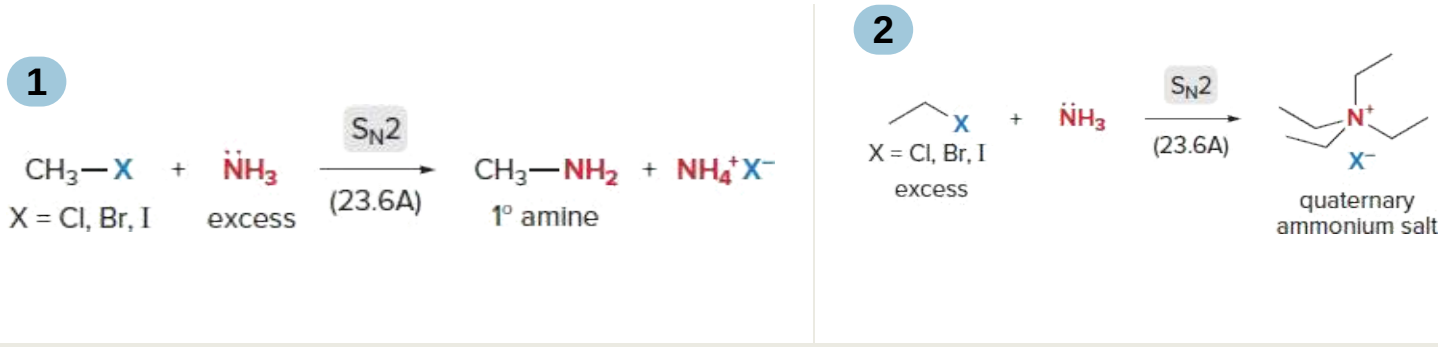
- **Alkylamines with a lone pair in an sp^3 hybrid orbital are more basic than those with a lone pair in an sp^2 hybrid orbital.**

Try Problems 23.36a, 23.40–23.42, 23.44.

KEY REACTIONS

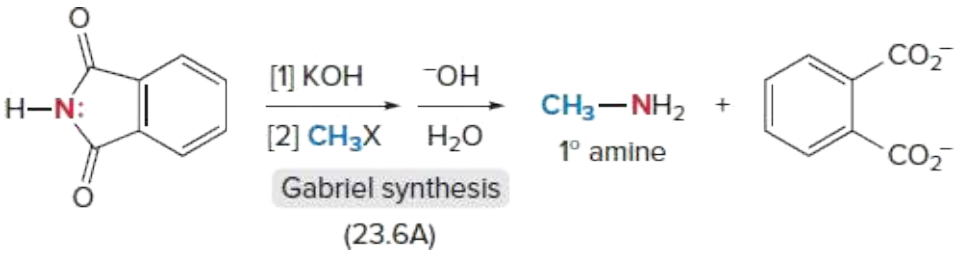
Preparation of Amines

[1] Direct nucleophilic substitution with NH_3 and amines



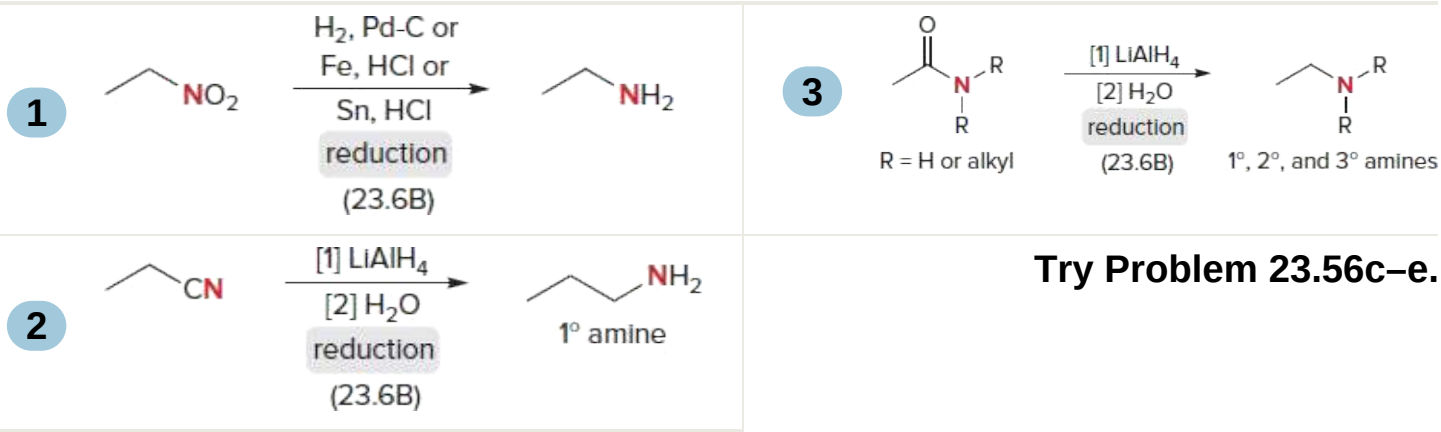
Try Problems 23.52d, 23.56a.

[2] Gabriel synthesis



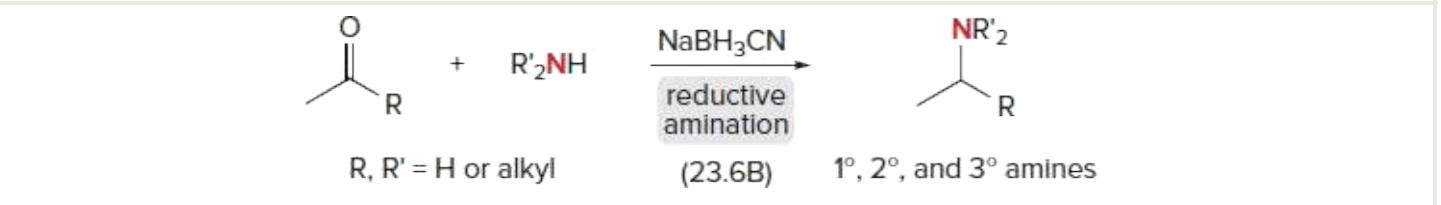
Try Problem 23.56b.

[3] Reduction methods



Try Problem 23.56c–e.

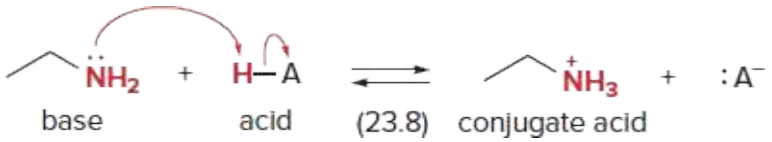
[4] Reductive amination



Try Problems 23.49, 23.50, 23.52j, 23.56h.

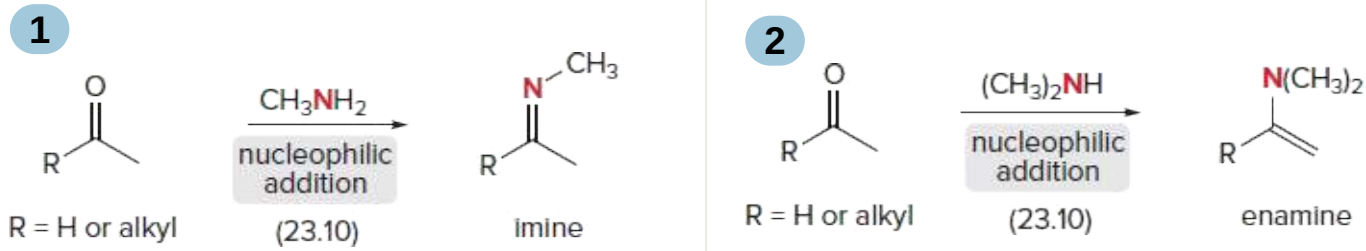
Reactions of Amines

[1] Reaction as a base



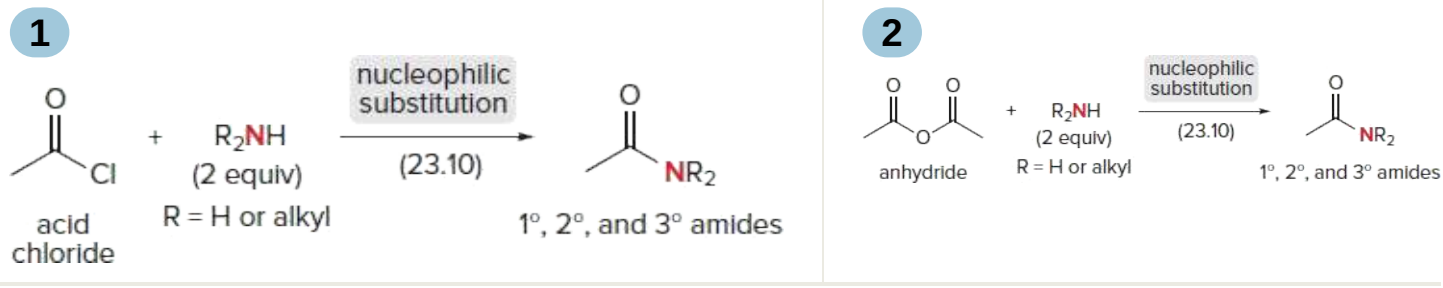
Try Problems 23.36b; 23.52a, g.

[2] Nucleophilic addition to aldehydes and ketones



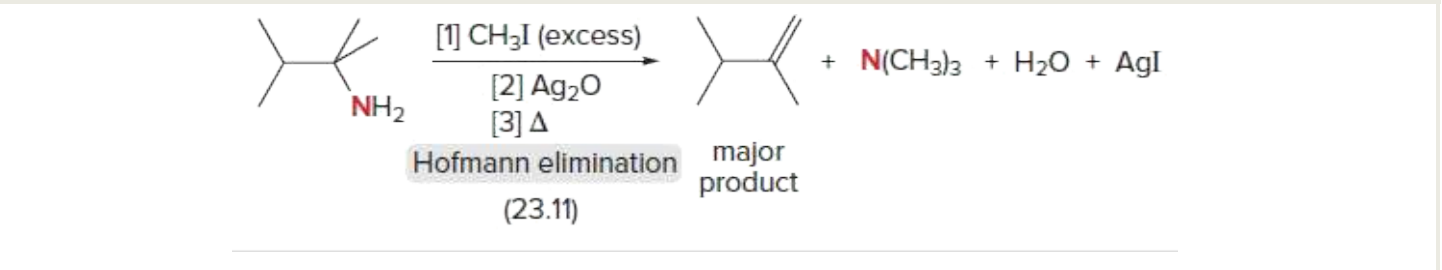
Try Problems 23.52e, 23.56i.

[3] Nucleophilic substitution with acid chlorides and anhydrides



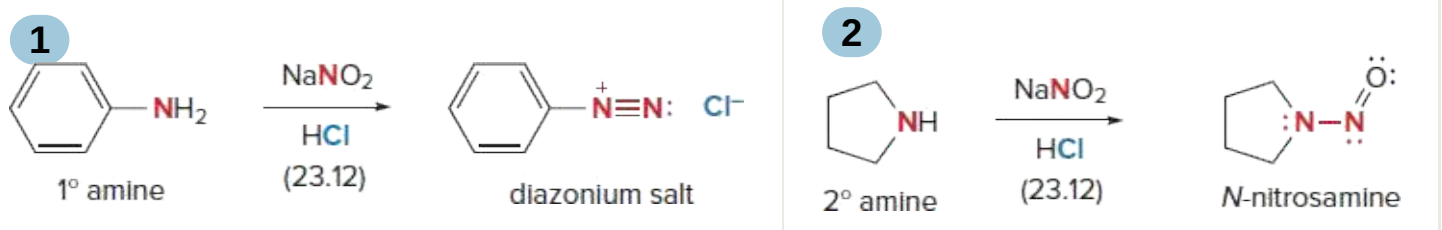
Try Problems 23.52b, c; 23.56f.

[4] Hofmann elimination



Try Problems 23.53, 23.54c, 23.55c, 23.56j, 23.57.

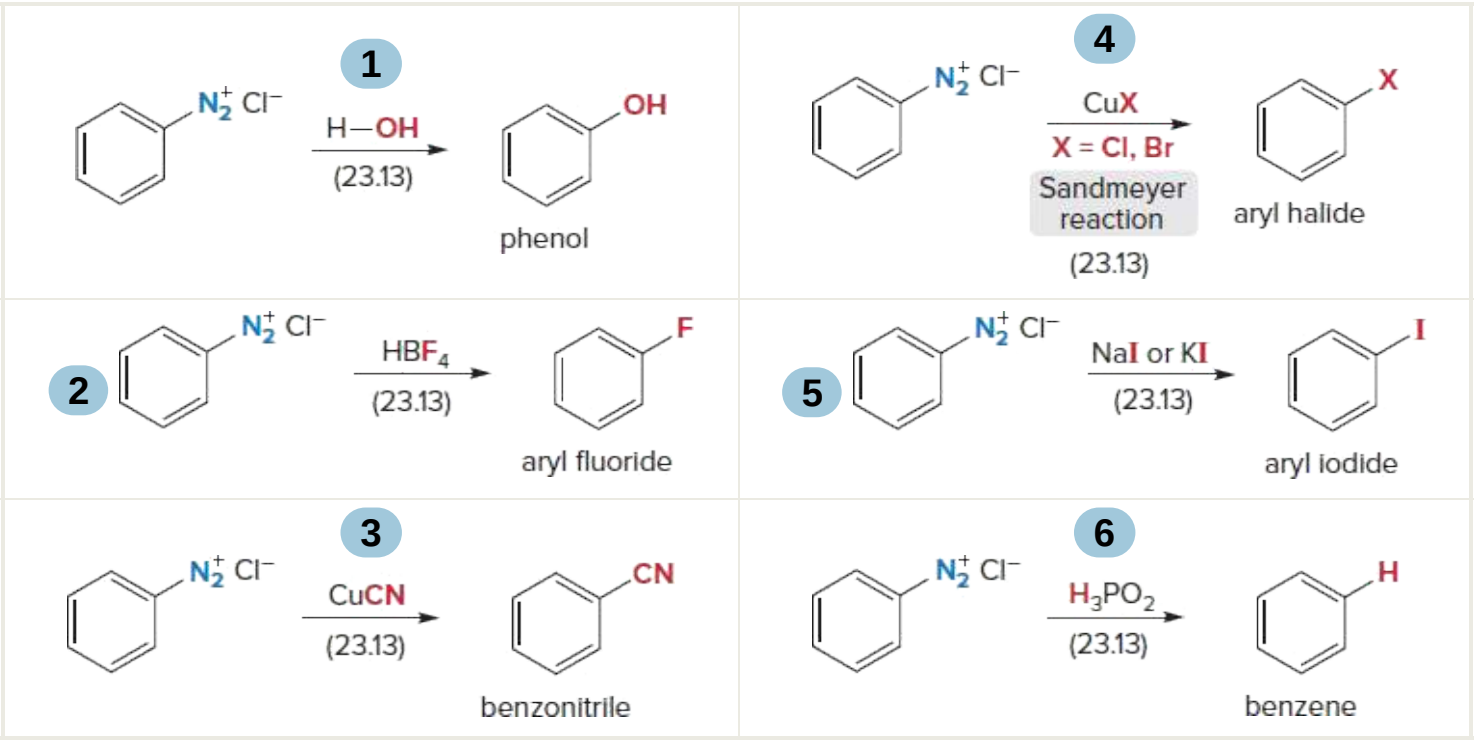
[5] Reaction with nitrous acid



Try Problems 23.52h, 23.56g.

Reactions of Diazonium Salts

[1] Substitution reactions



Try Problem 23.60a, b.

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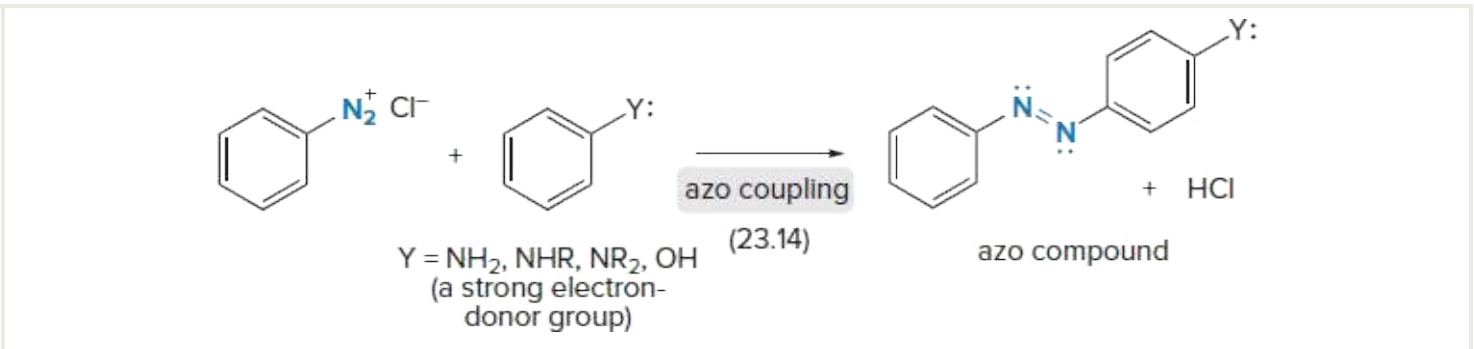
[2] Coupling to form azo compounds



Try Problem 23.60c.

KEY SKILLS

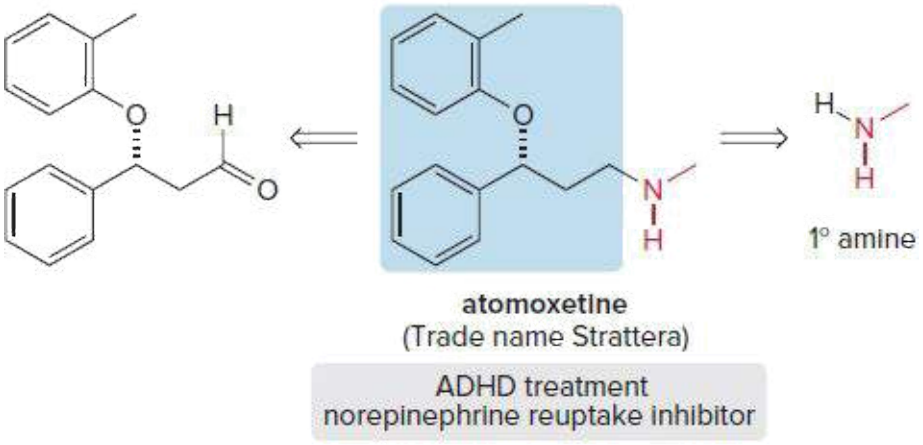
[1] Using retrosynthetic analysis in a reductive amination (23.6C); two possibilities

1 **Break the molecule into two components, using one alkyl group on N to form the carbonyl**

2 **Break the molecule into tv**

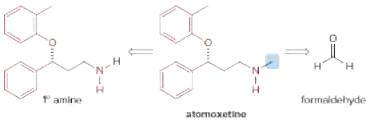
component.

components, using the other alkyl group on N form the carbon component.



atomoxetine
(Trade name Strattera)

ADHD treatment
norepinephrine reuptake inhibitor



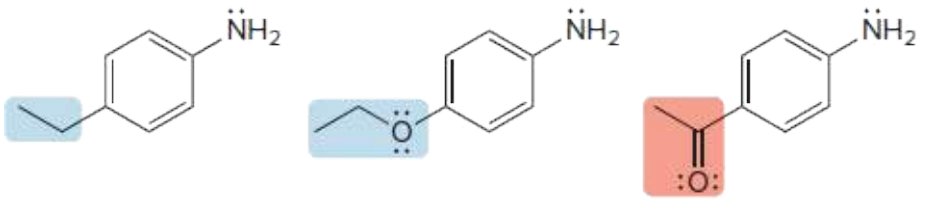
- Because atomoxetine has two different R groups bonded the N atom, eith R group can co from the carbon component.

See Sample Problem 23.2. Try Problems 23.48, 23.54b, 23.55b.

[2] Ranking arylamines in order of increasing basicity (23.9)

1 Identify whether the substituents are electron donating or electron withdrawing.

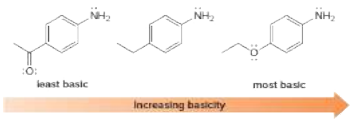
2 Rank the compounds.



p-ethylaniline
electron-donating group

p-ethoxyaniline
electron-donating group

p-aminoacetophenone
electron-withdrawing group



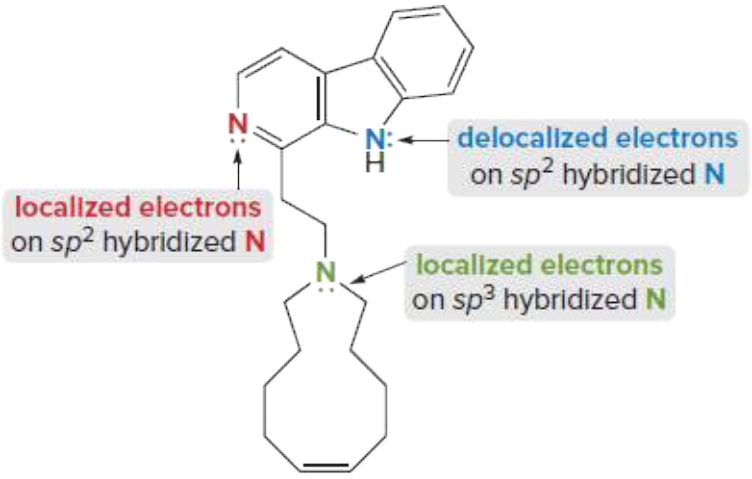
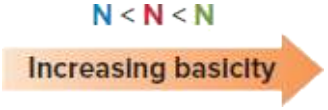
- The ethoxy group is more strongly electron donating than the ethyl group due to resonance.
- The acyl group is electron withdrawing.

- Arylamines wit electron-donor groups are mo basic than

	arylamines with electron withdrawing groups.

See Sample Problem 23.3. Try Problem 23.40b.

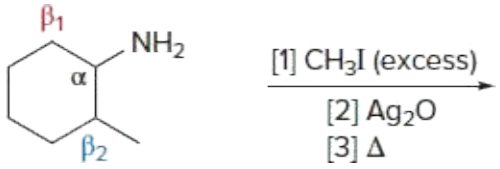
[3] Ranking N atoms in order of increasing basicity; example: manzamine C (23.9)

1 Identify the different types of nitrogen atoms.	2 Evaluate the basicity of the nitrogen atoms.
 **manzamine C** anticancer activity	• Aromatic heterocycles with a localized electron pair on N are more basic than those with a delocalized lone pair on the N atom. • The lone pair is localized on N, but N is sp^2 hybridized. Increasing percent *s*-character decreases basicity. • N has a localized lone pair and is sp^3 hybridized, making it the most basic site in the molecule. 

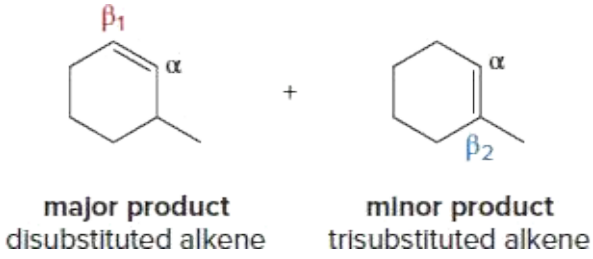
See Sample Problem 23.4. Try Problems 23.36a, 23.41, 23.42, 23.44.

[4] Drawing the major and minor product formed from Hofmann elimination (23.11)

1 **Identify the α and β carbons of the amine.**



2 **Draw the major and minor products.**



major product
disubstituted alkene

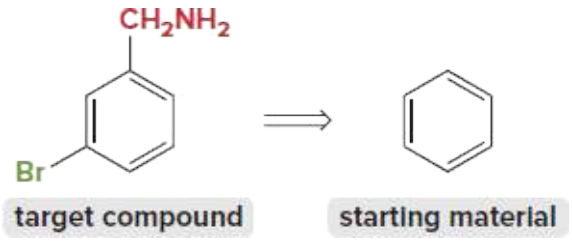
minor product
trisubstituted alkene

- **The major product has the less substituted double bond.**
- **The minor product has the more substituted double bond.**

See Sample Problem 23.5. Try Problems 23.53, 23.54c, 23.55c, 23.56j, 23.57.

[5] Devising a synthesis using diazonium salts (23.13)

1 **Compare the carbon skeletons and functional groups.**

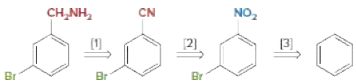


target compound → starting material

- **The groups are located meta to each other.**

2 **Work backwards.**

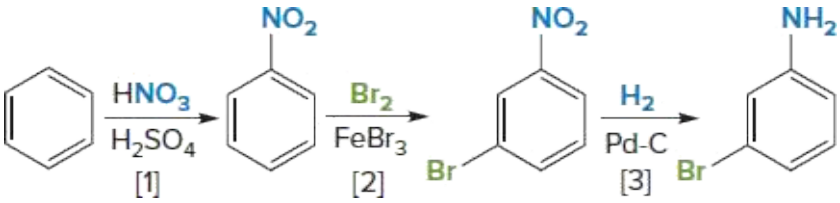
3 **Work forwards.**

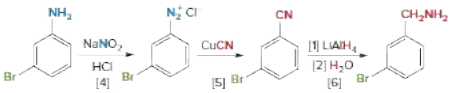


- **Nitration followed by bromination forms a meta, disubstituted benzene (Steps [1]–[**
- **Reduction of the NO group (Step [3]) forn a 1° arylamine.**

4 **Complete the**

synthesis.





- [1] Form the CH2NH2 group by reduction of CN.
- [2] Prepare the CN group from an NO2 group by a three-step sequence using a diazonium salt.
- [3] Introduce Br meta to NO2 by halogenation, and add the NO2 group by nitration.

- Diazotization of the NH_2 group followed reaction with CuCN (Steps [4]–[5]) forms nitrile.
- The nitrile is reduce form the CH_2NH_2 gr (Step [6]).

See Sample Problems 23.6 and 23.7. Try Problems 23.66–23.72.

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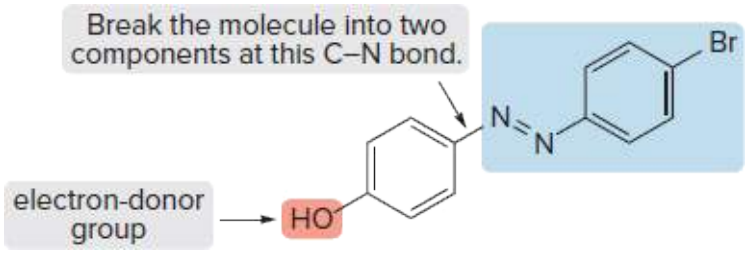
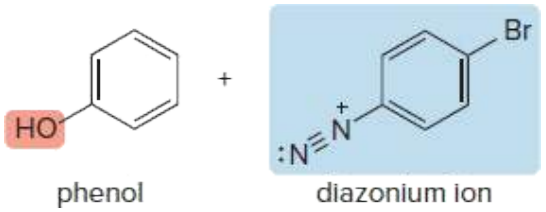
[6] Drawing the starting materials needed to synthesize an azo compound (23.14)

1 Break the molecule into two components at the specified C—N bond.

2 Draw the diazonium ion a the aromatic starting material with a strong electron-donor group.





- The diazonium ion must be bonded to the ring that is *not* bonded to the

electron-donor group.

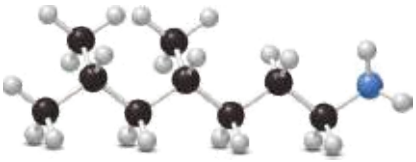
See Sample Problem 23.8. Try Problems 23.66c, 23.67c, 23.70c.

PROBLEMS

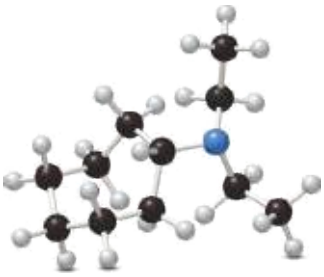
Problems Using Three-Dimensional Models

23.35 **Give a systematic or common name for each compound.**

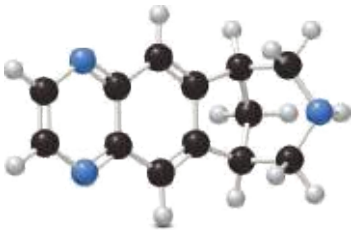
a.



b.



23.36 **Varenicline (trade name Chantix) is a drug used to help smokers quit their habit. (a) Which N atom in varenicline is most basic? Explain your choice. (b) What product is formed when varenicline is treated with HCl?**

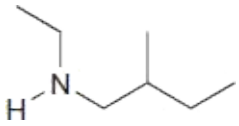


varenicline

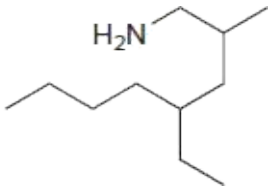
Nomenclature

23.37 **Give a systematic or common name for each compound.**

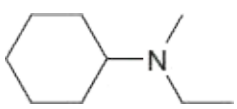
a.

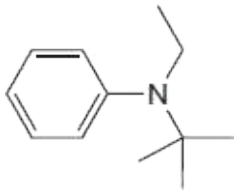


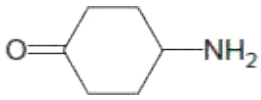
b.

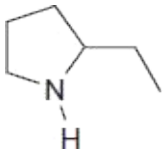


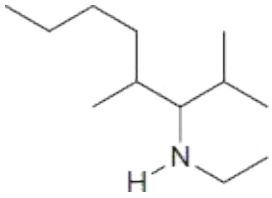
c.

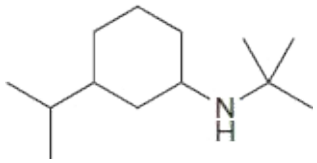


d. 

e. 

f. 

g. 

h. 

23.38 Draw the structure that corresponds to each name.

a. *N*-isobutylcyclopentanamine

b. tri-*tert*-butylamine

c. *N,N*-diisopropylaniline

d. *N*-methylpyrrole

e. *N*-methylcyclopentanamine

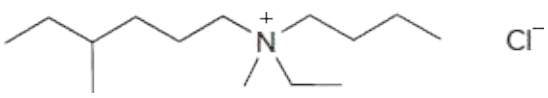
f. 3-methylhexan-2-amine

g. 2-*sec*-butylpiperidine

h. (*S*)-heptan-2-amine

Chiral Compounds

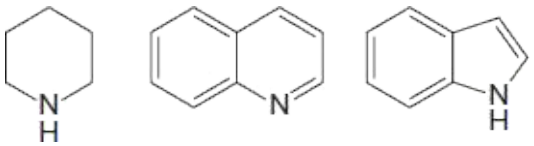
23.39 How many stereogenic centers are present in the following tetraalkylammonium salt? Draw all possible stereoisomers.



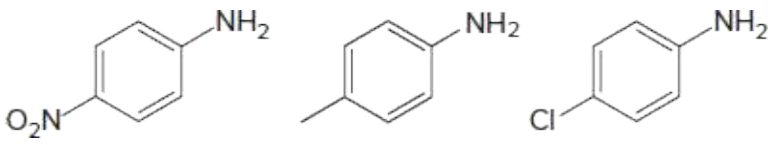
Basicity

23.40 Rank the compounds in each group in order of increasing basicity.

a.

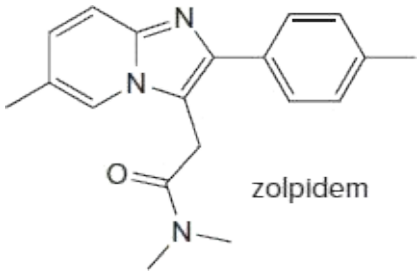


b.



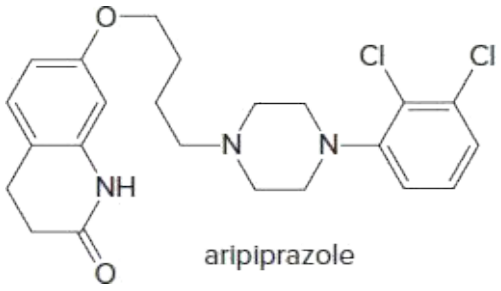
23.41 Decide which N atom in each molecule is most basic, and draw the product formed when each compound is treated with CH_3CO_2H. Zolpidem (trade name Ambien) is used to treat insomnia, whereas aripiprazole (trade name Abilify) is used to treat depression, schizophrenia, and bipolar disorders.

a.



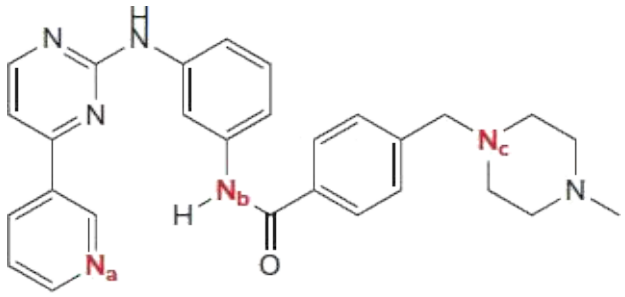
zolpidem

b.



aripiprazole

23.42 Rank the labeled N atoms in the anticancer drug imatinib (trade name Gleevec) in order of increasing basicity. Imatinib, sold as a salt with methanesulfonic acid (CH_3SO_3H), is used for the treatment of chronic myeloid leukemia as well as certain gastrointestinal tumors.



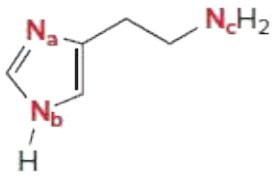
imatinib

23.43 Explain why pyrimidine is less basic than pyridine.

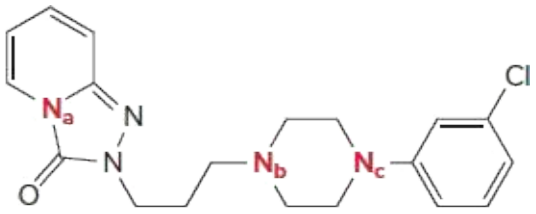
pyridine pyrimidine

23.44 Rank the labeled nitrogen atoms in each compound in order of

increasing basicity. Histamine (Section 23.5B) causes the runny nose and watery eyes associated with allergies, and trazodone is a drug used as a sedative and antidepressant.

a. 

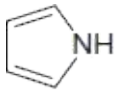
histamine

b. 

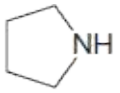
trazodone

23.45 Explain why *m*-nitroaniline is a stronger base than *p*-nitroaniline.

23.46 Why is pyrrole more acidic than pyrrolidine?



pyrrole
$pK_a = 23$

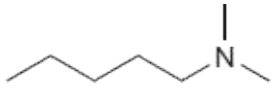


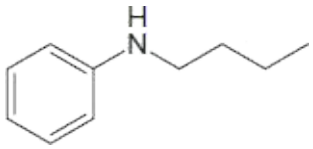
pyrrolidine
$pK_a = 44$

Preparation of Amines

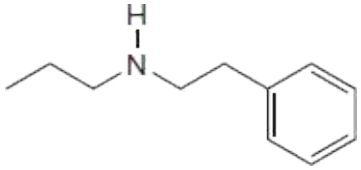
23.47 What amide(s) can be used to prepare each amine by reduction?

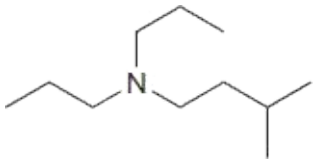
a.

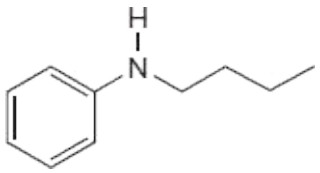
b. 

c. 

23.48 What carbonyl and nitrogen compounds are needed to make each compound by reductive amination? When more than one set of starting materials is possible, give all possible methods.

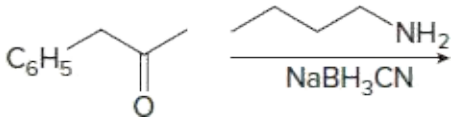
a. 

b. 

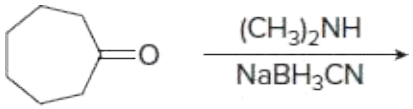
c. 

23.49 Draw the product of each reductive amination reaction.

a.

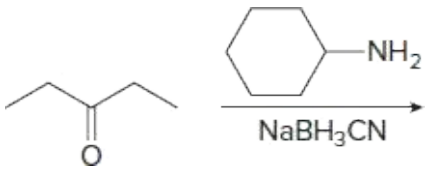


b.

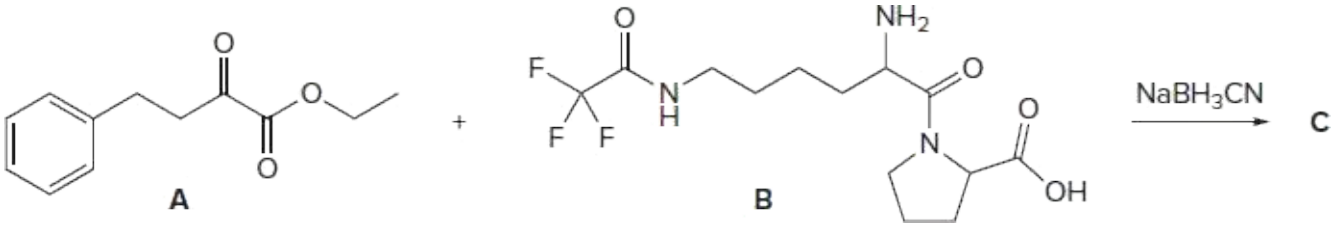


c.

d.



23.50 One step in the synthesis of lisinopril (Section 5.6, Problem 5.18), a drug used to treat high blood pressure, involves the reaction of A with B in the presence of a reducing agent to form C. What is the structure of C?



Extraction

23.51 How would you separate toluene ($C_6H_5CH_3$), benzoic acid ($C_6H_5CO_2H$), and aniline ($C_6H_5NH_2$) by an extraction procedure?

Reactions

23.52 Draw the products formed when *p*-methylaniline (*p*-$CH_3C_6H_4NH_2$) is treated with each reagent.

a. HCl

b. CH_3COCl

c. $(CH_3CO)_2O$

d. excess CH_3I

e. $(CH_3)_2C{=}O$

f. CH_3COCl, $AlCl_3$

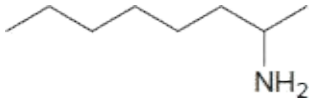
g. CH_3CO_2H

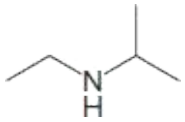
h. $NaNO_2$, HCl

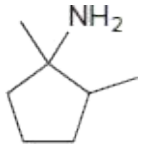
i. Part (b), then CH_3COCl, $AlCl_3$

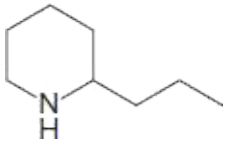
j. CH_3CHO, $NaBH_3CN$

23.53 Draw the products formed when each amine is treated with [1] CH_3I (excess); [2] Ag_2O; [3] Δ. Indicate the major product when a mixture results.

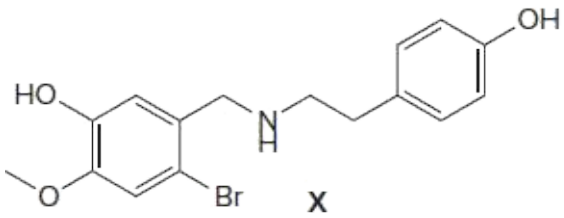
a. 

b. 

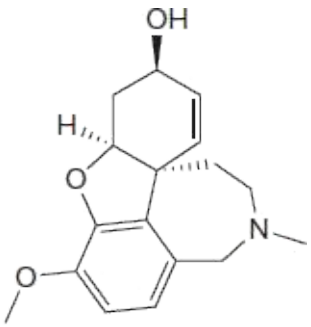
c. 

d. 

23.54 Answer the following questions about amine X, an intermediate in the synthesis of galantamine, a drug used to treat mild to moderate dementia.



X



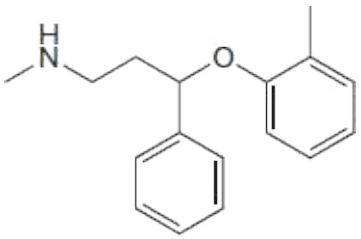
galantamine

a. What amides can be reduced to form X?

b. What starting materials can be used to form X by reductive amination? Draw all possible methods.

c. What products are formed by Hofmann elimination from X?

23.55 Answer the following questions about atomoxetine, a drug used to treat attention deficit hyperactivity disorder (ADHD).



atomoxetine

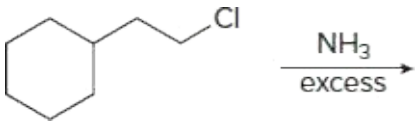
a. What amides can be reduced to form atomoxetine?

b. What starting materials can be used to form atomoxetine by reductive amination? Draw all possible methods.

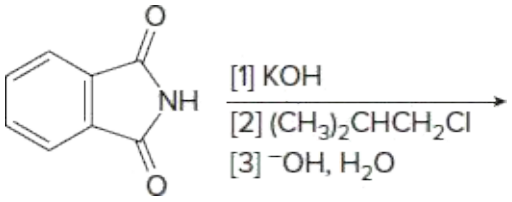
c. What products are formed by Hofmann elimination of atomoxetine?

23.56 Draw the organic products formed in each reaction.

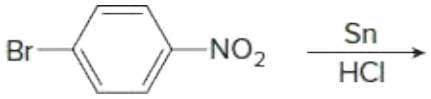
a.



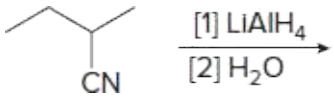
b.



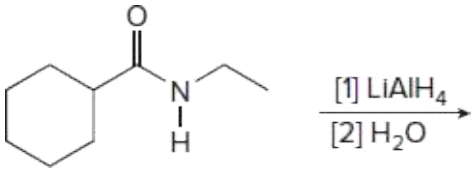
c.



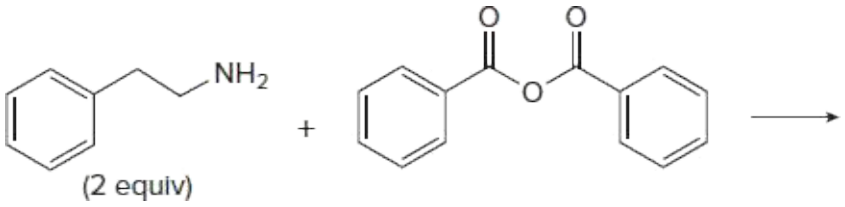
d.



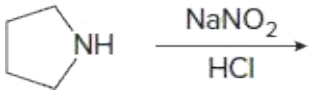
e.



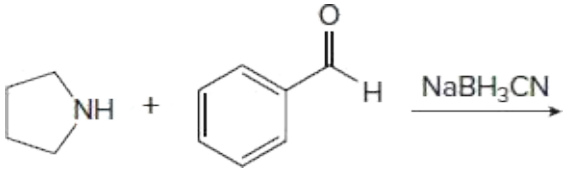
f.



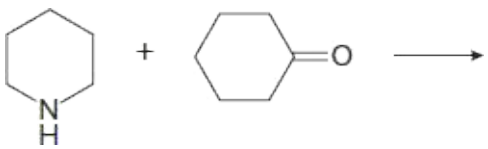
g.



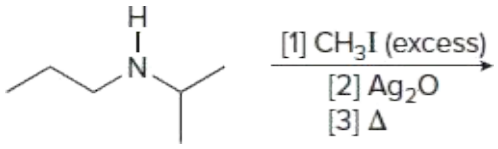
h.



i.

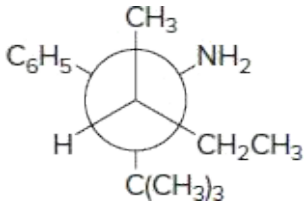


j.

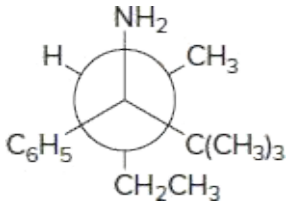


23.57 What is the major Hofmann elimination product formed from each amine?

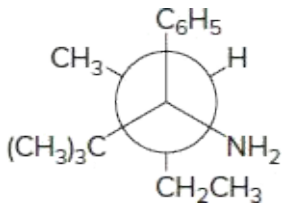
a.



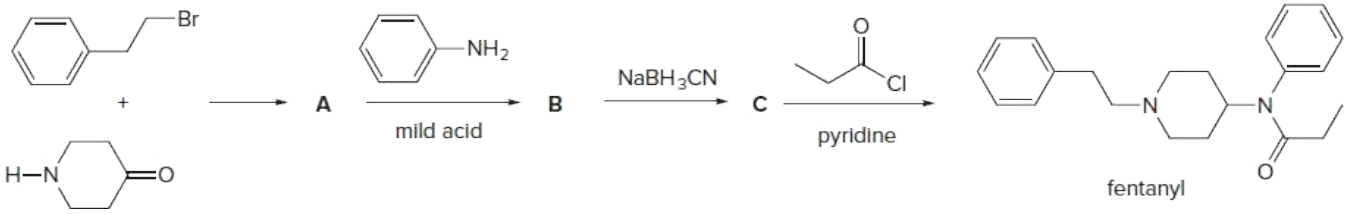
b.



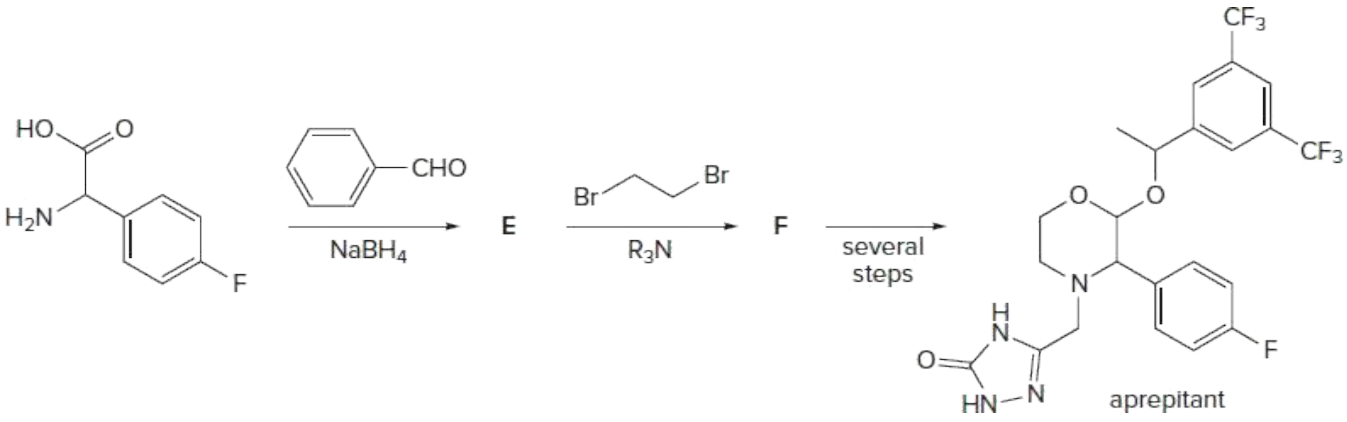
c.



23.58 Identify A, B, and C, three intermediates in the synthesis of the pain reliever and anesthetic fentanyl.



23.59 Aprepitant (trade name Emend) is used to prevent the acute nausea and vomiting caused by chemotherapy. Identify E and F, intermediates in the synthesis of aprepitant.

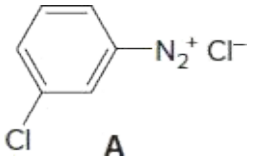


23.60 Draw the product formed when A is treated with each series of reagents.

a. [1] H_2O; [2] NaH; [3] CH_3Br

b. [1] CuCN; [2] DIBAL-H; [3] H_2O

c. [1] $C_6H_5NH_2$; [2] CH_3COCl



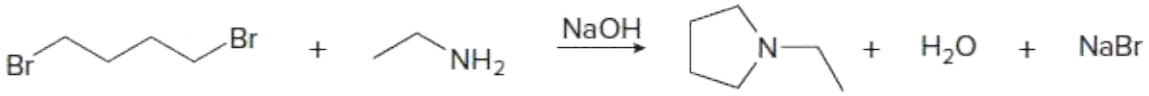
A

23.61 A chiral amine A having the *R* configuration undergoes Hofmann elimination to form an alkene B as the major product. B is oxidatively cleaved with ozone, followed by CH_3SCH_3, to form $CH_2{=}O$ and $CH_3CH_2CH_2CHO$. What are the structures of A and B?

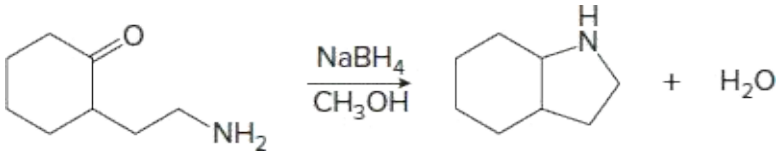
Mechanism

23.62 Draw a stepwise mechanism for each reaction.

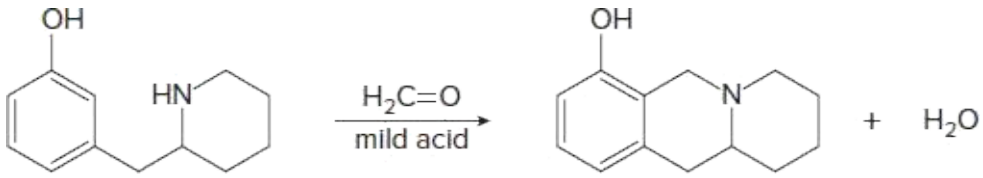
a.



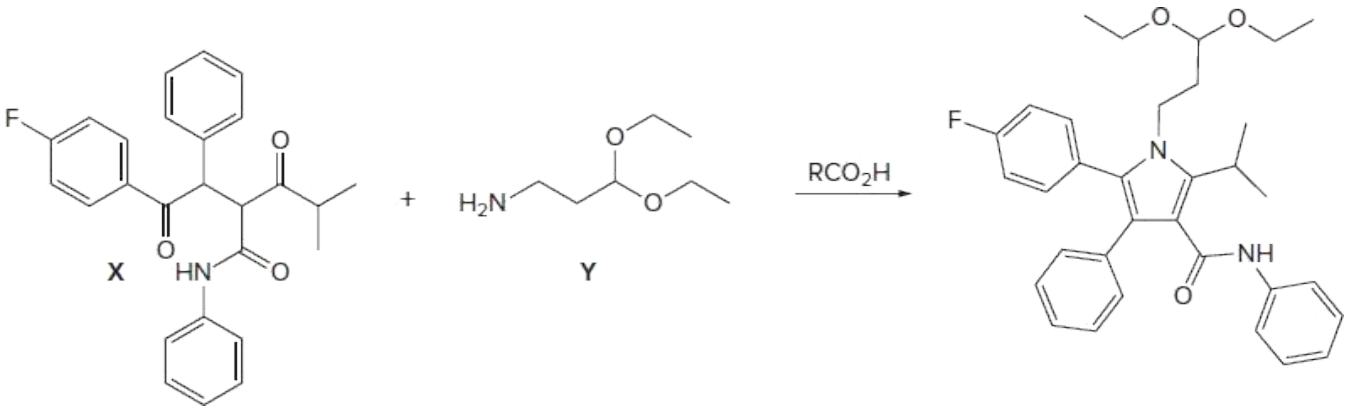
b.



23.63 Draw a stepwise mechanism for the following reaction.

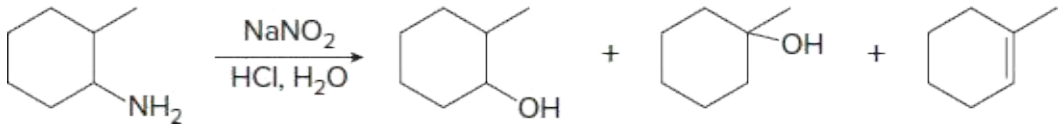


23.64 One synthesis of the cholesterol-lowering drug atorvastatin (trade name Lipitor, Section 29.8, Problem 21.52) involves the construction of the pyrrole by reaction of diketone X with amine Y. Draw a stepwise mechanism for this reaction.



23.65 Alkyl diazonium salts decompose to form carbocations, which go on to

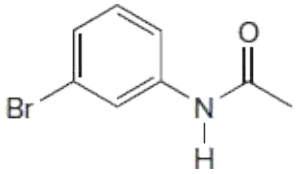
form products of substitution, elimination, and (sometimes) rearrangement. Keeping this in mind, draw a stepwise mechanism that forms all of the following products.



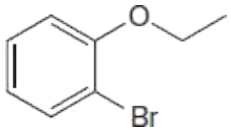
Synthesis

23.66 Devise a synthesis of each compound from benzene. You may use alcohols with one or two carbons and any inorganic reagents.

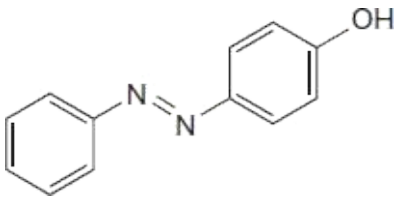
a.



b.

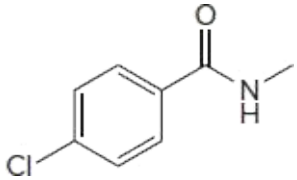


c.



23.67 Devise a synthesis of each compound from aniline ($C_6H_5NH_2$) as starting material.

a.



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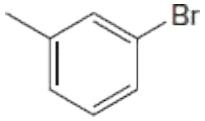

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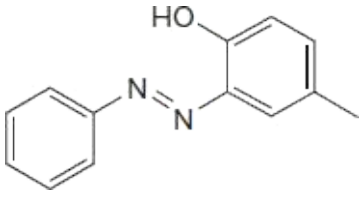


23.68 Devise at least three different methods to prepare *N*-methylbenzylamine ($PhCH_2NHCH_3$) from benzene, any one-carbon organic compounds, and any required reagents.

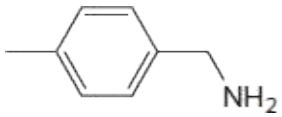
23.69 Safrole, which is isolated from sassafras (Problem 18.30), can be converted to the illegal stimulant MDMA (3,4-methylenedioxymethamphetamine, "Ecstasy") by a variety of methods. (a) Devise a synthesis that begins with safrole and uses a nucleophilic

substitution reaction to introduce the amine. (b) Devise a synthesis that begins with safrole and uses reductive amination to introduce the amine.

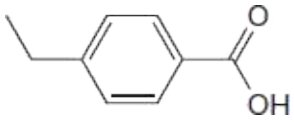
MDMA safrole

23.70 Synthesize each compound from benzene. Use a diazonium salt as one of the synthetic intermediates.

a.



b.



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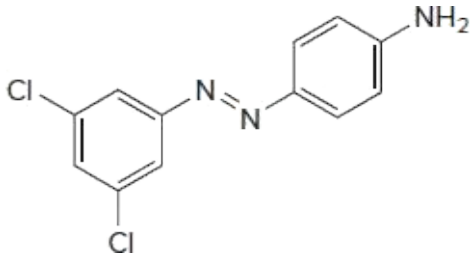
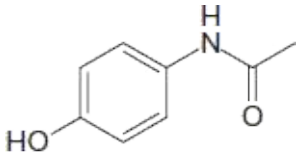


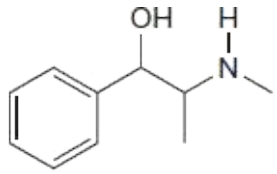
23.71 Devise a synthesis of each biologically active compound from benzene.

a.



acetaminophen
(analgesic)

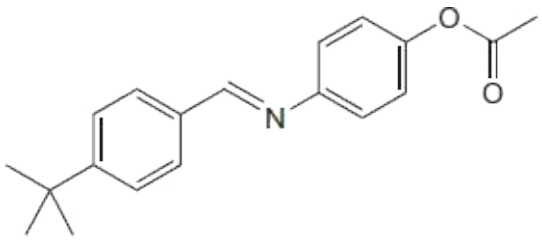
b.



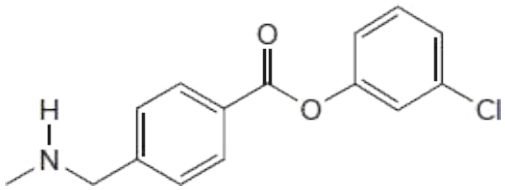
pseudoephedrine
(nasal decongestant)

23.72 Devise a synthesis of each compound from benzene, any organic alcohols having four or fewer carbons, and any required reagents.

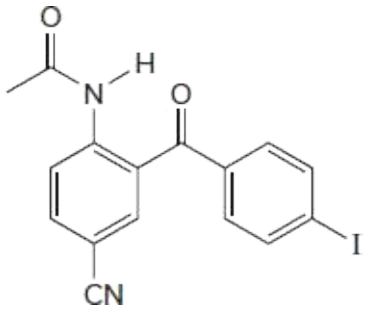
a.



b.



c.



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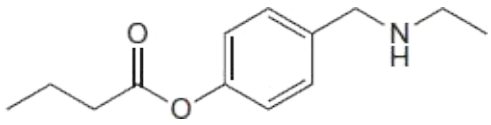
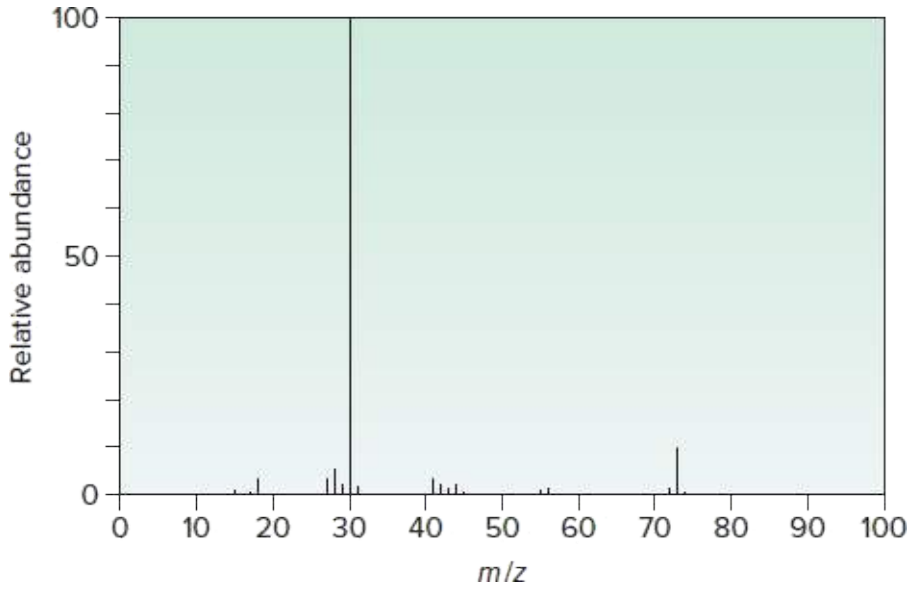


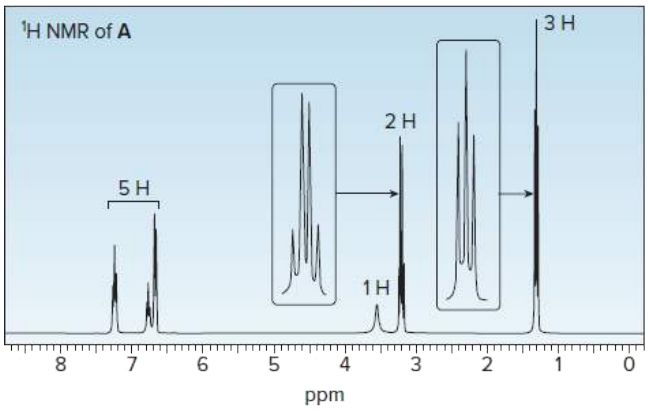
Spectroscopy

23.73 Identify the parent and propose a structure for the base peak in the mass spectrum of butan-1-amine.

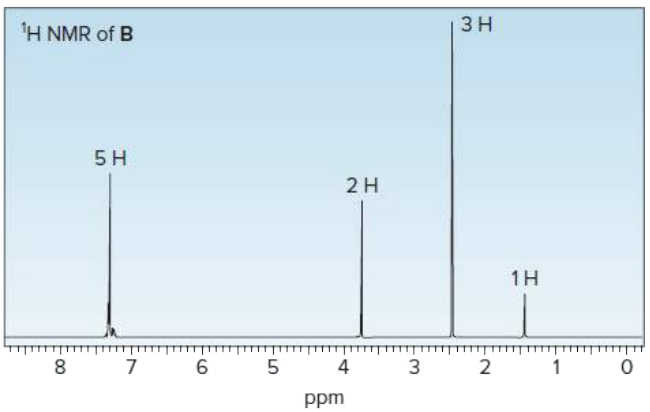


23.74 Three isomeric compounds, A, B, and C, all have molecular formula $C_8H_{11}N$. The ^1H NMR and IR spectral data of A, B, and C are given below. What are their structures?

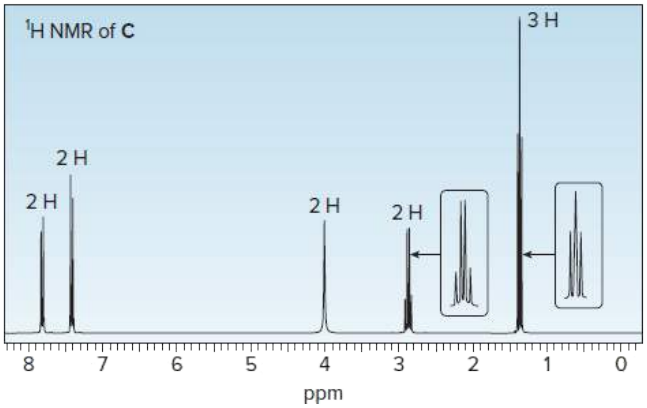
Compound **A:** IR peak at 3400 cm^{-1}



Compound **B:** IR peak at 3310 cm^{-1}

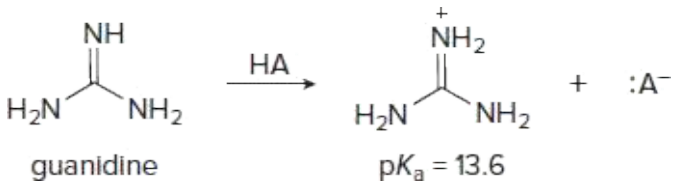


Compound **C:** IR peaks at 3430 and 3350 cm^{-1}



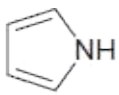
Challenge Problems

23.75 The pK_a of the conjugate acid of guanidine is 13.6, making it one of the strongest neutral organic bases. Offer an explanation.

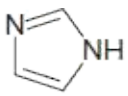


guanidine $pK_a = 13.6$

23.76 Rank the following compounds in order of increasing basicity and explain the order you chose.



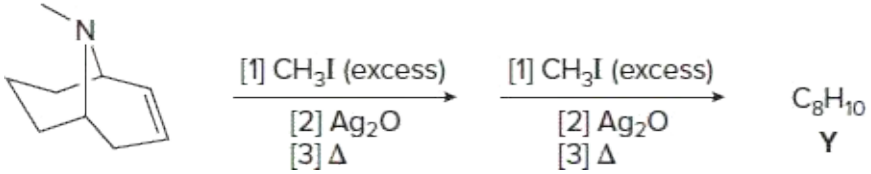
pyrrole



imidazole

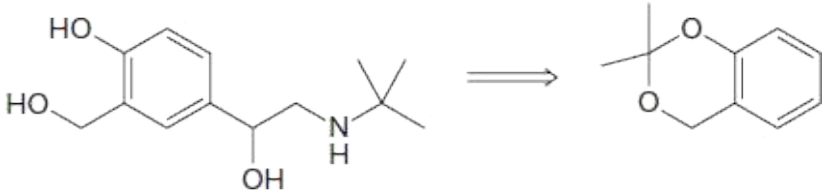
thiazole

23.77 Draw the product Y of the following reaction sequence. Y was an intermediate in the remarkable synthesis of cyclooctatetraene by Richard Willstatter in 1911.



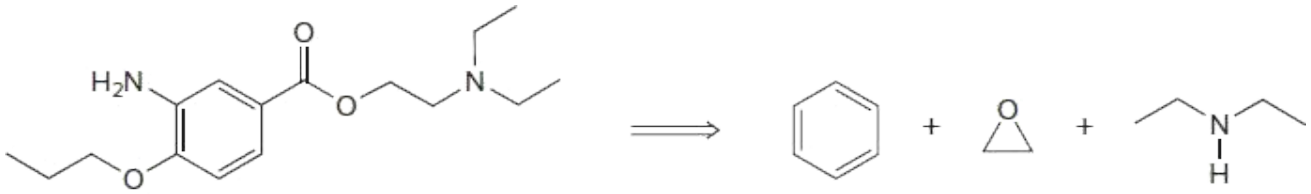
23.78 Devise a synthesis of each compound from the given starting material(s). Albuterol is a bronchodilator and proparacaine is a local anesthetic.

a.



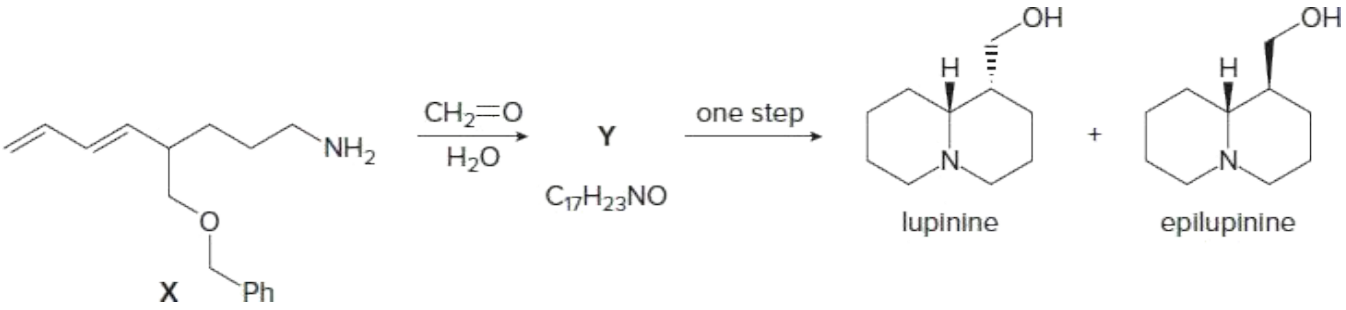
albuterol

b.



proparacaine

23.79 Heating compound X with aqueous formaldehyde forms Y ($C_{17}H_{23}NO$), which has been converted to a mixture of lupinine and epilupinine, alkaloids isolated from lupin, a perennial ornamental plant commonly seen on the roadside in parts of Alaska (Chapter 23 opener). Identify Y and explain how it is formed.



Carbon–Carbon Bond-Forming Reactions in Organic Synthesis

24

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24.1 Coupling reactions of organocuprate reagents
24.2 Suzuki reaction
24.3 Heck reaction
24.4 Carbenes and cyclopropane synthesis
24.5 Simmons–Smith reaction
24.6 Metathesis

Ingenol mebutate is an ester derived from ingenol, a natural product obtained from the sap of *Euphorbia peplus*, a type of milkweed native to Europe, northern Africa, and western Asia. Because ingenol derivatives exhibited useful biological activity and isolation from the natural source did not provide easy access to the material, scientists developed an efficient laboratory synthesis. A gel formulation of ingenol mebutate (trade name Picato) has been approved for the treatment of actinic keratosis, a skin condition resulting from over-exposure to the sun that may result in squamous cell carcinoma, a form of skin cancer. In Chapter 24, we learn about carbon–carbon bond-forming reactions that prepare complex compounds like ingenol.

Why Study…

Reactions That Form Carbon–Carbon Bonds?

To form the carbon skeletons of complex molecules, organic chemists need an extensive repertoire of carbon–carbon bond-forming reactions. In Chapter 17, for example, we learned about the reactions of organometallic reagents—organolithium reagents, Grignard reagents, and organocuprates—with carbonyl substrates. In Chapters 21 and 22, we studied the reactions of nucleophilic enolates that form new carbon–carbon bonds.

Chapter 24 presents more carbon–carbon bond-forming reactions that are especially useful tools in organic synthesis. Whereas previous chapters have concentrated on the reactions of one or two functional groups, the reactions in this chapter utilize a variety of starting materials and conceptually different reactions that form many types of

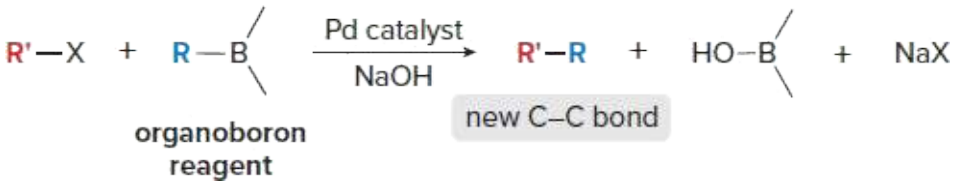
products. All follow one central theme: they form new carbon–carbon bonds under mild conditions, making them versatile synthetic methods.

24.1 Coupling Reactions of Organocuprate Reagents

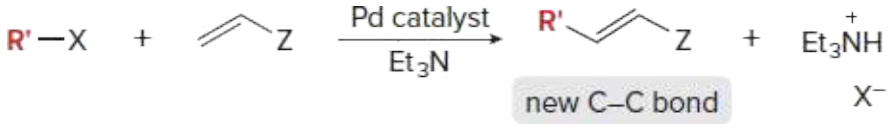
Several carbon–carbon bond-forming reactions involve the coupling of an organic halide (R′X) with an organometallic reagent or alkene. Three useful reactions are discussed in Sections 24.1–24.3:

[1] Reaction of an organic halide with an organocuprate reagent (Section 24.1)

[2] Suzuki reaction: Reaction of an organic halide with an organoboron reagent in the presence of a palladium catalyst (Section 24.2)



[3] Heck reaction: Reaction of an organic halide with an alkene in the presence of a palladium catalyst (Section 24.3)



A complete list of reactions that form C–C bonds appears in Appendix F.

24.1A General Features of Organocuprate Coupling Reactions

In addition to their reactions with acid chlorides, epoxides, and α,β-unsaturated carbonyl compounds (Sections 17.13–17.15), organocuprate reagents (R_2CuLi) also react with organic halides R′–X to form coupling products R–R′ that contain a new C–C bond. Only one R group of the organocuprate is transferred to form the product, while the other becomes part of RCu, a reaction by-product.

A variety of organic halides can be used, including methyl and 1° alkyl halides, as well as vinyl and aryl halides that contain X bonded to an sp^2 hybridized carbon. Some cyclic 2° alkyl halides give reasonable yields of product, but 3° alkyl halides are too sterically hindered. The halogen X in R′X may be Cl, Br, or I.

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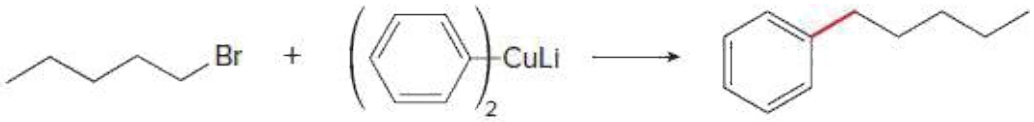
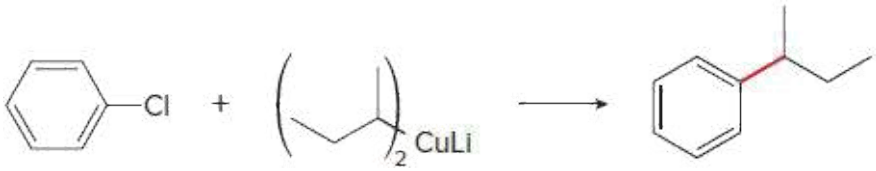
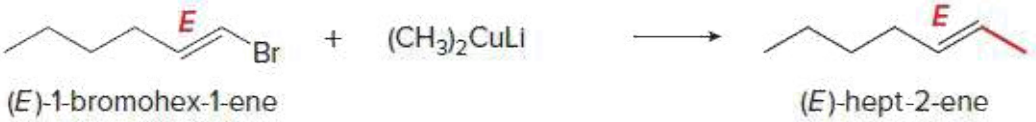
[1]



[2]



[3]



(*E*)-1-bromohex-1-ene (*E*)-hept-2-ene

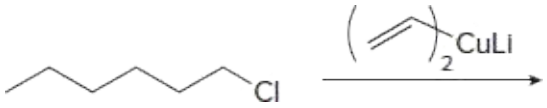
new C–C bonds in red

Coupling reactions with vinyl halides are stereospecific. For example, reaction of (*E*)-1-bromohex-1-ene with $(CH_3)_2CuLi$ forms (*E*)-hept-2-ene as the only stereoisomer (Equation [3]).

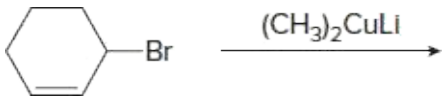
Problem 24.1

Draw the product of each coupling reaction.

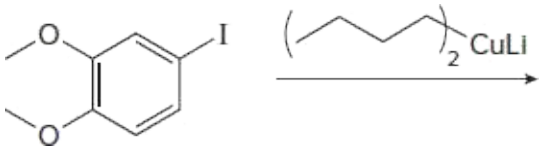
a.



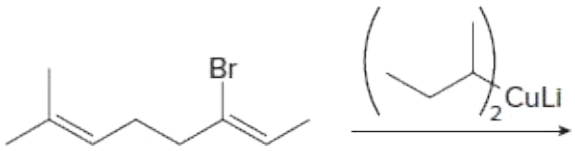
b.



c.

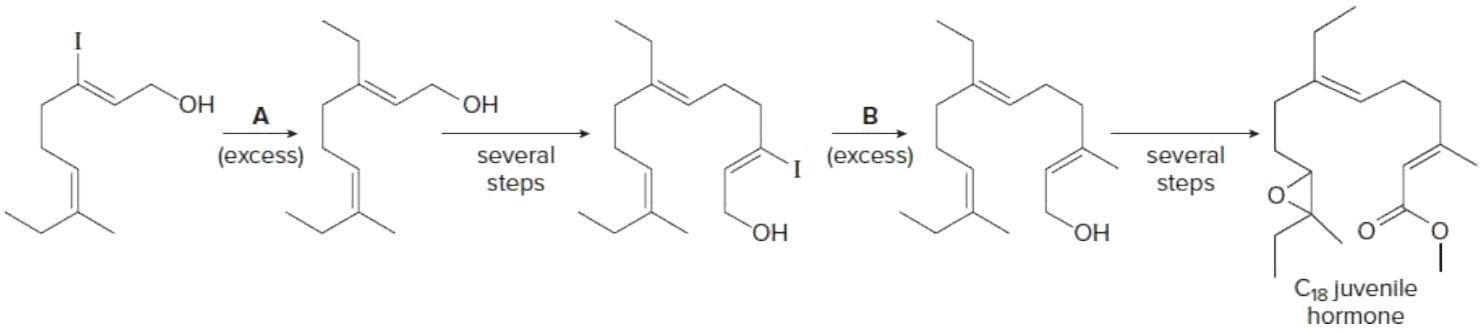


d.



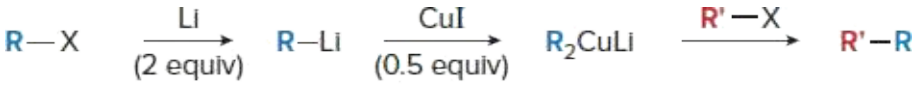
Problem 24.2

Identify reagents A and B in the following reaction scheme. This synthetic sequence was used to prepare the C_{18} juvenile hormone (Figure 17.6).



24.1B Using Organocuprate Couplings to Synthesize Hydrocarbons

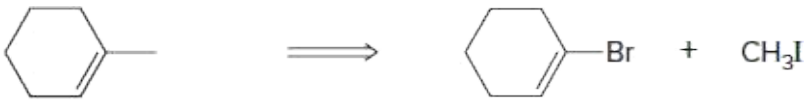
Because organocuprate reagents (R_2CuLi) are prepared in two steps from alkyl halides (RX), this method ultimately converts two organic halides (RX and R′X) to a hydrocarbon R–R′ with a new carbon–carbon bond. A hydrocarbon can often be made by two different routes, as shown in Sample Problem 24.1.



Two organic halides are needed as starting materials.

Sample Problem 24.1 Using an Organocuprate Coupling to Prepare a Hydrocarbon

Devise a synthesis of 1-methylcyclohexene from 1-bromocyclohexene and CH_3I.

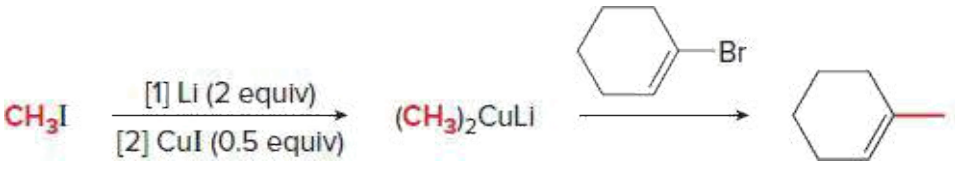


1-methylcyclohexene 1-bromocyclohexene

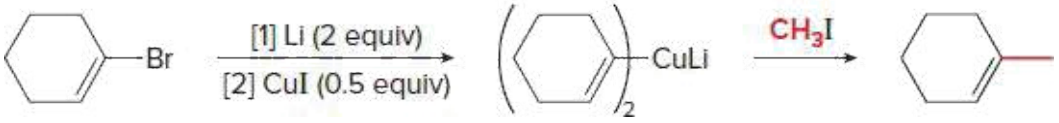
Solution

In this example, either halide can be used to form an organocuprate, which can then be coupled with the second halide.

Possibility [1]



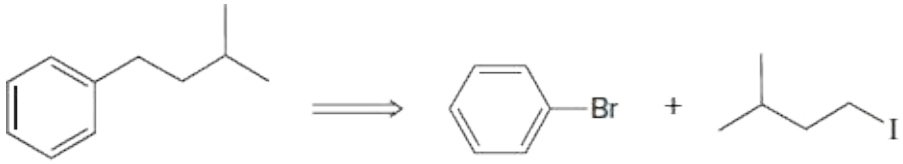
Possibility [2]



Problem 24.3

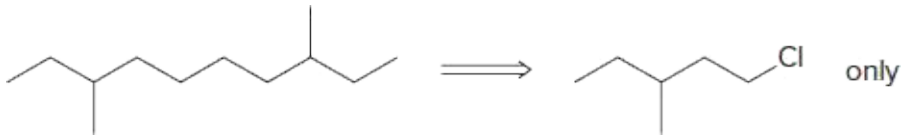
Synthesize each product from the given starting materials using an organocuprate coupling reaction.

a.



b.

c.



More Practice:

Try Problems 24.23, 24.26.

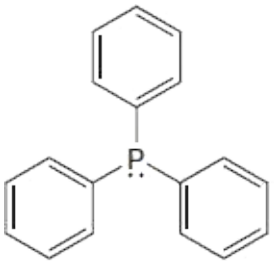
The mechanism of this reaction may vary with the identity of R′ in R′–X. Coupling occurs with organic halides having the halogen X on either an sp^3 or sp^1 hybridized carbon, so an S_N2 mechanism cannot explain all the observed results.

24.2 Suzuki Reaction

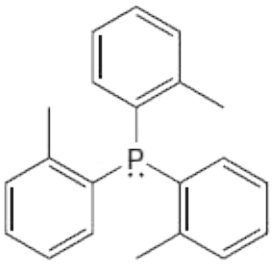
The Suzuki reaction is the first of two reactions that utilize a palladium catalyst and proceed by way of an intermediate organopalladium compound. The second is the Heck reaction (Section 14.3).

24.2A General Features of Reactions with Pd Catalysts

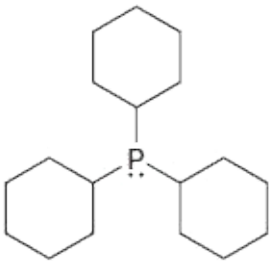
Reactions with palladium compounds share many common features with reactions involving other transition metals. During a reaction, palladium is coordinated to a variety of groups called ligands, which donate electron density to (or sometimes withdraw electron density from) the metal. A common electron-donating ligand is a phosphine, such as triphenylphosphine, tri(*o*-tolyl)phosphine, or tricyclohexylphosphine.



PPh_3
triphenylphosphine



$P(o\text{-tolyl})_3$
tri(*o*-tolyl)phosphine
abbreviated as **PAr_3**
Ar = an aryl group



PCy_3
tricyclohexylphosphine

A general ligand bonded to a metal is often designated as L. Pd bonded to four ligands is denoted as PdL_4.

Ac is the abbreviation for an acetyl group, $CH_3C{=}O$, so OAc (or ^-OAc) is the abbreviation for acetate, $CH_3CO_2^-$.

Organopalladium compounds—compounds that contain a carbon–palladium bond—are generally prepared in situ during the course of a reaction, from another palladium reagent such as $Pd(OAc)_2$ or $Pd(PPh_3)_4$. In most useful reactions, only a catalytic amount of palladium reagent is utilized.

Two common processes, called oxidative addition and reductive elimination, dominate many reactions of palladium compounds.

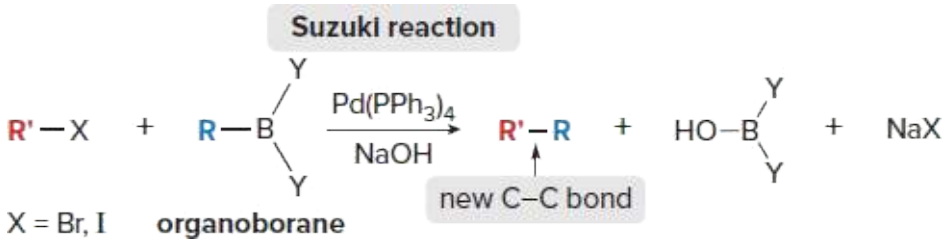
- ***Oxidative addition*** **is the addition of a reagent (such as RX) to a metal, often increasing the number of groups around the metal by two.**

- ***Reductive elimination*** **is the elimination of two groups that surround the metal, often forming new C–H or C–C bonds.**

Reaction mechanisms with palladium compounds are often multistep. During the course of a reaction, the identity of some groups bonded to Pd will be known with certainty, while the identity of other ligands might not be known. Consequently, only the crucial reacting groups around a metal are usually drawn and the other ligands are not specified.

24.2B Details of the Suzuki Reaction

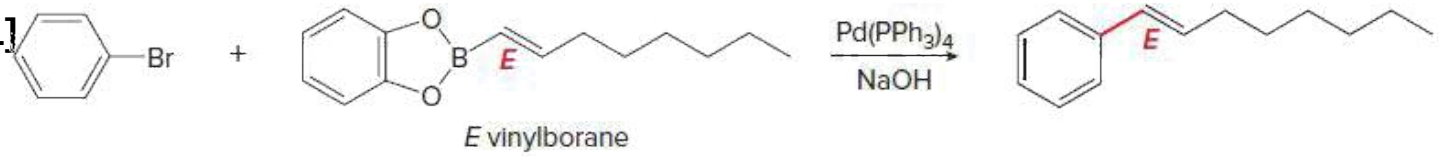
The Suzuki reaction is a palladium-catalyzed coupling of an organic halide (R′X) with an organoborane (RBY_2) to form a product (R–R′) with a new C–C bond. $Pd(PPh_3)_4$ is the typical palladium catalyst, and the reaction is carried out in the presence of a base such as NaOH or $NaOCH_2CH_3$.



Vinyl halides and aryl halides, both of which contain a halogen X bonded directly to an sp^2 hybridized carbon, are most often used, and the halogen is usually Br or I. The Suzuki reaction is completely stereospecific, as shown in Example [3]; a *Z* vinyl halide and an *E* vinylborane form a (*Z*, *E*)-1,3-diene.

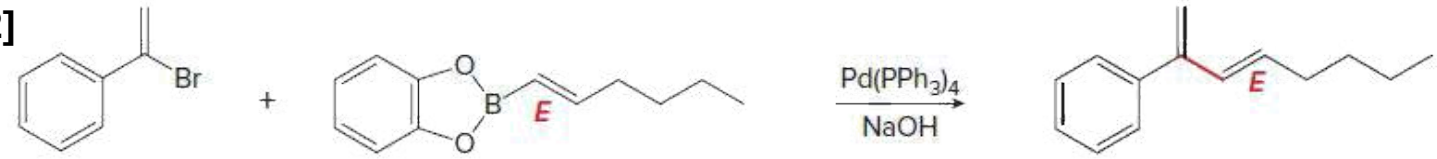
Page 1107

[1]



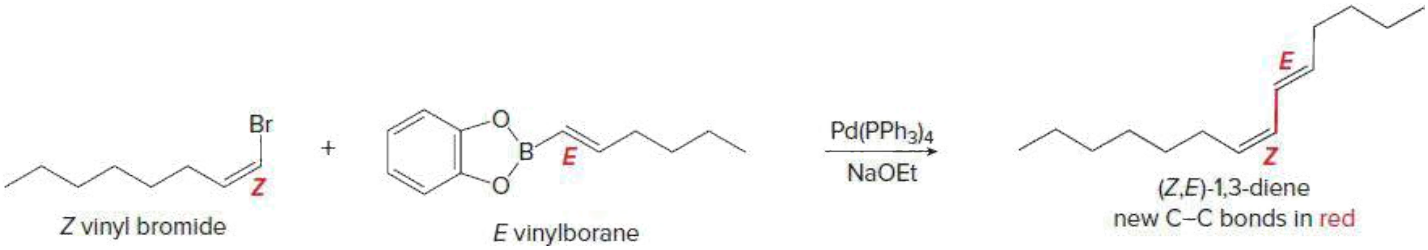
E vinylborane

[2]



E vinylborane

[3]



Z vinyl bromide

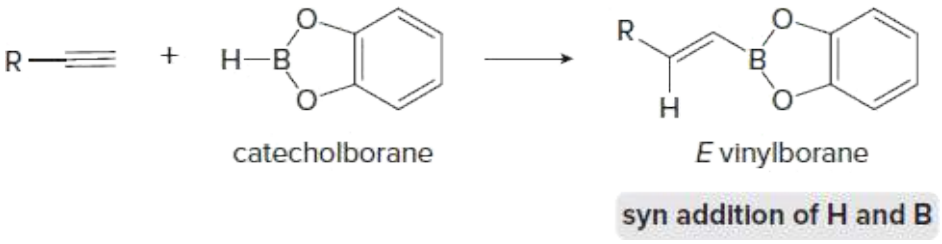
E vinylborane

(*Z*,*E*)-1,3-diene
new C–C bonds in red

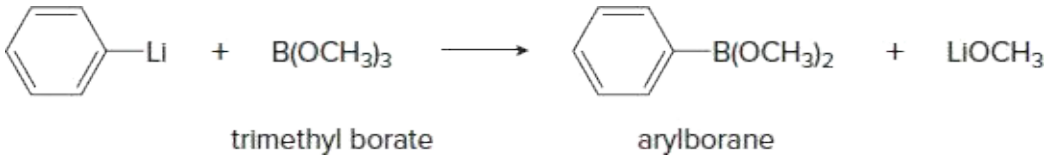
The organoboranes used in the Suzuki reaction are prepared from two sources.

- Vinylboranes, which have a boron atom bonded to a carbon–carbon double bond, are prepared by hydroboration of an alkyne using catecholborane, a commercially available reagent. Hydroboration adds the elements of H and B in a syn fashion to form an *E* vinylborane. With terminal alkynes, hydroboration

always places the boron atom on the *less substituted* terminal carbon.



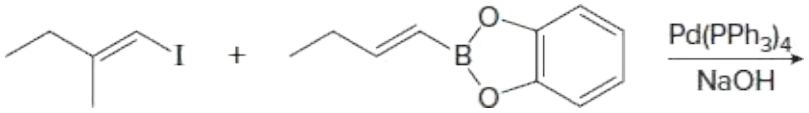
- Arylboranes, which have a boron atom bonded to a benzene ring, are prepared from organolithium reagents by reaction with trimethyl borate [$B(OCH_3)_3$].



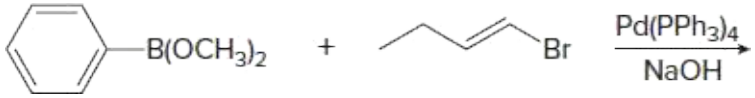
Problem 24.4

Draw the product of each reaction.

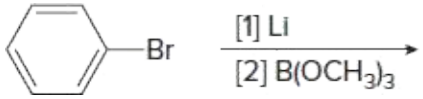
a.



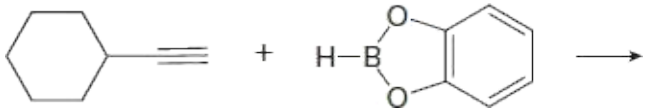
b.



c.



d.

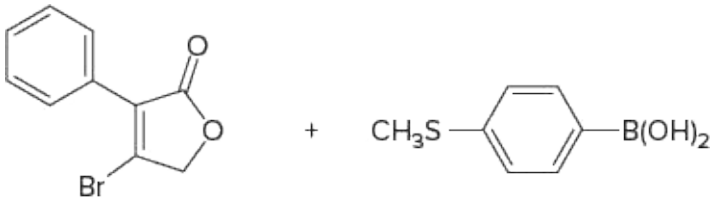


The structure of bombykol (Figure 24.1) the sex pheromone of the female silkworm moth *Bombyx mori*, was elucidated in 1959 using 6.4 mg of material obtained from 500,000 silkworm moths.

©Alon Meir/Alamy Stock Photo

Problem 24.5

One step in the synthesis of the nonsteroidal anti-inflammatory drug rofecoxib (trade name Vioxx) involves Suzuki coupling of A and B. What product is formed in this reaction?

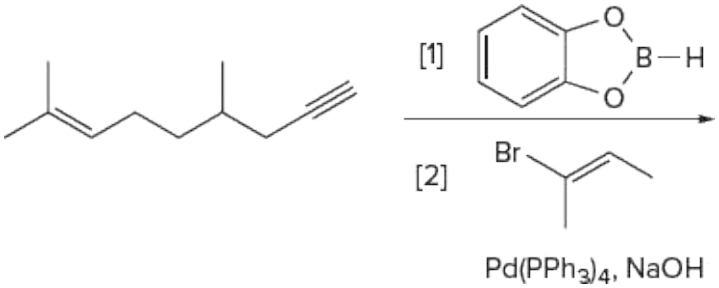


A **B**

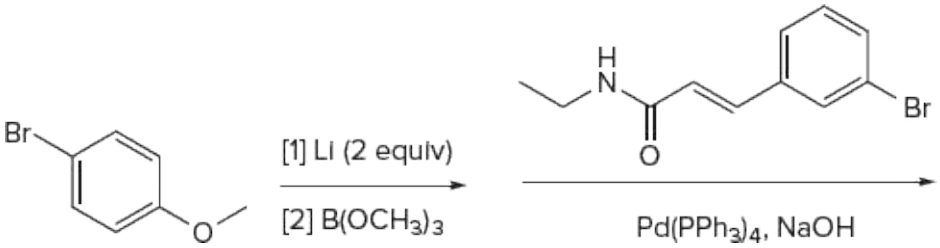
Problem 24.6

Draw the products formed in each reaction.

a.



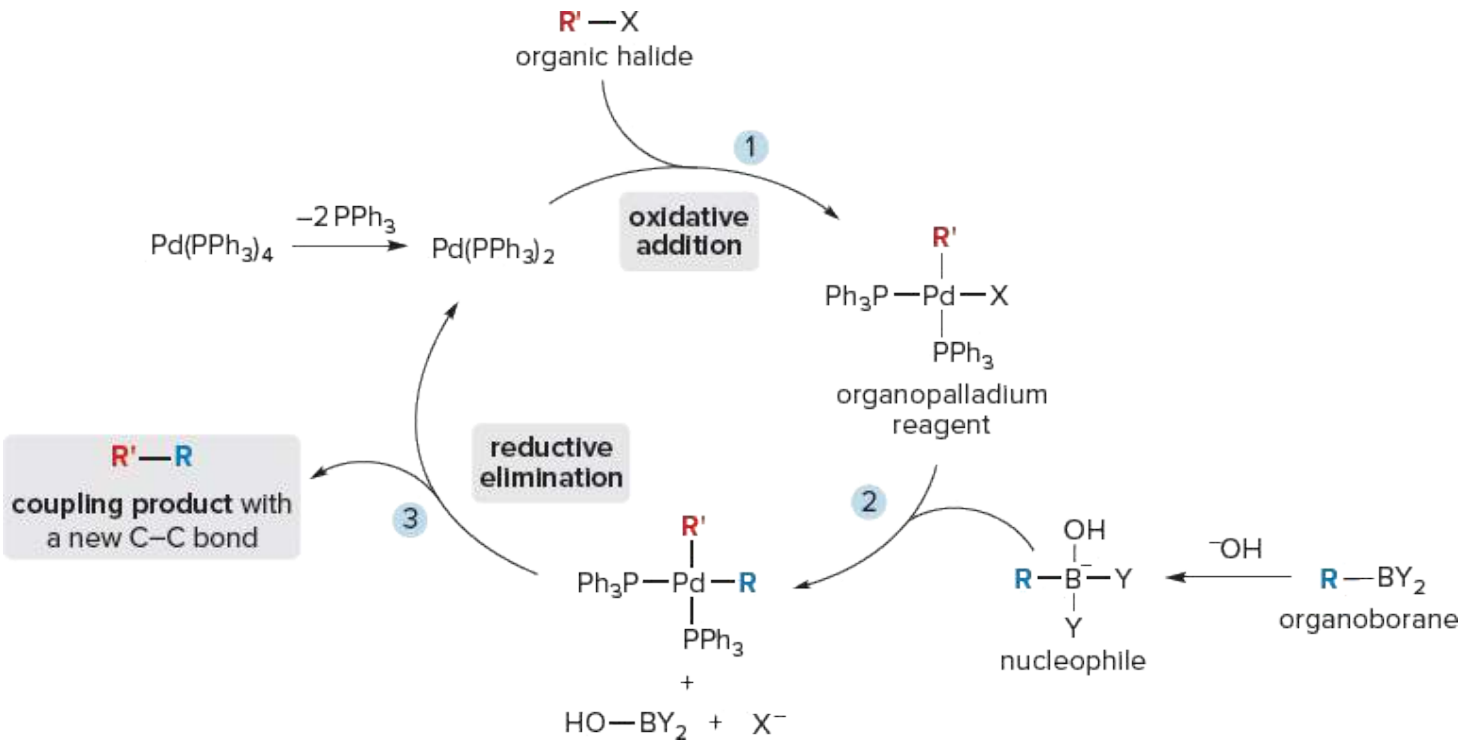
b.



The mechanism of the Suzuki reaction consists of oxidative addition of R′–X to the palladium catalyst, transfer of an alkyl group from the organoborane to palladium, and reductive elimination of R–R′, forming a new carbon–carbon bond. A general halide R′–X and organoborane R–BY_2 are used to illustrate this process in Mechanism 24.1. The mechanism is often written in a circle to emphasize that only a catalytic amount of palladium is needed, because the palladium reagent is regenerated during reductive elimination.

Page 1109

Mechanism 24.1 Suzuki Reaction



1. **Loss of two triphenylphosphine ligands from $Pd(PPh_3)_4$ forms $Pd(PPh_3)_2$, which undergoes oxidative addition of R′X to form an organopalladium reagent.**
2. **Reaction of the organoborane RBY_2 with ^-OH forms a nucleophilic boron intermediate that transfers an alkyl group from boron to palladium.**
3. **Reductive elimination of R′–R forms a new carbon–carbon bond, and the palladium catalyst $Pd(PPh_3)_2$ is regenerated.**

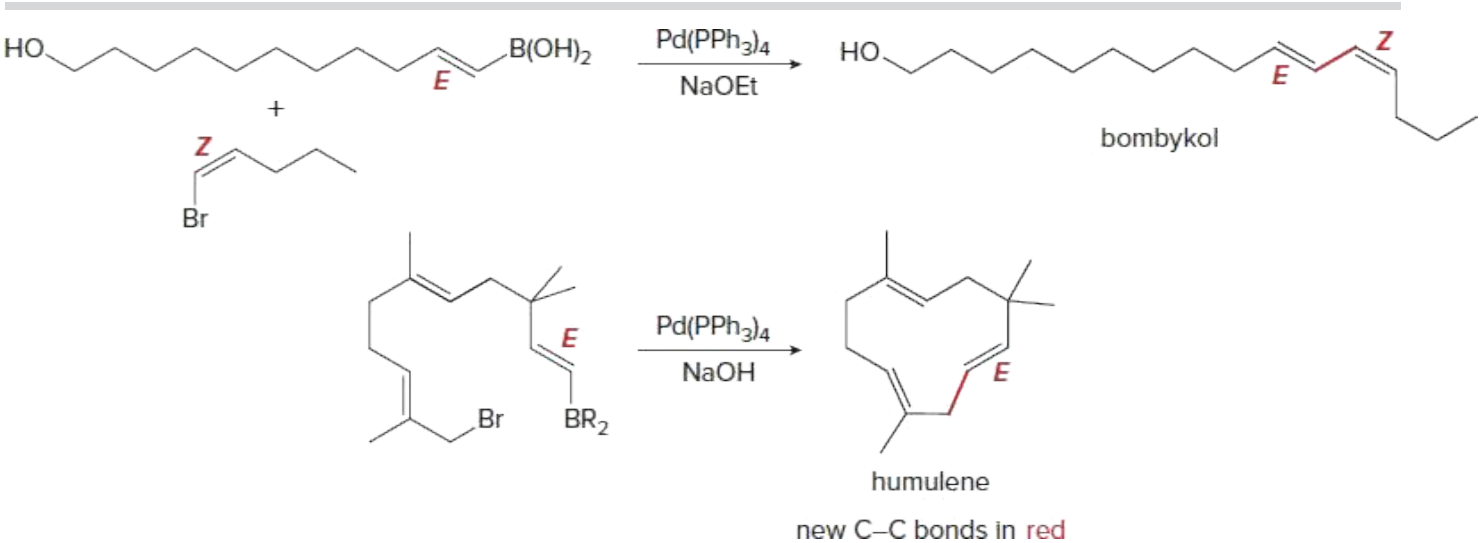


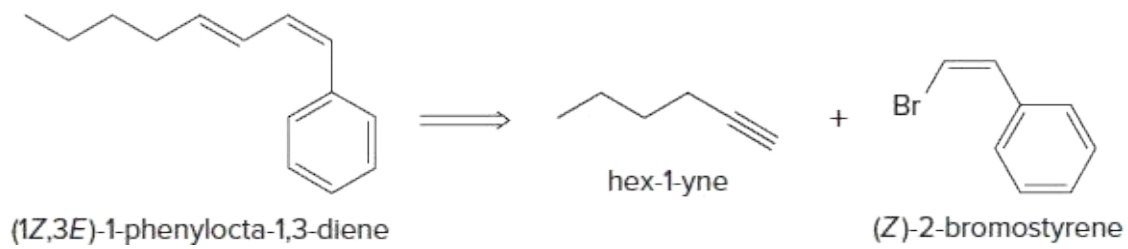
Figure 24.1 **Synthesis of two natural products using the Suzuki reaction**

The Suzuki reaction was a key step in the synthesis of bombykol, the sex pheromone of the female silkworm moth, and humulene, a lipid isolated from hops, as shown in Figure 14.1. The synthesis of humulene illustrates that an intramolecular Suzuki

reaction can form a ring. Sample Problem 14.1 shows how a conjugated diene can be prepared from an alkyne and vinyl halide using a Suzuki reaction.

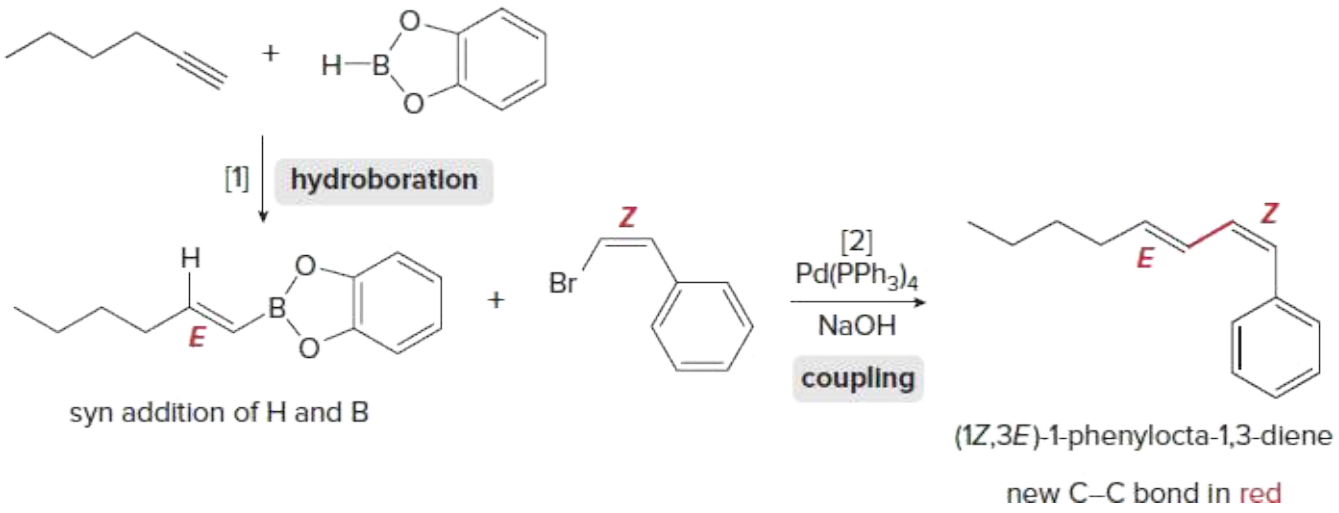
Sample Problem 24.2 Devising a Synthesis with a Suzuki Coupling

Devise a synthesis of (1*Z*,3*E*)-1-phenylocta-1,3-diene from hex-1-yne and (*Z*)-2-bromostyrene using a Suzuki coupling.



Solution

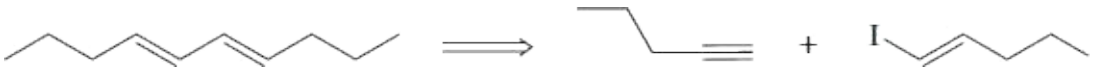
This synthesis can be accomplished in two steps. Hydroboration of hex-1-yne with catecholborane forms a vinylborane. Coupling of this vinylborane with (*Z*)-2-bromostyrene gives the desired 1,3-diene. The *E* configuration of the vinylborane and the *Z* configuration of the vinyl bromide are both *retained* in the product.



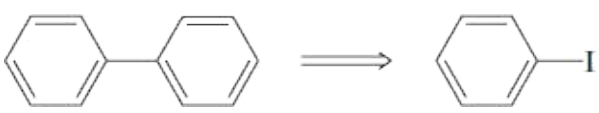
Problem 24.7

Synthesize each compound from the given starting materials.

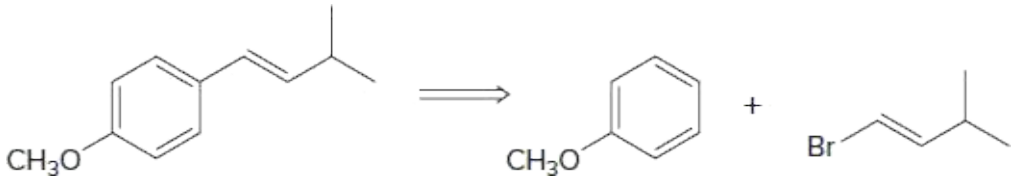
a.



b.



c.



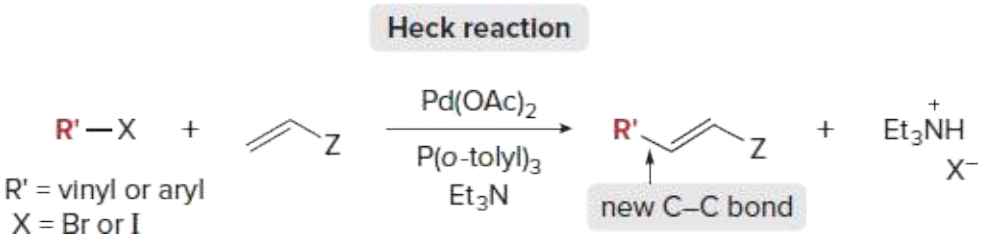
More Practice:

Try Problems 24.24, 24.47.

24.3 Heck Reaction

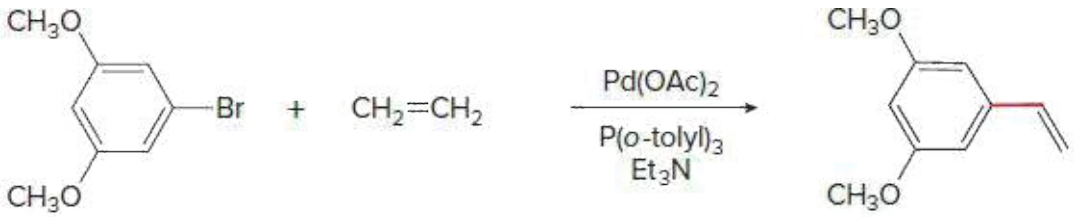
Richard Heck and Akira Suzuki won the 2010 Nobel Prize in Chemistry for the discovery of the carbon–carbon bond-forming reactions detailed in Sections 24.2 and 24.3.

The Heck reaction is a palladium-catalyzed coupling of a vinyl or aryl halide with an alkene to form a more highly substituted alkene with a new C–C bond. Palladium(II) acetate [$Pd(OAc)_2$] in the presence of a triarylphosphine [P(*o*-tolyl)$_3$] is the typical catalyst, and the reaction is carried out in the presence of a base such as triethylamine (Et_3N). The Heck reaction is a substitution reaction in which one H atom of the alkene starting material is replaced by the R′ group of the vinyl or aryl halide.

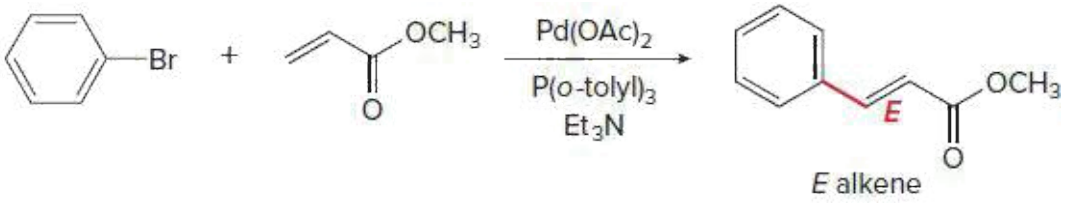


The alkene component is typically ethylene or a monosubstituted alkene (CH_2=CHZ), and the halogen X is usually Br or I. When Z = Ph, COOR, or CN in a monosubstituted alkene, the new C–C bond is formed on the *less* substituted carbon to afford a trans alkene. When a vinyl halide is used as the organic halide, the reaction is stereospecific, as shown in Example [3]; the *E* stereochemistry of the vinyl iodide is *retained* in the product.

[1]

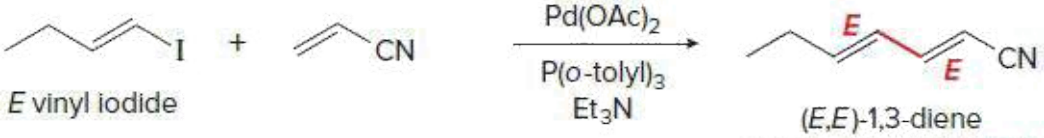


[2]



E alkene

[3]



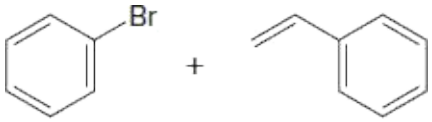
E vinyl iodide

(*E*,*E*)-1,3-diene
new C–C bonds in red

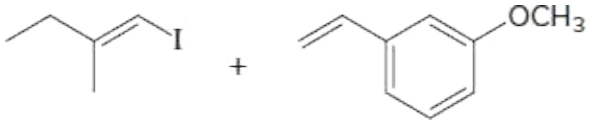
Problem 24.8

Draw the coupling product formed when each pair of compounds is treated with $Pd(OAc)_2$, P(*o*-tolyl)$_3$, and Et_3N.

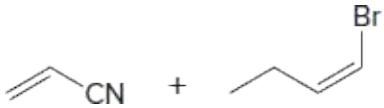
a.



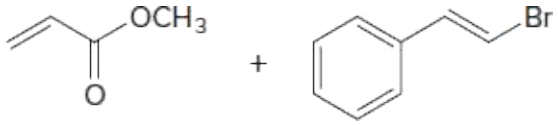
b.



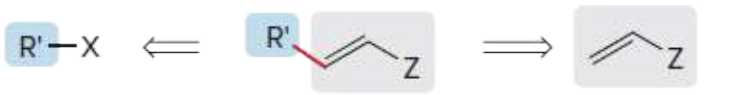
c.



d.



To use the Heck reaction in synthesis, you must determine what alkene and what organic halide are needed to prepare a given compound. To work backwards, locate the double bond with the aryl, COOR, or CN substituent, and break the molecule into two components at the end of the C=C *not* bonded to one of these substituents. Sample Problem 14.3 illustrates this retrosynthetic analysis.



vinyl or aryl halide

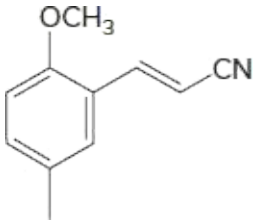
Heck reaction product

Z = Ph, CO_2R, CN

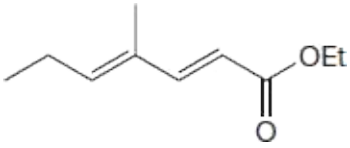
Sample Problem 24.3 Determining the Starting Materials Needed for a Heck Reaction

What starting materials are needed to prepare each alkene using a Heck reaction?

a.



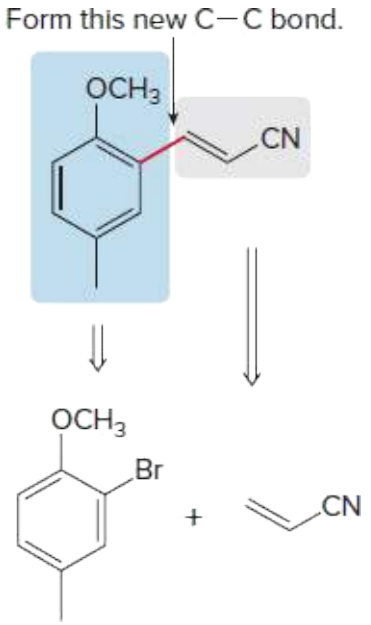
b.



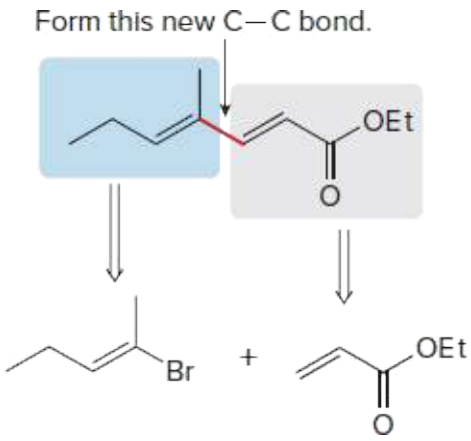
Solution

To prepare an alkene of general formula R′CH=CHZ by the Heck reaction, two starting materials are needed–an alkene (CH_2=CHZ) and a vinyl or aryl halide (R′X).

a.



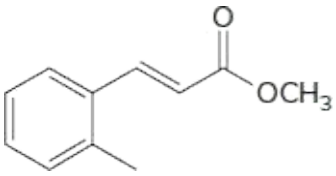
b.



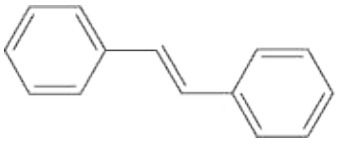
Problem 24.9

What starting materials are needed to prepare each compound using a Heck reaction?

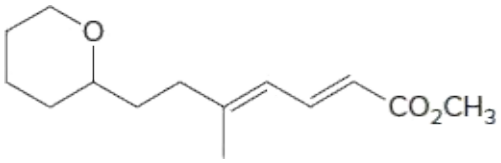
a.



b.



c.

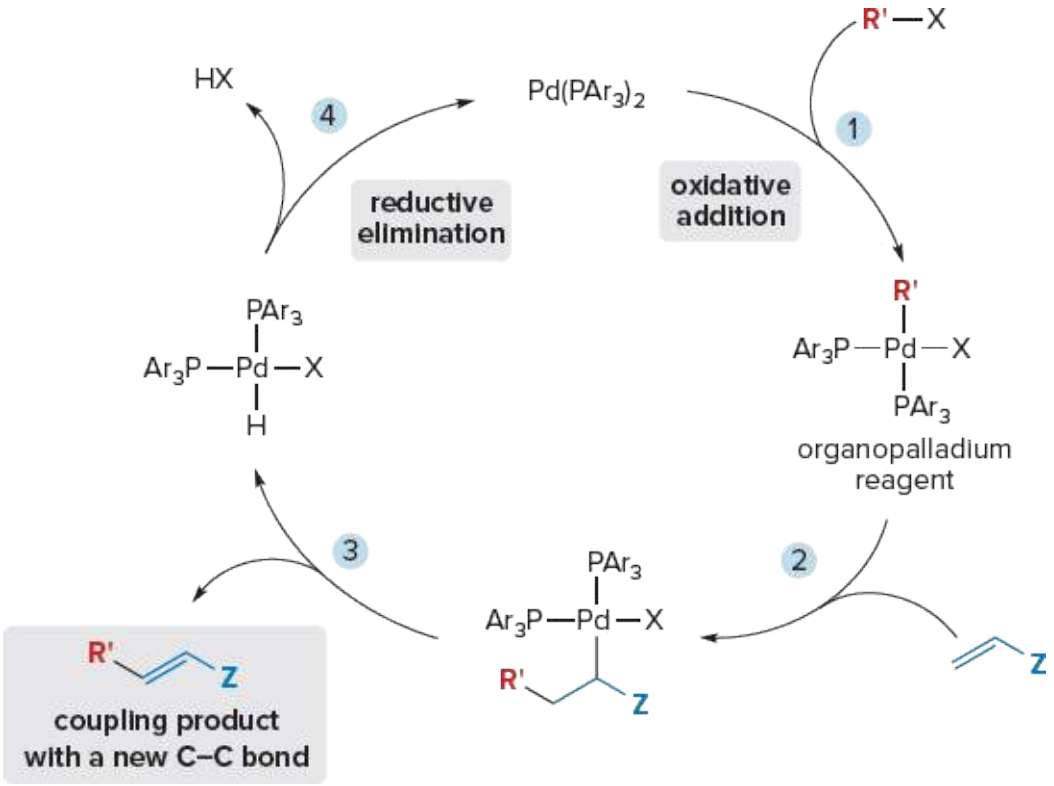


More Practice:

Try Problems 24.25, 24.49a.

The actual palladium catalyst in the Heck reaction is thought to contain a Page 1112 palladium atom bonded to two tri(*o*-tolyl)phosphine ligands, abbreviated as $Pd(PAr_3)_2$. In this way it resembles the divalent palladium catalyst used in the Suzuki reaction. The mechanism of the Heck reaction consists of oxidative addition of the halide R′X to the palladium catalyst, addition of the resulting organopalladium reagent to the alkene, and two successive eliminations. A general organic halide R′X and alkene CH_2=CHZ are used to illustrate the process in Mechanism 24.2, which is drawn in a circle to illustrate that the reaction is catalytic in palladium.

Mechanism 24.2 Heck Reaction

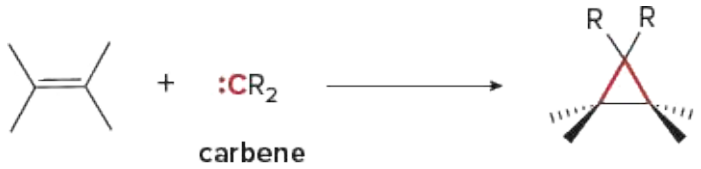


1. **Oxidative addition of R′X forms an organopalladium reagent.**
2. **Addition of R′ and Pd to the n bond of CH_2=CHZ places the Pd on the carbon with the Z substituent.**
3. **Elimination of H and Pd forms the π bond in the reaction product and transfers a hydrogen to Pd.**
4. **Reductive elimination of HX regenerates the palladium catalyst $Pd(PAr_3)_2$.**

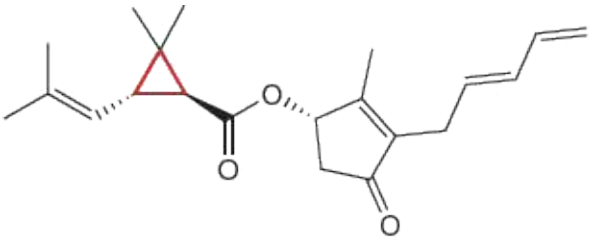
24.4 Carbenes and Cyclopropane Synthesis

Another method of carbon–carbon bond formation involves the conversion of alkenes to cyclopropane rings using carbene intermediates.

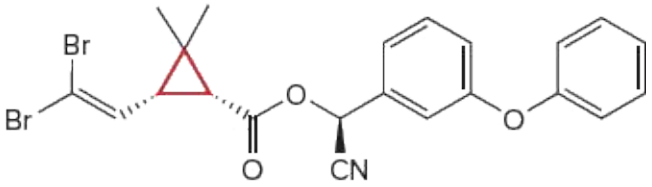
©McGraw-Hill Education/John Thoeming, photographer



Pyrethrin I and decamethrin both contain cyclopropane rings. Pyrethrin I is a naturally occurring biodegradable insecticide obtained from chrysanthemums, whereas decamethrin is a more potent synthetic analogue that is widely used as an insecticide in agriculture.



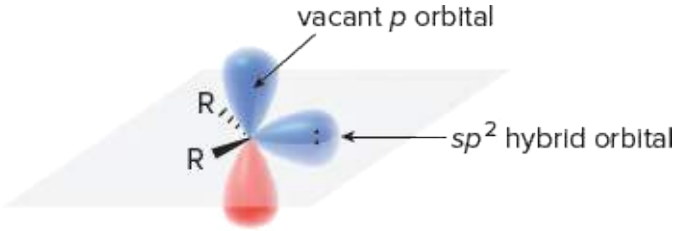
pyrethrin I



decamethrin

24.4A Carbenes

A *carbene*, R_2C:, is a neutral reactive intermediate that contains a divalent carbon surrounded by six electrons—the lone pair and two each from the two R groups. These three groups make the carbene carbon sp^2 hybridized, with a vacant *p* orbital extending above and below the plane containing the C and the two R groups. The lone pair of electrons occupies an sp^2 hybrid orbital.



The carbene carbon is sp^2 hybridized.

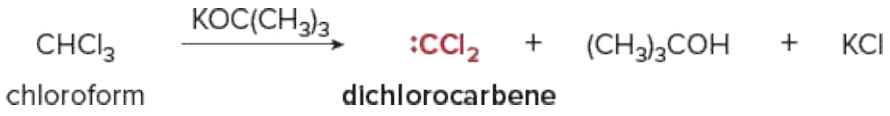
Carbenes share two features in common with carbocations and carbon radicals.

- **A carbene is highly reactive because carbon does not have an octet of electrons.**
- **A carbene is electron deficient, so it behaves as an electrophile.**

24.4B Preparation and Reactions of Dihalocarbenes

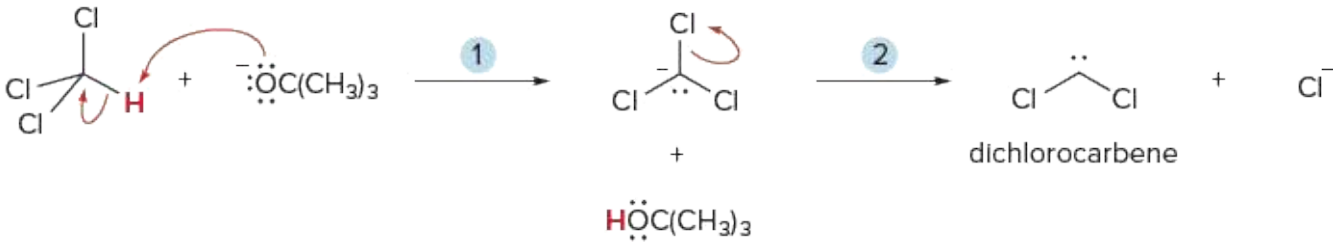
Dihalocarbenes, $:CX_1$, are especially useful reactive intermediates because they are readily prepared from trihalomethanes (CHX_3) by reaction with a strong base.

Treatment of chloroform, $CHCl_3$, with $KOC(CH_3)_3$ forms dichlorocarbene, $:CCl_1$.



Dichlorocarbene is formed by a two-step process that results in the elimination of the elements of H and Cl from the *same* carbon, as shown in Mechanism 14.3. Loss of two elements from the same carbon is called α elimination, to distinguish it from the β eliminations discussed in Chapter 8, in which two elements are lost from *adjacent* carbons.

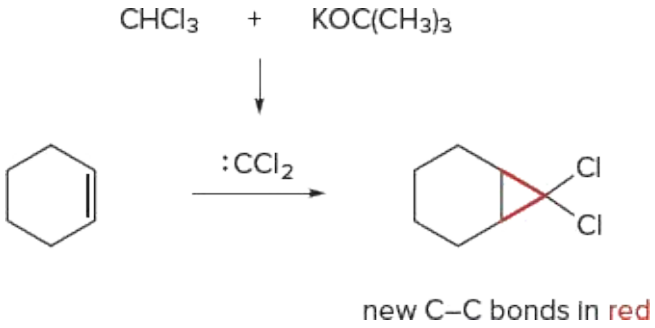
Mechanism 24.3 Formation of Dichlorocarbene



1 **Three electronegative Cl atoms acidify the C–H of $CHCl_3$, so it can be removed by strong base to form a carbanion.**

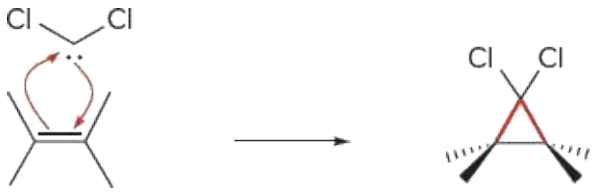
2 **Elimination of Cl^- forms the carbene.**

Dihalocarbenes are electrophiles, so they readily react with double bonds to afford cyclopropanes, forming two new carbon–carbon bonds.



Cyclopropanation is a concerted reaction, so both C–C bonds are formed in Page 1114 a single step, as shown in Mechanism 14.4.

Mechanism 24.4 Addition of Dichlorocarbene to an Alkene



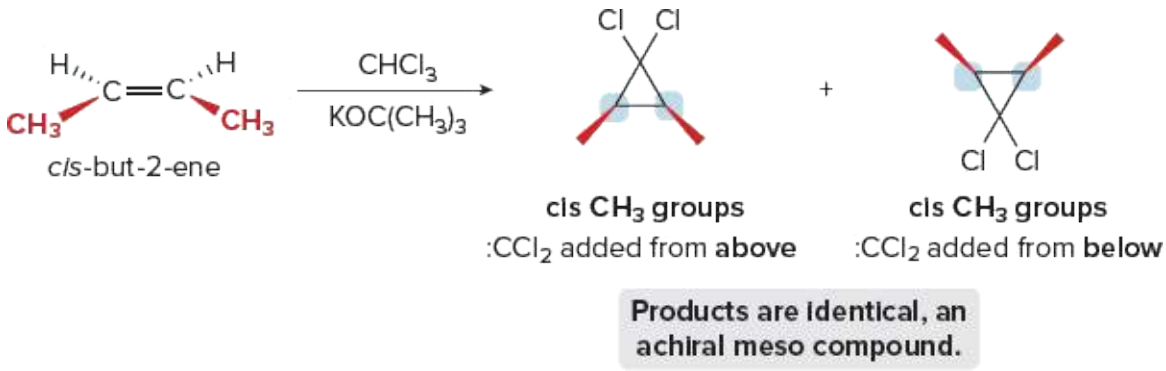
Carbene addition occurs in a syn fashion from either side of the planar double bond. The relative position of substituents in the alkene reactant is retained in the cyclopropane product. Carbene addition is thus a stereospecific reaction, because cis and trans alkenes yield different stereoisomers as products, as illustrated in Sample Problem 14.4.

Sample Problem 24.4 Drawing the Products of Carbene Addition

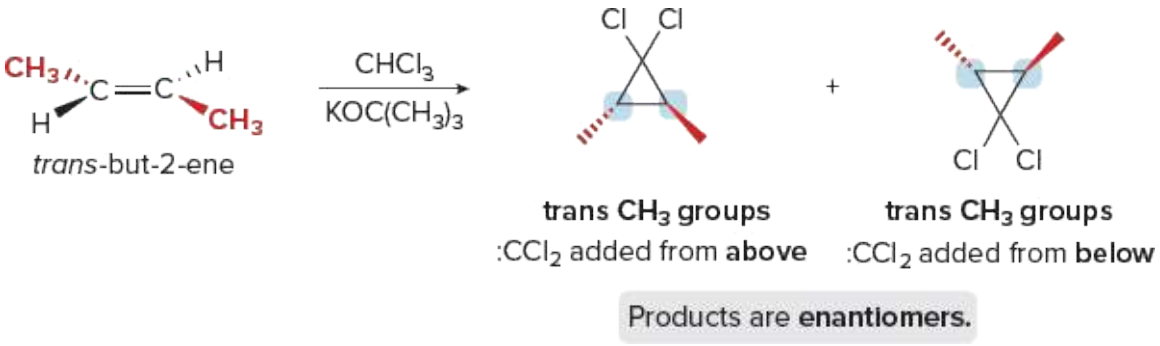
Draw the products formed when *cis*- and *trans*-but-2-ene are treated with $CHCl_3$ and $KOC(CH_3)_3$

Solution

To draw each product, add the carbene carbon from either side of the alkene, and keep all substituents in their original orientations. The cis methyl groups in *cis*-but-2-ene become cis substituents in the cyclopropane. Addition from either side of the alkene yields the same compound–an achiral meso compound that contains two stereogenic centers–labeled in blue.



The trans methyl groups in *trans*-but-2-ene become trans substituents in the cyclopropane. Addition from either side of the alkene yields an equal amount of two enantiomers–a racemic mixture.



Problem 24.10

Draw all stereoisomers formed when each alkene is treated with $CHCl_3$ and $KOC(CH_3)_3$.

a.

b.

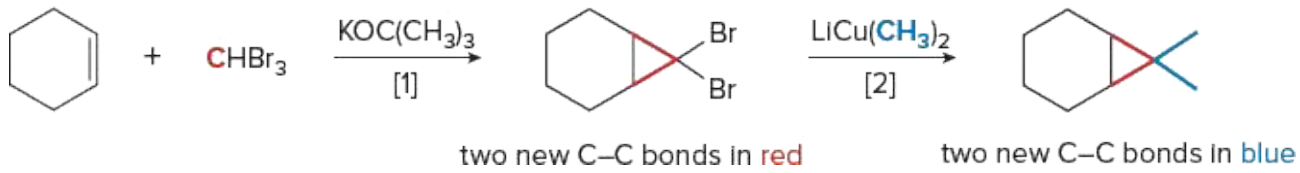
c.

More Practice:

Try Problems 24.30c, d; 24.39a.

Finally, *dihalo* cyclopropanes can be converted to *dialkyl* cyclopropanes by reaction with organocuprates (Section 14.1). For example, cyclohexene can be converted to a bicyclic product having four new C–C bonds by the following two-step sequence: cyclopropanation with dibromocarbene ($:CBr_2$) and reaction with lithium dimethylcuprate, $LiCu(CH_3)_2$.

Page 1115



Problem 24.11

What reagents are needed to convert 2-methylpropene $[(CH_3)_2C{=}CH_2]$ to each compound? More than one step may be required.

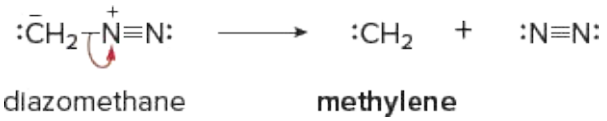
a.

b.

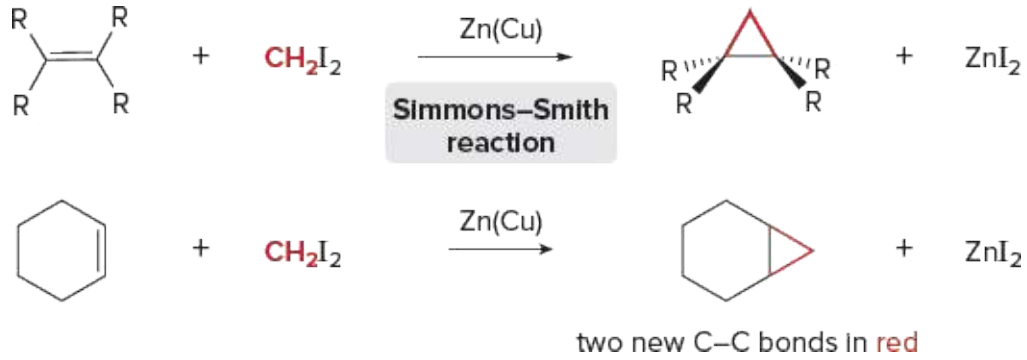
c.

24.5 Simmons–Smith Reaction

Although the reaction of dihalocarbenes with alkenes gives good yields of halogenated cyclopropanes, this is not usually the case with methylene, $:CH_2$, the simplest carbene. Methylene is readily formed by heating diazomethane, CH_1N_1, which decomposes and loses N_1, but the reaction of $:CH_1$ with alkenes often affords a complex mixture of products. Thus, this reaction cannot be reliably used for cyclopropane synthesis.

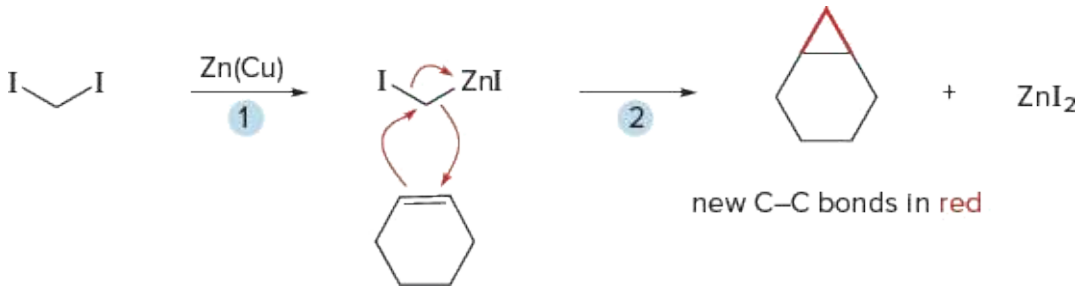


Nonhalogenated cyclopropanes can be prepared by the reaction of an alkene with diiodomethane, CH_2I_2, in the presence of a copper-activated zinc reagent called zinc–copper couple [Zn(Cu)]. This process, the Simmons–Smith reaction, is named for H. E. Simmons and R. D. Smith, DuPont chemists who discovered the reaction in 1959.



The Simmons–Smith reaction does not involve a free carbene. Rather, the reaction of CH_1I_1 with Zn(Cu) forms (iodomethyl)zinc iodide, which transfers a CH1 group to an alkene, as shown in Mechanism 14.5.

Mechanism 24.5 Simmons–Smith Reaction

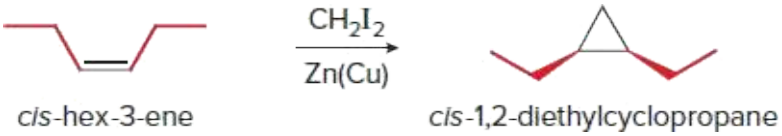


1 **Reaction of CH_2I_2 with zinc–copper couple forms ICH_2ZnI [(iodomethyl)zinc iodide], the Simmons–Smith reagent. This intermediate is called a *carbenoid*, because the CH_2 does not exist as a free carbene.**

2 **The Simmons–Smith reagent transfers a CH_2 to an alkene, forming two new C–C bonds.**

The Simmons–Smith reaction is stereospecific. The relative position of substituents in the alkene reactant is *retained* in the cyclopropane product, as shown for the conversion of *cis*-hex-3-ene to *cis*-1,2-diethylcyclopropane.

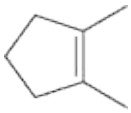
Page 1116



Problem 24.12

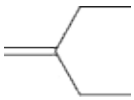
What product is formed when each alkene is treated with CH_2I_2 and Zn(Cu)?

a.



b.

c.



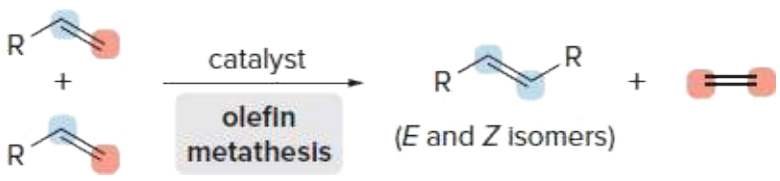
Problem 24.13

What stereoisomers are formed when trans-hex-3-ene is treated with CH_2I_2 and Zn(Cu)?

24.6 Metathesis

Recall from Section 10.1 that olefin is another name for an alkene.

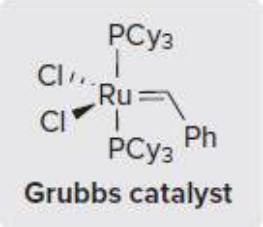
Alkene metathesis, more commonly called olefin metathesis, is a reaction between two alkene molecules that results in the interchange of the carbons of their double bonds. Two a and two π bonds are broken, and two new a and two new π bonds are formed.



24.6A General Features of Metathesis

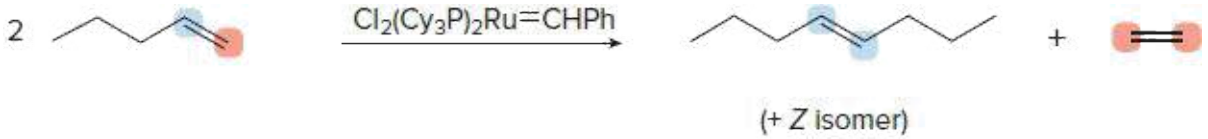
The word *metathesis* is derived from the Greek words *meta* (change) and *thesis* (position). The 2005 Nobel Prize in Chemistry was awarded to Robert Grubbs of the California Institute of Technology, Yves Chauvin of the Institut Français du Pétrole, and Richard Schrock of the Massachusetts Institute of Technology for their work on olefin metathesis.

Olefin metathesis occurs in the presence of a complex transition metal catalyst that contains a carbon–metal double bond. The metal is typically ruthenium (Ru), tungsten (W), or molybdenum (Mo). In a widely used catalyst, called Grubbs catalyst, the metal is Ru.

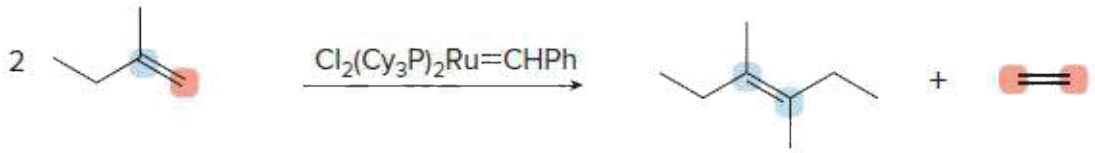


Grubbs catalyst

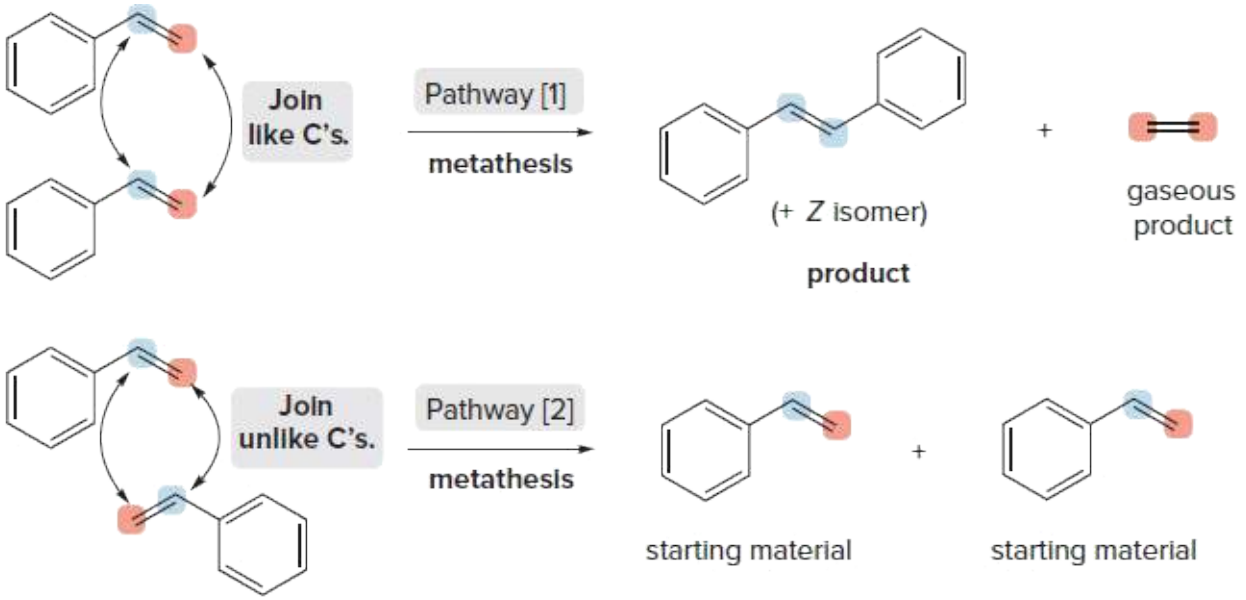
Olefin metathesis is an equilibrium process and, with many alkene substrates, a mixture of starting material and two or more alkene products is present at equilibrium, making the reaction useless for preparative purposes. With terminal alkenes, however, one metathesis product is $CH_2{=}CH_2$ (a gas), which escapes from the reaction mixture and drives the equilibrium to the right. As a result, monosubstituted alkenes ($RCH{=}CH_2$) and 2,2-disubstituted alkenes ($R_2C{=}CH_2$) are excellent metathesis substrates because high yields of a single alkene product are obtained, as shown in Equations [1] and [2].

[1] 

(+ *Z* isomer)

[2] 

(+ *Z* isomer)



- Overall reaction: **2 PhCH=CH_2 → PhCH=CHPh + CH_2=CH_2.**
- There are always two ways to join the C's of a single alkene to form metathesis products (Pathways [1] and [2]).
- When *like* C's of the alkene substrate are joined in the first reaction (Pathway [1]), PhCH=CHPh (in a cis and trans mixture) and CH_2=CH_2 are formed. Because CH_2=CH_2 escapes as a gas from the reaction mixture, only PhCH=CHPh is isolated as product.
- When *unlike* C's of PhCH=CH_2 are joined in the second reaction (Pathway [2]), starting material is formed, which can re-enter the catalytic cycle to form product by the first pathway.
- In this way, **a single constitutional isomer, PhCH=CHPh, is isolated.**

Figure 24.2 **Drawing the products of olefin metathesis using styrene (PhCH=CH_2) as starting material**

To draw the products of any metathesis reaction:

[1] Arrange two molecules of the starting alkene adjacent to each other as in Figure 24.2 where styrene (PhCH=CH_2) is used as the starting material.

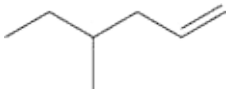
[2] Then, break the double bonds in the starting material and form two new double bonds using carbon atoms that were *not* previously bonded to each other in the starting alkenes.

There are always two ways to arrange the starting alkenes (Pathways [1] and [1] in Figure 14.1). In this example, the two products of the reaction, PhCH=CHPh and CH_1=CH_1, are formed in the first reaction pathway (Pathway [1]), whereas starting material is re-formed in the second pathway (Pathway [1]). Whenever the starting alkene is regenerated, it can go on to form product when the catalytic cycle is repeated.

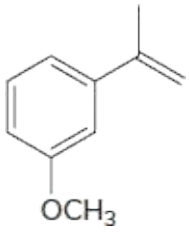
Problem 24.14

Draw the products formed when each alkene is treated with Grubbs catalyst.

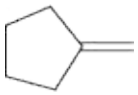
a.



b.



c.

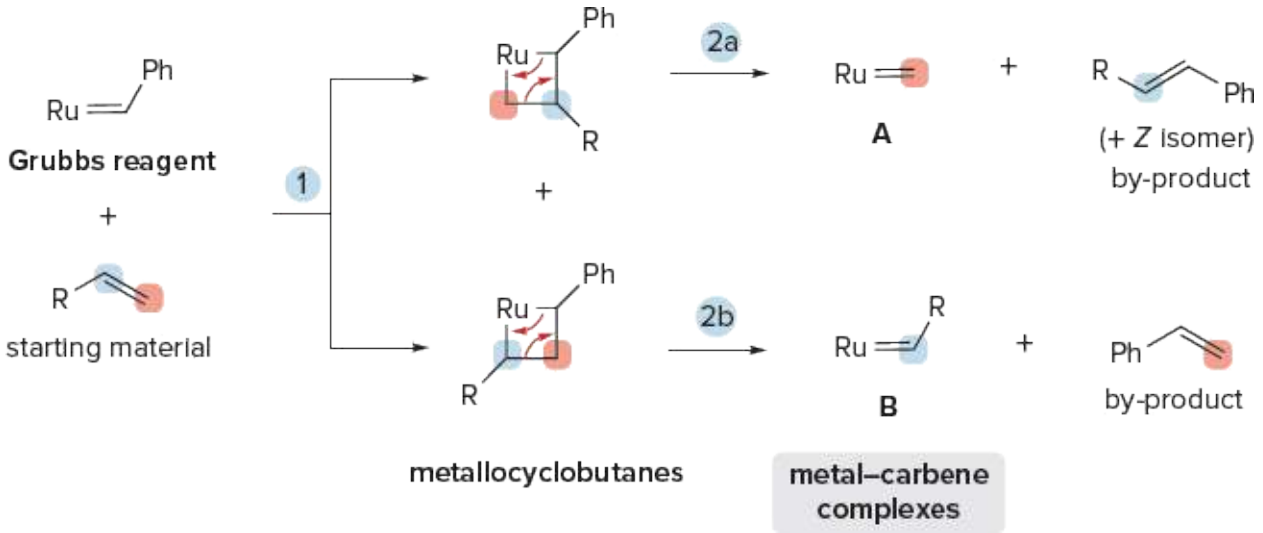


Problem 24.15

What products are formed when *cis*-pent-2-ene undergoes metathesis? Use this reaction to explain why metathesis of a 1,2-disubstituted alkene (RCH=CHR′) is generally not a practical method for alkene synthesis.

The mechanism for olefin metathesis is complex and involves metal–carbene intermediates—intermediates that contain a metal–carbon double bond. The mechanism is drawn for the reaction of a terminal alkene ($RCH{=}CH_1$) with Grubbs catalyst, abbreviated as Ru=CHPh, to form RCH=CHR and $CH_1{=}CH_1$. To begin metathesis, Grubbs catalyst reacts with the alkene substrate to form two new metal–carbenes A and B by a two-step process: addition of Ru=CHPh to the alkene to yield two different metallocyclobutanes (Step [1]), followed by elimination to form A and B (Steps [1a] and [1b]). The alkene by-products formed in this process (RCH=CHPh and $PhCH{=}CH_2$) are present in only a small amount because Grubbs reagent is used catalytically.

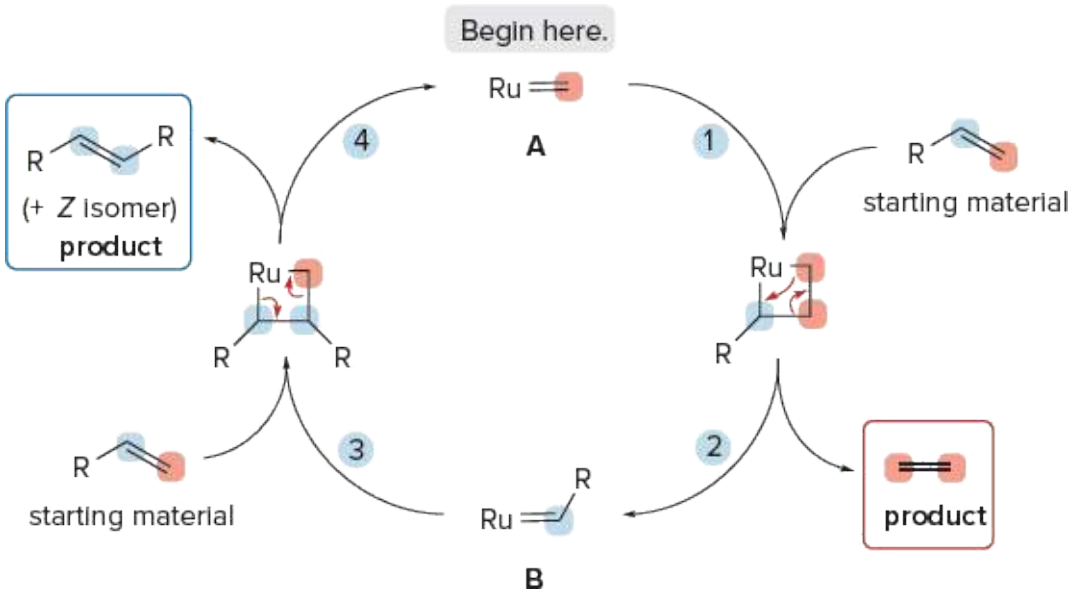
Page 1118



Each of these metal–carbene intermediates A and B then reacts with more starting

alkene to form metathesis products, as shown in Mechanism 24.6. As was seen in Mechanisms 24.1 and 24.2, this mechanism is often written in a circle to emphasize the catalytic cycle. The mechanism demonstrates how two molecules of $RCH{=}CH_2$ are converted to $RCH{=}CHR$ and $CH_2{=}CH_2$. The mechanism can be written beginning with reagent A or B, and all steps are equilibria.

Mechanism 24.6 Olefin Metathesis: 2 $RCH{=}CH_2$ → $RCH{=}CHR$ + $CH_2{=}CH_2$

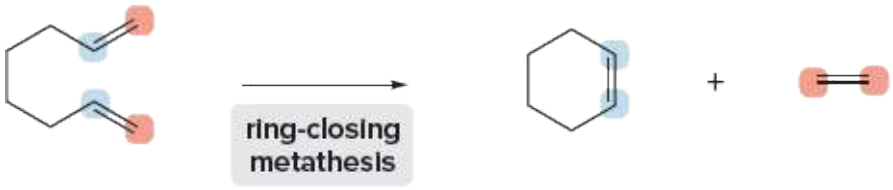


1. **Reaction of $Ru{=}CH_2$ (A) with $RCH{=}CH_2$ forms a metallocyclobutane. Ru can bond to either the more or less substituted end of the alkene, but product is formed only when Ru bonds to the *more* substituted end, as shown.**
2. **Elimination forms one metathesis product, $CH_2{=}CH_2$, and metal–carbene complex B.**
3. **Reaction of B with $RCH{=}CH_2$ forms a metallocyclobutane. Ru can bond to either the more or less substituted end of the alkene, but product is formed only when Ru bonds to the *less* substituted end, as shown.**
4. **Elimination forms the other metathesis product, $RCH{=}CHR$, and metal–carbene complex A. The catalyst is regenerated and the cycle begins again.**

24.6B Ring-Closing Metathesis

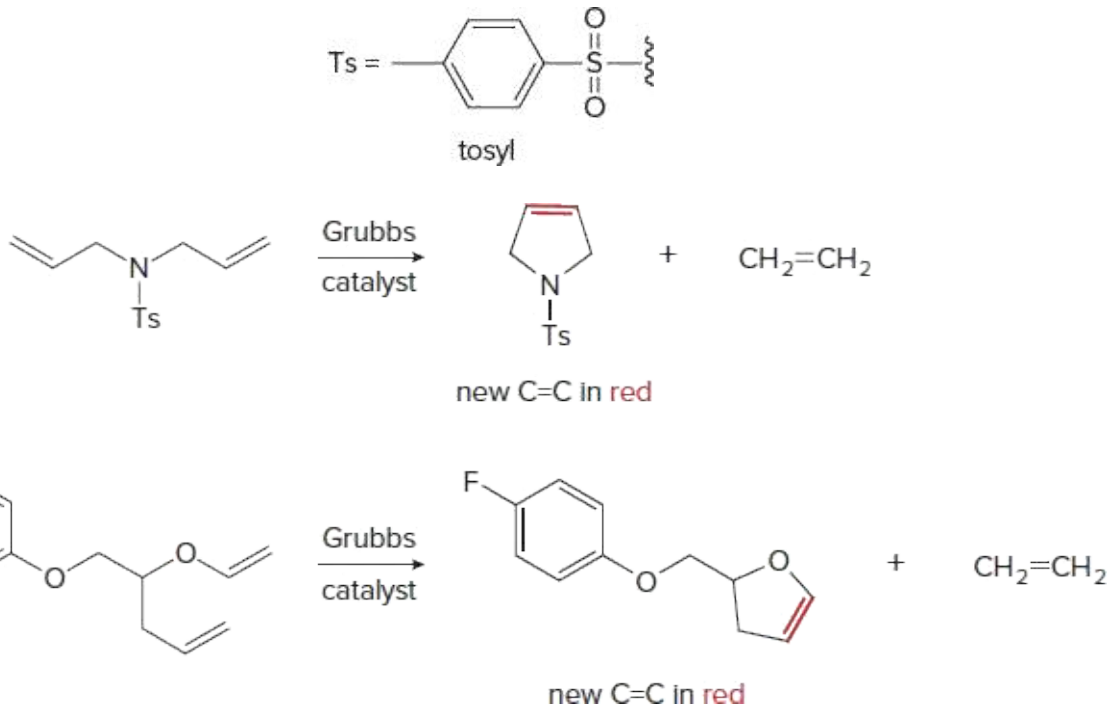
When a diene is used as starting material, ring closure occurs.

A metathesis reaction that forms a ring is called ring-closing metathesis (RCM).

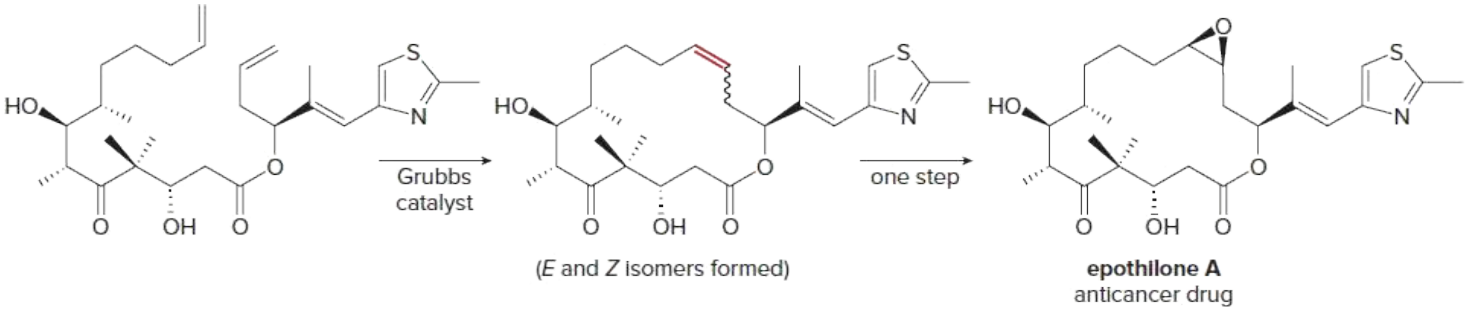


These reactions are typically run in very dilute solution, so that the two reactive ends of the *same* molecule have a higher probability of finding each other for reaction than two functional groups in *different* molecules. These high-dilution conditions thus favor intramolecular rather than intermolecular metathesis. Two examples are shown.

Page 1119



Because metathesis catalysts are compatible with the presence of many functional groups (such as OH, OR, and C=O) and because virtually any ring size can be prepared, metathesis has been used to prepare many complex natural products such as epothilone A, shown in Figure 14.3.



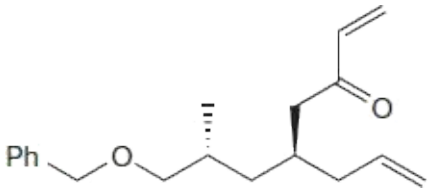
- **Epothilone A,** a promising anticancer agent, was first isolated from soil bacteria collected from the banks of the Zambezi River in South Africa.
- The new C–C bonds formed during metathesis are indicated in red. During metathesis, $CH_2{=}CH_2$ is also formed.

Figure 24.3 **Ring-closing metathesis in the synthesis of epothilone A**

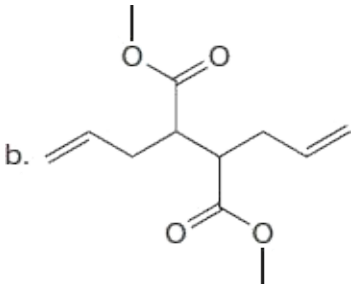
Problem 24.16

Draw the product formed from ring-closing metathesis of each compound.

a.

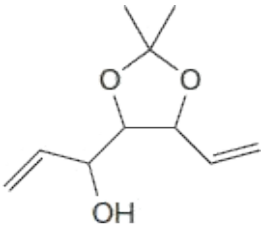


b.



Problem 24.17

What product is formed when B is treated with Grubbs catalyst under high-dilution conditions? This reaction was used in the synthesis of oleocanthal, an antioxidant isolated from olive oil (Problem 21.67).

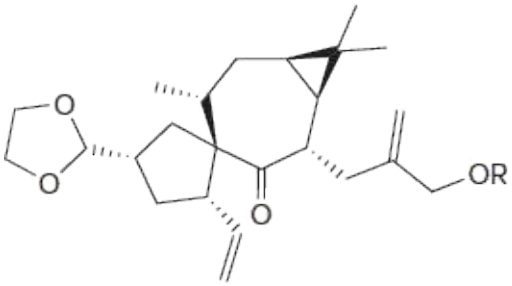


B

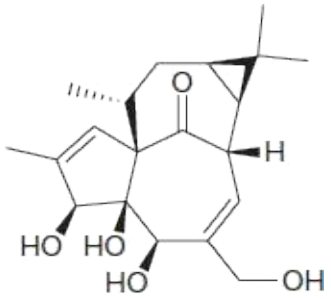
Ingenol (Problem 24.18) is isolated from the milky liquid obtained from *Euphorbia ingens*, a large cactus commonly called the candelabra tree, which is native to dry areas in southern Africa. ***©Papa Bravo/Shutterstock***

Problem 24.18

What product is formed by ring-closing metathesis of compound V, a key intermediate in the synthesis of ingenol, a natural product mentioned in the chapter opener?



V

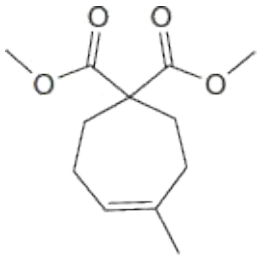


ingenol

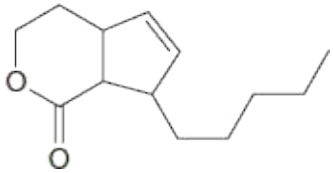
Sample Problem 24.5 Determining the Starting Material of a Ring-Closing Metathesis

What starting material is needed to synthesize each compound by a ring-closing metathesis reaction?

a.

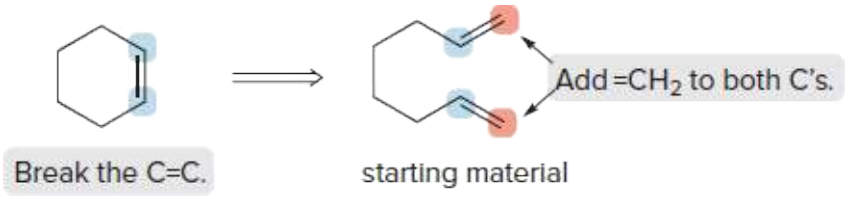


b.



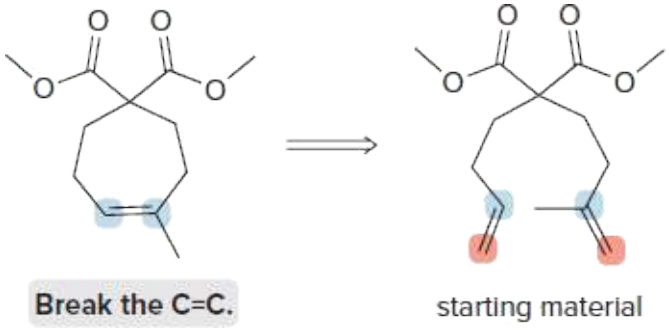
Solution

To work in the retrosynthetic direction, cleave the C=C in the product, and bond each carbon of the original alkene to a CH_2 group using a double bond.

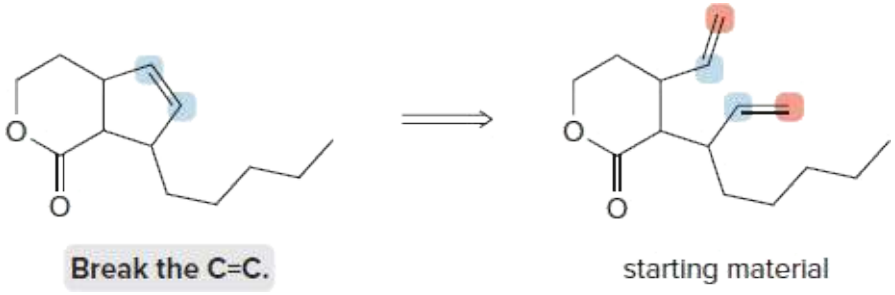


The resulting compound has a carbon chain with two terminal alkenes.

a.



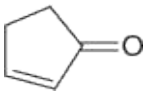
b.



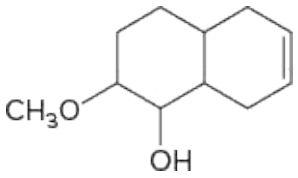
Problem 24.19

What starting material is needed to synthesize each compound by a ring-closing metathesis reaction?

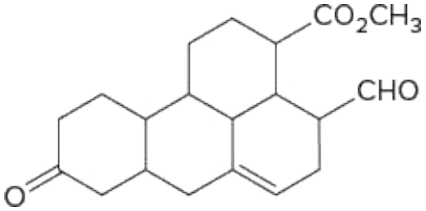
a.



b.



c.



More Practice:

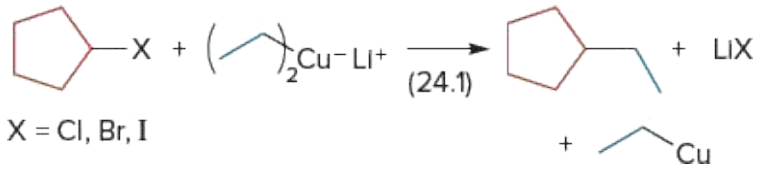
Try Problem 24.36.

Chapter 15 REVIEW

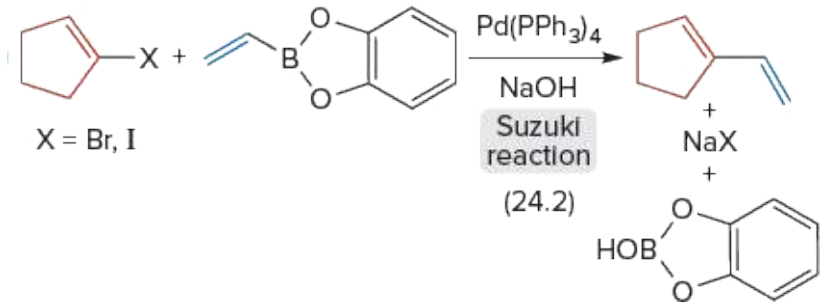
KEY REACTIONS

Coupling Reactions

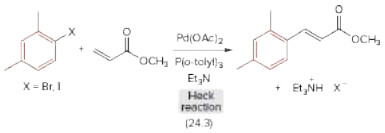
1



2



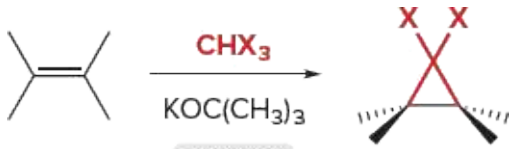
3



Try Problems 24.20; 24.22; 24.25; 24.27–24.29; 24.39b–d, g, h.

Cyclopropane Synthesis

1



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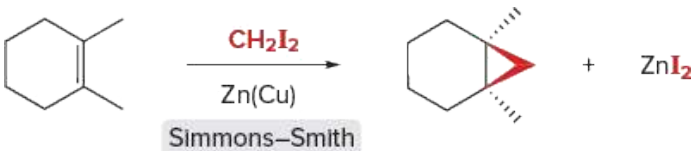

Try Problems 24.30; 24.31; 24.39a, f.

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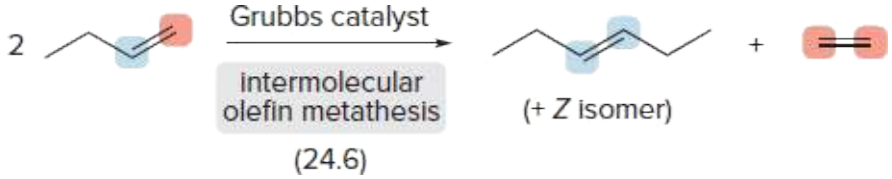
Metathesis

1



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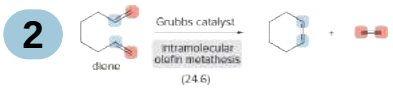
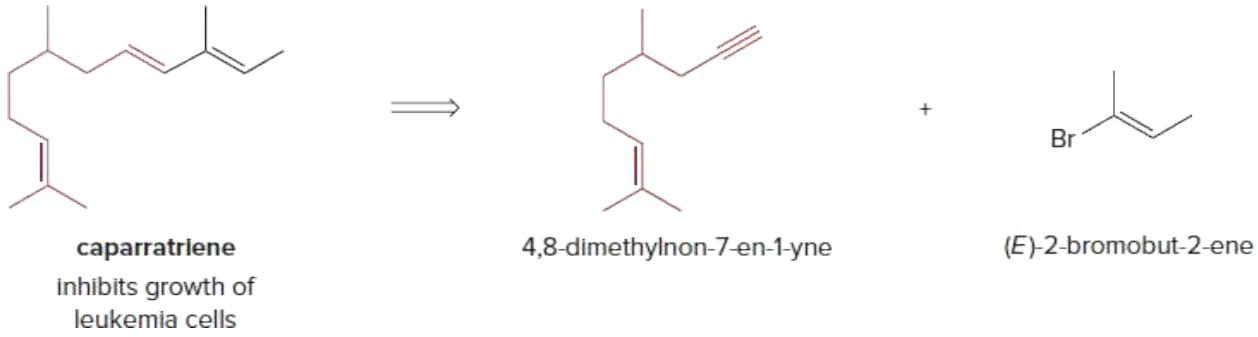


Try Problems 24.21, 24.32–24.35, 24.39e.

KEY SKILLS

[1] Devising a synthesis using a Suzuki coupling (24.2); example: caparratriene from 4,8-dimethyl-non-7-en-1-yne and (*E*)-2-bromobut-2-ene

1 **Compare the carbon skeletons and functional groups.**

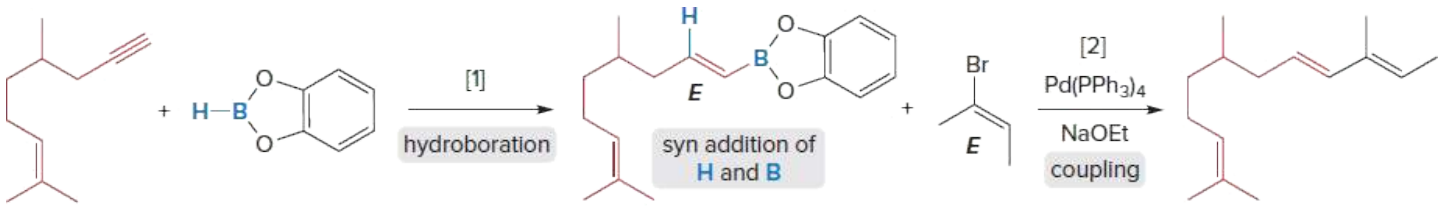


caparratriene
inhibits growth of leukemia cells

4,8-dimethylnon-7-en-1-yne

(*E*)-2-bromobut-2-ene

2 **Complete the synthesis in two steps.**



alkyne | catecholborane | vinylborane | vinyl bromide | caparratriene

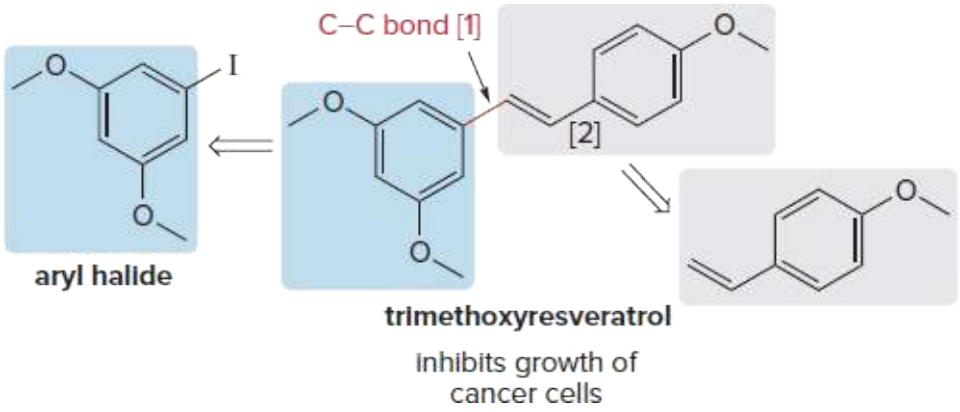
- **[1] Hydroboration of the alkyne with catecholborane forms a vinylborane.**
- **[2] Coupling of the vinylborane with the vinyl bromide gives the conjuga diene with retention of configuration.**

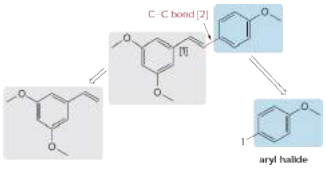
See Sample Problem 24.2. Try Problems 24.24, 24.47.

[2] Identifying the starting materials to synthesize an alkene using a Heck reaction (24.3); two possibilities

1 **Break the molecule into two components, and form C–C bond [1].**

2 **Break molecule i two components, and form C bond [2].**





- **Because trimethoxyresveratrol has two different aryl groups bonded to the central alkene, the compound can be broken at C–C bond [1] or [2].**

See Sample Problem 24.3. Try Problems 24.25, 24.49a.

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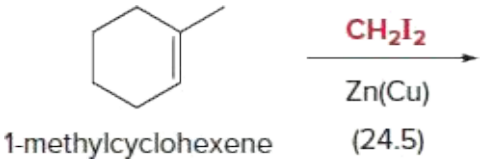
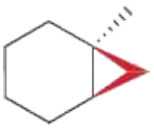
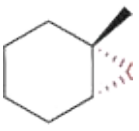
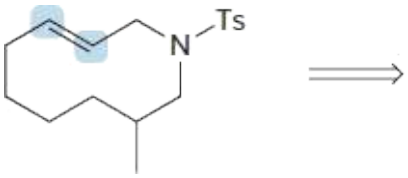
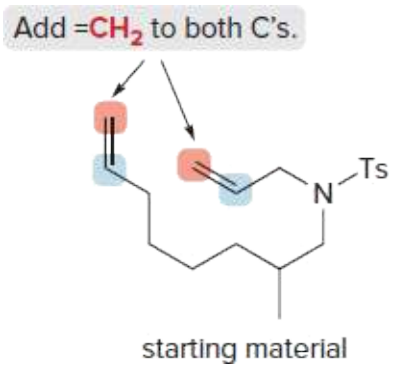
[3] Drawing all stereoisomers that form in a cyclopropanation (24.4–24.5); example: cyclopropanation of 1-methylcyclohexene

1 Use the reagents to identify the group added to the C=C.	**2** Add CH_2 from above the alkene.	**3** Add CH_2 from below the alkene.	**4** Determine stereochem of the prod
 1-methylcyclohexene			• **Both stereogenic centers opposite configurati** • **There is plane symmetry.** • **The compo**

			are enantiomer

See Sample Problem 24.4. Try Problems 24.30; 24.31; 24.39a, f.

[4] Identifying the starting material in a ring-closing metathesis reaction (24.6)

1 Identify the C=C bond.	2 Cleave the C=C bond, and add a CH_2 group to each carbon of the original alkene using a double bond.
	

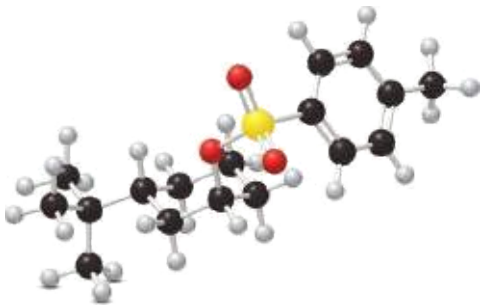
See Figure 24.3, Sample Problem 24.5. Try Problem 24.36.

PROBLEMS

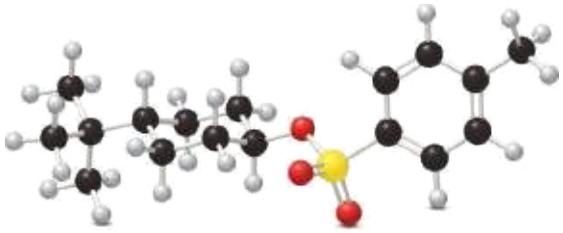
Problems Using Three-Dimensional Models

24.20 **In addition to organic halides, alkyl tosylates (R′OTs, Section 9.13) react with organocuprates (R_2CuLi) to form coupling products R–R′. When 2° alkyl tosylates are used as starting materials (R_2CHOTs), inversion of the configuration at a stereogenic center results. Keeping this in mind, draw the product formed when each compound is treated with $(CH_3)_2CuLi$.**

a.

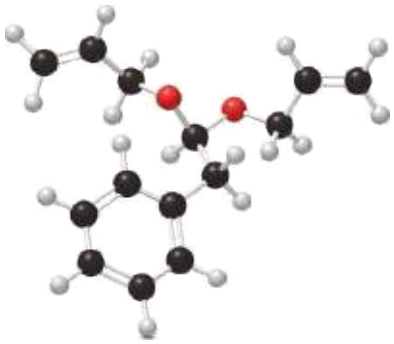


b.

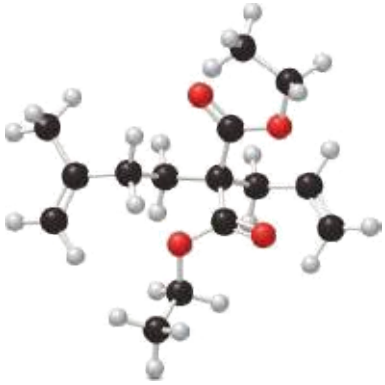


24.21 What product is formed by ring-closing metathesis of each compound?

a.



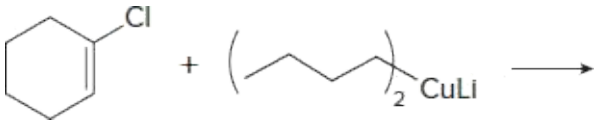
b.



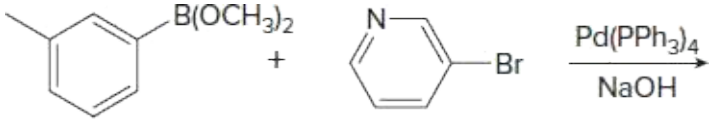
Coupling Reactions

24.22 Draw the products formed in each reaction.

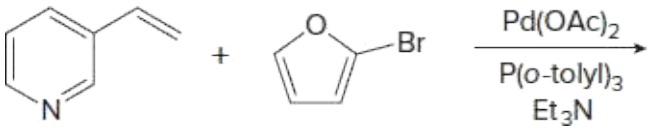
a.



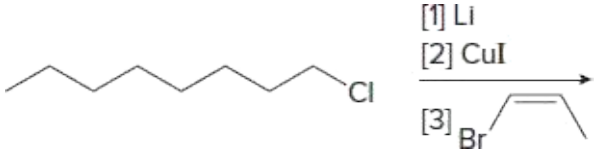
b.



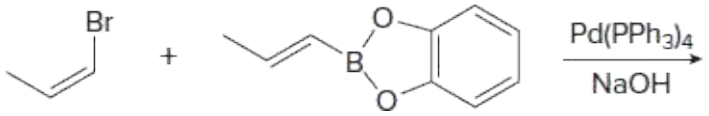
c.



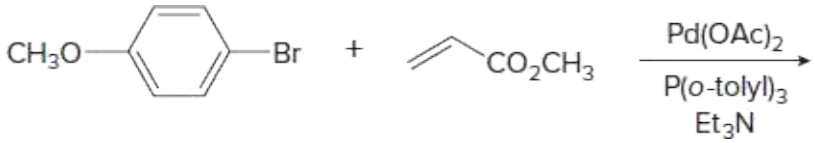
d.



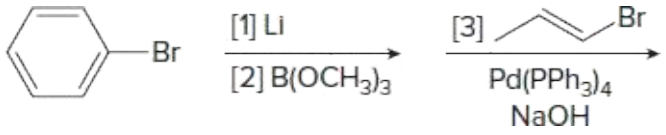
e.



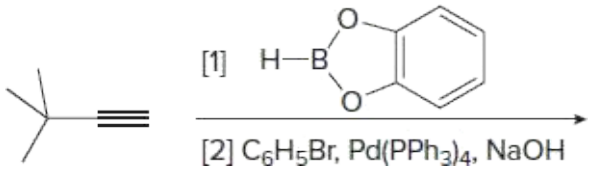
f.



g.

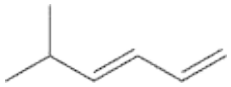


h.

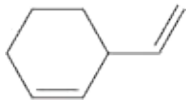


24.23 What organic halide is needed to convert lithium divinylcuprate [$(CH_2{=}CH)_2CuLi$] to each compound?

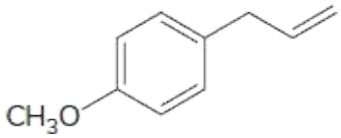
a.



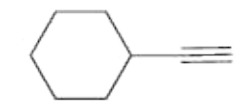
b.



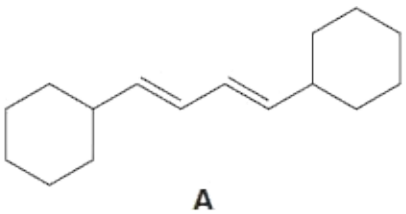
c.



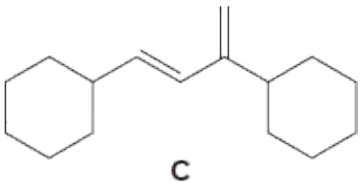
24.24 How can you convert ethynylcyclohexane to dienes A–C using a Suzuki reaction? You may use any other organic compounds and inorganic reagents. Is it possible to synthesize diene D using a Suzuki reaction? Explain why or why not.



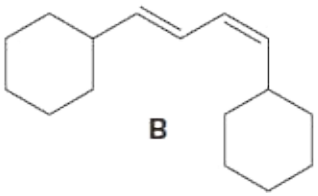
ethynylcyclohexane



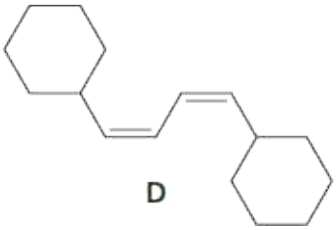
A



C



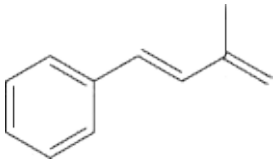
B



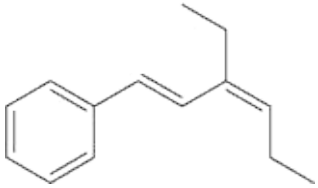
D

24.25 What compound is needed to convert styrene ($C_6H_5CH{=}CH_2$) to each product using a Heck reaction?

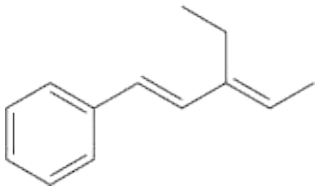
a.



b.

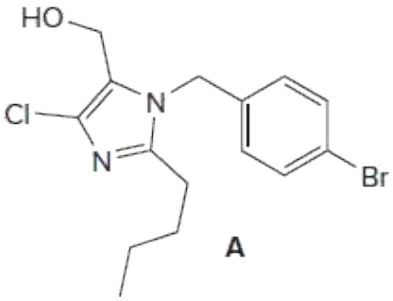


c.

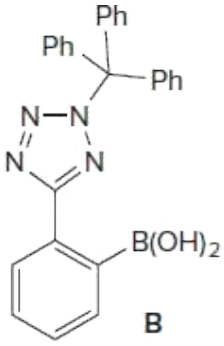


24.26 **What steps are needed to convert but-1-ene ($CH_3CH_2CH{=}CH_2$) to octane [$CH_3(CH_2)_6CH_3$] using a coupling reaction with an organocuprate reagent? All carbon atoms in octane must come from but-1-ene.**

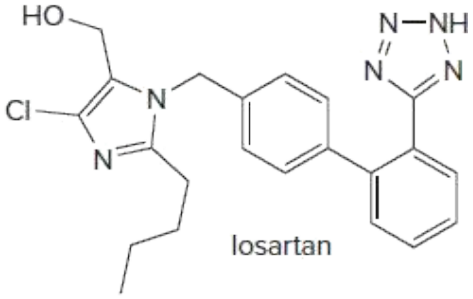
24.27 **What product is formed in the Suzuki coupling of A and B? This reaction was a key step in the synthesis of losartan, a drug used to treat hypertension.**



A

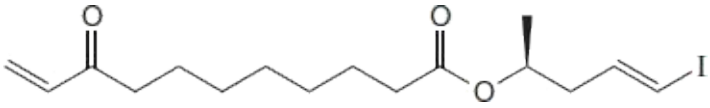


B

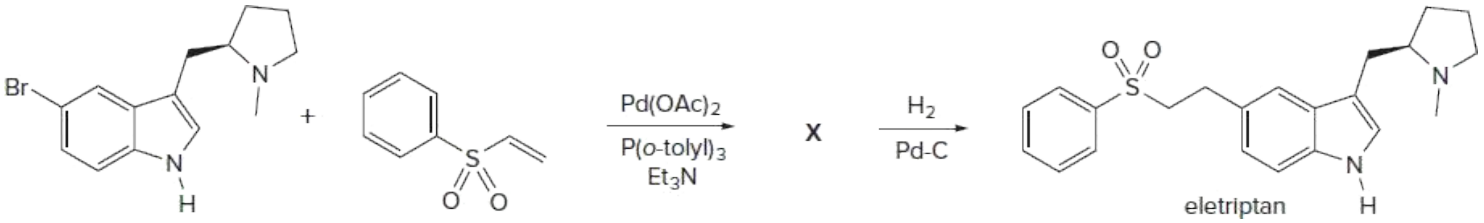


losartan

24.28 **Draw the product formed when the following compound undergoes an intramolecular Heck reaction. Indicate the stereochemistry at all double bonds and tetrahedral stereogenic centers.**



24.29 **Identify X, an intermediate that was converted to eletriptan (trade name Relpax), a drug used to treat migraines.**

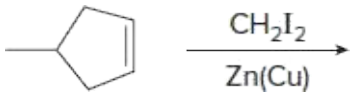


eletriptan

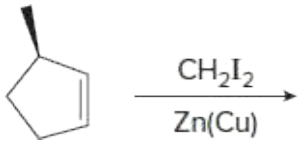
Cyclopropanes

24.30 **Draw the products (including stereoisomers) formed in each reaction.**

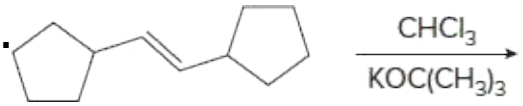
a.



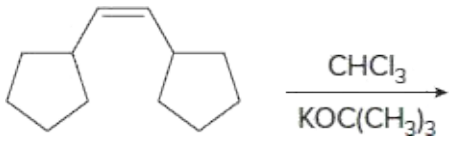
b.



C.



d.

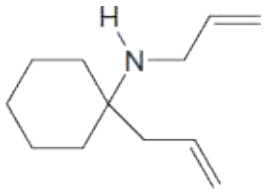


24.31 **Treatment of cyclohexene with $C_6H_5CHI_2$ and Zn(Cu) forms two stereoisomers of molecular formula $C_{13}H_{16}$. Draw their structures and explain why two compounds are formed.**

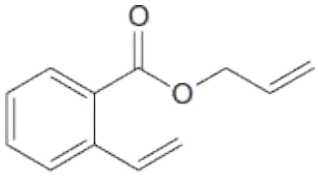
Metathesis

24.32 **What ring-closing metathesis product is formed when each substrate is treated with Grubbs catalyst under high-dilution conditions?**

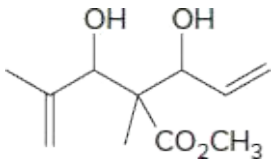
a.



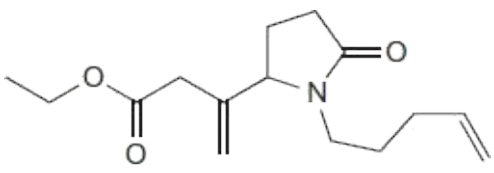
b.



c.



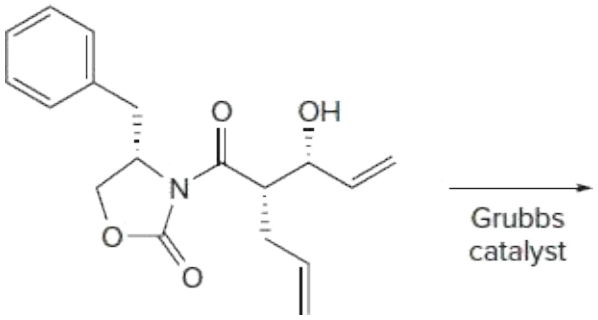
24.33 **What product is formed when A is treated with Grubbs catalyst under high-dilution conditions? This reaction was a key step in the synthesis of stemoamide, the naturally occurring amide described in the Chapter 21 opening paragraph.**



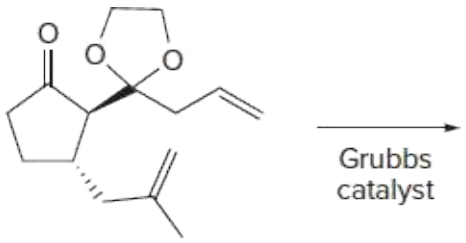
A

24.34 **Draw the products of each reaction carried out under high-dilution conditions. Indicate the stereochemistry at all stereogenic centers.**

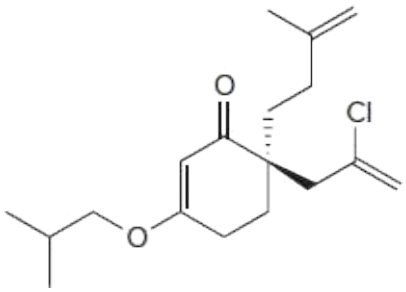
a.



b.

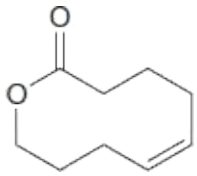


24.35 Draw the product when the following compound undergoes ring-closing metathesis.

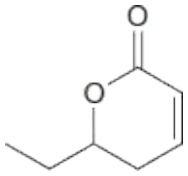


24.36 What starting material is needed to prepare each compound by a ring-closing metathesis reaction?

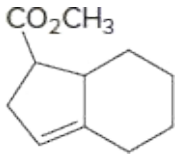
a.



b.

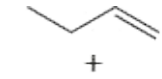


c.

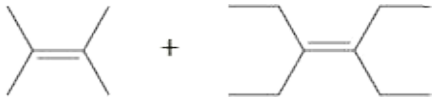


24.37 Metathesis reactions can be carried out with two *different* alkene substrates in one reaction mixture. Depending on the substitution pattern around the C=C, the reaction may lead to one major product or a mixture of many products. For each pair of alkene substrates, draw all metathesis products formed. (Disregard any starting materials that may also be present at equilibrium.) With reference to the three examples, discuss when alkene metathesis with two different alkenes is a synthetically useful reaction.

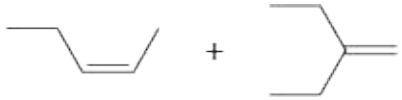
a.



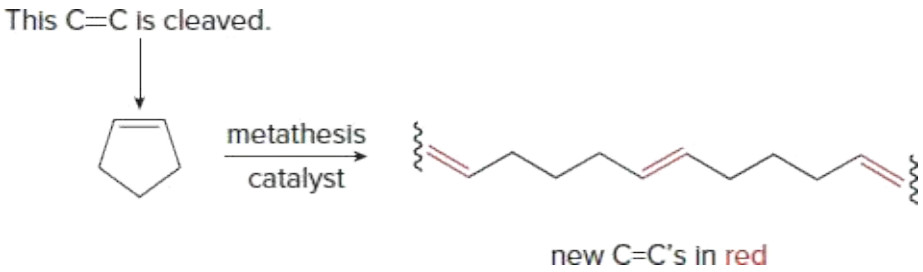
b.



c.



24.38 When certain cycloalkenes are used in metathesis reactions, ring-opening metathesis polymerization (ROMP) occurs to form a high-molecular-weight polymer, as shown with cyclopentene as the starting material. The reaction is driven to completion by relief of strain in the cycloalkene.



What products are formed by ring-opening metathesis polymerization of each alkene?

a.

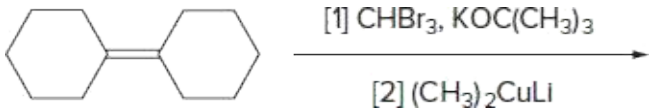
b.

c.

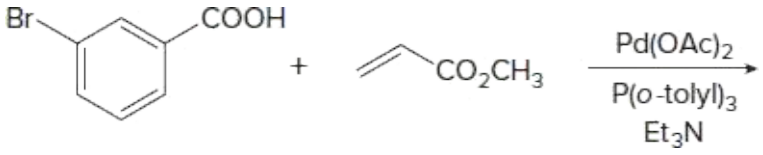
General Reactions

24.39 Draw the products formed in each reaction.

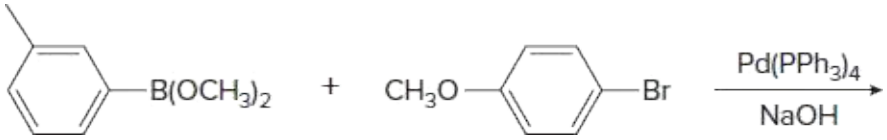
a.



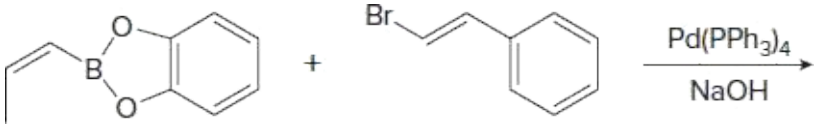
b.



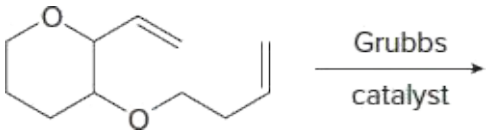
c.



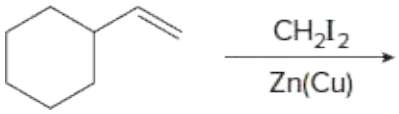
d.



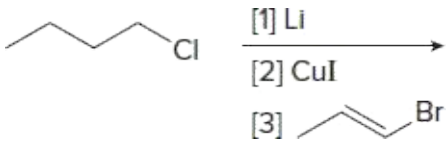
e.



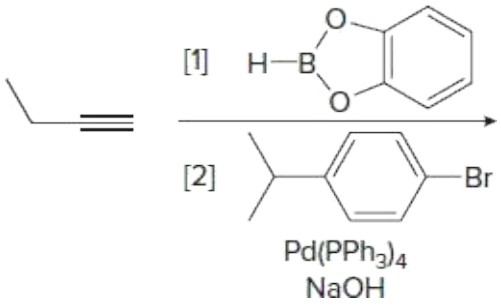
f.



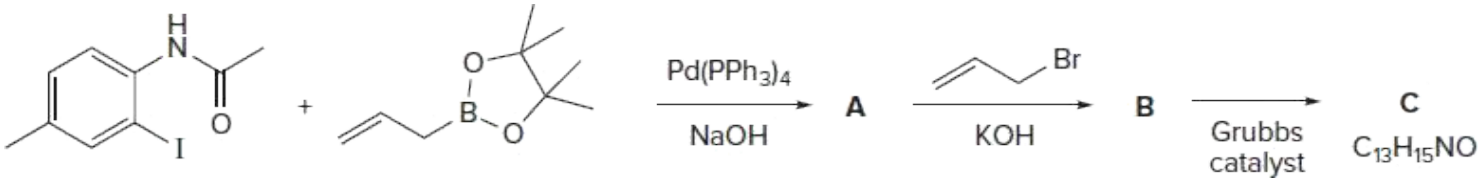
g.



h.

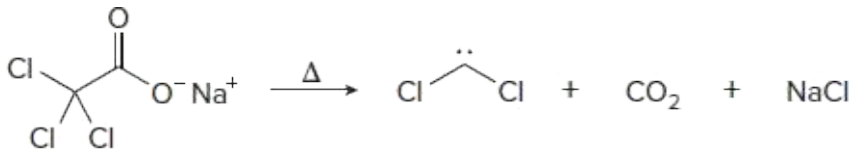


24.40 Identify compounds A–C in the following reaction scheme.



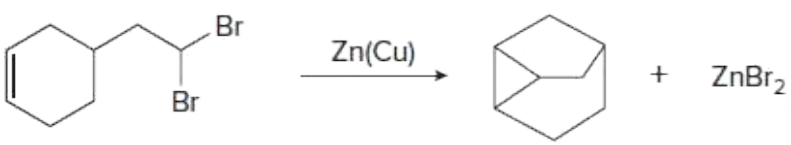
Mechanisms

24.41 In addition to using CHX_3 and base to synthesize dihalocarbenes (Section 24.4B), dichlorocarbene ($:CCl_2$) can be prepared by heating sodium trichloroacetate. Draw a stepwise mechanism for this reaction.



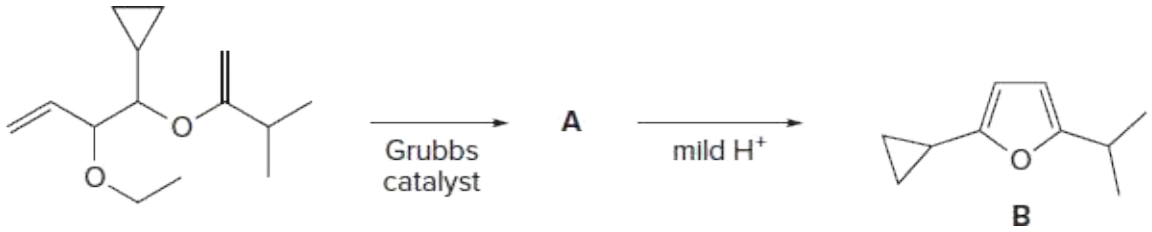
sodium trichloroacetate

24.42 Draw a stepwise mechanism for the following reaction.

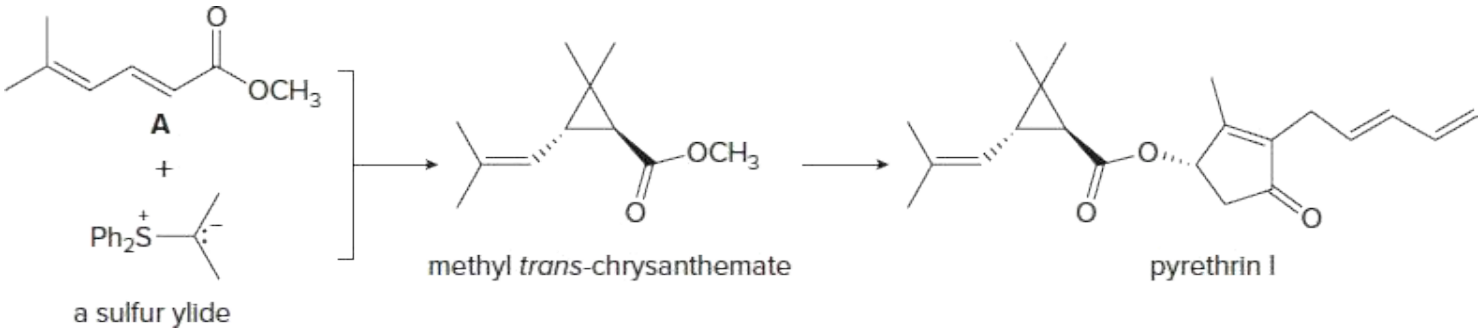


24.43 Identify A in the following reaction scheme, and draw a stepwise

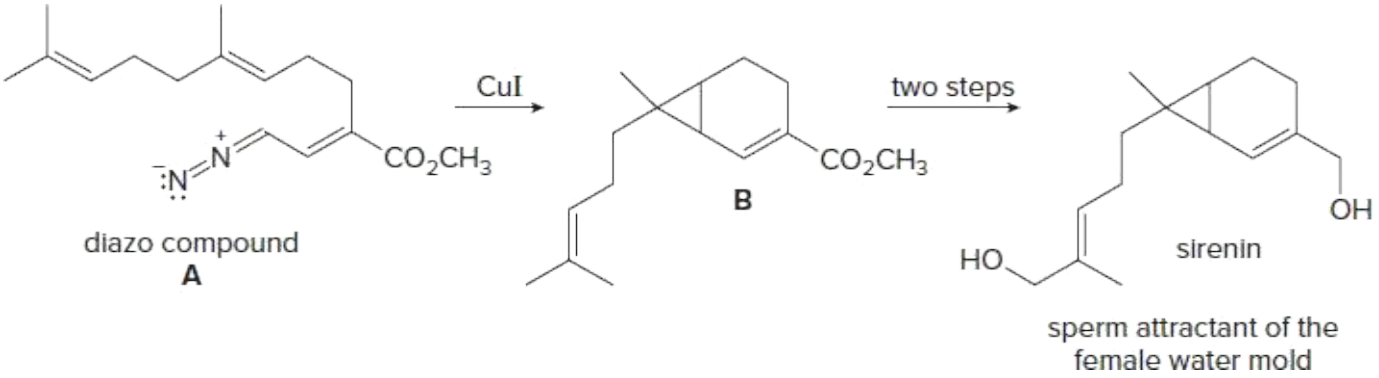
mechanism for the conversion of A to the furan B.



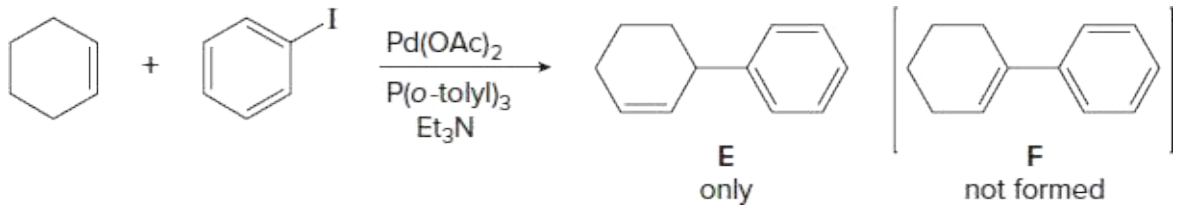
24.44 Sulfur ylides, like the phosphorus ylides of Chapter 18, are useful intermediates in organic synthesis. Methyl *trans*-chrysanthemate, an intermediate in the synthesis of the insecticide pyrethrin I (Section 24.4), can be prepared from diene A and a sulfur ylide. Draw a stepwise mechanism for this reaction.



24.45 Although diazomethane (CH_2N_2) is often not a useful reagent for preparing cyclopropanes, other diazo compounds give good yields of more complex cyclopropanes. Draw a stepwise mechanism for the conversion of diazo compound A to B, an intermediate in the synthesis of sirenin, the sperm attractant produced by the female gametes of the water mold *Allomyces.*



24.46 The reaction of cyclohexene with iodobenzene under Heck conditions forms E, a coupling product with the new phenyl group on the allylic carbon, but none of the "expected" coupling product F with the phenyl group bonded directly to the carbon–carbon double bond.

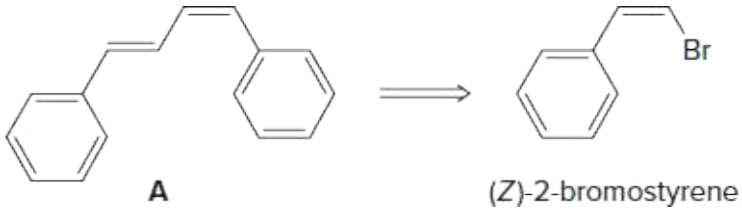


a. Draw a stepwise mechanism that illustrates how E is formed.

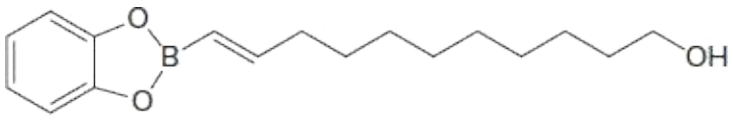
b. Step [2] in Mechanism 24.2 proceeds with syn addition of Pd and R′ to the double bond. What does the formation of E suggest about the stereochemistry of the elimination reaction depicted in Step [3] of Mechanism 24.2?

Synthesis

24.47 **Devise a synthesis of diene A from (Z)-2-bromostyrene as the only organic starting material. Use a Suzuki reaction in one step of the synthesis.**

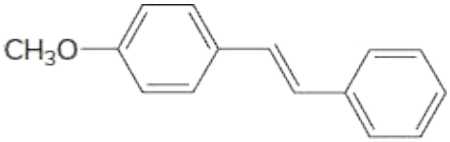


24.48 **Devise a synthesis of the given trans vinylborane, which can be used for bombykol synthesis (Figure 24.1). All of the carbon atoms in the vinylborane must come from acetylene, nonane-1,9-diol, and catecholborane.**

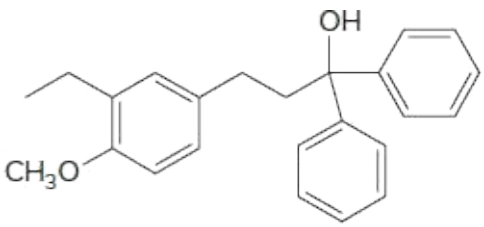


24.49 **Devise a synthesis of each compound using a Heck reaction as one step. You may use benzene, CH_2=$CHCO_2Et$, organic alcohols having one or two carbons, and any required inorganic reagents.**

a.

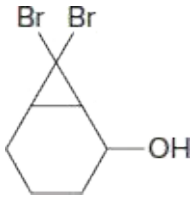


b.



24.50 Devise a synthesis of each compound from cyclohexene and any required organic compounds or inorganic reagents.

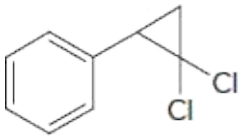
a.



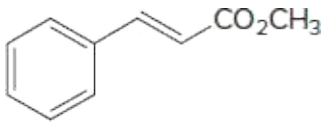
b.

24.51 Devise a synthesis of each compound from benzene. You may also use any organic compounds having four or fewer carbons and any required inorganic reagents.

a.

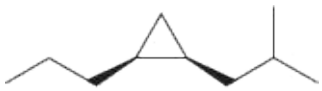


b.



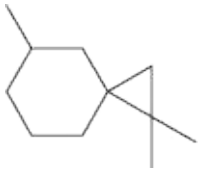
24.52 Devise a synthesis of each substituted cyclopropane. Use acetylene (HC=CH) as a starting material in part (a) and cyclohexanone as a starting material in part (b). You may use any other organic compounds and any needed reagents.

a.



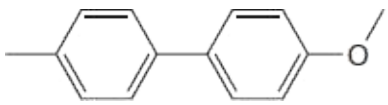
+ enantiomer

b.

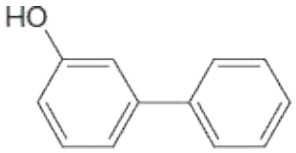


24.53 Biaryls, compounds containing two aromatic rings joined by a C–C bond, can often be efficiently made by two different Suzuki couplings; that is, either aromatic ring can be used to form the organoborane needed for coupling. In some cases, however, only one route is possible. With this in mind, synthesize each of the following biaryls using benzene as the starting material for each aromatic ring. When more than one route is possible, draw both of them. You may use any required organic or inorganic reagents.

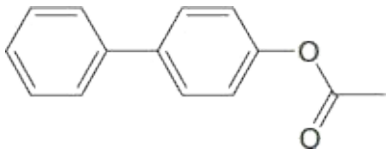
a.



b.

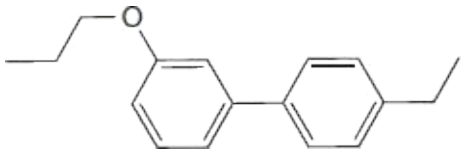


c.

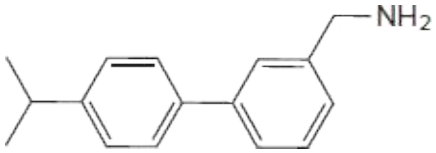


24.54 Devise a synthesis of each compound from benzene using a Suzuki reaction. You may also use organic alcohols having four or fewer carbons and any needed organic or inorganic reagents.

a.

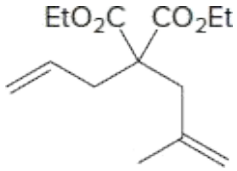


b.

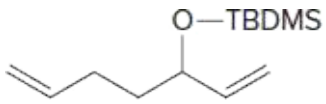


24.55 Draw the product formed from the ring-closing metathesis of each compound. Then, devise a synthesis of each metathesis starting material using any of the following compounds: $CH_2(CO_2Et)_2$, alcohols with four or fewer carbons, and any needed organic or inorganic reagents.

a.

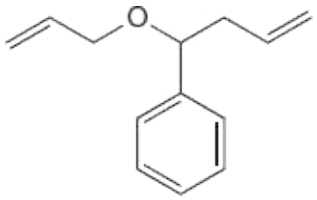


b.

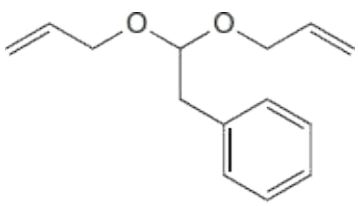


24.56 Draw the product formed from the ring-closing metathesis of each compound. Then, devise a synthesis of each metathesis starting material from benzene, alcohols with four or fewer carbons, and any needed organic or inorganic reagents.

a.



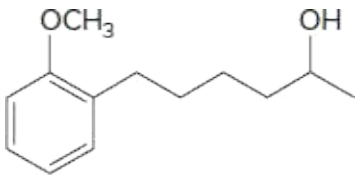
b.



24.57 Devise a synthesis of each of the following compounds. Besides inorganic reagents, you may use hydrocarbons and halides having ≤ 6 C's, and CH_2=CHCOOCH$_3$ as starting materials. Each synthesis must use

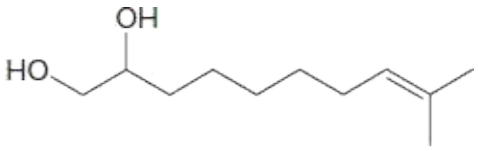
at least one of the carbon–carbon bond-forming reactions in this chapter.

a.



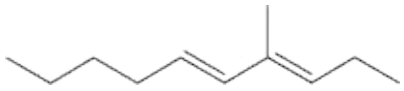
(two enantiomers)

b.

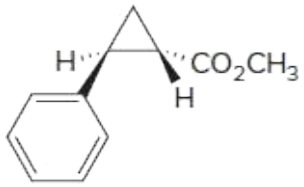


(two enantiomers)

c.



d.

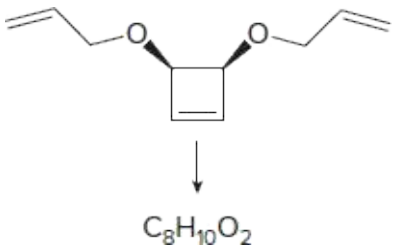


(+ enantiomer)

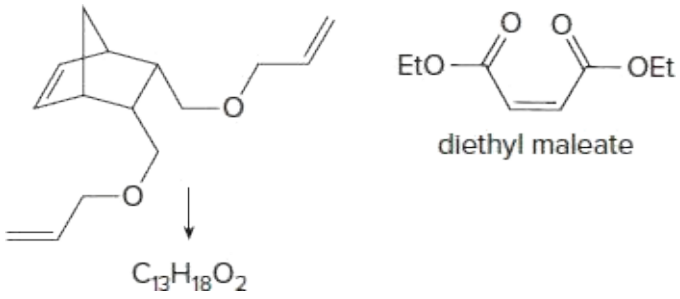
Challenge Problems

24.58 **Many variations of ring-closing metathesis have now been reported. Tandem ring–opening–ring-closing metathesis can occur with cyclic alkenes that contain two additional carbon–carbon double bonds. In this reaction, the cycloalkene is cleaved, and two new rings are formed. [1] What compounds are formed in this tandem reaction with the following substrates? [2] Devise a synthesis of the substrate in part (b) that uses a Diels–Alder reaction with diethyl maleate as the dienophile.**

a.



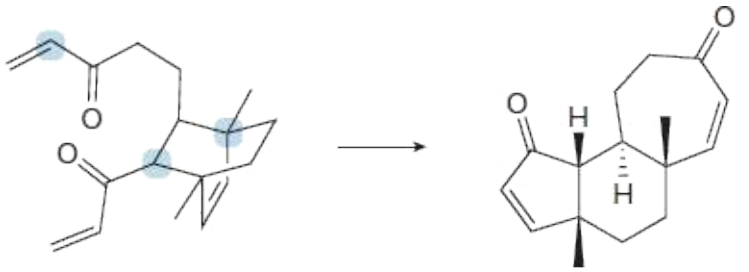
b.



diethyl maleate

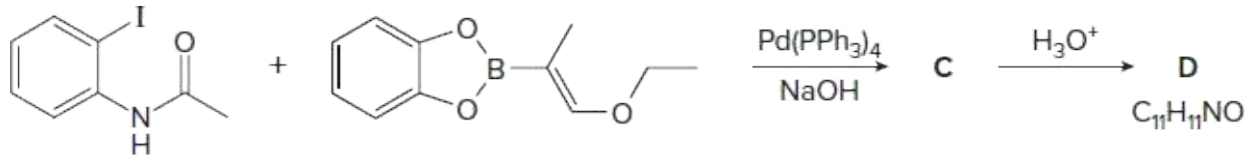
24.59 **The following conversion, carried out in the presence of Grubbs catalyst and ethylene gas, involves a cascade of metathesis reactions. Draw a reaction sequence that illustrates how the reactant is converted to the product Z, and indicate where each labeled atom in the reactant ends up**

in Z.



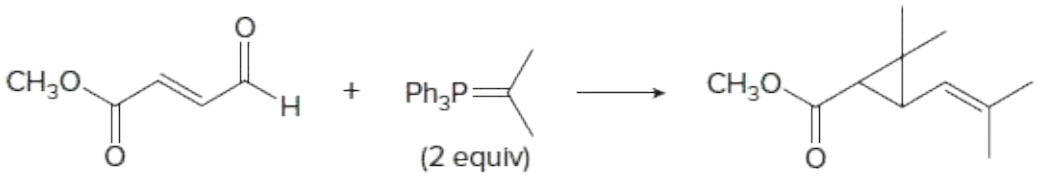
Z

24.60 Suzuki coupling of aryl iodide A and vinylborane B affords compound C, which is converted to D in the presence of aqueous acid. Identify compounds C and D and draw a stepwise mechanism for the conversion of C to D.



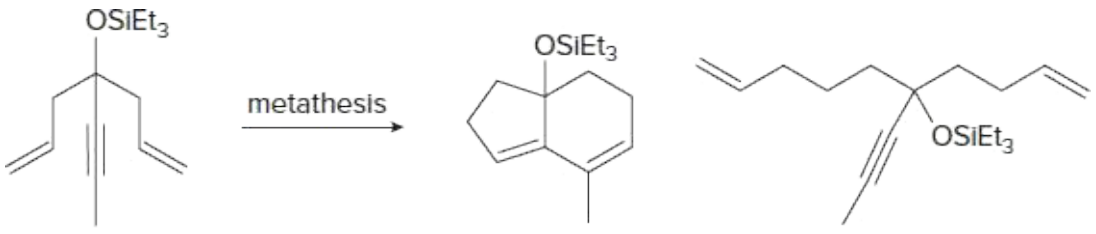
A B

24.61 Dimethyl cyclopropanes can be prepared by the reaction of an α, β-unsaturated carbonyl compound X with two equivalents of a Wittig reagent Y. Draw a stepwise mechanism for this reaction.



X Y

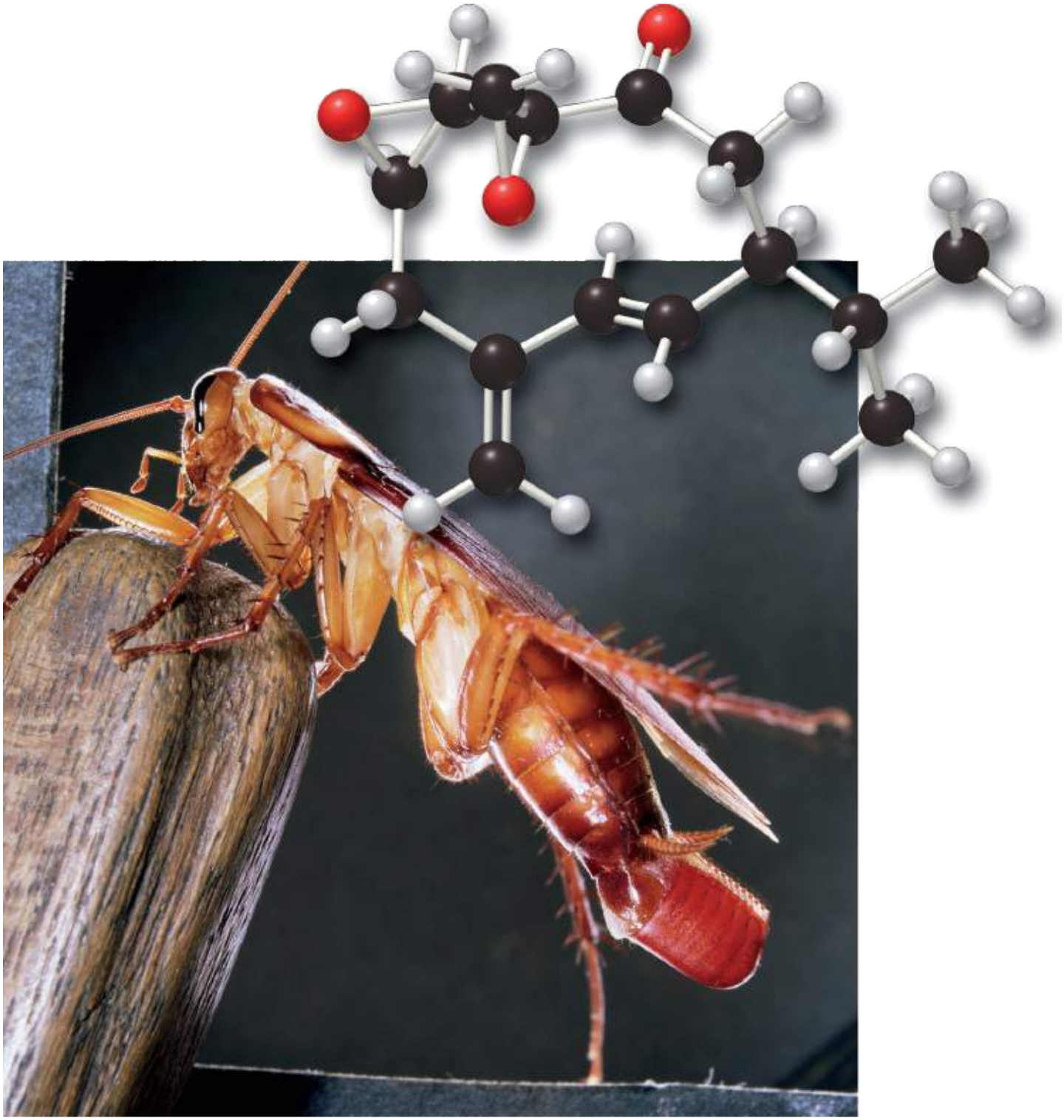
24.62 Dienynes undergo metathesis to afford fused bicyclic ring systems. (a) Explain how A is converted to B. (b) Keeping this reaction in mind, draw the two products formed by dienyne metathesis of C.



A B C

25

Pericyclic Reactions



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25.1 Types of pericyclic reactions
25.2 Molecular orbitals
25.3 Electrocyclic reactions
25.4 Cycloaddition reactions
25.5 Sigmatropic rearrangements
25.6 Summary of rules for pericyclic reactions

Periplanone B, an unusual diepoxide with a 10-membered ring, is a potent sex pheromone of the female American cockroach. Although periplanone B was isolated in 1952, its structure was not determined until 1976 using 200 μg of material obtained from more than 75,000 female cockroaches. This structure was confirmed by synthesis in 1979, and several subsequent syntheses have been reported. Key steps in an elegant 1984 synthesis of periplanone B involve pericyclic reactions, a group of powerful, stereospecific reactions discussed in Chapter 25.

Why Study…

Pericyclic Reactions?

Many of the reactions thus far encountered in our study of organic chemistry occur by way of reactive intermediates—cations, anions, and radicals. For example, the S_N1 reaction in Chapter 7 and electrophilic aromatic substitutions in Chapter 16 involve carbocations, while the aldol and Claisen reactions in Chapter 22 occur via enolate anions. Other reactions, such as the halogenation of alkanes and the polymerization of alkenes discussed in Chapter 13, take place via radical intermediates.

In Chapter 25, we learn about a small but versatile group of reactions, pericyclic reactions, which occurs in a concerted process—all bonds are broken and formed in a single step—with a cyclic transition state. The Diels–Alder reaction in Chapter 14 is an example of one type of pericyclic reaction. Pericyclic reactions involve π bonds, and they are governed by a set of rules that allows us to predict the identity and stereochemistry of the products formed. Consequently, pericyclic reactions are

valuable tools for synthesizing organic molecules.

25.1 Types of Pericyclic Reactions

Although most organic reactions take place by way of ionic or radical intermediates, a number of useful reactions occur in one-step processes that do *not* form reactive intermediates.

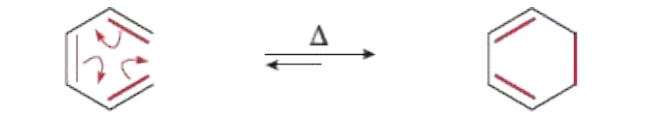
- **A pericyclic reaction is a concerted reaction that proceeds through a cyclic transition state.**

Stereospecific reactions were first discussed in Chapter 10.

Pericyclic reactions require light or heat and are completely stereospecific; that is, a particular stereoisomer of the reactant forms a particular stereoisomer of the product. There are three categories of pericyclic reactions: electrocyclic reactions, cycloadditions, and sigmatropic rearrangements.

An electrocyclic reaction is a reversible reaction that can involve ring closure or ring opening of one molecule of reactant to form one molecule of product.

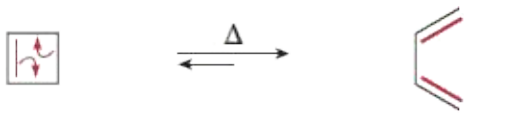
- **An electrocyclic ring closure is an intramolecular reaction that forms a cyclic product containing one more σ bond and one fewer π bond than the reactant.**



hexa-1,3,5-triene
3 π bonds

cyclohexa-1,3-diene
2 π bonds

- **An electrocyclic ring opening is a reaction in which a σ bond of a cyclic reactant is cleaved to form a conjugated product with one more π bond.**

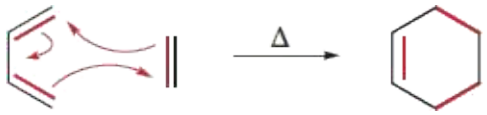


cyclobutene
1 π bond

buta-1,3-diene
2 π bonds

Cycloaddition reactions form a ring. The Diels–Alder reaction in Chapter 14 is one example of a cycloaddition.

- **A cycloaddition is a reaction between two compounds with π bonds to form a cyclic product with two new σ bonds.**



In contrast to electrocyclic reactions and cycloadditions, in which the number of π bonds differs in the reactants and products, the number of π bonds does *not* change in a sigmatropic rearrangement.

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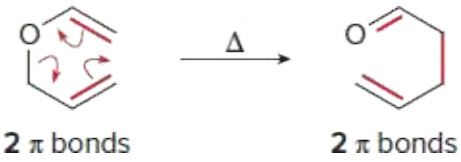
- **A sigmatropic rearrangement is a reaction in which a σ bond is broken in the reactant, the π bonds rearrange, and a σ bond is formed in the product.**



Hoffmann and Fukui received the 1981 Nobel Prize in Chemistry for developing theories that explain the course of pericyclic reactions.

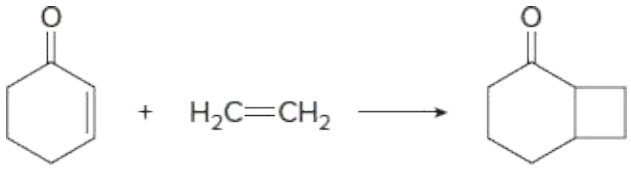
Two features determine the course of the reactions: the number of π bonds involved and whether the reaction occurs in the presence of heat (thermal conditions) or light (photochemical conditions). These reactions follow a set of rules based on orbitals and symmetry first proposed by R. B. Woodward and Roald Hoffmann in 1965, and derived from theory described by Kenichi Fukui in 1954.

To understand pericyclic reactions, we must review and expand upon what we learned about the molecular orbitals of systems with π bonds in Chapter 15.

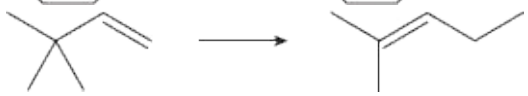
Problem 25.1

Classify each reaction as an electrocyclic reaction, a cycloaddition, or a sigmatropic rearrangement. Label the σ bonds that are broken or formed in each reaction.

a.

b. 

c.

d. 

25.2 Molecular Orbitals

In Section 15.9, we learned that molecular orbital (MO) theory describes bonds as the mathematical combination of atomic orbitals that forms a new set of orbitals called molecular orbitals (MOs). The number of atomic orbitals used *equals* the number of molecular orbitals formed.

Because pericyclic reactions involve π bonds, let's examine the molecular orbitals that result from *p* orbital overlap in ethylene, buta-1,3-diene, and hexa-1,3,5-triene—molecules that contain one, two, and three π bonds, respectively. Keep in mind that the two lobes of a *p* orbital are opposite in phase, with a node of electron density at the nucleus.

25.2A Ethylene

The π bond in ethylene (CH_2=CH_2) is formed by side-by-side overlap of two *p* orbitals on adjacent carbons. Two *p* orbitals can combine in two different ways. As shown in Figure 25.1, when two *p* orbitals of similar phase overlap, a π bonding molecular orbital (designated as ψ_1) results. Two electrons occupy this lower-energy bonding molecular orbital. When two *p* orbitals of opposite phase combine, a π* antibonding molecular orbital (designated as ψ_2*) results. A destabilizing node between the orbitals occurs when two orbitals of opposite phase combine.

25.2B Buta-1,3-diene

The two π bonds of buta-1,3-diene (CH_2=CH–CH=CH_2) are formed by overlap of four *p* orbitals on four adjacent carbons. As shown in Figure 25.2, four *p* orbitals can combine in four different ways to form four molecular orbitals designated as ψ_1–ψ_4. Two are bonding molecular orbitals (ψ_1 and ψ_2), and two are antibonding molecular orbitals (ψ_3* and ψ_4*). The two bonding MOs are *lower* in energy than the *p* orbitals from which they are formed, whereas the two antibonding MOs are *higher* in energy than the *p* orbitals from which they are formed. As the number of bonding interactions *decreases* and the number of nodes *increases*, the

energy of the molecular orbital *increases*.

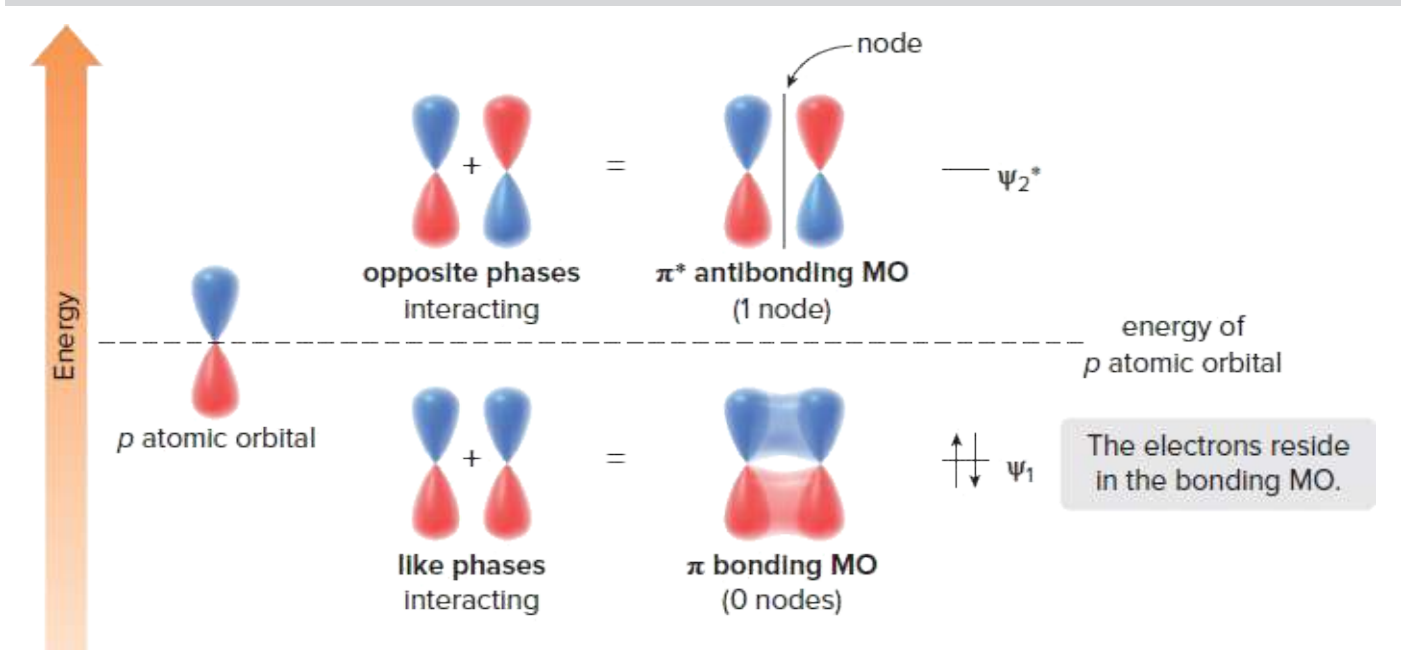
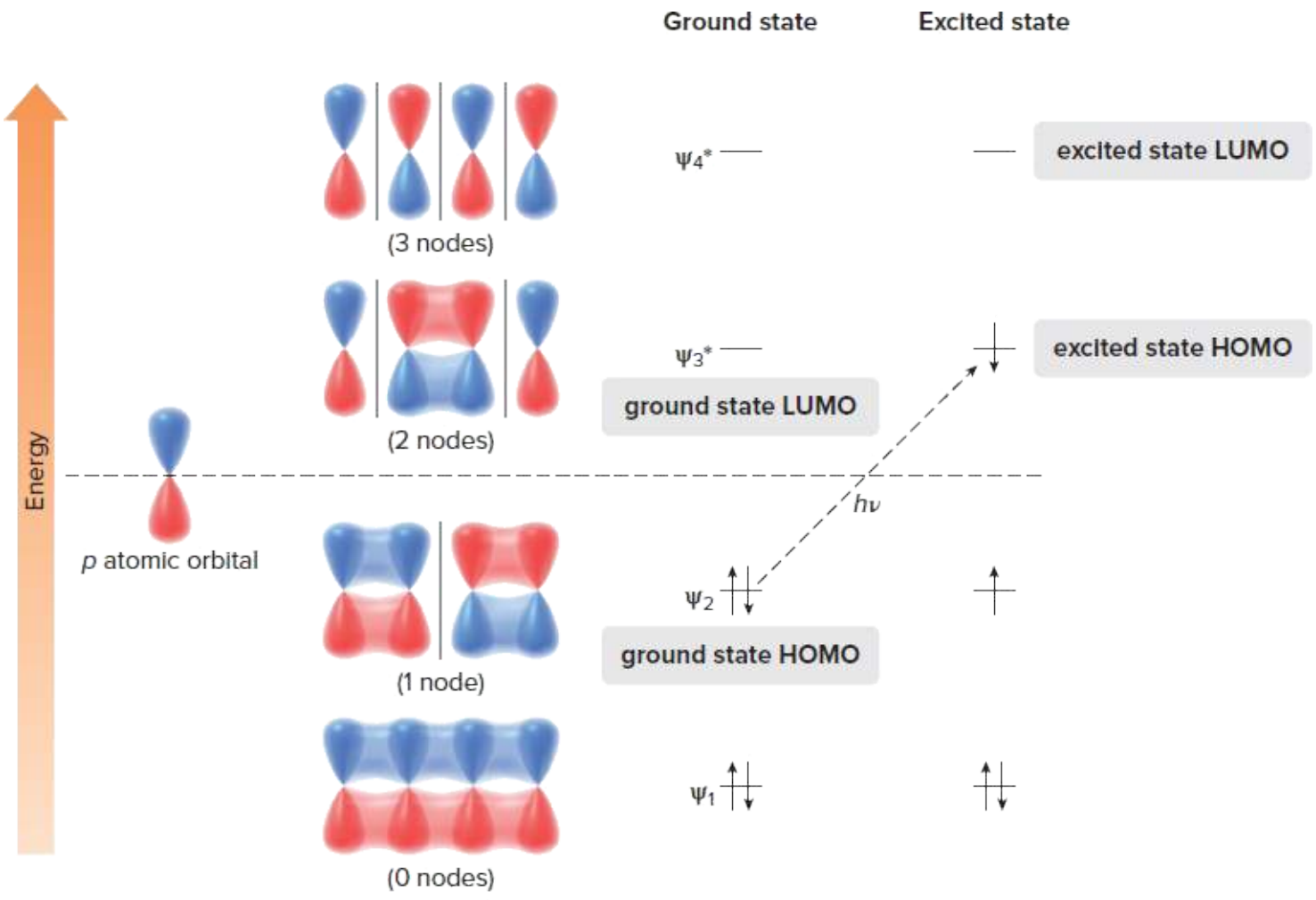


Figure 25.1 **The π and π* molecular orbitals of ethylene**



- The two lowest-energy molecular orbitals, ψ_1 and ψ_2, are **bonding MOs.**
- The two highest-energy molecular orbitals, ψ_3^* and ψ_4^*, are **antibonding MOs.**

Figure 25.2 **The four π molecular orbitals of buta-1,3-diene**

- **In the ground state electronic arrangement, the four π electrons occupy the two bonding molecular orbitals.**

Also recall from Section 15.9:

- **The highest-energy orbital that contains electrons is called the highest occupied molecular orbital (HOMO). In the ground state of buta-1,3-diene, Ψ_2 is the HOMO.**
- **The lowest-energy orbital that contains no electrons is called the lowest unoccupied molecular orbital (LUMO). In the ground state of buta-1,3-diene, Ψ_3^* is the LUMO.**

The thermal reactions discussed in Section 25.3B utilize reactants in their ground state electronic configuration.

When buta-1,3-diene absorbs light of appropriate energy, an electron is promoted from ψ_2 (the HOMO) to ψ_3^* (the LUMO) to form a higher-energy electronic configuration, the excited state. In the excited state, the HOMO is now ψ_3^*. In the photochemical reactions in Section 25.3C, the reactant is in its excited state. As a result, the HOMO is ψ_3^* and the LUMO is ψ_4^* for buta-1,3-diene.

All conjugated dienes can be described by a set of molecular orbitals that are similar to those drawn in Figure 25.2 for buta-1,3-diene.

Problem 25.2

For each molecular orbital in Figure 25.2, count the number of bonding interactions (interactions between adjacent orbitals of similar phase) and the number of nodes. (a) How do these two values compare for a bonding molecular orbital? (b) How do these two values compare for an antibonding molecular orbital?

25.2C Hexa-1,3,5-triene

The three π bonds of hexa-1,3,5-triene (CH_2=CH–CH=CH–CH=CH_2) are formed by overlap of six *p* orbitals on six adjacent carbons. As shown in Figure 25.3, six *p* orbitals can combine in six different ways to form six molecular orbitals designated as ψ_1–ψ_6. Three are bonding molecular orbitals (ψ_1–ψ_3), and three are antibonding molecular orbitals (ψ_4^*–ψ_6^*).

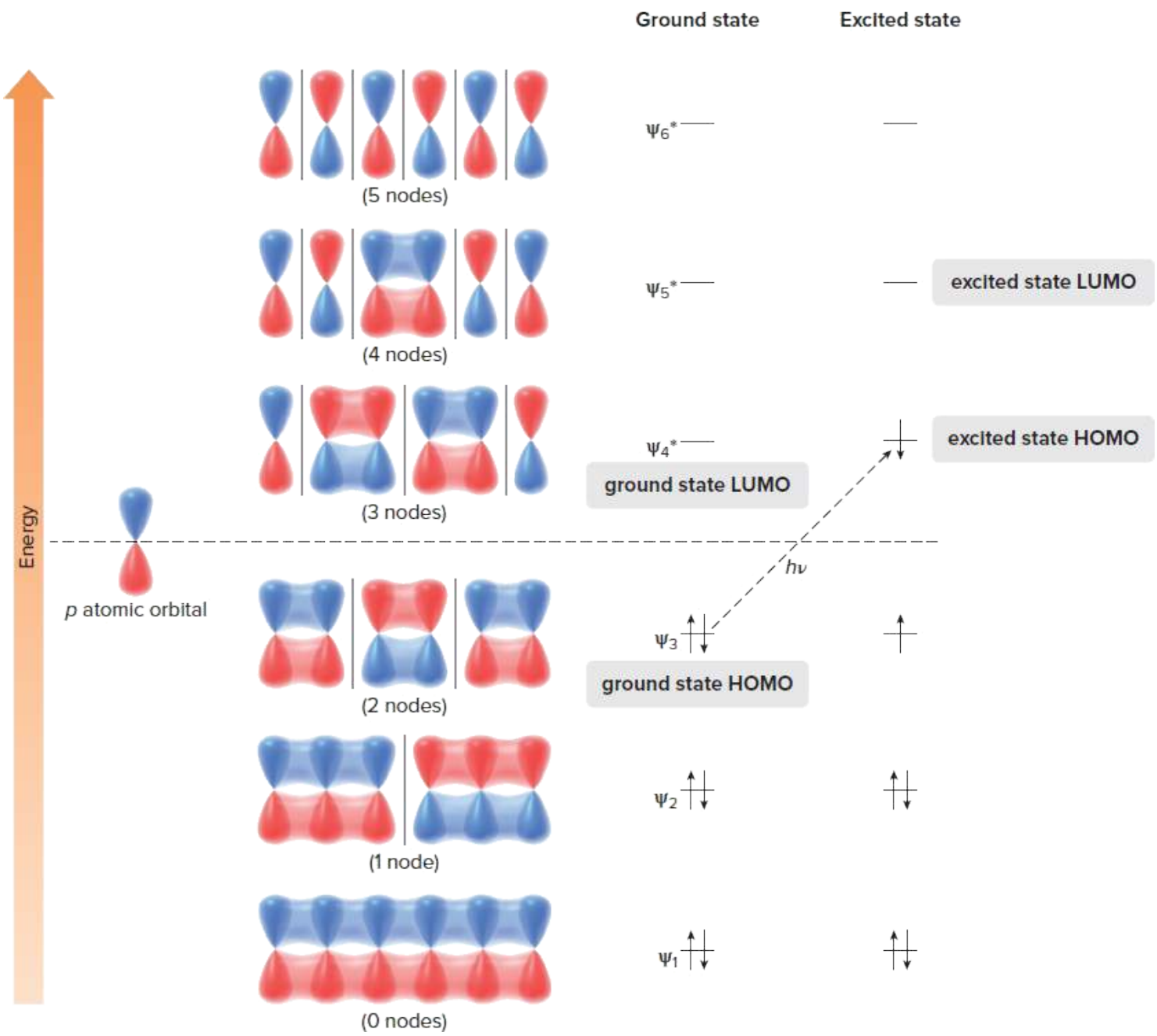


Figure 25.3 **The six π molecular orbitals of hexa-1,3,5-triene**

In the ground state electronic configuration, the six π electrons occupy the three bonding MOs, ψ_3 is the HOMO, and ψ_4^* is the LUMO. In the excited state, which results from promotion of an electron from ψ_3 to ψ_4^*, ψ_4^* is the HOMO and ψ_5^* is the LUMO.

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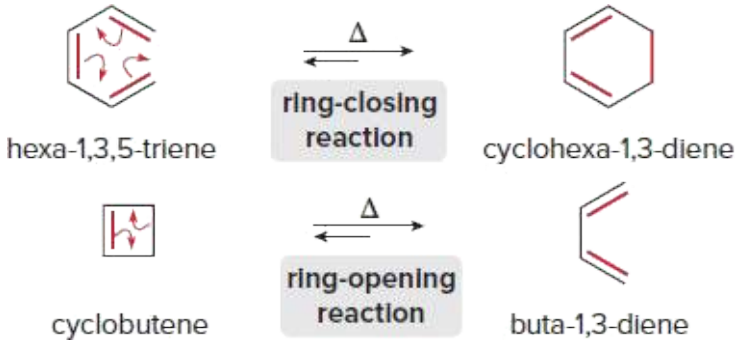
Problem 25.3

(a) Using Figure 25.2 as a guide, draw the molecular orbitals for hexa-2,4-diene. (b) Label the HOMO and the LUMO in the ground state. (c) Label the HOMO and the LUMO in the excited state.

25.3 Electrocyclic Reactions

An electrocyclic reaction is a reversible reaction that involves ring closure of a conjugated polyene to a cycloalkene, or ring opening of a cycloalkene to a conjugated polyene. For example, ring closure of hexa-1,3,5-triene forms cyclohexa-1,3-diene, a product with one more σ bond and one fewer π bond than the reactant. Ring opening of cyclobutene forms buta-1,3-diene, a product with one fewer σ bond and one more π bond than the reactant.



Arrows may be drawn in a clockwise or counterclockwise direction to show the flow of electrons.

- **To draw the product in each reaction, use curved arrows and *begin at a π bond.* Move the π electrons to an adjacent carbon–carbon bond and continue in a cyclic fashion.**

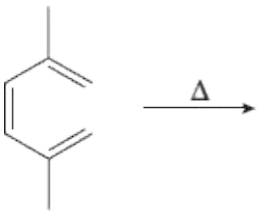
In a ring-closing reaction, this process forms a new σ bond that now joins the ends of the conjugated polyene. In a ring-opening reaction, this process breaks a σ bond to form a conjugated polyene with one more π bond.

Whether the reactant or product predominates at equilibrium depends on the ring size of the cyclic compound. Generally, a six-membered ring is favored over an acyclic triene at equilibrium. In contrast, an acyclic diene is favored over a strained four-membered ring.

Problem 25.4

Use curved arrows and draw the product of each electrocyclic reaction.

a.



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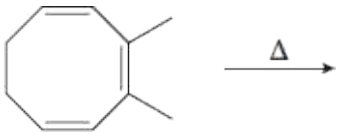
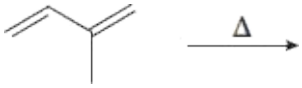
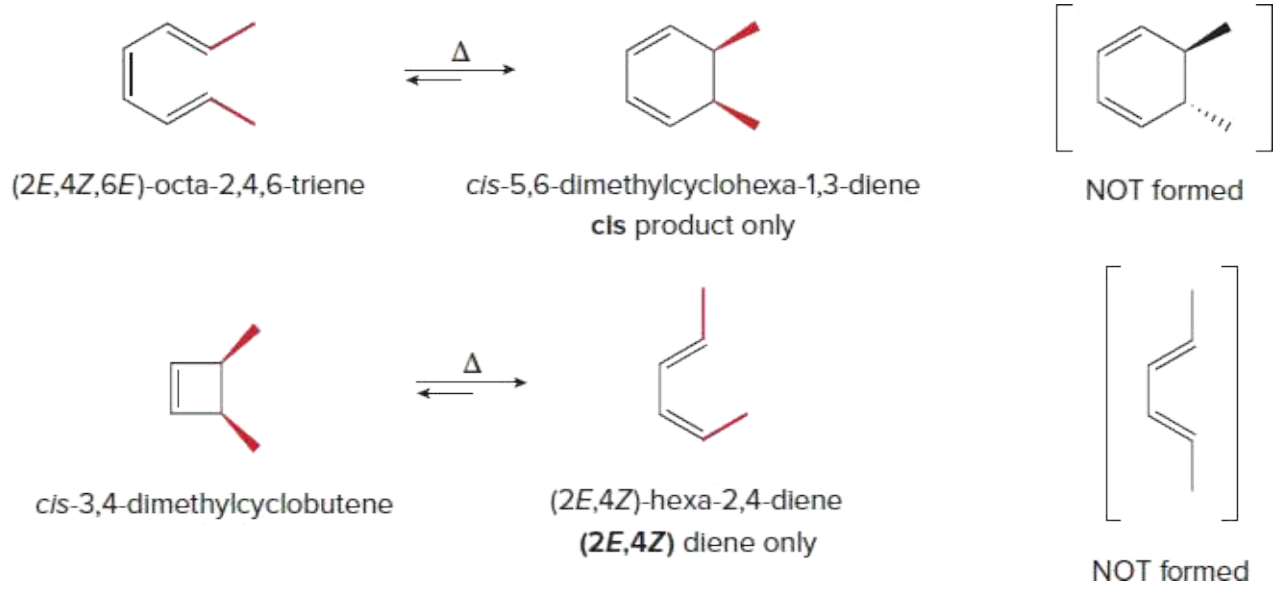


c.



25.3A Stereochemistry and Orbital Symmetry

Electrocyclic reactions are completely stereospecific. For example, ring closure of (2*E*,4*Z*,6*E*)-octa-2,4,6-triene yields a single product with cis methyl groups on the ring. Ring opening of *cis*-3,4-dimethylcyclobutene forms a single conjugated diene with one *Z* alkene and one *E* alkene.



Moreover, the stereochemistry of the product of an electrocyclic reaction depends on whether the reaction is carried out under thermal or photochemical reaction conditions—that is, with heat or light, respectively. Cyclization of (2*E*,4*E*)-hexa-2,4-diene with heat forms a cyclobutene with trans methyl groups, whereas cyclization with light forms a cyclobutene with cis methyl groups.

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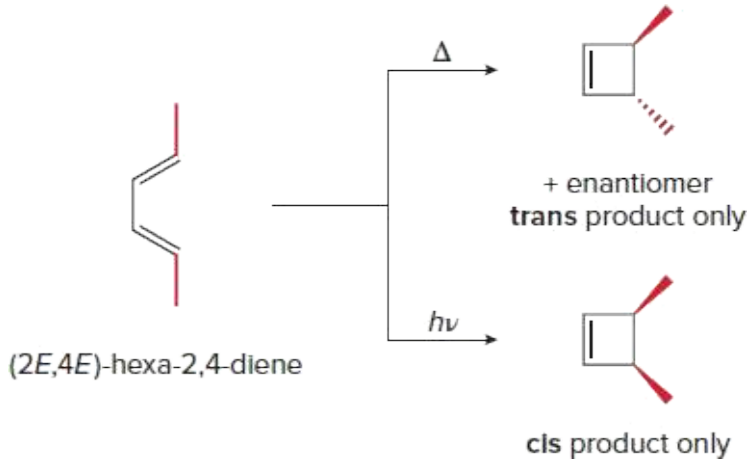
Electrocyclic ring closure generally forms either an achiral meso compound or a mixture of chiral enantiomers. When enantiomers form, only one enantiomer is drawn in these reactions.

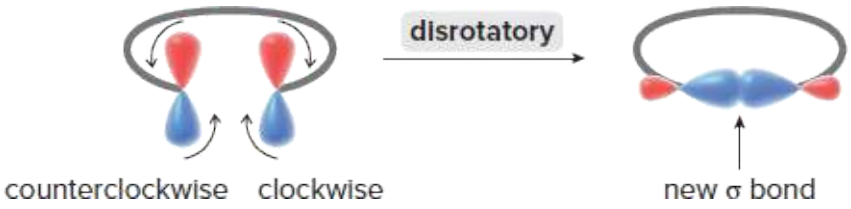


To understand these results, we must focus on the HOMO of the acyclic conjugated polyene that is either the reactant or product in an electrocyclic reaction. In particular, we must examine the *p* orbitals on the terminal carbons of the HOMO, and determine whether like phases of the orbitals are on the *same* side or on *opposite* sides of the molecule.

- **An electrocyclic reaction occurs only when like phases of orbitals can overlap to form a bond. Such a reaction is *symmetry allowed.***
- **An electrocyclic reaction cannot occur between lobes of opposite phase. Such a reaction is *symmetry forbidden.***

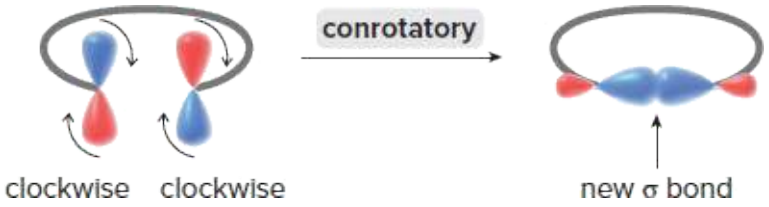
To form a bond, the *p* orbitals on the terminal carbons must rotate so that like phases can interact to form the new σ bond. Two modes of rotation are possible.

- **When like phases of the *p* orbitals are on the same side of the molecule, the two orbitals must rotate in *opposite* directions—one clockwise and one counterclockwise. Rotation in opposite directions is said to be *disrotatory.***



- **When like phases of the *p* orbitals are on opposite sides of the**

molecule, the two orbitals must rotate in the *same* direction—both clockwise or both counterclockwise. Rotation in the same direction is said to be *conrotatory.*



25.3B Thermal Electrocyclic Reactions

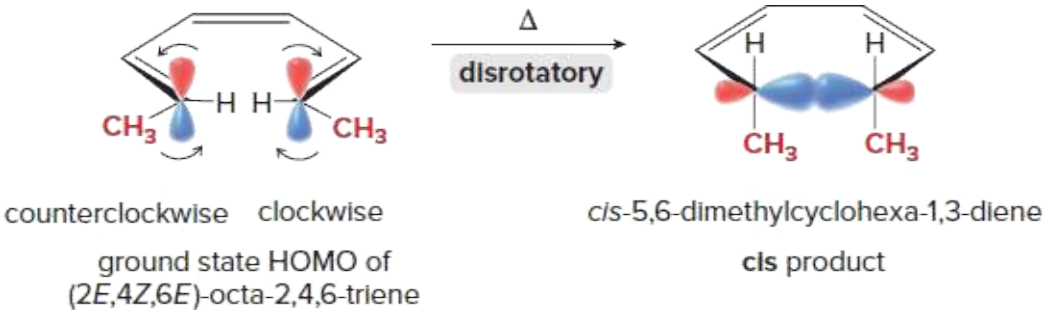
To explain the stereochemistry observed in electrocyclic reactions, we must examine the symmetry of the molecular orbital that contains the most loosely held π electrons. In a thermal reaction, we consider the HOMO of the ground state electronic configuration. Rotation occurs in a disrotatory or conrotatory fashion so that like phases of the *p* orbitals on the terminal carbons of this molecular orbital combine.

- **The number of double bonds in the conjugated polyene determines whether rotation is conrotatory or disrotatory.**

Two examples illustrate different outcomes.

Thermal electrocyclic ring closure of (2*E*,4*Z*,6*E*)-octa-2,4,6-triene yields a single product with cis methyl groups on the ring.

Only the *p* orbitals on the terminal carbons of the HOMO are drawn for clarity.



Cyclization occurs in a disrotatory fashion because the HOMO of a conjugated triene has like phases of the outermost *p* orbitals on the *same* side of the molecule (Figure 25.3). A disrotatory ring closure is symmetry allowed because like phases of the *p* orbitals overlap to form the new σ bond of the ring. In the disrotatory ring closure,

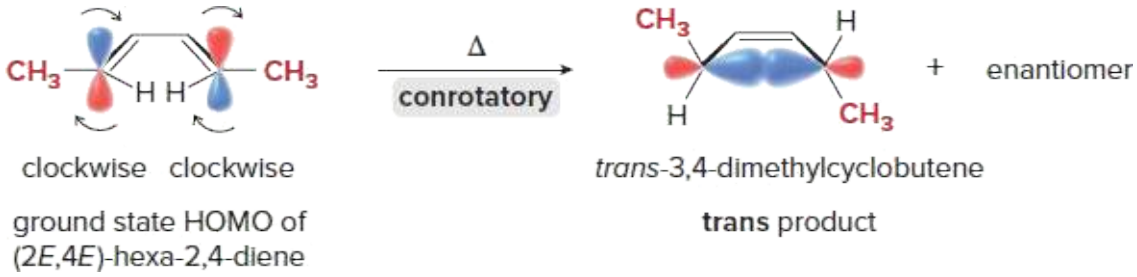
both methyl groups are pushed *down* (or *up*), making them *cis* in the product.

This is a specific example of the general process observed for conjugated polyenes with an *odd* number of π bonds. The HOMO of a conjugated polyene with an odd number of π bonds has like phases of the outermost *p* orbitals on the *same* side of the molecule. As a result:

- **Thermal electrocyclic reactions occur in a *disrotatory* fashion for a conjugated polyene with an *odd* number of π bonds.**

In contrast, thermal electrocyclic ring closure of (2*E*,4*E*)-hexa-2,4-diene forms a cyclobutene with trans methyl groups.

The conrotatory ring closure of (2*E*,4*E*)-hexa-2,4-diene is drawn with two clockwise rotations. The conrotatory ring closure could also be drawn with two counterclockwise rotations, leading to the enantiomer of the trans product drawn. Both enantiomers are formed in equal amounts.

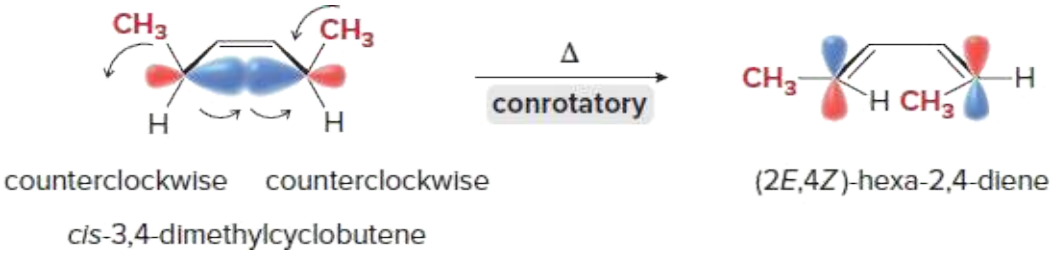


Cyclization occurs in a conrotatory fashion because the HOMO of a conjugated diene has like phases of the outermost *p* orbitals on *opposite* sides of the molecule (Figure 25.2). A conrotatory ring closure is symmetry allowed because like phases of the *p* orbitals overlap to form the new σ bond of the ring. In the conrotatory ring closure, one methyl group is pushed *down* and one methyl group is pushed *up*, making them *trans* in the product.

This is a specific example of the general process observed for conjugated polyenes with an *even* number of π bonds. The HOMO of a conjugated polyene with an even number of π bonds has like phases of the outermost *p* orbitals on *opposite* sides of the molecule. As a result:

- **Thermal electrocyclic reactions occur in a *conrotatory* fashion for a conjugated polyene with an *even* number of π bonds.**

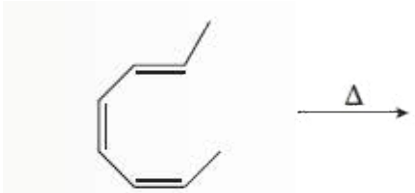
Because electrocyclic reactions are reversible, electrocyclic ring-opening reactions follow the same rules as electrocyclic ring closures. Thus, thermal ring opening of *cis*-3,4-dimethylcyclobutene—which ring opens to a diene with an *even* number of π bonds—occurs in a *conrotatory* fashion to form (2*E*,4*Z*)-hexa-2,4-diene as the only product.



Sample Problem 25.1 Drawing the Product of a Thermal Electrocyclic Ring Closure

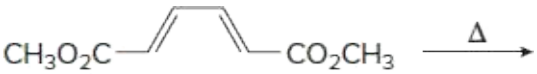
Draw the product of each thermal electrocyclic ring closure.

a.



(2*E*,4*Z*,6*Z*)-octa-2,4,6-triene

b.



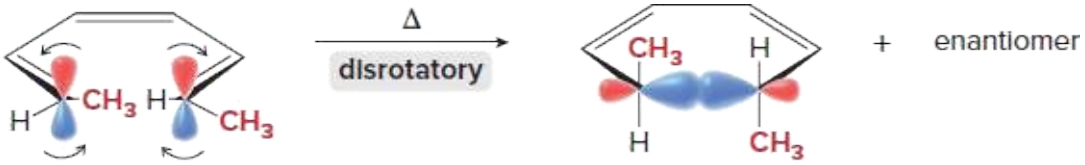
B

Solution

Count the number of π bonds in the conjugated polyene to determine the mode of ring closure in a thermal electrocyclic reaction.

- **A conjugated polyene with an odd number of π bonds undergoes disrotatory cyclization.**
- **A conjugated polyene with an even number of π bonds undergoes conrotatory cyclization.**

a. (2*E*,4*Z*,6*Z*)-Octa-2,4,6-triene contains three π bonds. The HOMO of a conjugated polyene with an *odd* number of π bonds has like phases of the outermost *p* orbitals on the *same* side of the molecule, and this results in *disrotatory* cyclization.



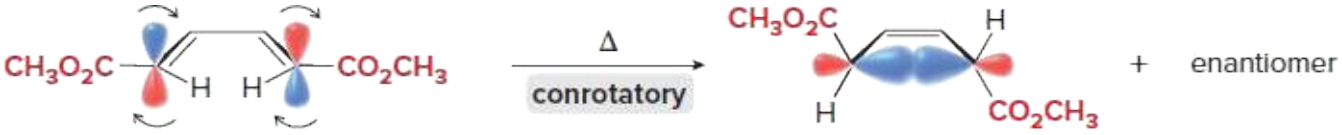
counterclockwise clockwise

(2*E*,4*Z*,6*Z*)-octa-2,4,6-triene

trans-5,6-dimethylcyclohexa-1,3-diene

trans product

b. Diene B contains two π bonds. The HOMO of a conjugated polyene with an *even* number of π bonds has like phases of the outermost *p* orbitals on *opposite* sides of the molecule, and this results in *conrotatory* cyclization.



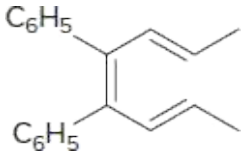
clockwise clockwise

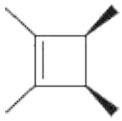
B

trans product

Problem 25.5

What product is formed when each compound undergoes thermal electrocyclic ring opening or ring closure? Label each process as conrotatory or disrotatory, and clearly indicate the stereochemistry around tetrahedral stereogenic centers and double bonds.

a. 

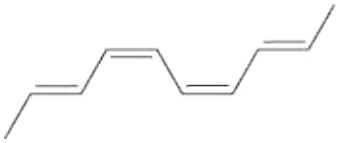
b. 

More Practice:

Try Problems 25.25a; 25.28; 25.31a, c; 25.34a; 25.50b.

Problem 25.6

What cyclic product is formed when each decatetraene undergoes thermal electrocyclic ring closure?

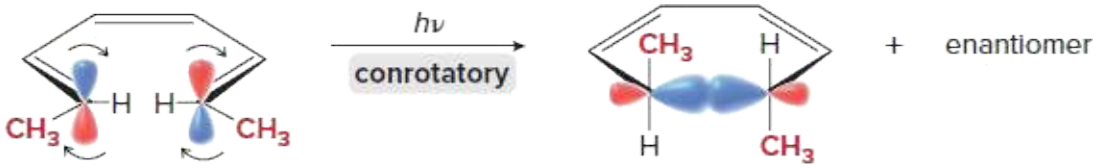
a. 

b.

25.3C Photochemical Electrocyclic Reactions

Photochemical electrocyclic reactions follow similar principles as those detailed in thermal reactions with one important difference: In photochemical reactions, we must consider the orbitals of the HOMO of the *excited* state to determine the course of the reaction. As a photon is absorbed, an electron in the ground state HOMO is excited to the ground state LUMO. As a result, the excited state HOMO is one energy level higher than before (see Figures 25.2 and 25.3). The excited state HOMO has the *opposite* orientation of the outermost *p* orbitals compared to the HOMO of the ground state. As a result, the method of ring closure of a photochemical electrocyclic reaction is *opposite* to that of a thermal electrocyclic reaction for the same number of π bonds.

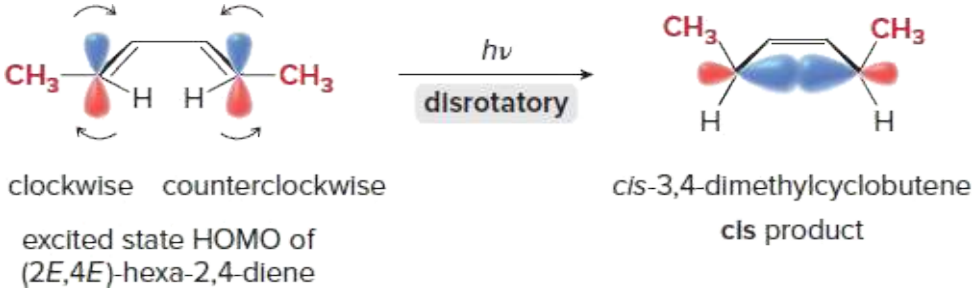
Photochemical electrocyclic ring closure of (2*E*,4*Z*,6*E*)-octa-2,4,6-triene yields a cyclic product with trans methyl groups on the ring.



Cyclization occurs in a conrotatory fashion because the excited state HOMO of a conjugated triene has like phases of the outermost *p* orbitals on the *opposite* sides of the molecule (Figure 25.3). In the conrotatory ring closure, one methyl group is pushed *down* and one methyl group is pushed *up*, making them *trans* in the product. This is a specific example of the general process observed for conjugated polyenes with an *odd* number of π bonds.

- **Photochemical electrocyclic reactions occur in a *conrotatory* fashion for a conjugated polyene with an *odd* number of π bonds.**

Photochemical electrocyclic ring closure of (2*E*,4*E*)-hexa-2,4-diene forms a cyclobutene with cis methyl groups.



Cyclization occurs in a disrotatory fashion because the excited state HOMO of a conjugated diene has like phases of the outermost *p* orbitals on the *same* side of the molecule (Figure 25.3). In the disrotatory ring closure, both methyl groups are pushed *down* (or *up*), making them *cis* in the product. This is a specific example of the general process observed for conjugated polyenes with an *even* number of π bonds.

- **Photochemical electrocyclic reactions occur in a *disrotatory* fashion for a conjugated polyene with an *even* number of π bonds.**

Problem 25.7

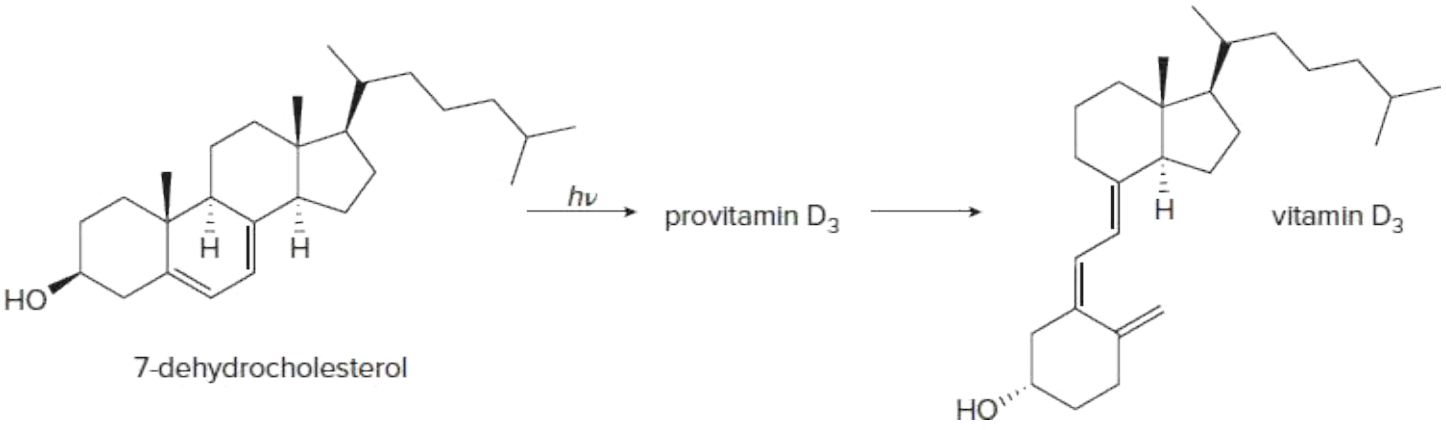
What product is formed when each compound in Problem 25.5 undergoes photochemical electrocyclic ring opening or ring closure? Label each process as conrotatory or disrotatory and clearly indicate the stereochemistry around tetrahedral stereogenic centers and double bonds.

Vitamin D (Problem 25.8) regulates calcium absorption, so adequate vitamin D levels are needed for proper bone growth. Vitamin D-fortified milk sold in the United States is produced by exposing milk to ultraviolet light. ***©McGraw-Hill Education/Mary Reeg, photographer***

Problem 25.8

Vitamin D_3, the most abundant of the D vitamins, is synthesized from 7-dehydrocholesterol, a compound found in milk and fatty fish such as salmon and mackerel. When the skin is exposed to sunlight, a photochemical electrocyclic ring

opening forms provitamin D_3, which is then converted to vitamin D_3 by a sigmatropic rearrangement (Section 25.5). Draw the structure of provitamin D_3.



25.3D Summary of Electrocyclic Reactions

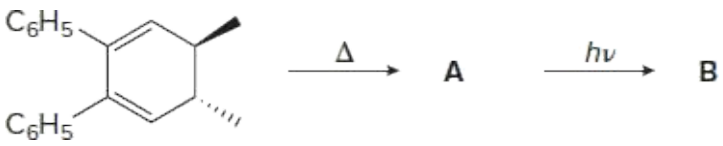
Table 25.1 summarizes the rules, often called the Woodward–Hoffmann rules, for electrocyclic reactions under thermal or photochemical reaction conditions. The number of π bonds refers to the acyclic conjugated polyene that is either the reactant or product of an electrocyclic reaction.

Table 25.1 Woodward–Hoffmann Rules for Electrocyclic Reactions

Number of π bonds	Thermal reaction	Photochemical reaction
Even	Conrotatory	Disrotatory
Odd	Disrotatory	Conrotatory

Sample Problem 25.2 Determining the Product of an Electrocyclic Reaction

Identify A and B in the following reaction sequence. Label each process as conrotatory or disrotatory.



Solution

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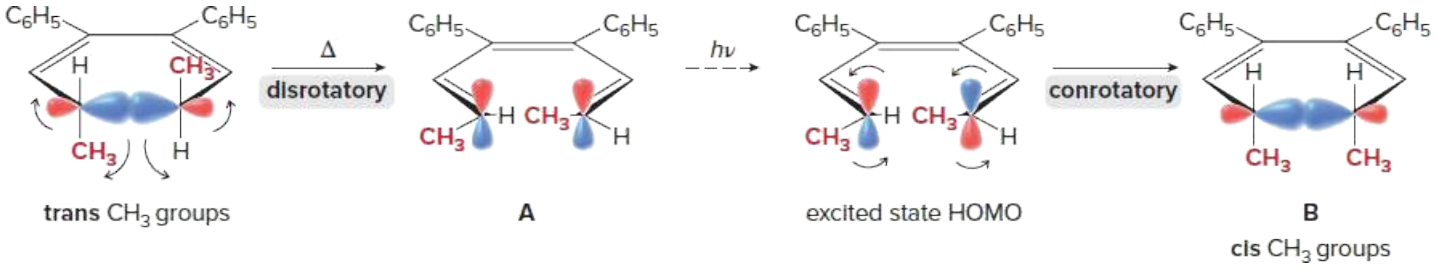
Ring opening of a cyclohexadiene forms a hexatriene with three π bonds. A conjugated polyene with an odd number of π bonds undergoes a thermal electrocyclic reaction in a disrotatory fashion (Table 25.1). The resulting hexatriene (A) then undergoes a photochemical electrocyclic reaction in a conrotatory fashion to form a cyclohexadiene with cis methyl groups (B).

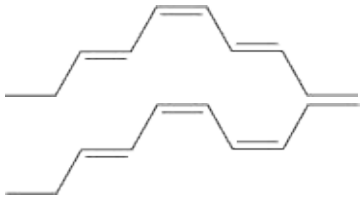


Problem 25.9

Draw the product formed when each triene undergoes electrocyclic reaction under [1] thermal conditions; [2] photochemical conditions.

a.

b.



More Practice:

Try Problems 25.25; 25.28–25.35; 25.50b, d.

Problem 25.10

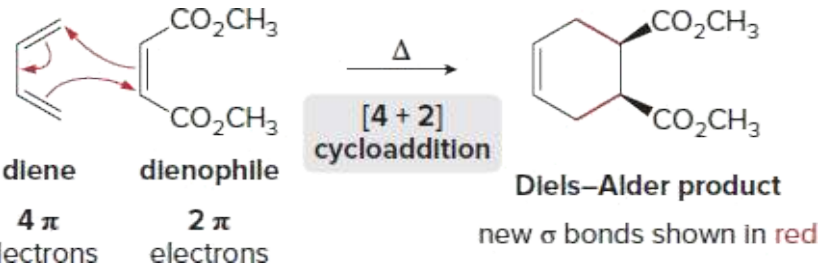
What product would be formed by the disrotatory cyclization of the given triene? Would this reaction occur under photochemical or thermal conditions?

25.4 Cycloaddition Reactions

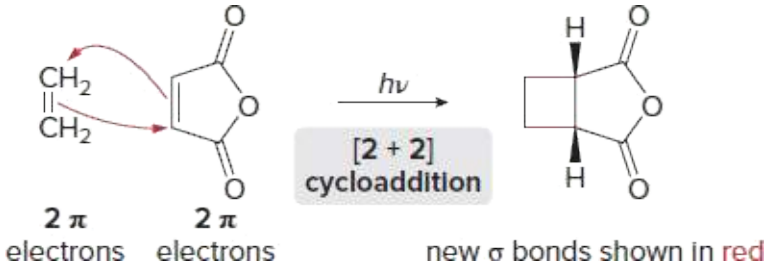
A cycloaddition is a reaction between two compounds with π bonds to form a cyclic product with two new σ bonds. Like electrocyclic reactions, cycloadditions are concerted, stereospecific reactions, and the course of the reaction is determined by the symmetry of the molecular orbitals of the reactants.

Cycloadditions can be initiated by heat (thermal conditions) or light (photochemical conditions). Cycloadditions are identified by the number of π electrons in the two reactants.

The Diels–Alder reaction is a thermal [4 + 2] cycloaddition that occurs between a diene with four π electrons and an alkene (dienophile) with two π electrons (Sections 14.12–14.14).

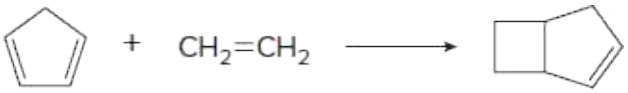


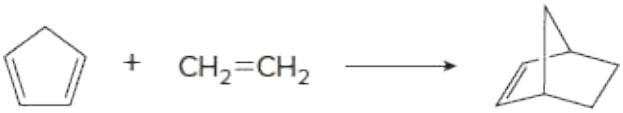
A photochemical [2 + 2] cycloaddition occurs between two alkenes, each with two π electrons, to form a cyclobutane. Thermal [2 + 2] cycloadditions do *not* take place.



Sample Problem 25.3 Classifying a Cycloaddition

What type of cycloaddition is shown in each equation?

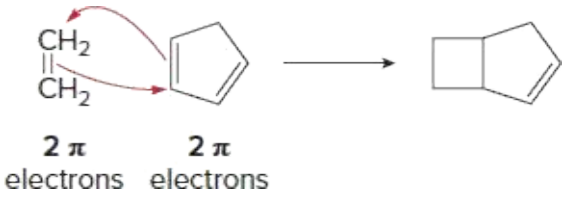
a. 

b. 

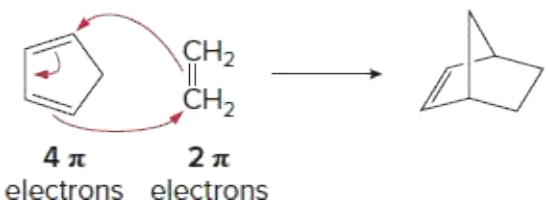
Solution

Count the number of π electrons *involved in each reactant* to classify the cycloaddition.

a. [2 + 2] Cycloaddition

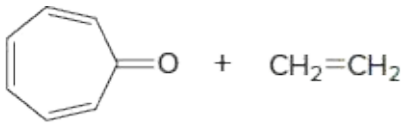


b. [4 + 2] Cycloaddition



Problem 25.11

Consider cycloheptatrienone and ethylene, and draw a possible product formed from each type of cycloaddition: (a) [2 + 2]; (b) [4 + 2]; (c) [6 + 2].



cycloheptatrienone

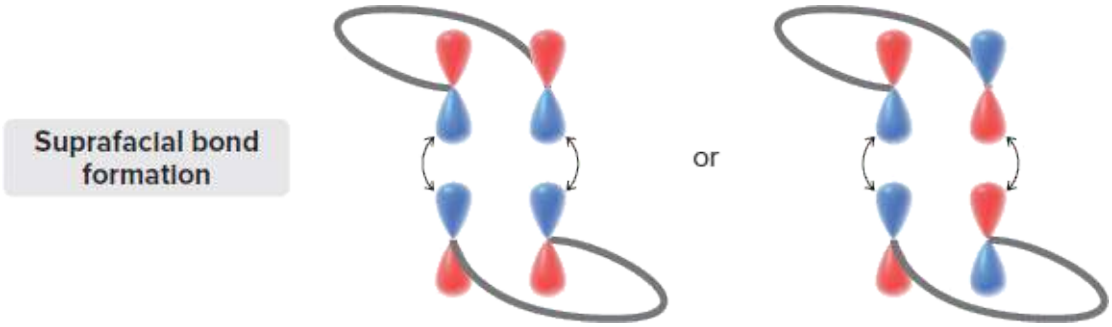
More Practice:

Try Problem 25.36.

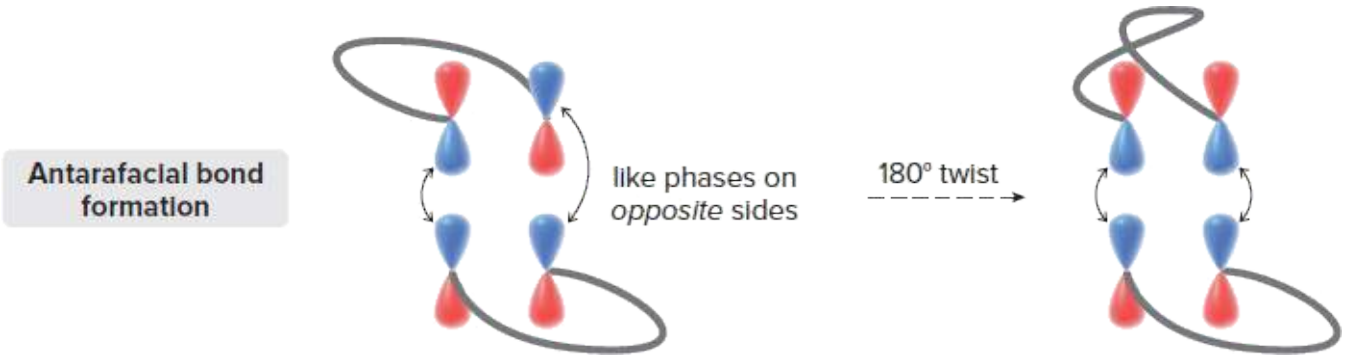
25.4A Orbital Symmetry and Cycloadditions

To understand cycloaddition reactions, we examine the *p* orbitals of the terminal carbons of both reactants. Bonding can take place only when like phases of both sets of *p* orbitals can combine. Two modes of reaction are possible.

- **A suprafacial cycloaddition occurs when like phases of the *p* orbitals of both reactants are on the *same* side of the π system, so that two bonding interactions result.**



- **An antarafacial cycloaddition occurs when one π system must *twist* to align like phases of the *p* orbitals of the terminal carbons of the reactants.**



Because of the geometrical constraints of small rings, cycloadditions that

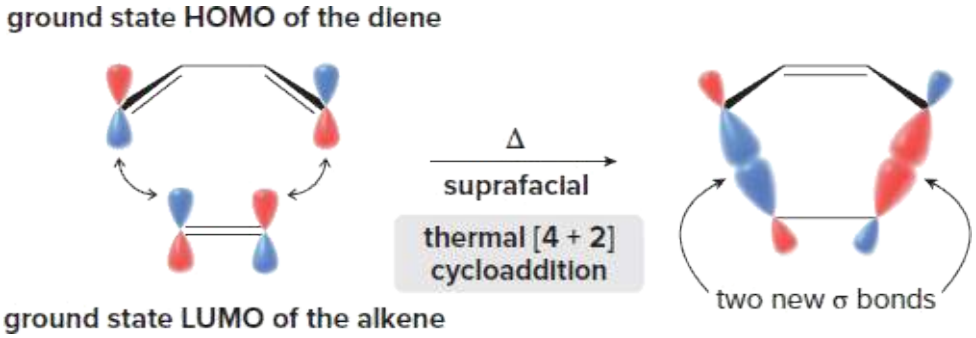
form four- or six-membered rings must take place by suprafacial pathways.

Because cycloaddition involves the donation of electron density from one reactant to another, one reactant donates its most loosely held electrons—those occupying its HOMO—to a vacant orbital that can accept electrons—the LUMO—of the second reactant. The HOMO of either reactant can be used for analysis.

- **In a cycloaddition, we examine the bonding interactions of the HOMO of one component with the LUMO of the second component.**

25.4B [4 + 2] Cycloadditions

To examine the course of a [4 + 2] cycloaddition, let's arbitrarily choose the HOMO of the diene and the LUMO of the alkene, and look at the symmetry of the *p* orbitals on the terminal carbons of both components. Because two bonding interactions result from overlap of the like phases of both sets of *p* orbitals, a [4 + 2] cycloaddition occurs readily by suprafacial reaction under thermal conditions.

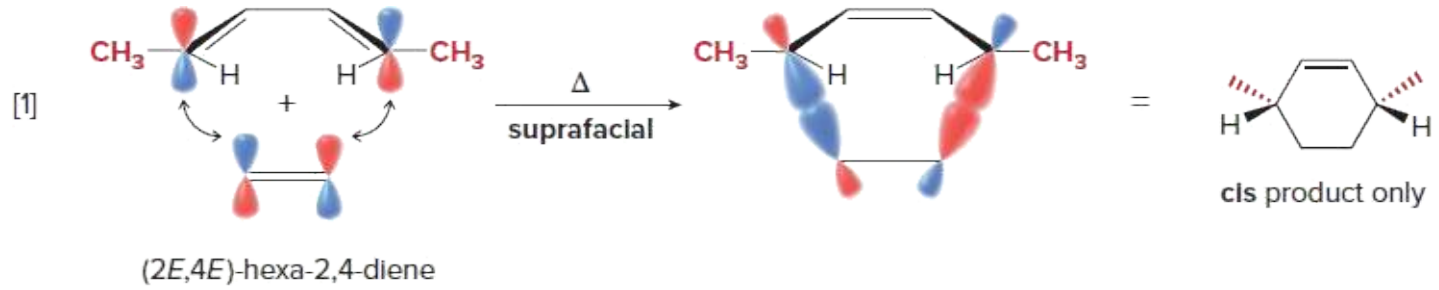


This is a specific example of a general cycloaddition involving an *odd* number of π bonds (three π bonds total, two from the diene and one from the alkene).

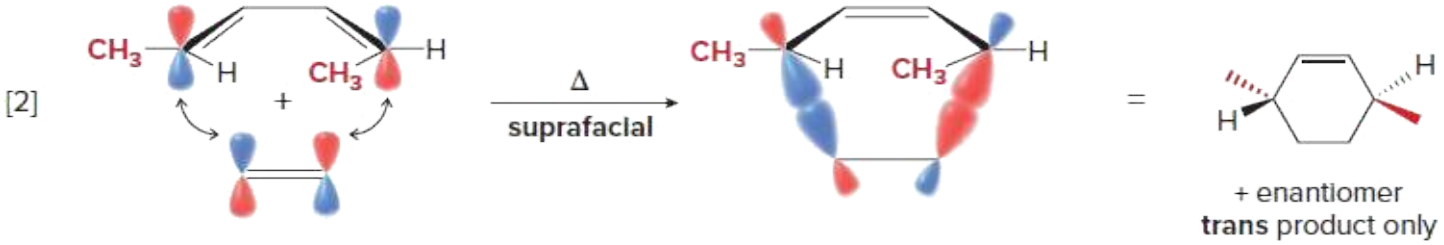
- **Thermal cycloadditions involving an *odd* number of π bonds proceed by a *suprafacial* pathway.**

In Section 14.13, we learned that the stereochemistry of the dienophile is retained in the Diels–Alder product.

Because a Diels–Alder reaction follows a concerted, suprafacial pathway, the stereochemistry of the diene is retained in the Diels–Alder product. As a result, reaction of (2*E*,4*E*)-hexa-2,4-diene with ethylene forms a cyclohexene with cis substituents (Reaction [1]), whereas reaction of (2*E*,4*Z*)-hexa-2,4-diene with ethylene forms a cyclohexene with trans substituents (Reaction [2]).



(2*E*,4*E*)-hexa-2,4-diene



(2*E*,4*Z*)-hexa-2,4-diene

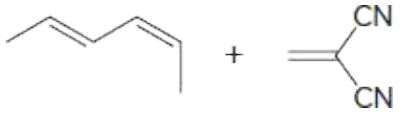
Problem 25.12

Show that a thermal suprafacial addition is symmetry allowed in a [4 + 2] cycloaddition by using the HOMO of the alkene and the LUMO of the diene.

Problem 25.13

Draw the product (including stereochemistry) formed from each pair of reactants in a thermal [4 + 2] cycloaddition reaction.

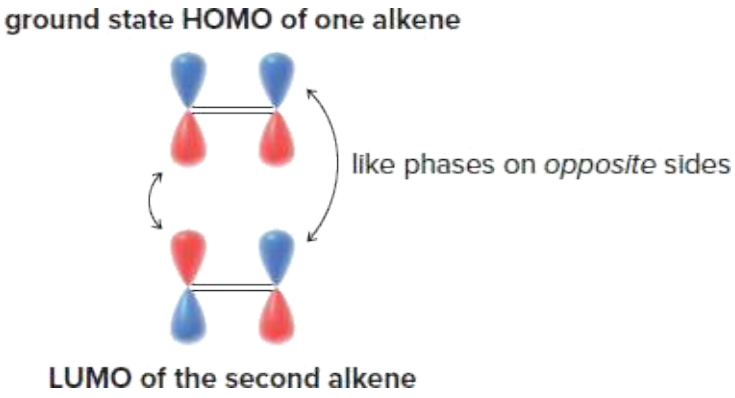
a.

b. 

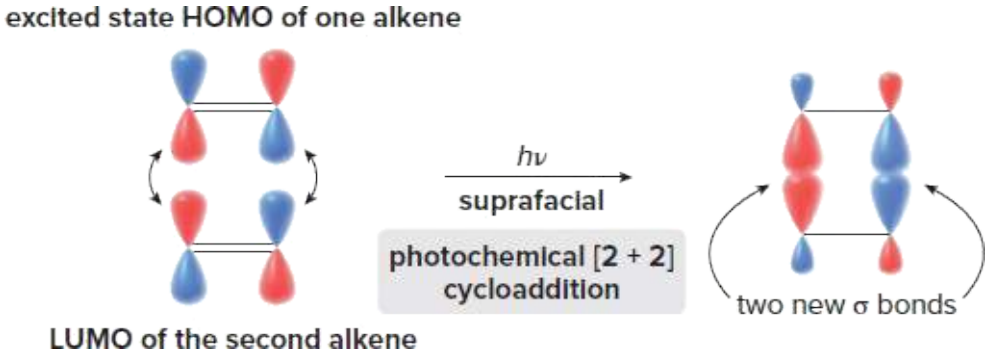
25.4C [2 + 2] Cycloadditions

In contrast to a [4 + 2] cycloaddition, a [2 + 2] cycloaddition does *not* occur under thermal conditions, but *does* take place photochemically. This result is explained by examining the symmetry of the HOMO and LUMO of the alkene reactants.

In a thermal [2 + 2] cycloaddition, like phases of the *p* orbitals on only one set of terminal carbons can overlap. For like phases to overlap on the other terminal carbon, the molecule must twist to allow for an antarafacial pathway. This process *cannot* occur to form small rings.



In a photochemical [2 + 2] cycloaddition, light energy promotes an electron from the ground state HOMO to form the excited state HOMO (designated as ψ_2^* in Figure 25.1). Interaction of this excited state HOMO with the LUMO of the second alkene then allows for overlap of the like phases of both sets of *p* orbitals. Two bonding interactions result and the reaction occurs by a suprafacial pathway.



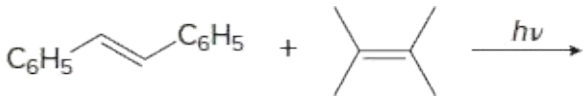
This is a specific example of a general cycloaddition involving an *even* number of π bonds (two π bonds total, one from each alkene).

- **Photochemical cycloadditions involving an *even* number of π bonds proceed by a *suprafacial* pathway.**

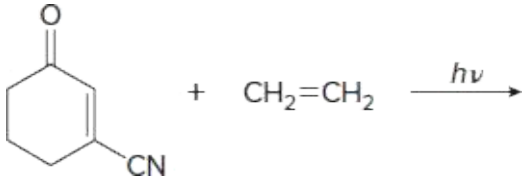
Problem 25.14

Draw the product formed in each cycloaddition.

a.



b.



25.4D Summary of Cycloaddition Reactions

Table 25.2 summarizes the Woodward–Hoffmann rules that govern cycloaddition reactions. The number of π bonds refers to the total number of π bonds from both

components of the cycloaddition. For a given number of π bonds, the mode of cycloaddition is always *opposite* in thermal and photochemical reactions.

Table 25.2 Woodward–Hoffmann Rules for Cycloaddition Reactions

Number of π bonds	Thermal reaction	Photochemical reaction
Even	Antarafacial	Suprafacial
Odd	Suprafacial	Antarafacial

Problem 25.15

Using the Woodward–Hoffmann rules, predict the stereochemical pathway for each cycloaddition: (a) a [6 + 4] photochemical reaction; (b) an [8 + 2] thermal reaction.

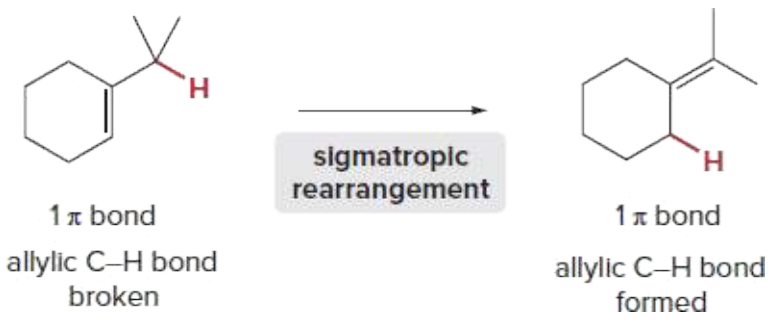
Problem 25.16

Using orbital symmetry, explain why a Diels–Alder reaction does not take place under photochemical reaction conditions.

25.5 Sigmatropic Rearrangements

A sigmatropic rearrangement is an intramolecular pericyclic reaction in which a σ bond is broken in a reactant, the π bonds rearrange, and a new σ bond is formed in the product.

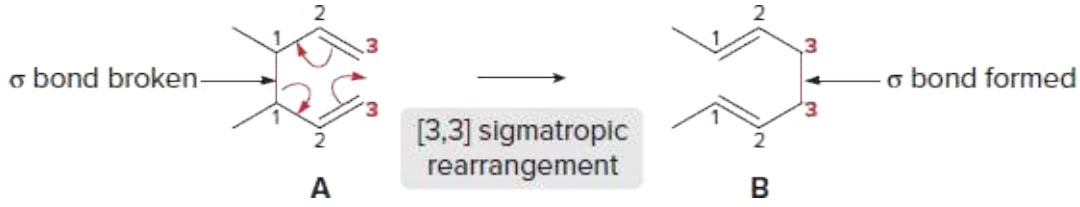
In a sigmatropic rearrangement, the number of π bonds in the reactant and product is constant, and the σ bonds broken and formed are allylic C–H, C–C, or C–Z bonds (Z = N, O, or S). A sigmatropic rearrangement that results in cleavage and formation of a C–H bond is shown.



Sigmatropic rearrangements are characterized by a set of numbers in brackets, [*n*,*m*], to indicate the location of the new σ bond relative to the broken σ bond. To designate a sigmatropic rearrangement:

- **Locate the σ bond broken in the reactant and label both atoms in the bond with "1's."**
- **Locate the new σ bond in the product, and count the number of atoms from the broken σ bond to the new σ bond for each fragment.**
- **Place both numbers in brackets, with the lower number first. In a rearrangement involving a C–H bond, the first number is always "1."**

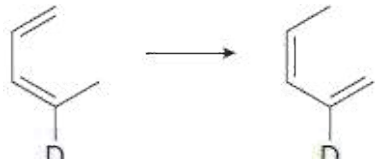
For example, a [3,3] sigmatropic rearrangement converts diene A to diene B when an allylic C–C bond in A is broken and a new allylic C–C bond is formed in B. Page 1147



Sample Problem 25.4 Determining the Type of Sigmatropic Rearrangement

What type of sigmatropic rearrangement is illustrated in each equation?

a.

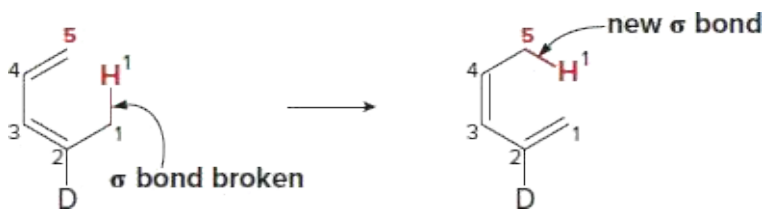


b.

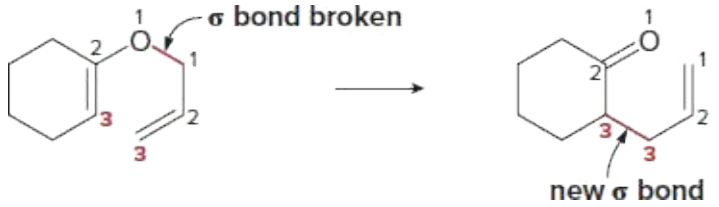
Solution

Locate the atoms in the broken σ bond and label them with 1's. Locate the atoms in the new σ bond, and count the number of atoms from the bond broken to the bond formed. When a C–H bond is broken, the first number in the [*n*,*m*] designation must be 1, because the H atom is bonded to no other atom.

a. A C–H bond is broken on the allylic C and a new C–H bond is formed on C5, so the reaction is a [1,5] sigmatropic rearrangement.



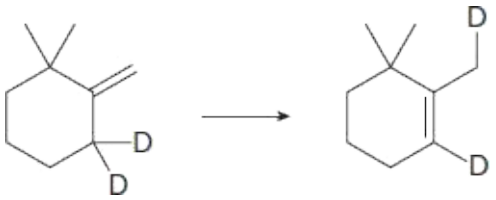
b. The reaction is a [3,3] sigmatropic rearrangement, because a C–O σ bond is broken and a new allylic C–C σ bond is formed between carbons that are three atoms removed from the broken bond.



Problem 25.17

What type of sigmatropic rearrangement is illustrated in each equation?

a.



b.

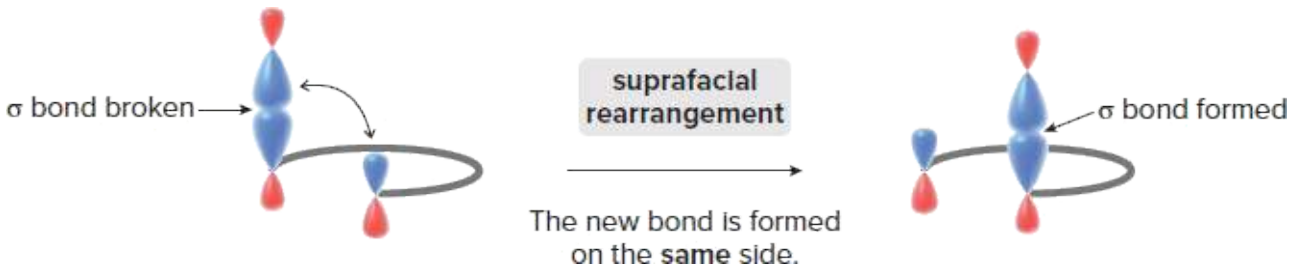
More Practice:

Try Problems 25.42, 25.49[2].

25.5A Sigmatropic Rearrangements and Orbital Symmetry

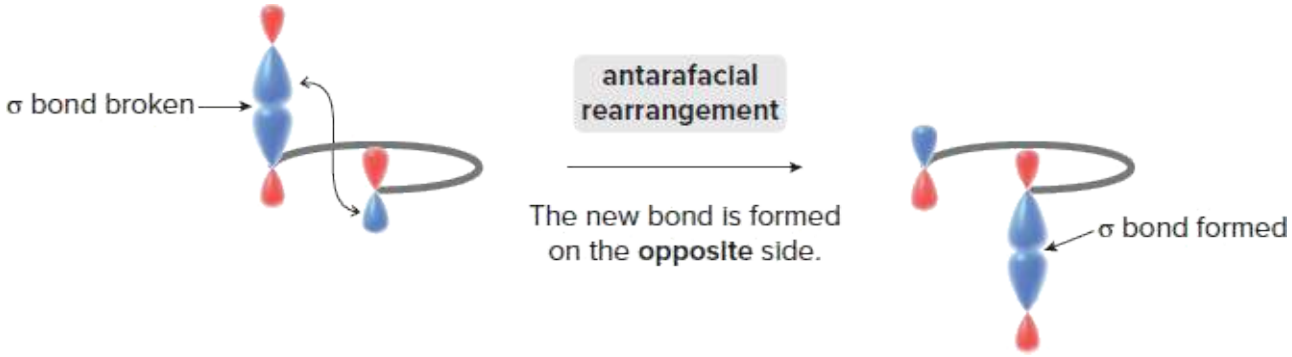
The stereochemistry of a sigmatropic rearrangement, like that of other pericyclic reactions, is determined by the symmetry of the orbitals involved in the reaction. In sigmatropic rearrangements, we consider the orbitals of the σ bond that is broken and the terminal *p* orbital of the π bond at which the new σ bond forms. Two modes of rearrangement are possible: suprafacial and antarafacial.

- **In a suprafacial rearrangement, the new σ bond forms on the *same* side of the π system as the broken σ bond.**



- **In an antarafacial rearrangement, the new σ bond forms on the *opposite***

side of the π system as the broken σ bond.

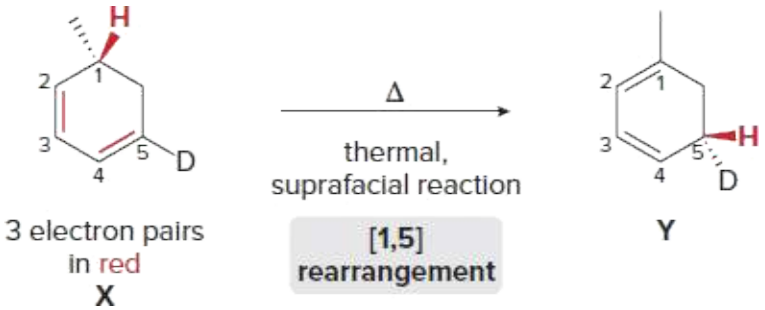


Sigmatropic rearrangements can occur under thermal or photochemical conditions, and follow the same rules observed in cycloaddition reactions. With sigmatropic rearrangements we count the total number of electron pairs in the σ bond that is broken and the π bonds that rearrange (Table 25.3). Because sigmatropic rearrangements involve cyclic transition states and small rings have geometrical constraints, reactions involving six or fewer atoms must take place by suprafacial pathways.

Table 25.3 Woodward–Hoffmann Rules for Sigmatropic Rearrangements

Number of electron pairs	Thermal reaction	Photochemical reaction
Even	Antarafacial	Suprafacial
Odd	Suprafacial	Antarafacial

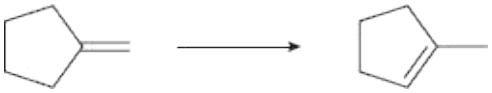
For example, a [1,5] sigmatropic rearrangement of X to Y involves three electron pairs, one from the σ bond that is broken and two from the π bonds that rearrange.



According to Table 25.3, this reaction must occur in a suprafacial mode under thermal conditions and in an antarafacial mode under photochemical conditions. Because this reaction involves only six atoms (including the H atom that migrates), it must take place under thermal conditions in a suprafacial fashion.

Sample Problem 25.5 Determining Whether a Sigmatropic Rearrangement Occurs Under Thermal or Photochemical Conditions

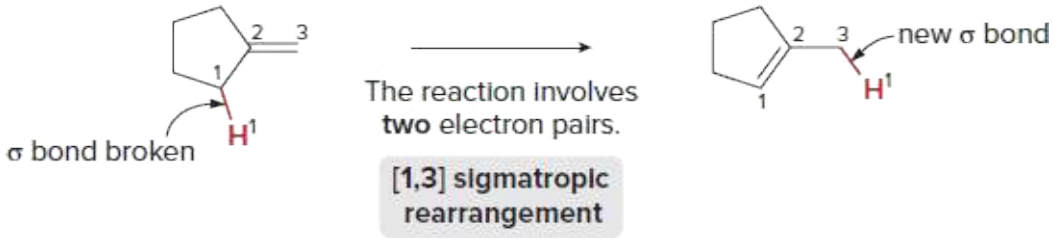
Classify the following sigmatropic rearrangement and determine whether it takes place readily under thermal or photochemical reaction conditions.



Solution

Page 1149

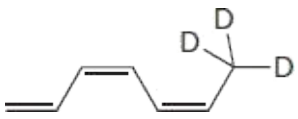
- **Classify the rearrangement as in Sample Problem 25.4: Label the atoms in the broken σ bond with 1's, locate the new σ bond, and count the number of atoms from the bond broken to the bond formed.**
- **Count the number of electron pairs involved in the reaction, and use Table 25.3 to determine the stereochemical pathway of the reaction. Keep in mind that reactions involving six or fewer atoms must take place by suprafacial pathways.**



This reaction is a [1,3] sigmatropic rearrangement, involving two electron pairs: the C–H σ bond broken and one π bond. Because the reaction involves four atoms, it must take place via a suprafacial pathway, which occurs under photochemical conditions.

Problem 25.18

(a) What product is formed from the [1,7] sigmatropic rearrangement of a deuterium in the following triene? (b) Does this reaction proceed in a suprafacial or antarafacial manner under thermal conditions? (c) Does this reaction proceed in a suprafacial or antarafacial manner under photochemical conditions?

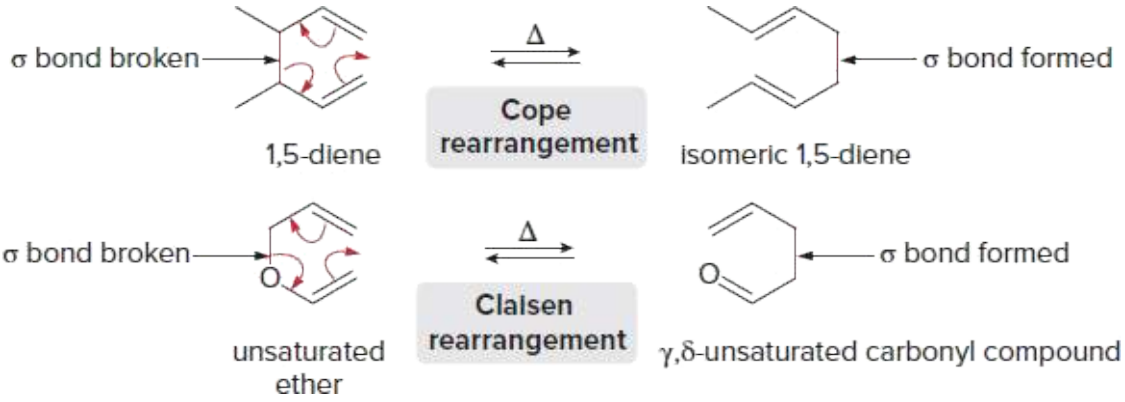


More Practice:

Try Problems 25.45, 25.49[2].

25.5B [3,3] Sigmatropic Rearrangements

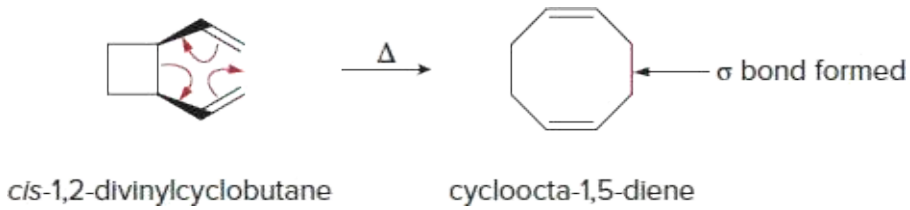
Two widely used [3,3] sigmatropic rearrangements in organic synthesis are the Cope rearrangement of a 1,5-diene to an isomeric 1,5-diene, and the Claisen rearrangement of an unsaturated ether to a γ,δ-unsaturated carbonyl compound.



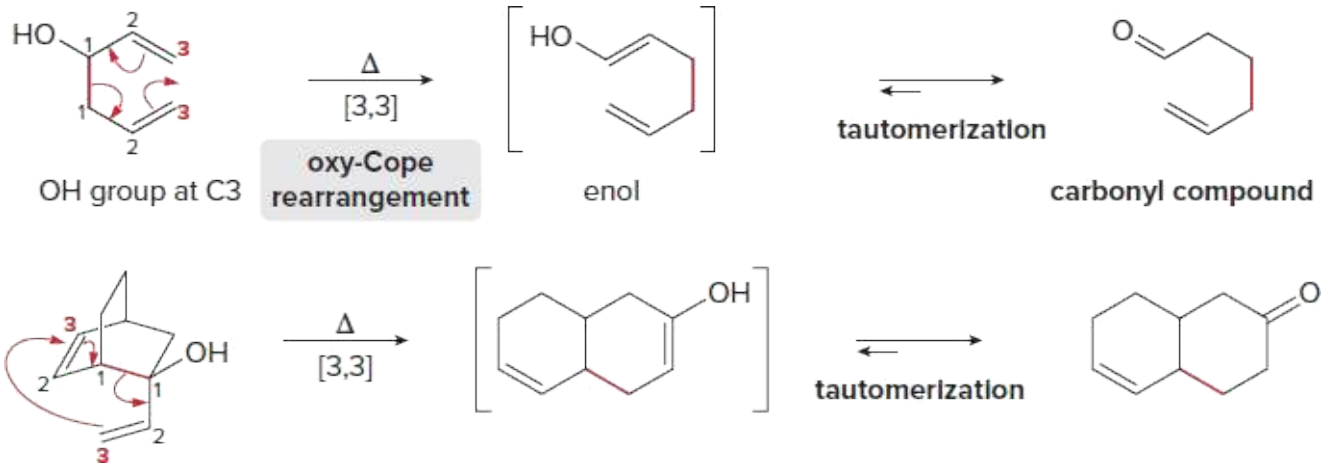
Both reactions involve three electron pairs—two π bonds and one σ bond—and six atoms, and take place readily in a suprafacial pathway under thermal conditions.

Cope Rearrangement

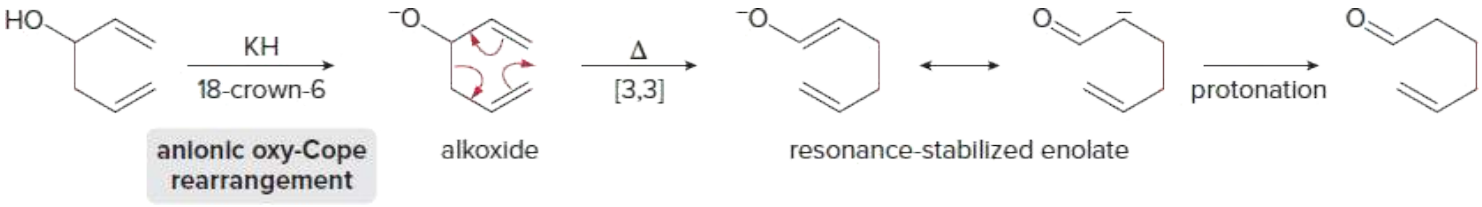
Because a Cope rearrangement involves isomeric 1,5-dienes as reactant and product, the more stable diene is favored at equilibrium. Useful Cope rearrangements occur when the reactant 1,5-diene is considerably less stable than the product, as in the case of *cis*-1,2-divinylcyclobutane, which rearranges to cycloocta-1,5-diene with loss of strain from the cyclobutane ring.



The oxy-Cope rearrangement is an especially powerful variation of a Cope rearrangement using an unsaturated alcohol. [3,3] Sigmatropic rearrangement forms an enol initially, which then tautomerizes to form a carbonyl group.

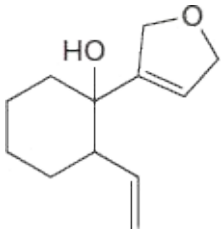


Moreover, *anionic* oxy-Cope rearrangements often give high yields of rearranged product under very mild reaction conditions. In an anionic oxy-Cope rearrangement, the unsaturated alcohol reactant is first treated with strong base, usually KH in the presence of 18-crown-6 (Section 9.5B), to form an alkoxide. [3,3] Sigmatropic rearrangement then yields a resonance-stabilized enolate, which is protonated to form a carbonyl product.



Sample Problem 25.6 Drawing the Product of a [3,3] Sigmatropic Rearrangement

Draw the product when the following compound undergoes a [3,3] sigmatropic rearrangement.



Solution

To draw the product of a [3,3] sigmatropic rearrangement:

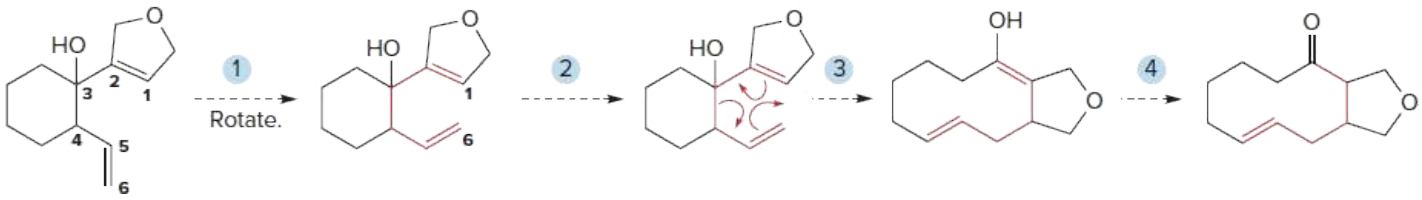
- **Locate the 1,5-diene unit, and draw the ends of the double bonds (C1 and C6) close to each other.**
- **Draw three arrows beginning with a π bond. Break two π bonds and one σ bond to draw the product.**
- **If an enol is formed, tautomerize the enol to a keto form.**

1 Identify the 1,5-diene, and place C1 and C6 close to each other.

2 **Draw three arrows,** beginning at a π bond.

3 Draw the product.

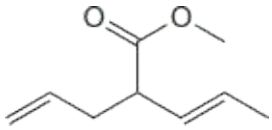
4 Tautomerize.



Problem 25.19

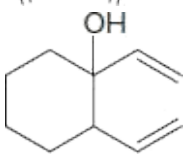
What product is formed from the Cope or oxy-Cope rearrangement of each starting material?

a.



b.

c.

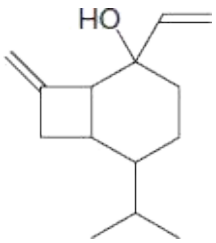


More Practice:

Try Problems 25.26a; 25.43b, c; 25.44; 25.47; 25.51b; 25.53b.

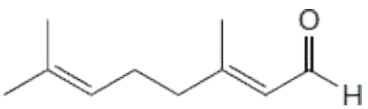
Problem 25.20

One step in the synthesis of periplanone B, the chapter-opening molecule, involves anionic oxy-Cope rearrangement of the following unsaturated alcohol. Draw the product that results after protonation of the intermediate enolate.



Problem 25.21

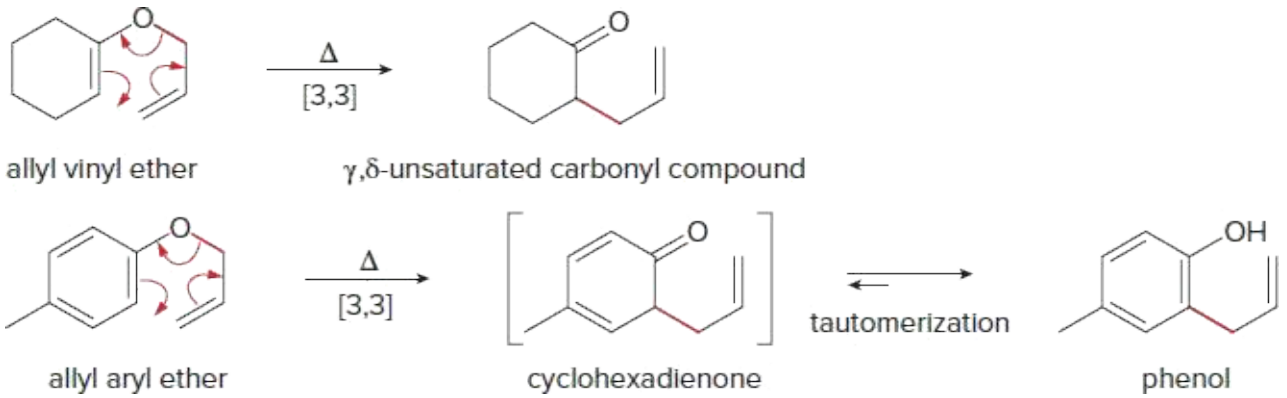
What compound forms geranial by a Cope rearrangement?



geranial

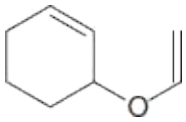
Claisen Rearrangement

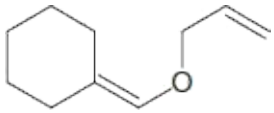
A Claisen rearrangement is a [3,3] sigmatropic rearrangement of an unsaturated ether, either an allyl vinyl ether or an allyl aryl ether. With an allyl vinyl ether, a γ,δ-unsaturated carbonyl compound is formed directly by the concerted rearrangement. With an allyl aryl ether, Claisen rearrangement initially generates a cyclohexadienone intermediate, which tautomerizes to a phenol that contains an allyl group ortho to the OH group.

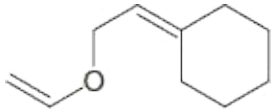


Problem 25.22

What product is formed from the Claisen rearrangement of each starting material?

a. 

b. 

c. 

Garsubellin A (Problem 25.23) is isolated from the wood of *Garcinia subelliptica*, a tree grown in Okinawa, Japan.

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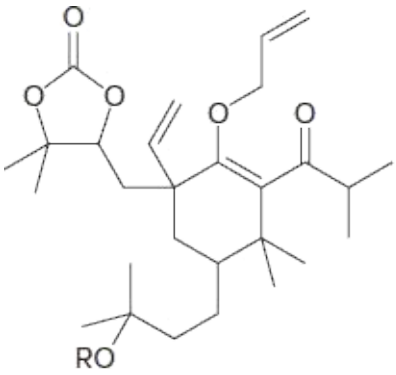
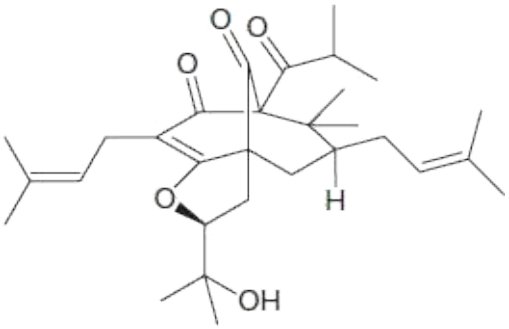
Problem 25.23

(a) What product is formed by the Claisen rearrangement of compound Z? (b) Using what you have learned about ring-closing metathesis in Chapter 24, draw the product formed when the product in part (a) is treated with Grubbs catalyst. These two reactions are key steps in the synthesis of garsubellin A, a biologically active natural product that stimulates the synthesis of the neurotransmitter acetylcholine. Compounds of this sort may prove to be useful drugs for the treatment of neurodegenerative diseases such as Alzheimer's disease.



Z



garsubellin A

25.6 Summary of Rules for Pericyclic Reactions

Table 25.4 summarizes the rules that govern pericyclic reactions, and in truth, this table holds a great deal of information. To keep track of this information, it may be helpful to learn one row in the table only, and then note the result when one or more conditions change. For example:

- **A *thermal* reaction involving an *even* number of electron pairs is *conrotatory* or *antarafacial.***
- **If *one* of the reaction conditions changes—either from thermal to photochemical or from an even to an odd number of electron pairs—the stereochemistry of the reaction changes to disrotatory or suprafacial.**
- **If *both* reaction conditions change—that is, a photochemical reaction with an odd number of electron pairs—the stereochemistry does *not* change.**

Table 25.4 Summary of the Stereochemical Rules for Pericyclic Reactions

Reaction conditions	Number of electron pairs	Stereochemistry

Thermal	Even	Conrotatory or antarafacial
	Odd	Disrotatory or suprafacial
Photochemical	Even	Disrotatory or suprafacial
	Odd	Conrotatory or antarafacial

Problem 25.24

Using the Woodward–Hoffmann rules in Table 25.4, predict the stereochemistry of each reaction.

a. a [6 + 4] thermal cycloaddition

b. photochemical electrocyclic ring closure of deca-1,3,5,7,9-pentaene

c. a [4 + 4] photochemical cycloaddition

d. a thermal [5,5] sigmatropic rearrangement

Chapter 25 REVIEW

KEY CONCEPTS

Woodward–Hoffmann rules for pericyclic reactions

1 Type of reaction	2 Number of electron pairs*	3 Thermal	4 Photochemical
Electrocyclic reactions (25.3)	Even	Conrotatory	Disrotatory
	Odd	Disrotatory	Conrotatory
Cycloaddition reactions (25.4)	Even	Antarafacial	Suprafacial
	Odd	Suprafacial	Antarafacial

Sigmatropic rearrangements (25.5)	**Even**	**Antarafacial**	**Suprafacial**
	Odd	**Suprafacial**	**Antarafacial**

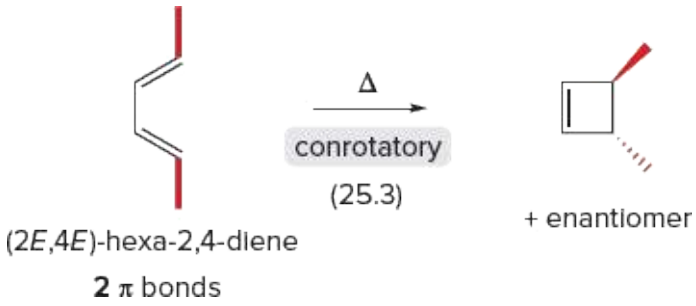
***In electrocyclic reactions, count the number of π bonds in the acyclic conjugated polyene that is either the reactant or the product. In cycloaddition reactions, count the total number of π bonds from both components of the cycloaddition. In sigmatropic rearrangements, count the σ bond that is broken and the π bonds that rearrange.**

See Tables 25.1–25.4.

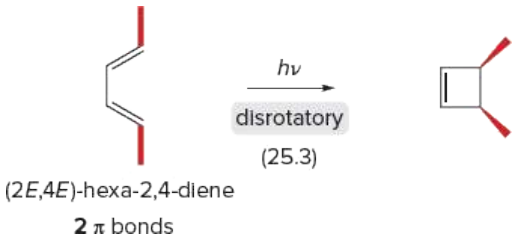
KEY REACTIONS

[1] Electrocyclic reactions

1



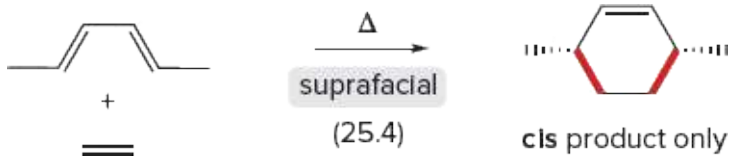
2



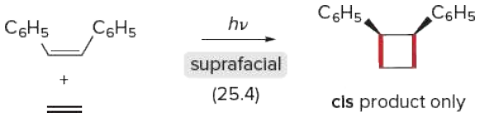
Try Problems 25.25; 25.28–25.35; 25.50b, d.

[2] Cycloaddition reactions

1



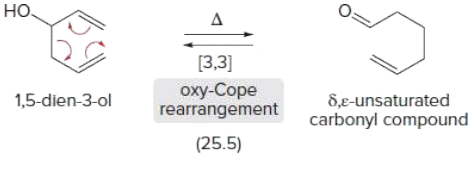
2



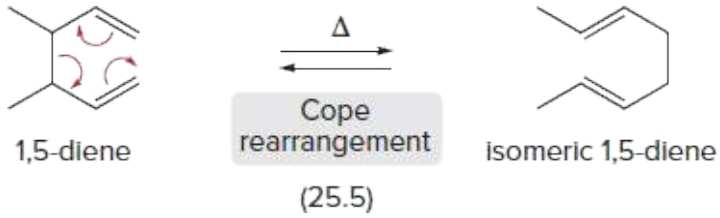
Try Problems 25.36–25.41; 25.50a, c; 25.51d; 25.53a.

[3] Sigmatropic rearrangements

3

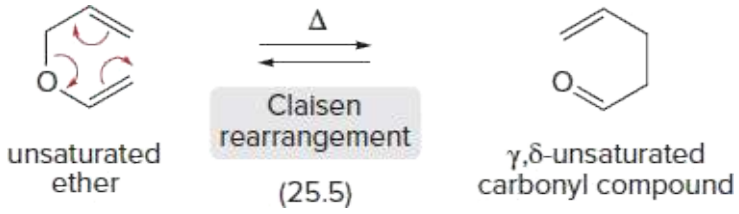


1



(25.5)

2



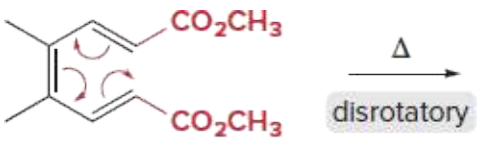
(25.5)

Try Problems 25.26, 25.43–25.48, 25.51a–c, 25.53b.

KEY SKILLS

[1] Identifying the product of a thermal electrocyclic ring closure, and labeling a process as conrotatory or disrotatory (25.3A)

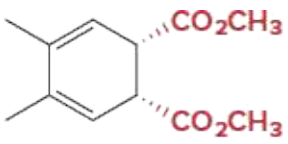
1 **Count the number of π bonds, and use Table 25.1 to determine if the process is conrotatory or disrotatory.**



3 π bonds

- **A conjugated polyene with an odd number of π bonds undergoes disrotatory cyclization.**
- **A conjugated polyene with an even number of π bonds undergoes conrotatory cyclization.**

2 **Draw the product.**

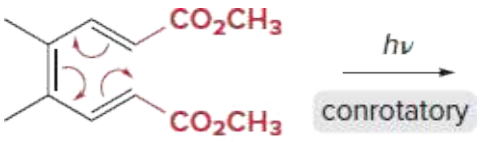
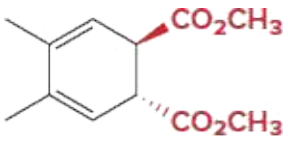


cis product only

- **In the disrotatory ring closure, both methyl ester groups are pushed *down* (or up), making them *cis* in the product.**

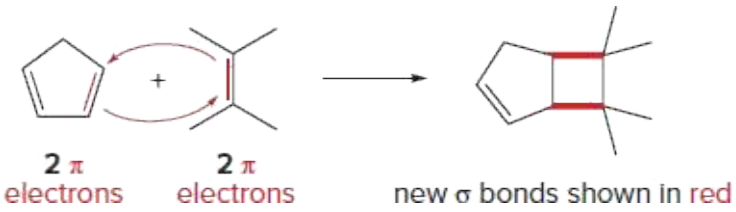
See Sample Problem 25.1 and Table 25.1. Try Problems 25.25a; 25.28; 25.31a, c, 25.34a; 25.50b.

[2] Identifying the product of a photochemical electrocyclic ring closure, and labeling a process as conrotatory or disrotatory (25.3C)

1 Count the number of π bonds to determine if the process is conrotatory or disrotatory.	2 Draw the product.
 3 π bonds	 **trans** product + enantiomer • In the conrotatory ring closure, one methyl ester group is pushed *down* and one methyl ester group is pushed *up*, making them *trans* in the product.

See Sample Problem 25.2 and Table 25.1. Try Problems 25.25b; 25.29; 25.30; 25.31b, d; 25.34b; 25.50d.

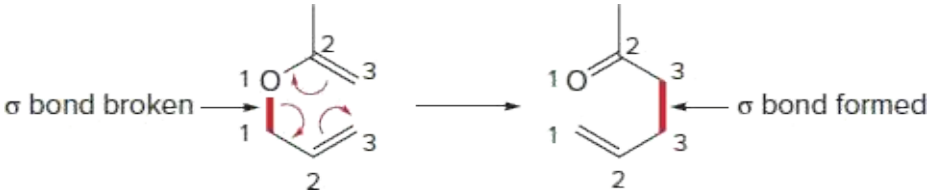
[3] Classifying the type of cycloaddition and determining whether it takes place under thermal or photochemical conditions (25.4)

1 Count the number of π electrons involved in each reactant.	2 Classify the cycloaddition.
	• photochemical [2 + 2] cycloaddition

See Sample Problem 25.3. Try Problem 25.36.

[4] Classifying a sigmatropic rearrangement (25.5)

1 Label the atoms in the broken σ bond with 1's, and count the number of atoms from the broken σ bond to the new σ bond for *each* fragment.	2 Place the numbers in brackets.



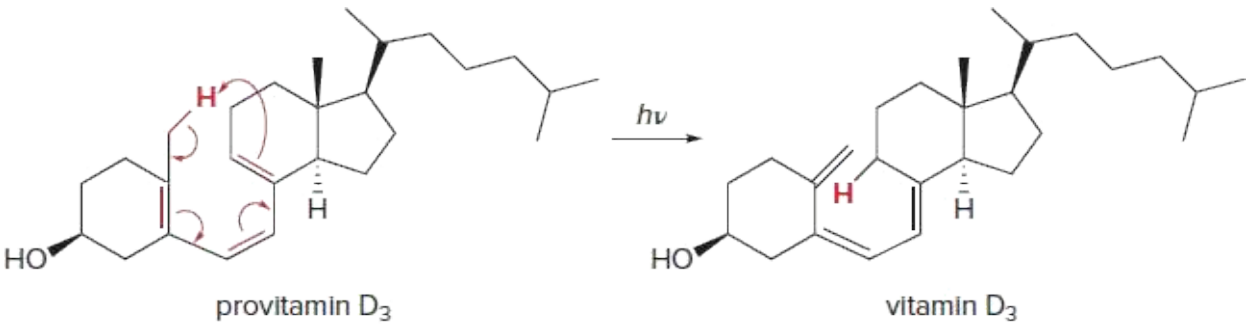
- **[3,3] sigmatropic rearrangement**

See Sample Problem 25.4. Try Problems 25.42, 25.49[2].

[5] Determining the stereochemical pathway of a sigmatropic rearrangement (25.5)

1 **Count the number of electron pairs involved in the reaction.**

2



provitamin D_3 vitamin D_3

The reaction involves **four** electron pairs.

-
-

See Sample Problem 25.5 and Table 25.3. Try Problem 25.45.

PROBLEMS

Problems Using Three-Dimensional Models

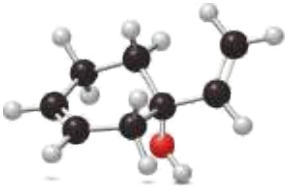
25.25 **(a) What product is formed when each compound undergoes a thermal electrocyclic ring opening? (b) What product is formed when each compound undergoes a photochemical electrocyclic ring opening?**

A

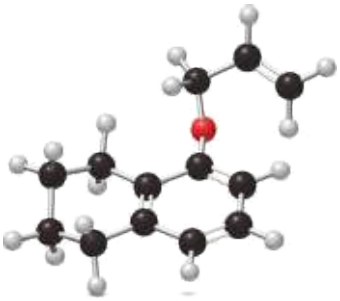
B

25.26 **What product is formed by the [3,3] sigmatropic rearrangement of each compound?**

a.



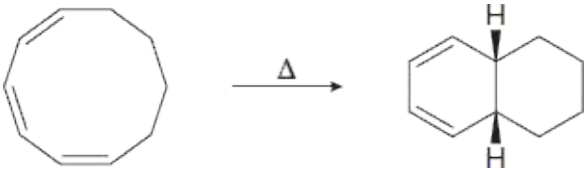
b.



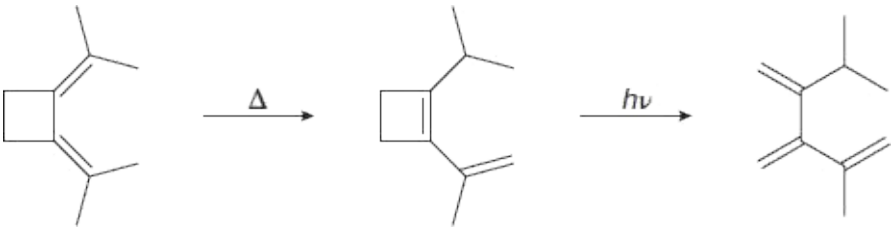
Types of Pericyclic Reactions

25.27 **Classify each pericyclic reaction as an electrocyclic reaction, cycloaddition, or sigmatropic rearrangement. Indicate whether the stereochemistry is conrotatory, disrotatory, suprafacial, or antarafacial.**

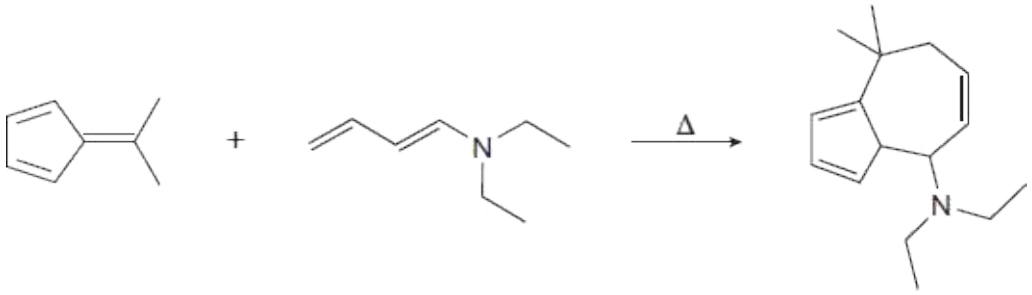
a.



b.



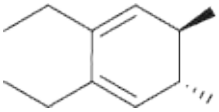
c.



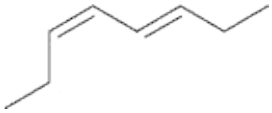
Electrocyclic Reactions

25.28 **What product is formed when each compound undergoes thermal electrocyclic ring opening or ring closure? Label each process as conrotatory or disrotatory, and clearly indicate the stereochemistry around tetrahedral stereogenic centers and double bonds.**

a.



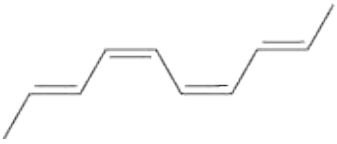
b.



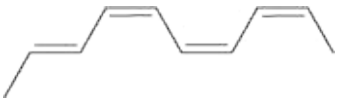
25.29 **What product is formed when each compound in Problem 25.28 undergoes photochemical electrocyclic reaction? Label each process as conrotatory or disrotatory, and clearly indicate the stereochemistry around tetrahedral stereogenic centers and double bonds.**

25.30 **What cyclic product is formed when each decatetraene undergoes photochemical electrocyclic ring closure?**

a.



b.



25.31 **Draw the product of each electrocyclic reaction.**

a. the thermal electrocyclic ring closure of (2*E*,4*Z*,6*Z*)-nona-2,4,6-triene

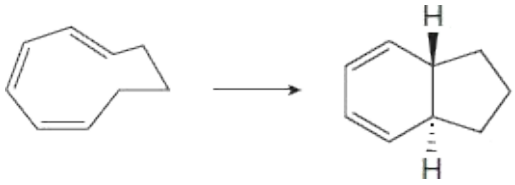
b. the photochemical electrocyclic ring closure of (2*E*,4*Z*,6*Z*)-nona-2,4,6-triene

c. the thermal electrocyclic ring opening of *cis*-5-ethyl-6-methylcyclohexa-1,3-diene

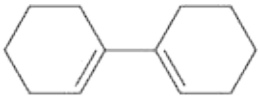
d. the photochemical electrocyclic ring opening of *trans*-5-ethyl-6-methylcyclohexa-1,3-diene

25.32 **Consider the following electrocyclic ring closure. Does the product form**

by a conrotatory or disrotatory process? Would this reaction occur under photochemical or thermal conditions?

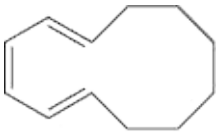


25.33 Draw the product formed when diene M undergoes disrotatory cyclization. Indicate the stereochemistry at new sp^3 hybridized carbons. Will the reaction occur under thermal or photochemical conditions?



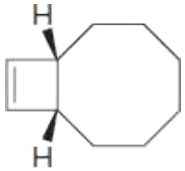
M

25.34 (a) What product is formed when triene N undergoes thermal electrocyclic ring closure? (b) What product is formed when triene N undergoes photochemical ring closure? (c) Label each process as conrotatory or disrotatory.



N

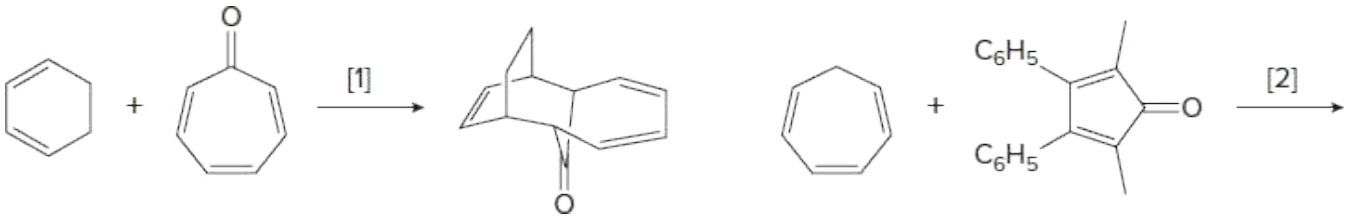
25.35 The bicyclic alkene P can be prepared by thermal electrocyclic ring closure from cyclodecadiene Q or by photochemical electrocyclic ring closure from cyclodecadiene R. Draw the structures of Q and R, and indicate the stereochemistry of the process by which each reaction occurs.



P

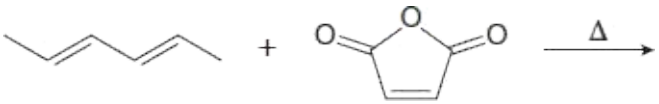
Cycloaddition Reactions

25.36 What type of cycloaddition occurs in Reaction [1]? Draw the product of a similar process in Reaction [2]. Would you predict that these reactions occur under thermal or photochemical conditions?

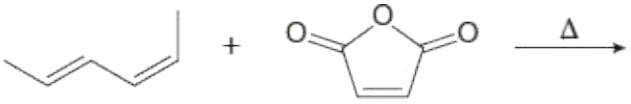


25.37 Draw the product of each Diels–Alder reaction, and indicate the stereochemistry at all stereogenic centers.

a.

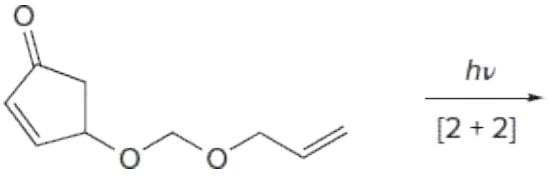


b.

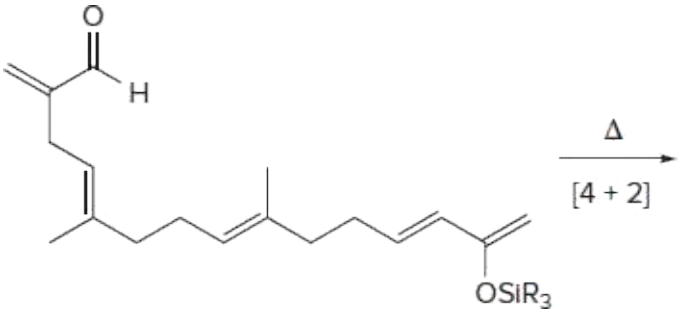


25.38 Draw the product of each intramolecular cycloaddition.

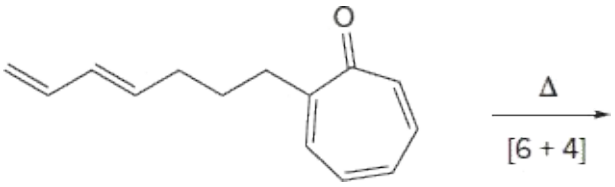
a.



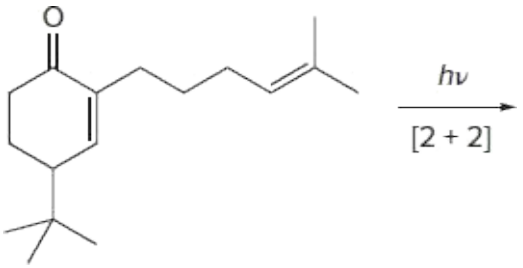
b.



c.

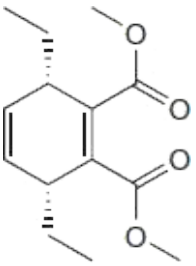


d.

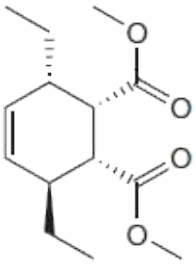


25.39 What starting materials are needed to synthesize each compound by a thermal [4 + 2] cycloaddition?

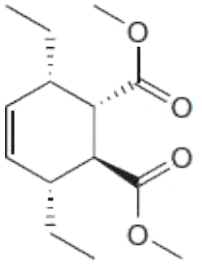
a.



b.

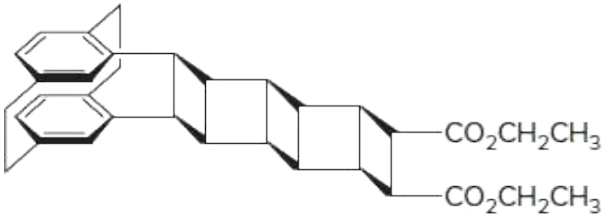


c.

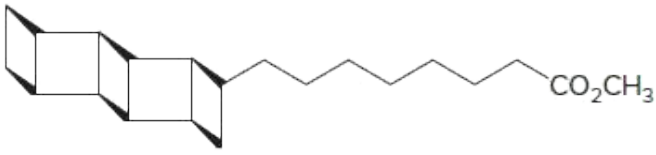


25.40 **Explain why heating buta-1,3-diene forms 4-vinylcyclohexene but not cycloocta-1,5-diene.**

25.41 **How can X be prepared from a constitutional isomer by a series of [2 + 2] cycloaddition reactions? Interest in molecules that contain several cyclobutane rings fused together has been fueled by the discovery of pentacycloanammoxic acid methyl ester, a lipid isolated from the membrane of organelles in the bacterium *Candidatus Brocadia anammoxidans.* The role of this unusual natural product is as yet unknown.**



X

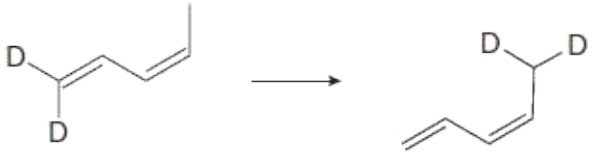


pentacycloanammoxic acid methyl ester

Sigmatropic Rearrangements

25.42 **What type of sigmatropic rearrangement is illustrated in each reaction?**

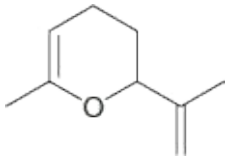
a.



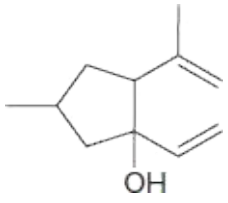
b.

25.43 **Draw the product of the [3,3] sigmatropic rearrangement of each compound.**

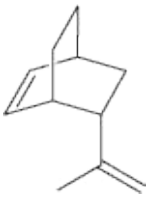
a.



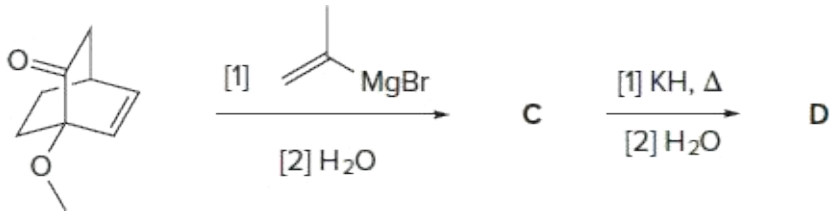
b.



c.

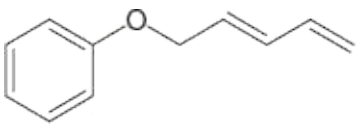


25.44 Draw the structure of C in the following reaction scheme, and show how C can be converted to D by a sigmatropic rearrangement.

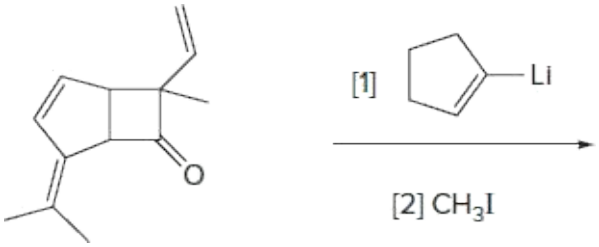


25.45 A solution of 5-methylcyclopenta-1,3-diene rearranges at room temperature to a mixture containing 1-methyl-, 2-methyl-, and 5-methylcyclopenta-1,3-diene. (a) Show how both isomeric products are formed from the starting material by a sigmatropic rearrangement involving a C–H bond. (b) Explain why 2-methylcyclopenta-1,3-diene is not formed directly from 5-methylcyclopenta-1,3-diene by a [1,3] rearrangement.

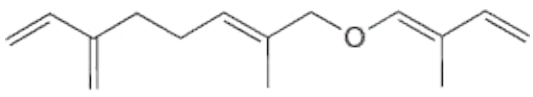
25.46 What product is formed from the [5,5] sigmatropic rearrangement of the following unsaturated ether?



25.47 Identify the product of the following two-step reaction sequence. The initial intermediate formed from Step [1] undergoes a [3,3] sigmatropic rearrangement prior to reaction with CH_3I.



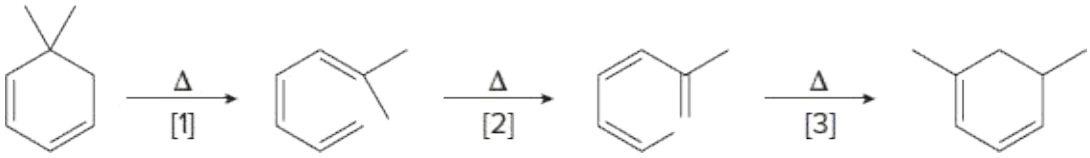
25.48 Heating A results in two successive [3,3] sigmatropic rearrangements—Claisen reaction followed by Cope reaction—to afford β-sinensal, a component of mandarin orange oil. What is the structure of β-sinensal?



A

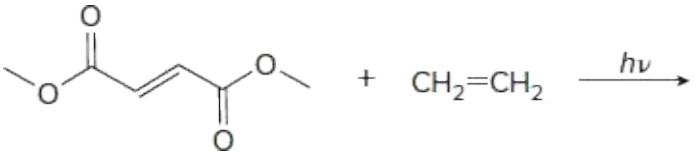
General Pericyclic Reactions

25.49 What type of pericyclic reaction is illustrated in each reaction?

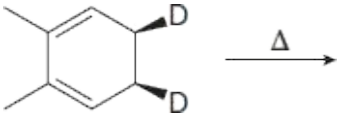


25.50 Draw the product formed (including stereochemistry) in each pericyclic reaction.

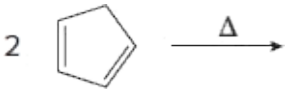
a.



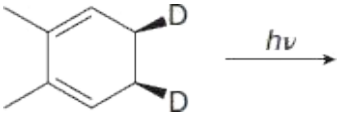
b.



c.

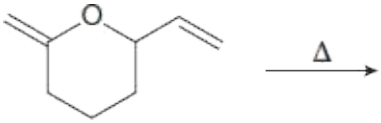


d.

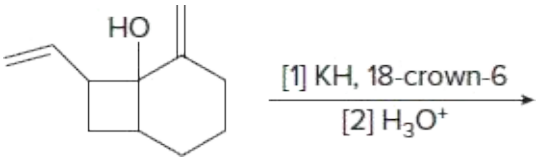


25.51 Draw the products of each reaction.

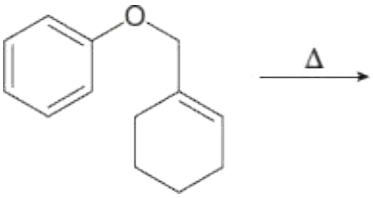
a.



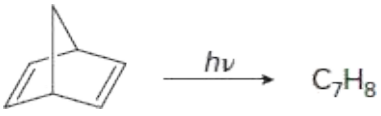
b.



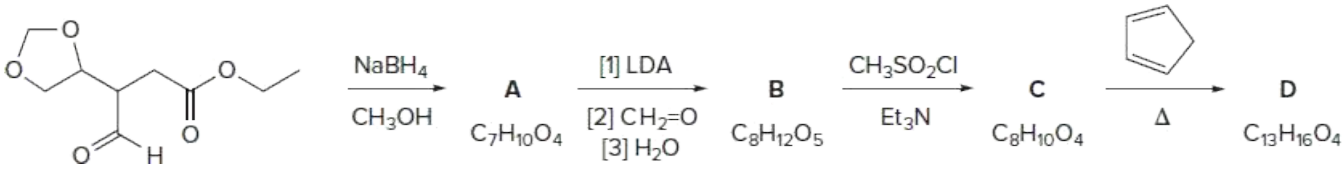
c.



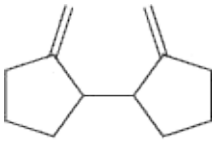
d.



25.52 Identify compounds A–D in the following reaction sequence.



25.53 With reference to diene A:



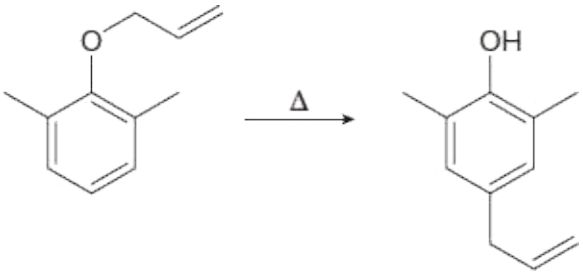
A

a. What product is formed when A undergoes a [2 + 2] cycloaddition?

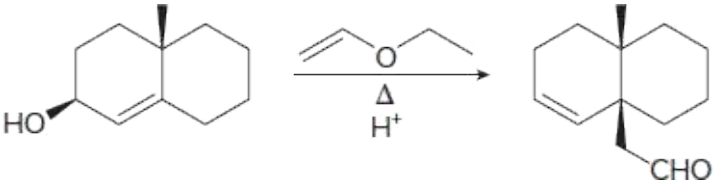
b. What product is formed when A undergoes a [3,3] sigmatropic rearrangement?

Mechanisms

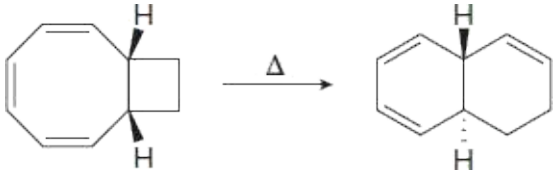
25.54 When both carbons ortho to the aryl oxygen are not bonded to hydrogen, an allyl aryl ether rearranges to a para-substituted phenol. Draw a stepwise mechanism for the following reaction, which contains two [3,3] sigmatropic rearrangements.



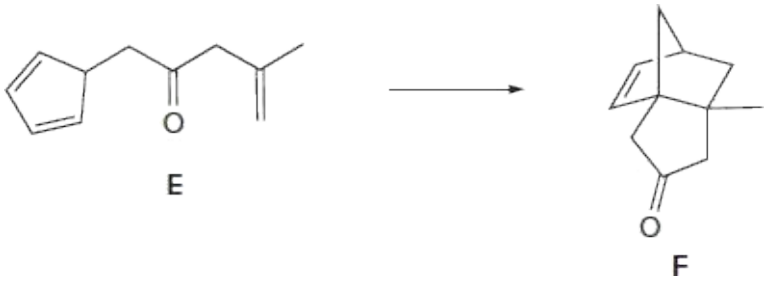
25.55 Draw a stepwise, detailed mechanism for the following reaction.



25.56 Show how the following starting material is converted to the given product by a series of two pericyclic reactions. Account for the observed stereochemistry.

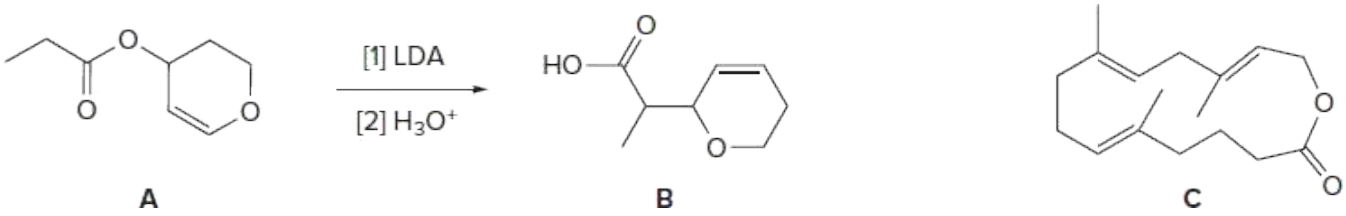


25.57 Use curved arrows to show how E is converted to F by a two-step reaction sequence consisting of a [1,5] sigmatropic rearrangement followed by a [4 + 2] cycloaddition.



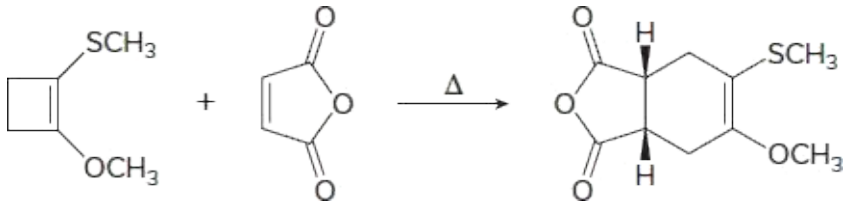
E F

25.58 **(a) Draw a stepwise mechanism for the conversion of A to B. (b) What product would be formed if C was exposed to similar reaction conditions?**

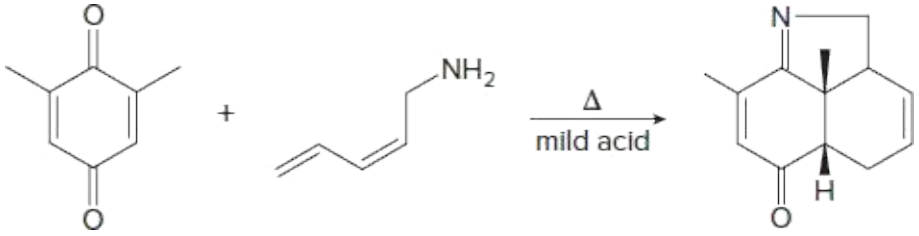


A B C

25.59 **Show how the following starting materials are converted to the given product by a series of two pericyclic reactions. Account for the observed stereochemistry.**

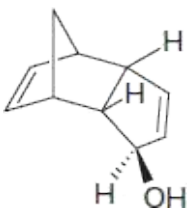


25.60 **Draw a stepwise, detailed mechanism for the following reaction.**

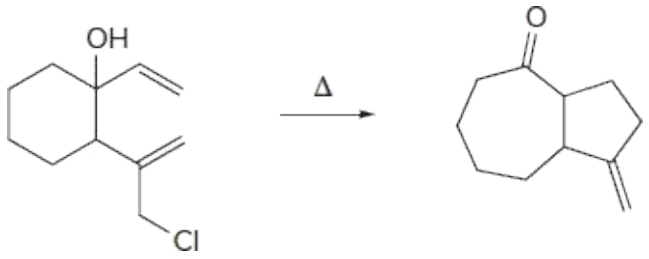


Challenge Problems

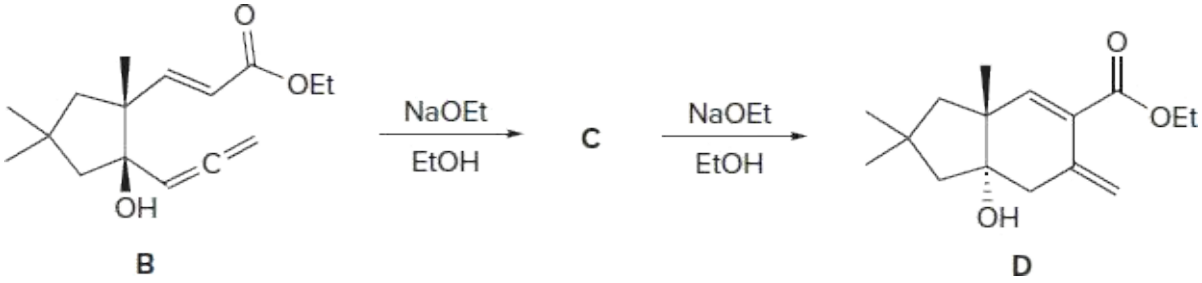
25.61 **What product is formed by [3,3] sigmatropic rearrangement of the following compound? Clearly indicate the stereochemistry around all tetrahedral stereogenic centers.**



25.62 **Draw a stepwise mechanism for the following reaction.**

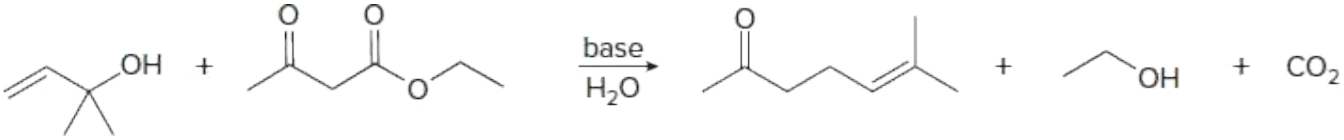


25.63 **(a) What is the structure of C, which is formed by oxy-Cope rearrangement of B with NaOEt? (b) Draw a stepwise mechanism for the conversion of C to the bicyclic alcohol D.**

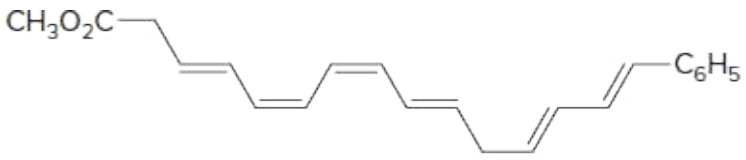


B D

25.64 **Draw a stepwise mechanism for the Carroll rearrangement, a reaction that prepares a γ,δ-unsaturated carbonyl compound from a β-keto ester and allylic alcohol in the presence of base.**



25.65 **The endiandric acids comprise a group of unsaturated carboxylic acids isolated from a tree that grows in the rainforests of eastern Australia. The methyl esters of endiandric acids D and E have been prepared from polyene Y by a series of two successive electrocyclic reactions: thermal ring closure of the conjugated tetraene followed by ring closure of the resulting conjugated triene. (a) Draw the structures (including stereochemistry) of the methyl esters of endiandric acids D and E. (b) The methyl ester of endiandric acid E undergoes an intramolecular [4 + 2] cycloaddition to form the methyl ester of endiandric acid A. Propose a possible structure for endiandric acid A.**



Y

Carbohydrates

26

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26.1 Introduction

26.2 Monosaccharides

26.3 The family of D-aldoses

26.4 The family of D-ketoses

26.5 Physical properties of monosaccharides

26.6 The cyclic forms of monosaccharides

26.7 Glycosides

26.8 Reactions of monosaccharides at the OH groups
26.9 Reactions at the carbonyl group—Oxidation and reduction
26.10 Reactions at the carbonyl group—Adding or removing one carbon atom
26.11 Disaccharides
26.12 Polysaccharides
26.13 Other important sugars and their derivatives

Sucrose, the carbohydrate commonly called table sugar, is composed of two simple sugars, glucose and fructose. Many mammals, birds, and insects use the sucrose in plants as a key food source. Although sugar has been produced for almost 2000 years, sucrose was an expensive luxury until the 1700s when worldwide demand led to the cultivation of large plantations of sugarcane around the globe. In Chapter 26, we learn about the properties and reactions of carbohydrates like sucrose.

Why Study…

Carbohydrates?

Chapters 26, 27, and 29 discuss *biomolecules*, organic compounds found in biological systems. You have already learned many facts about these compounds in previous chapters while you studied other organic compounds having similar properties. In Chapter 10 (Alkenes), for example, you learned that the presence of double bonds determines whether a fatty acid is part of a fat or an oil. In Chapter 19 (Carboxylic Acids and Nitriles), you learned that amino acids are the building blocks of proteins.

Chapter 26 focuses on carbohydrates, the largest group of biomolecules in nature, comprising ~50% of the earth's biomass. Chapter 27 concentrates on proteins (and the amino acids that compose them), whereas Chapter 29 explores lipids. These compounds are all organic molecules, so many of the same principles and chemical reactions that you have already studied will be examined once again. But, as you will see, each class of compound has its own unique features that we must learn as well.

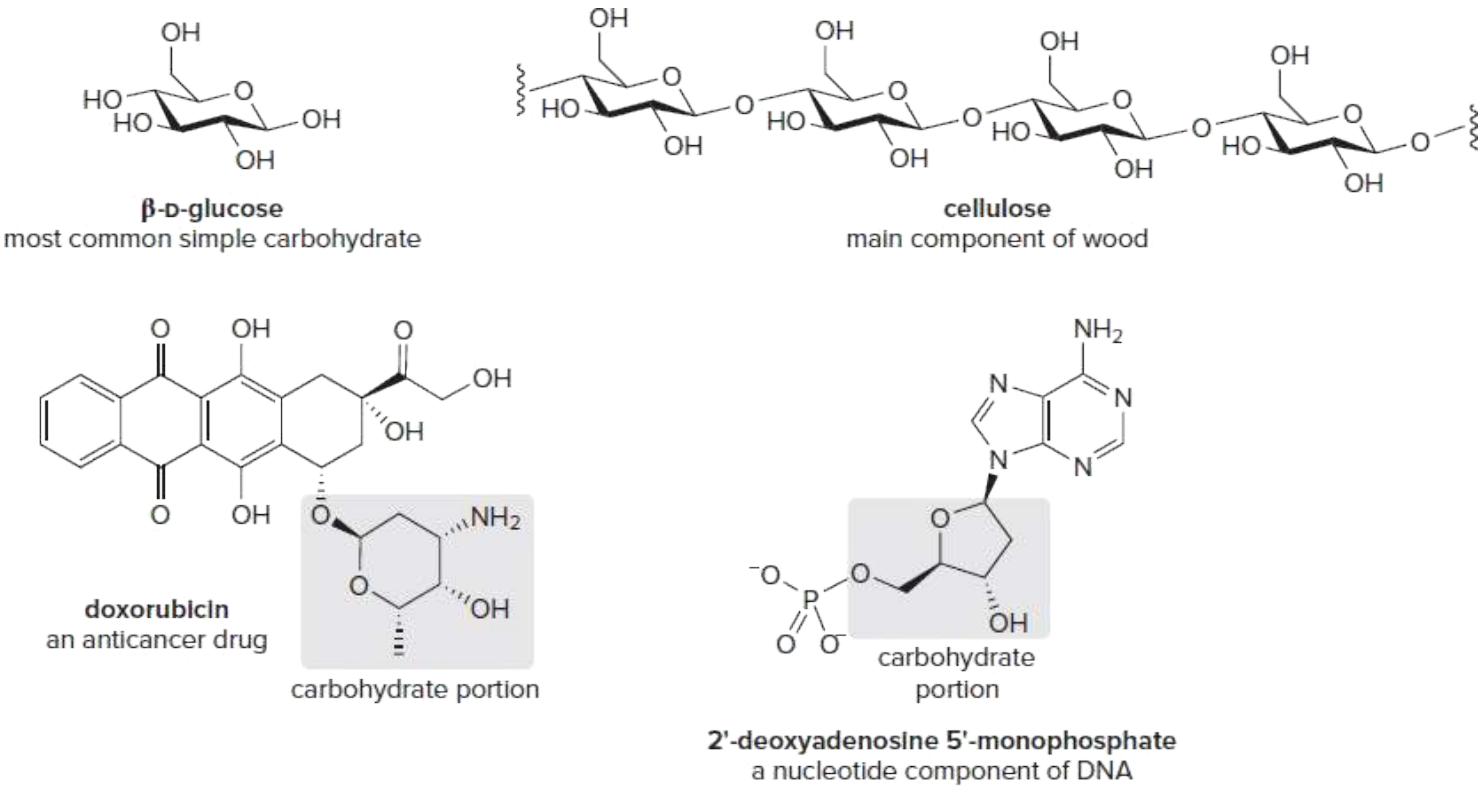
26.1 Introduction

Carbohydrates, commonly referred to as sugars and starches, are polyhydroxy aldehydes and ketones, or compounds that can be hydrolyzed to them. The cellulose in plant stems and tree trunks and the chitin in the exoskeletons of arthropods and mollusks are both complex carbohydrates. Four examples are shown in Figure 26.1. They include not only glucose and cellulose, but also doxorubicin (an anticancer drug) and 2′-deoxyadenosine 5′-monophosphate (a nucleotide base from DNA), both of which have a carbohydrate moiety as part of a larger molecule.

Carbohydrates were given their name because molecular formulas of simple carbohydrates could be written as $C_n(H_2O)_n$, making them hydrates of carbon.

Carbohydrates such as glucose and cellulose were discussed in Sections 5.1, 6.4, and 18.16.

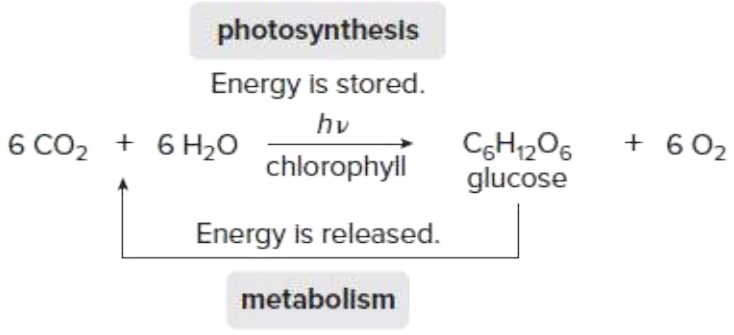
Carbohydrates are storehouses of chemical energy. They are synthesized in green plants and algae by photosynthesis, a process that uses the energy from the sun to convert carbon dioxide and water to glucose and oxygen. This energy is released when glucose is metabolized. The oxidation of glucose is a multistep process that forms carbon dioxide, water, and a great deal of energy (Section 6.4).



- These compounds illustrate the structural diversity of carbohydrates and their derivatives. **Glucose** is the most common simple sugar, whereas **cellulose,** which comprises wood, plant stems, and grass, is the most common carbohydrate in the plant world. **Doxorubicin,** an anticancer drug that has a carbohydrate ring as part of its structure, has been used in the treatment of leukemia, Hodgkin's disease, and cancers of the breast, bladder, and ovaries. **2'-Deoxyadenosine 5'-monophosphate** is one of the four nucleotides that form DNA.

Figure 26.1 **Some examples of carbohydrates**

Although the metabolism of lipids provides more energy per gram than the metabolism of carbohydrates, glucose is the preferred source when a burst of energy is needed during exercise. Glucose is water soluble, so it can be quickly and easily transported through the bloodstream to the tissues.



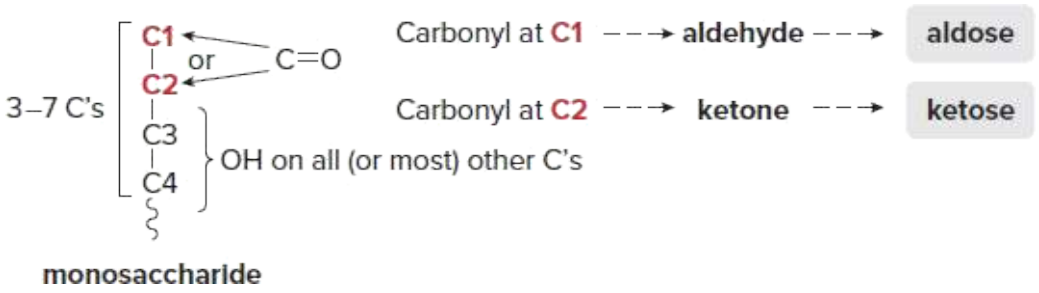
26.2 Monosaccharides

The simplest carbohydrates are called monosaccharides or simple sugars.

Monosaccharides have three to seven carbon atoms in a chain, with a carbonyl group at either the terminal carbon (C1) or the carbon adjacent to it (C2). In most carbohydrates, each of the remaining carbon atoms has a hydroxy group. Monosaccharides are often drawn vertically, with the carbonyl group at the top. When this convention is used, monosaccharides look different from molecules encountered in prior chapters.

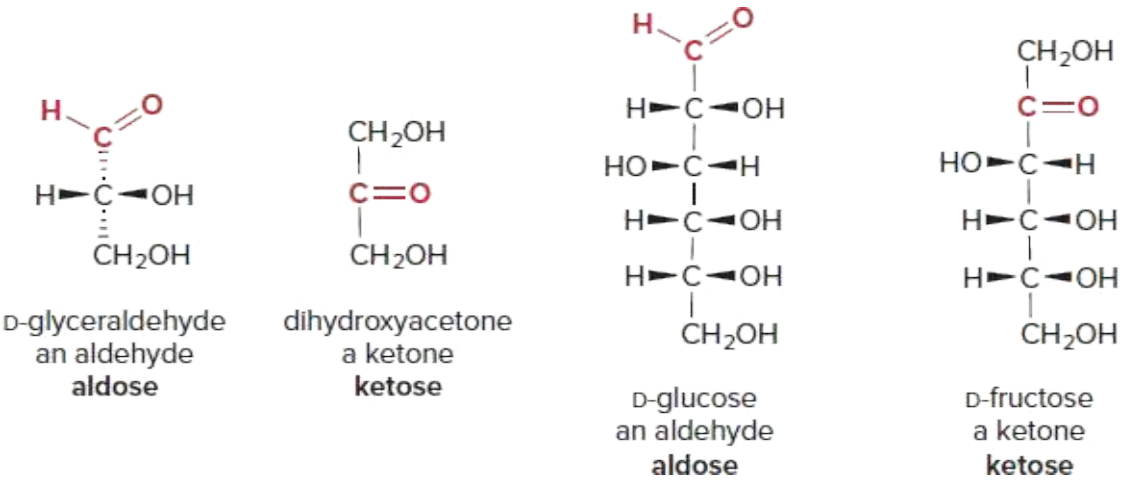
D-Fructose is almost twice as sweet as normal table sugar (sucrose) with about the same number of calories per gram. "Lite" food products use only half as much fructose as sucrose for the same level of sweetness, so they have fewer calories. ©*Jill Braaten*

Dihydroxyacetone is the active ingredient in many artificial tanning agents. ©*McGraw-Hill Education/Elite Images*



- **Monosaccharides with an aldehyde carbonyl group at C1 are called *aldoses*.**
- **Monosaccharides with a ketone carbonyl group at C2 are called *ketoses*.**

Several examples of simple carbohydrates are shown. D-Glyceraldehyde and dihydroxyacetone have the same molecular formula, so they are constitutional isomers, as are D-glucose and D-fructose.



All carbohydrates have common names. The simplest aldehyde, glyceraldehyde, and the simplest ketone, dihydroxyacetone, are the only monosaccharides whose names do not end in the suffix *-ose*. (The prefix "D-" is explained in Section 26.2C.)

A monosaccharide is called

- **a triose if it has 3 C's;**
- **a tetrose if it has 4 C's;**
- **a pentose if it has 5 C's;**
- **a hexose if it has 6 C's, and so forth.**

These terms are then combined with the words *aldose* and *ketose* to indicate both the number of carbon atoms in the monosaccharide and whether it contains an aldehyde or ketone. Thus, glyceraldehyde is an aldotriose (three C atoms

and an aldehyde), glucose is an aldohexose (six C atoms and an aldehyde), and fructose is a ketohexose (six C atoms and a ketone).

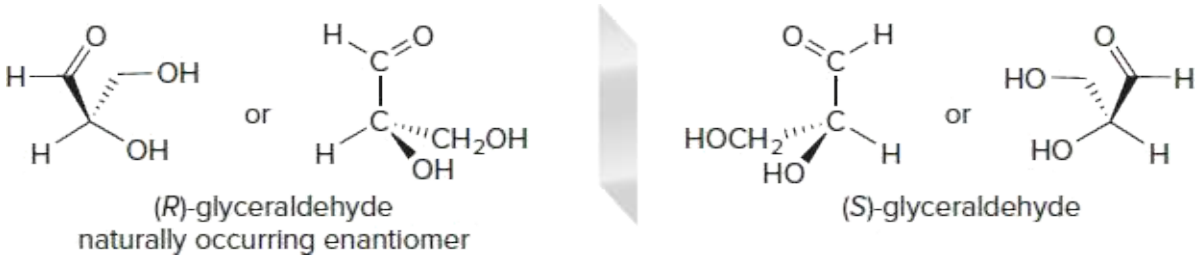
Problem 26.1

Draw the structure of (a) a ketotetrose; (b) an aldopentose; (c) an aldotetrose.

26.2A Fischer Projection Formulas

A striking feature of carbohydrate structure is the presence of stereogenic centers. All carbohydrates except for dihydroxyacetone contain one or more stereogenic centers.

The simplest aldehyde, glyceraldehyde, has one stereogenic center, so there are two possible enantiomers. Only the enantiomer with the *R* configuration occurs naturally.



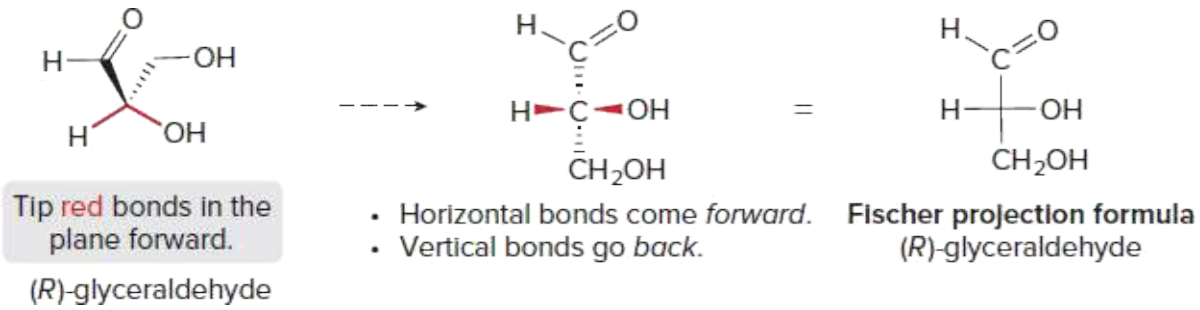
(*R*)-glyceraldehyde
naturally occurring enantiomer

(*S*)-glyceraldehyde

The stereogenic centers in sugars are often depicted following a different convention than is usually seen for other stereogenic centers. Instead of drawing a tetrahedron with two bonds in the plane, one in front of the plane and one behind it, the tetrahedron is tipped so that horizontal bonds come forward (drawn on wedges) and vertical bonds go behind (on dashed wedges). This structure is then abbreviated by a cross formula, also called a Fischer projection formula. In a Fischer projection formula:

- **A carbon atom is located at the intersection of the two lines of the cross.**
- **The horizontal bonds come forward, on wedges.**
- **The vertical bonds go back, on dashed wedges.**
- **In a carbohydrate, the aldehyde or ketone carbonyl is put at or near the top.**

Carbon atoms that are not stereogenic centers are generally drawn in. Using a Fischer projection formula, (*R*)-glyceraldehyde becomes:

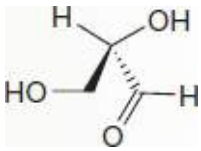


Do *not* rotate a Fischer projection formula in the plane of the page, because you might inadvertently convert a compound to its enantiomer. When using Fischer projections, it is usually best to convert them to structures with wedges and dashed wedges, and then manipulate them. Although a Fischer projection formula can be used for the stereogenic center in any compound, it is most commonly used for monosaccharides.

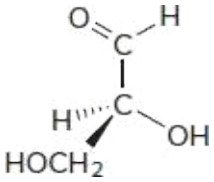
Sample Problem 26.1 Drawing a Fischer Projection Formula

Convert each compound to a Fischer projection formula.

a.



b.



Solution

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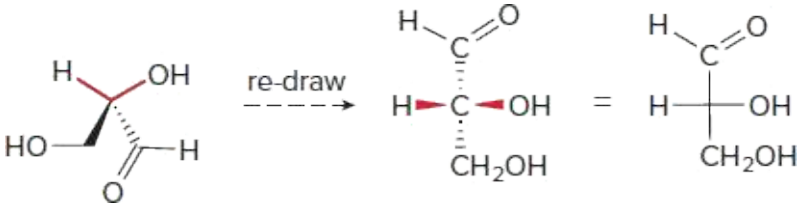
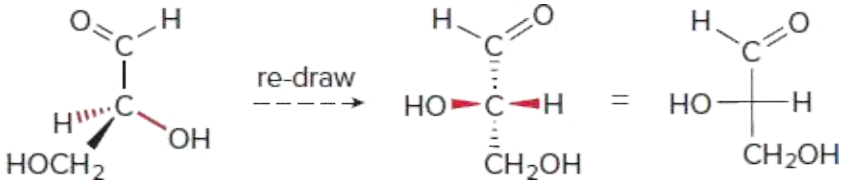
Rotate and re-draw each molecule to place the horizontal bonds in front of the plane and the vertical bonds behind the plane. Then use a cross to represent the stereogenic center.

a.

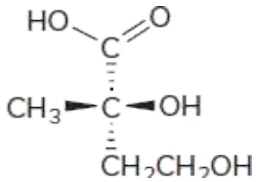


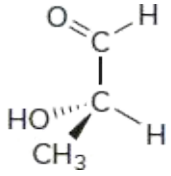
b.

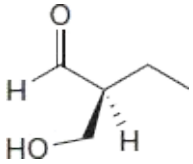


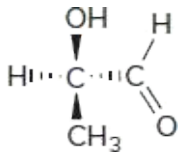
Problem 26.2

Draw each stereogenic center using a Fischer projection formula.

a. 

b. 

c. 

d. 

More Practice:

Try Problem 26.38.

R,S designations can be assigned to any stereogenic center drawn as a Fischer projection formula in the following manner:

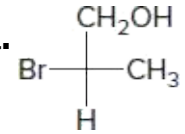
[1] Assign priorities (1 → 4) to the four groups bonded to the stereogenic center using the rules detailed in Section 5.6.

[2] When the lowest-priority group occupies a vertical bond—that is, it projects *behind* the plane on a dashed wedge—tracing a circle in the clockwise direction (from priority group 1 → 2 → 3) gives the *R* configuration. Tracing a circle in the counterclockwise direction gives the *S* configuration.

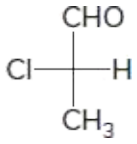
[3] When the lowest-priority group occupies a horizontal bond—that is, it projects *in front of* the plane on a wedge—reverse the answer obtained in Step [2] to designate the configuration.

Sample Problem 26.2 Labeling a Fischer Projection as *R* or *S*

Re-draw each Fischer projection formula using wedges and dashed wedges for the stereogenic center, and label the center as *R* or *S*.

a. 

b.



Solution

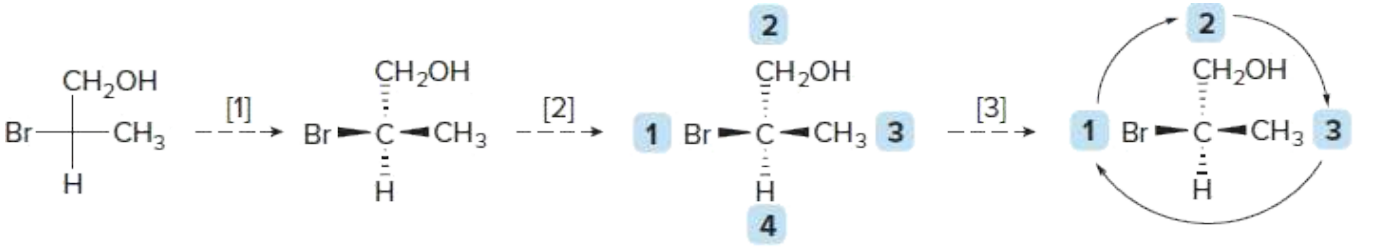
For each molecule:

[1] Convert the Fischer projection formula to a representation with wedges and dashed wedges.

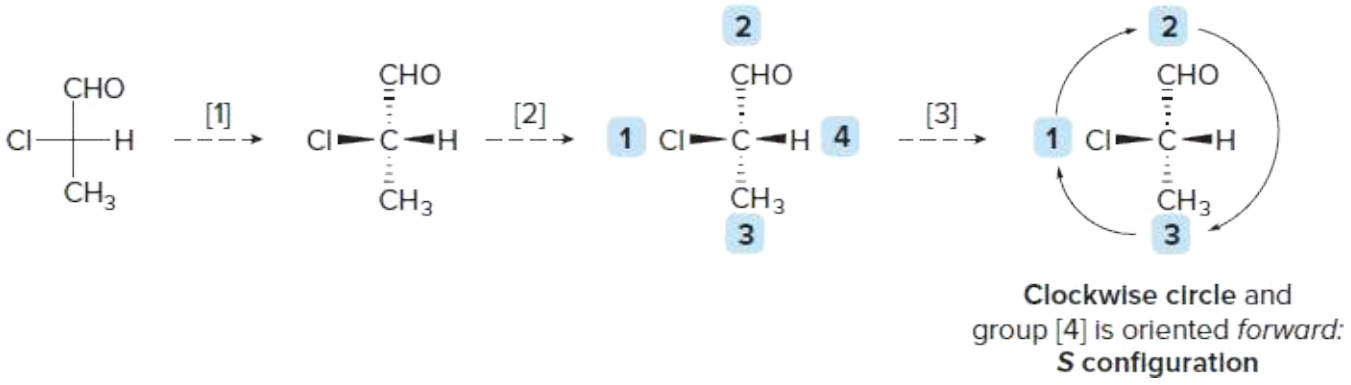
[2] Assign priorities (Section 5.6).

[3] Determine *R* or *S* in the usual manner. Reverse the answer if priority group [4] is oriented forward (on a wedge).

a.



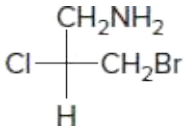
b.



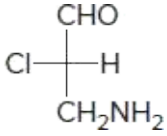
Problem 26.3

Label each stereogenic center as *R* or *S*.

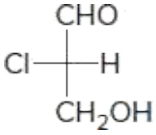
a.

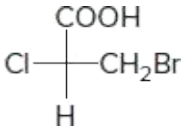


b.



c.



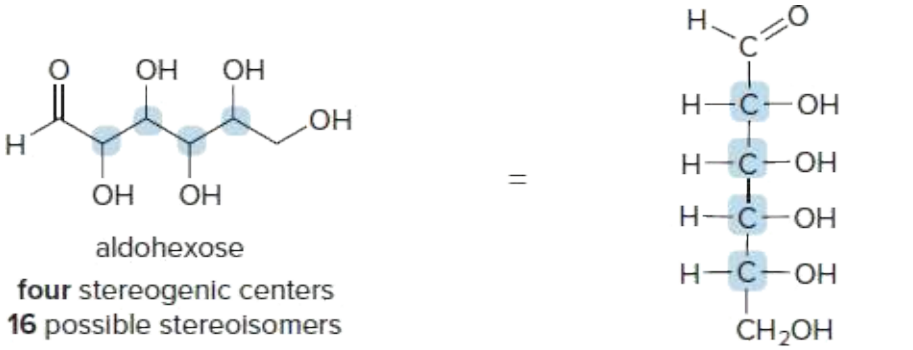
d. 

More Practice:

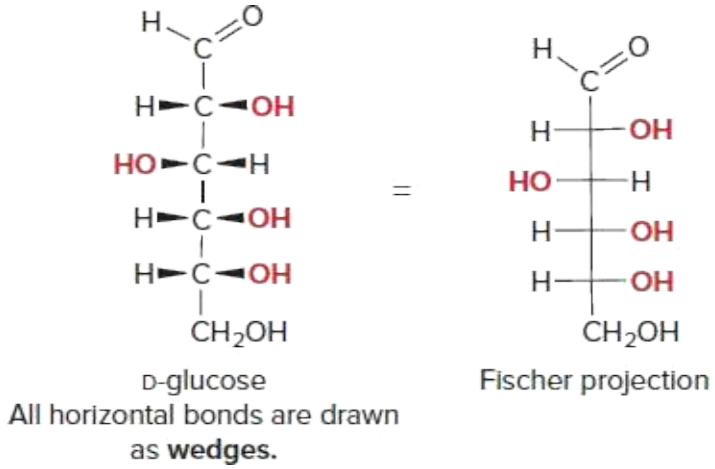
Try Problem 26.39.

26.2B Monosaccharides with More Than One Stereogenic Center

The number of possible stereoisomers of a monosaccharide increases exponentially with the number of stereogenic centers present. An aldohexose has four stereogenic centers, so it has $2^4 = 16$ possible stereoisomers, or eight pairs of enantiomers.



Fischer projection formulas are also used for compounds like aldohexoses that contain several stereogenic centers. In this case, the molecule is drawn with a vertical carbon skeleton and the stereogenic centers are stacked one above another. Using this convention, all horizontal bonds project *forward* (on wedges).



Although Fischer projections are commonly used to depict monosaccharides with many stereogenic centers, care must be exercised in using them, because they do not give a true picture of the three-dimensional structures they represent. Each stereogenic center is drawn in the

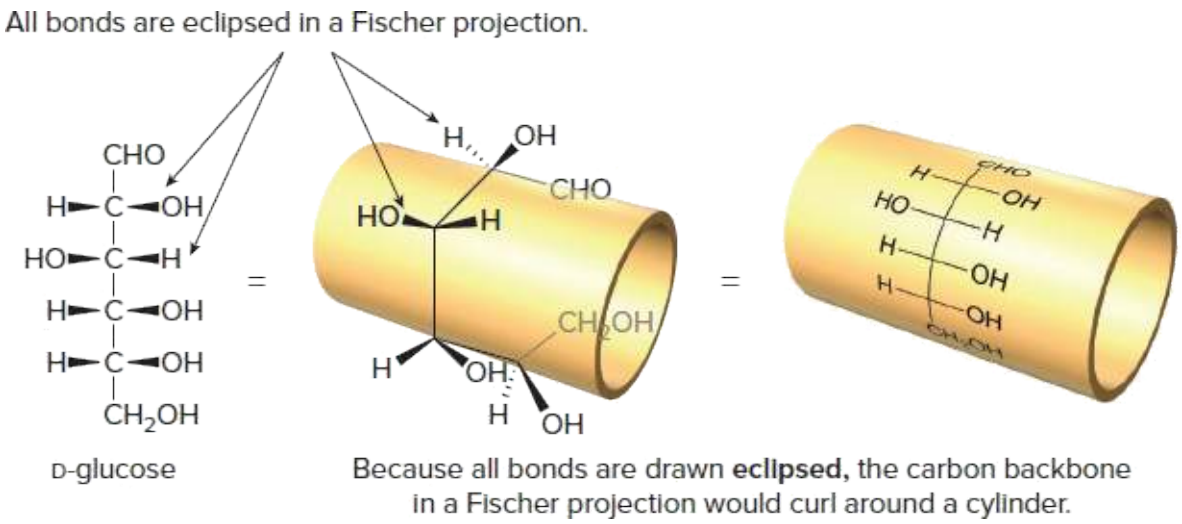


Figure 26.2 **A Fischer projection and the 3-D structure of glucose**

less stable eclipsed conformation, so the Fischer projection of glucose really represents the molecule in a cylindrical conformation, as shown in Figure 26.2.

Sample Problem 26.3 Converting a Ball-and-Stick Model to a Fischer Projection

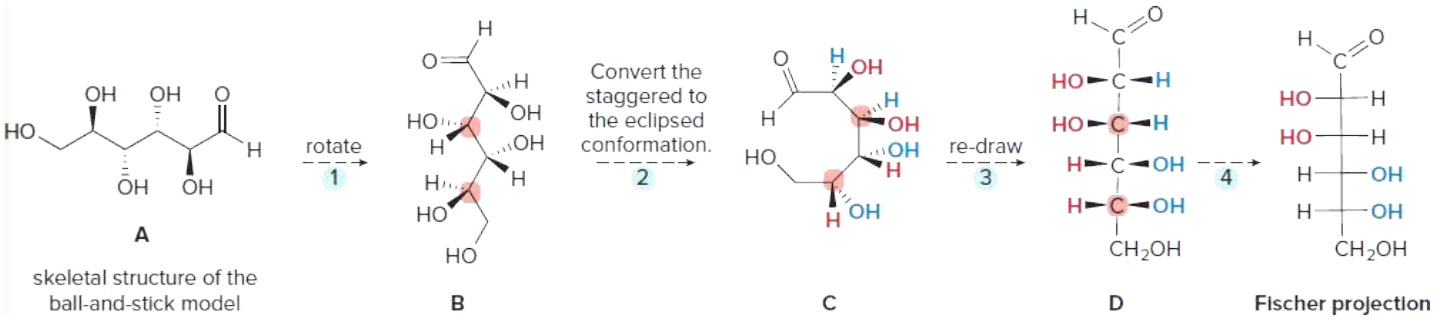
Convert the ball-and-stick model to a Fischer projection.

Solution

The ball-and-stick model is shown in the more stable staggered conformation, so it must be converted to the less stable eclipsed conformation used in a Fischer projection.

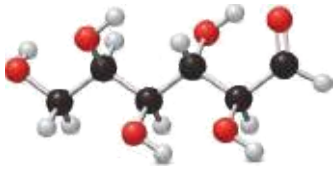
1. **Re-draw the model as a skeletal structure (A), and rotate it to place the carbonyl group at the top (B).**
2. **To convert the all-staggered form to the all-eclipsed form, rotate around the bonds in B to swing two carbons (labeled in red) 180°, forming C.**
3. **Re-draw C so that all bonds to H and OH on the four stereogenic centers are drawn on wedges, forming D. Groups that are on wedges in C (in red) are on the left side of the carbon skeleton in D, and groups on dashed wedges in C (in blue) are on the right side of the carbon skeleton in D.**

4 **Replace the wedges with crosses to form the Fischer projection.**



Problem 26.4

Convert the ball-and-stick model to a Fischer projection.



More Practice:

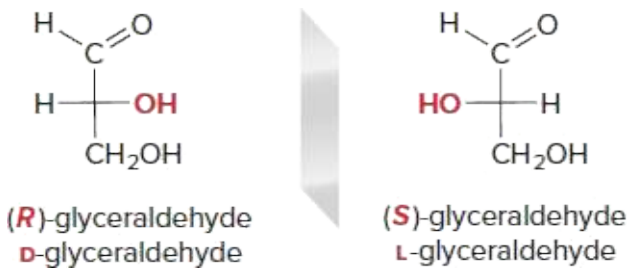
Try Problem 26.36.

Problem 26.5

Assign *R,S* designations to each stereogenic center in glucose.

26.2C D and L Monosaccharides

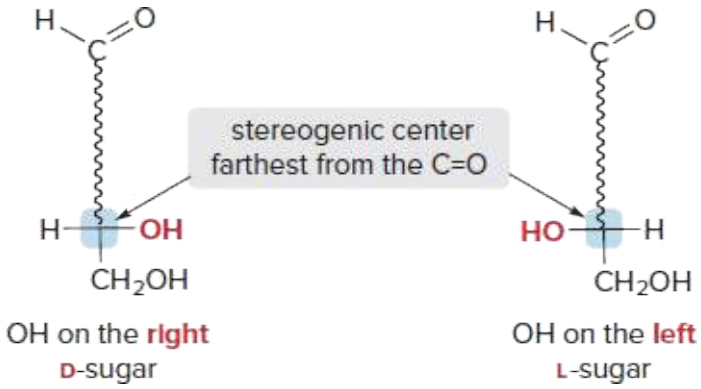
Although the prefixes *R* and *S* can be used to designate the configuration of stereogenic centers in monosaccharides, an older system of nomenclature uses the prefixes D- and L- instead. Naturally occurring glyceraldehyde with the *R* configuration is called the D-isomer. Its enantiomer, (*S*)-glyceraldehyde, is called the L-isomer.



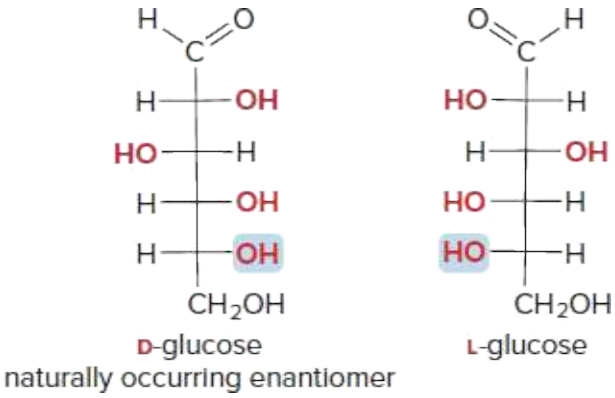
The letters D and L are used to label all monosaccharides, even those with multiple stereogenic centers. The configuration of the stereogenic center *farthest* from the carbonyl group determines whether a monosaccharide is D- or L-.

The two designations, D and *d*, refer to very different phenomena. The "D" designates the configuration around a stereogenic center in a monosaccharide. The "*d*," on the other hand, is an abbreviation for "dextrorotatory"; that is, a *d*-compound rotates the plane of polarized light in the clockwise direction. A D-sugar may be dextrorotatory or it may be levorotatory. There is no direct correlation between D and *d* or L and *l*.

- **A D-sugar has the OH group on the stereogenic center farthest from the carbonyl on the *right* in a Fischer projection (like D-glyceraldehyde).**
- **An L-sugar has the OH group on the stereogenic center farthest from the carbonyl on the *left* in a Fischer projection (like L-glyceraldehyde).**

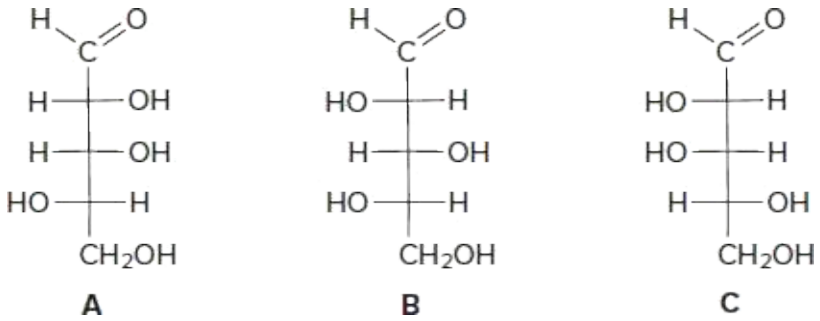


Glucose and all other naturally occurring sugars are D-sugars. L-Glucose, a compound that does not occur in nature, is the enantiomer of D-glucose. L-Glucose has the opposite configuration at *every* stereogenic center.



Problem 26.6

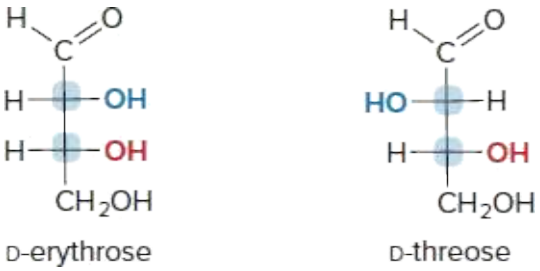
(a) Label compounds A, B, and C as D- or L-sugars. (b) How are compounds A and B related? A and C? B and C? Choose from enantiomers, diastereomers, or constitutional isomers.



26.3 The Family of D-Aldoses

Beginning with D-glyceraldehyde, one may formulate other D-aldoses having four, five, or six carbon atoms by adding carbon atoms (each bonded to H and OH), one at a time, between C1 and C2. Two D-aldotetroses can be formed from D-glyceraldehyde, one with the new OH group on the right and one with the new OH group on the left. Their names are D-erythrose and D-threose. They are two diastereomers, each with two stereogenic centers, labeled in blue.

The common name of each monosaccharide indicates both the number of atoms it contains and the configuration at each of the stereogenic centers. Because the common names are firmly entrenched in the chemical literature, no systematic method has ever been established to name these compounds.



Because each aldotetrose has two stereogenic centers, there are 2^2 or four possible stereoisomers. D-Erythrose and D-threose are two of them. The other two are their enantiomers, called L-erythrose and L-threose, respectively. The configuration around each stereogenic center is exactly the opposite in its enantiomer. All four stereoisomers of the aldotetroses are shown in Figure 26.3.

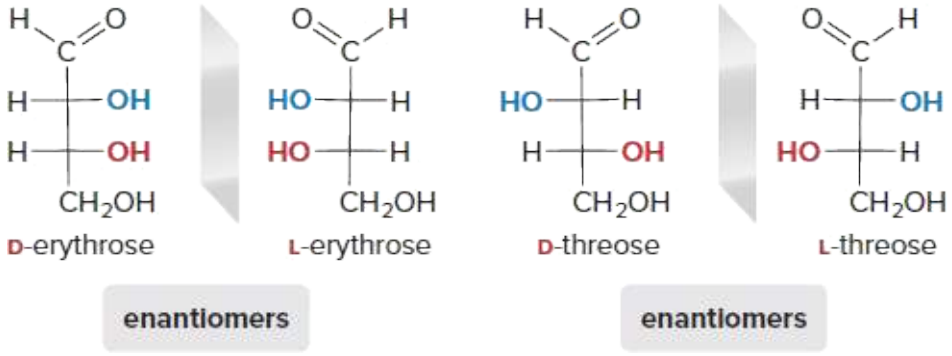


Figure 26.3 **The four stereoisomeric aldotetroses**

D-Ribose, D-arabinose, and D-xylose are all common aldopentoses in nature. D-Ribose is the carbohydrate component of RNA, the polymer that translates the genetic information of DNA for protein synthesis.

To continue forming the family of D-aldoses, we must add another carbon atom (bonded to H and OH) just below the carbonyl of either tetrose. Because there are *two* D-aldotetroses to begin with, and there are *two* ways to place the new OH (right or left), there are now *four* D-aldopentoses: D-ribose, D-arabinose, D-xylose, and D-lyxose. Each aldopentose now has *three* stereogenic centers, so there are $2^3 = 8$ possible stereoisomers, or four pairs of enantiomers. The D-enantiomer of each pair is shown in Figure 26.4.

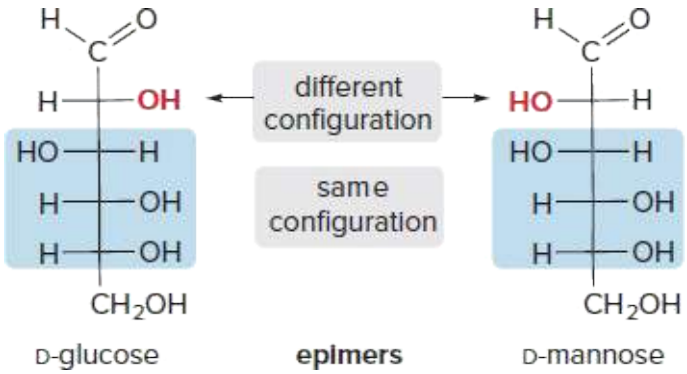
Finally, to form the D-aldohexoses, we must add another carbon atom (bonded to H and OH) just below the carbonyl of all the aldopentoses. Because there are *four* D-aldopentoses to begin with, and there are *two* ways to place the new OH (right or left), there are now *eight* D-aldohexoses. Each aldohexose now has *four* stereogenic centers, so there are $2^4 = 16$ possible stereoisomers, or eight pairs of enantiomers. Only the D-enantiomer of each pair is shown in Figure 26.4.

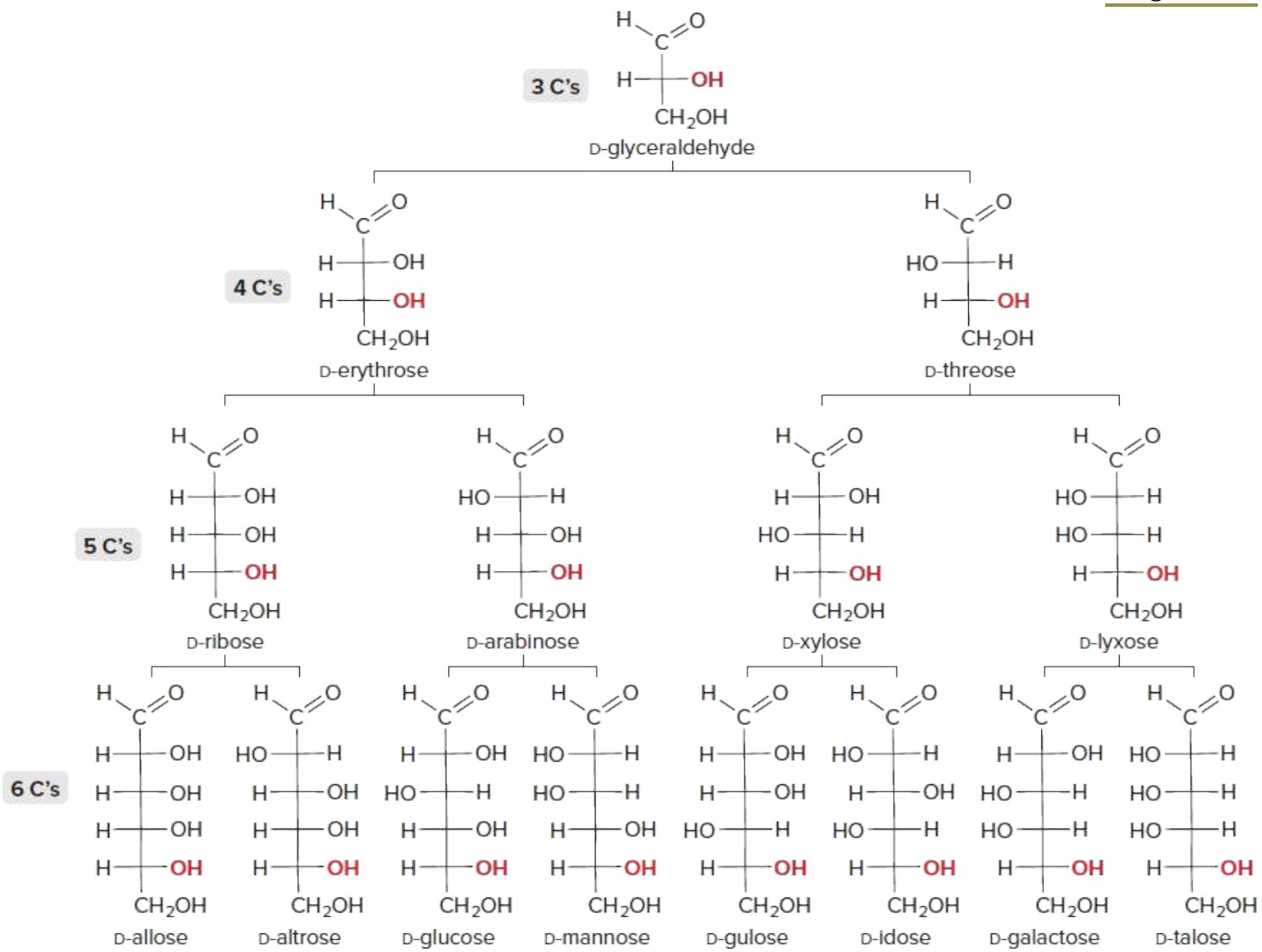
The tree of D-aldoses (Figure 26.4) is arranged in pairs of compounds that are bracketed together. Each pair of compounds, such as D-glucose and D-mannose, has the same configuration around all of its stereogenic centers except for one.

Of the D-aldohexoses, only D-glucose and D-galactose are common in nature. D-Glucose is by far the most abundant of all D-aldoses. D-Glucose comes from the hydrolysis of starch and cellulose, and D-galactose comes from the hydrolysis of

fruit pectins.

- **Two diastereomers that differ in the configuration around only one stereogenic center are called *epimers*.**





- All D-aldoses have the OH group on the stereogenic center farthest from the C=O (shown in red) on the **right.**

Figure 26.4 **The family of D-aldoses having three to six carbon atoms**

Problem 26.7

How many different aldoheptoses are there? How many are D-sugars? Draw all D-aldoheptoses having the R configuration at C2 and C3.

Problem 26.8

Draw two possible epimers of D-erythrose. Name each of these compounds using Figure 26.4.

26.4 The Family of D-Ketoses

The family of D-ketoses, shown in Figure 26.5, is formed from dihydroxyacetone by adding a new carbon (bonded to H and OH) between C2 and C3. Having a carbonyl group at C2 decreases the number of stereogenic centers in these monosaccharides, so that there are only four D-ketohexoses. The most common naturally occurring ketose is D-fructose.

Problem 26.9

Referring to the structures in Figures 26.4 and 26.5, classify each pair of compounds as enantiomers, epimers, diastereomers but not epimers, or constitutional isomers of each other.

a. D-allose and L-allose

b. D-altrose and D-gulose

c. D-galactose and D-talose

d. D-mannose and D-fructose

e. D-fructose and D-sorbose

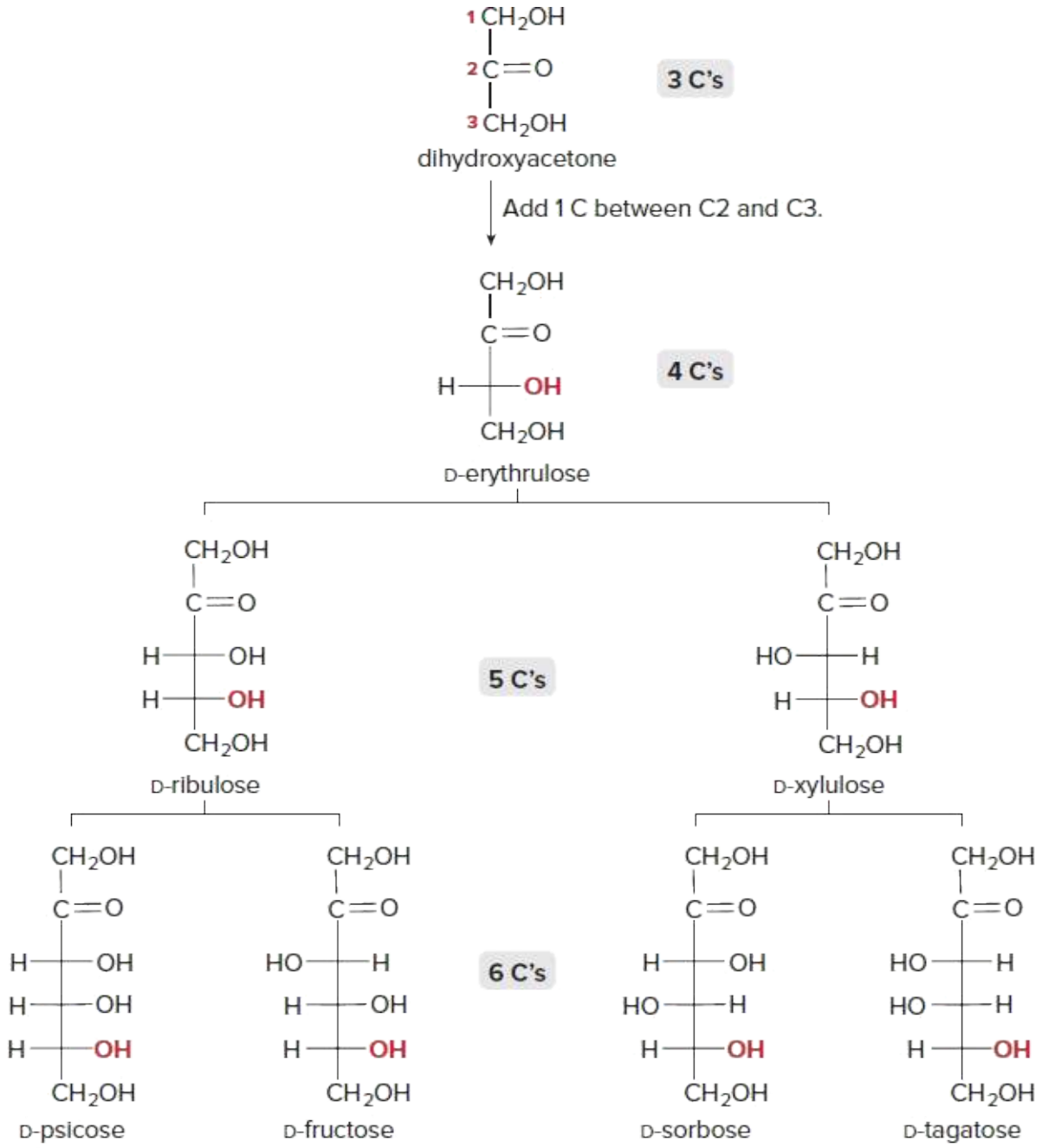
f. L-sorbose and L-tagatose

Problem 26.10

a. Draw the enantiomer of D-fructose.

b. Draw an epimer of D-fructose at C4. What is the name of this compound?

c. Draw an epimer of D-fructose at C5. What is the name of this compound?



- All D-ketoses have the OH group on the stereogenic center farthest from the C=O (shown in red) on the **right.**

Figure 26.5 **The family of D-ketoses having three to six carbon atoms**

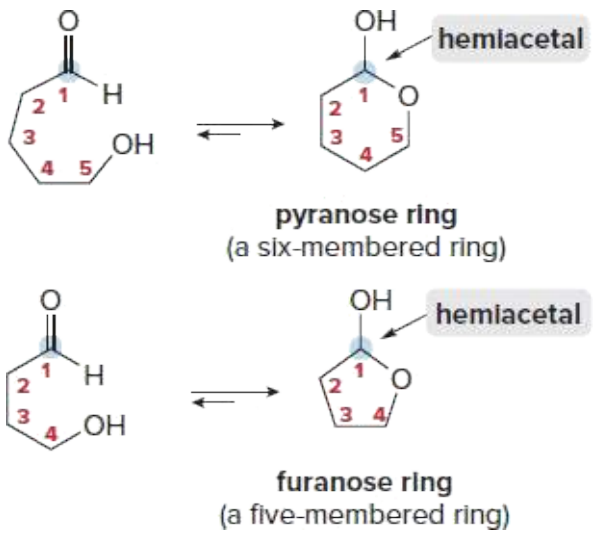
26.5 Physical Properties of Monosaccharides

Monosaccharides have these physical properties:

- They are all sweet tasting, but their relative sweetness varies a great deal.
- They are polar compounds with high melting points.
- The presence of so many polar functional groups capable of hydrogen bonding makes them water soluble.
- Unlike most other organic compounds, monosaccharides are so polar that they are insoluble in organic solvents like diethyl ether.

26.6 The Cyclic Forms of Monosaccharides

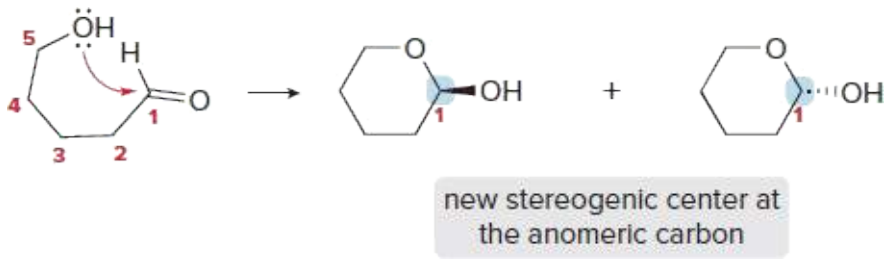
Although the monosaccharides in Figures 26.4 and 26.5 are drawn as acyclic carbonyl compounds containing several hydroxy groups, the hydroxy and carbonyl groups of monosaccharides can undergo intramolecular cyclization reactions to form hemiacetals having either five or six atoms in the ring. This process was first discussed in Section 18.15.



- **A six-membered ring containing an O atom is called a *pyranose* ring.**
- **A five-membered ring containing an O atom is called a *furanose* ring.**

Cyclization of a hydroxy carbonyl compound always forms a stereogenic center at the hemiacetal carbon, called the anomeric carbon. The two hemiacetals are called anomers.

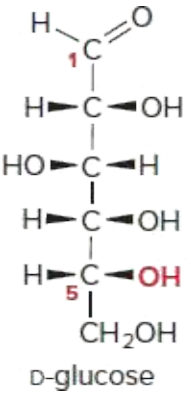
- **Anomers are stereoisomers of a cyclic monosaccharide that differ in the position of the OH group at the hemiacetal carbon.**



Cyclization forms the more stable ring size in a given molecule. The most common monosaccharides, the aldohexoses like glucose, typically form a pyranose ring, so our discussion begins with forming a cyclic hemiacetal from D-glucose.

26.6A Drawing Glucose as a Cyclic Hemiacetal

Which of the five OH groups in glucose is at the right distance from the carbonyl group to form a six-membered ring? The O atom on the stereogenic center farthest from the carbonyl (C5) is six atoms from the carbonyl carbon, placing it in the proper position for cyclization to form a pyranose ring.



The OH at C5 forms the pyranose ring.

To translate the acyclic form of glucose into a cyclic hemiacetal, we must draw the hydroxy aldehyde in a way that suggests the position of the atoms in the new ring, and then draw the ring. By convention the O atom in the new pyranose ring is drawn in the upper right corner of the six-membered ring.

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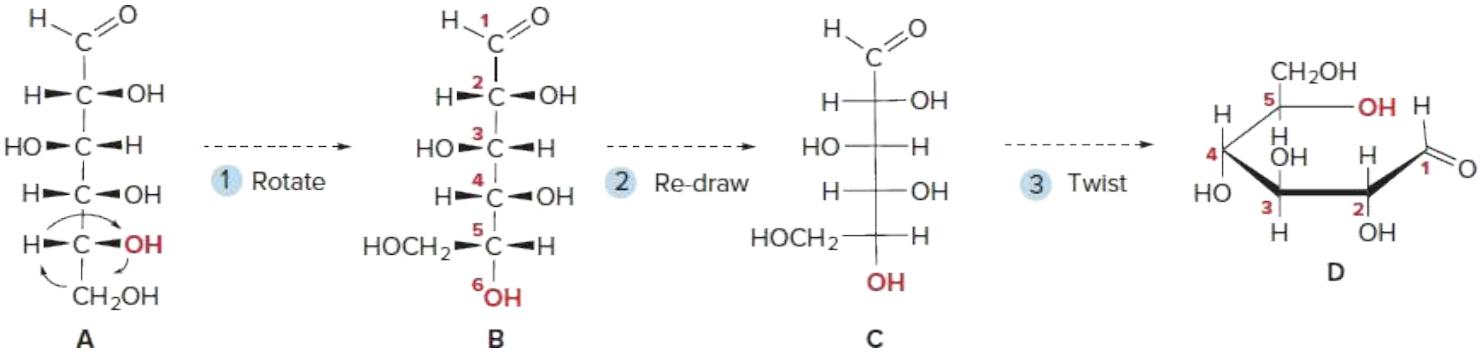
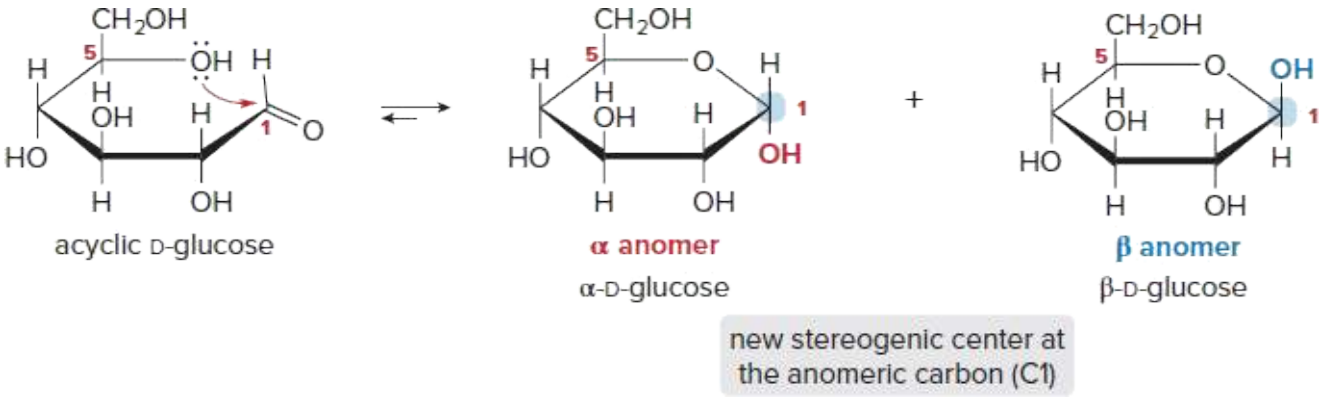
Rotating the groups on the bottom stereogenic center in A places all six atoms needed for the ring (including the OH) in a vertical line (B). Re-drawing this representation as a Fischer projection makes the structure appear less cluttered (C). Twisting this structure and rotating it 90° forms D. Structures A–D are four different ways of drawing the same acyclic structure of D-glucose.



We are now set to draw the cyclic hemiacetal formed by nucleophilic attack of the OH group on C5 on the aldehyde carbonyl. Because cyclization creates a new stereogenic center, there are two cyclic forms of D-glucose, an α anomer and a β anomer. All the original stereogenic centers retain their configuration in both of the products formed.

- **The α anomer of a D monosaccharide has the OH group drawn *down*, trans to the CH_2OH group at C5. The α anomer of D-glucose is called α-D-glucose, or α-D-glucopyranose (to emphasize the six-membered ring).**

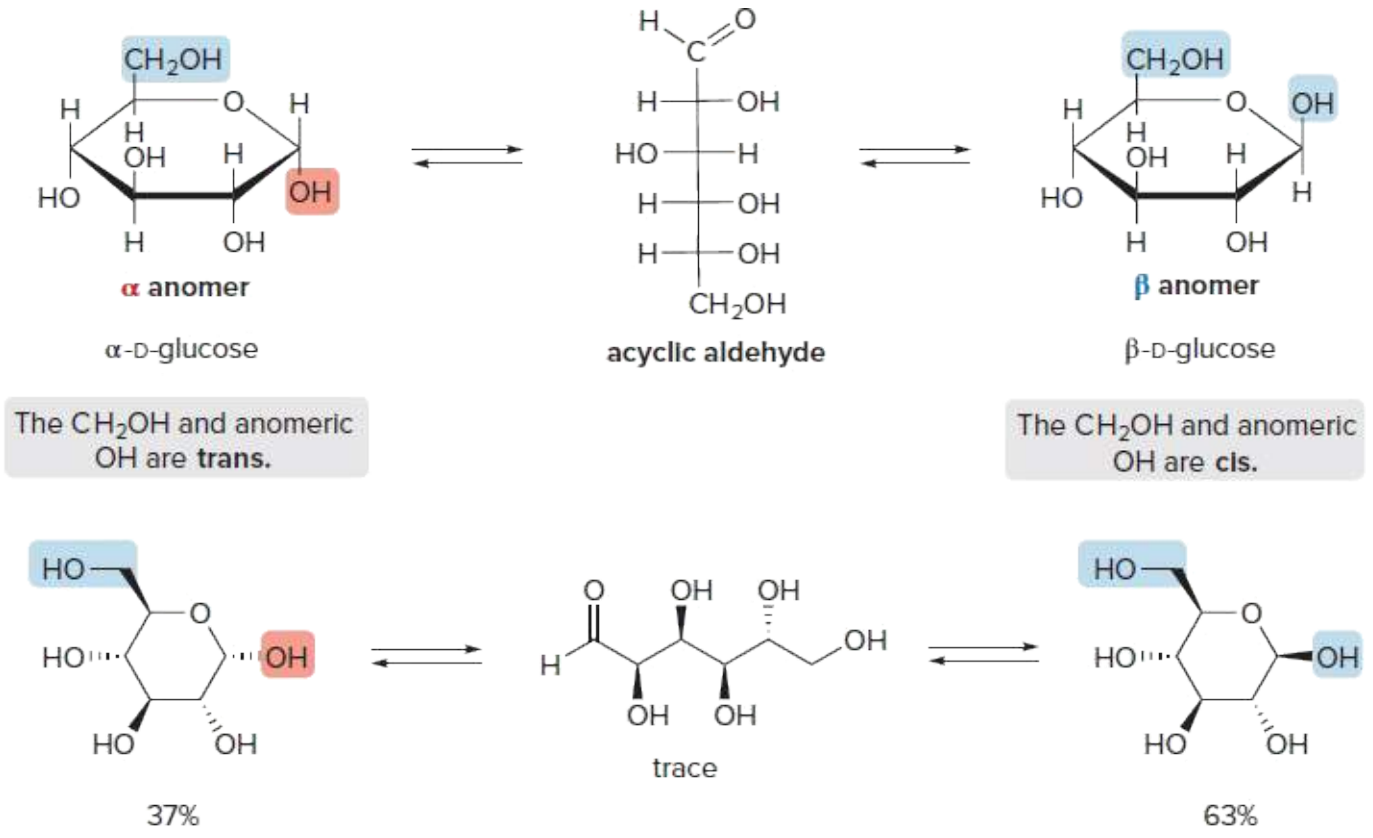
- **The β anomer of a D monosaccharide has the OH group drawn *up*, cis to the CH_2OH group at C5. The β anomer is called β-D-glucose, or β-D-glucopyranose (to emphasize the six-membered ring).**



The α anomer in any monosaccharide has the anomeric OH group and the CH_2OH group trans. The β anomer has the anomeric OH group and the CH_2OH group cis.

These flat, six-membered rings used to represent the cyclic hemiacetals of glucose and other sugars are called Haworth projections. The cyclic forms of glucose now have five stereogenic centers, the four from the starting hydroxy aldehyde and the new anomeric carbon. α-D-Glucose and β-D-glucose are diastereomers, because only the anomeric carbon has a different configuration.

The mechanism for this transformation is exactly the same as the mechanism that converts a hydroxy aldehyde to a cyclic hemiacetal (Mechanism 18.12). The acyclic aldehyde and two cyclic hemiacetals are all in equilibrium. Each cyclic hemiacetal can be isolated and crystallized separately, but when any one compound is placed in solution, an equilibrium mixture of all three forms results. This process is called mutarotation. At equilibrium, the mixture has 37% of the α anomer, 63% of the β anomer, and only trace amounts of the acyclic hydroxy aldehyde (Figure 26.6). Also shown are representations of the three forms of glucose using wedges and dashed wedges.



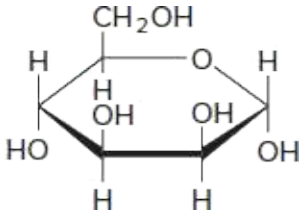
- Bonds above the ring in a Haworth projection are drawn as wedges.
- Bonds below the ring in a Haworth projection are drawn as dashed wedges.

Figure 26.6 **The three forms of glucose**

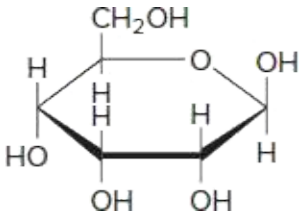
Problem 26.11

Label each Haworth projection as an α or β anomer, and convert the Haworth projection to a six-membered ring with wedges and dashed wedges.

a.



b.

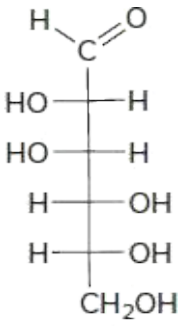


26.6B Haworth Projections

To convert an acyclic monosaccharide to a Haworth projection, follow a stepwise procedure.

How To Draw a Haworth Projection from an Acyclic Aldohexose

Example Convert D-mannose to a Haworth projection.



D-mannose

Step [1] Place the O atom in the upper right corner of a hexagon, and add the CH_2OH group on the first carbon counterclockwise from the O atom.

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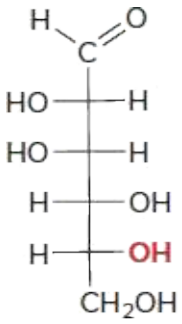
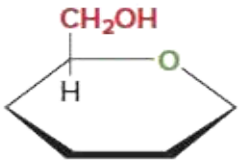
- For D-sugars, the CH_2OH group is drawn up. For L-sugars, the CH_2OH group is drawn down.



D-sugar

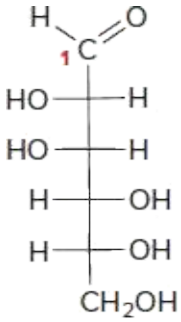
D-mannose

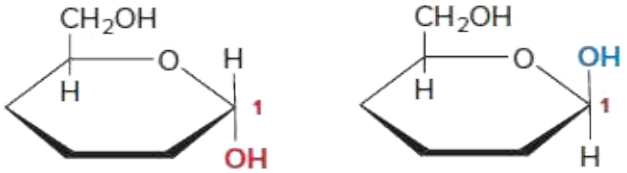


CH_2OH is drawn up.

Step [2] Place the anomeric carbon on the first carbon clockwise from the O atom.

- For an α anomer, the OH is drawn down in a D-sugar.
- For a β anomer, the OH is drawn up in a D-sugar.





α anomer

β anomer

The anomeric carbon is a new stereogenic center at C1.

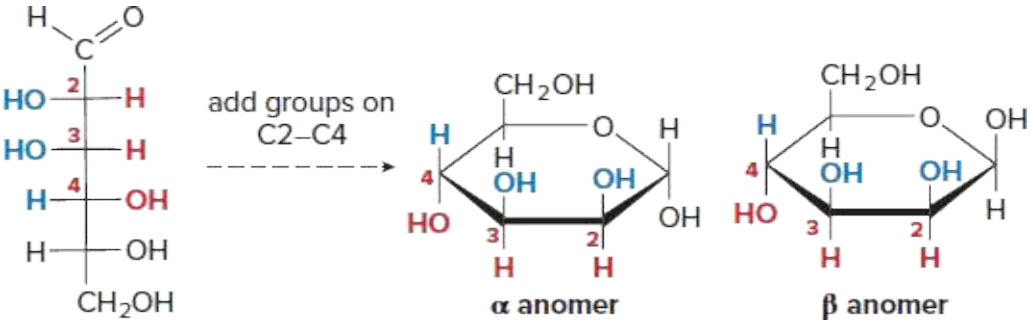
- Remember: The carbonyl carbon becomes the anomeric carbon (a new stereogenic center).

Step [3] Add the substituents at the three remaining stereogenic centers clockwise around the ring.

- The substituents on the right side of the Fischer projection are

drawn down.

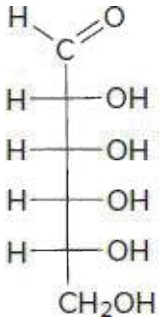
- The substituents on the left are drawn up.



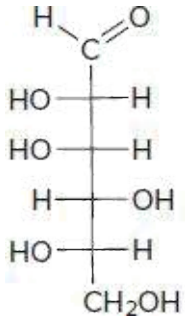
Problem 26.12

Convert each aldohexose to the indicated anomer using a Haworth projection.

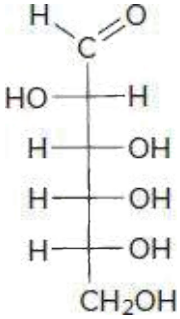
a. Draw the α anomer of:



b. Draw the α anomer of:



c. Draw the β anomer of:



Sample Problem 26.4 shows how to convert a Haworth projection back to the acyclic form of a monosaccharide. It doesn't matter whether the hemiacetal is the α or β anomer, because both anomers give the *same* hydroxy

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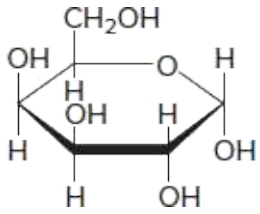
aldehyde.

Sample Problem 26.4 Converting a Haworth Projection to a Fischer Projection

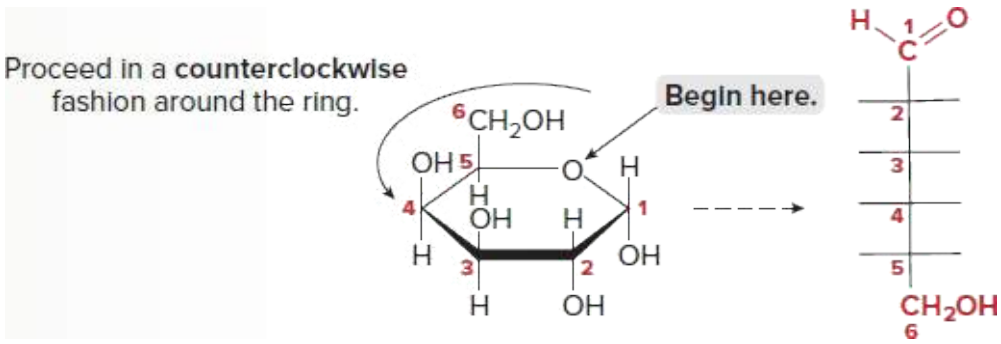
Convert the following Haworth projection to the acyclic form of the aldohexose.



Solution

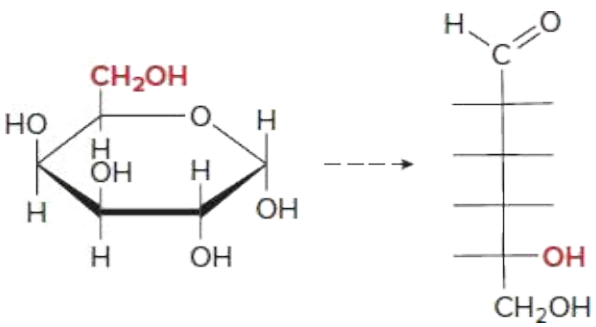
To convert the substituents to the acyclic form, start at the pyranose O atom, and work in a *counterclockwise* fashion around the ring, and from bottom-to-top along the chain.

[1] Draw the carbon skeleton, placing the CHO on the top and the CH_2OH on the bottom.



[2] Classify the sugar as D- or L-.

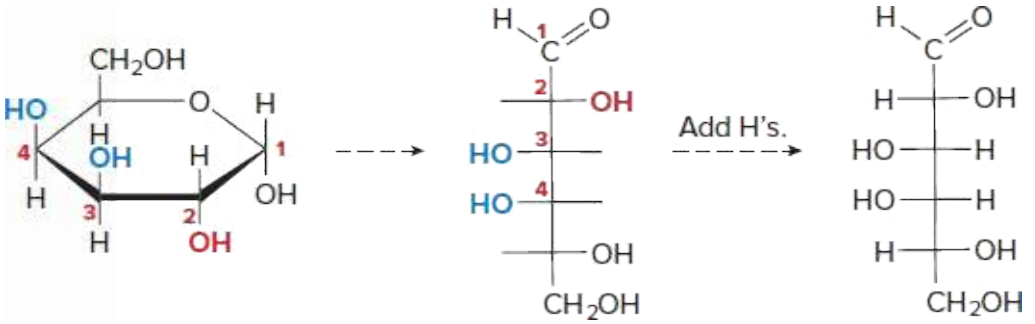
- **The CH_2OH is drawn up, so it is a D-sugar.**
- **A D-sugar has the OH group on the bottom stereogenic center on the right.**



[3] Add the three other stereogenic centers.

- **Up substituents go on the left.**

- **Down substituents go on the right.**

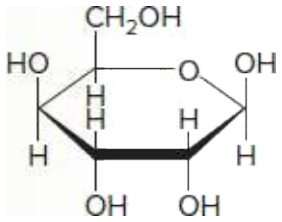


- **The anomeric carbon becomes the C=O at C1.**

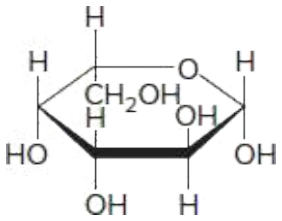
Problem 26.13

Convert each Haworth projection to its acyclic form.

a.



b.



More Practice:

Try Problem 26.45.

26.6C Three-Dimensional Representations for D-Glucose

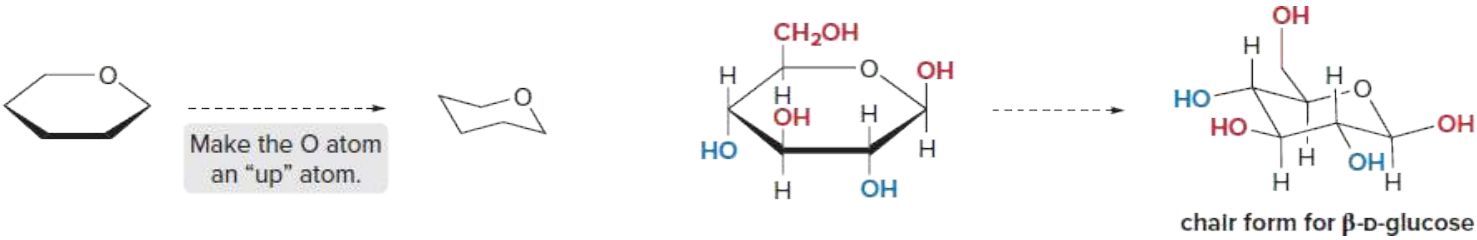
Because the chair form of a six-membered ring gives the truest picture of its three-dimensional shape, we must learn to convert Haworth projections to chair forms.

To convert a Haworth projection to a chair form:

- **Draw the pyranose ring with the O atom as an "up" atom.**
- **The "up" substituents in a Haworth projection become the "up" bonds (either axial or equatorial) on a given carbon atom on a puckered six-membered ring.**
- **The "down" substituents in a Haworth projection become the "down" bonds (either axial or equatorial) on a given carbon atom on a puckered**

six-membered ring.

As a result, the three-dimensional chair form of β-D-glucose is drawn in this manner:



Glucose has all substituents larger than a hydrogen atom in the more roomy equatorial positions, making it the most stable and thus most prevalent monosaccharide. The β anomer is the major isomer at equilibrium, moreover, because the hemiacetal OH group is in the equatorial position, too. Figure 26.7 shows both anomers of D-glucose drawn as chair conformations.

Problem 26.14

Convert each Haworth projection in Problem 26.13 to a three-dimensional representation using a chair pyranose ring.

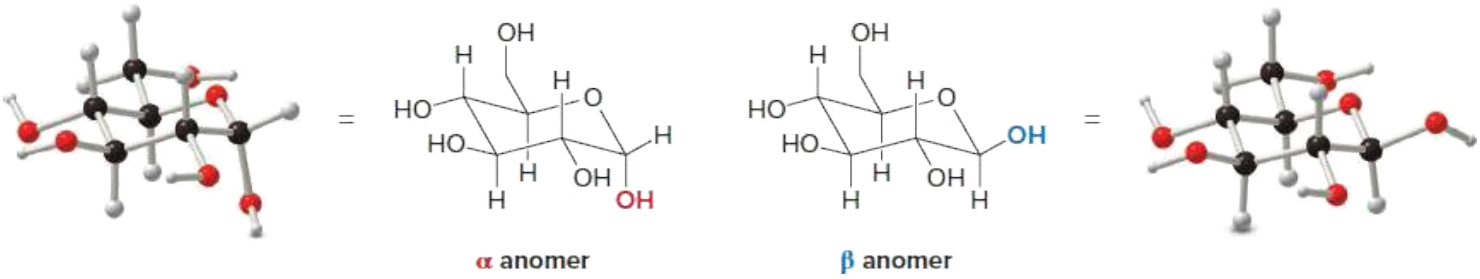


Figure 26.7 **Three-dimensional representations for both anomers of D-glucose**

26.6D Furanoses

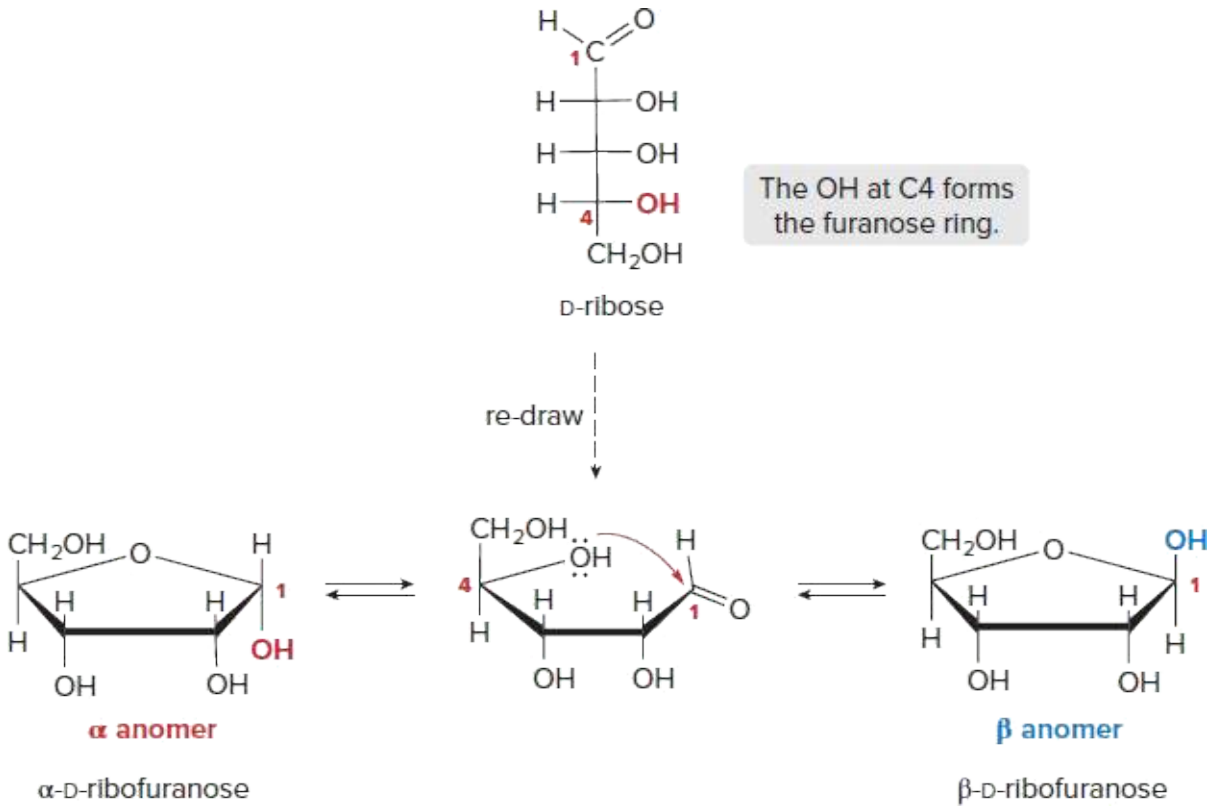
Certain monosaccharides—notably aldopentoses and ketohexoses—predominantly form furanose rings, rather than pyranose rings, in solution. The same principles apply to drawing these structures as for drawing pyranose rings, except the ring size is one atom smaller.

- **Cyclization always forms a new stereogenic center at the anomeric carbon, so two different anomers are possible. For a D-sugar, the OH group is drawn *down* in the α anomer and *up* in the β anomer.**

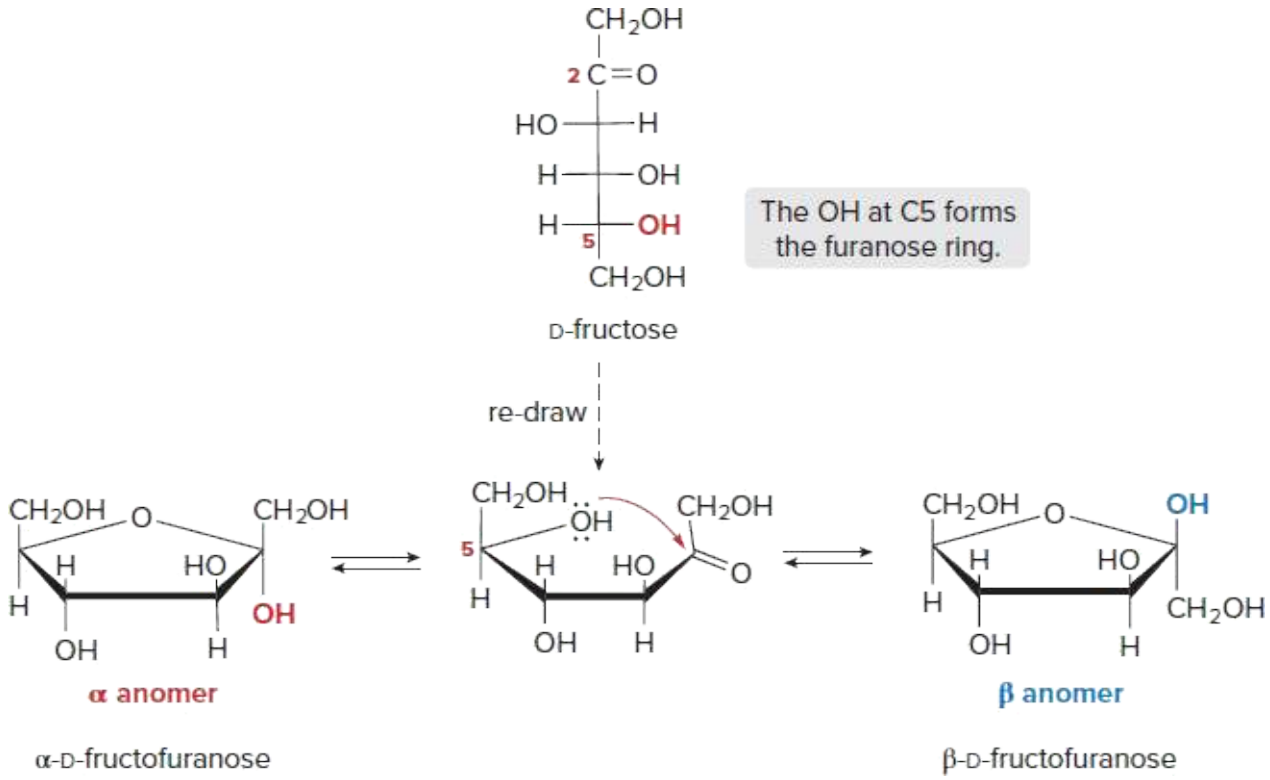
- **Use the same drawing conventions for adding substituents to the five-membered ring. With D-sugars, the CH_2OH group is drawn *up*.**

Honey was the first and most popular sweetening agent until it was replaced by sugar (from sugarcane) in modern times. Honey is a mixture consisting largely of D-fructose and D-glucose. ***©Anastasy Yarmolovich/iStockphoto/Getty Images***

With D-ribose, the OH group used to form the five-membered furanose ring is located on C4. Cyclization yields two anomers at the new stereogenic center, which are called α-D-ribofuranose and β-D-ribofuranose.



The same procedure can be used to draw the furanose form of D-fructose, the most common ketohexose. Because the carbonyl group is at C2 (instead of C1, as in the aldoses), the OH group at C5 reacts to form the hemiacetal in the five-membered ring. Two anomers are formed.



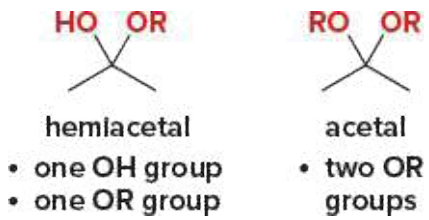
Problem 26.15

Aldotetroses exist in the furanose form. Draw both anomers of D-erythrose.

26.7 Glycosides

Because monosaccharides exist in solution in an equilibrium between acyclic and cyclic forms, they undergo three types of reactions:

Keep in mind the difference between a hemiacetal and an acetal:



- Reaction of the hemiacetal
- Reaction of the hydroxy groups
- Reaction of the carbonyl group

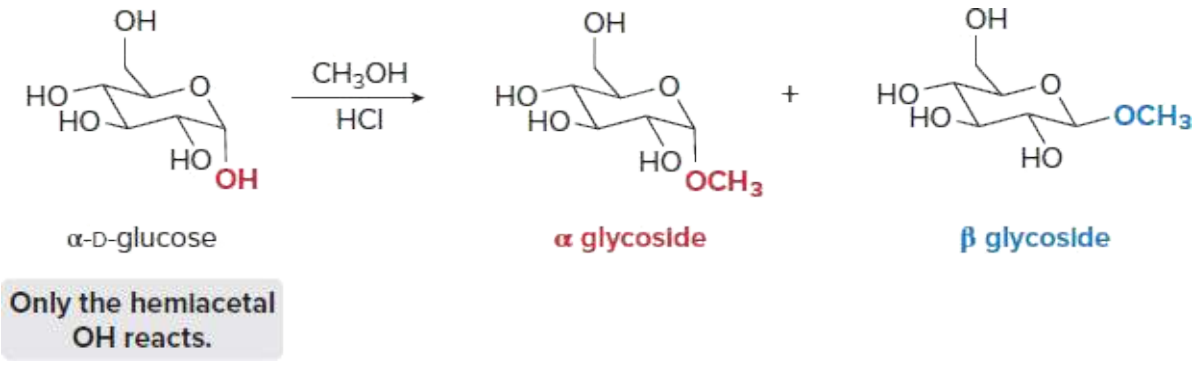
Even though the acyclic form of a monosaccharide may be present in only trace amounts, the equilibrium can be tipped in its favor by Le Châtelier's principle (Section

9.8). Suppose, for example, that the carbonyl group of the acyclic form reacts with a reagent, thus depleting its equilibrium concentration. The equilibrium will then shift to compensate for the loss, thus producing more of the acyclic form, which can react further.

Note, too, that monosaccharides have two different types of OH groups. Most are "regular" alcohols and, as such, undergo reactions characteristic of alcohols. The anomeric OH group, on the other hand, is part of a hemiacetal, giving it added reactivity.

26.7A Glycoside Formation

Treatment of a monosaccharide with an alcohol and HCl converts the hemiacetal to an acetal called a glycoside. For example, treatment of α-D-glucose with CH_3OH and HCl forms two glycosides that are diastereomers at the acetal carbon. The α and β labels are assigned in the same way as anomers: with a D-sugar, an α glycoside has the new OR group (OCH_3 group in this example) *down*, and a β glycoside has the new OR group *up*.



Mechanism 26.1 explains why a single anomer forms two glycosides. The reaction proceeds by way of a planar carbocation, which undergoes nucleophilic attack from two different directions to give a mixture of diastereomers. Because both α- and β-D-glucose form the same planar carbocation, each yields the same mixture of two glycosides.

The mechanism also explains why only the hemiacetal OH group reacts. Protonation of the hemiacetal OH, followed by loss of H_2O, forms a resonance-stabilized carbocation in Step [2]. A resonance-stabilized carbocation is *not* formed by loss of H_2O from any other OH group.

Unlike cyclic hemiacetals, glycosides are acetals, so they do *not* undergo mutarotation. When a single glycoside is dissolved in H_2O, it is *not* converted to an equilibrium mixture of α and β glycosides.

- **Glycosides are acetals with an alkoxy group (OR) bonded to the anomeric carbon.**

Problem 26.16

What glycosides are formed when each monosaccharide is treated with CH_3CH_2OH, HCl: (a) β-D-mannose; (b) α-D-gulose; (c) β-D-fructose?

Mechanism 26.1 Glycoside Formation

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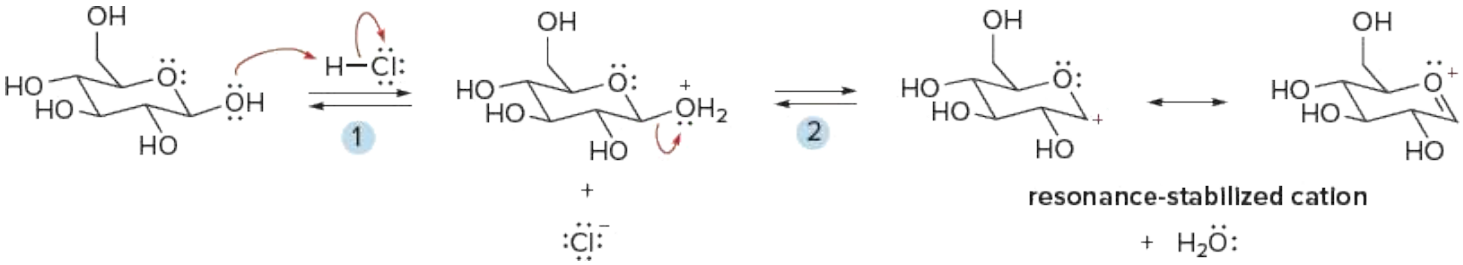
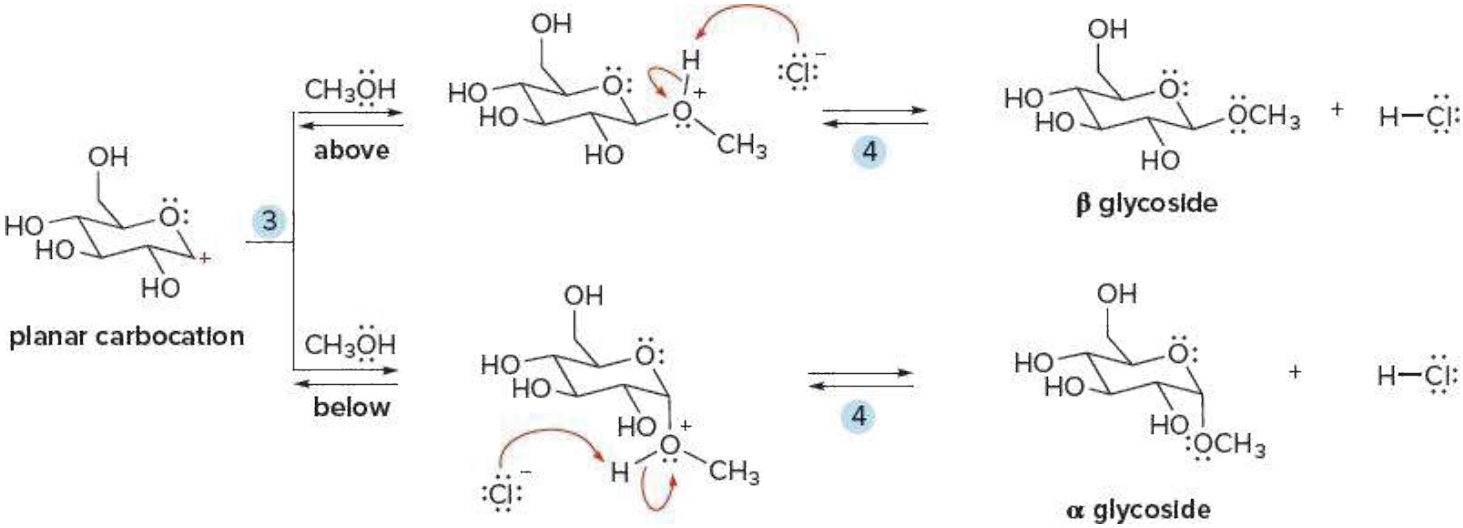
Part [1] Loss of H_2O from the hemiacetal



1 – 2 Protonation of the hemiacetal OH followed by loss of H_2O forms a resonance-stabilized carbocation.

Part [2] Formation of the glycosides

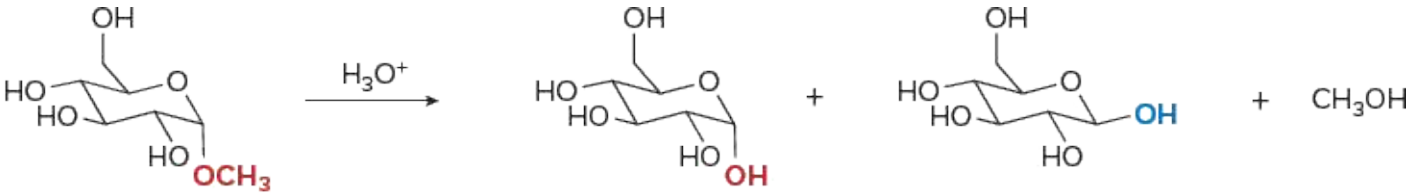


3 – 4 Nucleophilic attack by CH_3OH occurs from both sides of the planar carbocation to yield α and β glycosides after loss of a proton.

26.7B Glycoside Hydrolysis

Because glycosides are acetals, they are hydrolyzed with acid and water to cyclic hemiacetals and a molecule of alcohol. A mixture of two anomers is formed from a

single glycoside. For example, treatment of methyl α-D-glucopyranoside with aqueous acid forms a mixture of α- and β-D-glucose and methanol.

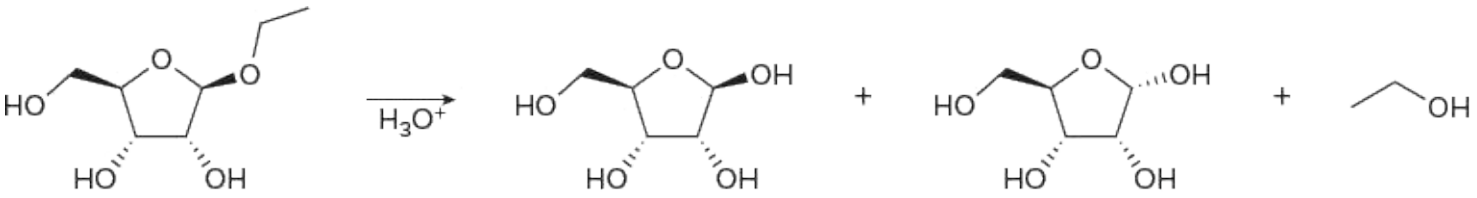


methyl α-D-glucopyranoside | α-D-glucose | β-D-glucose

The mechanism for glycoside hydrolysis is just the reverse of glycoside formation. It involves two parts: formation of a planar carbocation, followed by nucleophilic attack of H_2O to form anomeric hemiacetals, as shown in Mechanism 26.2.

Problem 26.17

Draw a stepwise mechanism for the following reaction.



Mechanism 26.2 Glycoside Hydrolysis

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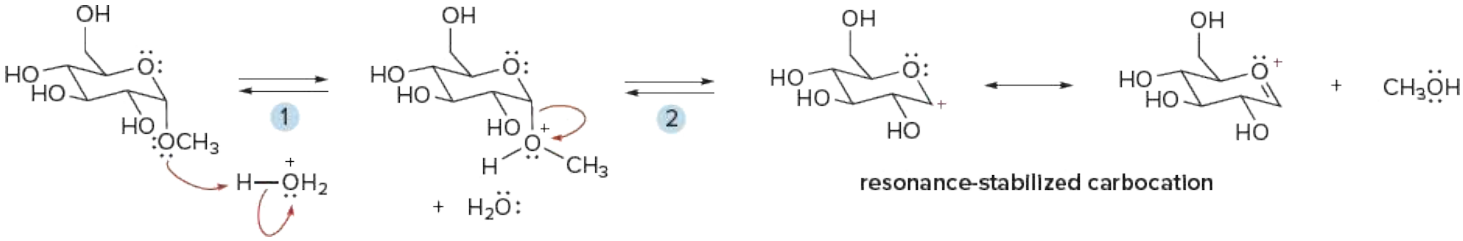
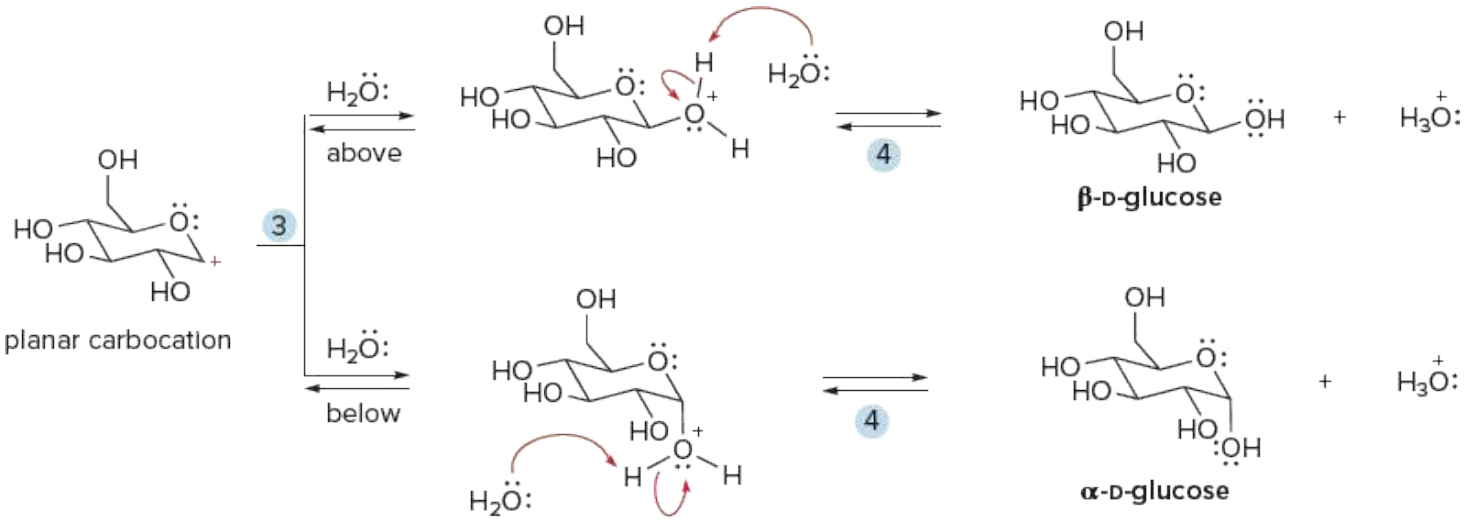
Part [1] Loss of CH_3OH from the glycoside



1 – 2 Protonation of the acetal OCH_3 followed by loss of CH_3OH forms a resonance-stabilized carbocation.

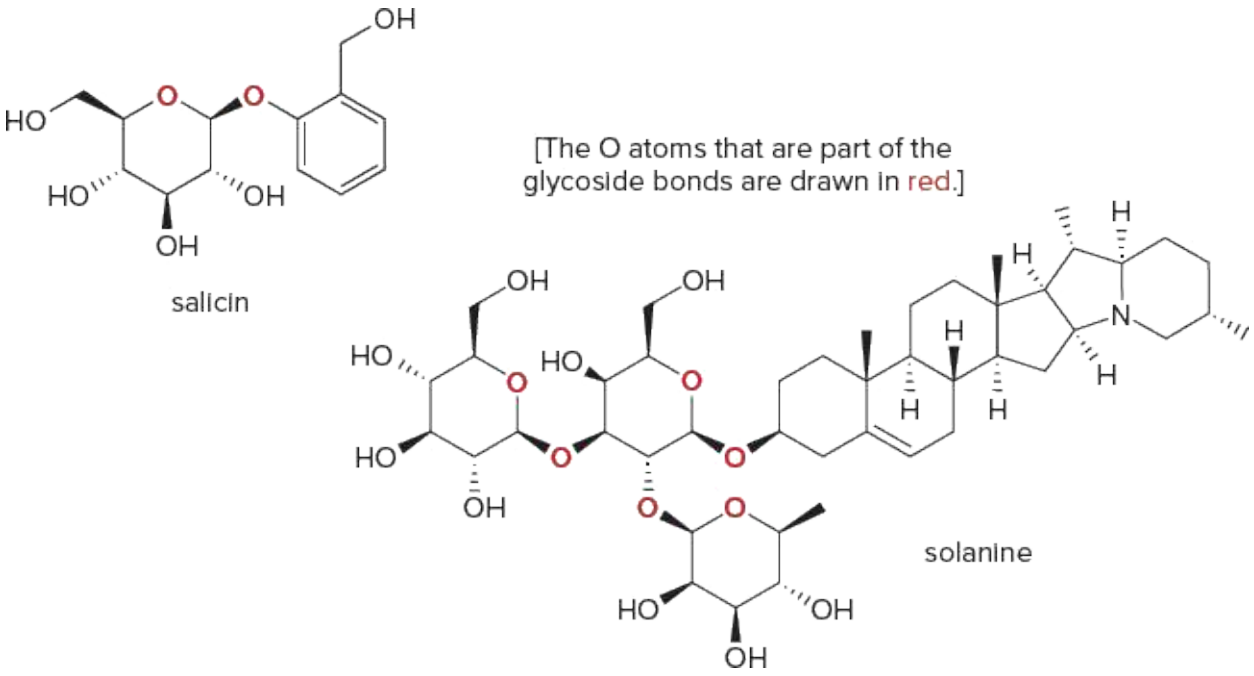
Part [2] Formation of the hemiacetals



3 – 4 Nucleophilic attack by H_2O occurs from both sides of the planar carbocation to yield α and β anomers after loss of a proton.

26.7C Naturally Occurring Glycosides

Salicin and solanine are two naturally occurring compounds that contain glycoside bonds as part of their structure. Salicin is an analgesic isolated from willow bark, and solanine is a poisonous compound produced in the leaves, stem, and green spots on the skin of potatoes. Solanine is also isolated from the berries of the deadly nightshade plant. It is believed that the role of the sugar rings in both salicin and solanine is to increase their water solubility.



The berries of the black nightshade plant (*Solanum nigrum*) are a source of the poisonous alkaloid solanine. ***©TunedIn by Westend61/Shutterstock***

Glycosides are common in nature. All disaccharides and polysaccharides are formed by joining monosaccharides together with glycosidic linkages. These compounds are discussed in detail beginning in Section 26.11.

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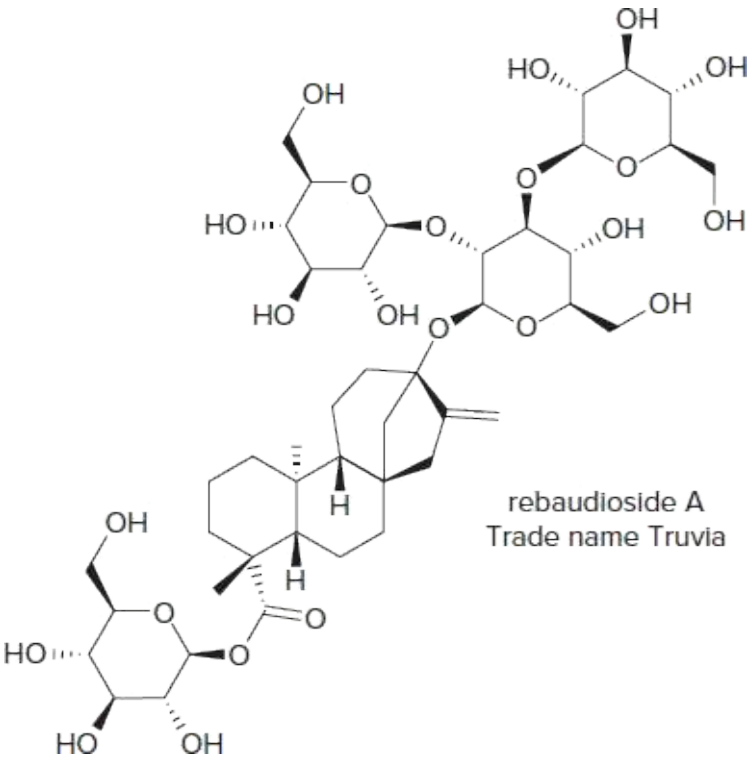
Problem 26.18

(a) Label all the O atoms that are part of a glycoside in rebaudioside A. Rebaudioside A, marketed under the trade name Truvia, is a sweet glycoside obtained from the stevia plant, which has been used for centuries in Paraguay to sweeten foods. (b) The alcohol or phenol formed from the hydrolysis of a glycoside is called an aglycon. What aglycon and monosaccharides are formed by the hydrolysis of rebaudioside A?



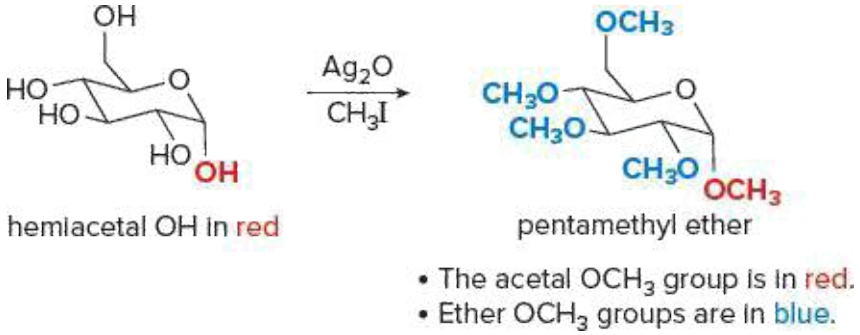
Rebaudioside A, a naturally occurring glycoside about 400 times sweeter than table sugar, is obtained from the leaves of the stevia plant, a shrub native to Central and South America.

©Linda Hall/Shutterstock

26.8 Reactions of Monosaccharides at the OH Groups

Because monosaccharides contain OH groups, they undergo reactions typical of alcohols—that is, they are converted to ethers and esters. Because the cyclic hemiacetal form of a monosaccharide contains an OH group, this form of a monosaccharide must be drawn as the starting material for any reaction that occurs at an OH group.

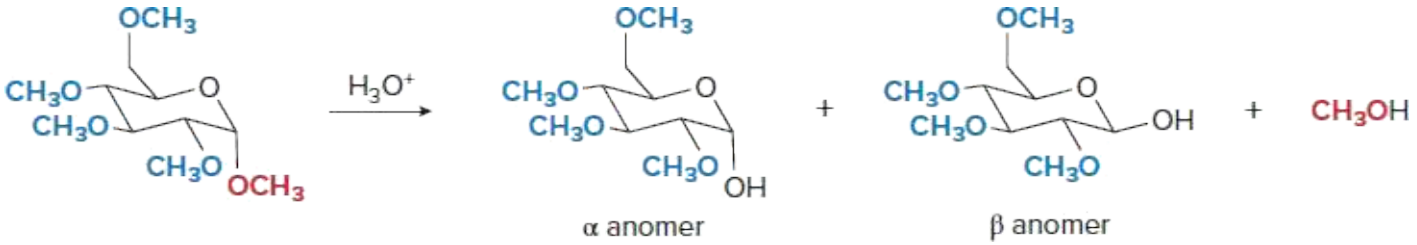
All OH groups of a cyclic monosaccharide are converted to ethers by treatment with base and an alkyl halide. For example, α-D-glucose reacts with silver(I) oxide (Ag_2O, a base) and excess CH_3I to form a pentamethyl ether.



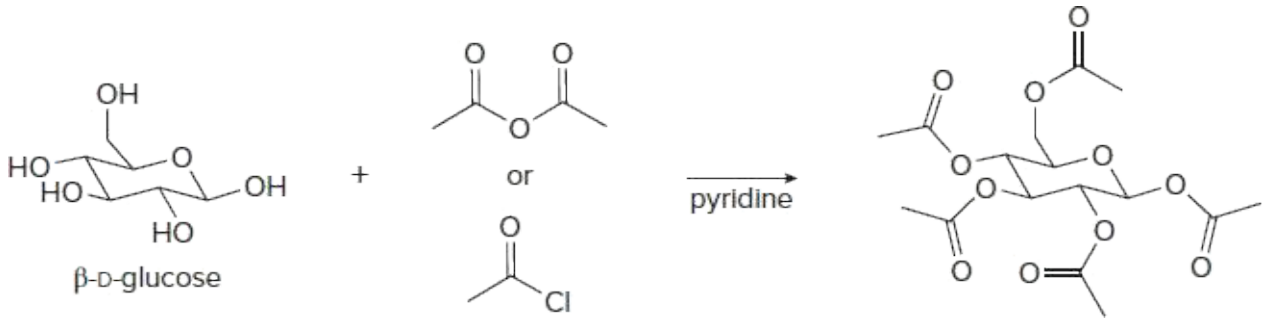
Ag_2O removes a proton from each alcohol, forming an alkoxide (RO^-), which then reacts with CH_3I in an S_N2 reaction. Because no C–O bonds are broken, the configuration of all substituents in the starting material is retained, forming a single product.

The product contains two different types of ether bonds. There are four “regular” ethers formed from the “regular” hydroxyls. The new ether from the hemiacetal is now part of an acetal—that is, a glycoside.

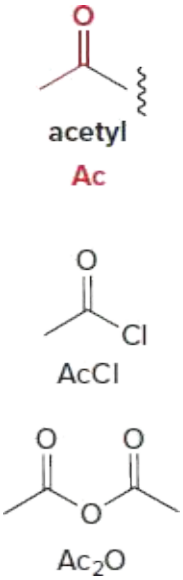
The four ether bonds that are *not* part of the acetal do not react with any reagents except strong acids like HBr and HI (Section 9.14). The acetal ether, on the other hand, is hydrolyzed with aqueous acid (Section 26.7B). Aqueous hydrolysis of a single glycoside (like the pentamethyl ether of α-D-glucose) yields both anomers of the product monosaccharide.

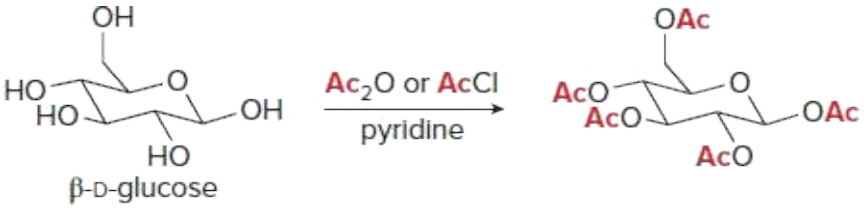


The OH groups of monosaccharides can also be converted to esters. For example, treatment of β-D-glucose with either acetic anhydride or acetyl chloride in the presence of pyridine (a base) converts all OH groups to acetate esters.



Because it is cumbersome and tedious to draw in all the atoms of the esters, the abbreviation Ac is used for the acetyl group, $CH_3C{=}O$. The esterification of β-D-glucose can then be written as follows:





Monosaccharides are so polar that they are insoluble in common organic solvents, making them difficult to isolate and use in organic reactions. Monosaccharide derivatives that have five ether or ester groups in place of the OH groups, however, are readily soluble in organic solvents.

Problem 26.19

Draw the products formed when β-D-galactose is treated with each reagent.

a. $Ag_2O + CH_3I$

b. $NaH + C_6H_5CH_2Cl$

c. The product in (b), then H_3O^+

d. Ac_2O + pyridine

e. C_6H_5COCl + pyridine

f. The product in (c), then C_6H_5COCl + pyridine

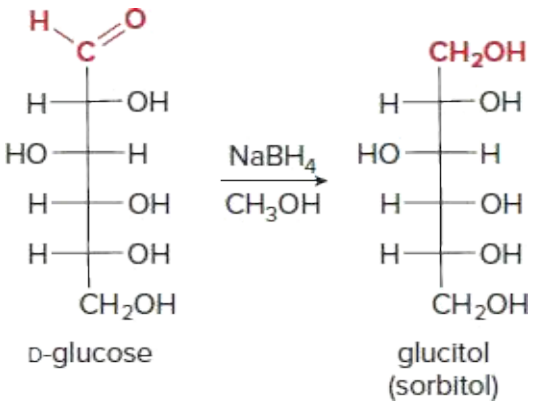
26.9 Reactions at the Carbonyl Group—Oxidation and Reduction

Oxidation and reduction reactions occur at the carbonyl group of monosaccharides, so they all begin with the monosaccharide drawn in the acyclic form. We will confine our discussion to aldoses as starting materials.

26.9A Reduction of the Carbonyl Group

Like other aldehydes, the carbonyl group of an aldose is reduced to a 1° alcohol using $NaBH_4$. This alcohol is called an alditol. For example, reduction of D-glucose with $NaBH_4$ in CH_3OH yields glucitol (also called sorbitol).

Glucitol occurs naturally in some fruits and berries. It is sometimes used as a substitute for sucrose (table sugar). With six polar OH groups capable of hydrogen bonding, glucitol is readily hydrated. It is used as an additive to prevent certain foods from drying out.

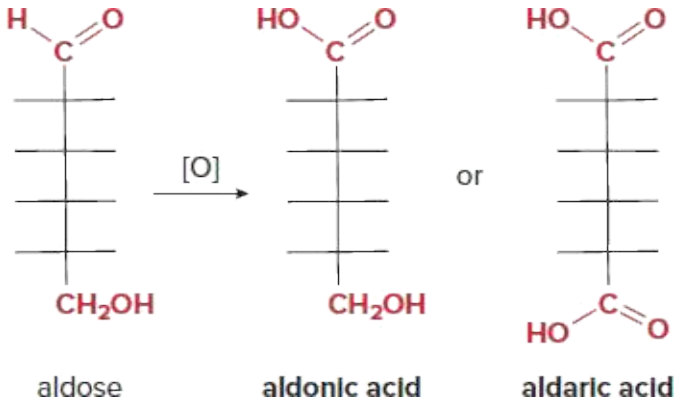


Problem 26.20

A 2-ketohexose is reduced with $NaBH_4$ in CH_3OH to form a mixture of D-galactitol and D-talitol. What is the structure of the 2-ketohexose?

26.9B Oxidation of Aldoses

Aldoses contain 1° and 2° alcohols and an aldehyde, all of which are oxidizable functional groups. Two different types of oxidation reactions are particularly useful —oxidation of the aldehyde to a carboxylic acid (an aldonic acid) and oxidation of both the aldehyde and the 1° alcohol to a diacid (an aldaric acid).

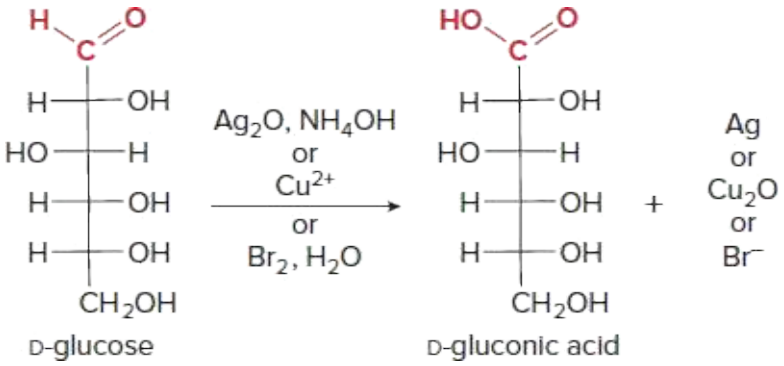


[1] Oxidation of the aldehyde to a carboxylic acid

The aldehyde carbonyl is the most easily oxidized functional group in an aldose, so a variety of reagents oxidize it to a carboxy group, forming an aldonic acid.

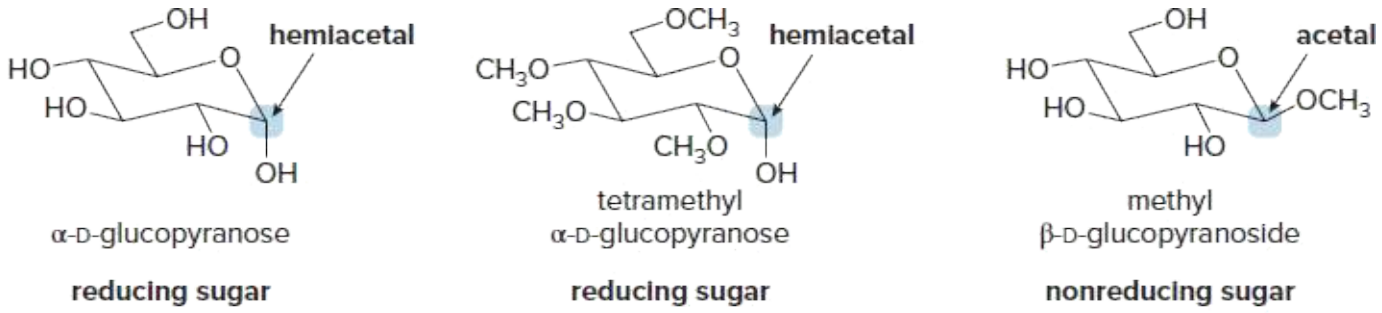
Three reagents used for this process produce a characteristic color change because the oxidizing agent is reduced to a colored product that is easily visible. As described in Section 17.8, Tollens reagent oxidizes aldehydes to carboxylic acids using Ag2O in NH4OH, and forms a mirror of Ag as a by-product. Benedict's and Fehling's reagents use a blue Cu^{2+} salt as an oxidizing agent, which is reduced to Cu_2O, a brick-red solid. Unfortunately, none of these reagents gives a high yield of aldonic acid. When the

aldonic acid is needed to carry on to other reactions, $Br_2 + H_2O$ is used as the oxidizing agent.



- **Any carbohydrate that exists as a *hemiacetal* is in equilibrium with a small amount of acyclic aldehyde, so it is oxidized to an aldonic acid.**
- **Glycosides are acetals, not hemiacetals, so they are *not* oxidized to aldonic acids.**

Carbohydrates that can be oxidized with Tollens, Benedict's, or Fehling's reagent are called reducing sugars. Those that do not react with these reagents are called nonreducing sugars. Figure 26.8 shows examples of reducing and nonreducing sugars.



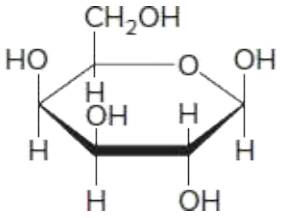
- Carbohydrates containing a hemiacetal are in equilibrium with an acyclic aldehyde, making them **reducing sugars.**
- Glycosides are acetals, so they are *not* in equilibrium with any acyclic aldehyde, making them **nonreducing sugars.**

Figure 26.8 **Examples of reducing and nonreducing sugars**

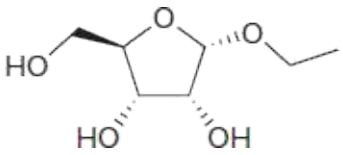
Problem 26.21

Classify each compound as a reducing or nonreducing sugar.

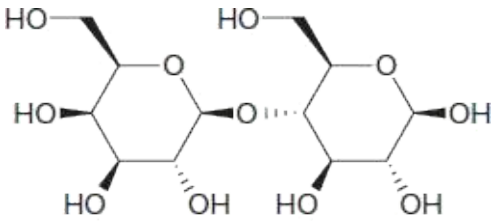
a.



b.



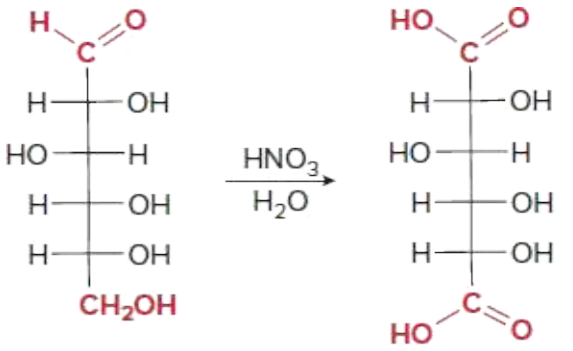
c.



lactose

[2] Oxidation of both the aldehyde and 1° alcohol to a diacid

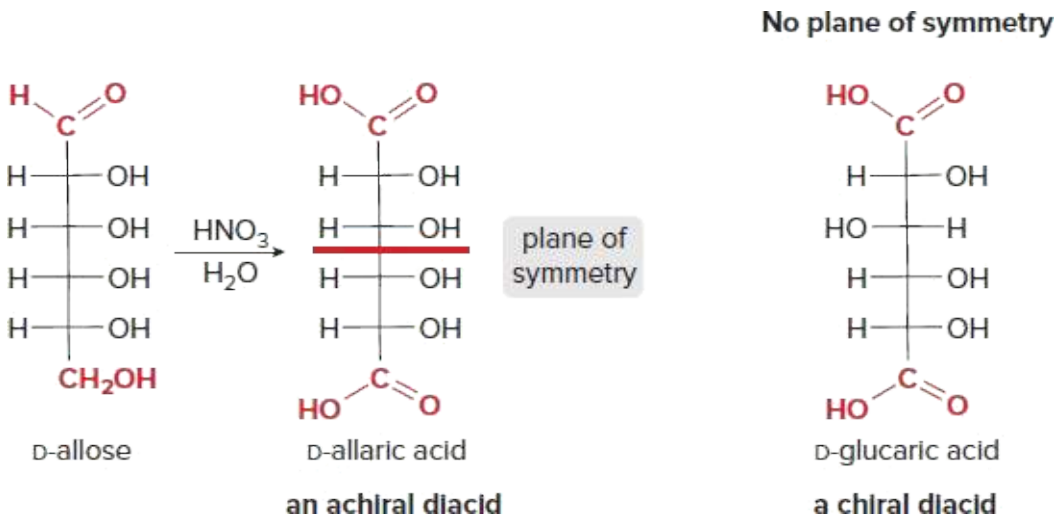
Both the aldehyde and 1° alcohol of an aldose are oxidized to carboxy groups by treatment with warm nitric acid, forming an aldaric acid. Under these conditions, D-glucose is converted to D-glucaric acid.



D-glucose

D-glucaric acid
an aldaric acid

Because aldaric acids have identical functional groups on both terminal carbons, some aldaric acids contain a plane of symmetry, making them achiral molecules. For example, oxidation of D-allose forms an achiral, optically inactive aldaric acid. This contrasts with D-glucaric acid formed from glucose, which has no plane of symmetry and is thus still optically active.



Problem 26.22

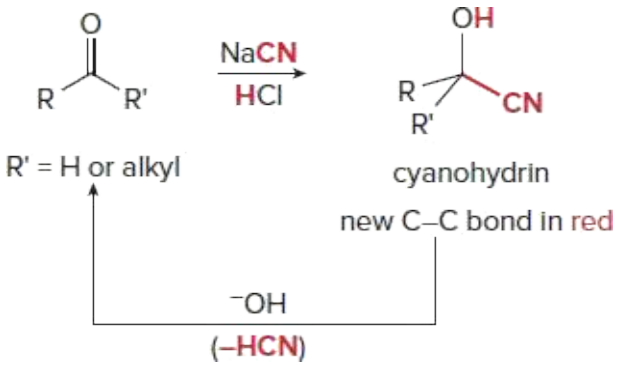
Draw the products formed when D-arabinose is treated with each reagent: (a) Ag_2O, NH_4OH; (b) Br_2, H_2O; (c) HNO_3, H_2O.

Problem 26.23

Which aldoses are oxidized to optically inactive aldaric acids: (a) D-erythrose; (b) D-lyxose; (c) D-galactose?

26.10 Reactions at the Carbonyl Group—Adding or Removing One Carbon Atom

Two common procedures in carbohydrate chemistry result in adding or removing one carbon atom from the skeleton of an aldose. The Wohl degradation shortens an aldose chain by one carbon, whereas the Kiliani–Fischer synthesis lengthens it by one. Both reactions involve cyanohydrins as intermediates. Recall from Section 18.8 that cyanohydrins are formed from aldehydes by addition of the elements of HCN. Cyanohydrins can also be re-converted to carbonyl compounds by treatment with base.



- **Forming a cyanohydrin adds one carbon to a carbonyl group.**
- **Re-converting a cyanohydrin to a carbonyl compound removes one**

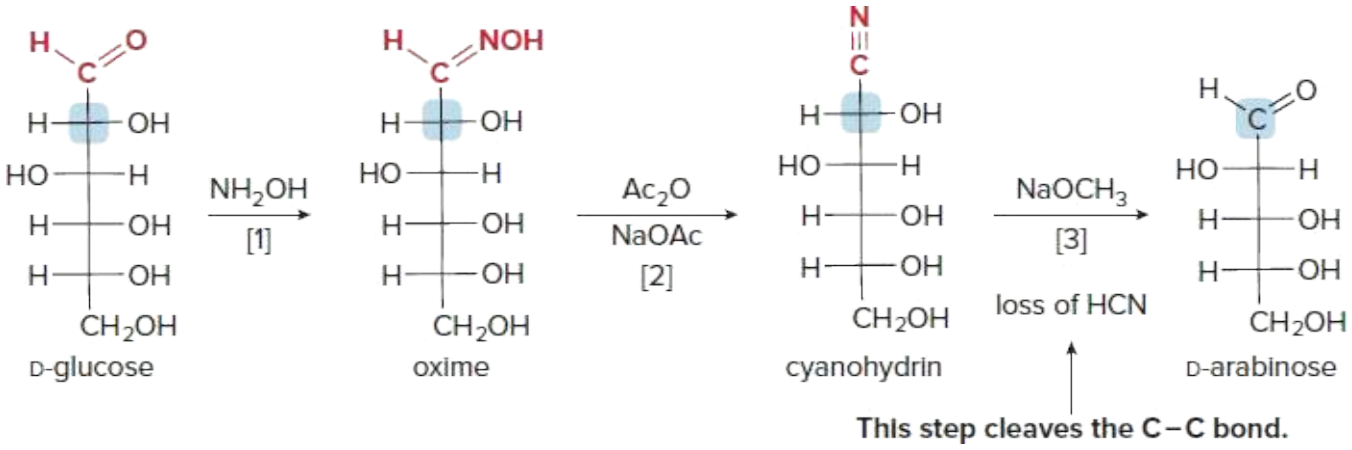
carbon.

26.10A The Wohl Degradation

The Wohl degradation is a stepwise procedure that shortens the length of an aldose chain by cleavage of the C1–C2 bond. As a result, an aldohexose is converted to an aldopentose having the same configuration at its bottom three stereogenic centers (C3–C5). For example, the Wohl degradation converts D-glucose to D-arabinose.

The Wohl degradation consists of three steps, illustrated here beginning with D-glucose.

Page 1188



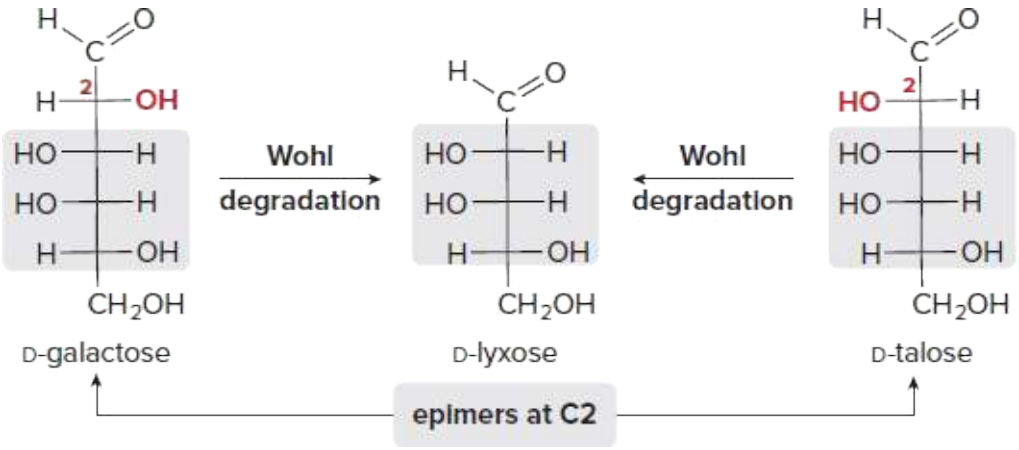
[1] Treatment of D-glucose with hydroxylamine (NH_2OH) forms an oxime by nucleophilic addition. This reaction is analogous to the formation of imines discussed in Section 18.10.

[2] Dehydration of the oxime to a nitrile occurs with acetic anhydride (Ac_2O) and sodium acetate (NaOAc). The nitrile product is a cyanohydrin.

[3] Treatment of the cyanohydrin with base results in loss of the elements of HCN to form an aldehyde having one fewer carbon.

The Wohl degradation converts a stereogenic center at C2 in the original aldose to an sp^2 hybridized C=O. As a result, a pair of aldoses that are epimeric at C2, such as D-galactose and D-talose, yield the *same* aldose (D-lyxose, in this case) upon Wohl

degradation.

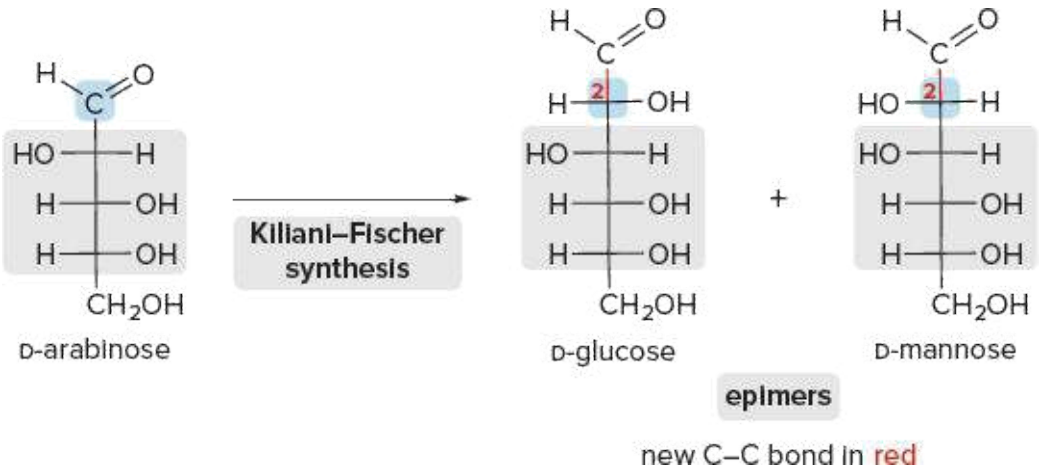


Problem 26.24

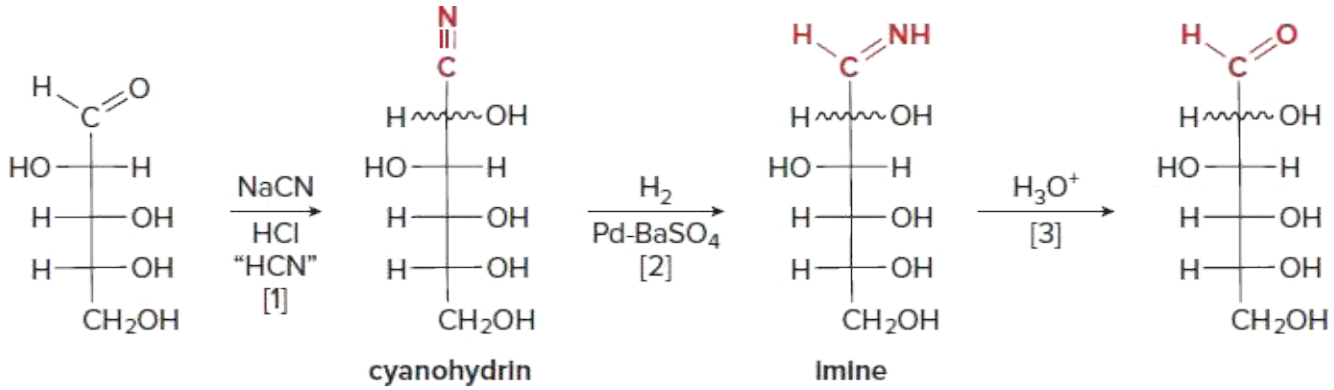
What two aldoses yield D-xylose on Wohl degradation?

26.10B The Kiliani–Fischer Synthesis

The Kiliani–Fischer synthesis lengthens a carbohydrate chain by adding one carbon to the aldehyde end of an aldose, thus forming a new stereogenic center at C2 of the product. The product consists of epimers that differ only in their configuration about the one new stereogenic center. For example, the Kiliani–Fischer synthesis converts D-arabinose to a mixture of D-glucose and D-mannose.



The Kiliani–Fischer synthesis, shown here beginning with D-arabinose, consists of three steps. "Squiggly" lines are meant to indicate that two different stereoisomers are formed at the new stereogenic center. As with the Wohl degradation, the key intermediate is a cyanohydrin.



[1] Treating an aldose with NaCN and HCl adds the elements of HCN to the carbonyl group, forming a cyanohydrin and a new carbon–carbon bond. Because the sp^2 hybridized carbonyl carbon is converted to an sp^3 hybridized carbon with four different groups, a new stereogenic center is formed in this step.

[2] Reduction of the nitrile with H_2 and Pd-$BaSO_4$, a poisoned Pd catalyst, forms an imine.

[3] Hydrolysis of the imine with aqueous acid forms an aldehyde that has one more carbon than the aldose that began the sequence.

Note that the Wohl degradation and the Kiliani–Fischer synthesis are conceptually opposite transformations.

- **The Wohl degradation *removes* a carbon atom from the aldehyde end of an aldose. Two aldoses that are epimers at C2 form the *same* product.**
- **The Kiliani–Fischer synthesis *adds* a carbon to the aldehyde end of an aldose, forming *two epimers* at C2.**

Problem 26.25

What aldoses are formed when the following aldoses are subjected to the Kiliani–Fischer synthesis: (a) D-threose; (b) D-ribose; (c) D-galactose?

26.10C Determining the Structure of an Unknown Monosaccharide

The reactions in Sections 26.9–26.10 can be used to determine the structure of an unknown monosaccharide, as shown in Sample Problem 26.5.

Sample Problem 26.5 Determining the Structure of an Unknown Aldose

A D-aldopentose A is oxidized to an optically inactive aldaric acid with HNO_3. A is formed by the Kiliani–Fischer synthesis of a D-aldotetrose B, which is

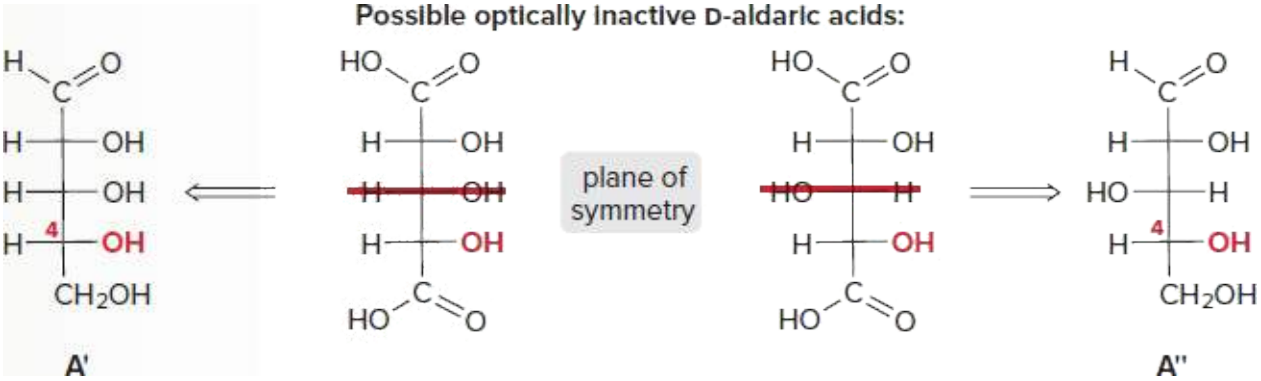
also oxidized to an optically inactive aldaric acid with HNO_3. What are the structures of A and B?

Solution

Use each fact to determine the relative orientation of the OH groups in the D-aldopentose.

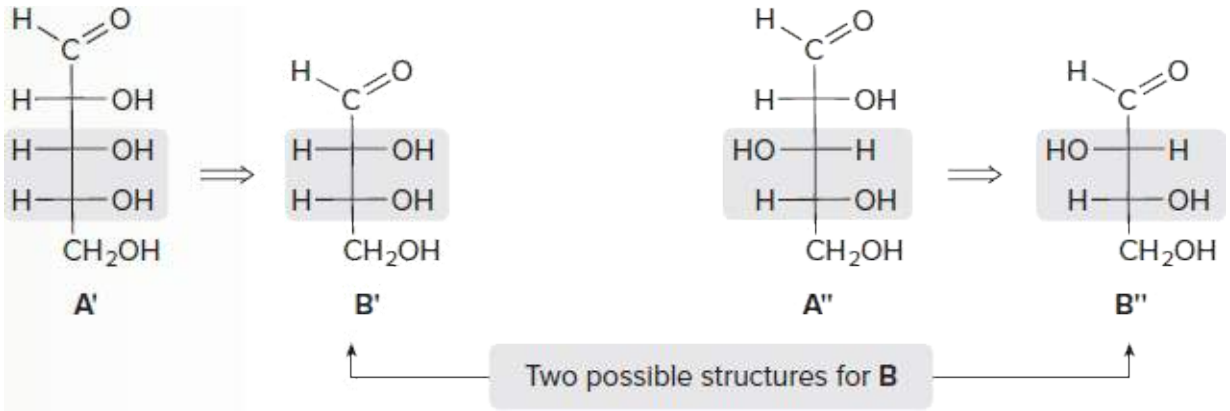
Fact [1] **A D-aldopentose A is oxidized to an optically *inactive* aldaric acid with HNO_3.**

An optically inactive aldaric acid must contain a plane of symmetry. Because the OH group on C4 must be on the right for the D-sugar, there are only two ways to arrange the OH groups in a five-carbon D-aldaric acid. Thus, only two structures are possible for A, labeled A′ and A″.



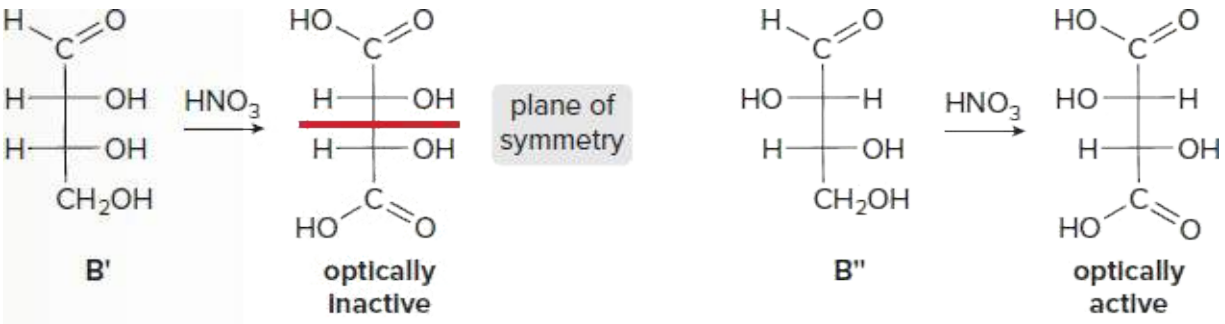
Fact [2] **A is formed by the Kiliani–Fischer synthesis from a D-aldotetrose B.**

A′ and A″ are each prepared from a D-aldotetrose (B′ and B″) that has the same configuration at the bottom two stereogenic centers.

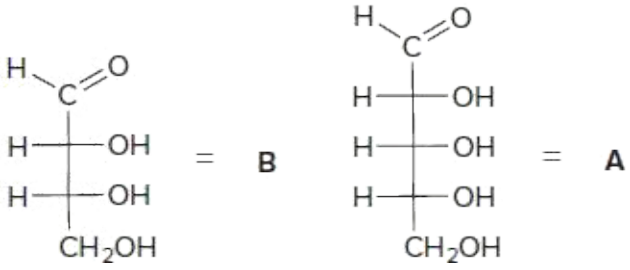


Fact [3] The D-aldotetrose is oxidized to an optically *inactive* aldaric acid upon treatment with HNO_3.

Only the aldaric acid from B′ has a plane of symmetry, making it optically inactive. Thus, B′ is the correct structure for the D-aldotetrose B, and therefore A′ is the structure of the D-aldopentose A.



Answer:



Problem 26.26

A D-aldopentose A is oxidized to an optically inactive aldaric acid. On Wohl degradation, A forms an aldotetrose B that is oxidized to an optically active aldaric acid. What are the structures of A and B?

More Practice:

Try Problems 26.64–26.66.

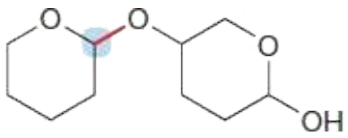
Problem 26.27

A D-aldohexose A is formed from an aldopentose B by the Kiliani–Fischer synthesis. Reduction of A with $NaBH_4$ forms an optically inactive alditol. Oxidation of B forms an optically active aldaric acid. What are the structures of A and B?

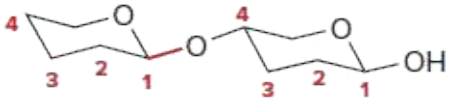
26.11 Disaccharides

Disaccharides contain two monosaccharides joined by a glycosidic linkage. The general

features of a disaccharide include the following:



disaccharide
glycosidic linkage in red
acetal carbon labeled in blue



1→4-β-glycosidic linkage

[1] Two monosaccharide rings may be five- or six-membered, but six-membered rings are much more common. The two rings are connected by an O atom that is part of an acetal, called a glycosidic linkage, which may be oriented α or β.

[2] The glycoside is formed from the anomeric carbon of one monosaccharide and any OH group on the other monosaccharide. All disaccharides have one acetal, plus either a hemiacetal or another acetal.

[3] With pyranose rings, the carbon atoms in each ring are numbered beginning with the anomeric carbon. The most common disaccharides contain two monosaccharides in which the hemiacetal carbon of one ring (Cl) is joined to C4 of the other ring.

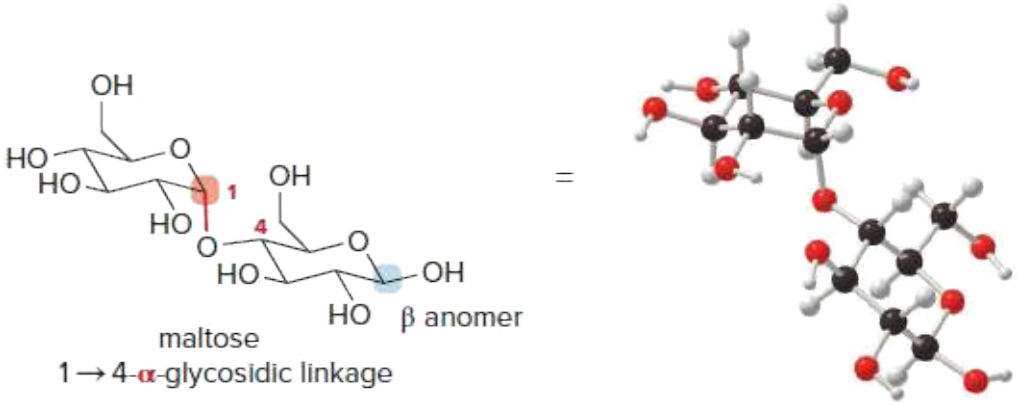
The three most abundant disaccharides are maltose, lactose, and sucrose.

26.11A Maltose

Maltose, a disaccharide formed by the hydrolysis of starch, is found in germinated grains such as barley. Maltose contains two glucose units joined by a 1→4-α-glycoside bond. Maltose contains one acetal carbon (in red) and one hemiacetal carbon (in blue).

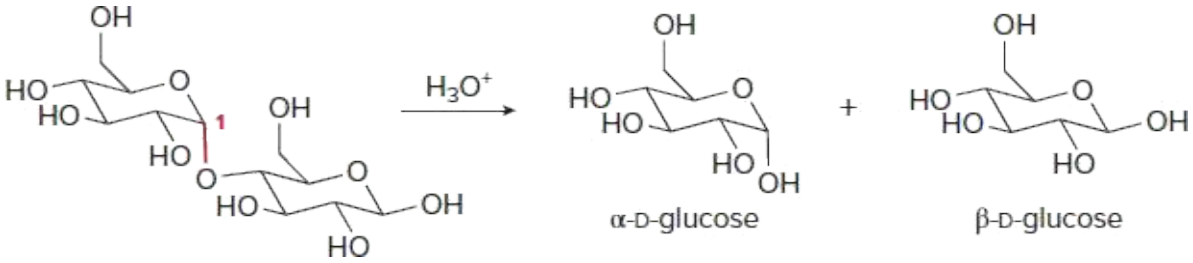
Maltose gets its name from malt, the liquid obtained from barley and other cereal grains.

©Mir141/Shutterstock



Because one glucose ring of maltose still contains a hemiacetal, it exists as a mixture of α and β anomers. Only the β anomer is shown. Maltose exhibits two properties of all carbohydrates that contain a hemiacetal: it undergoes mutarotation, and it reacts with oxidizing agents, making it a reducing sugar.

Hydrolysis of maltose forms two molecules of glucose. The C1–O bond is cleaved in this process, and a mixture of glucose anomers forms. The mechanism for this hydrolysis is exactly the same as the mechanism for glycoside hydrolysis in Section 26.7B.



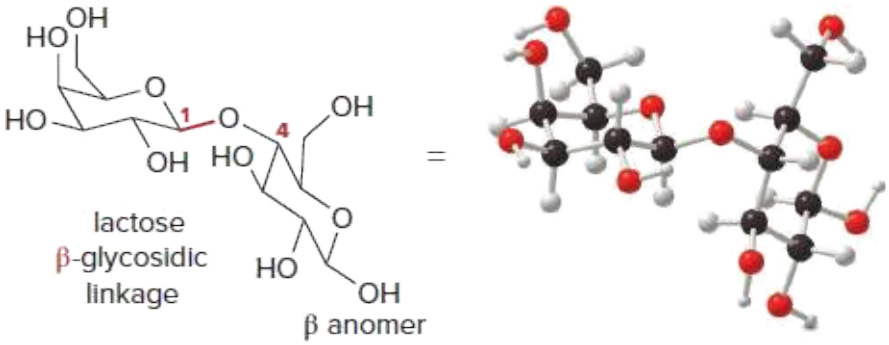
Problem 26.28

Draw the α anomer of maltose. What products are formed on hydrolysis of this form of maltose?

26.11B Lactose

Lactose is the principal disaccharide found in milk from both humans and cows. Unlike many mono- and disaccharides, lactose is not appreciably sweet. Lactose consists of one galactose and one glucose unit, joined by a 1→4-β-glycoside bond from the anomeric carbon of galactose to C4 of glucose.

Milk contains the disaccharide lactose. ***©McGraw-Hill Education/Elite Images***



Like maltose, lactose also contains a hemiacetal, so it exists as a mixture of α and β anomers. The β anomer is drawn. Lactose undergoes mutarotation, and it reacts with oxidizing agents, making it a reducing sugar.

Lactose is digested in the body by first cleaving the 1→4-β-glycoside bond using the enzyme *lactase*. Many individuals, mainly of Asian and African descent, lack adequate amounts of lactase, so they are unable to digest and absorb lactose. This condition, lactose intolerance, is associated with abdominal cramping and recurrent diarrhea when milk and dairy products are ingested.

Problem 26.29

Cellobiose, a disaccharide obtained by the hydrolysis of cellulose, is composed of two glucose units joined by a 1→4-β-glycoside bond. What is the structure of cellobiose?

26.11C Sucrose

Sucrose, the disaccharide mentioned in the chapter opener that is found in sugarcane

and used as table sugar (Figure 26.9), is the most common disaccharide in nature. It contains one glucose unit and one fructose unit.

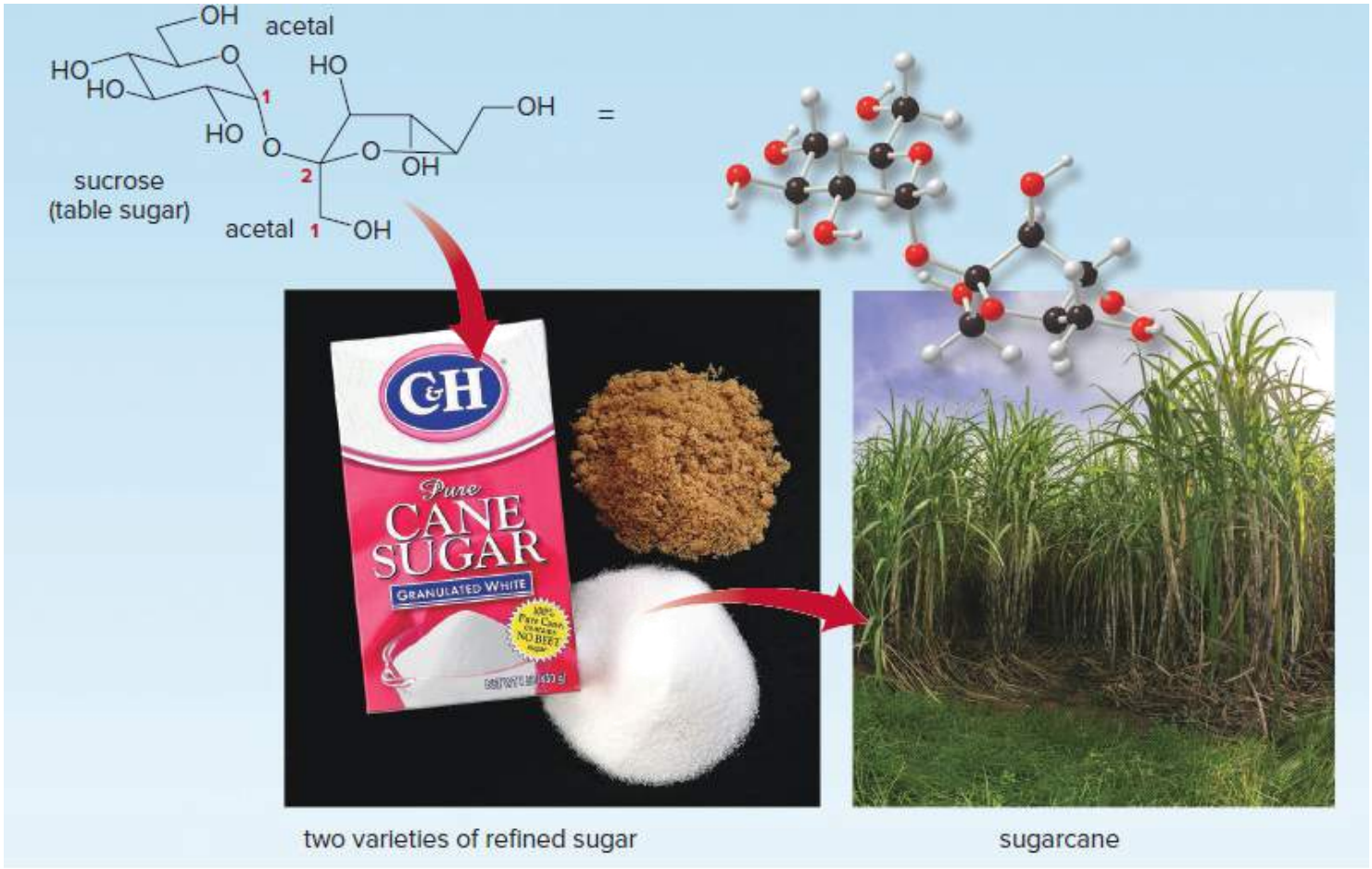


Figure 26.9 **Sucrose**

The structure of sucrose has several features that make it different from maltose and lactose. Sucrose contains one six-membered ring (glucose) and one five-membered ring (fructose), whereas both maltose and lactose contain two six-membered rings. In sucrose the six-membered glucose ring is joined by an α-glycosidic bond to C2 of a fructofuranose ring. The numbering in a fructofuranose is different from the numbering in a pyranose ring. The anomeric carbon is now designated as C2, so the anomeric carbons of the glucose and fructose rings are both used to form the glycosidic linkage.

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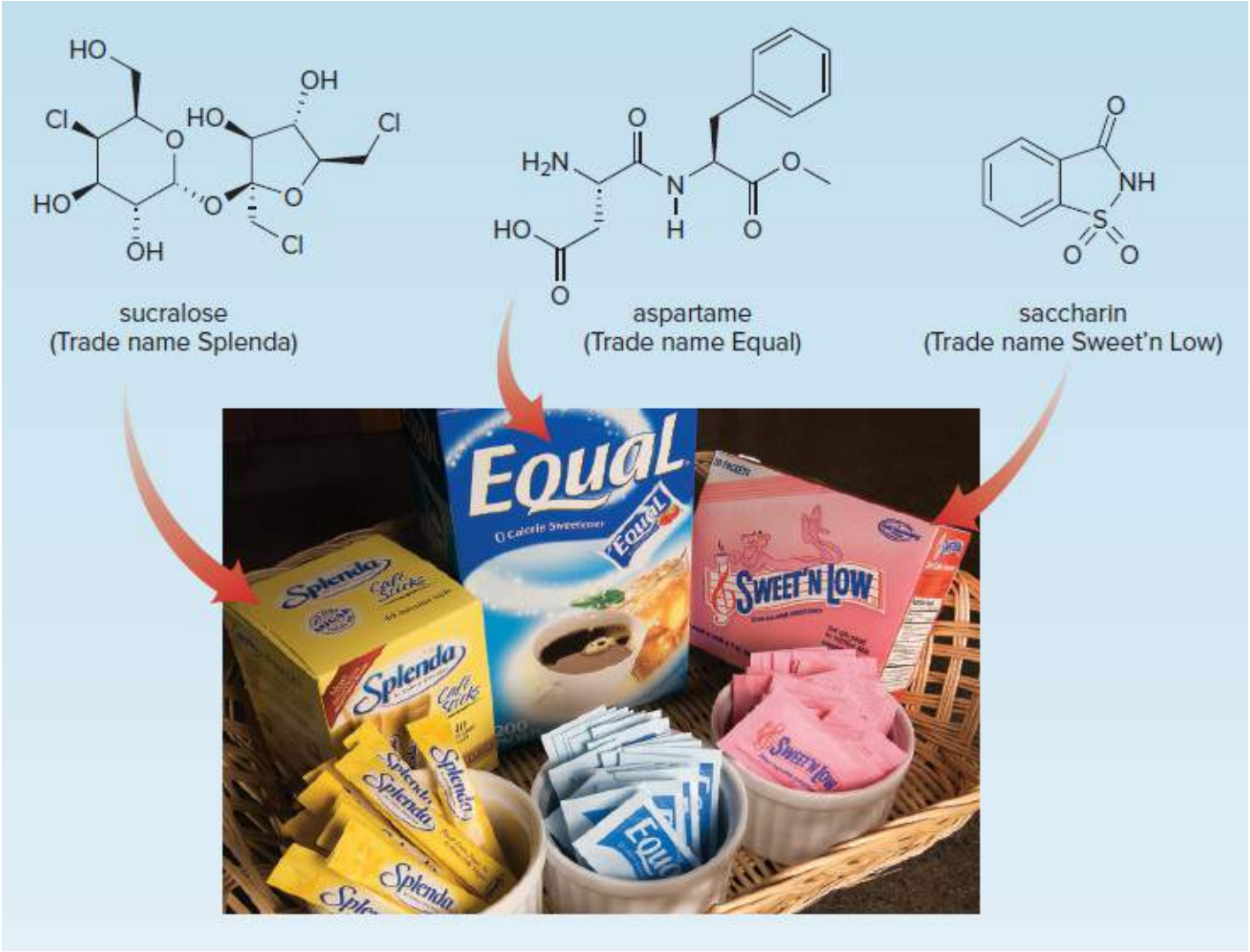
As a result, sucrose contains two acetals but no hemiacetal. Sucrose, therefore, is a nonreducing sugar and it does *not* undergo mutarotation.

Sucrose's pleasant sweetness has made it a widely used ingredient in baked goods, cereals, bread, and many other products. It is estimated that the average American ingests 100 lb of sucrose annually. Like other carbohydrates, however, sucrose contains many calories. To reduce caloric intake while maintaining sweetness, a variety

of artificial sweeteners have been developed. These include sucralose, aspartame, and saccharin (Figure 26.10). These compounds are much sweeter than sucrose, so only a small amount of each compound is needed to achieve the same level of perceived sweetness.



- The sweetness of these three artificial sweeteners was discovered accidentally. The sweetness of sucralose was discovered in 1976 when a chemist misunderstood his superior, and he *tasted* rather than *tested* his compound. Aspartame was discovered in 1965 when a chemist licked his dirty fingers in the lab and tasted its sweetness. Saccharin, the oldest-known artificial sweetener, was discovered in 1879 by a chemist who failed to wash his hands after working in the lab. Saccharin was not used extensively until sugar shortages occurred during World War I. Although there were concerns in the 1970s that saccharin causes cancer, there is no proven link between cancer occurrence and saccharin intake at normal levels. *©McGraw-Hill Education/Jill Braaten, photographer*

Figure 26.10 **Artificial sweeteners**

26.12 Polysaccharides

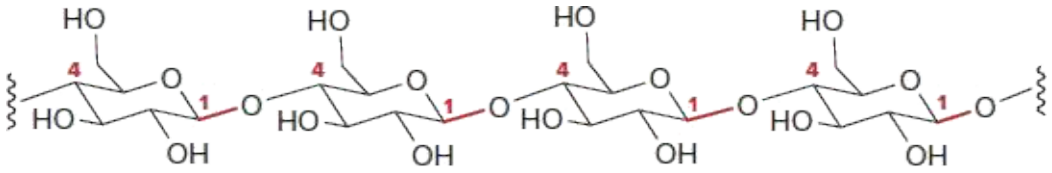
Polysaccharides contain three or more monosaccharides joined together. Three prevalent polysaccharides in nature are cellulose, starch, and glycogen, each of which

consists of repeating glucose units joined by different glycosidic bonds.

26.12A Cellulose

The structure of cellulose was discussed in Section 5.1.

Cellulose is found in the cell walls of nearly all plants, where it gives support and rigidity to wood and plant stems. Cotton is essentially pure cellulose.

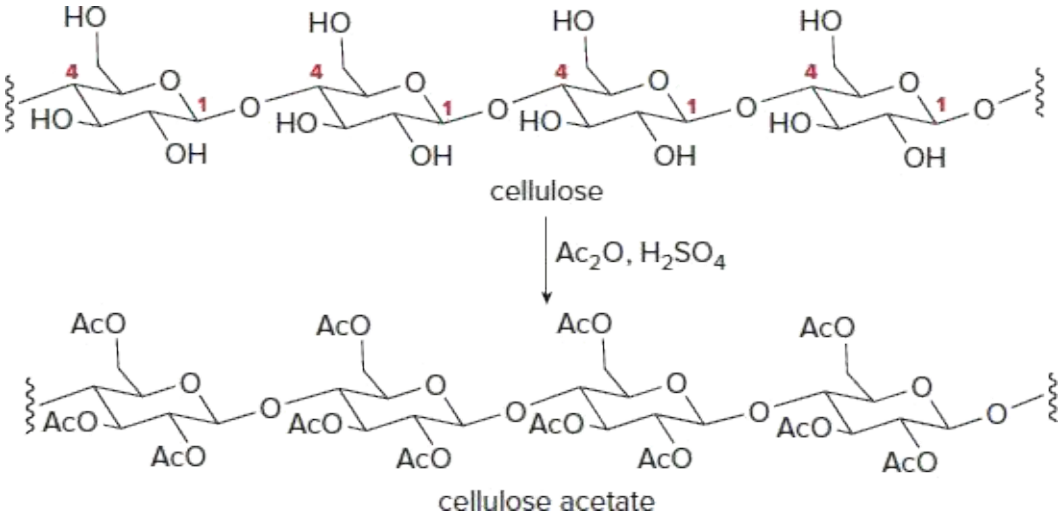


cellulose
1→4-β-glycosidic linkages in red

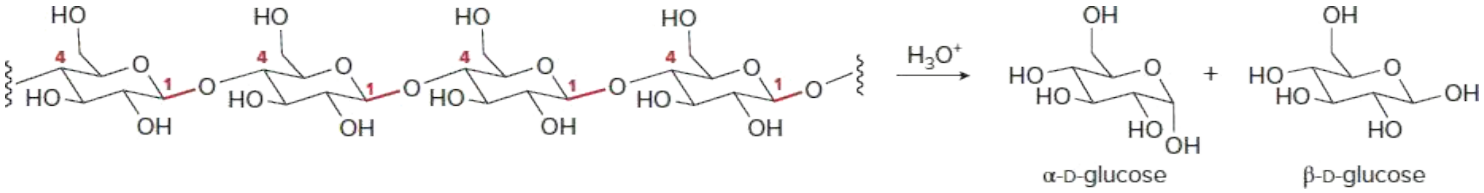
Ball-and-stick models showing the three-dimensional structures of cellulose and starch were given in Figure 5.2.

Cellulose is an unbranched polymer composed of repeating glucose units joined in a 1→4-β-glycosidic linkage. The β-glycosidic linkage forms long linear chains of cellulose molecules that stack in sheets, creating an extensive three-dimensional array. A network of intermolecular hydrogen bonds between the chains and sheets means that only the few OH groups on the surface are available to hydrogen bond to water, making this very polar compound water insoluble.

Cellulose acetate, a cellulose derivative, is made by treating cellulose with acetic anhydride and sulfuric acid. The resulting product has acetate esters in place of every OH group. Cellulose acetate is spun into fibers that are used for fabrics called *acetates*, which have a deep luster and satin appearance.



Cellulose can be hydrolyzed to glucose by cleaving all the β-glycosidic bonds, yielding both anomers of glucose.



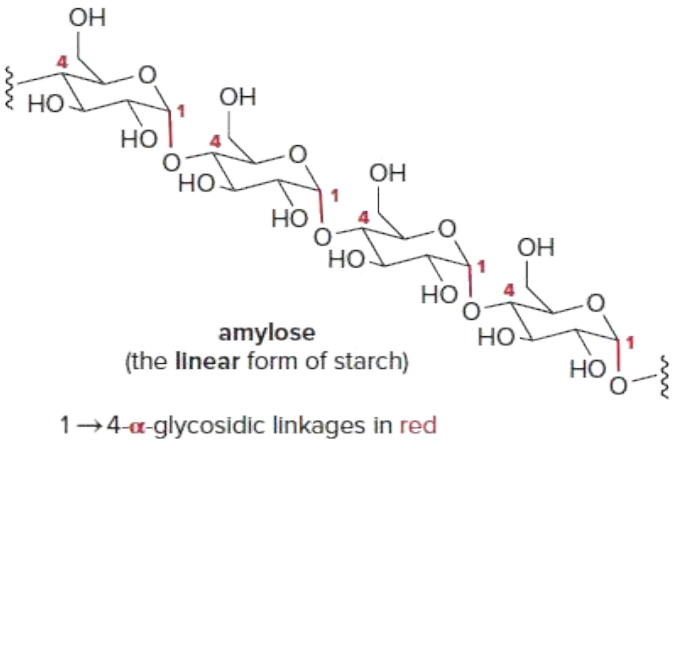
A β-glycosidase is the general name of an enzyme that hydrolyzes a β-glycoside linkage.

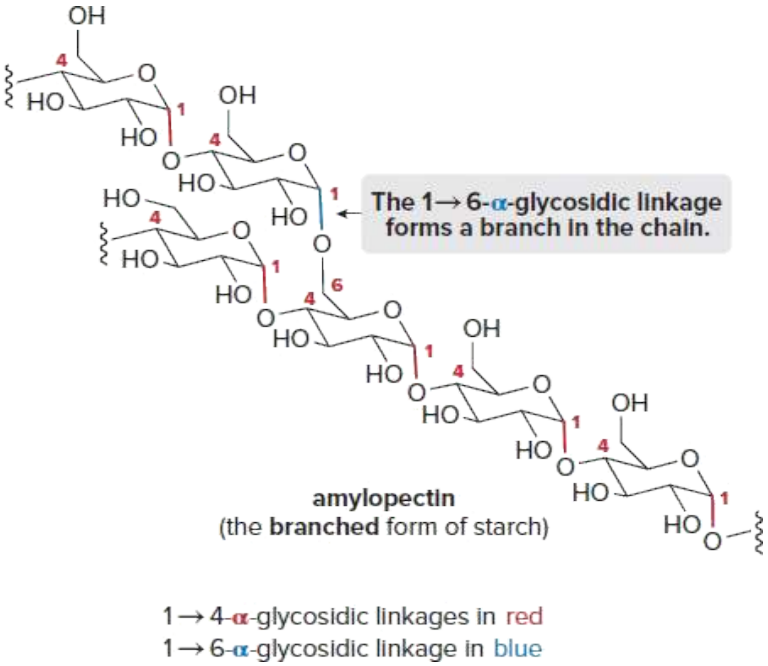
In cells, the hydrolysis of cellulose is accomplished by an enzyme called a β-glucosidase, which cleaves all the β-glycoside bonds formed from glucose. Humans do not possess this enzyme and therefore cannot digest cellulose. Ruminant animals, on the other hand, such as cattle, deer, and camels, have bacteria containing a β-glucosidase in their digestive systems, so they can derive nutritional benefit from eating grass and leaves.

26.12B Starch

Starch is the main carbohydrate found in the seeds and roots of plants. Corn, rice, wheat, and potatoes are common foods that contain a great deal of starch.

Starch is a polymer composed of repeating glucose units joined in α-glycosidic linkages. Both starch and cellulose are polymers of glucose, but starch contains α glycoside bonds, whereas cellulose contains β glycoside bonds. The two common forms of starch are amylose and amylopectin.





Amylose, which comprises about 20% of starch molecules, has an unbranched skeleton of glucose molecules with 1→4-α-glycoside bonds. Because of this linkage, an amylose chain adopts a helical arrangement, giving it a very different three-dimensional shape from the linear chains of cellulose. Amylose was first described in Section 5.1.

Amylopectin, which comprises about 80% of starch molecules, likewise consists of a backbone of glucose units joined in α-glycosidic bonds, but it also contains considerable branching along the chain. The linear linkages of amylopectin are formed by 1→4-α-glycoside bonds, similar to amylose. The branches are linked to the chain with 1→6-α-glycosidic linkages.

Both forms of starch are water soluble. Because the OH groups in these starch molecules are not buried in a three-dimensional network, they are more available for hydrogen bonding with water molecules, leading to greater water solubility than cellulose has.

The ability of amylopectin to form branched polymers is a unique feature of carbohydrates. Other types of polymers in the cell, such as the proteins discussed in Chapter 27, occur in nature only as linear molecules.

α-Glycosidase is the general name of an enzyme that hydrolyzes an α-glycoside linkage.

Both amylose and amylopectin are hydrolyzed to glucose with cleavage of the glycosidic bonds. The human digestive system has the necessary α-glucosidase enzymes needed to catalyze this process. Bread and pasta made from wheat flour, rice,

and corn tortillas are all sources of starch that are readily digested.

26.12C Glycogen

Glycogen is the major form in which polysaccharides are stored in animals. Glycogen, a polymer of glucose containing α-glycosidic bonds, has a branched structure similar to amylopectin, but the branching is much more extensive.

Glycogen is stored principally in the liver and muscle. When glucose is needed for energy in the cell, glucose units are hydrolyzed from the ends of the glycogen polymer, and then further metabolized with the release of energy. Because glycogen has a highly branched structure, there are many glucose units at the ends of the branches that can be cleaved whenever the body needs them.

Problem 26.30

Draw the structure of: (a) a polysaccharide formed by joining D-mannose units in 1→4-β-glycosidic linkages; (b) a polysaccharide formed by joining D-glucose units in 1→6-α-glycosidic linkages. The polysaccharide in (b) is dextran, a component of dental plaque.

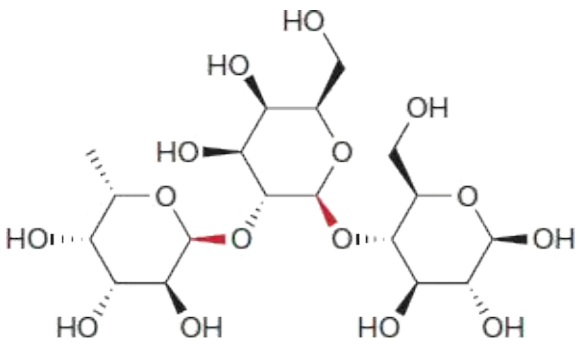
26.12D Human Milk Oligosaccharides

Human milk oligosaccharides (HMOs), a group of carbohydrates found in breast milk, contain three or four monosaccharides joined together. 2′-Fucosyllactose is the most prevalent component, comprising about 30% of all HMOs. The two glycosidic linkages that join the three monosaccharides together are shown in red.

The World Health Organization recommends that children are exclusively breast fed until six months of age, and then nursed along with other forms of nutrition until a child is two

years old. ***©Daniel C. Smith***

An oligosaccharide is a carbohydrate with a small number of monosaccharides—generally three to ten—joined together.



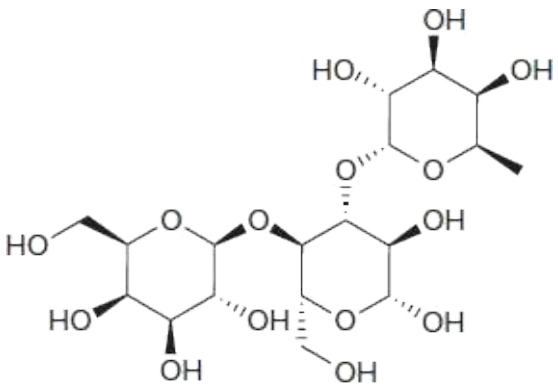
2'-fucosyllactose

HMOs, often called the fiber of breast milk, are not hydrolyzed by the gastric juices of the stomach, nor are they absorbed in the intestines. They nonetheless play a key role in the health of a newborn, by helping to establish the presence of beneficial bacteria in the infant's colon. Moreover, harmful pathogens attach to the surface of HMOs and are eliminated in the feces of the nursing infant.

Ongoing research continues to study the hundreds of unique components of human breast milk in an effort to understand its benefits to both the mother and the child, even after infancy.

Problem 26.31

3-Fucosyllactose is another HMO found in breast milk. (a) Locate any acetal and hemiacetal. (b) What products are formed when 3-fucosyllactose is hydrolyzed in aqueous acid?



3-fucosyllactose

26.13 Other Important Sugars and Their Derivatives

Many other examples of simple and complex carbohydrates with useful properties exist in the biological world. In Section 26.13, we examine some carbohydrates that contain nitrogen atoms.

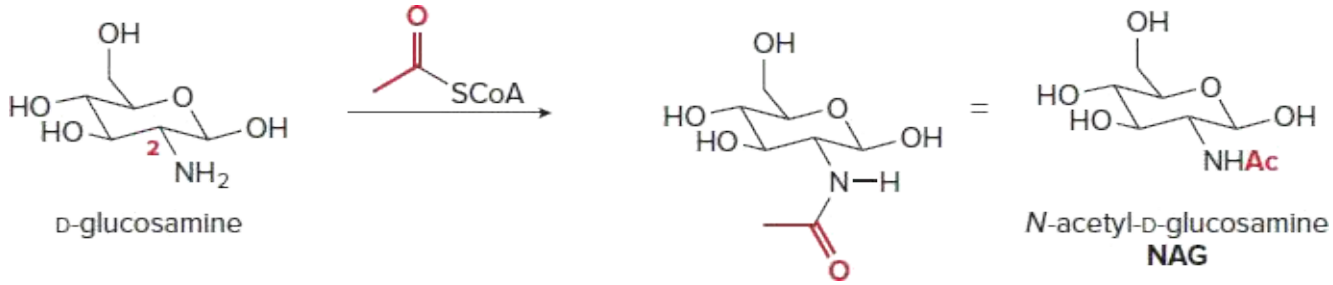
26.13A Amino Sugars and Related Compounds

Amino sugars contain an NH_2 group instead of an OH group at a non-anomeric carbon. The most common amino sugar in nature, D-glucosamine, is formally derived from D-glucose by replacing the OH at C2 with NH_2. Although it is not classified as a drug, and therefore not regulated by the U.S. Food and Drug Administration, glucosamine is available in many over-the-counter treatments for osteoarthritis.

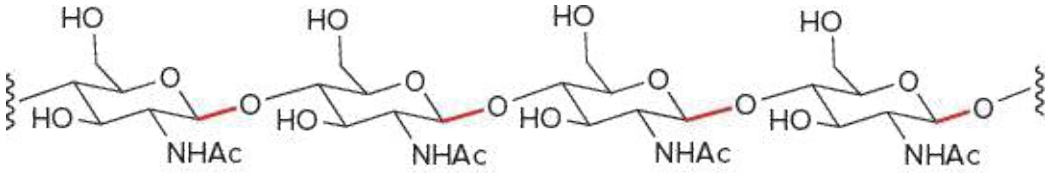
Dietary supplements containing glucosamine are used by individuals suffering from osteoarthritis.
©McGraw-Hill Education/Jill Braaten, photographer

The rigidity of a crab shell is due to chitin, a high-molecular-weight carbohydrate molecule. Chitin-based coatings have

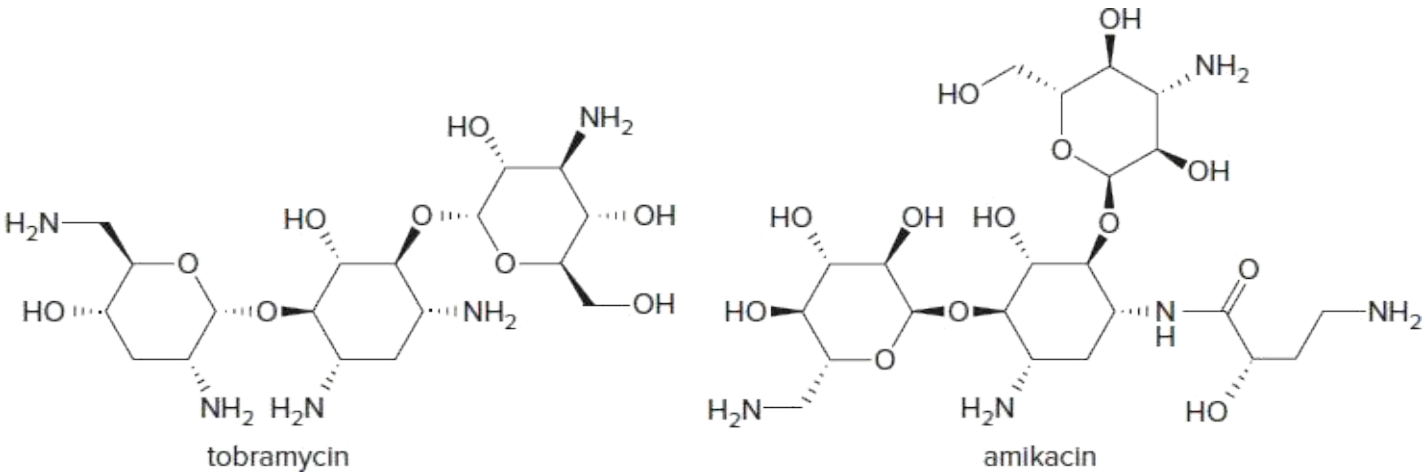
found several commercial applications, such as extending the shelf life of fruits. Processing plants now convert the shells of crabs, lobsters, and shrimp to chitin and various derivatives for use in many consumer products. ***©Comstock Images/Stockbyte/Getty Images***



Acetylation of glucosamine with acetyl CoA (Section 20.16) forms *N*-acetyl-D-glucosamine, abbreviated as NAG. Chitin, the second most abundant carbohydrate polymer, is a polysaccharide formed from NAG units joined together in 1→4-β-glycosidic linkages. Chitin is identical in structure to cellulose, except that each OH group at C2 is now replaced by $NHCOCH_3$. The exoskeletons of lobsters, crabs, and shrimp are composed of chitin. Like those of cellulose, chitin chains are held together by an extensive network of hydrogen bonds, forming water-insoluble sheets.



Several trisaccharides containing amino sugars are potent antibiotics used in the treatment of certain severe and recurrent bacterial infections. These compounds, such as tobramycin and amikacin, are called aminoglycoside antibiotics.



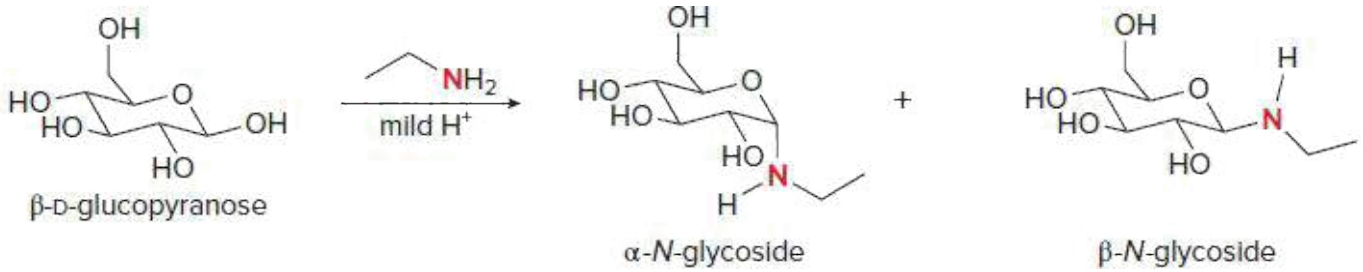
Problem 26.32

Treating chitin with H_2O, ^-OH hydrolyzes its amide linkages, forming a compound called chitosan. What is the structure of chitosan? Chitosan has been used in shampoos, fibers for sutures, and wound dressings.

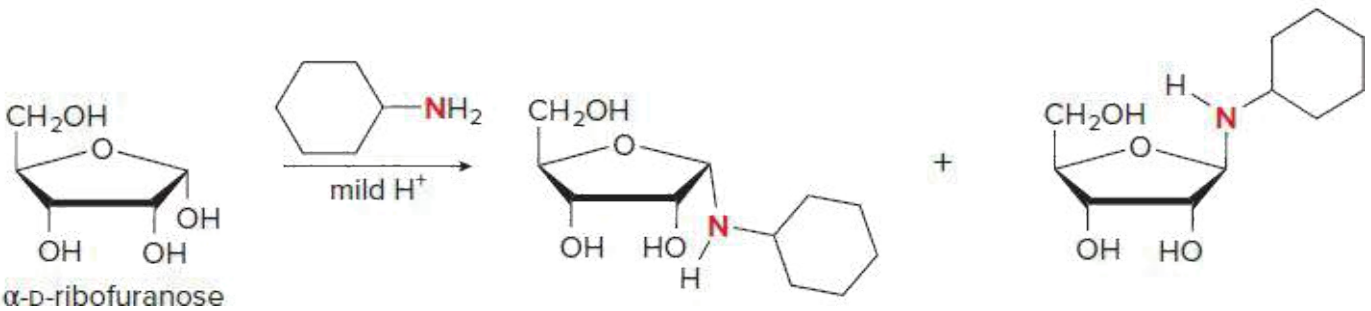
26.13B *N*-Glycosides

N-Glycosides are formed when a monosaccharide is reacted with an amine in the presence of mild acid (Reactions [1] and [2]).

[1]



[2]

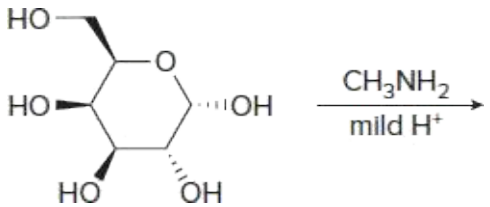


The mechanism of *N*-glycoside formation is analogous to the mechanism for glycoside formation, and both anomers of the *N*-glycoside are formed as products.

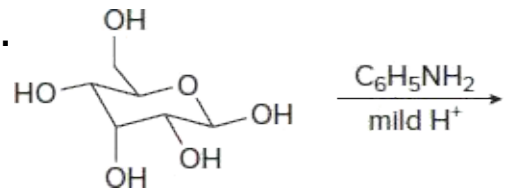
Problem 26.33

Draw the products of each reaction.

a.



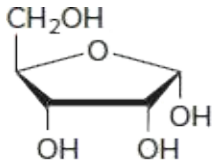
b.



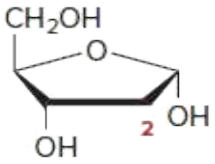
The prefix *deoxy* means "without oxygen."

The *N*-glycosides of two sugars, D-ribose and 2-deoxy-D-ribose, are especially

noteworthy, because they form the building blocks of RNA and DNA, respectively. 2-Deoxyribose is so named because it lacks an OH group at C2 of ribose.



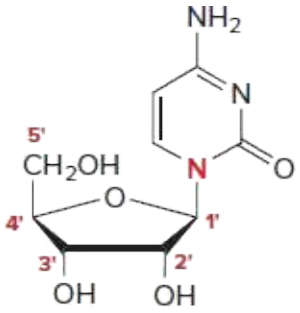
D-ribose



2-deoxy-D-ribose

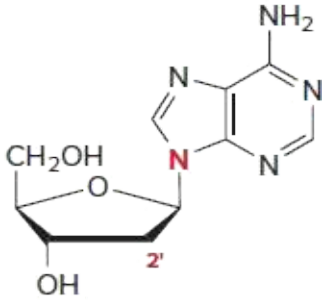
- **Reaction of D-ribose with certain amine heterocycles forms *N*-glycosides called ribonucleosides.**
- **This same reaction of 2-deoxy-D-ribose forms deoxyribonucleosides.**

An example of a ribonucleoside and a deoxyribonucleoside are drawn. These *N*-glycosides have the β orientation. Numbering in the sugar ring begins at the anomeric carbon (1′), and proceeds in a clockwise fashion around the ring.



cytidine

a ribonucleoside

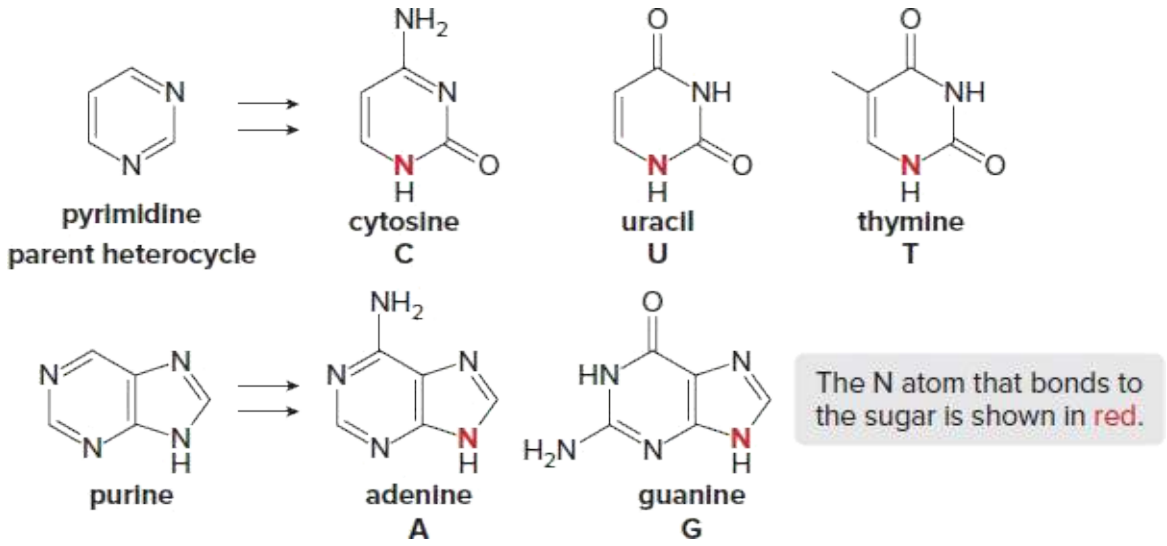


2-deoxyadenosine

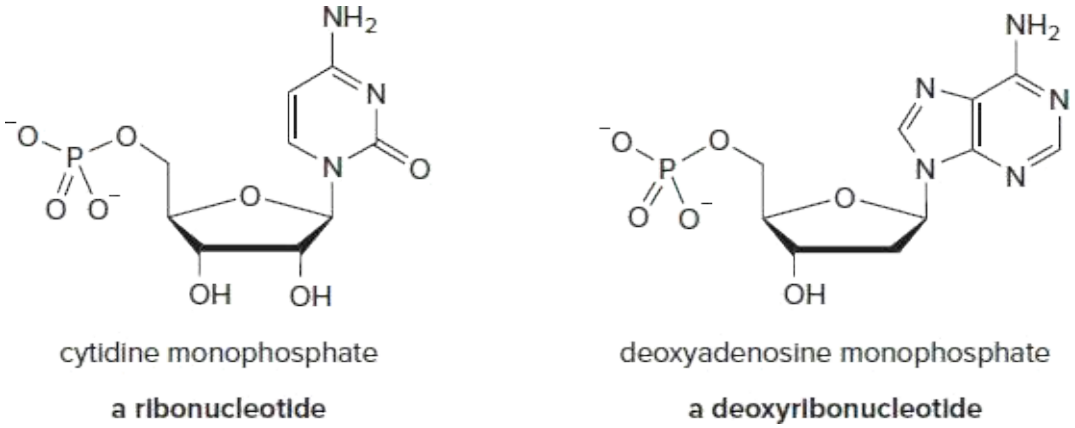
a deoxyribonucleoside

Only five common nitrogen heterocycles are used to form these nucleosides. Page 1199 Three compounds have one ring and are derived from a nitrogen heterocycle called pyrimidine. Two are bicyclic and are derived from a nitrogen heterocycle called purine. These five amines are referred to as *bases*. Each base is designated by a one-letter abbreviation, as shown in the names and structures drawn. Uracil (U) occurs only in ribonucleosides, and thymine (T) occurs only in deoxyribonucleosides.

- **Each nucleoside has two parts, a sugar and a base, joined by a β *N*-glycosidic linkage.**

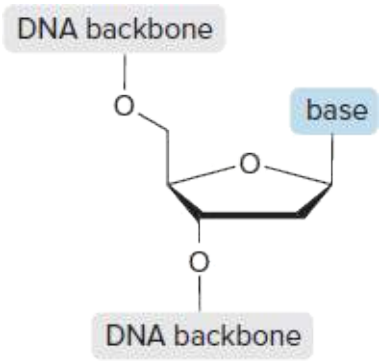


When one OH group of the sugar nucleus is bonded to a phosphate, the derivatives are called ribonucleotides and deoxyribonucleotides.



- **Ribonucleotides are the building blocks of the polymer ribonucleic acid, or RNA, the messenger molecules that convert genetic information to proteins.**
- **Deoxyribonucleotides are the building blocks of the polymer deoxyribonucleic acid, or DNA, the molecules that are responsible for the storage of all genetic information.**

Short segments of both RNA and DNA are shown in Figure 26.11. Note the central role of the sugar moiety in both RNA and DNA. The sugar residues are bonded to two phosphate groups, thus connecting the chain of RNA or DNA together. The sugar residues are also bonded to the nitrogen base via the anomeric carbon.



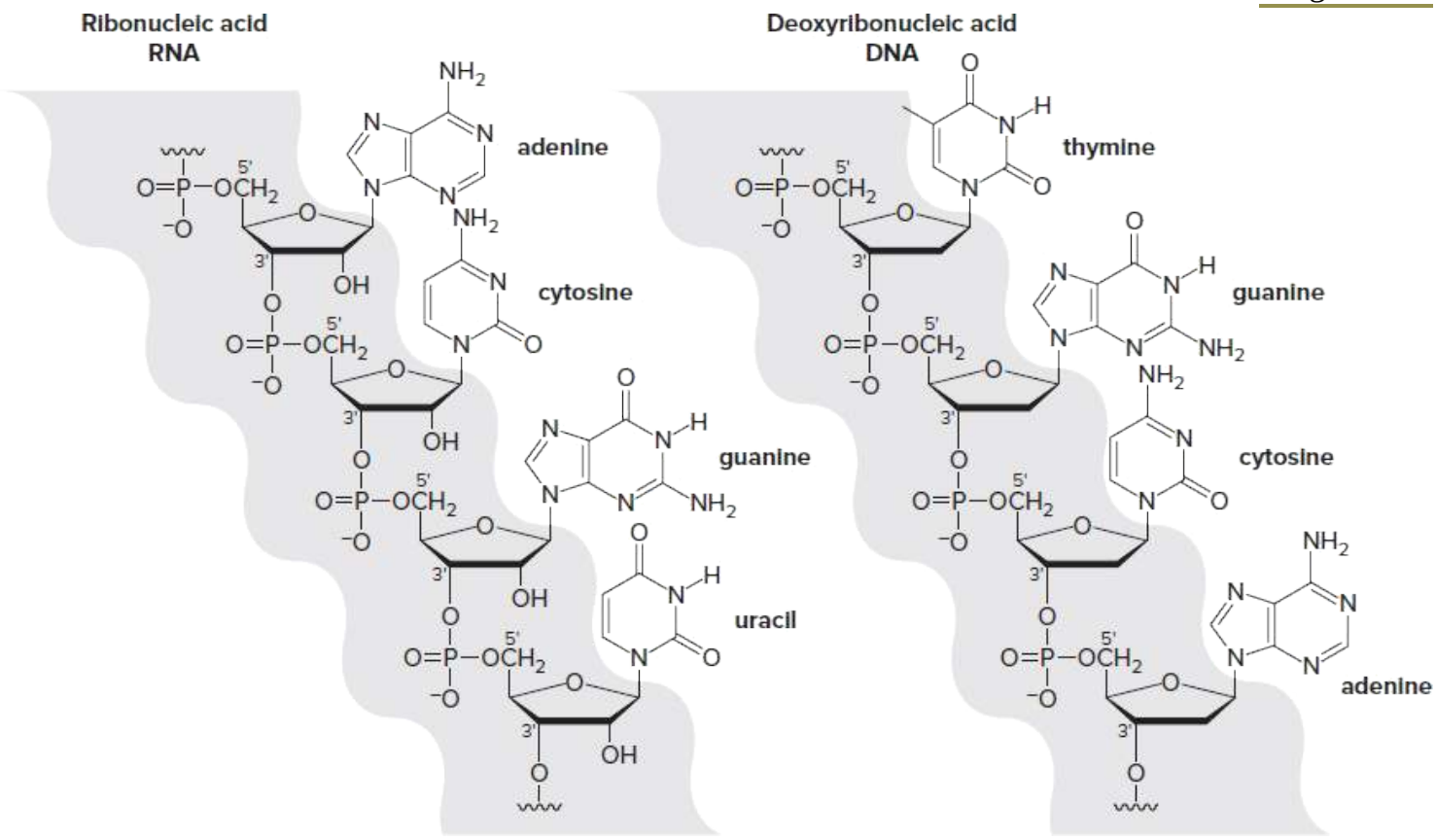
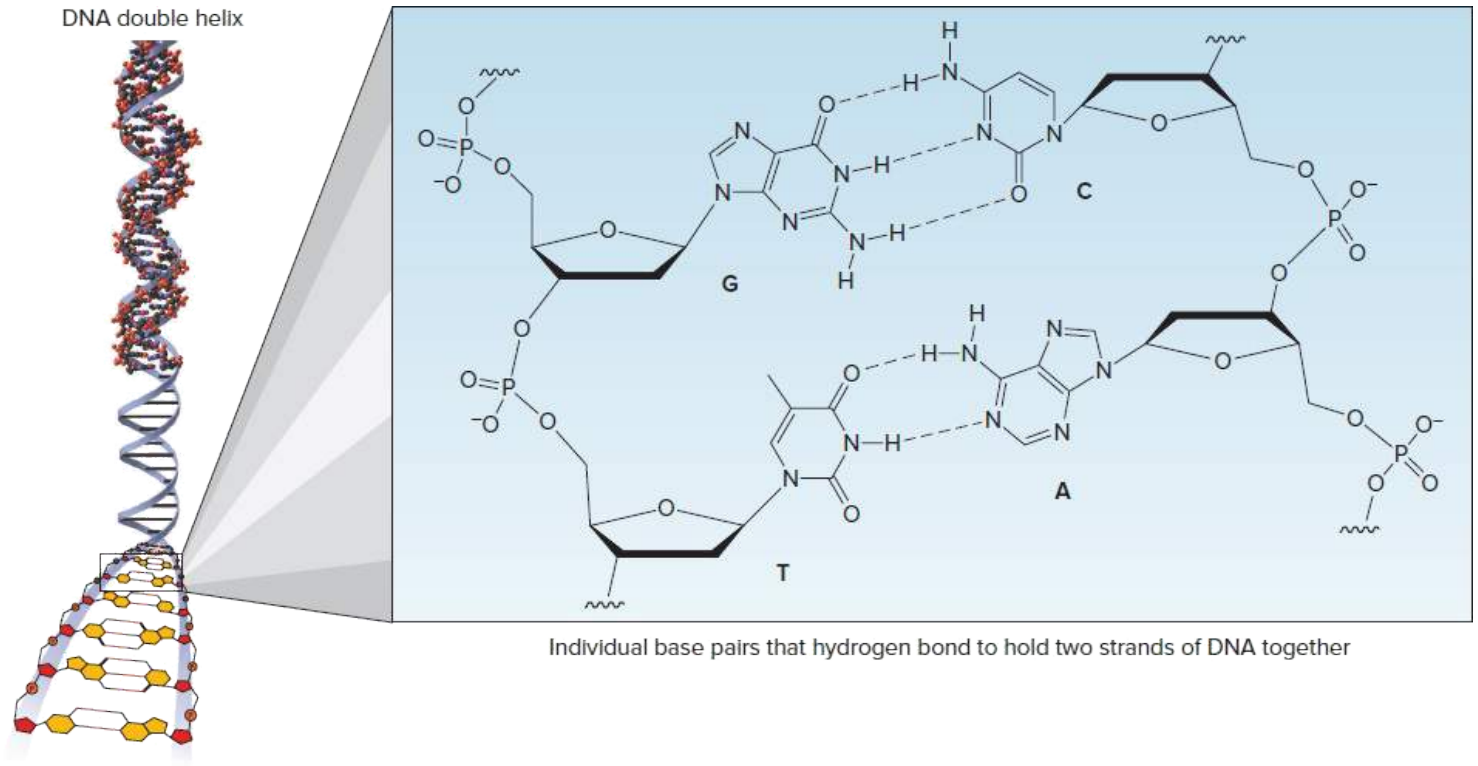


Figure 26.11 **Short segments of RNA and DNA**

DNA is composed of two polynucleotide strands that wind around each other to form a double helix, resembling a spiral ladder. The sides of the ladder are composed of the sugar–phosphate backbone of the polymer and the rungs are composed of the bases, as shown in Figure 26.12.



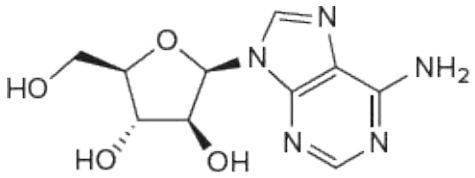
- Two polynucleotide strands form the double helix of DNA. The backbone of each polymer strand is composed of sugar–phosphate residues. Hydrogen bonding of base pairs (A–T and C–G) holds the two strands of DNA together.

Figure 26.12 **DNA—A double helix**

The nitrogen bases on one strand of DNA hydrogen bond to nitrogen bases on the other strand. A purine base on one strand hydrogen bonds with a pyrimidine base on the other strand. Two types of bases, called base pairs, hydrogen bond to each other: adenine hydrogen bonds with thymine (A–T), and cytosine hydrogen bonds with guanine (C–G). Page 1201

Problem 26.34

Novel antiviral agents isolated from Caribbean sponges led to the development of vidarabine, the first nucleoside drug used to treat herpes infections. (a) What monosaccharide and base are present in vidarabine? (b) Draw the structure of cytarabine, an anticancer nucleoside composed of cytosine and the same monosaccharide unit.



vidarabine

Problem 26.35

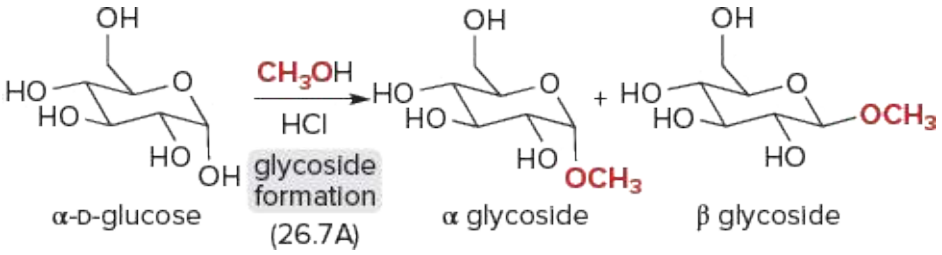
(a) Why can't two purine bases (A and G) form a base pair and hydrogen bond to each other on two strands of DNA in the double helix? (b) Why is hydrogen bonding between guanine and cytosine more favorable than hydrogen bonding between guanine and thymine?

Chapter 26 REVIEW

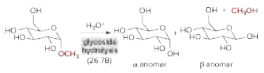
KEY REACTIONS

[1] Reactions of monosaccharides involving the hemiacetal

1



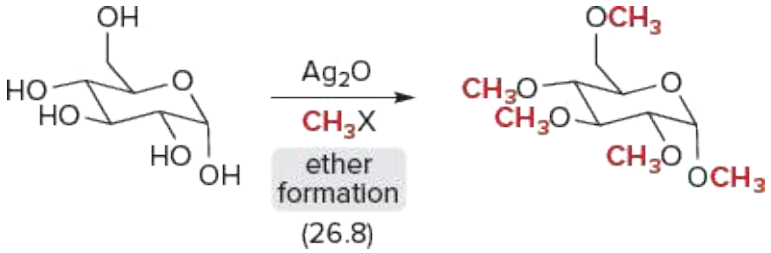
2



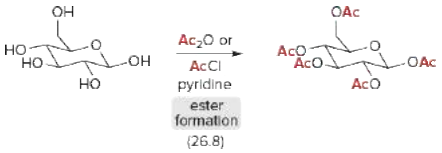
Try Problems 26.49b, d; 26.50a; 26.51.

[2] Reactions of monosaccharides at the OH groups

1



2

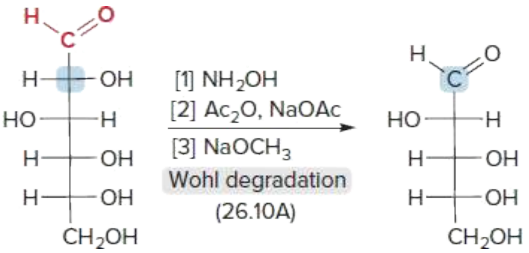


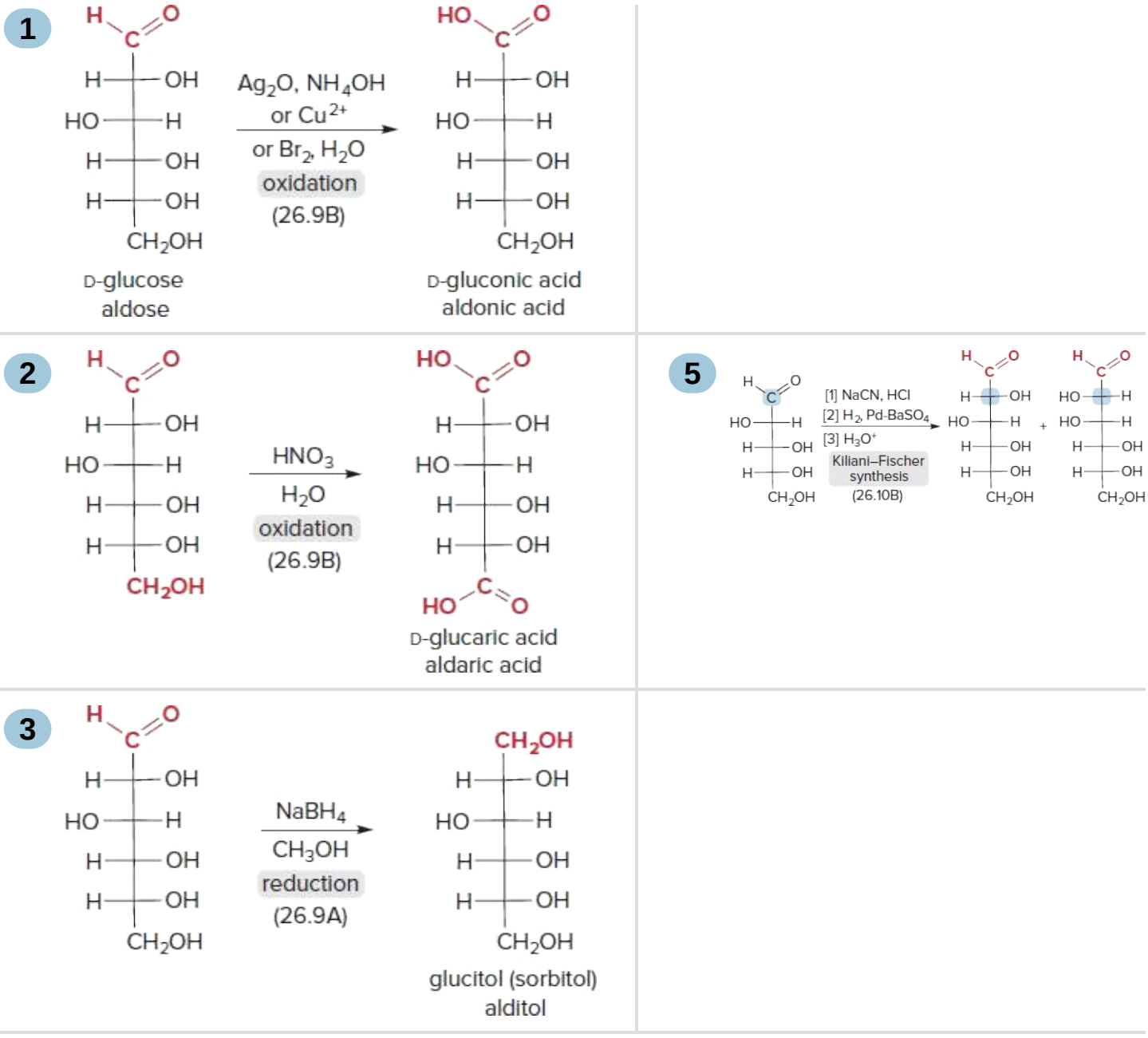
Try Problems 26.49a, c; 26.50g.

Page 1202

[3] Reactions of monosaccharides at the carbonyl group

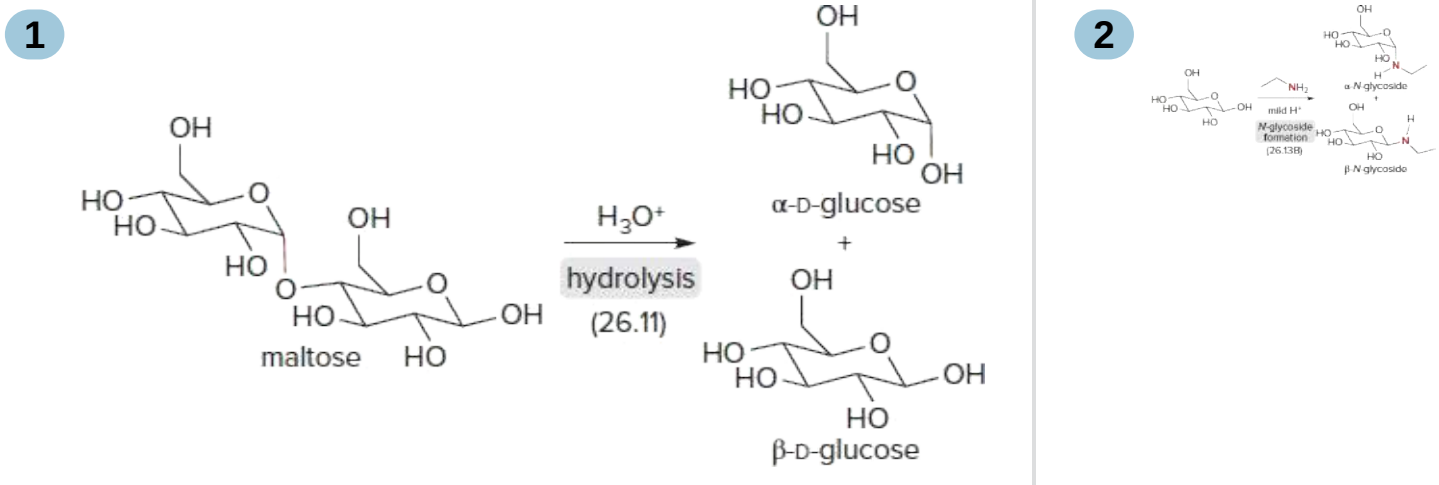
4





Try Problems 26.50b–f; 26.53c–e; 26.54c, d; 26.55–26.57; 26.59.

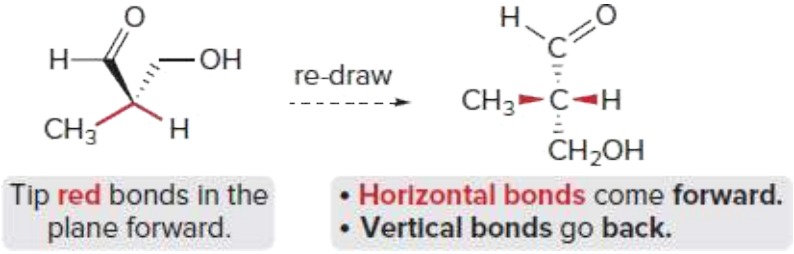
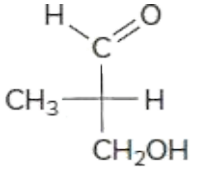
[4] Other reactions



Try Problems 26.50h, 26.51, 26.60, 26.69c, 26.71c.

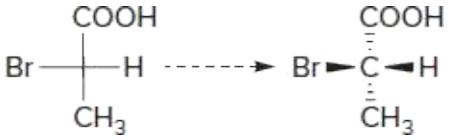
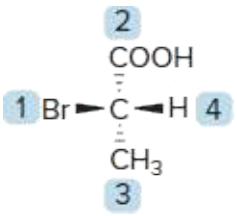
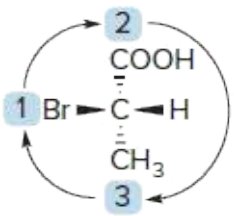
KEY SKILLS

[1] Converting a compound to a Fischer projection formula (26.2A); example: (S)-3-hydroxy-2-methylpropanal

1 Rotate and re-draw the molecule to place the horizontal bonds in front of the plane and the vertical bonds behind the plane.	**2** Use a cross to represent the stereogenic center.
 Tip red bonds in the plane forward. • Horizontal bonds come forward. • Vertical bonds go back.	 Fischer projection

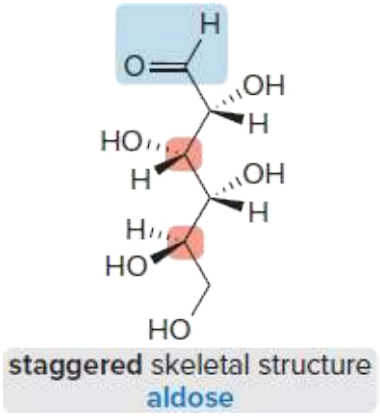
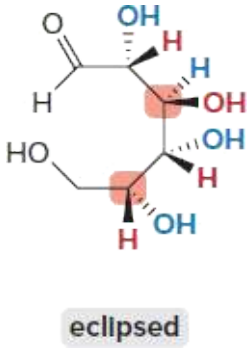
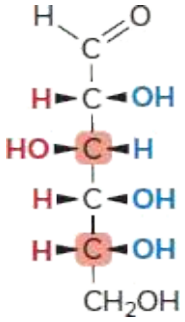
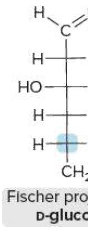
See Sample Problem 26.1. Try Problem 26.38.

[2] Re-drawing a Fischer projection, and labeling the stereogenic center as *R* or *S* (26.2A)

1 Convert the Fischer projection formula to a representation with wedges and dashed wedges.	**2** Assign priorities.	**3** Determine *R* or S.
		 Clockwise circle and group [4] is oriented forward: ***S* configuration**
• The horizontal bonds are drawn with wedges, and the vertical bonds are drawn with dashed wedges.		• Reverse the answer if priority group [4] is oriented forward (on a wedge.)

See Sample Problem 26.2. Try Problem 26.39.

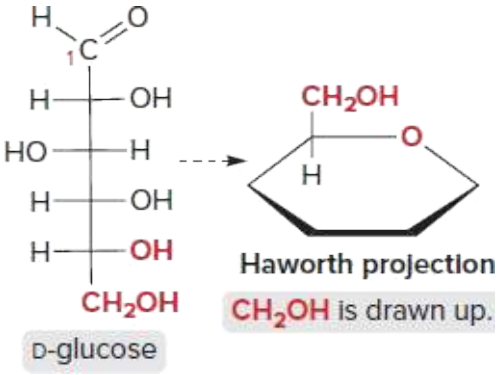
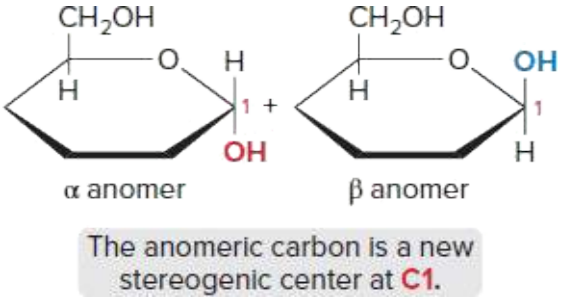
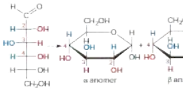
[3] Converting a skeletal structure to a Fischer projection (26.2A); example: D-glucose

1 Draw the structure with the carbonyl group at the top.	2 Convert the staggered to the eclipsed conformation.	3 Re-draw all bonds to H and OH on stereogenic centers as wedges.	4 Repla wedg with cross form Fisch proje
 staggered skeletal structure aldose	 eclipsed		 Fischer pro D-gluco
	• Rotate around the bonds to swing two carbons (labeled in red) 180°.	• Groups on wedges (in red) are drawn on the left, and groups on dashed wedges (in blue) are drawn on the right.	• This suga beca the bond the stere cente farth from carb grou draw the ri

See Sample Problem 26.3. Try Problem 26.36.

[4] Drawing a Haworth projection from an acyclic aldohexose (26.6); example:

D-glucose

1	2	3
Place the O atom in the upper right corner of a hexagon, and add the CH_2OH on the first carbon counterclockwise from the O atom.	Place the anomeric carbon on the first carbon clockwise from the O atom.	Add substitu at the t remainir stereoge centers clockwis around ring.
		
• For D-sugars, the CH_2OH group is drawn up. • For L-sugars, the CH_2OH group is drawn down.	• Anomers differ in configuration at the hemiacetal OH group. • For an α anomer, the OH is drawn down in a D-sugar. • For a β anomer, the OH is drawn up in a D-sugar.	• The substitu on the side of Fischer projectio are dr down. • The substitu on the are dr up.

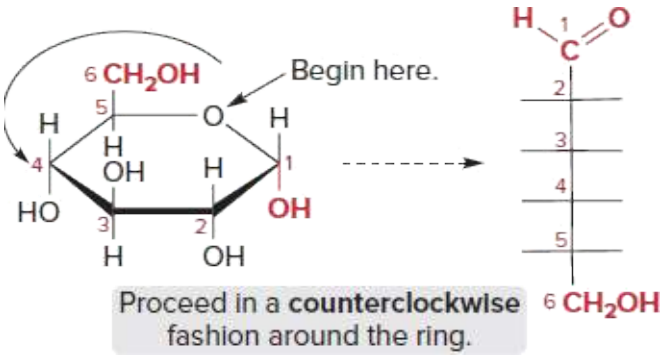
See *How To*, p. 1175. Try Problems 26.42, 26.43a, 26.53a, 26.54a.

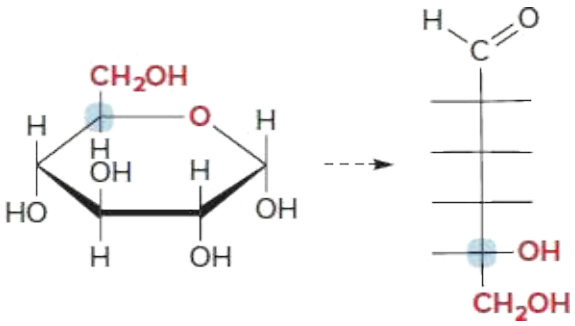
[5] Converting a Haworth projection to its acyclic form (26.6B); example: D-glucose

1	2	3
Draw the carbon skeleton,	Classify the sugar as D-	

placing the CHO on the top and the CH_2OH on the bottom.

or L-.





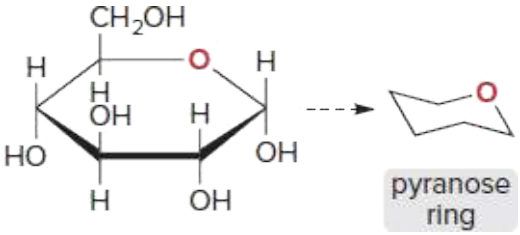
- The CH2OH is drawn up in the Haworth projection, so it is a D-sugar.
- In a Fisher projection, the OH group on the bottom stereogenic center is on the right in a D-sugar.

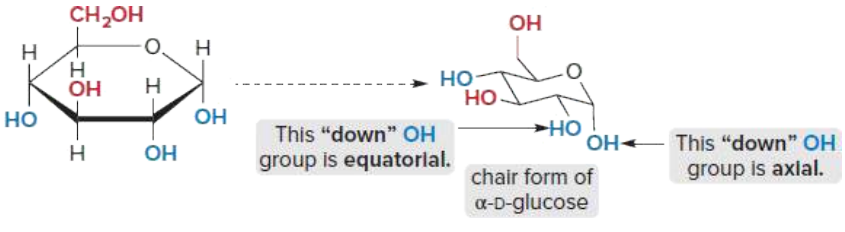
See Sample Problem 26.4. Try Problems 26.37a, 26.45.

[6] Converting a Haworth projection to a chair form (26.6C); example: D-glucose

1 Draw the pyranose ring with the O atom as an "up" atom.

2 Draw the "up" substituents in the Haworth projection as the "up" bonds on the chair, and draw the "down" substituents in the Haworth projection as the "down" bonds on the chair.

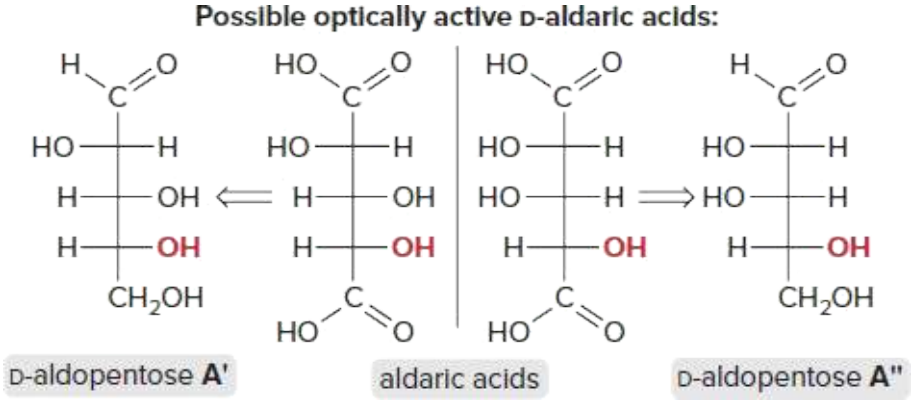




Try Problems 26.44, 26.53b, 26.54b.

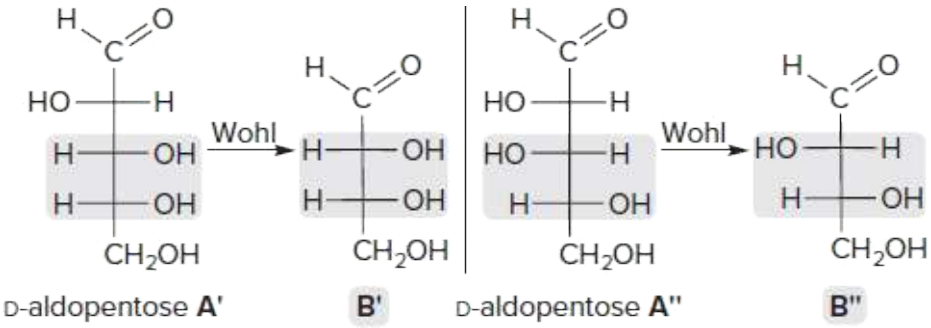
[7] Determining the structure of an unknown D-aldopentose given a set of facts (26.9–26.10)

1 **Use Fact [1]: A D-aldopentose A is oxidized to an optically active aldaric acid with HNO_3.**



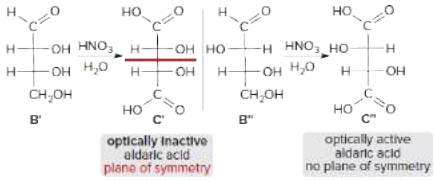
- **A′ and A″ are two possible structures for A, because their aldaric acids have no plane of symmetry.**

2 **Use Fact [2]: On Wohl degradation, A forms a D-aldotetrose B.**



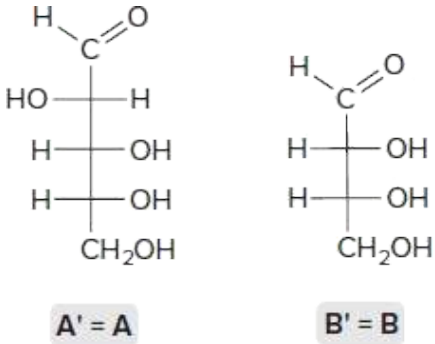
- **B′ and B″ are two possible structures for B.**

3 **Use Fact [3]: The D-aldotetrose B is oxidized to an optically inactive aldaric acid.**



- **The oxidation product of B′ is optically inactive, because it has a plane of symmetry.**

4 **Draw the unknown D-aldopentose A and D-aldotetrose B using Facts [1]–[3].**



- **The precursor of C′ is B′, and thus A′ = A.**

See Sample Problem 26.5. Try Problems 26.64–26.66.

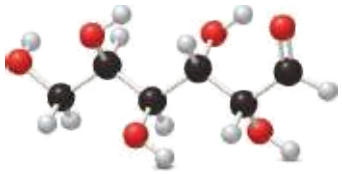
PROBLEMS

Problems Using Three-Dimensional Models

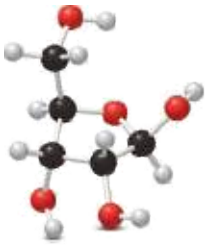
26.36 **Convert each ball-and-stick model to a Fischer projection.**

a.

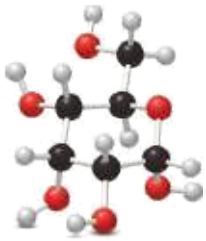
b.



26.37 **(a) Convert each cyclic monosaccharide to a Fischer projection of its acyclic form. (b) Name each monosaccharide. (c) Label the anomer as α or β.**



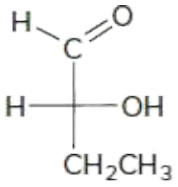
A



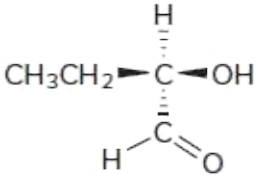
B

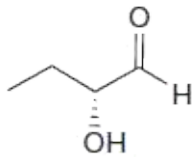
Fischer Projections

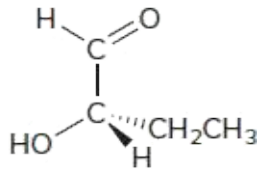
26.38 **Classify each compound as identical to A or its enantiomer.**



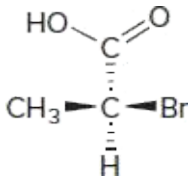
A

a. 

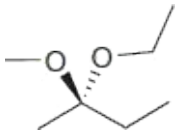
b. 

c. 

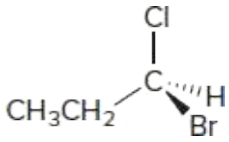
26.39 **Convert each compound to a Fischer projection, and label each stereogenic center as *R* or *S*.**

a. 

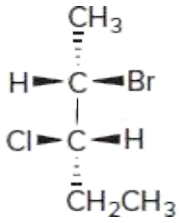
b.



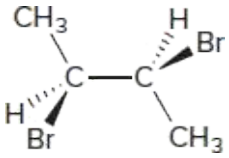
c.



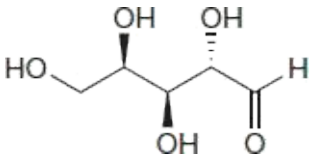
d.



e.



f.



Monosaccharide Structure and Stereochemistry

26.40 For D-arabinose:

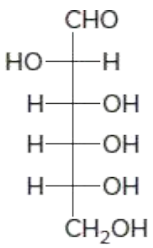
a. Draw its enantiomer.

b. Draw an epimer at C3.

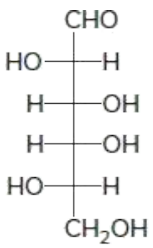
c. Draw a diastereomer that is not an epimer.

d. Draw a constitutional isomer that still contains a carbonyl group.

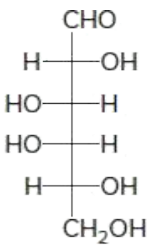
26.41 Consider the following six compounds (A–F).



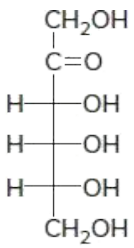
A



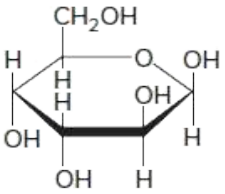
B



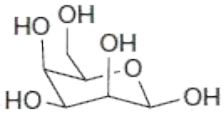
C



D



E



F

How are the two compounds in each pair related? Choose from enantiomers, epimers, diastereomers but not epimers, constitutional isomers, and identical compounds.

a. A and B

b. A and C

c. B and C

d. A and D

e. E and F

26.42 Draw a Haworth projection for each compound using the structures in Figures 26.4 and 26.5.

a. β-D-talopyranose

b. α-D-galactopyranose

c. α-D-tagatofuranose

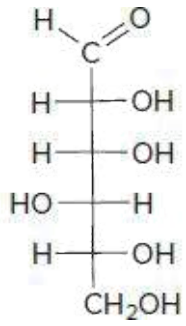
26.43 Draw the structure of each compound and name it using the information in Figure 26.4.

a. the α anomer of a monosaccharide that is epimeric with D-glucose at C4 using a Haworth projection

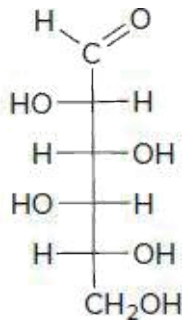
b. the β anomer of a monosaccharide that is epimeric with D-gulose at C2 using a chair pyranose

26.44 Draw both pyranose anomers of each aldohexose using a three-dimensional representation with a chair pyranose. Label each anomer as α or β.

a.

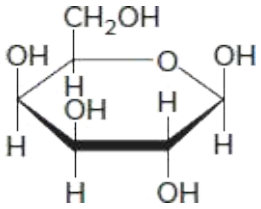


b.

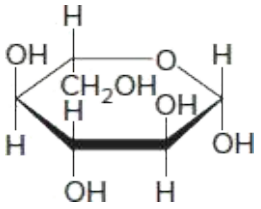


26.45 Convert each cyclic monosaccharide to its acyclic form.

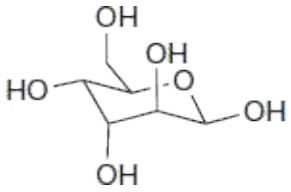
a.



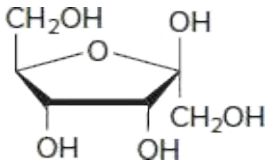
b.



c.

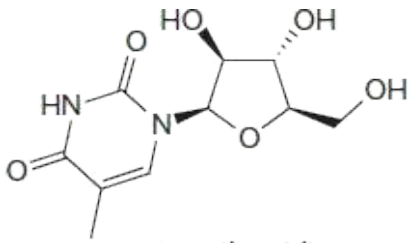


d.



26.46 **The most stable conformation of the pyranose ring of most D-aldohexoses places the largest group, CH_2OH, in the equatorial position. An exception to this is the aldohexose D-idose. Draw the two possible chair conformations of either the α or β anomer of D-idose. Explain why the more stable conformation has the CH_2OH group in the axial position.**

26.47 **Spongothymidine is an *N*-glycoside isolated from *Tectitethya crypta*, a shallow-water Caribbean sponge. Identify the base and monosaccharide that compose spongothymidine, and draw the structure of the monosaccharide using a Fischer projection formula.**

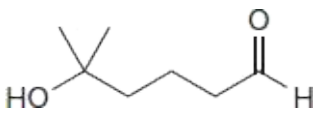


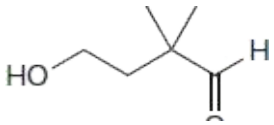
spongothymidine

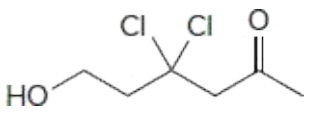
Monosaccharide Reactions

26.48 **Draw the structure (including stereochemistry) of the cyclic hemiacetal(s) formed when each hydroxy carbonyl compound is treated with aqueous acid.**

a.



b. 

c. 

26.49 **Draw the products formed when α-D-gulose is treated with each reagent.**

a. CH_3I, Ag_2O

b. CH_3OH, HCl

c. Ac_2O, pyridine

d. The product in (a), then H_3O^+

e. The product in (b), then Ac_2O, pyridine

f. The product in (d), then $C_6H_5CH_2Cl$, Ag_2O

26.50 **Draw the products formed when D-altrose is treated with each reagent.**

a. $(CH_3)_2CHOH$, HCl

b. $NaBH_4$, CH_3OH

c. Br_2, H_2O

d. HNO_3, H_2O

e. [1] NH_2OH; [2] $(CH_3CO)_2O$, $NaOCOCH_3$; [3] $NaOCH_3$

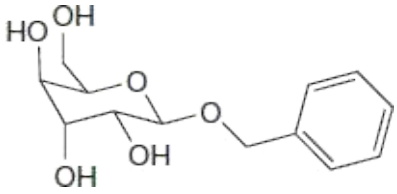
f. [1] NaCN, HCl; [2] H_2, Pd-$BaSO_4$; [3] H_3O^+

g. CH_3I, Ag_2O

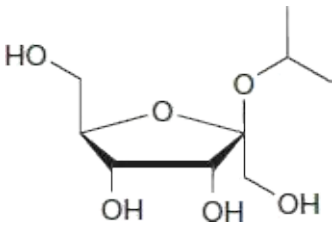
h. $C_6H_5CH_2NH_2$, mild H^+

26.51 **What aglycon and monosaccharides are formed when salicin and solanine (Section 26.7C) are each hydrolyzed with aqueous acid?**

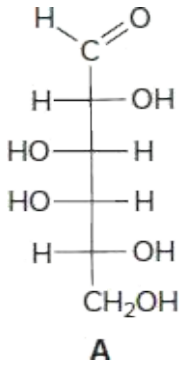
26.52 **Draw a Fischer projection of the monosaccharide from which each of the following glycosides was prepared.**

a. 

b.



26.53 Answer the following questions about monosaccharide A.



A

a. **Draw the α anomer of A in a Haworth projection.**

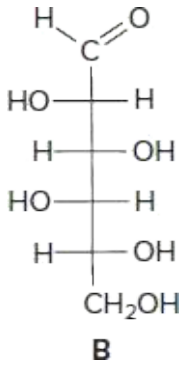
b. **Draw the β anomer of A in a three-dimensional representation using a chair conformation.**

c. **What two aldoses yield A in a Wohl degradation?**

d. **What product is formed when A undergoes a Wohl degradation?**

e. **What product is formed when A reacts with Ag_2O in NH_4OH?**

26.54 Answer the following questions about monosaccharide B.



B

a. **Draw the β anomer of B in a Haworth projection.**

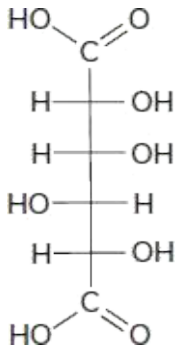
b. **Draw the α anomer of B in a three-dimensional representation using a chair conformation.**

c. **What products are formed when B undergoes the Kiliani–Fischer synthesis?**

d. **What product is formed when B is treated with $NaBH_4$ in CH_3OH?**

e. Draw the disaccharide formed when two molecules of B are joined by a 1→4-β-glycosidic linkage.

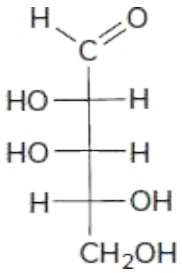
26.55 Draw the structure of two different aldohexoses that yield the following aldaric acid when oxidized with HNO_3. Use Figure 26.4 to name each aldohexose.



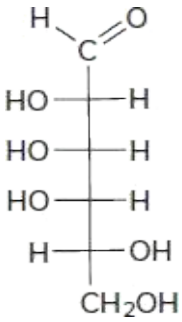
26.56 Treatment of D-glucose with $NaBH_4$ gives an alditol A. What L-aldohexose also yields A when treated with $NaBH_4$?

26.57 What products are formed when each compound undergoes a Kiliani–Fischer synthesis?

a.

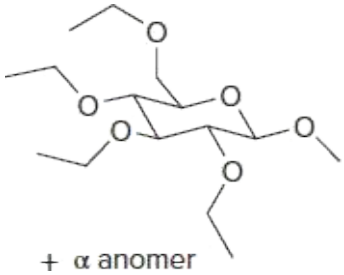


b.

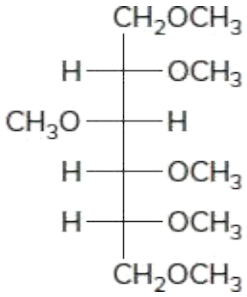


26.58 How would you convert D-glucose to each compound? More than one step is required.

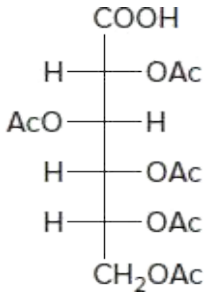
a.



b.



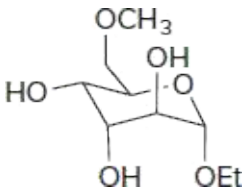
c.



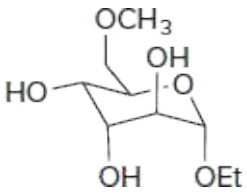
26.59 **Which D-aldopentoses are reduced to optically inactive alditols using $NaBH_4$, CH_3OH?**

26.60 **What products are formed when each compound is treated with aqueous acid?**

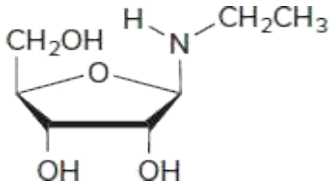
a.



b.

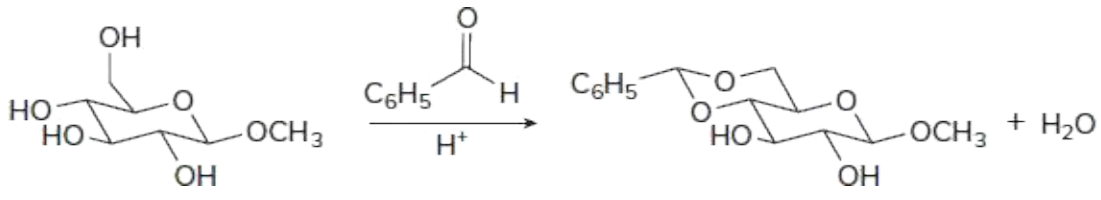


c.

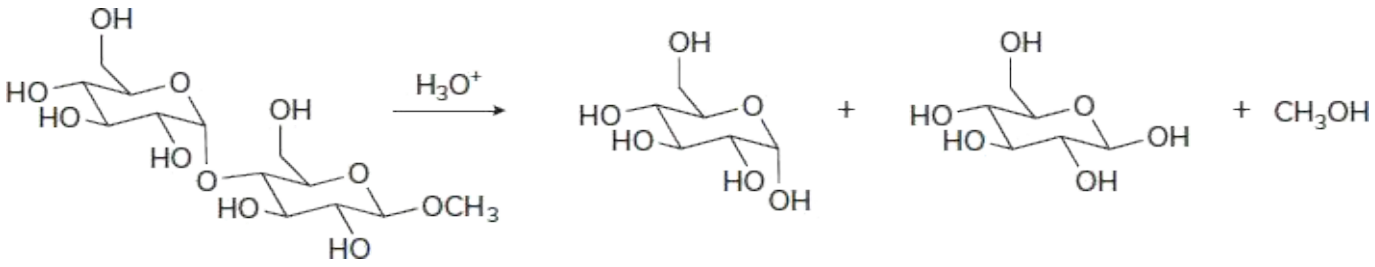


Mechanisms

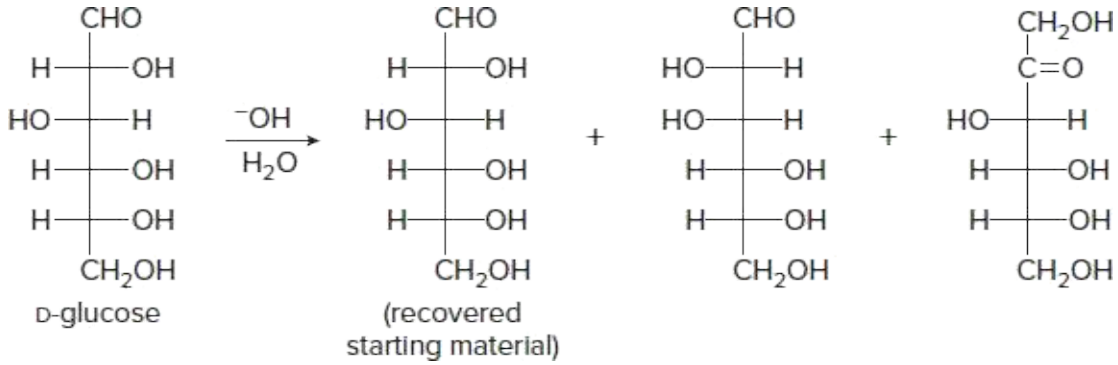
26.61 **Draw a stepwise mechanism for the following reaction.**



26.62 **Draw a stepwise mechanism for the following hydrolysis.**



26.63 **The following isomerization reaction, drawn using D-glucose as starting material, occurs with all aldohexoses in the presence of base. Draw a stepwise mechanism that illustrates how each compound is formed.**



Identifying Monosaccharides

26.64 **Which D-aldopentose is oxidized to an optically active aldaric acid and undergoes the Wohl degradation to yield a D-aldotetrose that is oxidized to an optically active aldaric acid?**

26.65 **Identify compounds A–D. A D-aldopentose A is oxidized with HNO_3 to an optically inactive aldaric acid B. A undergoes the Kiliani–Fischer synthesis to yield C and D. C is oxidized to an optically active aldaric acid. D is oxidized to an optically inactive aldaric acid.**

26.66 **A D-aldopentose A is reduced to an optically active alditol. Upon Kiliani–Fischer synthesis, A is converted to two D-aldohexoses, B and C. B is oxidized to an optically inactive aldaric acid. C is oxidized to an optically active aldaric acid. What are the structures of A–C?**

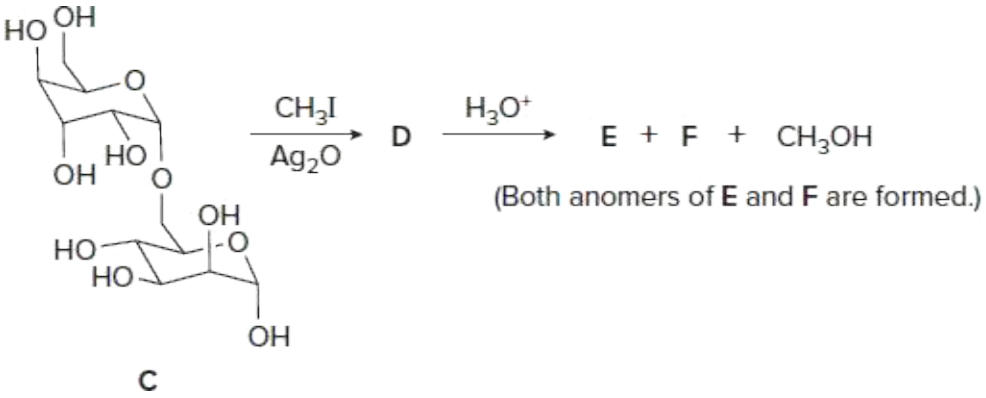
Disaccharides and Polysaccharides

26.67 **Draw the structure of a disaccharide formed from two mannose units joined by a 1 → 4-α-glycosidic linkage.**

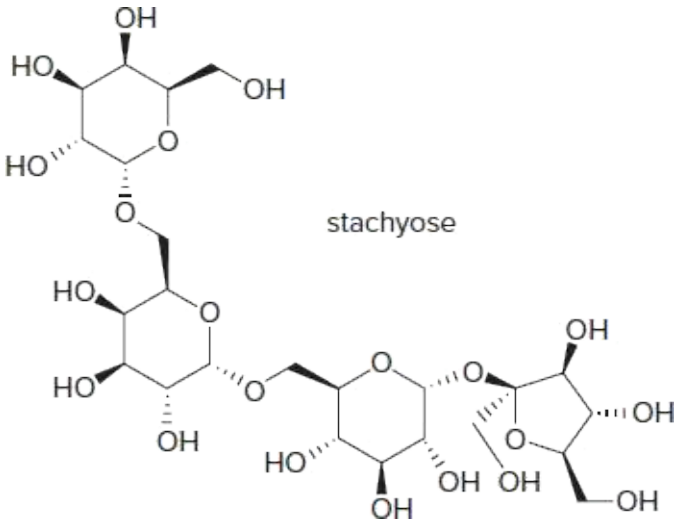
26.68 **a. Identify the glycosidic linkage in disaccharide C, classify the**

glycosidic bond as α or β, and use numbers to designate its location.

b. Identify the lettered compounds in the following reaction.



26.69 Consider the tetrasaccharide stachyose drawn below. Stachyose is found in white jasmine, soybeans, and lentils. Because humans cannot digest it, its consumption causes flatulence.



a. Label all glycoside bonds.

b. Classify each glycosidic linkage as α or β and use numbers to designate its location between two rings (e.g., 1→4-β).

c. What products are formed when stachyose is hydrolyzed with H_3O^+?

d. Is stachyose a reducing sugar?

e. What product is formed when stachyose is treated with excess CH_3I, Ag_2O?

f. What products are formed when the product in (e) is treated with H_3O^+?

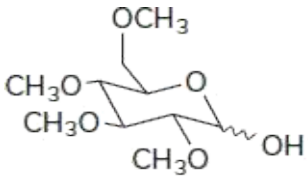
26.70 Deduce the structure of the disaccharide isomaltose from the following data.

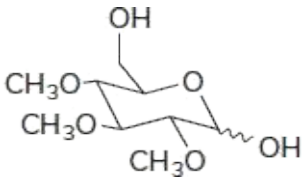
[1] Hydrolysis yields D-glucose exclusively.

[2] Isomaltose is cleaved with α-glycosidase enzymes.

[3] Isomaltose is a reducing sugar.

[4] Methylation with excess CH_3I, Ag_2O and then hydrolysis with H_3O^+ forms two products:





(Both anomers are present.)

26.71 Draw the structure of each of the following compounds.

a. a polysaccharide formed by joining D-glucosamine in 1→6-α-glycosidic linkages

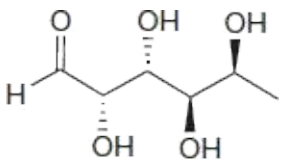
b. a disaccharide formed by joining D-mannose and D-glucose in a 1→4-β-glycosidic linkage using mannose's anomeric carbon

c. an α-*N*-glycoside formed from D-arabinose and $C_6H_5CH_2NH_2$

d. a ribonucleoside formed from D-ribose and thymine

Challenge Problems

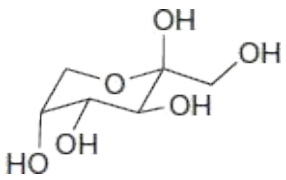
26.72 (a) Draw the more stable chair form of fucose, an essential monosaccharide needed in the diet and a component of carbohydrates on mammalian and plant cell surfaces. (b) Classify fucose as a D- or L-monosaccharide. (c) What two structural features are unusual in fucose?



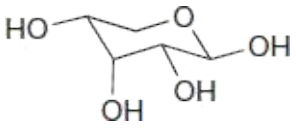
fucose

26.73 As we have seen in Chapter 26, monosaccharides can be drawn in a variety of ways, and in truth, often a mixture of cyclic compounds is present in a solution. Identify each monosaccharide, including its proper D,L designation, drawn in a less-than-typical fashion.

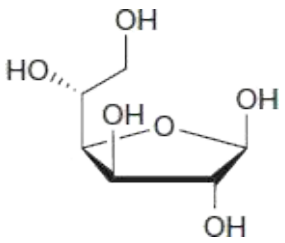
a.



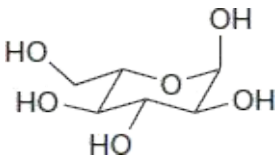
b.



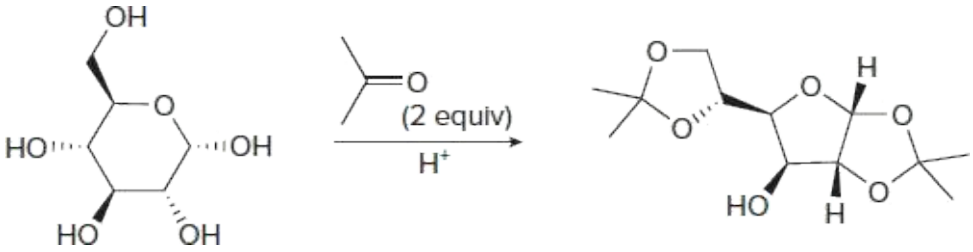
c.



d.



26.74 Draw a stepwise mechanism for the following reaction.



Amino Acids and Proteins

27

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27.1 Amino acids

27.2 Synthesis of amino acids

27.3 Separation of amino acids

27.4 Enantioselective synthesis of amino acids

27.5 Peptides

27.6 Peptide sequencing

27.7 Peptide synthesis
27.8 Automated peptide synthesis
27.9 Protein structure
27.10 Important proteins

Oxytocin, a peptide consisting of nine amino acids, is a hormone that causes cervical dilation in preparation for childbirth and uterine contractions during labor, and it also stimulates the flow of milk in nursing mothers. Oxytocin was the first peptide hormone synthesized, a feat for which Vincent du Vigneaud was awarded the 1955 Nobel Prize in Chemistry. Oxytocin, sold under the trade name Pitocin, is used to induce labor and to stop bleeding after a delivery. In Chapter 27, we learn about peptides like oxytocin and the amino acids that comprise them.

Why Study…

Amino Acids and Proteins?

Of the four major groups of biomolecules—lipids, carbohydrates, nucleic acids, and proteins—proteins have the widest array of functions. Keratin and collagen, for example, are part of a large group of structural proteins that form long insoluble fibers, giving strength and support to tissues. Hair, horns, hooves, and fingernails are all made up of keratin. Collagen is found in bone, connective tissue, tendons, and cartilage. Enzymes are proteins that catalyze and regulate all aspects of cellular function. Membrane proteins transport small organic molecules and ions across cell membranes. Insulin, the hormone that regulates blood glucose levels, fibrinogen and thrombin, which form blood clots, and hemoglobin, which transports oxygen from the lungs to tissues, are all proteins.

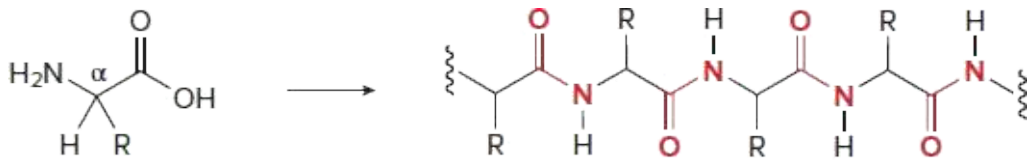
In Chapter 27 we discuss proteins and their primary components, the amino acids.

Amino acids were first discussed in Section 19.11.

27.1 Amino Acids

Naturally occurring amino acids have an amino group (NH_2) bonded to the α carbon of a carboxy group (COOH), so they are called α-amino acids.

- **All proteins are polyamides formed by joining amino acids together.**



27.1A General Features of α-Amino Acids

The 20 amino acids that occur naturally in proteins differ in the identity of the R group bonded to the α carbon. The R group is called the side chain of the amino acid.

The simplest amino acid, called glycine, has R = H. All other amino acids (R ≠ H) have a stereogenic center on the α carbon. As is true for monosaccharides, the prefixes D and L are used to designate the configuration at the stereogenic center of amino acids. Common, naturally occurring amino acids are called l-amino acids. Their enantiomers, D-amino acids, are rarely found in nature. These general structures are shown in Figure 27.1. According to *R*,*S* designations, all L-amino acids except cysteine have the *S* configuration.

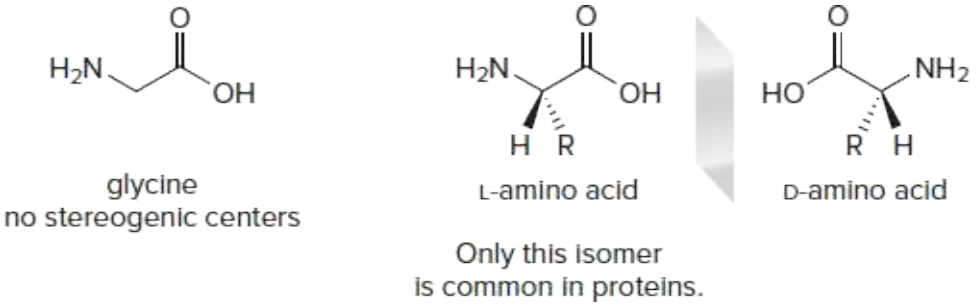


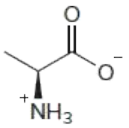
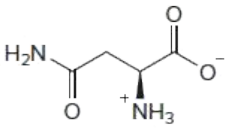
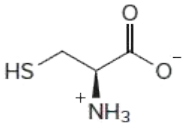
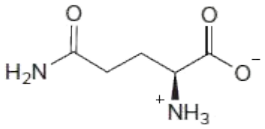
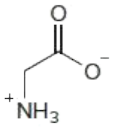
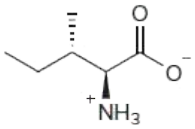
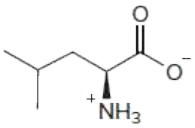
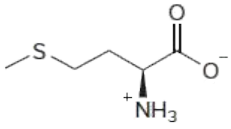
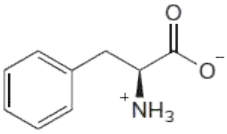
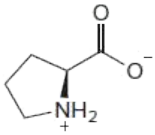
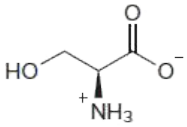
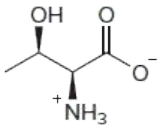
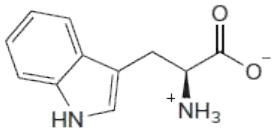
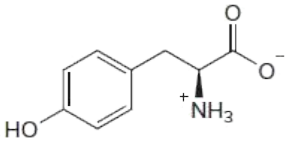
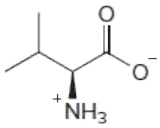
Figure 27.1 **The general features of an α-amino acid**

All amino acids have common names. These names can be represented by either a one-letter or a three-letter abbreviation. Figure 27.2 is a listing of the 20 naturally occurring amino acids, with their abbreviations. Note the variability in the R groups. A side chain can be a simple alkyl group, or it can have additional functional groups such as OH, SH, COOH, or NH_2.

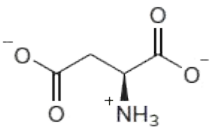
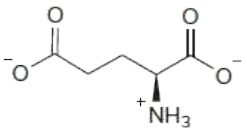
- **Amino acids with an additional COOH group in the side chain are called *acidic* amino acids.**

- **Those with an additional basic N atom in the side chain are called *basic* amino acids.**
- **All others are neutral amino acids.**

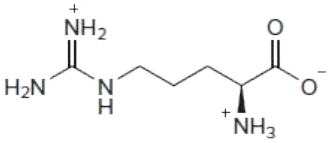
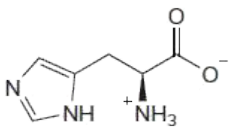
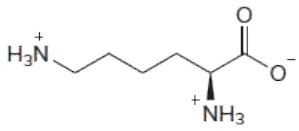
Neutral amino acids

Name	Structure	Abbreviations
Alanine		Ala A
Asparagine		Asn N
Cysteine		Cys C
Glutamine		Gln Q
Glycine		Gly G
Isoleucine*		Ile I
Leucine*		Leu L
Methionine*		Met M
Phenylalanine*		Phe F
Proline		Pro P
Serine		Ser S
Threonine*		Thr T
Tryptophan*		Trp W
Tyrosine		Tyr Y
Valine*		Val V

Acidic amino acids

Name	Structure	Abbreviations
Aspartic acid		Asp D
Glutamic acid		Glu E

Basic amino acids

Name	Structure	Abbreviations
Arginine*		Arg R
Histidine*		His H
Lysine*		Lys K

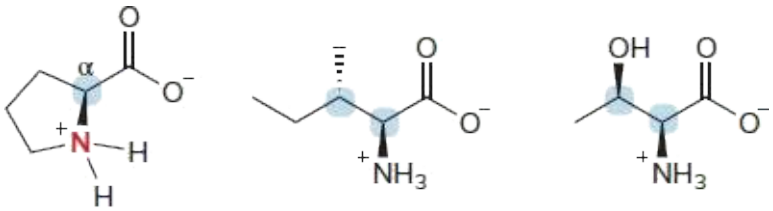
Essential amino acids are labeled with an asterisk (*).

Figure 27.2 **The 20 naturally occurring amino acids**

Look closely at the structures of proline, isoleucine, and threonine.

The essential amino acid leucine is sold as a dietary supplement that is used by body builders to help prevent muscle loss and heal muscle tissue after injury. ©*Jill Braaten*

- All amino acids are 1° amines except for proline, which has its N atom in a five-membered ring, making it a 2° amine.
- Isoleucine and threonine contain an additional stereogenic center at the β carbon, so there are four possible stereoisomers, only one of which is naturally occurring.



L-proline
2° amine

L-isoleucine

L-threonine

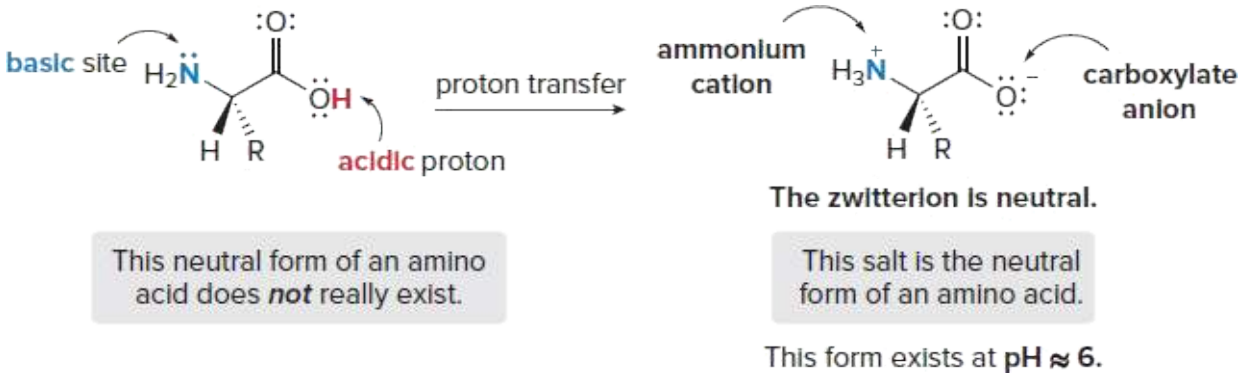
Humans can synthesize only 10 of these 20 amino acids. The remaining 10 are called essential amino acids because they must be obtained from the diet. These are labeled with an asterisk in Figure 27.2.

Problem 27.1

Draw the other three stereoisomers of L-isoleucine, and label the stereogenic centers as *R* or *S*.

27.1B Acid–Base Behavior

Recall from Section 19.11B that an amino acid has both an acidic and a basic functional group, so proton transfer forms a salt called a zwitterion.



The structures in Figure 27.2 show the charged form of the amino acids at the physiological pH of the blood.

- **Amino acids do not exist to any appreciable extent as uncharged neutral compounds. They exist as salts, giving them high melting points and making them water soluble.**

Amino acids exist in different charged forms, as shown in Figure 27.3, depending on the pH of the aqueous solution in which they are dissolved. For neutral amino acids, the overall charge is +1, 0, or −1. Only at pH ~6 does the zwitterionic form exist.

The –COOH and $-NH_3^+$ groups of an amino acid are ionizable, because they can lose a proton in aqueous solution. As a result, they have different pK_a values. The pK_a of the –COOH group is typically ~2, whereas that of the $-NH_3^+$ group is ~9, as shown in Table 27.1.

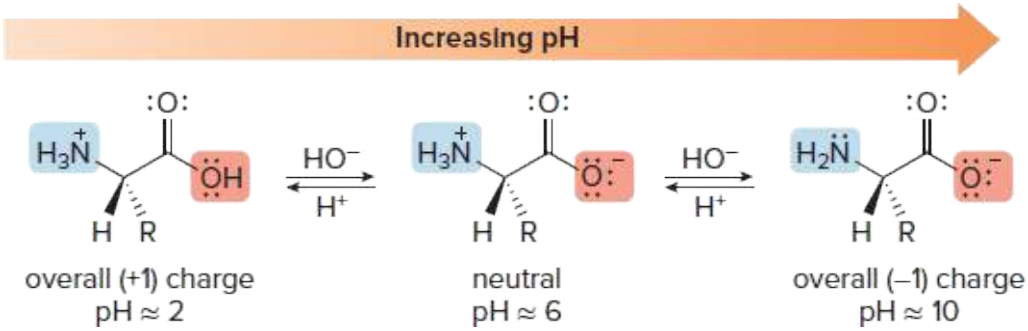


Figure 27.3 How the charge of a neutral amino acid depends on the pH

Table 27.1 pK_a Values for the Ionizable Functional Groups of an α-Amino Acid

Amino acid	α-COOH	α-NH_3^+	Side chain	p*I*
Alanine	**2.35**	**9.87**	**–**	**6.11**
Arginine	**2.01**	**9.04**	**12.48**	**10.76**
Asparagine	**2.02**	**8.80**	**–**	**5.41**
Aspartic acid	**2.10**	**9.82**	**3.86**	**2.98**
Cysteine	**2.05**	**10.25**	**8.00**	**5.02**
Glutamic acid	**2.10**	**9.47**	**4.07**	**3.08**
Glutamine	**2.17**	**9.13**	**–**	**5.65**
Glycine	**2.35**	**9.78**	**–**	**6.06**
Histidine	**1.77**	**9.18**	**6.10**	**7.64**
Isoleucine	**2.32**	**9.76**	**–**	**6.04**
Leucine	**2.33**	**9.74**	**–**	**6.04**
Lysine	**2.18**	**8.95**	**10.53**	**9.74**
Methionine	**2.28**	**9.21**	**–**	**5.74**
Phenylalanine	**2.58**	**9.24**	**–**	**5.91**
Proline	**2.00**	**10.60**	**–**	**6.30**
Serine	**2.21**	**9.15**	**–**	**5.68**
Threonine	**2.09**	**9.10**	**–**	**5.60**
Tryptophan	**2.38**	**9.39**	**–**	**5.88**
Tyrosine	**2.20**	**9.11**	**10.07**	**5.63**
Valine	**2.29**	**9.72**	**–**	**6.00**

Some amino acids, such as aspartic acid and lysine, have acidic or basic side chains. These additional ionizable groups complicate somewhat the acid–base behavior of these amino acids. Table 27.1 lists the pK_a values for these acidic and basic side chains as well.

Table 27.1 also lists the isoelectric points (p*I*) for all of the amino acids. Recall from Section 19.11C that the isoelectric point is the pH at which an amino acid exists primarily in its neutral form, and that it can be calculated from the average of the pK_a

values of the α-COOH and α-NH_3^+ groups (for neutral amino acids only).

Problem 27.2

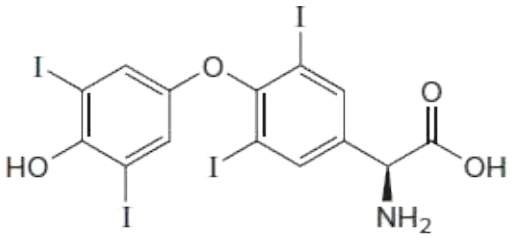
What form exists at the isoelectric point of each of the following amino acids: (a) valine; (b) leucine; (c) proline; (d) glutamic acid?

Problem 27.3

Explain why the pK_a of the –NH_3^+ group of an α-amino acid is lower than the pK_a of the ammonium ion derived from a 1° amine (RNH_3^+). For example, the pK_a of the –NH_3^+ group of alanine is 9.87 but the pK_a of $CH_3NH_3^+$ is 10.63.

Problem 27.4

L-Thyroxine, a thyroid hormone and oral medication used to treat thyroid hormone deficiency, is an amino acid that does not exist in proteins. Draw the zwitterionic form of L-thyroxine.



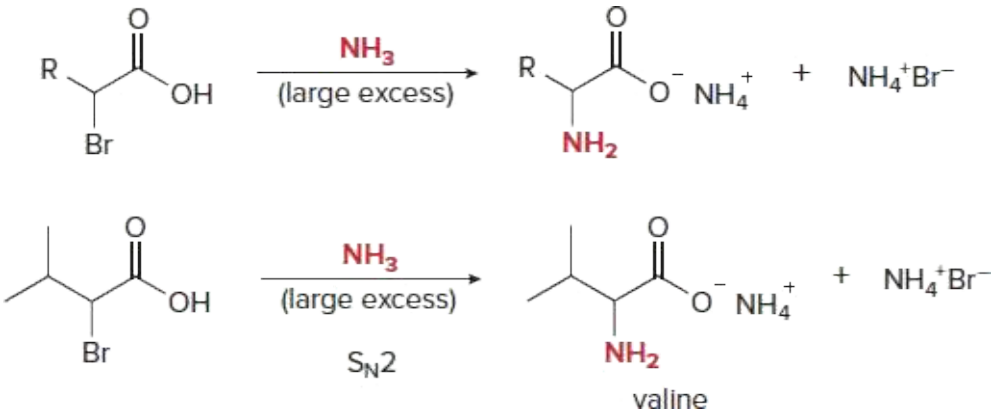
L-thyroxine

27.2 Synthesis of Amino Acids

Amino acids can be prepared in a variety of ways in the laboratory. Three methods are described, each of which is based on reactions learned in previous chapters.

27.2A S_N2 Reaction of α-Halo Acids with NH_3

The most direct way to synthesize an α-amino acid is by S_N2 reaction of an α-halo carboxylic acid with a large excess of NH_3.



Although the alkylation of ammonia with simple alkyl halides does not generally afford high yields of 1° amines (Section 23.6A), this reaction using α-halo carboxylic acids *does* form the desired amino acids in good yields. In this case, the amino group in the product is both less basic and more sterically crowded than other 1° amines, so that a single alkylation occurs and the desired amino acid is obtained.

Problem 27.5

What α-halo carbonyl compound is needed to synthesize each amino acid: (a) glycine; (b) isoleucine; (c) phenylalanine?

27.2B Alkylation of a Diethyl Malonate Derivative

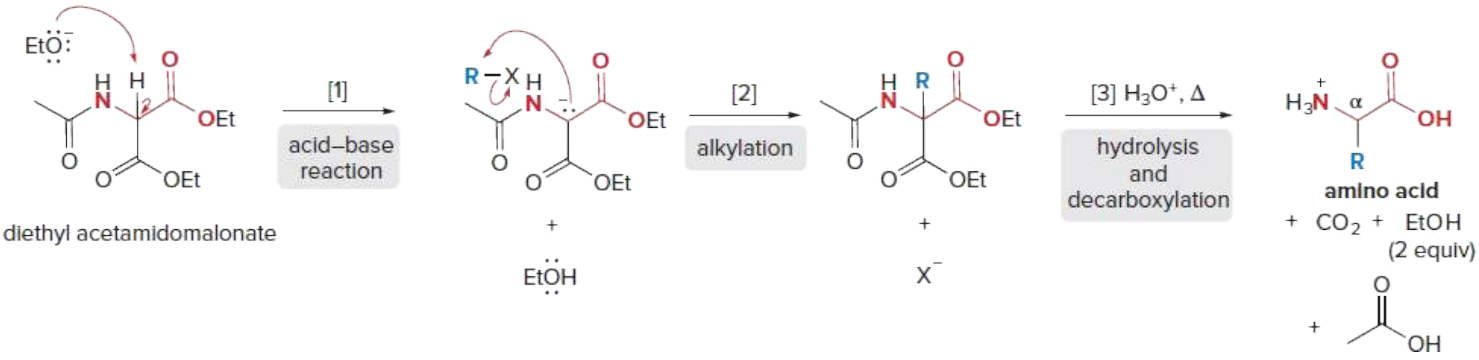
The second method for preparing amino acids is based on the malonic ester synthesis. Recall from Section 21.9 that this synthesis converts diethyl malonate to a carboxylic acid with a new alkyl group on its α carbon atom.

diethyl malonate

This reaction can be adapted to the synthesis of α-amino acids by using a commercially available derivative of diethyl malonate as starting material. This compound, diethyl acetamidomalonate, has a nitrogen atom on the α carbon, which ultimately becomes the NH_2 group on the α carbon of the amino acid.

diethyl acetamidomalonate

The malonic ester synthesis consists of three steps, and so does this variation to prepare an amino acid.

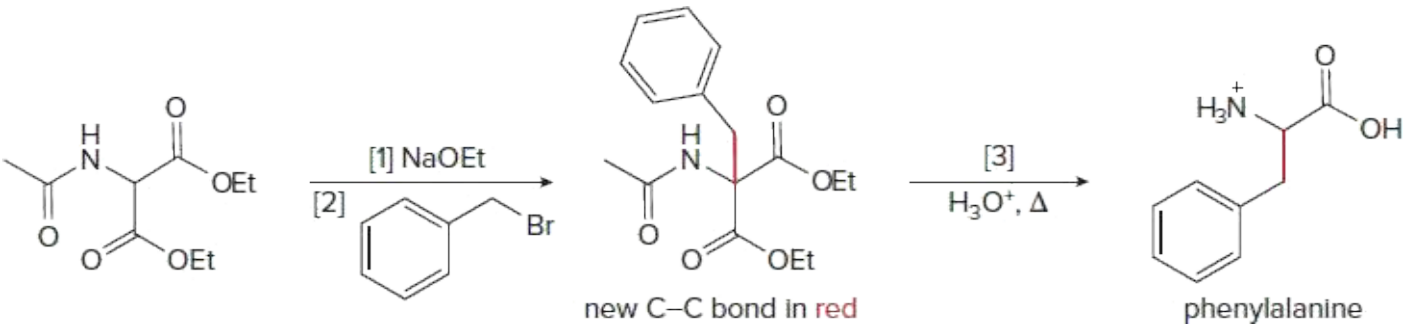


[1] Deprotonation of diethyl acetamidomalonate with NaOEt forms an enolate by removal of the acidic proton between the two carbonyl groups.

[2] Alkylation of the enolate with an unhindered alkyl halide (usually CH_3X or RCH_2X) forms a substitution product with a new R group on the α carbon.

[3] Heating the alkylation product with aqueous acid results in hydrolysis of both esters and the amide, followed by decarboxylation to form the amino acid.

Phenylalanine, for example, can be synthesized as follows:



The charge on the amino acid product (+1, −1, or 0) depends on the reaction conditions. Phenylalanine bears a net positive charge because the last step in its synthesis uses strong acid.

Problem 27.6

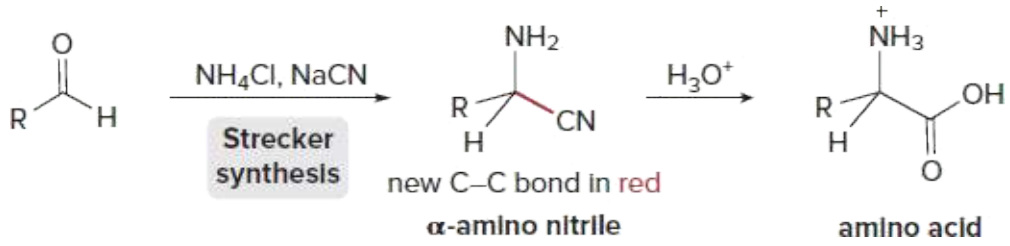
The enolate derived from diethyl acetamidomalonate is treated with each of the following alkyl halides. After hydrolysis and decarboxylation, what amino acid is formed: (a) CH_3I; (b) $(CH_3)_2CHCH_2Cl$; (c) $CH_3CH_2CH(CH_3)Br$?

Problem 27.7

What amino acid is formed when $CH_3CONHCH(CO_2Et)_2$ is treated with the following series of reagents: [1] NaOEt; [2] $CH_2{=}O$; [3] H_3O^+, Δ?

27.2C Strecker Synthesis

The third method, the Strecker amino acid synthesis, converts an aldehyde to an amino acid by a two-step sequence that *adds* one carbon atom to the aldehyde carbonyl. Treating an aldehyde with NH_4Cl and NaCN first forms an α-amino nitrile, which can then be hydrolyzed in aqueous acid to an amino acid.



The Strecker synthesis of alanine, for example, is as follows:

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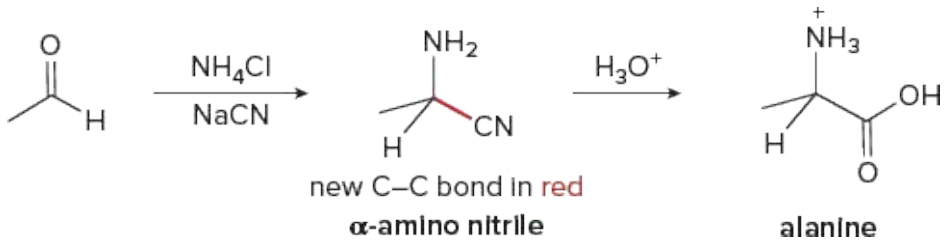
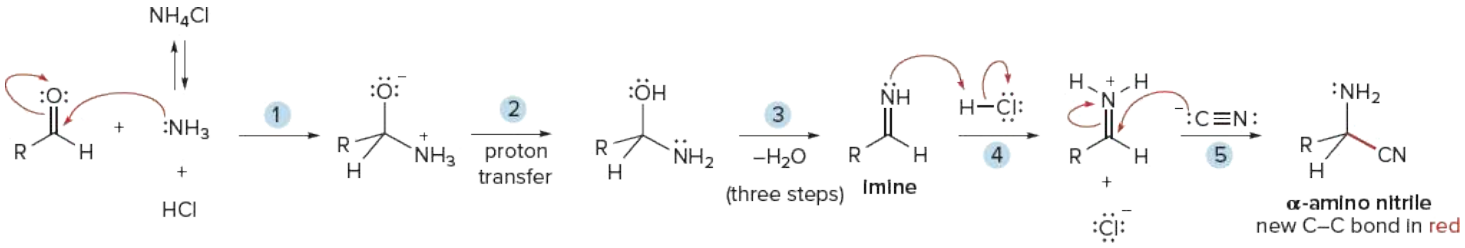


Mechanism 27.1 for the formation of the α-amino nitrile from an aldehyde (the first step in the Strecker synthesis) consists of nucleophilic addition of NH_3 to form an imine, followed by addition of cyanide to the C=N bond. Both parts are related to earlier mechanisms involving imines (Section 18.10) and cyanohydrins (Section 18.8).

Mechanism 27.1 Formation of an α-Amino Nitrile



1 – 3 Nucleophilic attack of NH_3 followed by proton transfer and loss of H_2O forms an imine. Loss of H2O occurs by the same threestep process outlined in Mechanism 18.5.

4 – 5 Protonation of the imine followed by nucleophilic attack of ^-CN gives the α-amino nitrile.

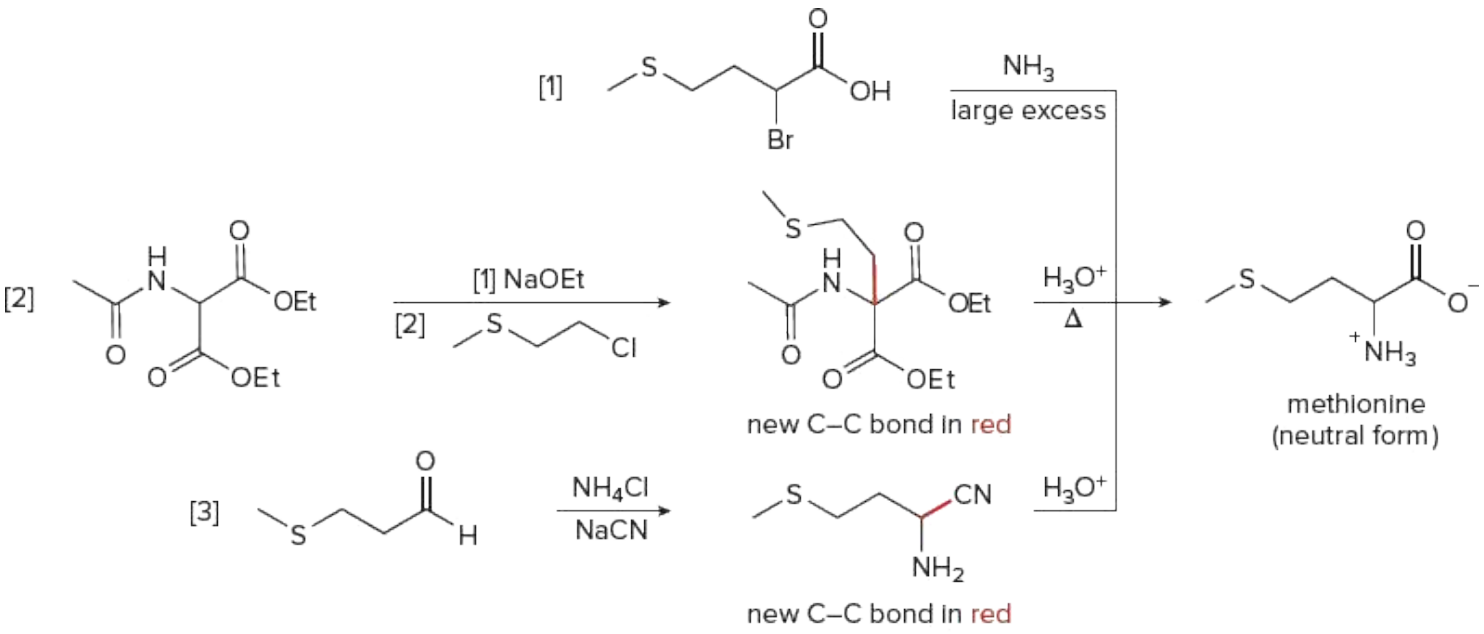
The details of the second step of the Strecker synthesis, the hydrolysis of a nitrile

(RCN) to a carboxylic acid (RCOOH), have already been presented in Section 19.12A.

Figure 27.4 shows how the amino acid methionine can be prepared by all three methods in Section 27.2.

Problem 27.8

What aldehyde is needed to synthesize each amino acid by the Strecker synthesis: (a) valine; (b) leucine; (c) phenylalanine?



Three methods of amino acid synthesis:

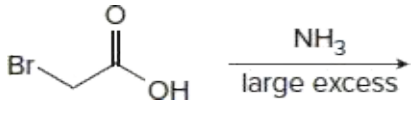
[1] **S_N2 reaction** using an α-halo carboxylic acid
[2] **Alkylation of diethyl acetamidomalonate**
[3] **Strecker synthesis**

Figure 27.4 **The synthesis of methionine by three different methods**

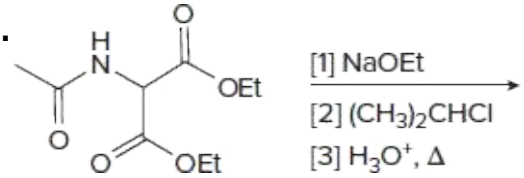
Problem 27.9

Draw the products of each reaction.

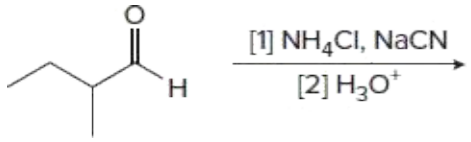
a.



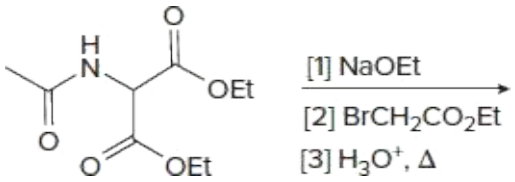
b.



c.



d.



27.3 Separation of Amino Acids

No matter which of the preceding methods is used to synthesize an amino acid, all three yield a racemic mixture. Naturally occurring amino acids exist as a single enantiomer, however, so the two enantiomers obtained must be separated if they are to be used in biological applications. This is not an easy task. Two enantiomers have the same physical properties, so they cannot be separated by common physical methods, such as distillation or chromatography. Moreover, they react in the same way with achiral reagents, so they cannot be separated by chemical reactions either.

Nonetheless, strategies have been devised to separate two enantiomers using physical separation techniques and chemical reactions. We examine two different strategies in Section 27.3. Then, in Section 27.4, we will discuss a method that affords optically active amino acids without the need for separation.

- **The separation of a racemic mixture into its component enantiomers is called *resolution*. Thus, a racemic mixture is *resolved* into its component enantiomers.**

27.3A Resolution of Amino Acids

The oldest and perhaps still the most widely used method to separate enantiomers exploits the following fact: enantiomers have the *same* physical properties, but diastereomers have *different* physical properties. Thus, a racemic mixture can be resolved using the following general strategy.

[1] Convert a pair of enantiomers to a pair of diastereomers, which are now separable because they have different melting points and boiling points.

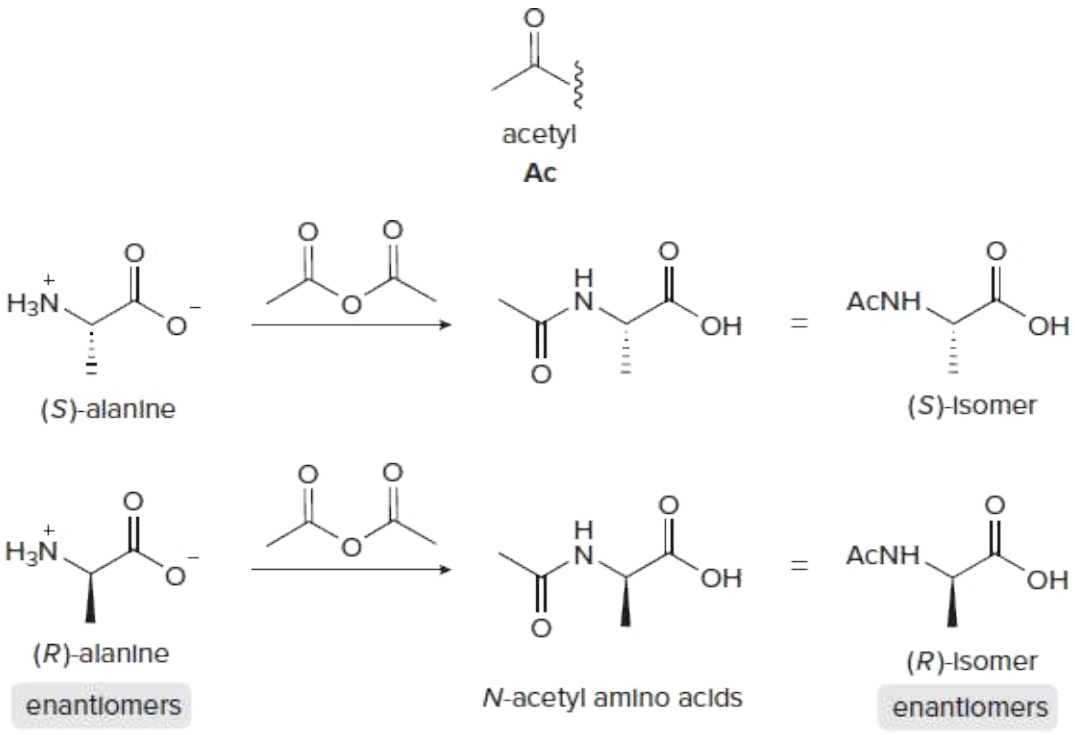
[2] Separate the diastereomers.

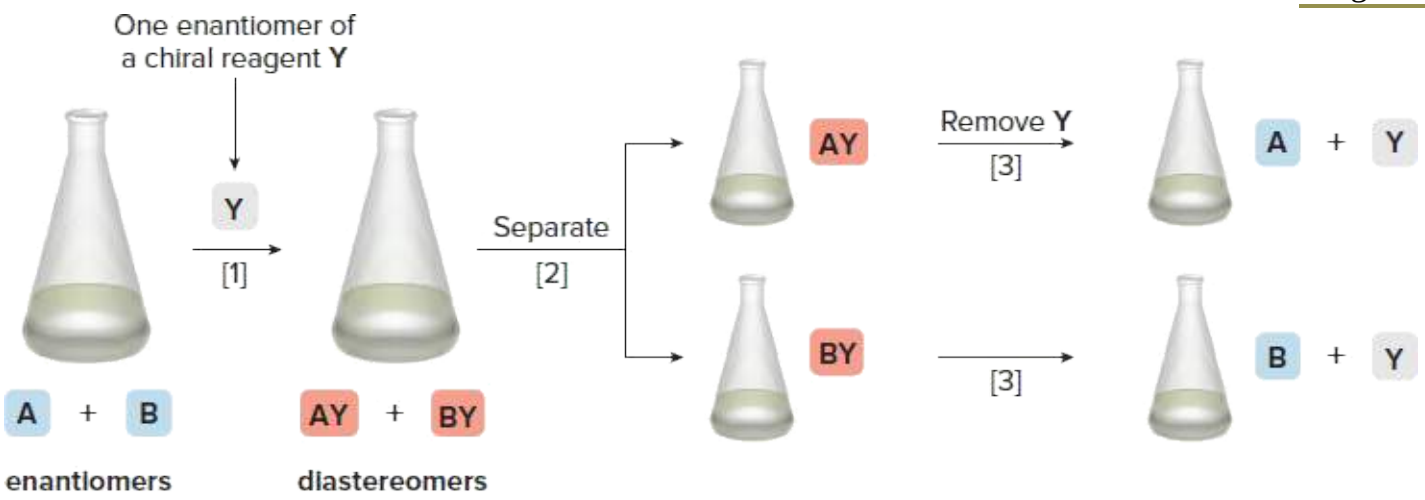
[3] Re-convert each diastereomer to the original enantiomer, now separated from the other.

This general three-step process is illustrated in Figure 27.5.

To resolve a racemic mixture of amino acids such as (*R*)- and (*S*)-alanine, the racemate is first treated with acetic anhydride to form *N*-acetyl amino acids. Each of these amides contains one stereogenic center and they are still enantiomers, so they are *still*

inseparable.





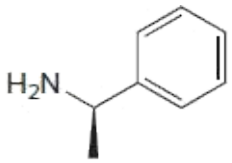
Enantiomers A and B can be separated by reaction with a single enantiomer of a chiral reagent, Y. The process of resolution requires three steps:

[1] Reaction of enantiomers **A** and **B** with **Y** forms two diastereomers, **AY** and **BY.**
[2] Diastereomers **AY** and **BY** have different physical properties, so they can be separated by physical methods such as fractional distillation or crystallization.
[3] **AY** and **BY** are then re-converted to **A** and **B** by a chemical reaction. The two enantiomers **A** and **B** are now separated from each other, and resolution is complete.

Figure 27.5 Resolution of a racemic mixture by converting it to a mixture of diastereomers

Both enantiomers of *N*-acetyl alanine have a free carboxy group that can react with an amine in an acid–base reaction. If a chiral amine is used, such as (*R*)-α-methylbenzylamine, the two salts formed are diastereomers, *not* enantiomers.

Diastereomers can be physically separated from each other, so the compound that converts enantiomers to diastereomers is called a resolving agent. Either enantiomer of the resolving agent can be used.

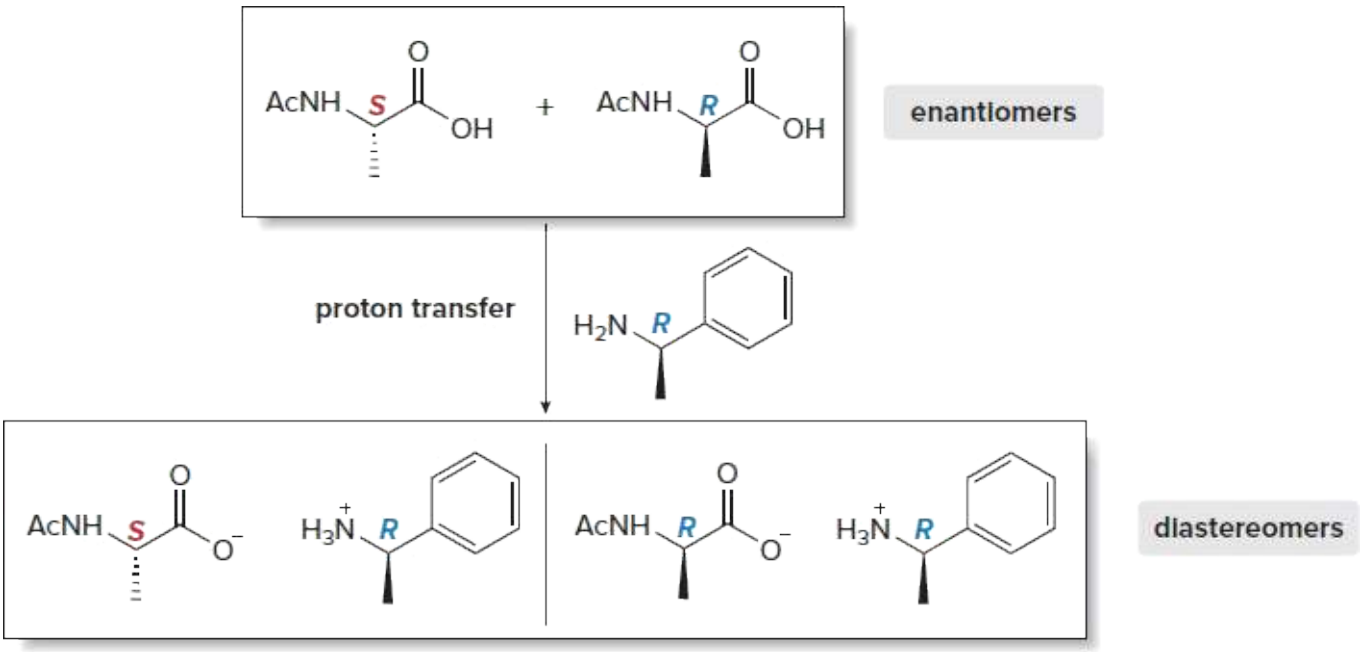


(*R*)-α-methylbenzylamine

a resolving agent

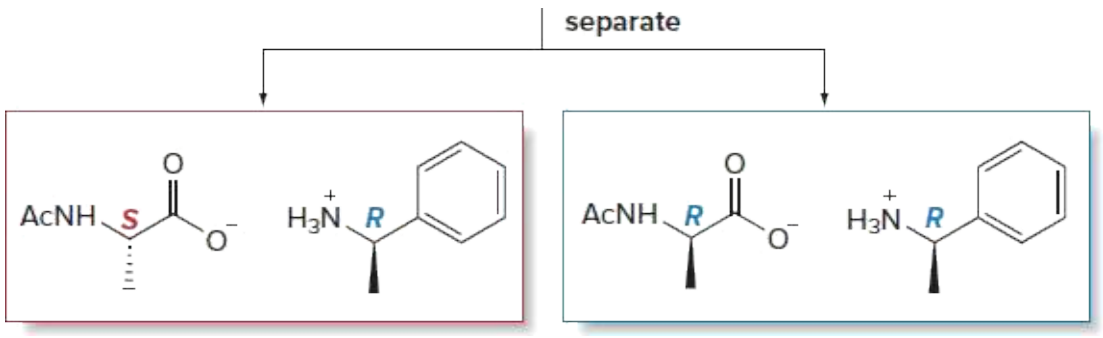
How To Use (*R*)-α-Methylbenzylamine to Resolve a Racemic Mixture of Amino Acids

Step [1] React both enantiomers of an *N*-acetyl amino acid with the *R* isomer of the chiral amine.

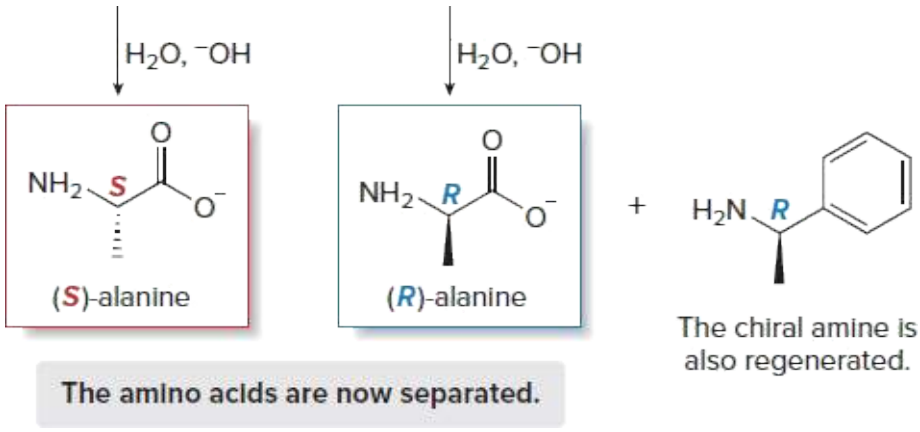


These salts have the *same* configuration around one stereogenic center, but the *opposite* configuration about the other stereogenic center.

Step [2] Separate the diastereomers.



Step [3] Regenerate the amino acid by hydrolysis of the amide.



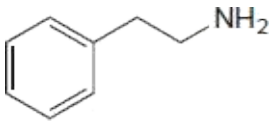
Step [1] is just an acid–base reaction in which the racemic mixture of *N*-acetyl alanines reacts with the same enantiomer of the resolving agent, in this case (*R*)-α-methylbenzylamine. The salts that form are diastereomers, *not* enantiomers, because they have the same configuration about one stereogenic center, but the opposite configuration about the other stereogenic center.

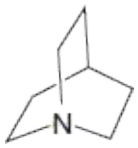
In Step [2], the diastereomers are separated by some physical technique, such as crystallization or distillation.

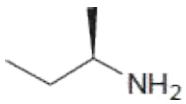
In Step [3], the amides can be hydrolyzed with aqueous base to regenerate the amino acids. The amino acids are now separated from each other. The optical activity of the amino acids can be measured and compared to their known rotations to determine the purity of each enantiomer.

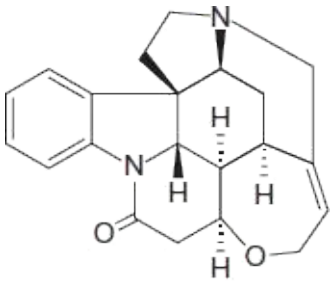
Problem 27.10

Which of the following amines can be used to resolve a racemic mixture of amino acids?

a. 

b. 

c. 

d. 

strychnine
(a powerful poison)

Problem 27.11

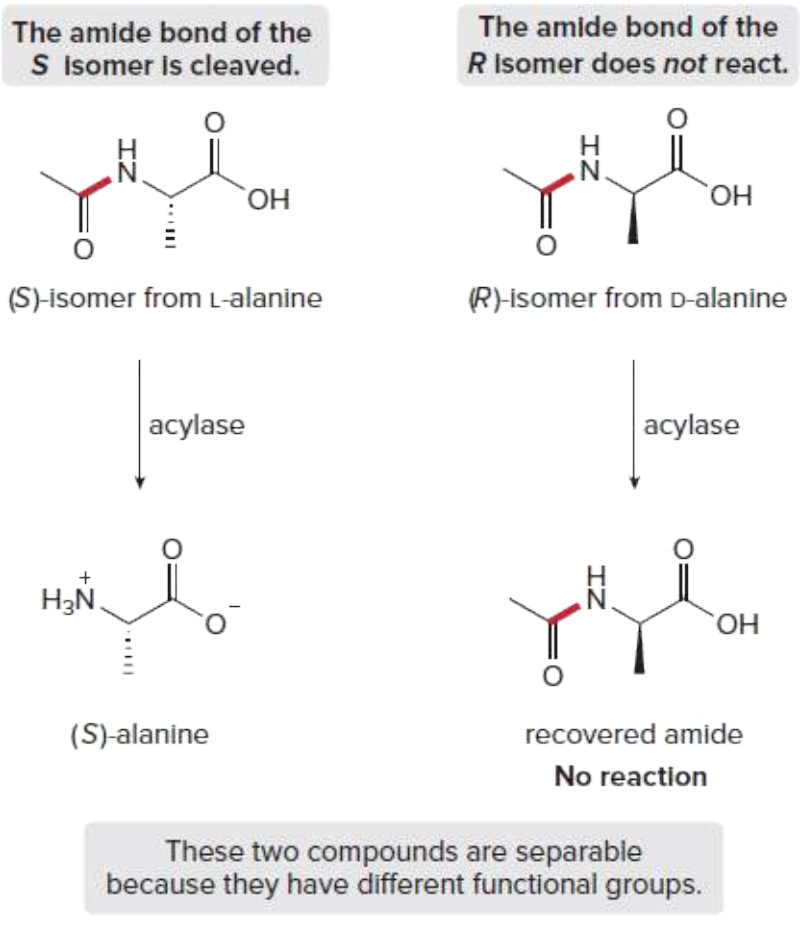
Write out a stepwise sequence that shows how a racemic mixture of leucine enantiomers can be resolved into optically active amino acids using (*R*)-α-methylbenzylamine.

27.3B Kinetic Resolution of Amino Acids Using Enzymes

A second strategy used to separate amino acids is based on the fact that two enantiomers react differently with chiral reagents. An enzyme is typically used as the chiral reagent.

To illustrate this strategy, we begin again with the two enantiomers of *N*-acetyl alanine, which were prepared by treating a racemic mixture of (*R*)- and (*S*)-alanine with acetic anhydride (Section 27.3A). Enzymes called acylases hydrolyze amide bonds, such as those found in *N*-acetyl alanine, but only for amides of L-amino acids. Thus, when a racemic mixture of *N*-acetyl alanines is treated with an acylase, only the amide of L-alanine (the *S* stereoisomer) is hydrolyzed to generate L-alanine, whereas the amide of D-alanine (the *R* stereoisomer) is untouched. The reaction mixture now consists of one amino acid and one *N*-acetyl amino acid. Because they have different functional groups with different physical properties, they can be physically separated.

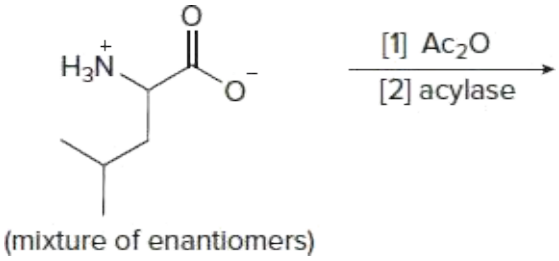
Page 1223



- **Separation of two enantiomers by a chemical reaction that selectively occurs for only one of the enantiomers is called *kinetic resolution*.**

Problem 27.12

Draw the organic products formed in the following reaction.



(mixture of enantiomers)

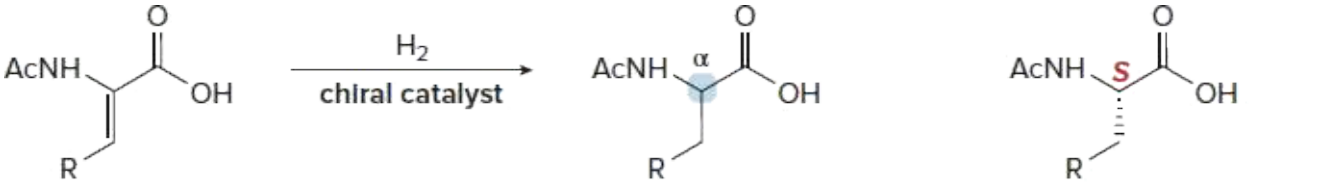
27.4 Enantioselective Synthesis of Amino Acids

Although the two methods introduced in Section 27.3 for resolving racemic mixtures of amino acids make enantiomerically pure amino acids available for further research, half of the reaction product is useless because it has the undesired configuration. Moreover, each of these procedures is costly and time-consuming.

If we use a chiral reagent to synthesize an amino acid, however, it is possible to favor the formation of the desired enantiomer over the other, without having to resort to a resolution. For example, single enantiomers of amino acids have been prepared by using enantioselective (or asymmetric) hydrogenation reactions. The success of this approach depends on finding a chiral catalyst, in much the same way that a chiral catalyst is used for the Sharpless asymmetric epoxidation (Section 12.15).

The necessary starting material is an alkene. Addition of H_2 to the double bond forms an *N*-acetyl amino acid with a new stereogenic center on the α carbon to the carboxy group. With proper choice of a chiral catalyst, the naturally occurring *S* configuration can be obtained as product.

Page 1224



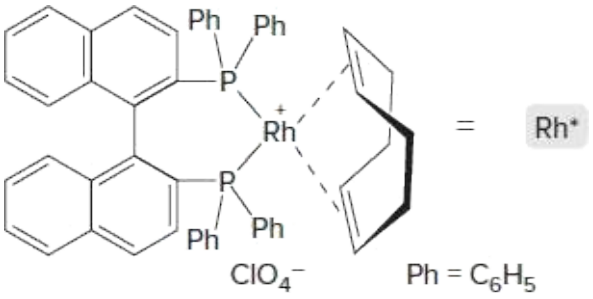
achiral alkene

new stereogenic center on the α carbon

With proper choice of catalyst, the naturally occurring *S* isomer is formed.

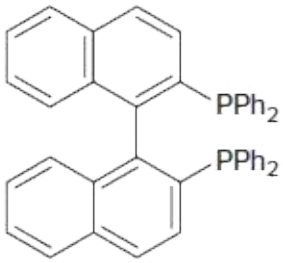
Several chiral catalysts with complex structures have now been developed for this purpose. Many contain rhodium as the metal, complexed to a chiral molecule

containing one or more phosphorus atoms. One example, abbreviated simply as Rh*, is drawn below.



chiral hydrogenation catalyst

This catalyst is synthesized from a rhodium salt and a phosphorus compound, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP). It is the BINAP moiety (Figure 27.6) that makes the catalyst chiral.



2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

BINAP

3-D model of BINAP

- The two naphthalene rings are oriented at right angles to each other, creating a rigid shape that makes the molecule chiral.

Figure 27.6 **The structure of BINAP**

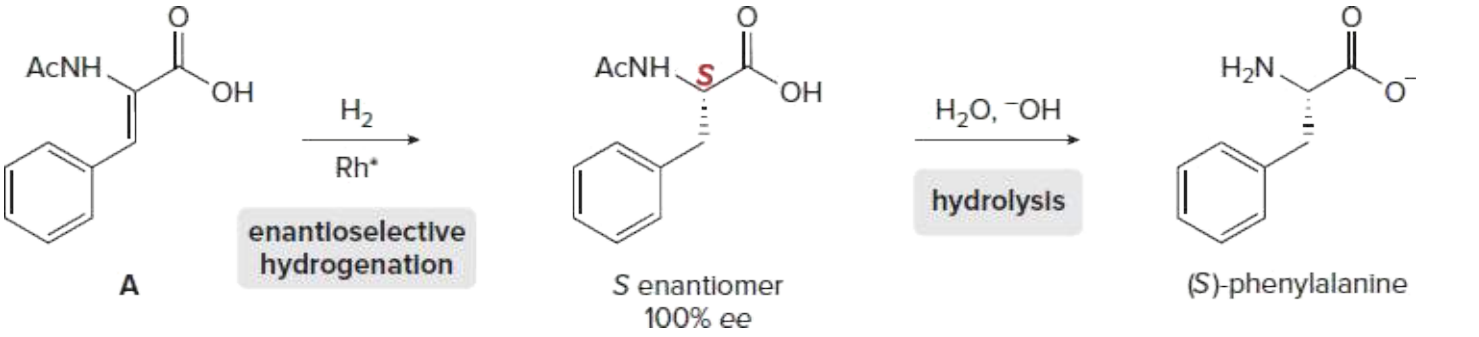
Ryoji Noyori shared the 2001 Nobel Prize in Chemistry for developing methods for asymmetric hydrogenation reactions using the chiral BINAP catalyst.

Twistoflex and helicene (Section 15.5) are two more aromatic compounds whose shape makes them chiral.

BINAP is one of a small number of molecules that is chiral even though it has no tetrahedral stereogenic centers. Its shape makes it a chiral molecule. The two naphthalene rings of the BINAP molecule are oriented at almost 90° to each other to minimize steric interactions between the hydrogen atoms on adjacent rings. This rigid

three-dimensional shape makes BINAP nonsuperimposable on its mirror image, and thus it is a chiral compound.

Enantioselective hydrogenation can be used to synthesize a single stereoisomer of phenylalanine. Treating achiral alkene A with H_2 and the chiral rhodium catalyst Rh* forms the *S* isomer of *N*-acetyl phenylalanine in 100% *ee*. Hydrolysis of the acetyl group on nitrogen then yields a single enantiomer of phenylalanine.



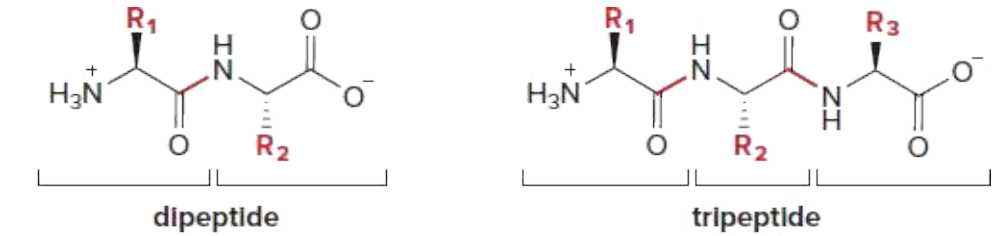
Problem 27.13

What alkene is needed to synthesize each amino acid by an enantioselective hydrogenation reaction using H_2 and Rh*: (a) alanine; (b) leucine; (c) glutamine?

27.5 Peptides

When amino acids are joined by amide bonds, they form larger molecules called peptides and proteins.

- **A *dipeptide* has two amino acids joined together by *one* amide bond.**
- **A *tripeptide* has three amino acids joined together by *two* amide bonds.**



Two amino acids joined together. Three amino acids joined together.

[Amide bonds are drawn in red.]

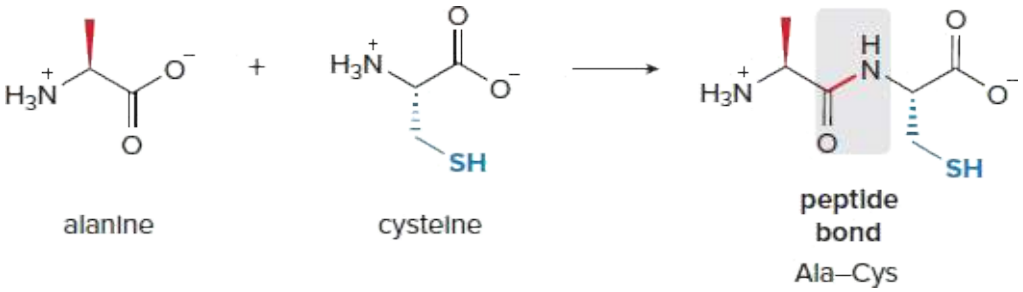
Polypeptides and proteins both have many amino acids joined in long linear chains, but the term protein is usually reserved for polymers of more than 40 amino acids.

- **The amide bonds in peptides and proteins are called *peptide bonds*.**
- **The individual amino acids are called *amino acid residues*.**

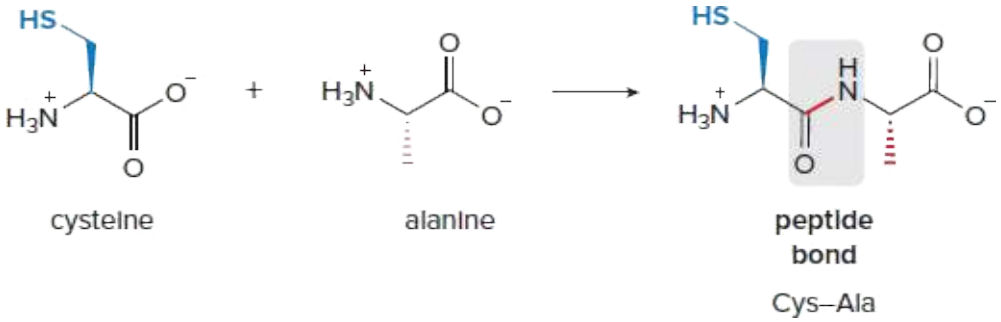
27.5A Simple Peptides

To form a dipeptide, the amino group of one amino acid forms an amide bond with the carboxy group of another amino acid. Because each amino acid has both an amino group and a carboxy group, two different dipeptides can be formed. This is illustrated with alanine and cysteine.

[1] The COO– group of alanine can combine with the NH_3^+ group of cysteine.



[2] The COO^- group of cysteine can combine with the NH_3^+ group of alanine.



These compounds are constitutional isomers of each other. Both have a free amino group (protonated as $NH3^+$) at one end of their chains and a free carboxy group (deprotonated as a carboxylate anion, COO^-) at the other.

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- **The amino acid with the free amino group is called the *N-terminal amino acid*.**
- **The amino acid with the free carboxy group is called the *C-terminal amino acid*.**

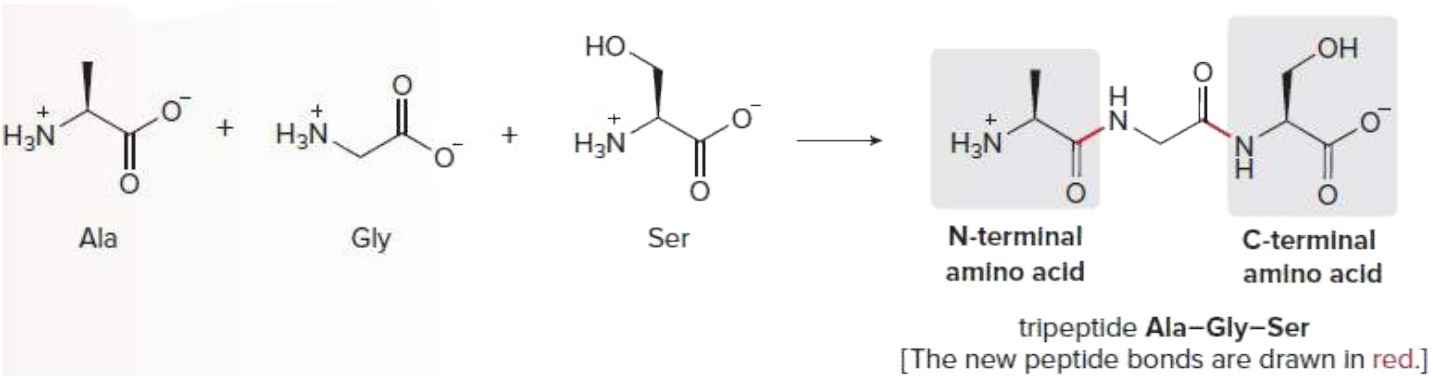
By convention, the *N*-terminal amino acid is always written at the *left* end of the chain and the C-terminal amino acid at the *right*. The peptide can be abbreviated by writing the one- or three-letter symbols for the amino acids in the chain from the *N*-terminal to the C-terminal end. Thus, Ala–Cys has alanine at the N-terminal end and cysteine at the C-terminal end, whereas Cys–Ala has cysteine at the N-terminal end and alanine at the C-terminal end. Sample Problem 27.1 shows how this convention applies to a tripeptide.

Sample Problem 27.1 Drawing the Structure of a Peptide from Three-Letter Symbols

Draw the structure of the following tripeptide, and label its N-terminal and C-terminal amino acids: Ala–Gly–Ser.

Solution

Draw the structures of the amino acids in order from left to right, placing the COO^- of one amino acid *next* to the NH_3^+ group of the adjacent amino acid. Always draw the NH_3^+ group on the *left* and the COO^- group on the *right.* Then, join adjacent COO^- and NH_3^+ groups together in amide bonds to form the tripeptide.



tripeptide **Ala–Gly–Ser**
[The new peptide bonds are drawn in red.]

The N-terminal amino acid is alanine, and the C-terminal amino acid is serine.

Problem 27.14

Draw the structure of each peptide. Label the N-terminal and C-terminal amino acids and all amide bonds.

a. Val–Glu

b. Gly–His–Leu

c. M–A–T–T

More Practice:

Try Problems 27.28a; 27.51; 27.52b, d.

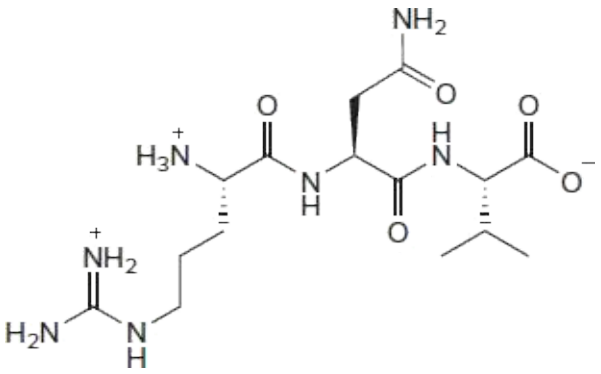
The tripeptide in Sample Problem 27.1 has one N-terminal amino acid, one C-terminal amino acid, and two peptide bonds.

- No matter how many amino acid residues are present, there is only *one* N-terminal amino acid and *one* C-terminal amino acid.
- For *n* amino acids in the chain, the number of amide bonds is *n* − 1.

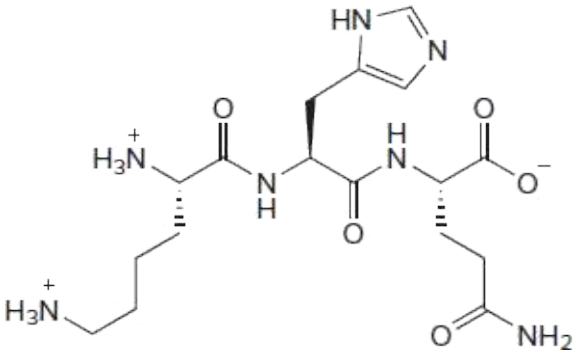
Problem 27.15

Name each peptide using both the one-letter and the three-letter abbreviations for the names of the component amino acids.

a.



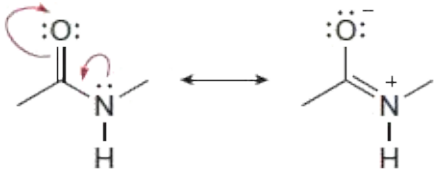
b.



Recall from Section 14.6 that buta-1,3-diene can also exist as s-cis and s-trans conformations. In buta-1,3-diene, the s-cis conformation has the two double bonds on the same side of the single bond (dihedral angle = 0°), whereas the s-trans conformation has them on opposite sides (dihedral angle = 180°).

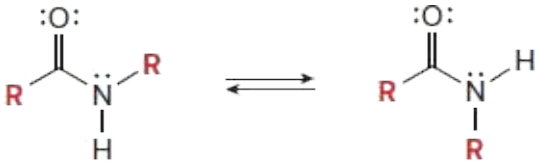
27.5B The Peptide Bond

The carbonyl carbon of an amide is sp^2 hybridized and has trigonal planar geometry. A second resonance structure can be drawn that delocalizes the nonbonded electron pair on the N atom. Amides are more resonance stabilized than other acyl compounds, so the resonance structure having the C=N makes a significant contribution to the hybrid.



two resonance structures for the peptide bond

Resonance stabilization has important consequences. Rotation about the C–N bond is restricted because it has partial double-bond character. As a result, there are two possible conformations.

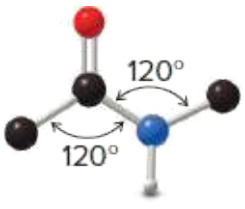


s-trans *s*-cis

- **The s-trans conformation has the two R groups oriented on *opposite* sides of the C–N bond.**
- **The s-cis conformation has the two R groups oriented on the *same* side of the C–N bond.**
- **The *s*-trans conformation of a peptide bond is typically more stable than the *s*-cis, because the *s*-trans has the two bulky R groups located farther from each other.**

The planar geometry of the peptide bond is analogous to the planar geometry of ethylene (or any other alkene), where the double bond between sp^2 hybridized carbon atoms makes all of the bond angles ~120° and puts all six atoms in the same plane.

A second consequence of resonance stabilization is that all six atoms involved in the peptide bond lie in the same plane. All bond angles are ~120°, and the C=O and N–H bonds are oriented 180° from each other.

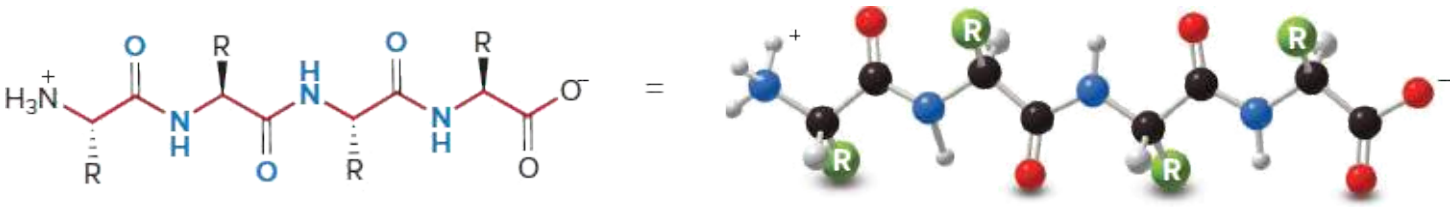


These six atoms lie in a plane.

The structure of a tetrapeptide illustrates the results of these effects in a long peptide

chain.

- **The s-trans arrangement makes a long chain with a zigzag arrangement.**
- **In each peptide bond, the N–H and C=O bonds lie parallel and at 180° with respect to each other.**



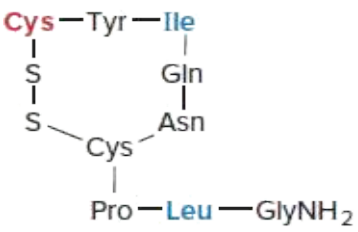
tetrapeptide

27.5C Interesting Peptides

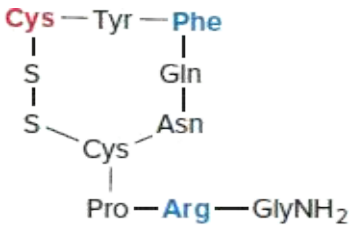
Even relatively simple peptides can have important biological functions. Bradykinin, for example, is a peptide hormone composed of nine amino acids. It stimulates smooth muscle contraction, dilates blood vessels, and causes pain. Bradykinin is a component of bee venom.

Arg–Pro–Pro–Gly–Phe–Ser–Pro–Phe–Arg
bradykinin

Oxytocin and vasopressin are nonapeptide hormones, too. Their sequences Page 1228 are identical except for two amino acids, yet this is enough to give them very different biological activities. As mentioned in the chapter opener, oxytocin induces labor by stimulating the contraction of uterine muscles, and it stimulates the flow of milk in nursing mothers. Vasopressin, on the other hand, controls blood pressure by regulating smooth muscle contraction. The N-terminal amino acid in both hormones is a cysteine residue, and the C-terminal residue is glycine. Instead of a free carboxy group, both peptides have an NH_2 group in place of OH, so this is indicated with the additional NH_2 group drawn at the end of the chain.



oxytocin

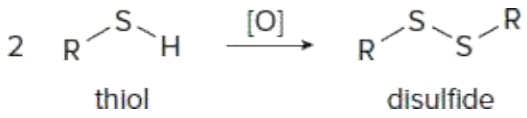


vasopressin

- The N-terminal amino acid is labeled in red.
- The amino acids that differ are labeled in blue.

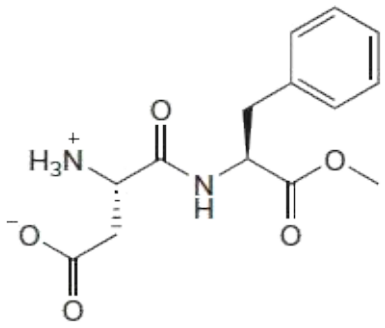
The oxidation of thiols to disulfides was discussed in Section 9.15.

The structure of both peptides includes a disulfide bond, a form of covalent bonding in which the –SH groups from two cysteine residues are oxidized to form a sulfur–sulfur bond. In oxytocin and vasopressin, the disulfide bonds make the peptides cyclic.



thiol disulfide

The artificial sweetener aspartame (Figure 26.10) is the methyl ester of the dipeptide Asp–Phe. This synthetic peptide is 180 times sweeter (on a gram-for-gram basis) than sucrose (common table sugar). Both of the amino acids in aspartame have the naturally occurring L-configuration. If the D-amino acid is substituted for either Asp or Phe, the resulting compound tastes bitter.



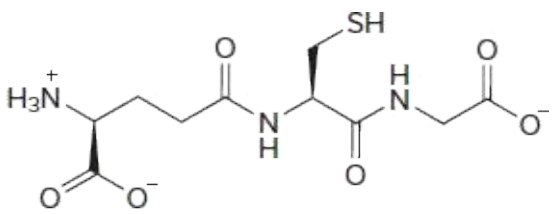
aspartame
the methyl ester of Asp–Phe
a synthetic artificial sweetener

Problem 27.16

Draw the structure of leu-enkephalin, a pentapeptide that acts as an analgesic and opiate, and has the following sequence: Tyr–Gly–Gly–Phe–Leu. (The structure of a related peptide, met-enkephalin, appeared in Section 20.5B.)

Problem 27.17

Glutathione, a powerful antioxidant that destroys harmful oxidizing agents in cells, is composed of glutamic acid, cysteine, and glycine, and has the following structure:



glutathione

a. What product is formed when glutathione reacts with an oxidizing agent?

b. What is unusual about the peptide bond between glutamic acid and cysteine?

27.6 Peptide Sequencing

To determine the structure of a peptide, we must know not only what amino acids comprise it, but also the sequence of the amino acids in the peptide chain. Although mass spectrometry has become an increasingly powerful method for the analysis of high-molecular-weight proteins (Section A.5C), chemical methods to determine peptide structure are still widely used and presented in this section.

27.6A Amino Acid Analysis

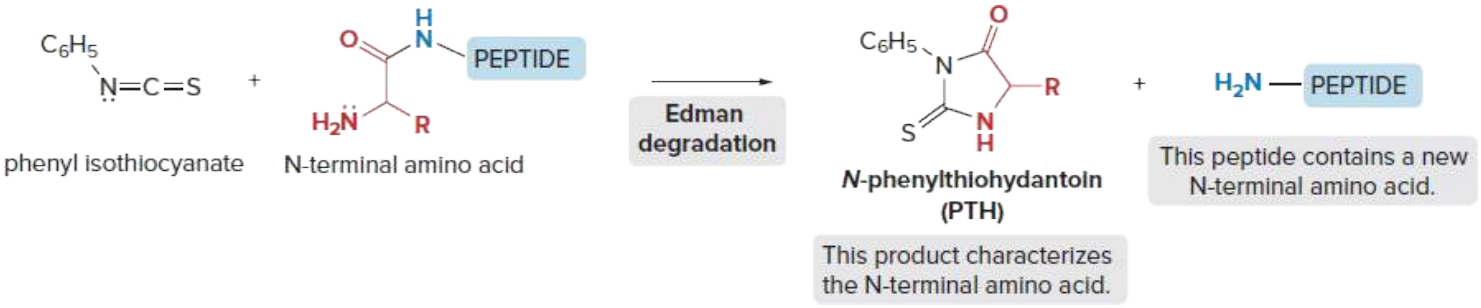
The structure determination of a peptide begins by analyzing the total amino acid composition. The amide bonds are first hydrolyzed by heating with hydrochloric acid for 24 h to form the individual amino acids. The resulting mixture is then separated using high-performance liquid chromatography (HPLC), a technique in which a solution of amino acids is placed on a column and individual amino acids move through the column at characteristic rates, often dependent on polarity.

This process determines both the identity of the individual amino acids and the amount of each present, but it tells nothing about the order of the amino acids in the peptide. For example, complete hydrolysis and HPLC analysis of the tetrapeptide Gly–Gly–Phe–Tyr would indicate the presence of three amino acids—glycine, phenylalanine, and tyrosine—and show that there are twice as many glycine residues as phenylalanine or tyrosine residues. The exact order of the amino acids in the peptide chain must then be determined by additional methods.

27.6B Identifying the N-Terminal Amino Acid—The Edman Degradation

To determine the sequence of amino acids in a peptide chain, a variety of procedures are often combined. One especially useful technique is to identify the N-terminal amino acid using the Edman degradation. In the Edman degradation, amino acids are cleaved one at a time from the N-terminal end, the identity of the amino acid determined, and the process repeated until the entire sequence is known. Automated sequencers using this methodology are now available to sequence peptides containing up to about 50 amino acids.

The Edman degradation is based on the reaction of the nucleophilic NH_2 group of the N-terminal amino acid with the electrophilic carbon of phenyl isothiocyanate, $C_6H_5N{=}C{=}S$. When the N-terminal amino acid is removed from the peptide chain, two products are formed: an *N*-phenylthiohydantoin (PTH) and a new peptide with one *fewer* amino acid.



The *N*-phenylthiohydantoin derivative contains the atoms of the N-terminal amino acid. This product identifies the N-terminal amino acid in the peptide because the PTH derivatives of all 20 naturally occurring amino acids are known and characterized. The new peptide formed in the Edman degradation has one fewer amino acid than the original peptide. Moreover, it contains a new N-terminal amino acid, so the process can be repeated.

Mechanism 27.2 illustrates some of the key steps of the Edman degradation. The nucleophilic N-terminal NH_2 group adds to the electrophilic carbon of phenyl isothiocyanate to form an *N*-phenylthiourea, the product of nucleophilic addition (Part [1]). Intramolecular cyclization followed by elimination results in cleavage of the terminal amide bond in Part [2] to form a new peptide with one fewer amino acid. A sulfur heterocycle, called a thiazolinone, is also formed, which rearranges by a multistep pathway to form an *N*-phenylthiohydantoin. The R group in this product identifies the amino acid located at the N-terminal end.

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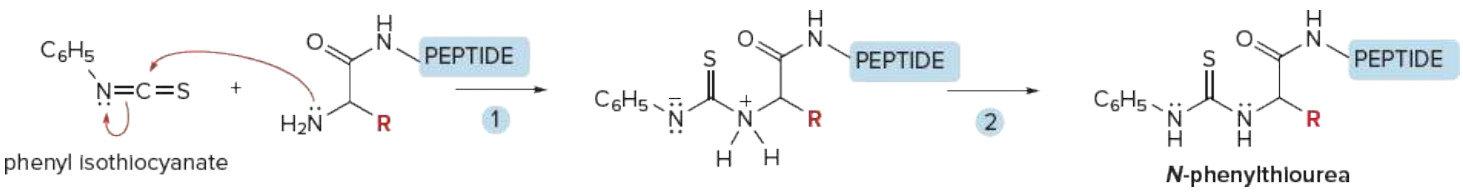
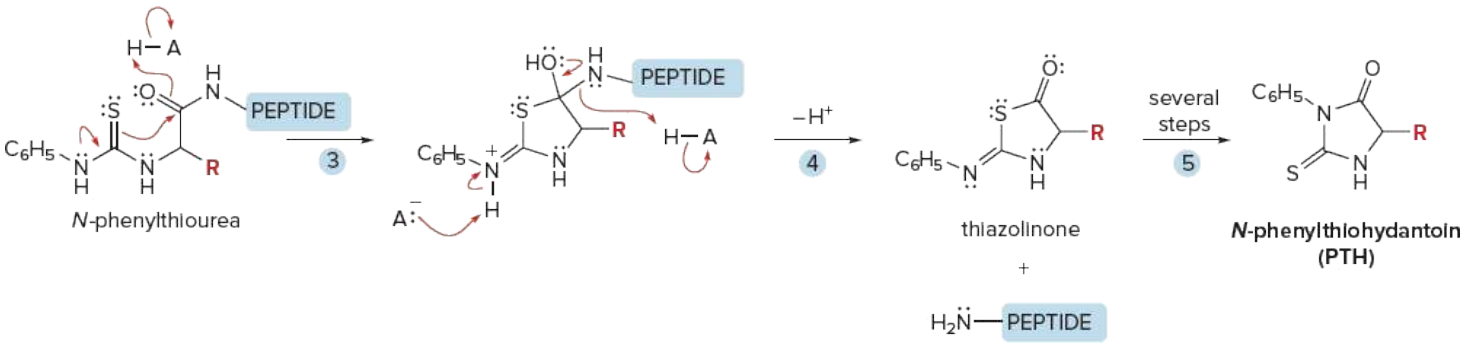
Mechanism 27.2 Edman Degradation

Part [1] Formation of an *N*-phenylthiourea



1 – 2 Addition of the amino group of the N-terminal amino acid to phenyl isothiocyanate followed by proton transfer forms an *N*-phenylthiourea.

Part [2] Formation of the N-terminal amino acid and *N*-phenylthiohydantoin (PTH)



3 **Nucleophilic addition of the S atom to the amide carbonyl forms a five-membered ring.**

4 **Loss of the amino group forms two products—a thiazolinone ring and a peptide chain that contains one fewer amino acid than the original peptide.**

5 **The thiazolinone rearranges by a multistep pathway to form an *N*-phenylthiohydantoin (PTH) that contains the original amino acid.**

In theory a protein of any length can be sequenced using the Edman degradation, but in practice, the accumulation of small quantities of unwanted by-products limits sequencing to proteins having fewer than approximately 50 amino acids.

Problem 27.18

Draw the structure of the *N*-phenylthiohydantoin formed by initial Edman degradation of each peptide: (a) Ala–Gly–Phe–Phe; (b) Val–Ile–Tyr.

27.6C Partial Hydrolysis of a Peptide

Additional structural information can be obtained by cleaving some, but not all, of the amide bonds in a peptide. Partial hydrolysis of a peptide with acid forms smaller fragments in a random fashion. Sequencing these peptides and identifying sites of overlap can be used to determine the sequence of the complete peptide, as shown in Sample Problem 27.2.

Sample Problem 27.2 Determining the Amino Acid Sequence of a Peptide Using Partial Hydrolysis

Give the amino acid sequence of a hexapeptide that contains the amino

acids Ala, Val, Ser, Ile, Gly, Tyr, and forms the following fragments when partially hydrolyzed with HCl: Gly–Ile–Val, Ala–Ser–Gly, and Tyr–Ala.

Solution

Looking for points of overlap in the sequences of the smaller fragments shows how the fragments should be pieced together. In this example, the fragment Ala–Ser–Gly contains amino acids common to the two other fragments, thus showing how the three fragments can be joined together.

Problem 27.19

Give the amino acid sequence of an octapeptide that contains the amino acids Tyr, Ala, Leu (2 equiv), Cys, Gly, Glu, and Val, and forms the following fragments when partially hydrolyzed with HCl: Val–Cys–Gly–Glu, Ala–Leu–Tyr, and Tyr–Leu–Val–Cys.

More Practice:

Try Problem 27.57.

Peptides can also be hydrolyzed at specific sites using enzymes. The enzyme carboxypeptidase catalyzes the hydrolysis of the amide bond nearest the C-terminal end, forming the C-terminal amino acid and a peptide with one fewer amino acid. In this way, carboxypeptidase is used to identify the C-terminal amino acid.

Other enzymes catalyze the hydrolysis of amide bonds formed with specific amino acids. For example:

- **Trypsin catalyzes the hydrolysis of amides with a carbonyl group that is part of the basic amino acids arginine and lysine.**
- **Chymotrypsin hydrolyzes amides with carbonyl groups that are part of the aromatic amino acids phenylalanine, tyrosine, and tryptophan.**

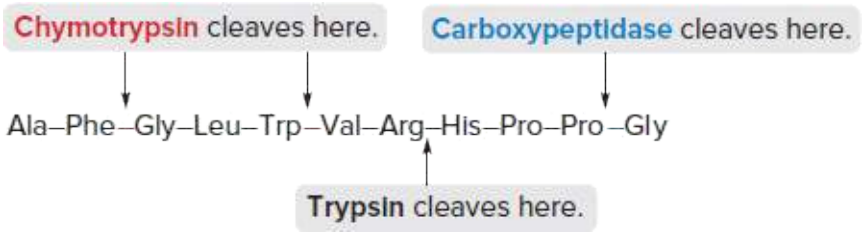


Table 27.2 summarizes these enzyme specificities used in peptide sequencing.

Table 27.2 Cleavage Sites of Specific Enzymes in Peptide Sequencing

Enzyme	Site of cleavage
Carboxypeptidase	Amide bond nearest to the C-terminal amino acid
Chymotrypsin	Amide bond with a carbonyl group from Phe, Tyr, or Trp
Trypsin	Amide bond with a carbonyl group from Arg or Lys

Problem 27.20

(a) What products are formed when each peptide is treated with trypsin? (b) What products are formed when each peptide is treated with chymotrypsin?

[1] Gly–Ala–Phe–Leu–Lys–Ala

[2] Phe–Tyr–Gly–Cys–Arg–Ser

[3] Thr–Pro–Lys–Glu–His–Gly–Phe–Cys–Trp–Val–Val–Phe

Sample Problem 27.3 Deducing the Sequence of a Peptide

Deduce the sequence of a pentapeptide that contains the amino acids Ala, Glu, Gly, Ser, and Tyr, from the following experimental data. Edman degradation cleaves Gly from the pentapeptide, and carboxypeptidase forms Ala and a tetrapeptide. Treatment of the pentapeptide with chymotrypsin forms a dipeptide and a tripeptide. Partial hydrolysis forms Gly, Ser, and the tripeptide Tyr–Glu–Ala.

Solution

Use each result to determine the location of an amino acid in the pentapeptide.

Experiment		Result
• Edman degradation identifies the N-terminal amino acid–in this case, Gly.	→	Gly– _ – _ – _ – _

- **Carboxypeptidase identifies the C-terminal amino acid (Ala) when it is cleaved from the end of the chain.** → Gly– _ – _ – _ –**Ala**
- **Chymotrypsin cleaves amide bonds that contain a carbonyl group from an aromatic amino acid–Tyr in this case. Because a dipeptide and a tripeptide are obtained after treatment with chymotrypsin, Tyr must be the C-terminal amino acid of either the di- or tripeptide. As a result, Tyr must be either the second or third amino acid in the pentapeptide chain.** → Gly–**Tyr**– _ – _ –Ala
  or
  Gly– _ –**Tyr**– _ –Ala
- **Partial hydrolysis forms the tripeptide Tyr–Glu–Ala. Because Ala is the C-terminal amino acid, this result identifies the last three amino acids in the chain.** → Gly– _ –**Tyr–Glu**–Ala
- **The last amino acid, Ser, must be located at the only remaining position, the second amino acid in the pentapeptide, and the complete sequence is determined.** → Gly–**Ser**–Tyr–Glu–Ala

Problem 27.21

Deduce the sequence of a heptapeptide that contains the amino acids Ala, Arg, Glu, Gly, Leu, Phe, and Ser, from the following experimental data. Edman degradation cleaves Leu from the heptapeptide, and carboxypeptidase forms Glu and a hexapeptide. Treatment of the heptapeptide with chymotrypsin forms a hexapeptide and a single amino acid. Treatment of the heptapeptide with trypsin forms a pentapeptide and a dipeptide. Partial hydrolysis forms Glu, Leu, Phe, and the tripeptides Gly–Ala–Ser and Ala–Ser–Arg.

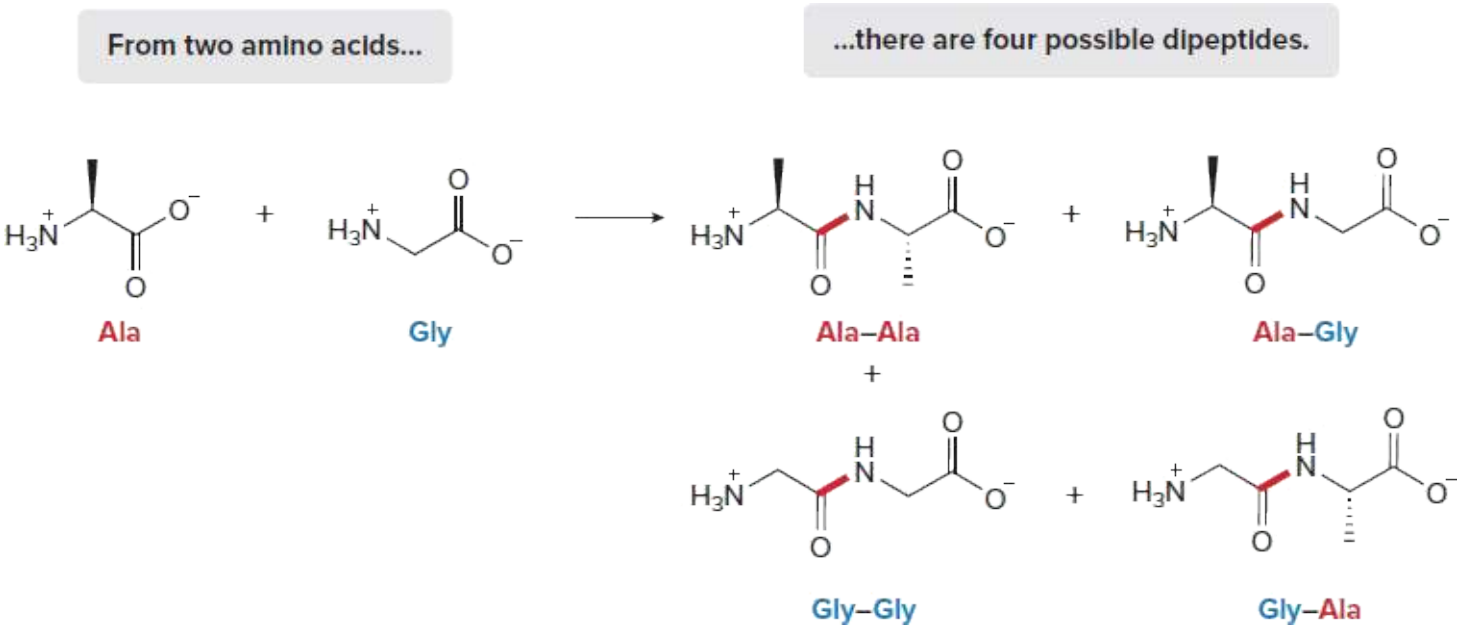
More Practice:

Try Problems 27.56–27.60.

27.7 Peptide Synthesis

The synthesis of a specific dipeptide, such as Ala–Gly from alanine and glycine, is complicated because both amino acids have two functional groups. As a result, four

products—namely, Ala–Ala, Ala–Gly, Gly–Gly, and Gly–Ala—are possible.

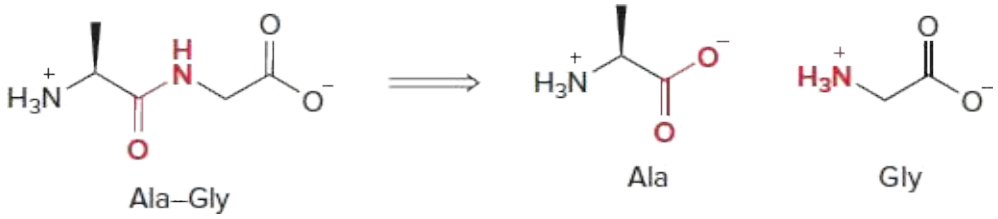


How do we selectively join the COOH group of alanine with the NH_2 group of glycine? Page 1233

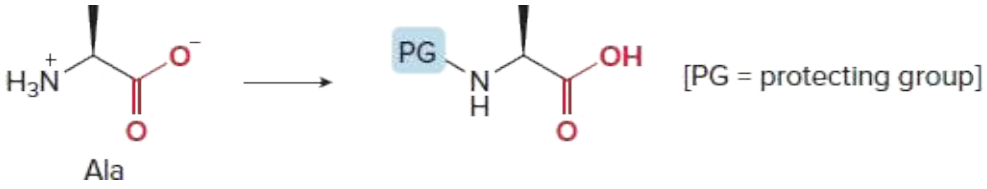
- **Protect the functional groups that we don't want to react, and then form the amide bond.**

How To Synthesize a Dipeptide from Two Amino Acids

Example

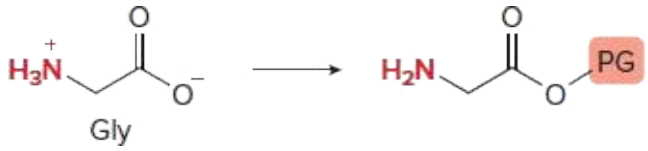


Step [1] Protect the NH_2 group of alanine.



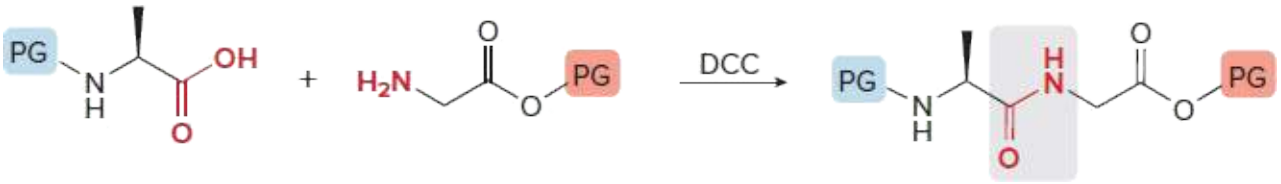
- **In the neutral amino acid, the NH_2 group exists largely as an ammonium ion, $-NH_3^+$.**

Step [2] Protect the COOH group of glycine.

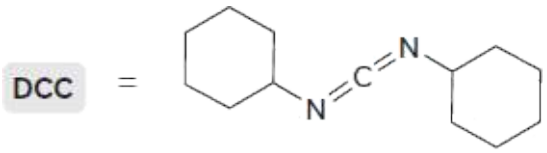


- **In the neutral amino acid, the COOH group exists largely as a carboxylate anion, $-COO^-$.**

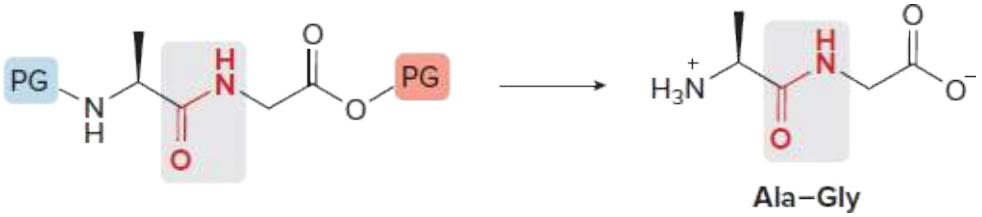
Step [3] Form the amide bond with DCC.



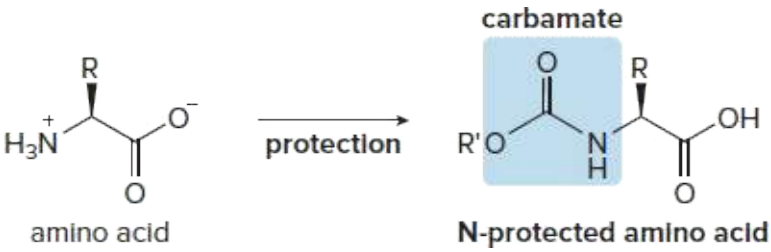
Dicyclohexylcarbodiimide (DCC) is a reagent commonly used to form amide bonds (see Section 20.9D). DCC makes the OH group of the carboxylic acid a better leaving group, thus activating the carboxy group toward nucleophilic attack.



Step [4] Remove one or both protecting groups.

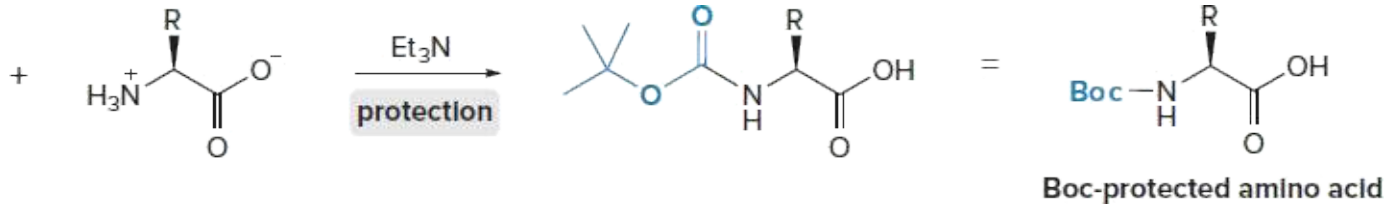


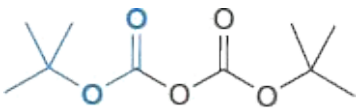
Two widely used amino protecting groups convert an amine to a carbamate, Page 1234 a functional group having a carbonyl bonded to both an oxygen and a nitrogen atom. Because the N atom of the carbamate is bonded to a carbonyl group, the protected amino group is no longer nucleophilic.



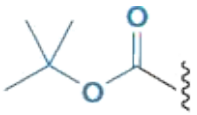
For example, the *tert*-butoxycarbonyl protecting group, abbreviated as Boc, is formed

by reacting the amino acid with di-*tert*-butyl dicarbonate in a nucleophilic acyl substitution reaction.



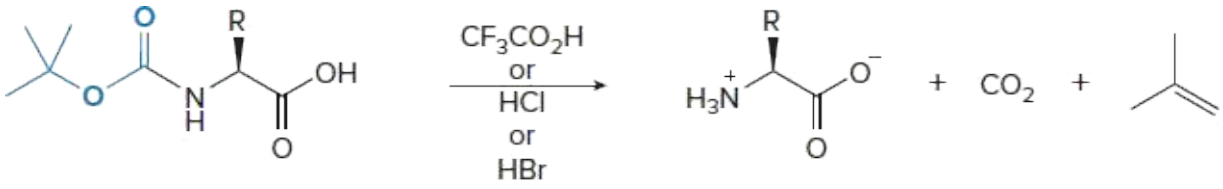


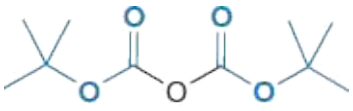
di-*tert*-butyl dicarbonate



tert-butoxycarbonyl
Boc

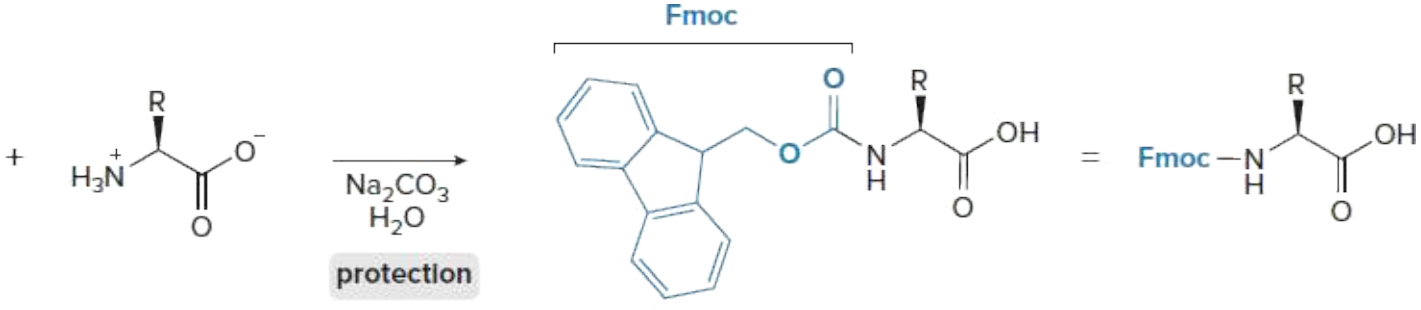
To be a useful protecting group, the Boc group must be removed under reaction conditions that do not affect other functional groups in the molecule. It can be removed with an acid such as trifluoroacetic acid, HCl, or HBr.

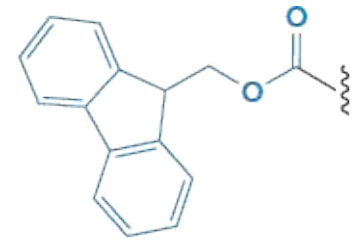




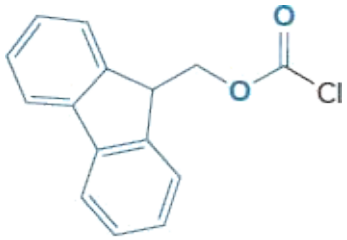
(Boc)$_2$O

A second amino protecting group, the 9-fluorenylmethoxycarbonyl protecting group, abbreviated as Fmoc, is formed by reacting the amino acid with 9-fluorenylmethyl chloroformate in a nucleophilic acyl substitution reaction.



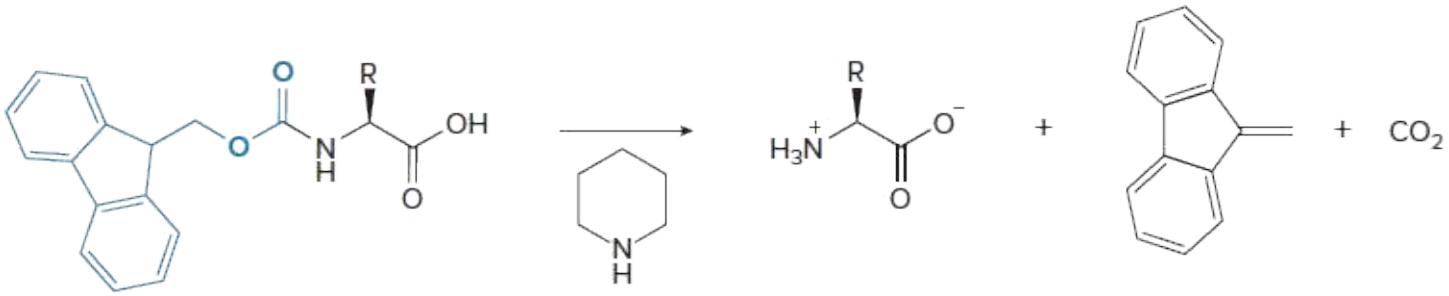


9-fluorenylmethoxycarbonyl
Fmoc



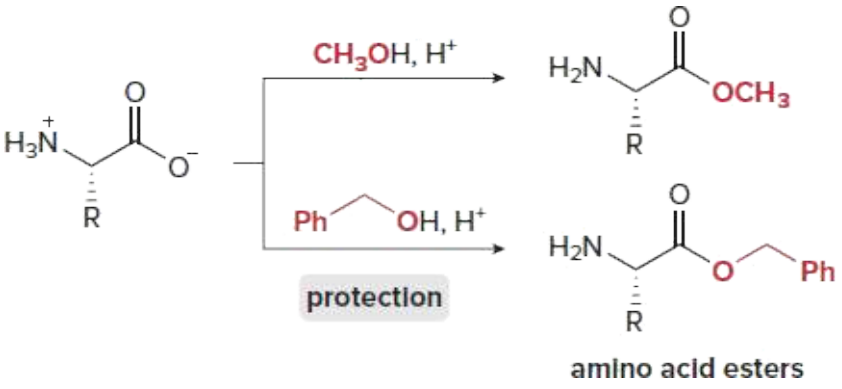
9-fluorenylmethyl
chloroformate
Fmoc—Cl

Although the Fmoc protecting group is stable to most acids, it can be removed by treatment with base (NH_3 or an amine).

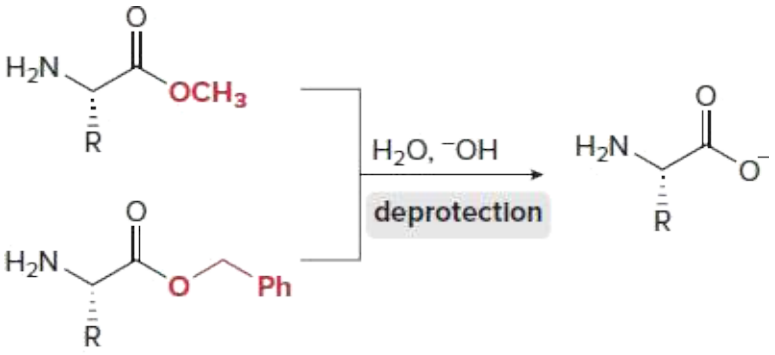


The carboxy group is usually protected as a methyl or benzyl ester by reaction with an alcohol and an acid.

Page 1235

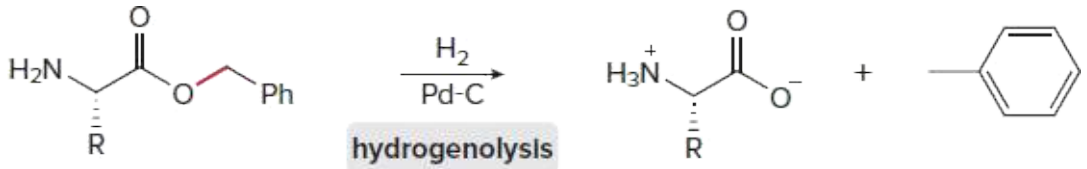


These esters are usually removed by hydrolysis with aqueous base.



amino acid esters

One advantage of using a benzyl ester for protection is that it can also be removed with H_2 in the presence of a Pd catalyst. This process is called hydrogenolysis. These conditions are especially mild, because they avoid the use of either acid or base. Benzyl esters can also be removed with HBr in acetic acid.

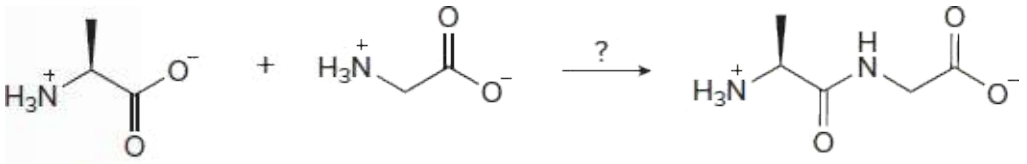


The benzylic C–O bond (in red) is cleaved.

The specific reactions needed to synthesize the dipeptide Ala–Gly are illustrated in Sample Problem 27.4.

Sample Problem 27.4 Devising the Synthesis of a Dipeptide

Draw out the steps in the synthesis of the dipeptide Ala–Gly.

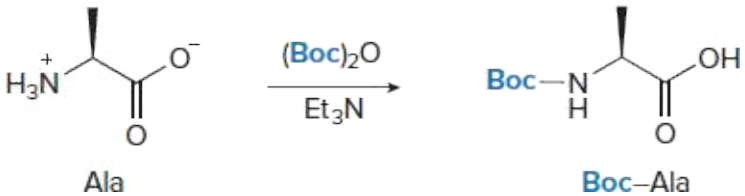


Ala Gly Ala–Gly

Solution

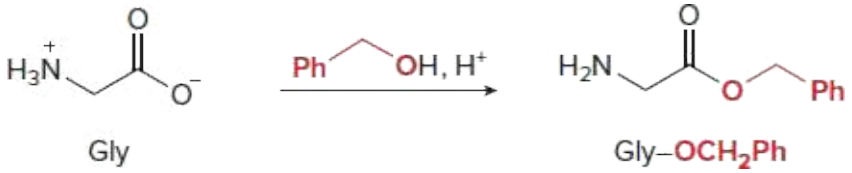
Page 1236

Step [1] Protect the NH_2 group of alanine using a Boc group.

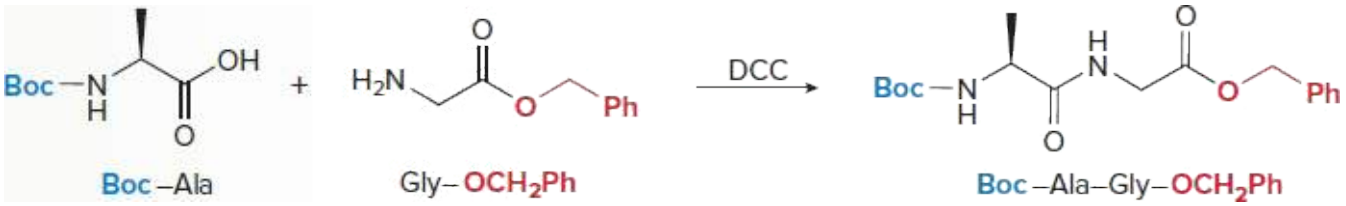


Ala Boc–Ala

Step [2] Protect the COOH group of glycine as a benzyl ester.

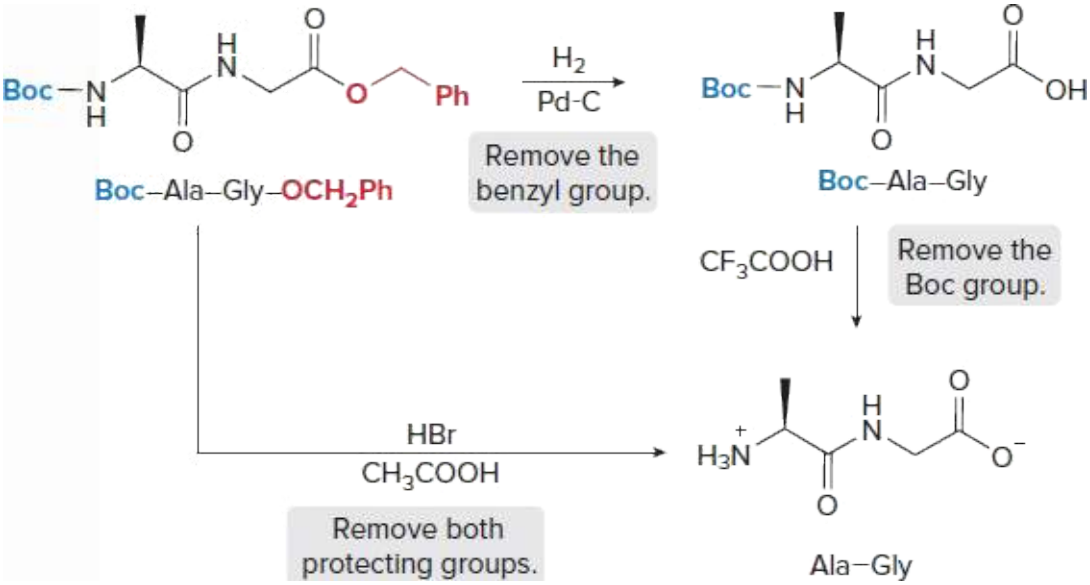


Step [3] Form the amide bond with DCC.



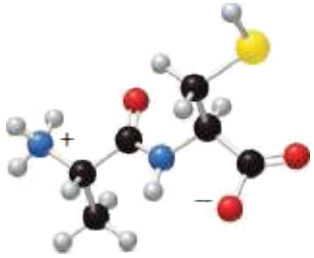
Step [4] Remove one or both protecting groups.

The protecting groups can be removed in a stepwise fashion or in a single reaction.



Problem 27.22

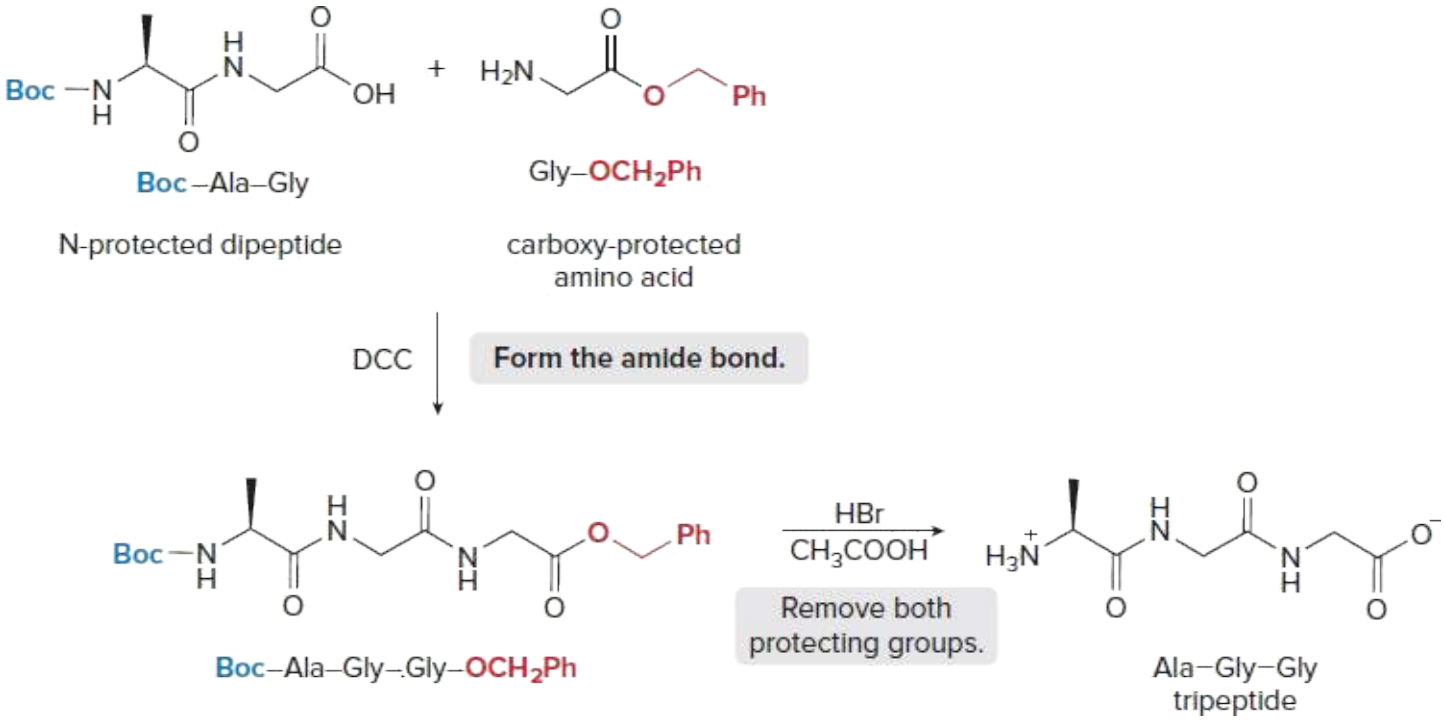
Devise a synthesis of the following dipeptide from amino acid starting materials.



More Practice:

Try Problems 27.29, 27.62.

This method can be applied to the synthesis of tripeptides and even larger polypeptides. After the protected dipeptide is prepared in Step [3], only one of the protecting groups is removed, and this dipeptide is coupled to a third amino acid with one of its functional groups protected, as illustrated in the following equations.



Problem 27.23

Devise a synthesis of each peptide from amino acid starting materials: (a) Leu–Val; (b) Ala–Ile–Gly.

Development of the solid phase technique earned Merrifield the 1984 Nobel Prize in Chemistry and has made possible the synthesis of many polypeptides and proteins.

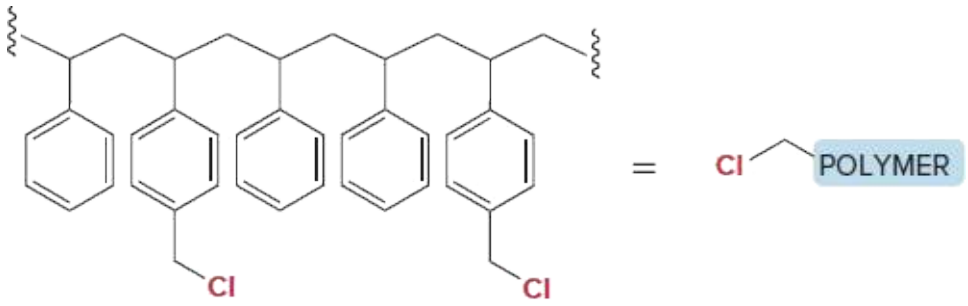
27.8 Automated Peptide Synthesis

The method described in Section 27.7 works well for the synthesis of small peptides. It is extremely time-consuming to synthesize larger proteins by this strategy, however, because each step requires isolation and purification of the product. The synthesis of larger polypeptides is usually accomplished by using the solid phase technique originally developed by R. Bruce Merrifield of Rockefeller University.

In the Merrifield method, an amino acid is attached to an insoluble polymer. Amino acids are sequentially added, one at a time, thereby forming successive peptide bonds. Because impurities and by-products are not attached to the polymer chain, they are

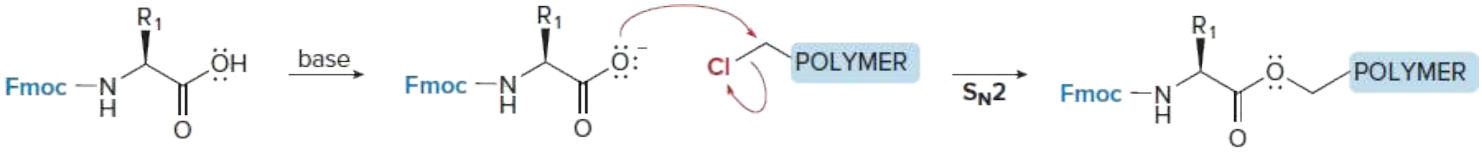
removed simply by washing them away with a solvent at each stage of the synthesis.

A commonly used polymer is a polystyrene derivative that contains $-CH_2Cl$ groups bonded to some of the benzene rings in the polymer chain. The Cl atoms serve as handles that allow attachment of amino acids to the chain.



polystyrene derivative with Cl leaving groups

An Fmoc-protected amino acid is attached to the polymer at its carboxy group by an S_N2 reaction.

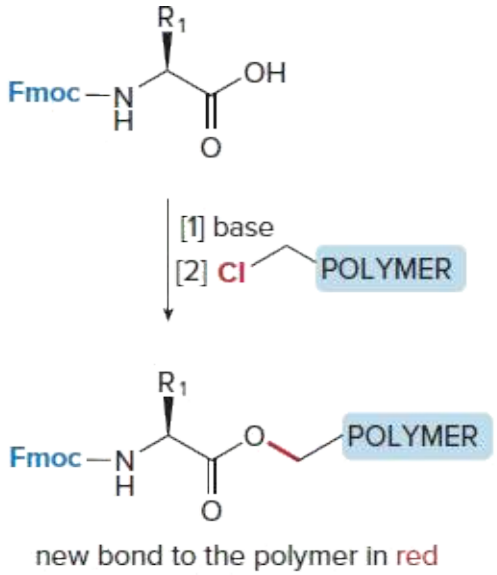


The amino acid is now bound to the insoluble polymer.

Once the first amino acid is bound to the polymer, additional amino acids Page 1238 can be added sequentially. The steps of the solid phase peptide synthesis technique are illustrated in the accompanying scheme. In the last step, HF cleaves the polypeptide chain from the polymer.

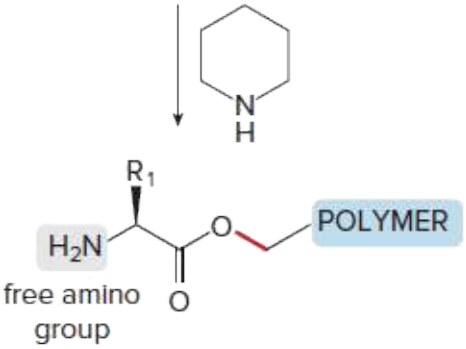
How To Synthesize a Peptide Using the Merrifield Solid Phase Technique

Step [1]
Attach an Fmoc-protected amino acid to the polymer.

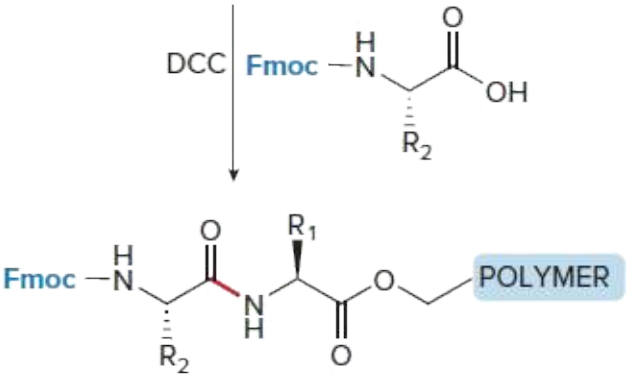


new bond to the polymer in red

Step [2]
Remove the protecting group.

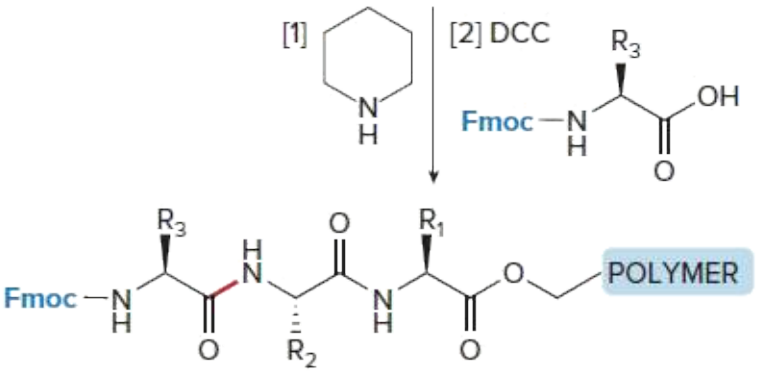


Step [3]
Form the amide bond with DCC.



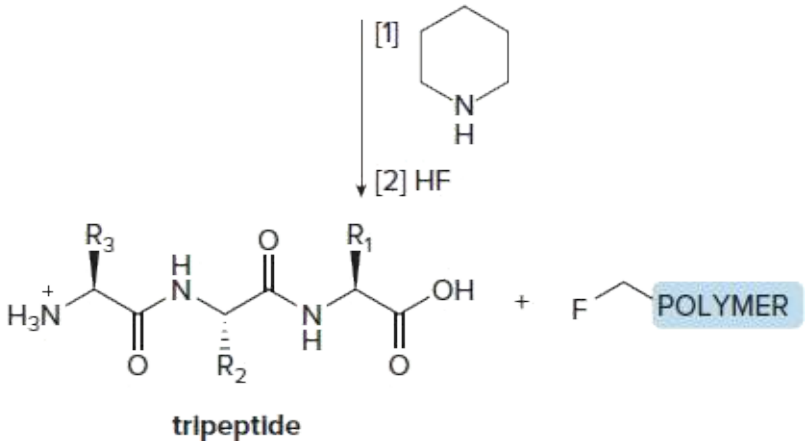
new amide bond in red

Step [4]
Repeat Steps [2] and [3].



new amide bond in red

Step [5]
Remove the protecting group and detach the peptide from the polymer.



tripeptide

The Merrifield method has now been completely automated, so it is possible to purchase peptide synthesizers that automatically carry out all of the above operations and form polypeptides in high yield in a matter of hours, days, or weeks, depending on the length of the chain of the desired product. For example, the protein ribonuclease, which contains 128 amino acids, has been prepared by this technique in an overall yield of 17%. This remarkable synthesis involved 369 separate reactions, and thus the yield of each individual reaction was > 99%.

Problem 27.24

Outline the steps needed to synthesize the tetrapeptide Ala–Leu–Ile–Gly using the Merrifield technique.

27.9 Protein Structure

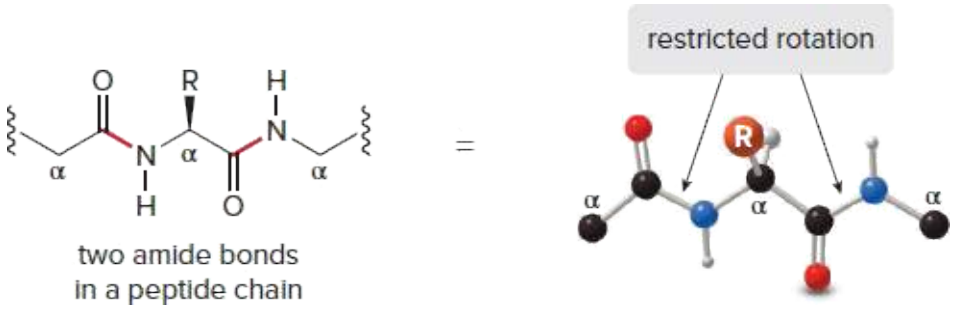
Now that you have learned some of the chemistry of amino acids, it's time to study proteins, the large polymers of amino acids that are responsible for so much of the structure and function of all living cells. We begin with a discussion of the primary, secondary, tertiary, and quaternary structure of proteins.

27.9A Primary Structure

The *primary structure* of proteins is the particular sequence of amino acids that is joined by peptide bonds. The most important element of this primary structure is the amide bond.

- **Rotation around the amide C–N bond is *restricted* because of electron delocalization, and the s-trans conformation is the more stable arrangement.**
- **In each peptide bond, the N–H and C=O bonds are directed 180° from**

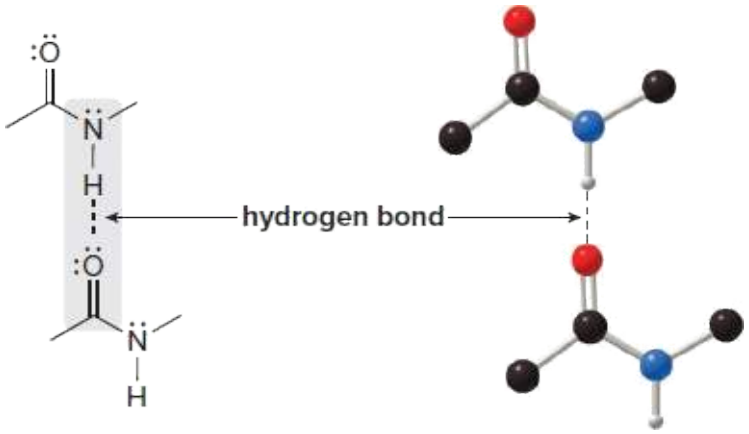
each other.



Although rotation about the amide bonds is restricted, rotation about the other σ bonds in the protein backbone is not. As a result, the peptide chain can twist and bend into a variety of different arrangements that constitute the secondary structure of the protein.

27.9B Secondary Structure

The three-dimensional conformations of localized regions of a protein are called its *secondary structure*. These regions arise due to hydrogen bonding between the N–H proton of one amide and the C=O oxygen of another. Two arrangements that are particularly stable are called the α-helix and the β-pleated sheet.



α-Helix

The α-helix forms when a peptide chain twists into a right-handed or clockwise spiral, as shown in Figure 27.7. Four important features of the α-helix are as follows:

[1] Each turn of the helix has 3.6 amino acids.

[2] The N–H and C=O bonds point along the axis of the helix. All C=O bonds point in one direction, and all N–H bonds point in the opposite direction.

[3] The C=O group of one amino acid is hydrogen bonded to an N–H group four amino acid residues farther along the chain. Thus, hydrogen bonding occurs between two amino acids *in the same chain*. Note, too, that the hydrogen bonds

are parallel to the axis of the helix.

[4] The R groups of the amino acids extend outward from the core of the helix.

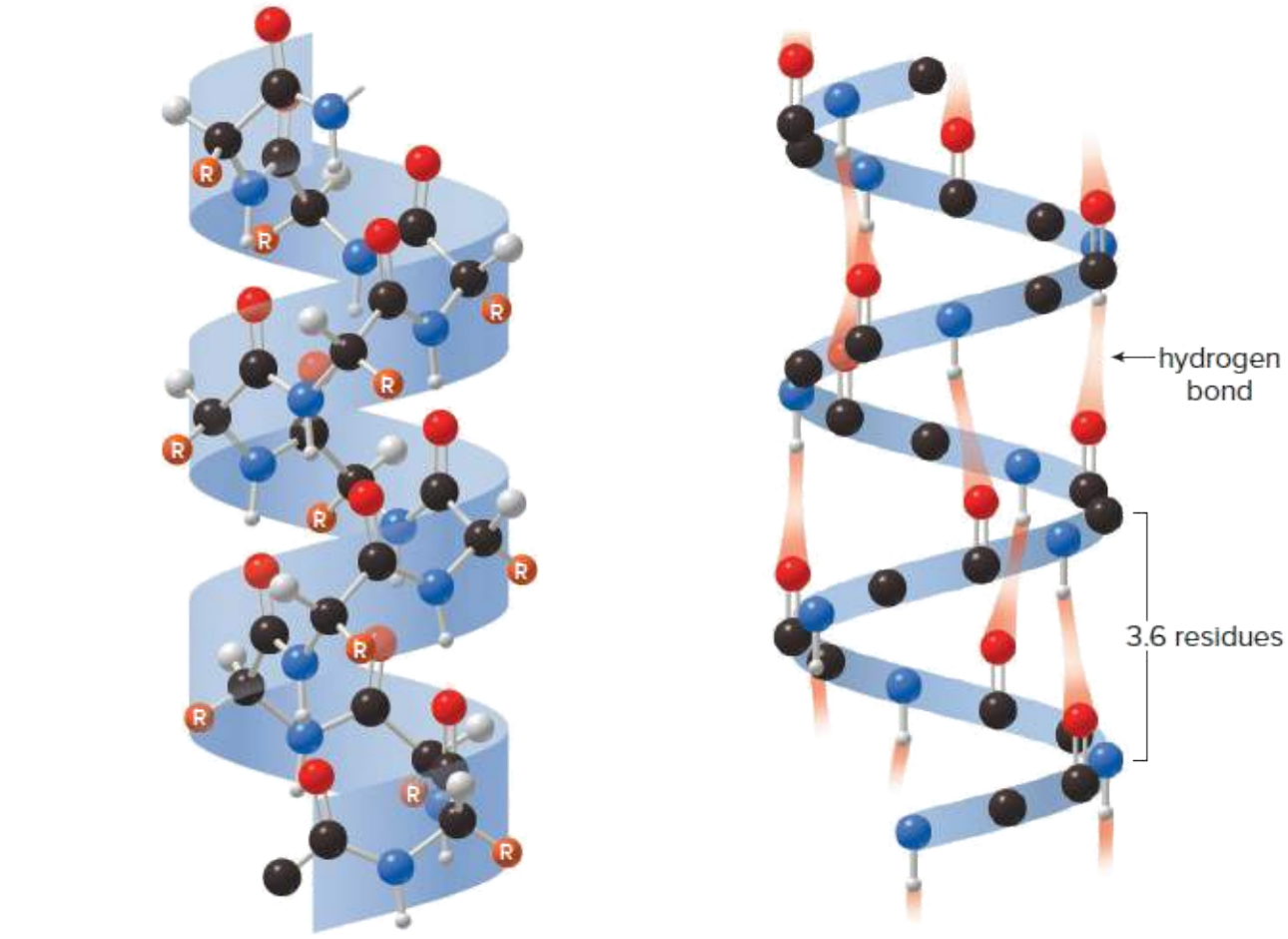


Figure 27.7 **Two different illustrations of the α-helix**

An α-helix can form only if there is rotation about the bonds at the α carbon of the amide carbonyl group, and not all amino acids can do this. For example, proline, the amino acid whose nitrogen atom forms part of a five-membered ring, is more rigid than other amino acids, and its C_α–N bond cannot rotate the necessary amount. Additionally, it has no N–H proton with which to form an intramolecular hydrogen bond to stabilize the helix. Thus, proline cannot be part of an α-helix.

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Both the myosin in muscle and α-keratin in hair are proteins composed almost entirely of α-helices.

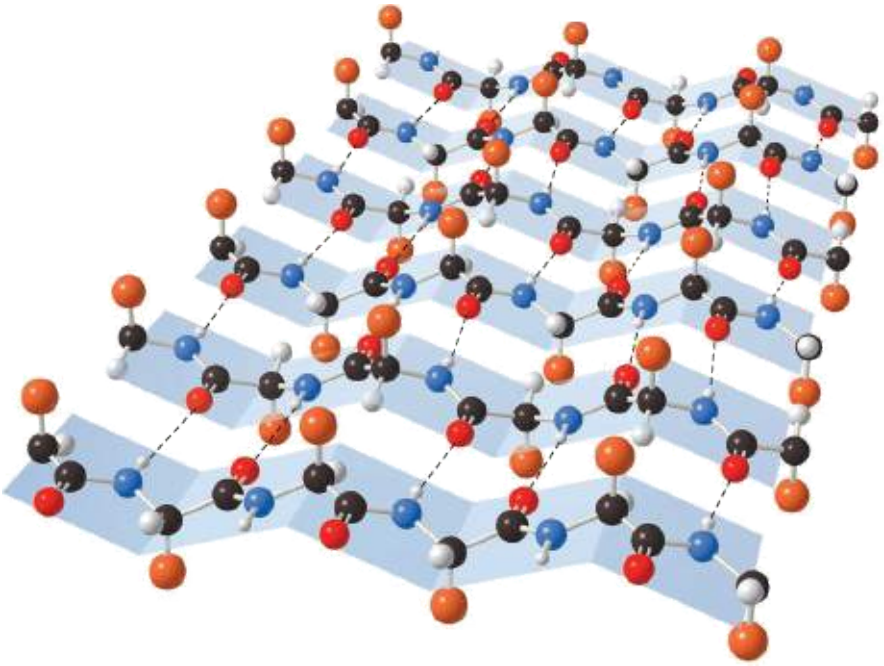
β-Pleated Sheet

The β-pleated sheet secondary structure forms when two or more peptide chains, called strands, line up side-by-side, as shown in Figure 27.8. All β-pleated sheets have the following characteristics:

[1] The C=O and N–H bonds lie in the plane of the sheet.

[2] Hydrogen bonding often occurs between the N–H and C=O groups of nearby amino acid residues.

[3] The R groups are oriented above and below the plane of the sheet, and alternate from one side to the other along a given strand.



- The β-pleated sheet consists of extended strands of the peptide chains held together by hydrogen bonding. The C=O and N–H bonds lie in the plane of the sheet, and the R groups (shown as orange balls) alternate above and below the plane.

Figure 27.8 **Three-dimensional structure of the β-pleated sheet**

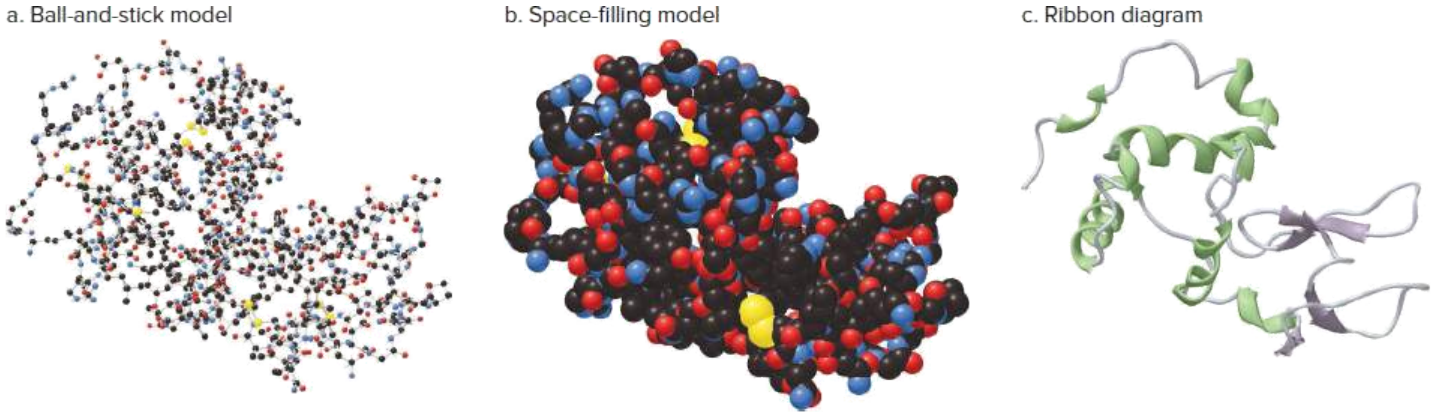
The β-pleated sheet arrangement most commonly occurs with amino acids with small R groups, like alanine and glycine. With larger R groups, steric interactions prevent the chains from getting close together, so the sheet cannot be stabilized by hydrogen bonding.

Most proteins have regions of α-helix and β-pleated sheet, in addition to other regions that cannot be characterized by either of these arrangements. Shorthand symbols are often used to indicate regions of a protein that have α-helix or β-pleated sheet. A flat helical ribbon is used for the α-helix, and a flat wide arrow is used for the β-pleated sheet. These representations are often used in ribbon diagrams to illustrate protein structure.

α-helix shorthand

β-pleated sheet shorthand

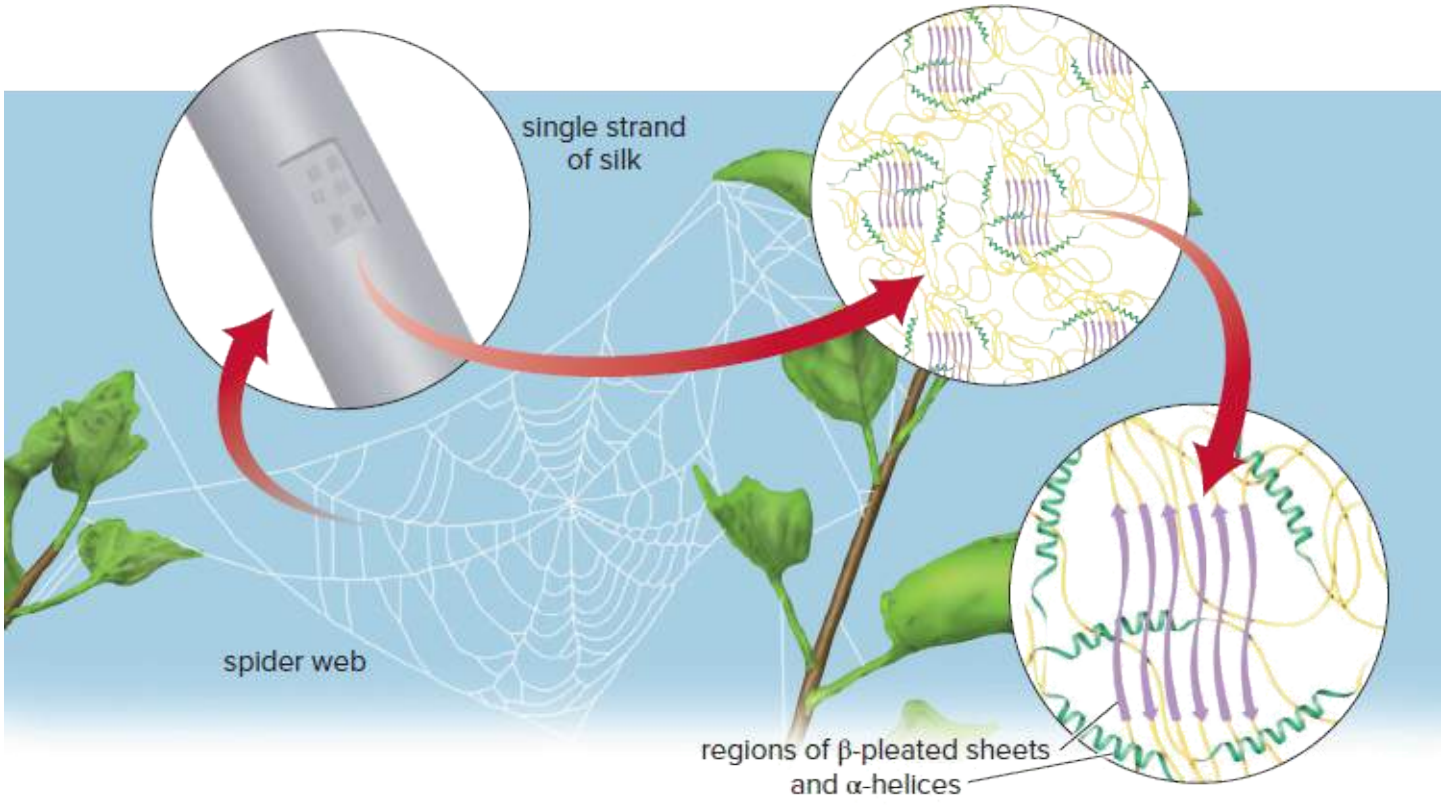
Proteins are drawn in a variety of ways to illustrate different aspects of their structure. Figure 27.9 illustrates three different representations of the protein lysozyme, an enzyme found in both plants and animals. Lysozyme catalyzes the hydrolysis of bonds in bacterial cell walls, weakening them, often causing the bacteria to burst.



(a) The ball-and-stick model of lysozyme shows the protein backbone with color-coded C, N, O, and S atoms. Individual amino acids are most clearly located using this representation. (b) The space-filling model uses color-coded balls for each atom in the backbone of the enzyme and illustrates how the atoms fill the space they occupy. (c) The ribbon diagram shows regions of α-helix and β-pleated sheet that are not clearly in evidence in the other two representations.

Figure 27.9 **Lysozyme**

Spider dragline silk is a strong yet elastic protein because it has regions of β-pleated sheet and regions of α-helix (Figure 27.10). α-Helical regions impart elasticity to the silk because the peptide chain is twisted (not fully extended), so it can stretch. β-Pleated sheet regions are almost fully extended, so they can't be stretched further, but their highly ordered three-dimensional structure imparts strength to the silk. Thus, spider silk suits the spider by comprising both types of secondary structure with beneficial properties.



- Spider silk has regions of α-helix and β-pleated sheet that make it both strong and elastic. The green coils represent the α-helical regions, and the purple arrows represent the β-pleated sheet regions. The yellow lines represent other areas of the protein that are neither α-helix nor β-pleated sheet.

Figure 27.10 **Different regions of secondary structure in spider silk**

27.9C Tertiary and Quaternary Structure

The three-dimensional shape adopted by the entire peptide chain is called its *tertiary structure*. A peptide generally folds into a conformation that maximizes its stability. In the aqueous environment of the cell, proteins often fold in such a way as to place a large number of polar and charged groups on their outer surface, to maximize the dipole–dipole and hydrogen bonding interactions with water. This generally places most of the nonpolar side chains in the interior of the protein, where van der Waals interactions between these hydrophobic groups help stabilize the molecule, too.

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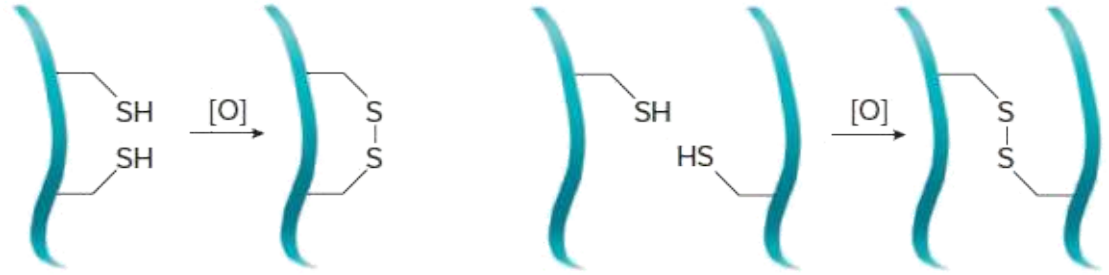
In addition, polar functional groups hydrogen bond with each other (not just water), and amino acids with charged side chains like $-COO^-$ and $-NH_3^+$ can stabilize tertiary structure by electrostatic interactions.

Finally, disulfide bonds are the only covalent bonds that stabilize tertiary structure. As previously mentioned, these strong bonds form by oxidation of two cysteine residues on either the same polypeptide chain or another polypeptide chain of the same protein.



disulfide bond between two SH groups on the *same* chain

disulfide bond between two SH groups on *different* chains

The nonapeptides oxytocin and vasopressin (Section 27.5C) contain intramolecular disulfide bonds. Insulin, on the other hand, consists of two separate polypeptide chains (A and B) that are covalently linked by two intermolecular disulfide bonds, as shown in Figure 27.11. The A chain, which also has an intramolecular disulfide bond, has 21 amino acid residues, whereas the B chain has 30.

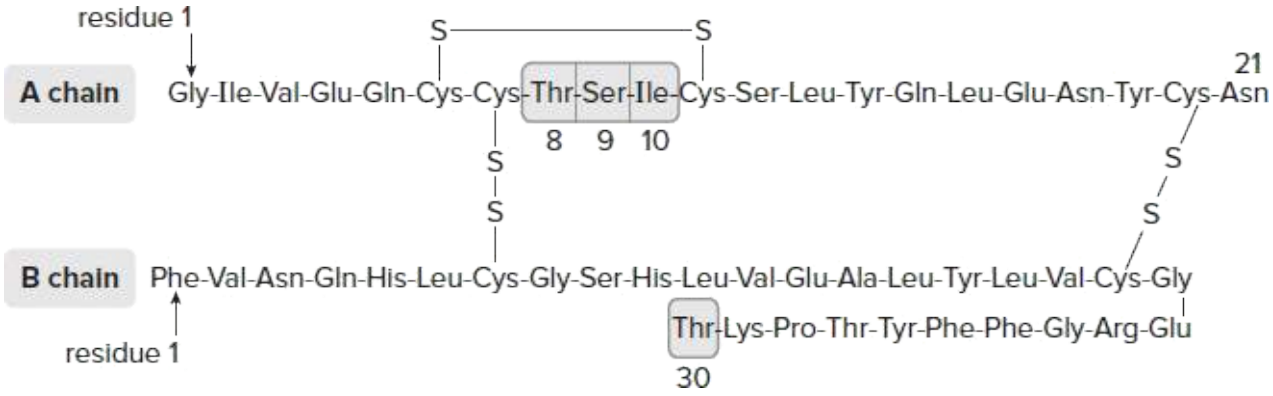
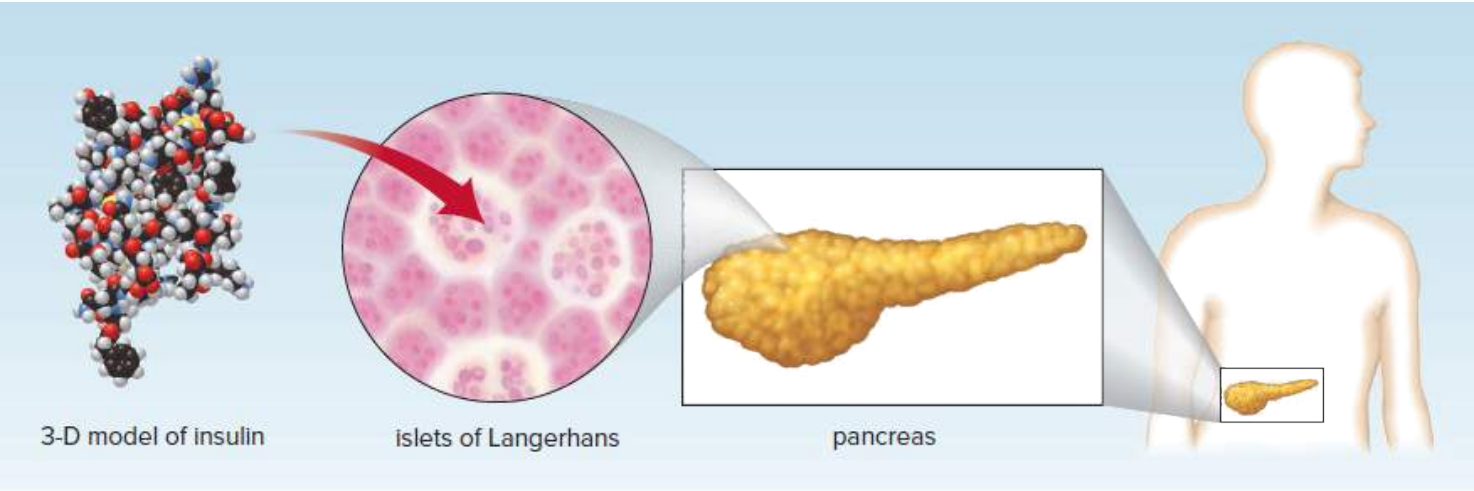


Figure 27.11 **Insulin**

Insulin is a small protein consisting of two polypeptide chains (designated as the A and B chains) held together by two disulfide bonds. An additional disulfide bond joins two cysteine residues within the A chain.



Synthesized by groups of cells in the pancreas called the islets of Langerhans,

insulin is the protein that regulates the levels of glucose in the blood. Insufficiency of insulin results in diabetes. Many of the abnormalities associated with this disease can be controlled by the injection of insulin. Until the availability of human insulin through genetic engineering techniques, all insulin used by diabetics was obtained from pigs and cattle. The amino acid sequences of these insulin proteins is slightly different from that of human insulin. Pig insulin differs in one amino acid only, whereas bovine insulin has three different amino acids. This is shown in the accompanying table.

	Chain A			Chain B
Position of residue →	**8**	**9**	**10**	**30**
Human insulin	**Thr**	**Ser**	**Ile**	**Thr**
Pig insulin	**Thr**	**Ser**	**Ile**	**Ala**
Bovine insulin	**Ala**	**Ser**	**Val**	**Ala**

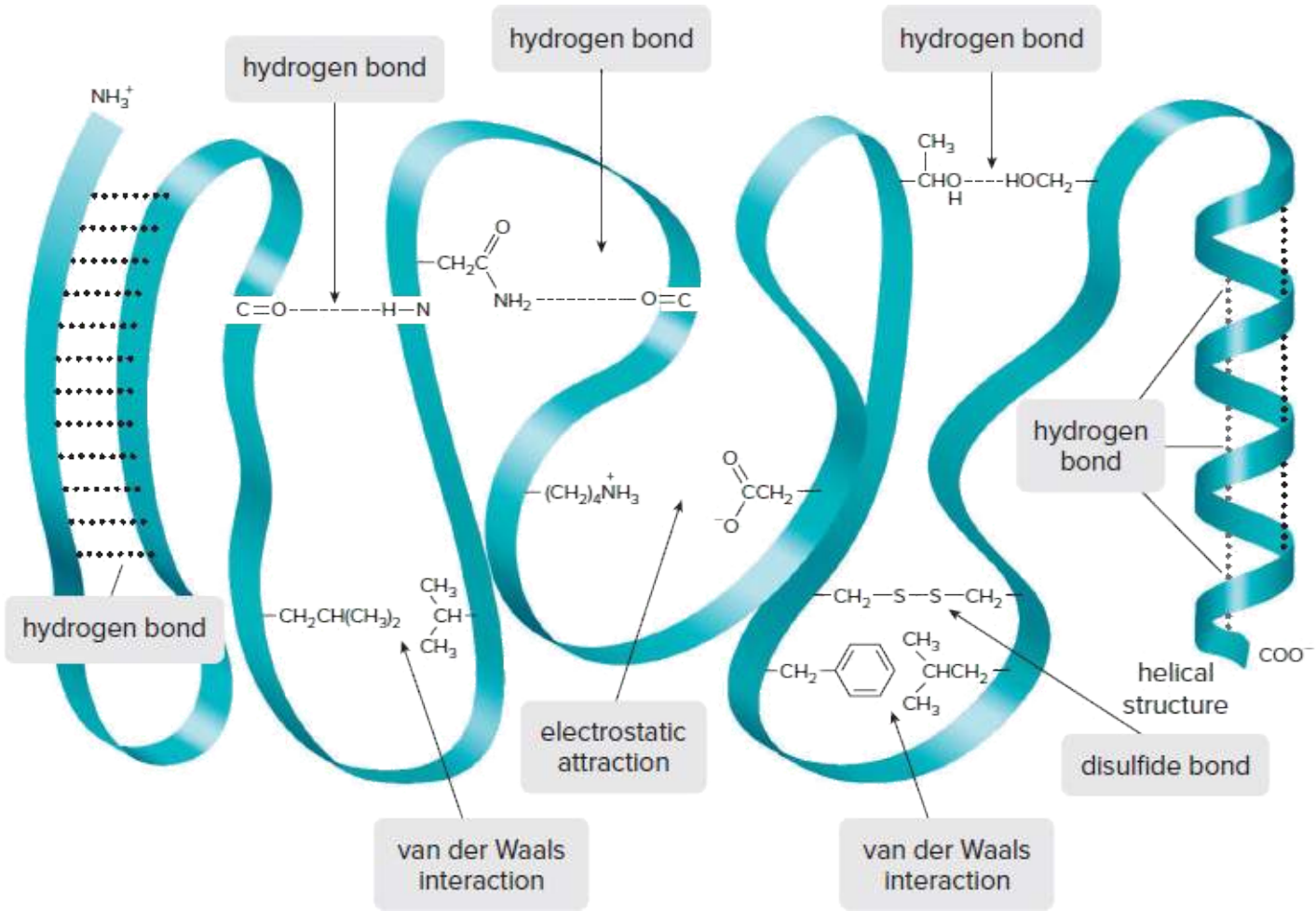


Figure 27.12 **The stabilizing interactions in secondary and tertiary protein structure**

Figure 27.12 schematically illustrates the many different kinds of intramolecular forces that stabilize the secondary and tertiary structures of polypeptide chains.

The shape adopted when two or more folded polypeptide chains aggregate into one protein complex is called the *quaternary structure* of the protein. Each individual polypeptide chain is called a subunit of the overall protein. Hemoglobin, for example, consists of two α and two β subunits held together by intermolecular forces in a compact three-dimensional shape. The unique function of hemoglobin is possible only when all four subunits are together.

The four levels of protein structure are summarized in Figure 27.13.

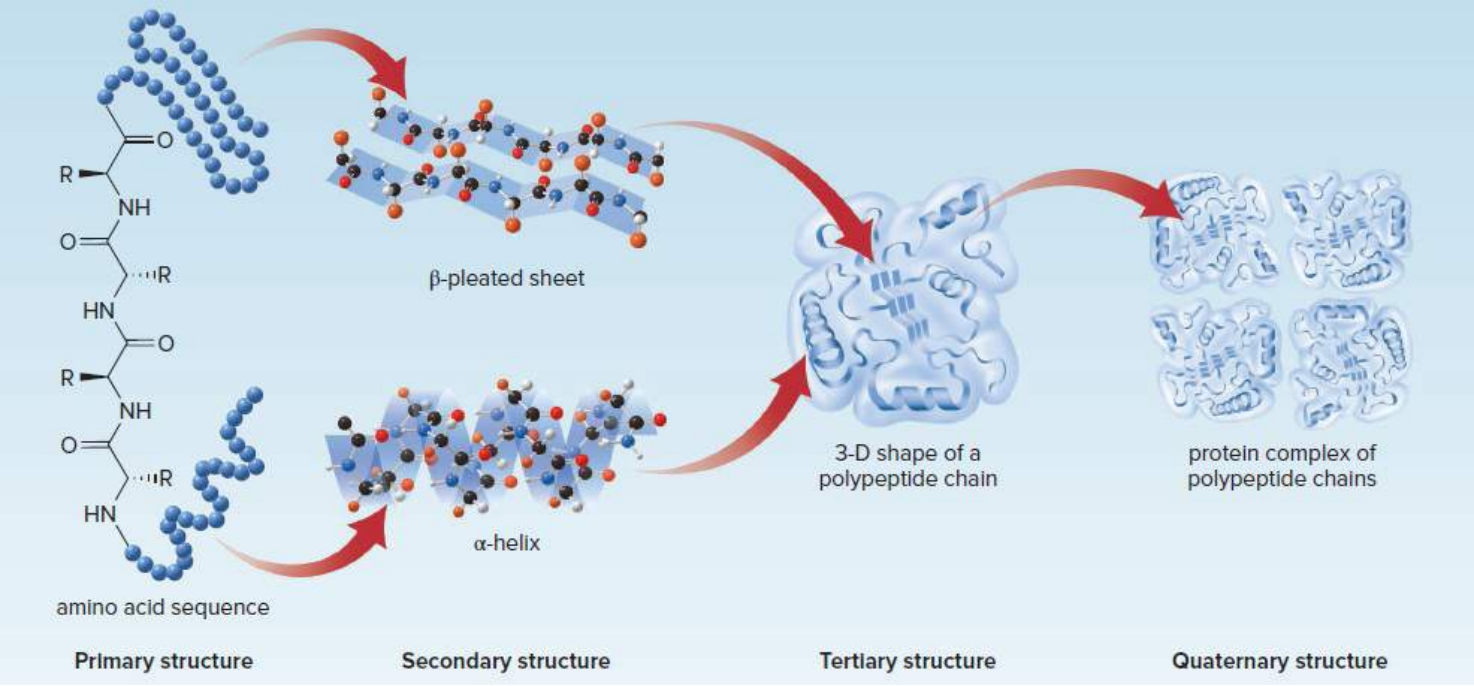


Figure 27.13 **The primary, secondary, tertiary, and quaternary structure of proteins**

Problem 27.25

Which peptide in each pair has side chains that exhibit predominantly van der Waals forces?

a. Met–Gly–Leu–Phe–Gln–Ala or Lys–Gly–Arg–Tyr–Trp–Glu

b. Tyr–Asp–Leu–Lys–His or Phe–Asn–Leu–Leu–Met

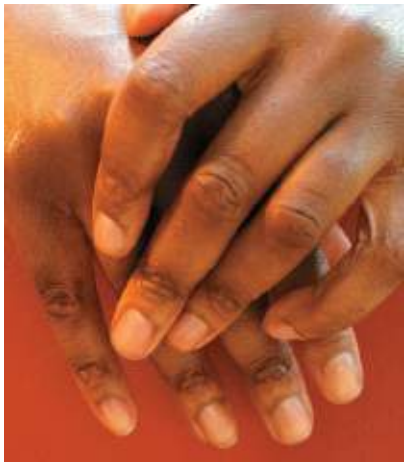
Problem 27.26

The fibroin proteins found in silk fibers consist of large regions of β-pleated sheets stacked one on top of another. (a) Explain why having a glycine at every other residue allows the β-pleated sheets to stack on top of each other. (b) Why are silk fibers insoluble in water?

27.10 Important Proteins

Proteins are generally classified according to their three-dimensional shapes.

- Fibrous proteins are composed of long linear polypeptide chains that are bundled together to form rods or sheets. These proteins are insoluble in water and serve structural roles, giving strength and protection to tissues and cells.
- Globular proteins are coiled into compact shapes with hydrophilic outer surfaces that make them water soluble. Enzymes and transport proteins are globular to make them soluble in the blood and other aqueous environments in cells.



The many disulfide bonds in the proteins that compose fingernails make nails strong and hard. ©*Diffused Productions/Alamy Stock Photo*

27.10A α-Keratins

α-Keratins are the proteins found in hair, hooves, nails, skin, and wool. They are composed almost exclusively of long sections of α-helix units, having large numbers of alanine and leucine residues. Because these nonpolar amino acids extend outward from the α-helix, these proteins are very water insoluble. Two α-keratin helices coil around each other, forming a structure called a supercoil or superhelix. These, in turn, form larger and larger bundles of fibers, ultimately forming a strand of hair, as shown schematically in Figure 27.14.

α-Keratins also have a number of cysteine residues, and because of this, disulfide bonds are formed between adjacent helices. The number of disulfide bridges determines the strength of the material. Claws, horns, and fingernails have extensive networks of disulfide bonds, making them extremely hard.

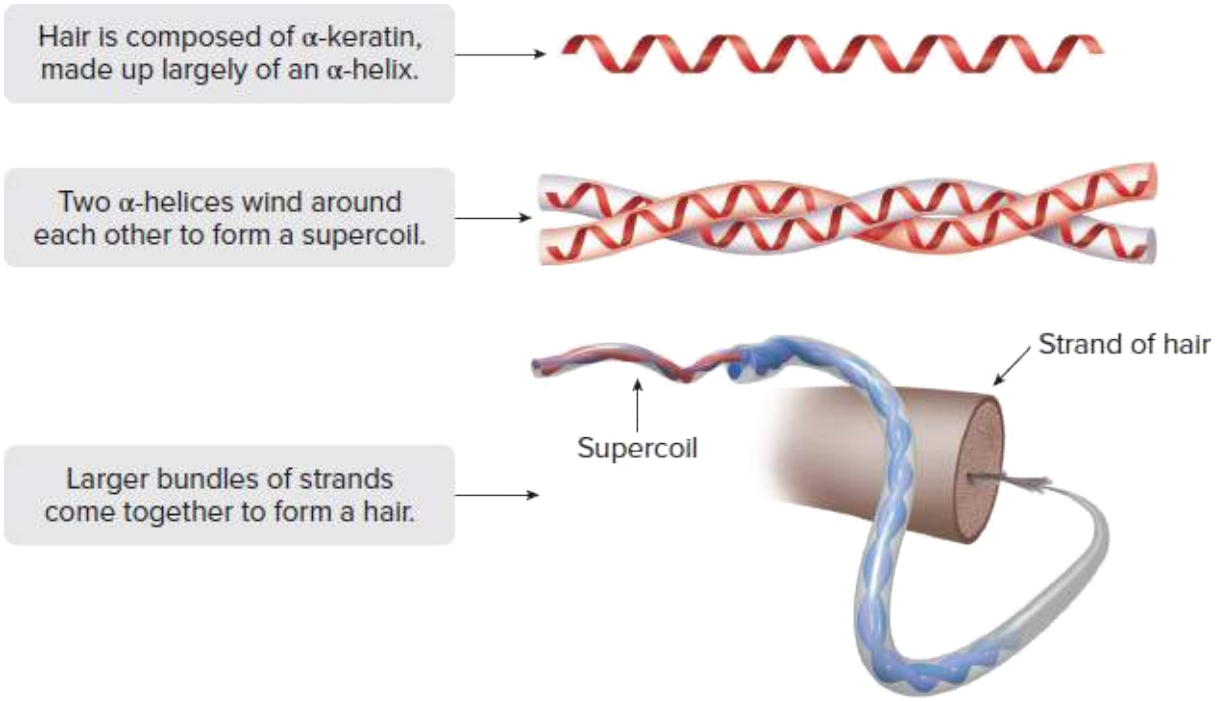


Figure 27.14 **Anatomy of a hair—It begins with α-keratin.**

Straight hair can be made curly by cleaving the disulfide bonds in α-keratin, and then rearranging and re-forming them, as shown schematically in Figure 27.15. First, the disulfide bonds in the straight hair are reduced to thiol groups, so the bundles of α-keratin chains are no longer held in their specific "straight" orientation. Then, the hair is wrapped around curlers and treated with an oxidizing agent that converts the thiol groups back to disulfide bonds, now with twists and turns in the keratin backbone. This makes the hair look curly and is the chemical basis for a "permanent."

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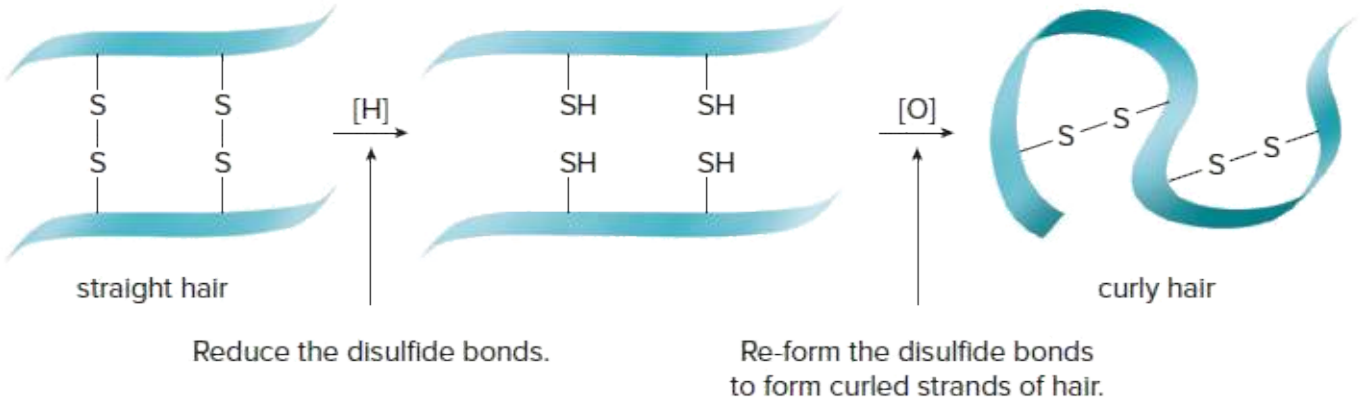
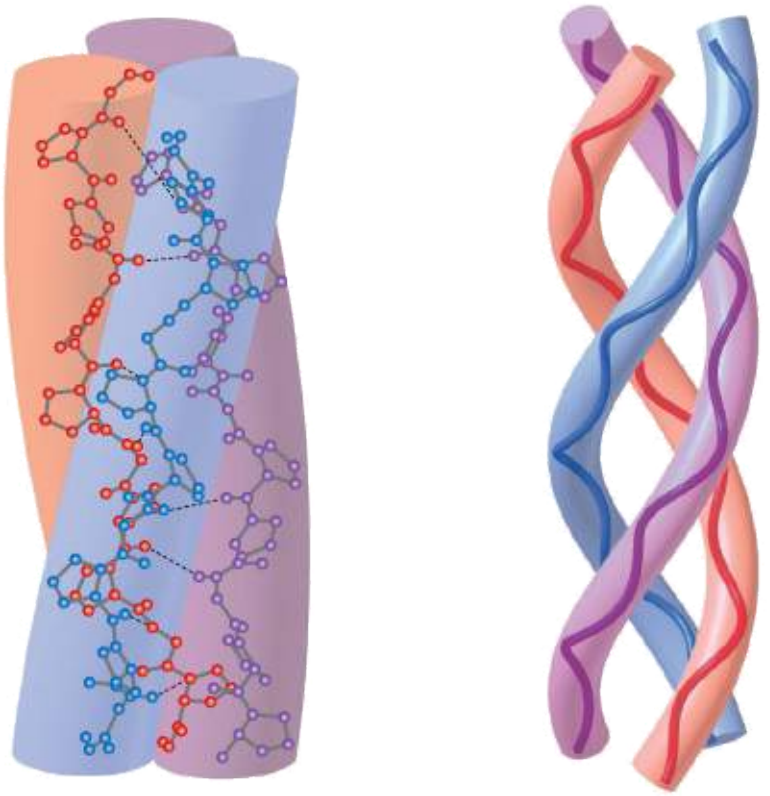


- To make straight hair curly, the disulfide bonds holding the α-helical chains together are cleaved by reduction. This forms free thiol groups (–SH). The hair is turned around curlers and then an oxidizing agent is applied. This re-forms the disulfide bonds in the hair, but between different thiol groups, now giving it a curly appearance.

Figure 27.15 **The chemistry of a "permanent"—Making straight hair curly**

27.10B Collagen

Collagen, the most abundant protein in vertebrates, is found in connective tissues such as bone, cartilage, tendons, teeth, and blood vessels. Glycine and proline account for a large fraction of its amino acid residues, whereas cysteine accounts for very little. Because of the high proline content, it cannot form a right-handed α-helix. Instead, it forms an elongated left-handed helix, and then three of these helices wind around each other to form a right-handed superhelix or triple helix. The side chain of glycine is only a hydrogen atom, so the high glycine content allows the collagen superhelices to lie compactly next to each other, thus stabilizing the superhelices via hydrogen bonding. Two views of the collagen superhelix are shown in Figure 27.16.



- In collagen, three polypeptide chains having an unusual left-handed helix wind around each other in a right-handed triple helix. The high content of small glycine residues allows the chains to lie close to each other, permitting hydrogen bonding between the chains.

Figure 27.16 **Two different representations for the triple helix of collagen**

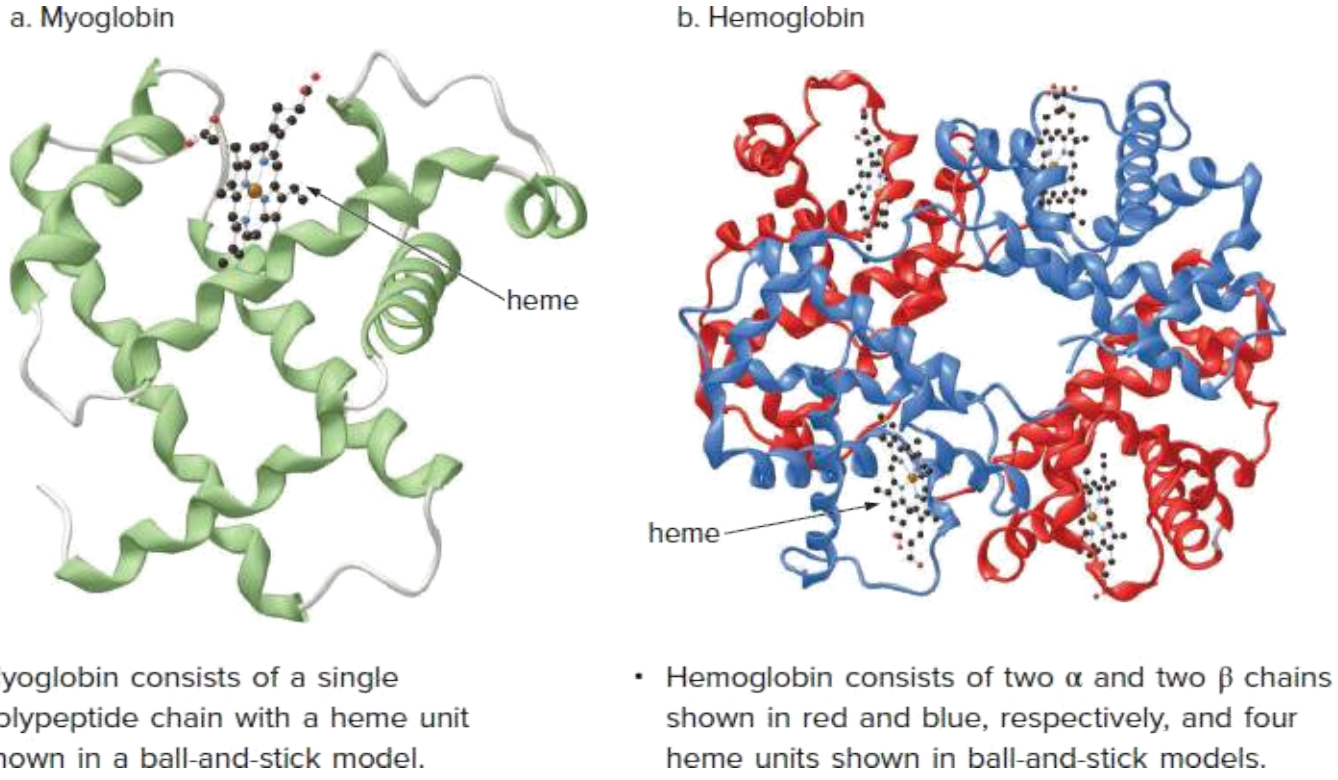
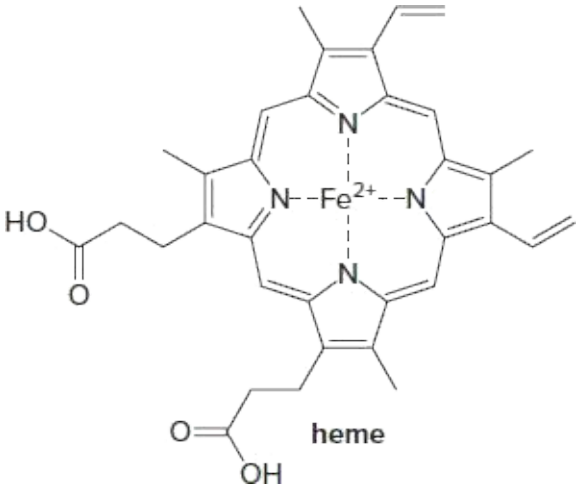


Figure 27.17 **Protein ribbon diagrams for myoglobin and hemoglobin**

27.10C Hemoglobin and Myoglobin

Hemoglobin and myoglobin, two globular proteins, are called conjugated proteins because they are composed of a protein unit and a nonprotein molecule called a prosthetic group. The prosthetic group in hemoglobin and myoglobin is heme, a complex organic compound containing the Fe^{2+} ion complexed with a nitrogen heterocycle called a porphyrin. The Fe^{2+} ion of hemoglobin and myoglobin binds oxygen in the blood. Hemoglobin, which is present in red blood cells, transports oxygen to wherever it is needed in the body, whereas myoglobin stores oxygen in tissues. Ribbon diagrams for myoglobin and hemoglobin are shown in Figure 27.17.



Myoglobin has 153 amino acid residues in a single polypeptide chain. It has eight

separate α-helical sections that fold back on one another, with the prosthetic heme group held in a cavity inside the polypeptide. Most of the polar residues are found on the outside of the protein so that they can interact with the water solvent. Spaces in the interior of the protein are filled with nonpolar amino acids. Myoglobin binds oxygen in the blood and stores it in the tissues.

Hemoglobin consists of four polypeptide chains (two α subunits and two β subunits), each of which carries a heme unit. Hemoglobin has more nonpolar amino acids than myoglobin. When each subunit is folded, some of these remain on the surface. The van der Waals attraction between these hydrophobic groups is what stabilizes the quaternary structure of the four subunits.

The high concentration of myoglobin in a whale's muscles allows it to remain underwater for long periods of time.
©Daniel C. Smith

Carbon monoxide is poisonous because it binds to the Fe^{2+} of hemoglobin Page 1248 more strongly than does oxygen. Hemoglobin complexed with CO cannot carry O_2 from the lungs to the tissues. Without O_2 in the tissues for metabolism, cells cannot function, so they die.

The properties of all proteins depend on their three-dimensional shape, and their shape depends on their primary structure—that is, their amino acid sequence. This is particularly well exemplified by comparing normal hemoglobin with sickle cell hemoglobin, a mutant variation in which a single amino acid of both β subunits is changed from glutamic acid to valine. The replacement of one acidic amino acid (Glu) with one nonpolar amino acid (Val) changes the shape of hemoglobin, which has profound effects on its function. Deoxygenated red blood cells with sickle cell hemoglobin become elongated and crescent shaped, and they are unusually fragile. As a result, they do not flow easily through capillaries, causing pain and inflammation, and they break open easily, leading to severe anemia and organ damage. The end result

is often a painful and premature death.

This disease, called sickle cell anemia, is found almost exclusively among people originating from central and western Africa, where malaria is an enormous health problem. Sickle cell hemoglobin results from a genetic mutation in the DNA sequence that is responsible for the synthesis of hemoglobin. Individuals who inherit this mutation from both parents develop sickle cell anemia, whereas those who inherit it from only one parent are said to have the sickle cell trait. They do not develop sickle cell anemia, and they are more resistant to malaria than individuals without the mutation. This apparently accounts for this detrimental gene being passed on from generation to generation.

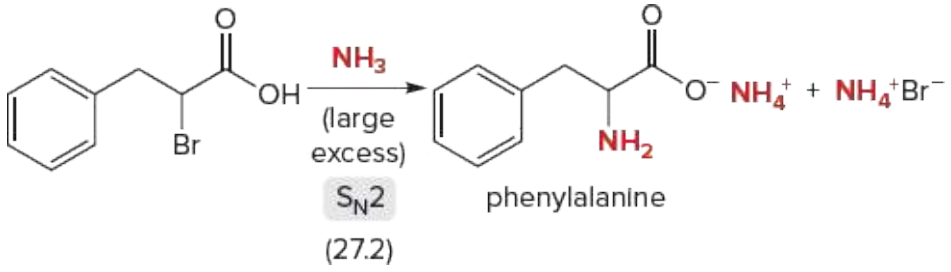
When red blood cells take on a "sickled" shape in persons with sickle cell disease, they occlude capillaries (causing organ injury) and they break easily (leading to profound anemia). This devastating illness results from the change of a single amino acid in hemoglobin. Note the single sickled cell surrounded by red cells with normal morphology. ***Source: CDC/Sickle Cell Foundation of Georgia: Jackie George, Beverly Sinclair/photo by Janice Haney Carr***

Chapter 27 REVIEW

KEY CONCEPTS

[1] Synthesis of amino acids

1



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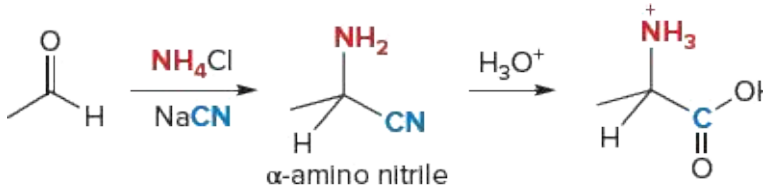

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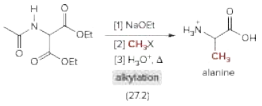

Try Problems 27.38–27.41.

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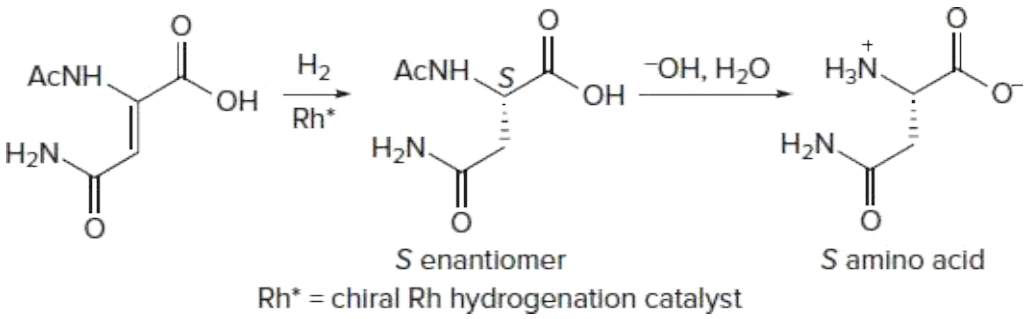
[2] Enantioselective hydrogenation (27.4)



Try Problem 27.49b.

[3] Adding and removing protecting groups for amino acids (27.7)

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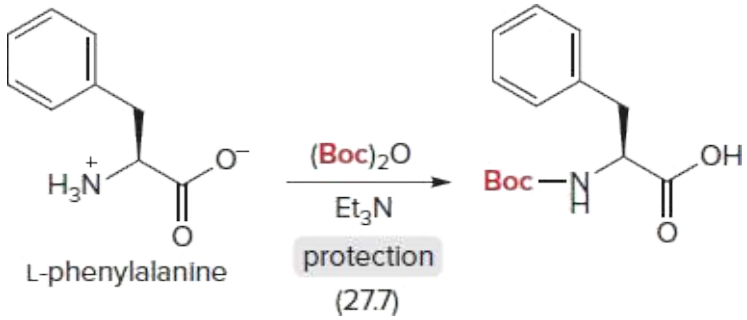

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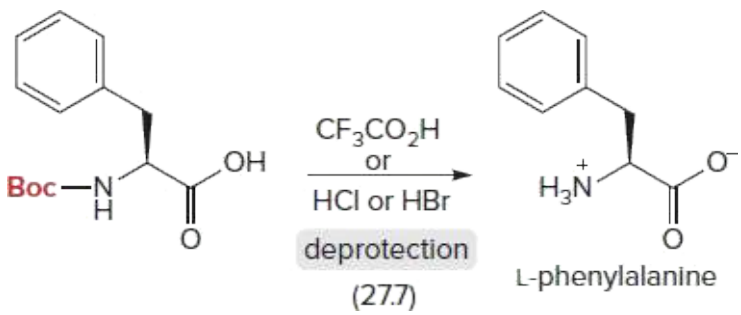

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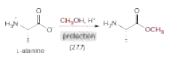

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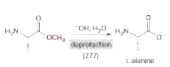

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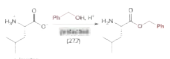

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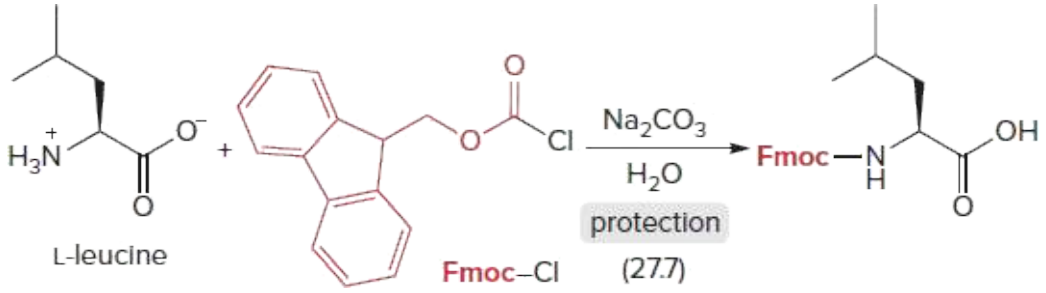

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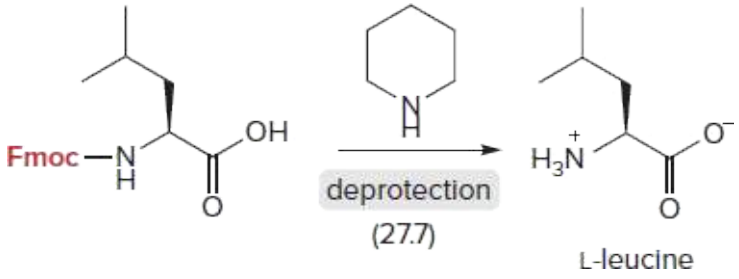

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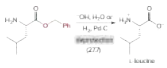
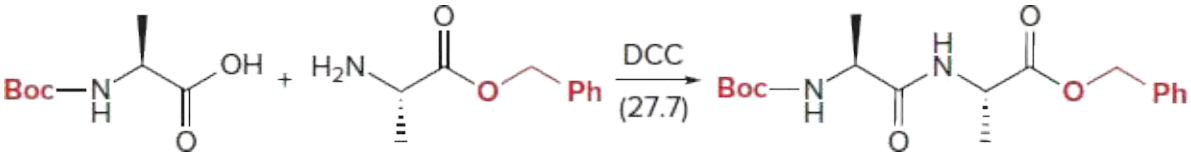


Try Problems 27.45a, d; 27.61.

[4] Amide formation with DCC



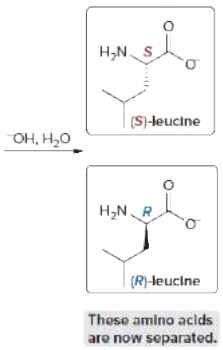
KEY SKILLS

[1] Using (*R*)-α-methylbenzylamine to resolve a racemic mixture of amino acids (27.3A); example: separation of L- and D-leucine

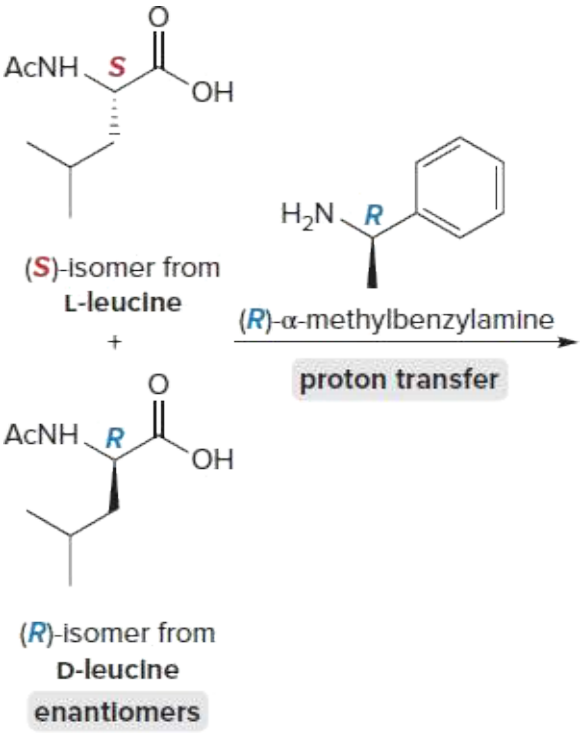
1 **React both enantiomers of an *N*-acetyl amino acid with the *R* isomer of the chiral amine.**

2 **Separate the diastereomers.**

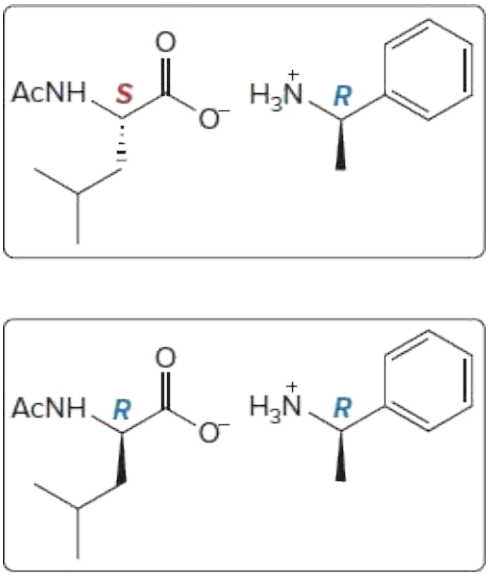
3 **Regene the ami acid by hydroly of the amide.**



These amino acids are now separated.



- **Enantiomers cannot be physically separated because they have the same physical properties.**



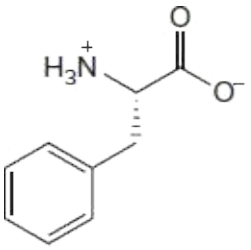
diastereomers

- **These salts are diastereomers.**
- **Diastereomers have different physical properties, so they can be physically separated.**

See *How To*, p. 1221. Try Problems 27.46–27.48.

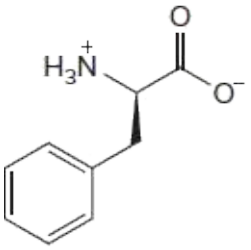
[2] Using enzymes to kinetically resolve a racemic mixture of amino acids (27.3B); example: separation of L- and D-phenylalanine

1 **Acetylate both enantiomers of an amino acid with Ac_2O.**	**2** **React both enantiomers of an *N*-acetyl amino acid with an acylase enzyme.**	**3** **Separate the amino acid from the acetylated amino acid.**



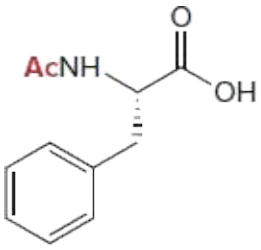
L-phenylalanine

Ac_2O

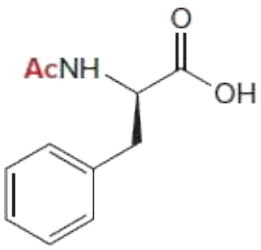


D-phenylalanine

enantiomers

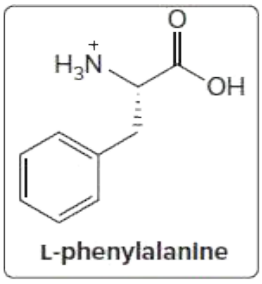


acylase



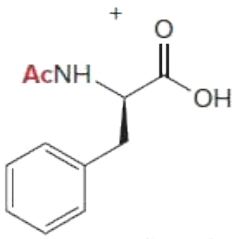
enantiomers

- **Acylases selectively hydrolyze amides of L-amino acids.**



L-phenylalanine

+



recovered amide

No reaction

These two **compounds** are **separable** because they have **different functional groups.**

- **Separation of two enantiomers by a chemical reaction that selectively occurs for only one of the enantiomers is called *kinetic resolution.***

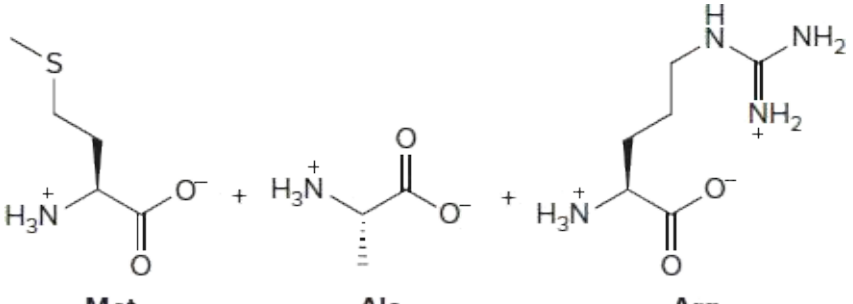
Try Problem 27.49a.

Page 1251

[3] Drawing the structure of a tripeptide, and labeling its N-terminal and C-terminal amino acids (27.5); example: Met–Ala–Arg

1 **Draw the structures of the amino acids in order from left to right, placing the COO^- of one amino acid *next* to the NH_3^+ group of the adjacent amino acid.**

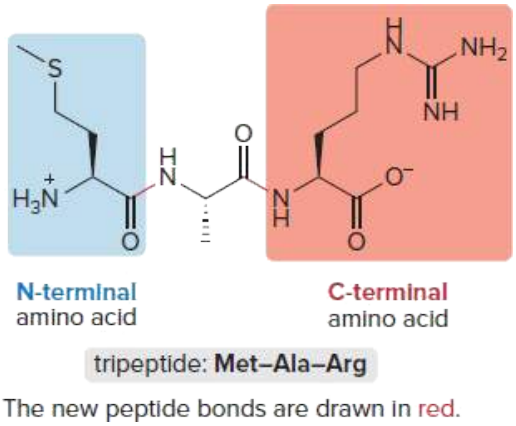
2 **Join adjacent COO^- and NH_3^+ groups together in amide bonds to form the tripeptide.**



Met **Ala** **Arg**

- **Always draw the NH_3^+ group on the *left***

and the COO^- group on the *right.*



- The N-terminal amino acid is methionine, and the C-terminal amino acid is arginine.

See Sample Problem 27.1. Try Problems 27.51; 27.52b, d.

[4] Giving the amino acid sequence of a hexapeptide that contains the amino acids Gly, Pro, Val, Ser, Leu, His, and forms the following fragments when partially hydrolyzed with HCl: Ser–Val, Pro–His–Gly, Val–Leu–Pro (27.6)

1 Look for points of overlap.	2 Piece the fragments together.
common amino acids Ser–Val Val–Leu–Pro Pro–His–Gly	Ser–Val–Leu–Pro–His–Gly hexapeptide

See Sample Problem 27.2. Try Problem 27.57.

[5] Deducing the sequence of a pentapeptide that contains the amino acids Phe, Ile, Ala, Lys, Gly (27.6C)

1 Identify the N-terminal amino acid by Edman degradation.	2 Identify the C-terminal amino acid by carboxypeptidase cleavage.	3 Identify the possible location of Lys or Arg, if applicable, from trypsin cleavage.	4

Ala–__–__–__–__

Ala–__–__–__–Ile

- If a tripeptide and a dipeptide are obtained:

  Ala–Lys–__–__–Ile

  or

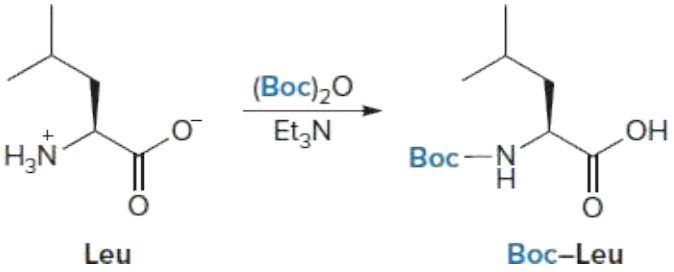
  Ala–__–Lys–__–Ile

- I A P a c

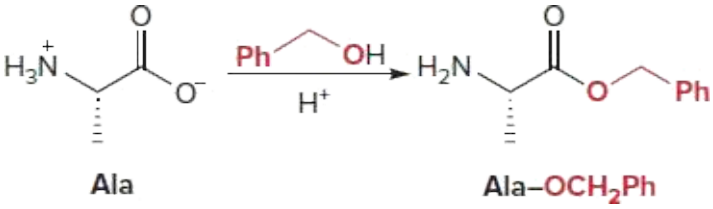
See Sample Problem 27.3, Table 27.2. Try Problems 27.56–27.60.

[6] Synthesizing a dipeptide from two amino acids (27.7): example: Leu–Ala

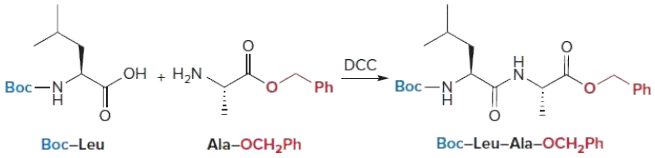
1 **Protect the NH_2 group of the N-terminal amino acid.**



2 **Protect the COOH group of the C-terminal amino acid.**

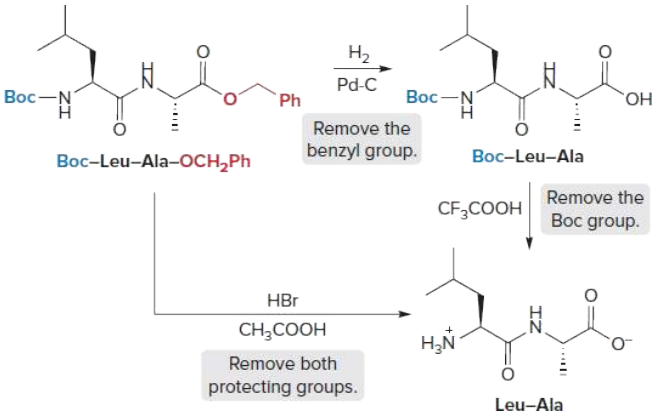


3 **Form the amide bond with DCC.**



- **DCC makes the OH group of the carboxylic acid a better leaving group, thus activating the carboxy group toward nucleophillic attack.**

4 **Remove one or both protecting groups.**



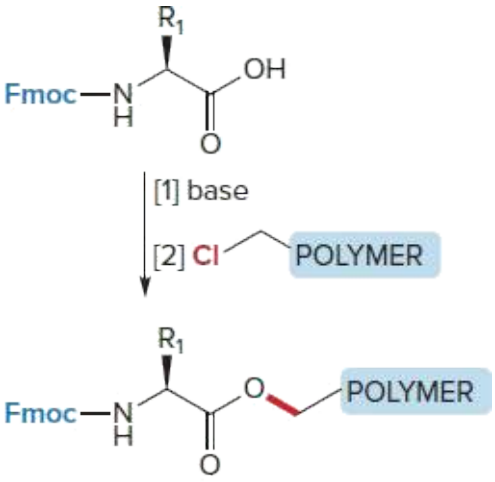
See *How To*, p. 1233, and Sample Problem 27.4. Try Problems 27.29, 27.62.

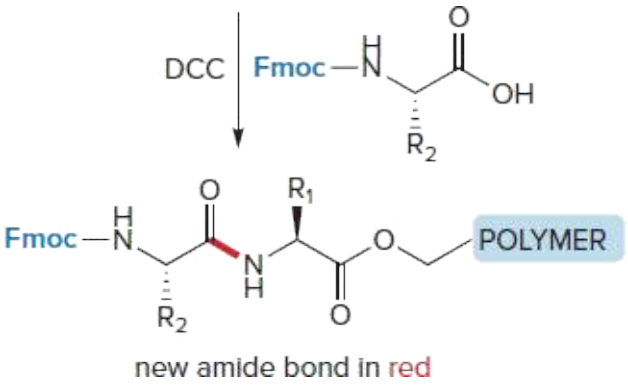
[7] Synthesizing a tripeptide using the Merrifield solid phase technique (27.8)

1 **Attach an Fmoc-**

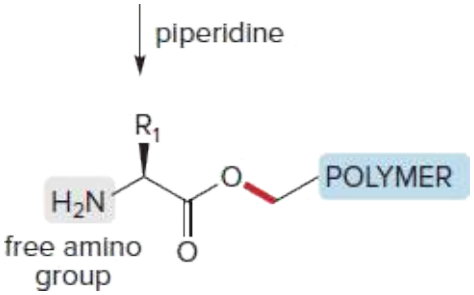
3 **Form the amide bond with DCC.**

protected amino acid to the polymer.

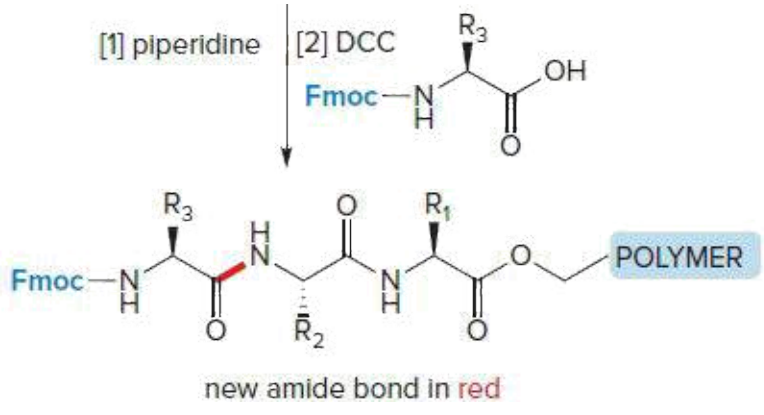




2 **Remove the protecting group.**



4 **Repeat Steps [2] and [3].**

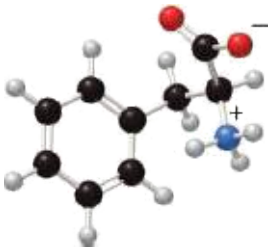


See *How To*, p. 1238. Try Problems 27.30, 27.63.

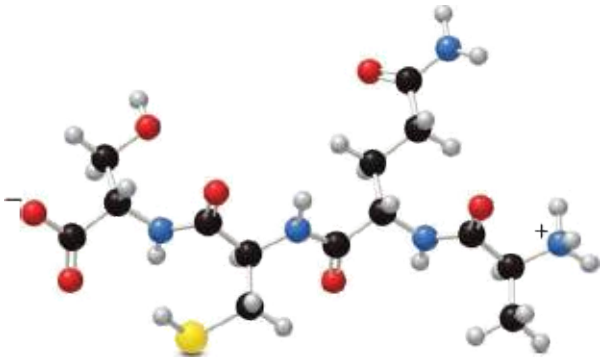
PROBLEMS

Problems Using Three-Dimensional Models

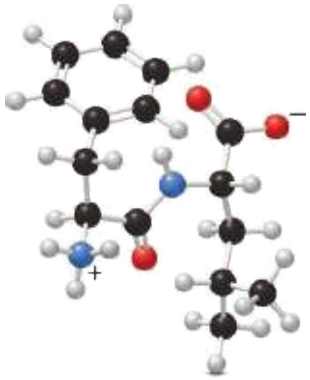
27.27 **Draw the product formed when the following amino acid is treated with each reagent: (a) CH_3OH, H^+; (b) CH_3COCl, pyridine; (c) HCl (1 equiv); (d) NaOH (1 equiv); (e) $C_6H_5N=C=S$.**



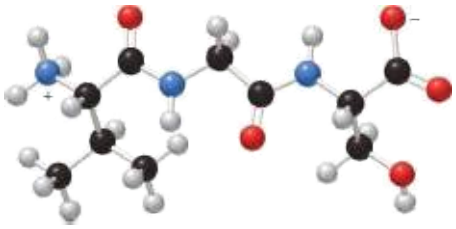
27.28 **With reference to the following peptide: (a) Identify the N-terminal and C-terminal amino acids. (b) Name the peptide using one-letter abbreviations. (c) Label all the amide bonds in the peptide backbone.**



27.29 **Devise a synthesis of the following dipeptide from amino acid starting materials.**



27.30 **Write out the steps needed to synthesize the following peptide using the Merrifield method.**

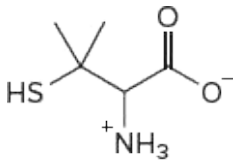


Amino Acids

27.31

a. (*S*)-Penicillamine, an amino acid that does not occur in proteins, is used as a copper chelating agent to treat Wilson's disease, an inherited defect in copper metabolism. (*R*)-Penicillamine is toxic, sometimes causing blindness. Draw the structures of (*R*)- and (*S*)-penicillamine.

b. What disulfide is formed from oxidation of (*S*)-penicillamine?



penicillamine

27.32 Histidine is classified as a basic amino acid because one of the N atoms in its five-membered ring is readily protonated by acid. Which N atom in histidine is protonated and why?

27.33 Tryptophan is not classified as a basic amino acid even though it has a heterocycle containing a nitrogen atom. Why is the N atom in the five-membered ring of tryptophan not readily protonated by acid?

27.34 What is the structure of each amino acid at its isoelectric point: (a) alanine; (b) methionine; (c) aspartic acid; (d) lysine?

Page 1254

27.35 What is the predominant form of each of the following amino acids at pH = 1? What is the overall charge on the amino acid at this pH? (a) threonine; (b) methionine; (c) aspartic acid; (d) arginine

27.36 What is the predominant form of each of the following amino acids at pH = 11? What is the overall charge on the amino acid? (a) valine; (b) proline; (c) glutamic acid; (d) lysine

27.37 a. Draw the structure of the tripeptide A–A–A, and label the two ionizable functional groups.

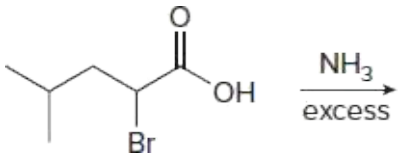
b. What is the predominant form of A–A–A at pH = 1?

c. The pK_a values for the two ionizable functional groups (3.39 and 8.03) differ considerably from the pK_a values of alanine (2.35 and 9.87; see Table 27.1). Account for the observed pK_a differences.

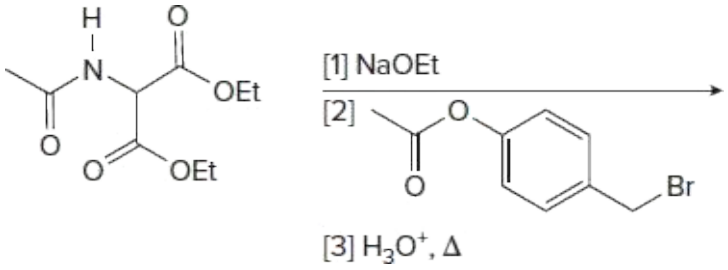
Synthesis and Reactions of Amino Acids

27.38 Draw the organic products formed in each reaction.

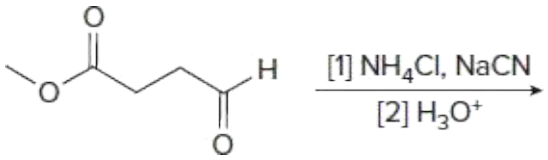
a.



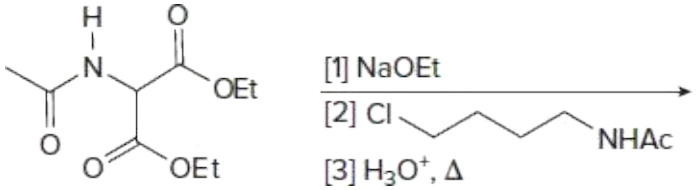
b.



c.



d.

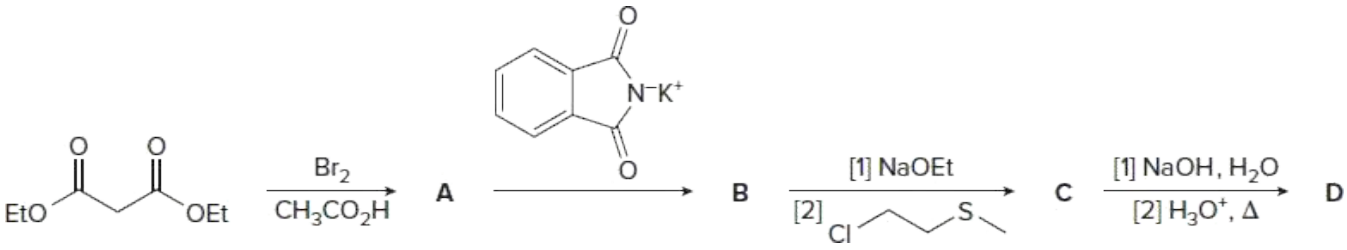


27.39 What alkyl halide is needed to synthesize each amino acid from diethyl acetamidomalonate: (a) Asn; (b) His; (c) Trp?

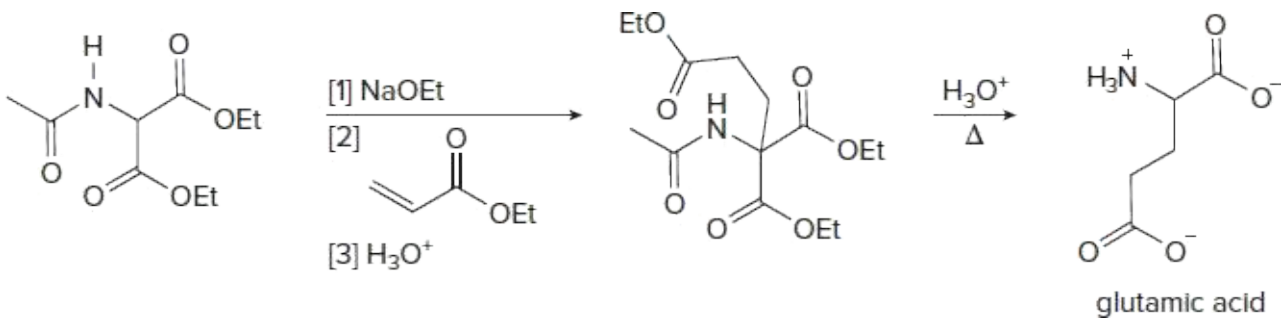
27.40 Devise a synthesis of threonine from diethyl acetamidomalonate.

27.41 Devise a synthesis of each amino acid from acetaldehyde (CH_3CHO): (a) glycine; (b) alanine.

27.42 Identify the lettered intermediates in the following reaction scheme. This is an alternative method to synthesize amino acids, based on the Gabriel synthesis of 1° amines (Section 23.6A).

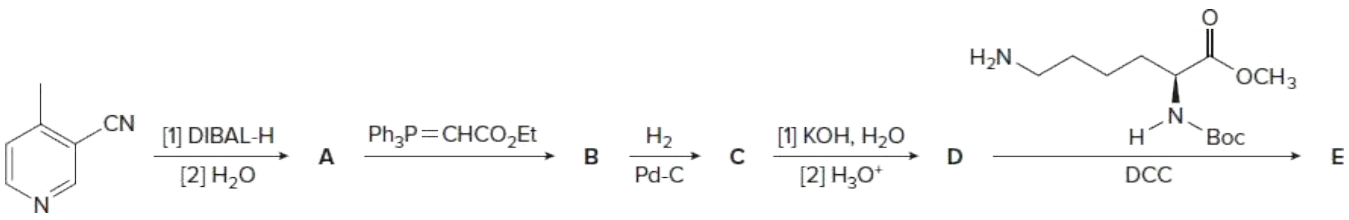


27.43 Glutamic acid is synthesized by the following reaction sequence. Draw a stepwise mechanism for Steps [1]–[3].

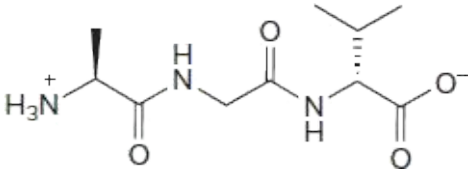


glutamic acid

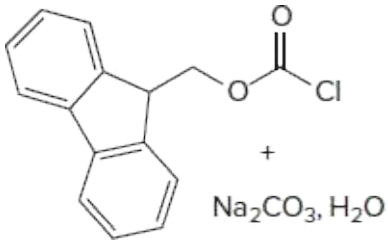
27.44 Identify A–E in the following reaction sequence.



27.45 Draw the product when the following tripeptide is treated with each reagent.



a.



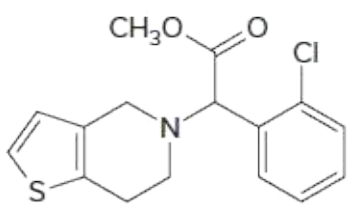
b. H_3O^+

c. C_6H_5NCS

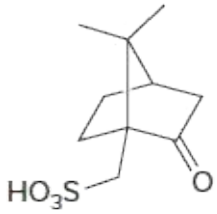
d. CH_3OH, H^+

Resolution; The Synthesis of Chiral Amino Acids

27.46 Write out a scheme for the resolution of the two enantiomers of the antiplatelet drug clopidogrel with 10-camphorsulfonic acid.

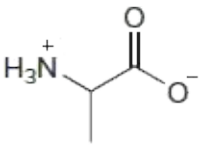


clopidogrel

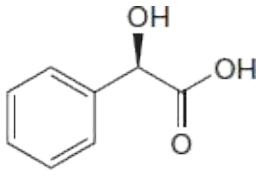


10-camphorsulfonic acid

27.47 Another strategy used to resolve amino acids involves converting the carboxy group to an ester and then using a *chiral carboxylic acid* to carry out an acid–base reaction at the free amino group. Using a racemic mixture of alanine enantiomers and (*R*)-mandelic acid as resolving agent, write out the steps showing how a resolution process would occur.

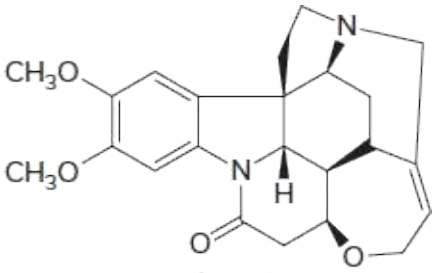


alanine
(two enantiomers)



(*R*)-mandelic acid

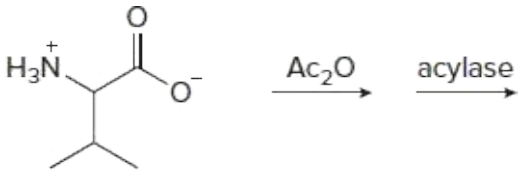
27.48 Brucine is a poisonous alkaloid obtained from *Strychnos nux vomica*, a tree that grows in India, Sri Lanka, and northern Australia. Write out a resolution scheme similar to the one given in Section 27.3A, which shows how a racemic mixture of phenylalanine can be resolved using brucine.



brucine

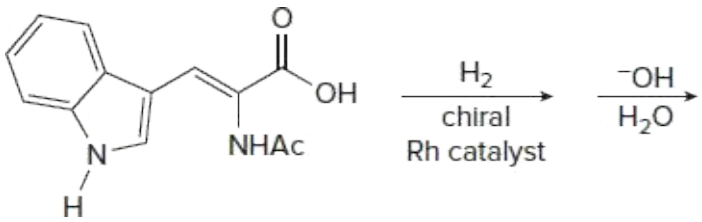
27.49 Draw the organic products formed in each reaction.

a.

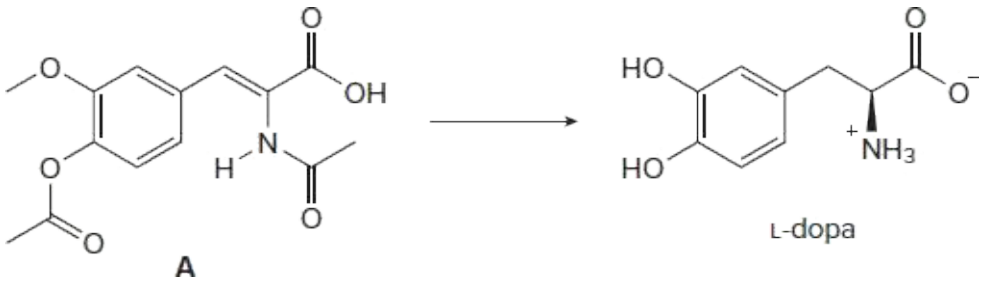


racemic mixture

b.



27.50 What steps are needed to convert A to L-dopa, an uncommon amino acid that is effective in treating Parkinson's disease? These steps are the key reactions in the first commercial asymmetric synthesis using a chiral transition metal catalyst. This process was developed at Monsanto in 1974.



A

L-dopa

27.51 **Draw the structure for each peptide: (a) Phe–Ala; (b) Gly–Gln; (c) Lys–Gly; (d) R–H.**

27.52 **For the tetrapeptide Asp–Arg–Val–Tyr:**

a. Name the peptide using one-letter abbreviations.

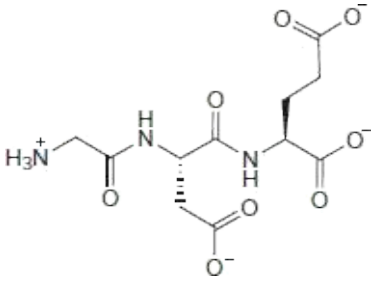
b. Draw the structure.

c. Label all amide bonds.

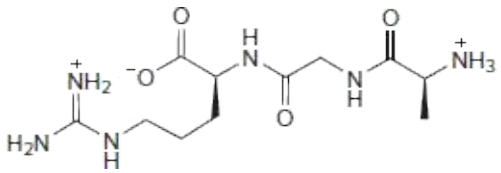
d. Label the N-terminal and C-terminal amino acids.

27.53 **Name each peptide using both the three-letter and one-letter abbreviations of the component amino acids.**

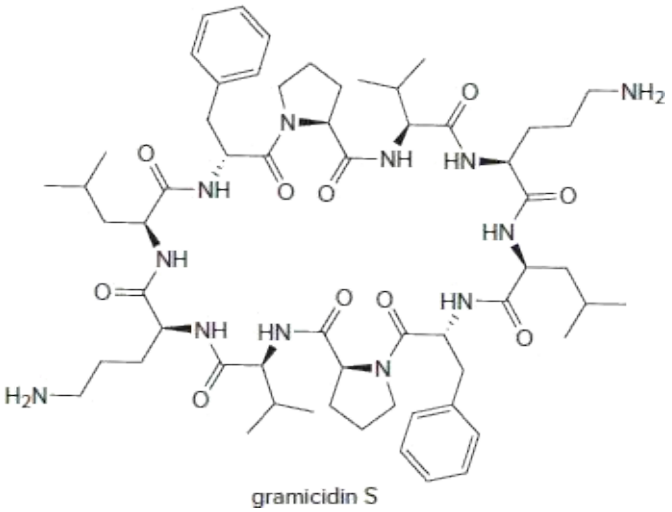
a.



b.



27.54 **Gramicidin S, a topical antibiotic produced by the bacterium *Bacillus brevis*, is a cyclic decapeptide formed from five amino acids. Draw the structures of the amino acids that form gramicidin S, and explain why this compound possesses two unusual structural features.**

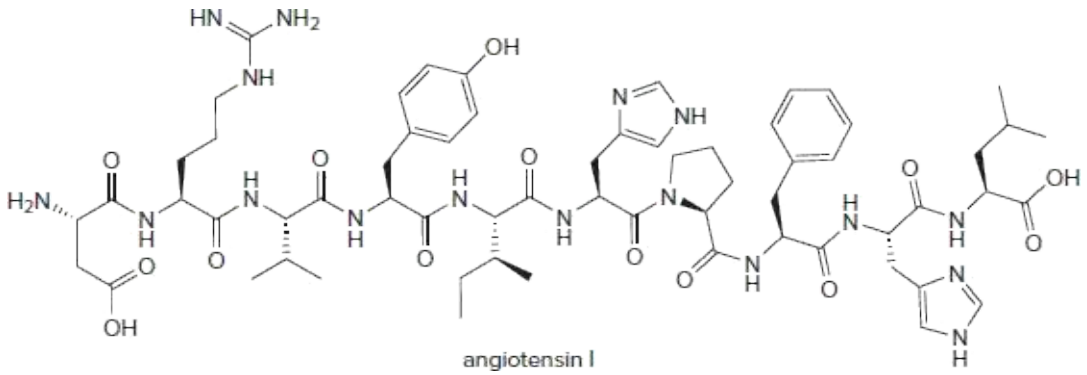


gramicidin S

27.55 **The dynorphins are a group of opioid peptides that play an important role in changes in the brain associated with cocaine addiction. One of these peptides, dynorphin A, contains the following amino acid sequence: Tyr–Gly–Gly–Phe–Leu–Arg–Arg–Ile–Arg–Pro–Lys–Leu–Lys. Draw the amino acids and peptide fragments formed when dynorphin A**

is treated with each reagent or enzyme: (a) chymotrypsin; (b) trypsin; (c) carboxypeptidase; (d) $C_6H_5N{=}C{=}S$.

27.56 Consider the decapeptide angiotensin I.



angiotensin I

a. What products are formed when angiotensin I is treated with trypsin?

b. What products are formed when angiotensin I is treated with chymotrypsin?

c. Treatment of angiotensin I with ACE (the angiotensin-converting enzyme) cleaves only the amide bond with the carbonyl group derived from phenylalanine to afford two products. The larger polypeptide is angiotensin II, a hormone that narrows blood vessels and increases blood pressure. Give the amino acid sequence of angiotensin II using three-letter abbreviations. ACE inhibitors are drugs that lower blood pressure by inhibiting the ACE enzyme (Problem 5.18).

27.57 Give the amino acid sequence of each peptide using the fragments obtained by partial hydrolysis of the peptide with acid.

a. a tetrapeptide that contains Ala, Gly, His, and Tyr, which is hydrolyzed to the dipeptides His–Tyr, Gly–Ala, and Ala–His

b. a pentapeptide that contains Glu, Gly, His, Lys, and Phe, which is hydrolyzed to His–Gly–Glu, Gly–Glu–Phe, and Lys–His

27.58 Glucagon, a hormone with 29 amino acids, is secreted by the pancreas. When the concentration of glucose in the bloodstream is too low, glucagon stimulates the liver to convert glycogen to glucose, thus increasing the blood glucose concentration. Deduce the amino acid sequence of glucagon from the following data. Treatment of glucagon with chymotrypsin forms: Thr–Ser–Asp–Tyr, Leu–Met–Asn–Thr, His–Ser–Gln–Gly–Thr–Phe, Ser–Lys–Tyr, Val–Gln–Trp, Leu–Asp–Ser–Arg–Arg–Ala–Gln–Asp–Phe. Treatment of glucagon with trypsin forms: Arg, Tyr–Leu–Asp–Ser–Arg, Ala–Gln–Asp–Phe–Val–Gln–Trp–Leu–Met–Asn–

Thr, His–Ser–Gln–Gly–Thr–Phe–Thr–Ser–Asp–Tyr–Ser–Lys.

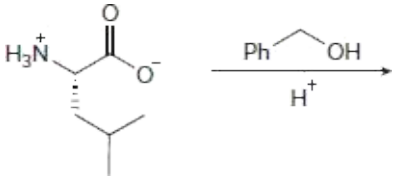
27.59 Use the given experimental data to deduce the sequence of an octapeptide that contains the following amino acids: Ala, Gly (2 equiv), His (2 equiv), Ile, Leu, and Phe. Edman degradation cleaves Gly from the octapeptide, and carboxypeptidase forms Leu and a heptapeptide. Partial hydrolysis forms the following fragments: Ile–His–Leu, Gly, Gly–Ala–Phe–His, and Phe–His–Ile.

27.60 An octapeptide contains the following amino acids: Arg, Glu, His, Ile, Leu, Phe, Tyr, and Val. Carboxypeptidase treatment of the octapeptide forms Phe and a heptapeptide. Treatment of the octapeptide with chymotrypsin forms two tetrapeptides, A and B. Treatment of A with trypsin yields two dipeptides, C and D. Edman degradation cleaves the following amino acids from each peptide: Glu (octapeptide), Glu (A), Ile (B), Glu (C), and Val (D). Partial hydrolysis of tetrapeptide B forms Ile–Leu in addition to other products. Deduce the structure of the octapeptide and fragments A–D.

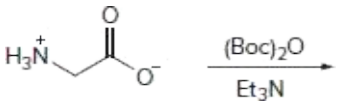
Peptide Synthesis

27.61 Draw the organic products formed in each reaction.

a.

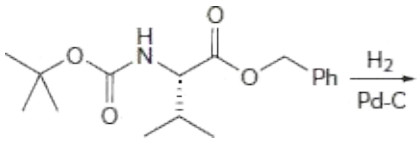


b.



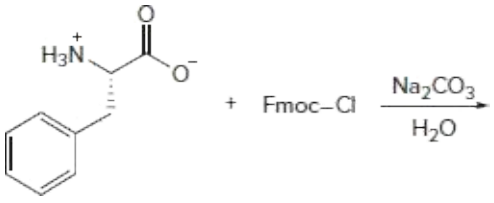
c. product in (a) + product in (b) $\xrightarrow{DCC}$

d.



e. product in (d) $\xrightarrow{CF_3COOH}$

f.



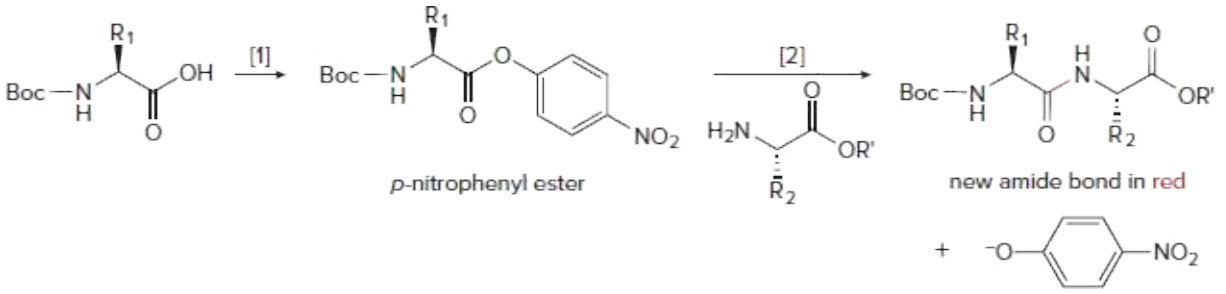
27.62 Draw all the steps in the synthesis of each peptide from individual amino acids: (a) Gly–Ala; (b) Ile–Ala–Phe.

27.63 Write out the steps for the synthesis of each peptide using the Merrifield method: (a) Ala–Leu–Phe–Phe; (b) Phe–Gly–Ala–Ile.

27.64 Another method to form a peptide bond involves a two-step process:

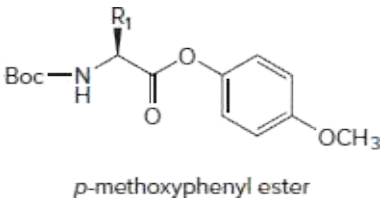
[1] Conversion of a Boc-protected amino acid to a *p*-nitrophenyl ester.

[2] Reaction of the *p*-nitrophenyl ester with an amino acid ester.



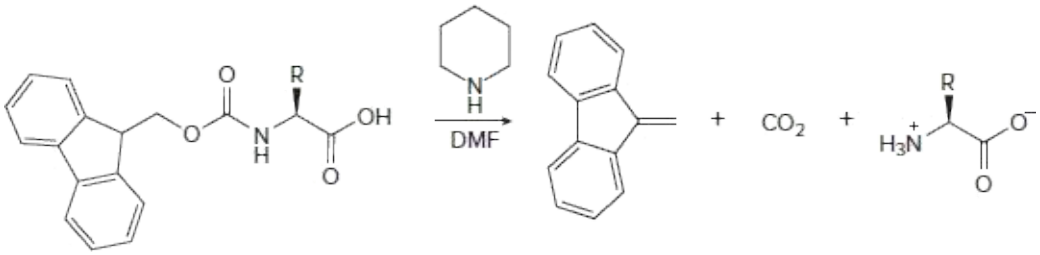
a. Why does a *p*-nitrophenyl ester "activate" the carboxy group of the first amino acid to amide formation?

b. Would a *p*-methoxyphenyl ester perform the same function? Why or why not?



p-methoxyphenyl ester

27.65 Draw the mechanism for the reaction that removes an Fmoc group from an amino acid under these conditions:



Proteins

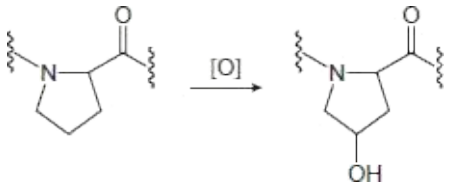
27.66 Which of the following amino acids are typically found in the interior of a globular protein, and which are typically found on the surface: (a) phenylalanine; (b) aspartic acid; (c) lysine; (d) isoleucine; (e) arginine; (f) glutamic acid?

27.67 Decide if the side chains of the following peptides are nonpolar or polar, and label the hydrophobic and hydrophilic end of each peptide.

a. VLLFGEDEK

b. RKYSFLGAA

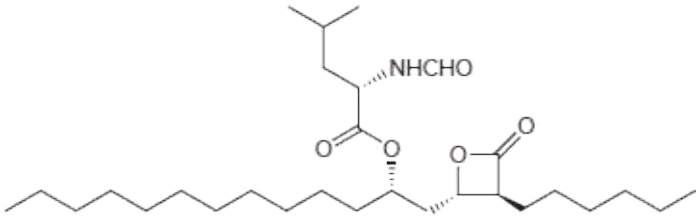
27.68 **After the peptide chain of collagen has been formed, many of the proline residues are hydroxylated on one of the ring carbon atoms. Why is this process important for the triple helix of collagen?**



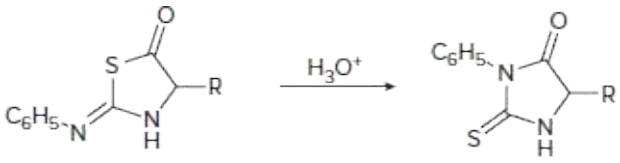
Challenge Problems

27.69 **Devise a stepwise synthesis of the tripeptide Val–Leu–Val from 3-methylbutanal [$(CH_3)_2CHCH_2CHO$] as the only organic starting material. You may also use any required inorganic or organic reagents.**

27.70 **The anti-obesity drug orlistat works by irreversibly inhibiting pancreatic lipase, an enzyme responsible for the hydrolysis of triacylglycerols in the intestines, so that they are excreted without metabolism. Inhibition occurs by reaction of orlistat with a serine residue of the enzyme, forming a covalently bound, inactive enzyme product. Draw the structure of the product formed during inhibition.**



27.71 **As shown in Mechanism 27.2, the final steps in the Edman degradation result in rearrangement of a thiazolinone to an *N*-phenylthiohydantoin. Draw a stepwise mechanism for this acid-catalyzed reaction.**



thiazolinone *N*-phenylthiohydantoin

28

Synthetic Polymers

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28.1 Introduction
28.2 Chain-growth polymers—Addition polymers
28.3 Anionic polymerization of epoxides
28.4 Ziegler–Natta catalysts and polymer stereochemistry
28.5 Natural and synthetic rubbers
28.6 Step-growth polymers—Condensation polymers
28.7 Polymer structure and properties
28.8 Green polymer synthesis
28.9 Polymer recycling and disposal

Polyethylene terephthalate (PET) is a synthetic polymer formed by the reaction of ethylene glycol ($HOCH_2CH_2OH$) and terephthalic acid. Because PET is lightweight and impervious to air and moisture, it is commonly used for transparent soft drink containers. PET is also used to produce synthetic fibers, sold under the trade name Dacron. Of the six most common synthetic polymers, PET is the most easily recycled, in part because beverage bottles that bear the recycling code "1" are composed almost entirely of PET. Recycled polyethylene terephthalate is used for fleece clothing and carpeting. In Chapter 28, we learn about the preparation and properties of synthetic polymers like polyethylene terephthalate.

Why Study…

Synthetic Polymers?

Chapter 28 discusses polymers, large organic molecules composed of repeating units—called monomers—that are covalently bonded together. Polymers occur naturally, as in the polysaccharides and proteins of Chapters 26 and 27, respectively, or they are synthesized in the laboratory.

This chapter concentrates on synthetic polymers, and expands on the material already

presented in Chapters 13 and 20. Thousands of synthetic polymers have now been prepared. Whereas some exhibit properties that mimic naturally occurring compounds, many others have unique properties. Although all polymers are large molecules, the size and branching of the polymer chain and the identity of the functional groups all contribute to determining an individual polymer's properties, thus making it suited for a particular product.

A polymer is a large organic molecule composed of repeating units—called monomers—that are covalently bonded together. The word *polymer* is derived from the Greek words *poly* + *meros* meaning "many parts."

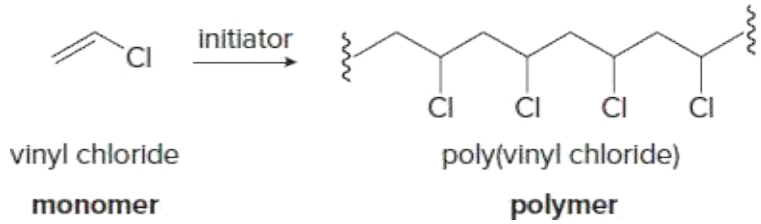
Polymerization is the joining together of monomers to make polymers.

28.1 Introduction

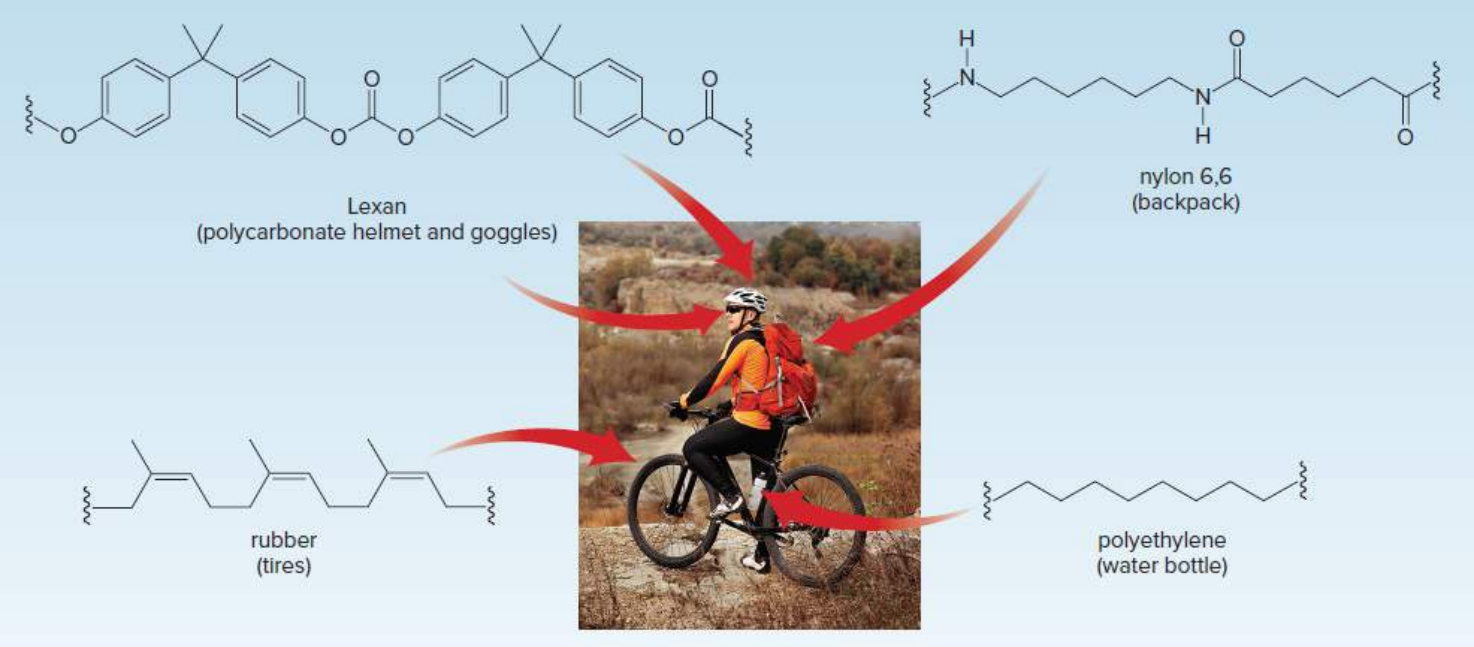
Synthetic polymers are perhaps more vital to the fabric of modern society than any other group of compounds prepared in the laboratory. Nylon backpacks and polyester clothing, car bumpers and CD cases, milk jugs and grocery bags, artificial heart valves and condoms—all these products and innumerable others are made of synthetic polymers. Since 1976, the U.S. production of synthetic polymers has exceeded its steel production. Figure 28.1 illustrates several consumer products and the polymers from which they are made.

Synthetic polymers can be classified as chain-growth or step-growth polymers.

- **Chain-growth polymers, also called addition polymers, are prepared by chain reactions.**



These compounds are formed by adding monomers to the growing end of a polymer chain. The conversion of vinyl chloride to poly(vinyl chloride) is an example of chain-growth polymerization. These reactions were introduced in Section 13.14.



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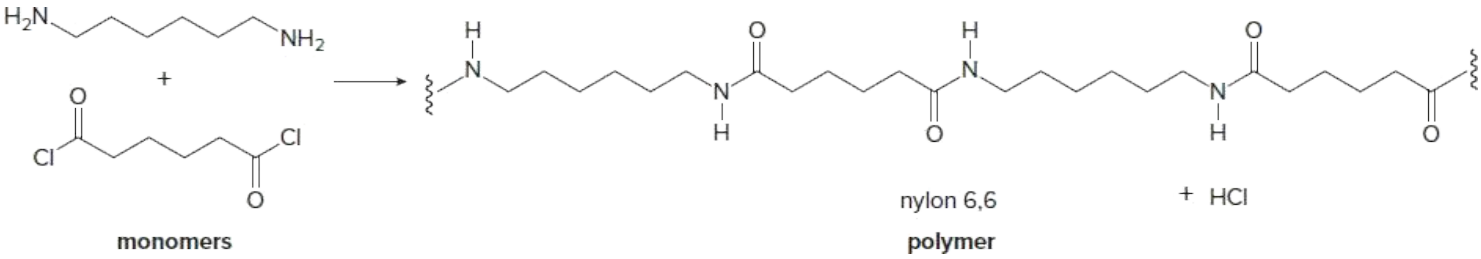
• We are surrounded by synthetic polymers in our daily lives. This cyclist rides on synthetic rubber tires, drinks from a polyethylene water bottle, wears a protective Lexan helmet and goggles, and uses a lightweight nylon backpack.

Figure 28.1 **Polymers in some common consumer products**

- **Step-growth polymers, also called condensation polymers, are formed when monomers containing two functional groups come together and lose a small molecule such as H_2O or HCl.**



In this method, any two reactive molecules can combine, so the monomer is not necessarily added to the end of a growing chain. Step-growth polymerization is used to prepare polyamides and polyesters, as discussed in Section 20.15.

In contrast to many of the organic molecules encountered in Chapters 1–23, which have molecular weights much less than 1000 grams per mole (g/mol), polymers generally have high molecular weights, ranging from 10,000 to 1,000,000 grams per mole (g/mol). Synthetic polymers are really mixtures of individual polymer chains of varying lengths, so the reported molecular weight is an average value based on the average size of the polymer chain.

By convention, we often simplify the structure of a polymer by placing brackets around

the repeating unit that forms the chain, as shown in Figure 28.2.

Problem 28.1

Give the shorthand structures of poly(vinyl chloride) and nylon 6,6 in Section 28.1.

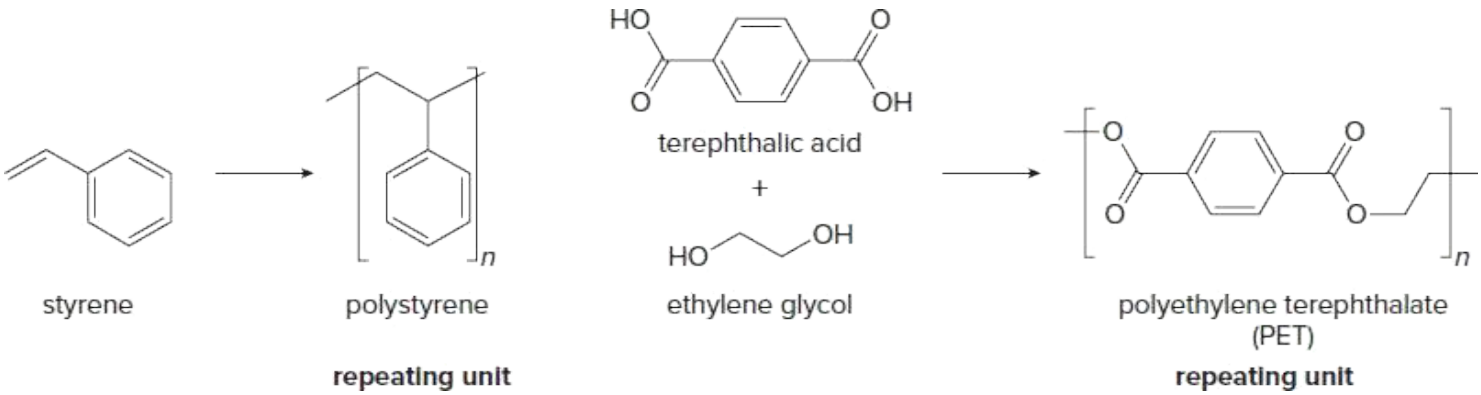
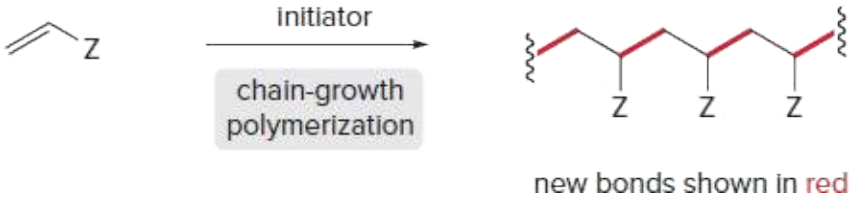


Figure 28.2 **Drawing a polymer in a shorthand representation**

28.2 Chain-Growth Polymers—Addition Polymers

Chain-growth polymerization is a chain reaction that converts an organic starting material, usually an alkene, to a polymer via a reactive intermediate—a radical, cation, or anion.



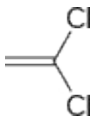
- **The alkene can be ethylene (CH_2=CH_2) or a derivative of ethylene (CH_2=CHZ or CH_2=CZ_2).**
- **The substituent Z (in part) determines whether radicals, cations, or anions are formed as intermediates.**
- **An initiator–a radical, cation, or anion–is needed to begin polymerization.**
- **Because chain-growth polymerization is a chain reaction, the mechanism involves initiation, propagation, and termination (Section 13.4).**

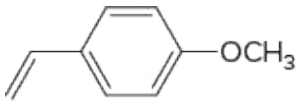
In most chain-growth polymerizations, an initiator adds to the carbon–carbon double bond of one monomer to form a reactive intermediate, which then reacts with another molecule of monomer to build the chain. Polymerization of

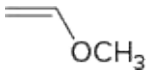
CH_2=CHZ results in a carbon chain having the Z substituents on every other carbon atom.

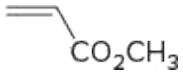
Problem 28.2

What polymer is formed by chain-growth polymerization of each monomer?

a. 

b. 

c. 

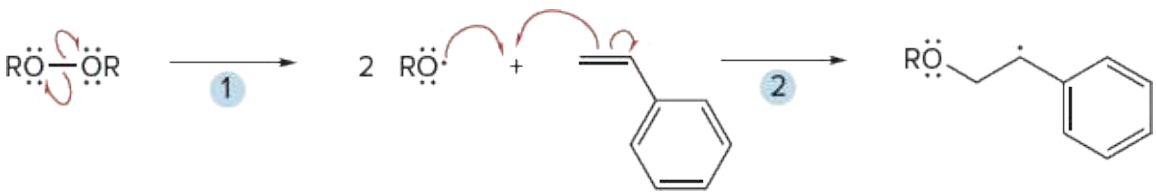
d. 

28.2A Radical Polymerization

Radical polymerization of alkenes was first discussed in Section 13.14, and is included here to emphasize its relationship to other methods of chain-growth polymerization. The initiator is often a peroxy radical (RO·), formed by cleavage of the weak O–O bond in an organic peroxide, ROOR. Mechanism 28.1 is written with styrene (CH_2=CHPh) as the starting material.

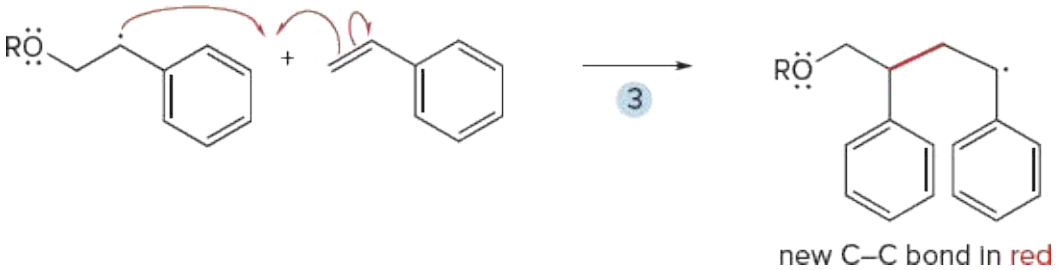
Mechanism 28.1 Radical Polymerization of CH_2=CHPh

Part [1] Initiation



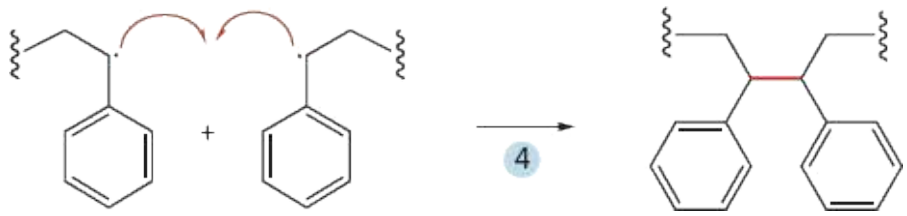
1 – 2 Initiation with ROOR occurs in two steps–homolysis of the weak O–O bond and addition of RO· to the alkene to form a carbon radical.

Part [2] Propagation



3 **Chain propagation consists of a single step. The carbon radical adds to another alkene to form a new C–C bond and another carbon radical. Addition forms the radical with the unpaired electron on the atom with the Z substituent. Step [3] occurs repeatedly to grow the polymer chain.**

Part [3] Termination



4 **Termination of the chain occurs when any two radicals combine to form a bond.**

Radical polymerization of $CH_2{=}CHZ$ is favored by Z substituents that stabilize a radical by electron delocalization. Each addition step occurs to put the intermediate radical on the carbon bearing the Z substituent. With styrene as the starting material, the intermediate radical is benzylic and highly resonance stabilized. Figure 28.3 shows several monomers used in radical polymerization reactions.

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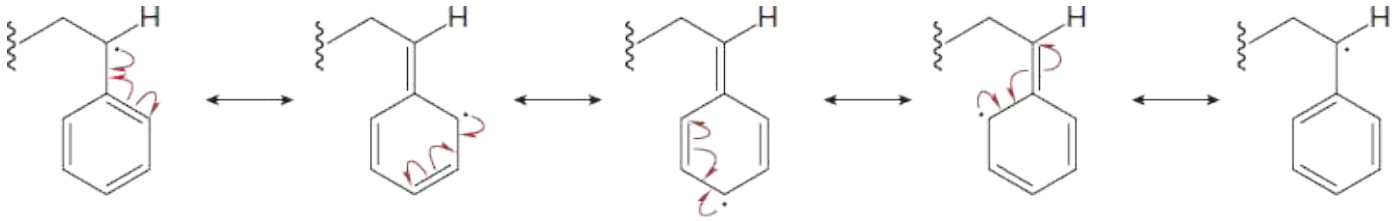
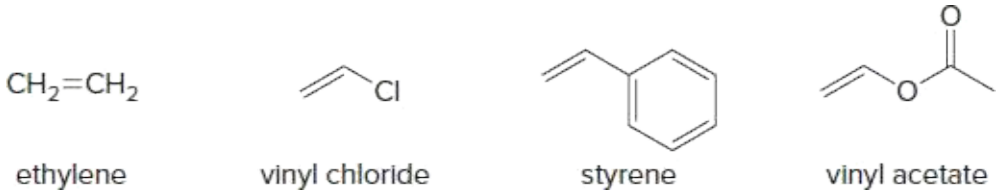


five resonance structures for the **benzylic radical**



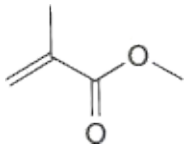
ethylene vinyl chloride styrene vinyl acetate

Figure 28.3 **Monomers used in radical polymerization reactions**

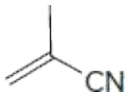
Problem 28.3

What polymer is formed by the radical polymerization of each monomer?

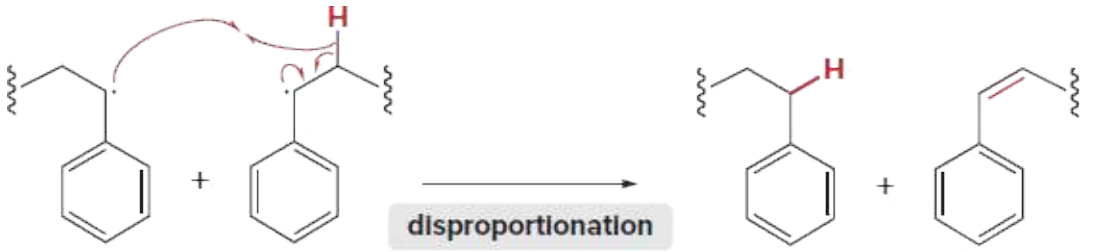
a.



b.



Chain termination can occur by radical coupling, as shown in Mechanism 28.1. Chain termination can also occur by disproportionation, a process in which a hydrogen atom is transferred from one polymer radical to another, forming a new C–H bond on one polymer chain, and a double bond on the other.

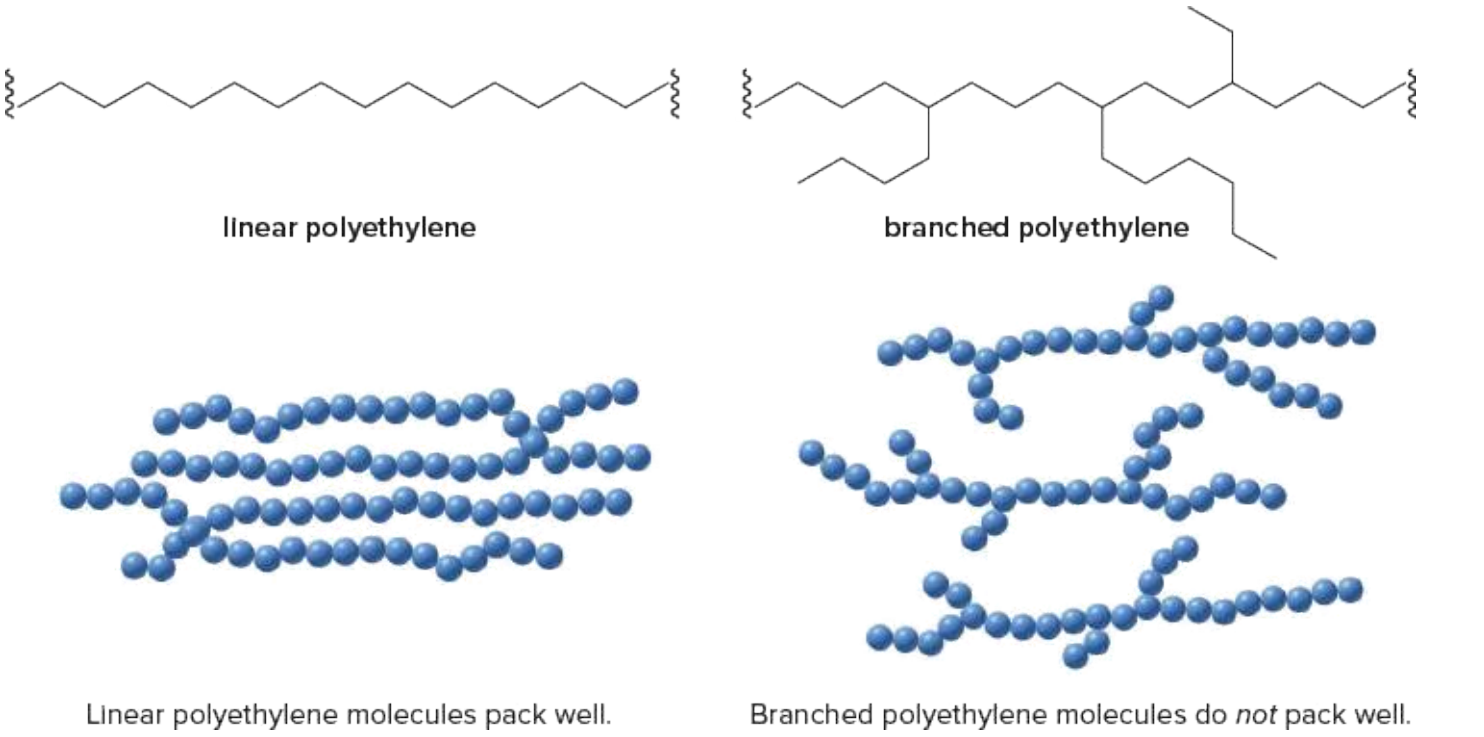


new C–H bond and π bond in red

HDPE is used in milk containers and water jugs, whereas LDPE is used in plastic bags and insulation.

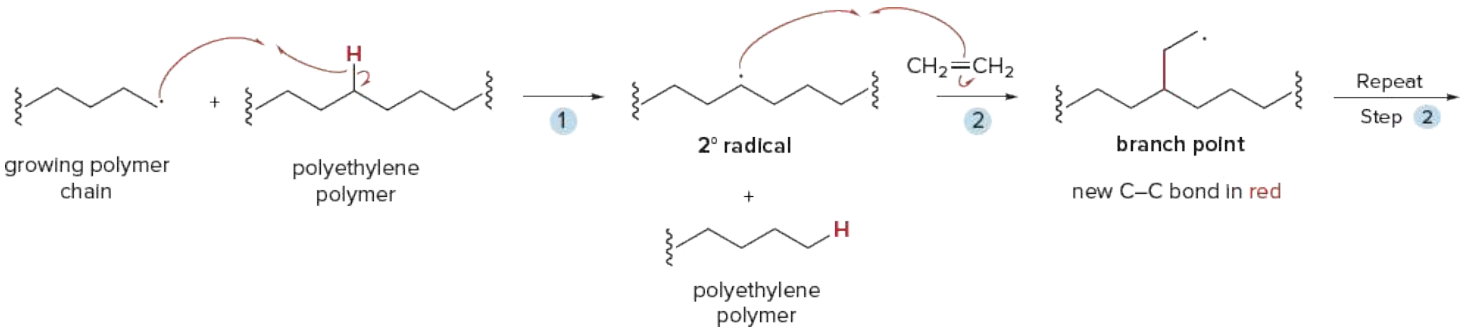
28.2B Chain Branching

The choice of reaction parameters greatly affects the properties of a synthetic polymer. In Section 13.14, we learned that there are two common types of polyethylene: high-density polyethylene (HDPE) and low-density polyethylene (LDPE). High-density polyethylene, which consists of long chains of CH_2 groups joined together in a linear fashion, is strong and hard because the linear chains pack well, resulting in strong van der Waals interactions. Low-density polyethylene, on the other hand, consists of long carbon chains with many branches along the chain. Branching prohibits the chains from packing well, so LDPE has weaker intermolecular interactions, making it a much softer, pliable material.



Branching occurs when a radical on one growing polyethylene chain abstracts a hydrogen atom from a CH_2 group in another polymer chain, as shown in Mechanism 28.2. The new 2° radical then continues chain propagation by adding to another molecule of ethylene, thus forming a branch point.

Mechanism 28.2 Forming Branched Polyethylene During Radical Polymerization

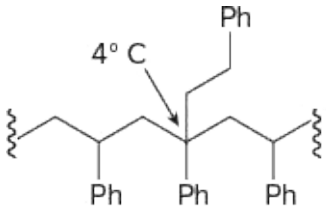


1 **Abstraction of a H atom from an existing polymer chain forms a 2° radical in the middle of the polymer chain.**

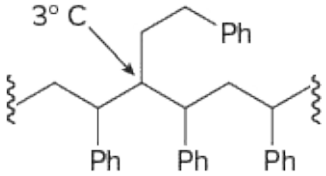
2 **Addition of the radical to another molecule of ethylene forms a new radical and a branch point along the polymer chain. Step [2] occurs repeatedly, and a long branch grows off the original polymer chain.**

Problem 28.4

Explain why radical polymerization of styrene forms branched chains with 4° carbons as in A, but none with 3° carbons as in B.



A



B

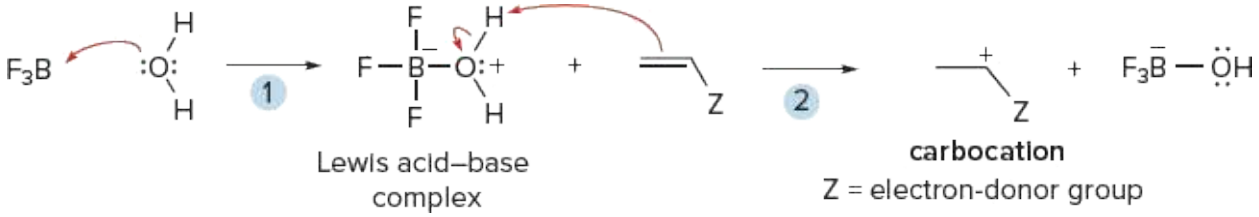
28.2C Ionic Polymerization

Chain-growth polymerization can also occur by way of cationic or anionic intermediates. Cationic polymerization is an example of electrophilic addition to an alkene involving carbocations. Cationic polymerization occurs with alkene monomers that have substituents capable of stabilizing intermediate carbocations, such as alkyl groups or other electron-donor groups. The initiator is an electrophile such as a proton source or Lewis acid.

Mechanism 28.3 illustrates cationic polymerization of the general monomer CH_2=CHZ using $BF_3 \cdot H_2O$, the Lewis acid–base complex formed from BF_3 and H_2O, as the initiator.

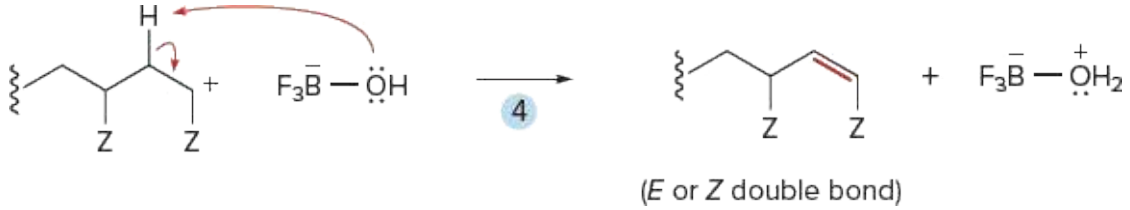
Mechanism 28.3 Cationic Polymerization of CH_2=CHZ

Part [1] Initiation



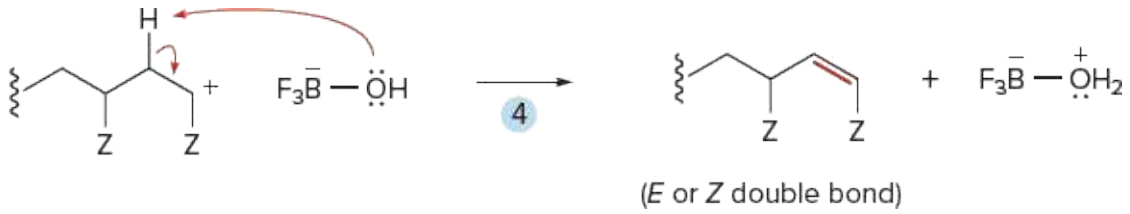
1 – 2 Electrophilic addition of H^+ from $BF_3 \cdot H_2O$ forms a carbocation.

Part [2] Propagation



3 The carbocation adds to another alkene to form a new C–C bond. Addition forms a carbocation stabilized by an electron-donor Z group. Step [3] occurs repeatedly to grow the polymer chain.

Part [3] Termination



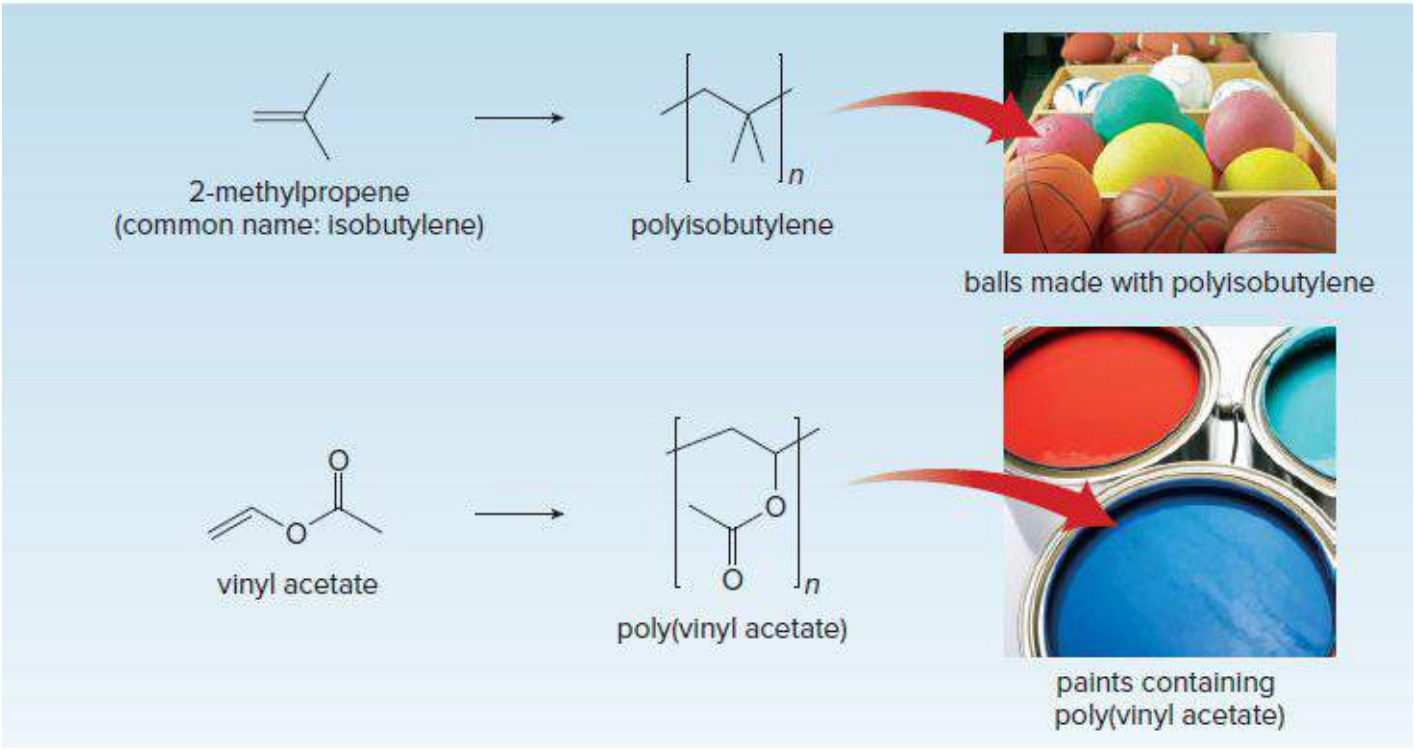
(*E* or *Z* double bond)

4 **Loss of a proton forms a new π bond and terminates the chain.**

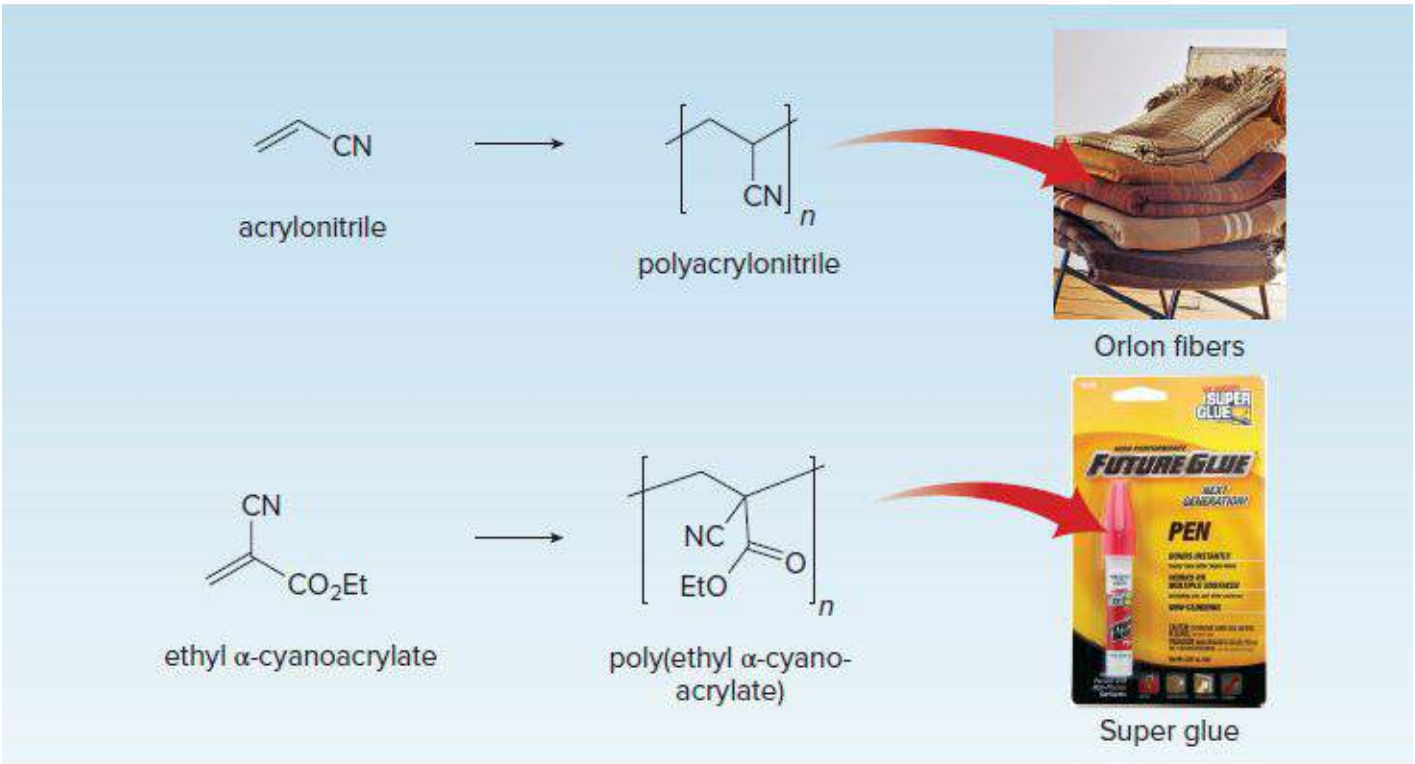
Because cationic polymerization involves carbocations, addition follows Markovnikov's rule to form the more stable, more substituted carbocation. Chain termination can occur by a variety of pathways, such as loss of a proton to form an alkene. Examples of alkene monomers that undergo cationic polymerization are shown in Figure 28.4.

Monomer	⟶	Polymer	Consumer product

- Polymers formed by **cationic** polymerization



- Polymers formed by **anionic** polymerization



- A chain-growth polymer is named by adding the prefix *poly* to the name of the monomer from which it is made. When the name of the monomer contains two words, this name is enclosed in parentheses and preceded by the prefix *poly*.

©Dynamicgraphics/JupiterImages; ©Fuse/Corbis/Getty Images;
©Fernando Bengoe/Corbis/Getty Images; ©McGraw-Hill Education/John Thoeming, photographer

Figure 28.4 **Common polymers formed by ionic chain-growth polymerization**

Problem 28.5

Explain why cationic polymerization is an effective method of polymerizing $CH_2=C(CH_3)_2$ but not $CH_2=CH_2$.

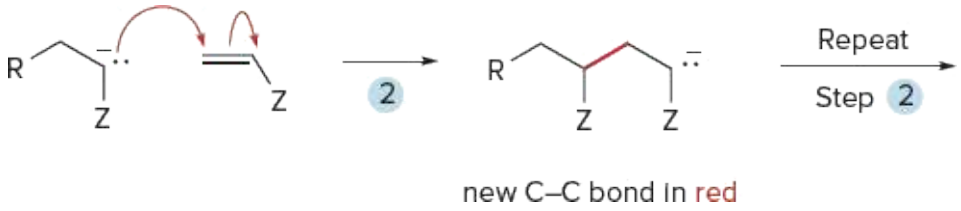
Although alkenes readily react with electron-deficient radicals and electrophiles, alkenes do *not* generally react with anions and other nucleophiles. Consequently, anionic polymerization takes place only with alkene monomers that contain electron-withdrawing groups such as COR, COOR, or CN, which can stabilize an intermediate negative charge. The initiator is a strong nucleophile, such as an organolithium reagent, RLi. Mechanism 28.4 illustrates anionic polymerization of the general monomer $CH_2=CHZ$.

Mechanism 28.4 Anionic Polymerization of $CH_2=CHZ$

Part [1] Initiation

1 **Nucleophilic addition of RLi forms a carbanion stabilized by an electron-withdrawing group Z.**

Part [2] Propagation



2 **The carbanion adds to another alkene to form a new C–C bond. Addition forms a new carbanion with the negative charge adjacent to the Z substituent. Step [2] occurs repeatedly to grow the polymer chain.**

Part [3] Termination

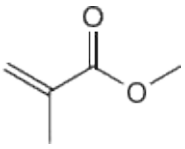
3 **An acid–base reaction with H_2O or another electrophile terminates the**

chain.

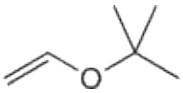
In contrast to other types of chain-growth polymerization, there are no efficient methods of terminating the chain mechanism in anionic polymerization. The reaction continues until all the initiator and monomer have been consumed, so that the end of each polymer chain contains a carbanion (Step [2] in Mechanism 28.4). Anionic polymerization is often called living polymerization because polymerization will begin again if more monomer is added at this stage. To terminate anionic polymerization, an electrophile such as H_2O or CO_2 must be added. Examples of alkene monomers that undergo anionic polymerization are shown in Figure 28.4.

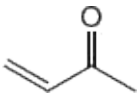
Problem 28.6

Which method of ionic polymerization—cationic or anionic—is preferred for each monomer? Explain your choices.

a. 

b.

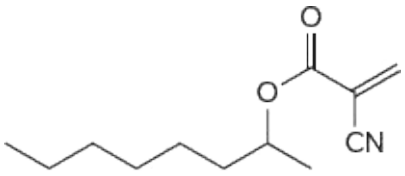
c. 

d. 

Dermabond (Problem 28.7) is a clear liquid containing 2-octyl cyanoacrylate, which polymerizes in moist air to form a tissue adhesive used to close wounds. ©*McGraw-Hill Education*

Problem 28.7

Draw the structure of Dermabond, the trade name for the polymer formed by anionic polymerization of 2-octyl cyanoacrylate.



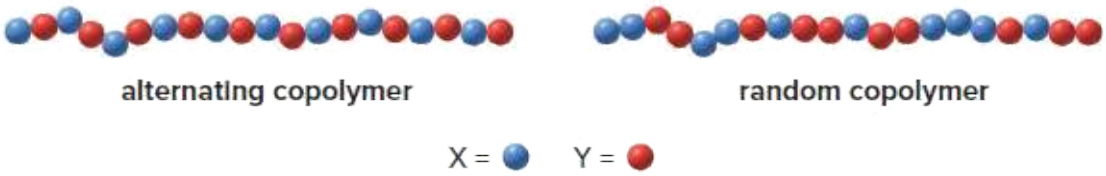
2-octyl cyanoacrylate

Problem 28.8

Explain why styrene (CH_2=CHPh) can be polymerized to polystyrene by all three methods of chain-growth polymerization.

28.2D Copolymers

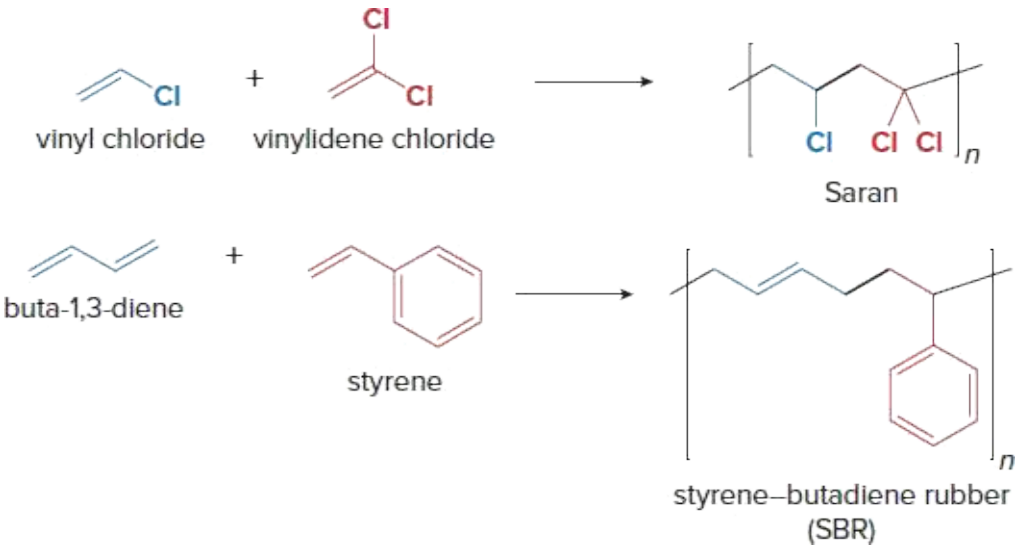
All polymers discussed thus far are homopolymers, because they have been prepared by the polymerization of a single monomer. Copolymers, on the other hand, are polymers prepared by joining two or more monomers (X and Y) together.



- **An *alternating copolymer* is formed when X and Y alternate regularly along the chain.**
- **A *random copolymer* is formed when X and Y are randomly distributed along the chain.**

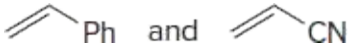
The structure of the copolymer depends on the relative amount and reactivity of X and Y, as well as the conditions used for polymerization.

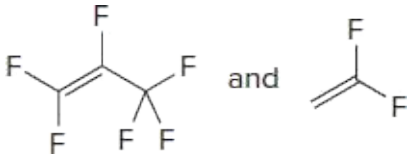
Several copolymers are commercially important and used in a wide range of consumer products. The copolymer of vinyl chloride and vinylidene chloride forms Saran, the film used in the well-known plastic food wrap. Copolymerization of buta-1,3-diene and styrene forms styrene–butadiene rubber (SBR), the polymer used almost exclusively in automobile tires.



Problem 28.9

Draw the alternating copolymer formed from each set of monomers.

a. 

b. 

Problem 28.10

ABS, a widely produced copolymer used in crash helmets, small appliances, and toys, is formed from three monomers–acrylonitrile (CH_2=CHCN), buta-1,3-diene (CH_2=CH–CH=CH_2), and styrene (CH_2=CHPh). Draw a possible structure for ABS.

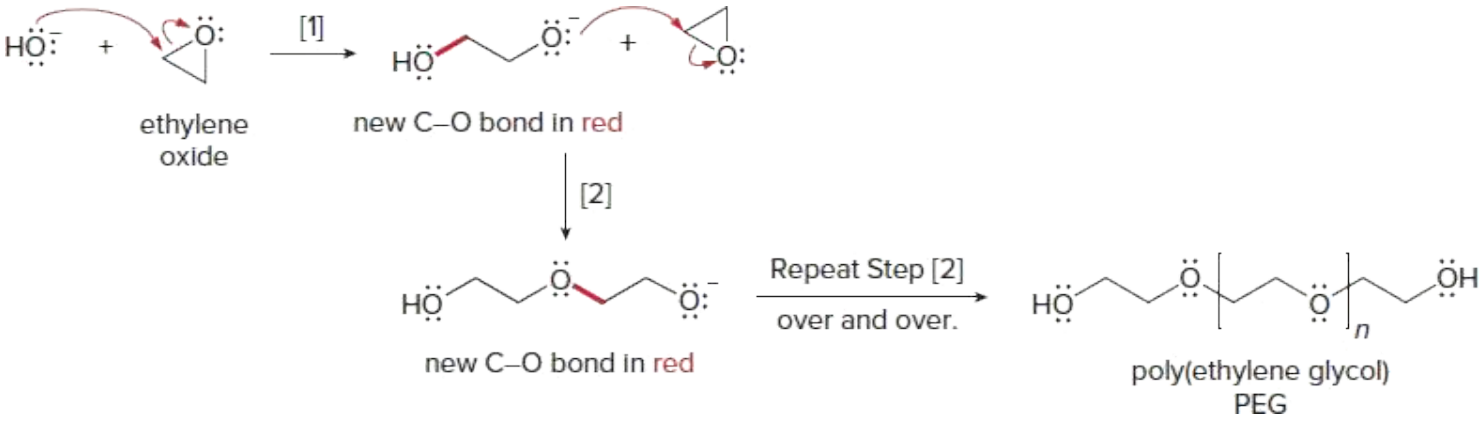
Lego bricks are made from the copolymer ABS (Problem 28.10). ©*Savushkin/Getty Images*

28.3 Anionic Polymerization of Epoxides

Alkene monomers are the most common starting materials in chain-growth polymerizations, but epoxides can also serve as starting materials, forming polyethers.

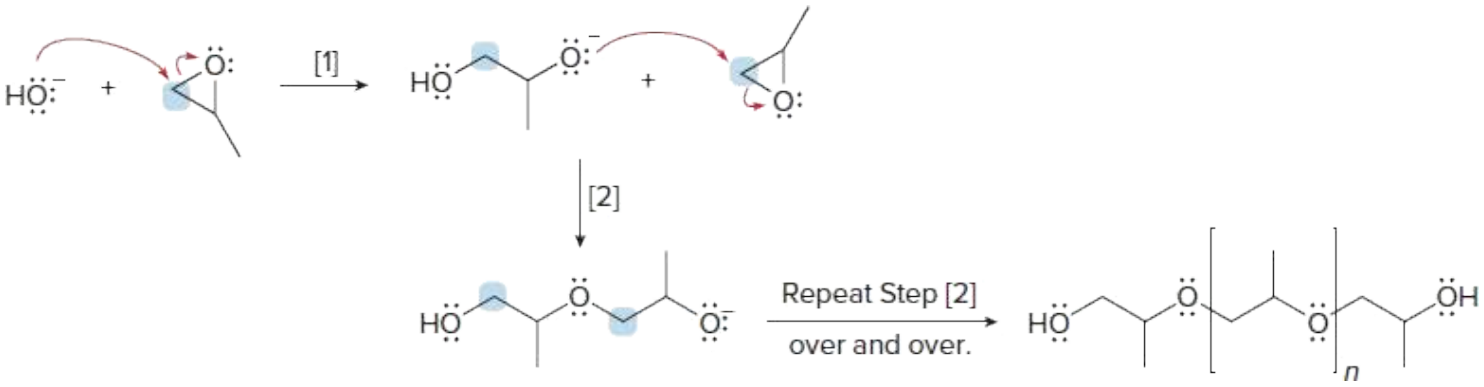
The strained three-membered ring of an epoxide is readily opened with a nucleophile (such as $^-$OH or $^-$OR) to form an alkoxide, which can then ring open another epoxide monomer to build the polymer chain. Unlike the other methods of chain-growth polymerization that join monomers with C–C bonds, this process forms new C–O bonds in the polymer backbone.

For example, the ring opening of ethylene oxide with a $^-$OH initiator affords an alkoxide nucleophile, which propagates the chain by reacting with more ethylene oxide. This process yields poly(ethylene glycol), PEG, a polymer used in lotions and creams. The many C–O bonds in these polymers make them highly water soluble.



The ring opening of epoxides with nucleophiles was first discussed in Section 9.15.

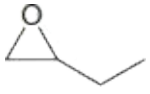
Under anionic conditions, the ring opening follows an S_N2 mechanism. Thus, the ring opening of an unsymmetrical epoxide occurs at the more accessible, less substituted carbon, labeled in blue.

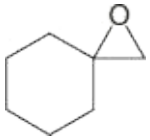


Problem 28.11

What polymer is formed by anionic polymerization of each monomer?

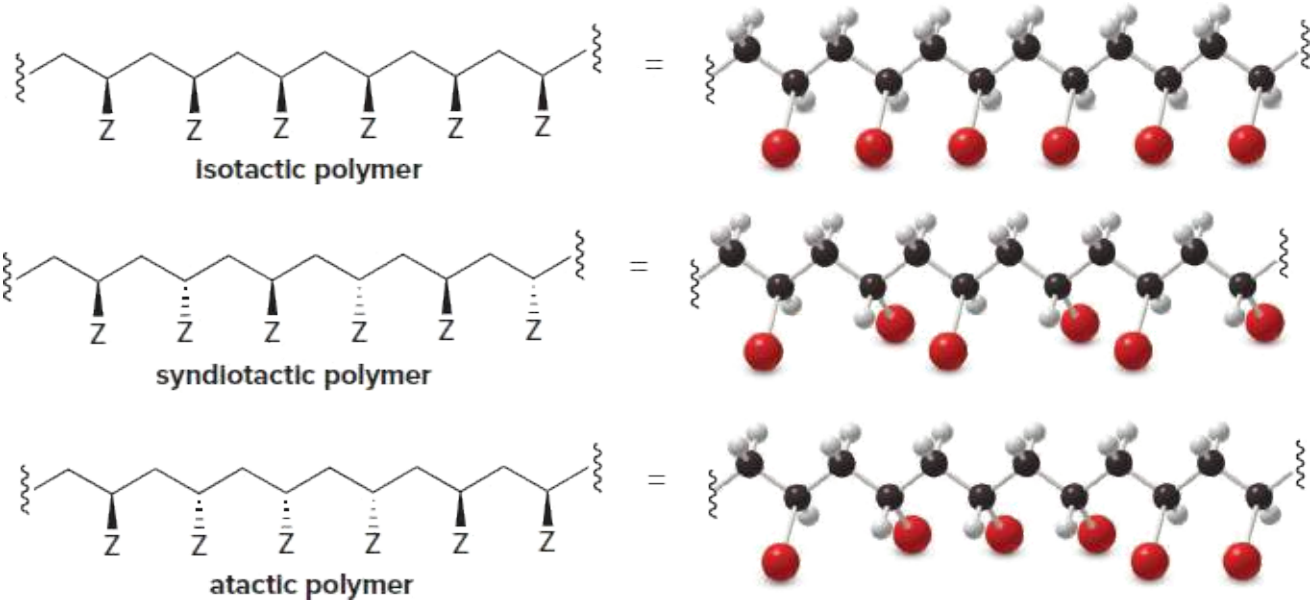
a.



b. 

28.4 Ziegler–Natta Catalysts and Polymer Stereochemistry

Polymers prepared from monosubstituted alkene monomers (CH_2=CHZ) can exist in three different configurations, called isotactic, syndiotactic, and atactic:



- **An *isotactic* polymer has all Z groups on the same side of the carbon backbone.**
- **A *syndiotactic* polymer has the Z groups alternating from one side of the carbon chain to the other.**
- **An *atactic* polymer has the Z groups oriented randomly along the polymer chain.**

The more regular arrangement of the Z substituents in isotactic and Page 1270 syndiotactic polymers allows them to pack together better, making the polymer stronger and more rigid. In contrast, the chains of an atactic polymer tend to pack less closely together, resulting in a lower-melting, softer polymer. Radical polymerization often affords an atactic polymer, but the particular reaction conditions can greatly affect the stereochemistry of the polymer formed.

In 1953, Karl Ziegler and Giulio Natta developed a new method of polymerizing alkene monomers using a metal catalyst to promote chain-growth polymerization. These catalysts, now called Ziegler–Natta catalysts, offer two advantages over other methods

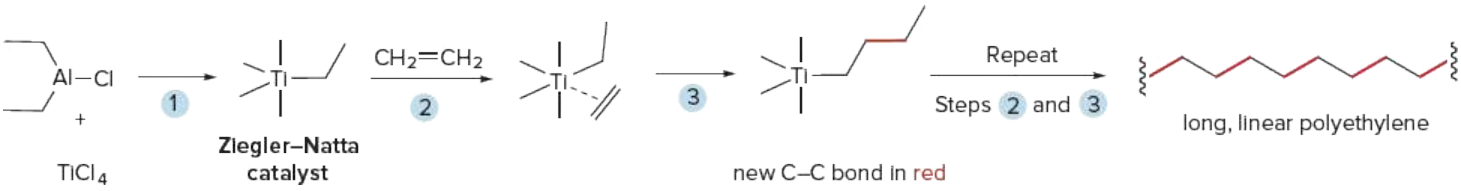
of chain-growth polymerization.

- **The stereochemistry of the polymer is easily controlled. Polymerization affords isotactic, syndiotactic, or atactic polymers depending on the catalyst.**
- **Long, linear chains of polymer are prepared without significant branching. Radicals are not formed as reactive intermediates, so intermolecular hydrogen abstraction, which leads to chain branching, does not occur.**

Ziegler and Natta received the 1963 Nobel Prize in Chemistry for their pioneering work on polymerization catalysts.

Many different Ziegler–Natta catalysts are used for polymerization, but most consist of an organoaluminum compound such as $(CH_3CH_2)_2AlCl$ and $TiCl_4$, a Lewis acid. The active catalyst is thought to be an alkyl titanium compound, formed by transfer of an ethyl group from $(CH_3CH2)_2AlCl$ to $TiCl_4$, although many mechanistic details are not known with certainty. It is generally agreed that the alkene monomer coordinates to an alkyl titanium complex, and then inserts into the Ti–C bond to form a new carbon–carbon bond, as shown in Mechanism 28.5.

Mechanism 28.5 Ziegler–Natta Polymerization of $CH_2=CH_2$



1. **Reaction of the organoaluminum compound with $TiCl_4$ forms the Ziegler–Natta catalyst with a Ti–C bond.**
2. **An alkene monomer coordinates with the Ti complex.**
3. **Insertion of $CH_2=CH_2$ into the Ti–C bond forms a new C–C bond. Repeating Steps [2] and [3] over and over yields the long polymer chain.**

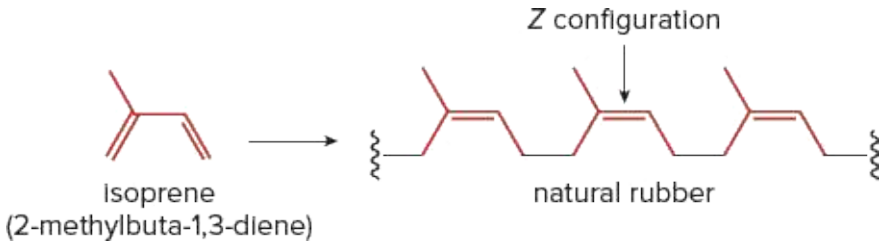
Dyneema, the strongest fabric known, is made of ultra high-density polyethylene and is used for ropes, nets, bulletproof vests, and crash helmets. ©*DSM Dyneema*

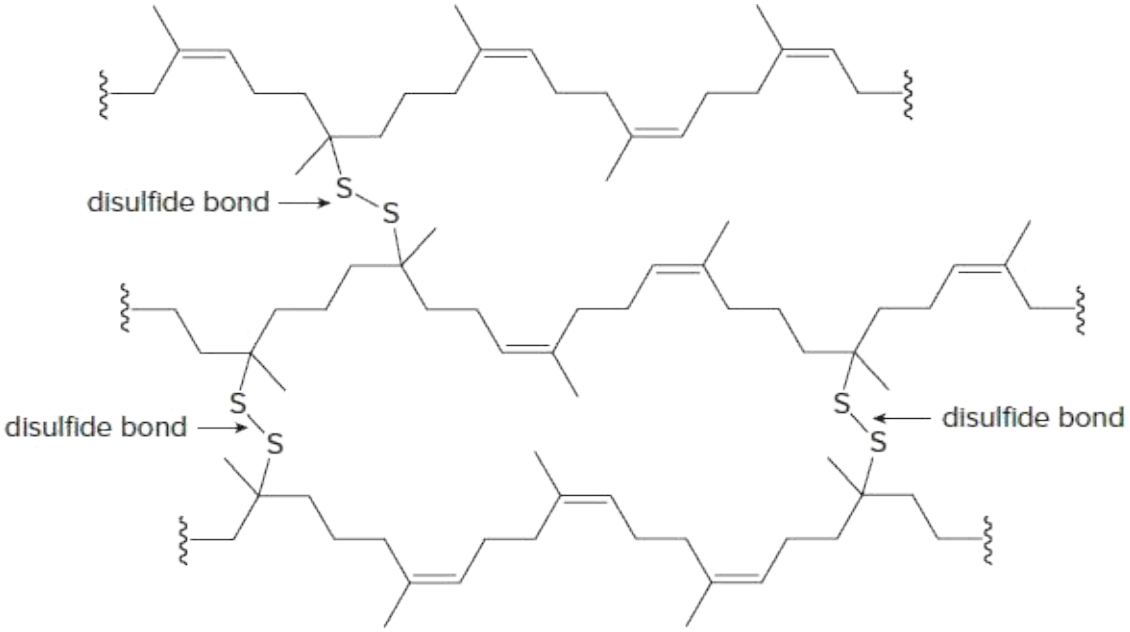
The Ziegler–Natta polymerization of ethylene forms high-density polyethylene, HDPE, composed of long linear carbon chains that pack closely together, forming a rigid polymer. By using specialized manufacturing techniques that force the polymer chains to pack closely in the solid phase as a set of linear extended chains, this material is converted to ultra high-density polyethylene, a synthetic organic material stronger than steel.

Recently developed Ziegler–Natta polymerizations utilize zirconium complexes that are soluble in the reaction solvents typically used, so they are homogeneous catalysts. Reactions that use these soluble catalysts are called coordination polymerizations.

28.5 Natural and Synthetic Rubbers

Natural rubber is composed of repeating five-carbon units, in which all the double bonds have the *Z* configuration. Because natural rubber is a hydrocarbon, it is water insoluble and thus useful for waterproofing. The *Z* double bonds cause bends and kinks in the polymer chain, making it a soft material.





• Vulcanized rubber contains many disulfide bonds that cross-link the hydrocarbon chains together.

Figure 28.5 **Vulcanized rubber**

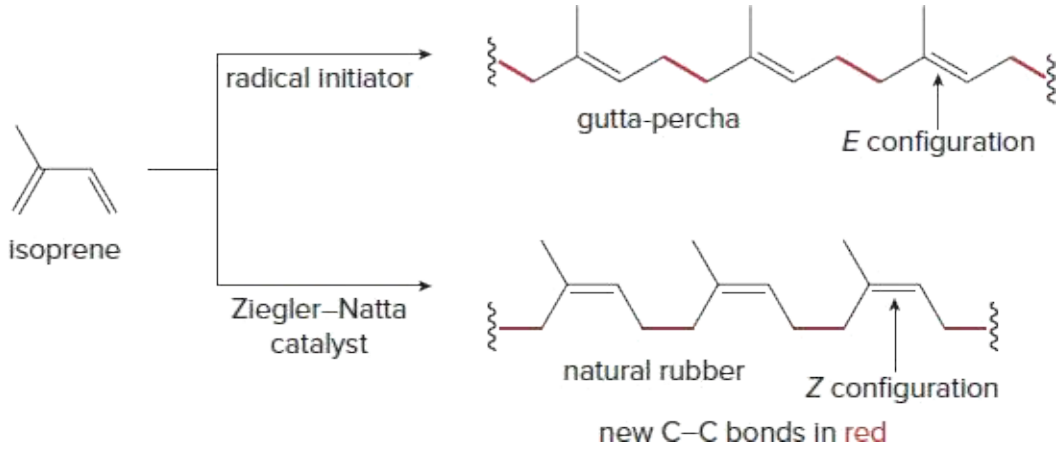
Natural rubber is obtained from latex that oozes from cuts made to the bark of the rubber tree. Waterproof latex is the rubber tree's natural protection, exuded in response to an injury. Although rubber was produced exclusively in Brazil until the late 1800s, today most of the world's rubber comes from plantations in Southeast Asia, Sri Lanka, and Indonesia.

©Suphatthra China/Shutterstock

Gutta-percha, a much harder material than natural rubber obtained from latex, is used in golf ball casings.

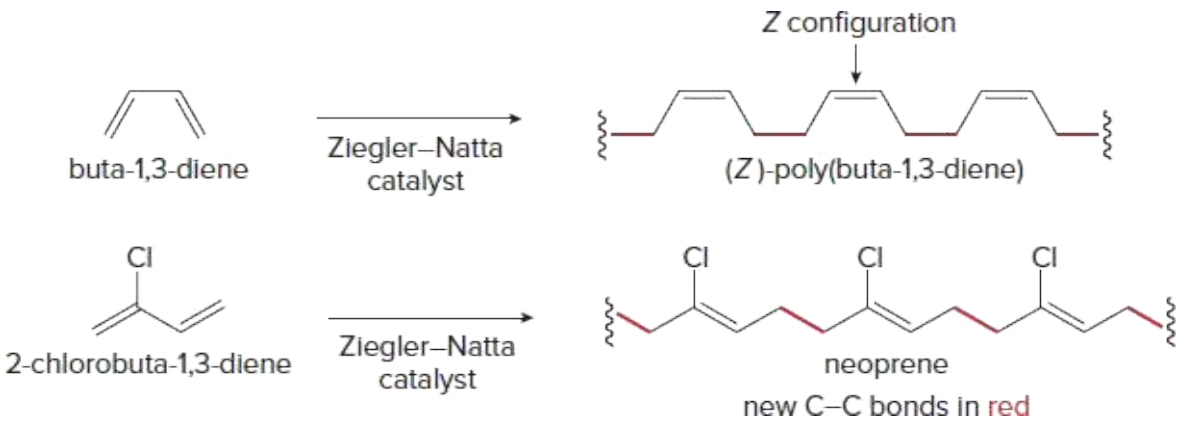
The degree of cross-linking affects the rubber's properties. Harder rubber used for automobile tires has more cross-linking than the softer rubber used for rubber bands.

The polymerization of isoprene under radical conditions forms a stereoisomer of natural rubber called gutta-percha, in which all the double bonds have the *E* configuration. Gutta-percha is also a naturally occurring polymer, although considerably less common than its *Z* stereoisomer. Polymerization of isoprene with a Ziegler–Natta catalyst forms natural rubber with all the double bonds having the desired *Z* configuration.



Natural rubber is too soft to be a useful material for most applications. Moreover, when natural rubber is stretched, the chains become elongated and slide past each other until the material pulls apart. In 1839, Charles Goodyear discovered that mixing hot rubber with sulfur produced a stronger and more elastic material. This process, called vulcanization, results in cross-linking of the hydrocarbon chains by disulfide bonds, as shown in Figure 28.5. When the polymer is stretched, the chains no longer can slide past each other and tearing does not occur. Vulcanized rubber is an *elastomer*, a polymer that stretches when stressed but then returns to its original shape when the stress is alleviated.

Other synthetic rubbers can be prepared by the polymerization of different 1,3-dienes using Ziegler–Natta catalysts. For example, the polymerization of buta-1,3-diene affords (Z)-poly(buta-1,3-diene), and the polymerization of 2-chlorobuta-1,3-diene yields neoprene, a polymer used in wet suits and tires.

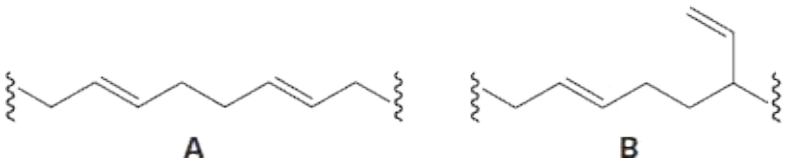


Problem 28.12

Assign the *E* or *Z* configuration to the double bonds in neoprene. Draw a stereoisomer of neoprene in which all the double bonds have the opposite configuration.

Problem 28.13

The polymerization of CH_2=CHCH=CH_2 under radical conditions affords products A and B. Draw a mechanism that accounts for their formation.



28.6 Step-Growth Polymers—Condensation Polymers

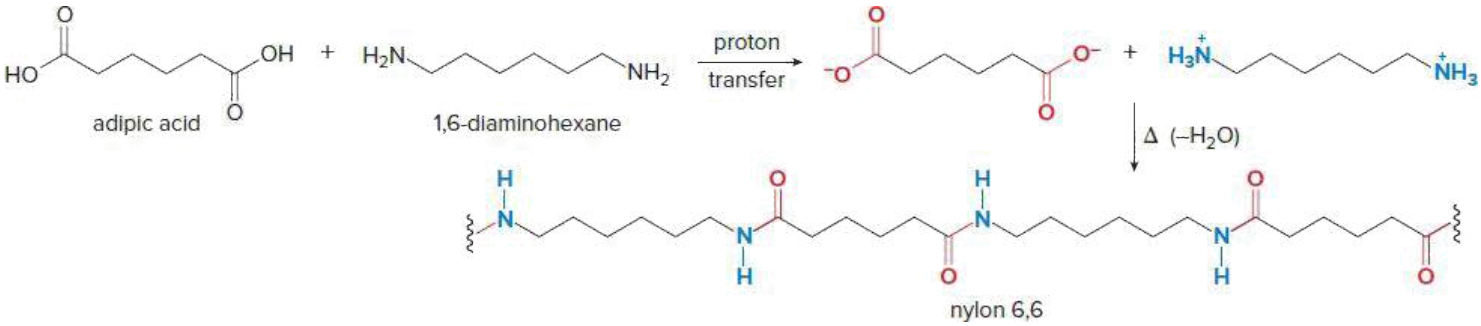
Step-growth polymers, the second major class of polymers, are formed when monomers containing two functional groups come together and lose a small molecule such as H_2O or HCl. Commercially important step-growth polymers include:

- Polyamides
- Polyesters
- Polyurethanes
- Polycarbonates
- Epoxy resins

Nylon 6,6 is used in many products including parachutes and clothing.

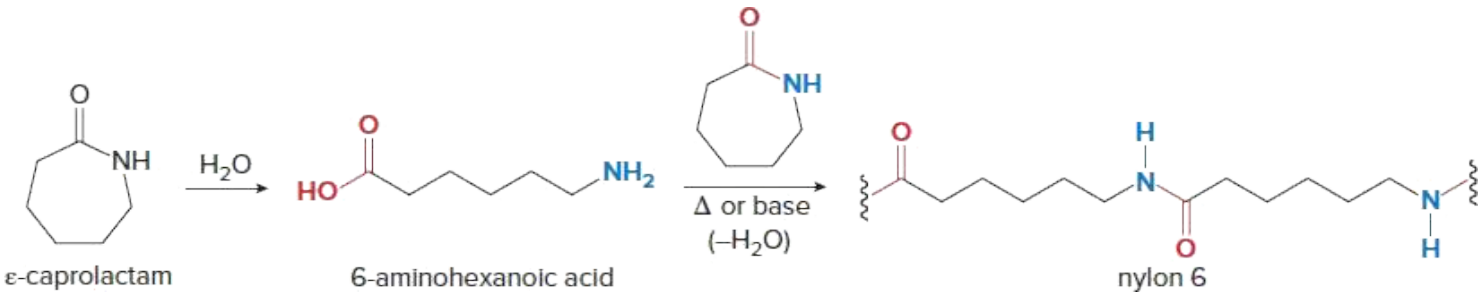
28.6A Polyamides

Nylons are polyamides formed by step-growth polymerization. In Section 20.15A, we learned that nylon 6,6 can be prepared by the reaction of a diacid chloride and a diamine. Nylon 6,6 can also be prepared by heating adipic acid and 1,6-diaminohexane. A Brønsted–Lowry acid–base reaction forms a diammonium salt, which loses H_2O at high temperature. In both methods, each starting material has two identical functional groups.



Nylon 6, trade name Perlon, is used to make rope and tire cord.

Nylon 6 is another polyamide, which is made by heating an aqueous solution of ε-caprolactam. The seven-membered ring of the lactam (a cyclic amide) is opened to form 6-aminohexanoic acid, the monomer that reacts with more lactam to form the polyamide chain. This step-growth polymerization thus begins with a single difunctional monomer that has two *different* functional groups, NH_2 and COOH.

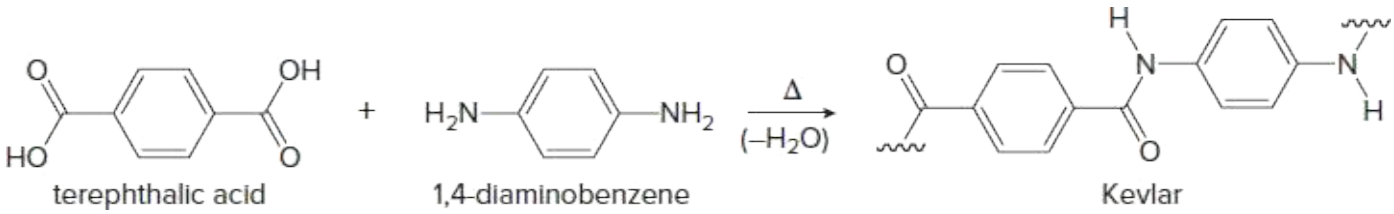


Kevlar is a polyamide formed from terephthalic acid and 1,4-diaminobenzene. The aromatic rings of the polymer backbone make the chains less flexible, resulting in a very strong material.

Armadillo bicycle tires reinforced with Kevlar are hard to pierce with sharp objects, so a cyclist rarely gets a flat tire.

©Specialized Bicycle Components

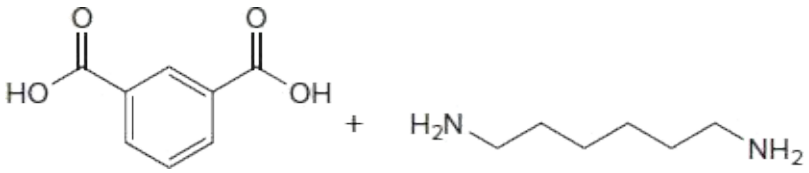
Kevlar is light in weight compared to other materials that are similar in strength, so it is used in many products, such as bulletproof vests, army helmets, and the protective clothing used by firefighters.



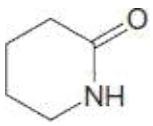
Problem 28.14

What polyamide is formed from each monomer or pair of monomers?

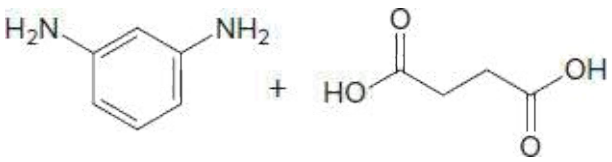
a.



b.

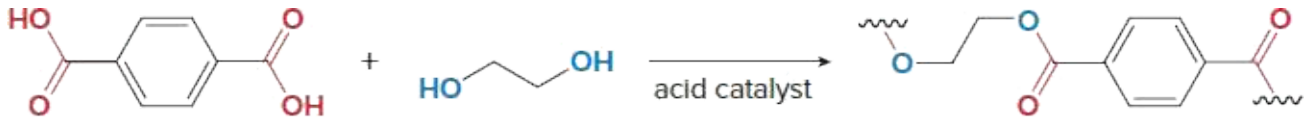


c.

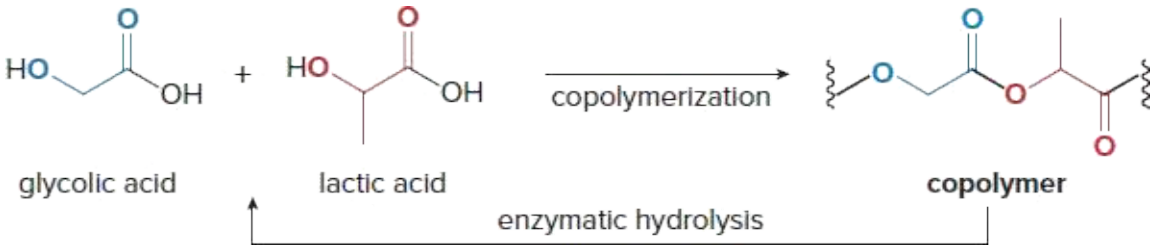


28.6B Polyesters

Polyesters are formed by step-growth polymerization using nucleophilic acyl substitution reactions, as we learned in Section 20.15B. For example, the reaction of terephthalic acid and ethylene glycol forms polyethylene terephthalate (PET), the chapter-opening molecule.

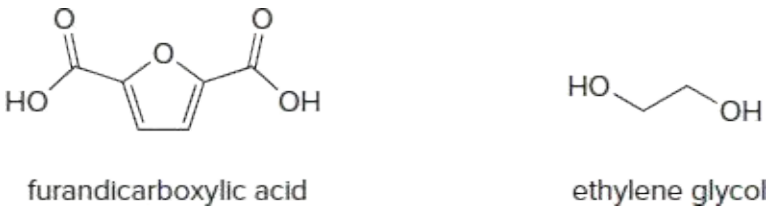


PET is a very stable material, but some polyesters are more readily hydrolyzed to carboxylic acids and alcohols in aqueous medium, making them suited for applications in which slow degradation is useful. For example, copolymerization of glycolic acid and lactic acid forms a copolymer used by surgeons in dissolving sutures. Within weeks, the copolymer is hydrolyzed to the monomers from which it was prepared, which are metabolized readily by the body. These sutures are used internally to hold tissues together while healing and scar formation occur.



Problem 28.15

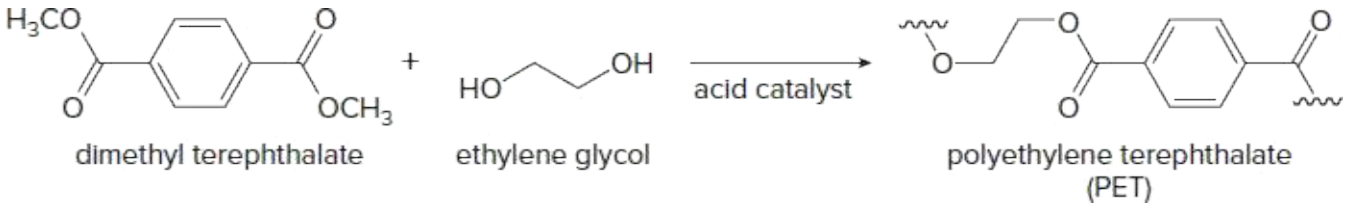
Draw the structure of PEF, polyethylene furanoate, a condensation polymer formed from furandicarboxylic acid and ethylene glycol. PEF, which can be synthesized from precursors that are obtained from renewable resources, has many of the same properties as polyethylene terephthalate (PET).



Problem 28.16

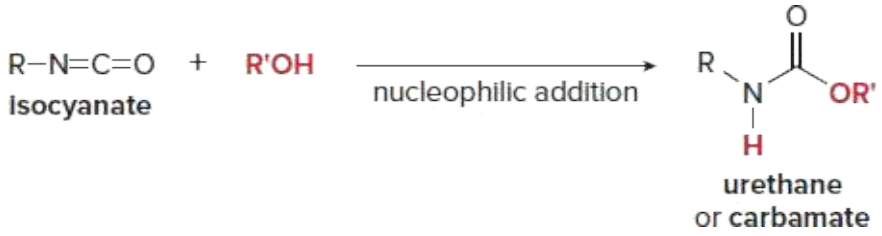
Polyethylene terephthalate is also prepared by the transesterification of dimethyl terephthalate with ethylene glycol. Draw the mechanism for this nucleophilic acyl

substitution.

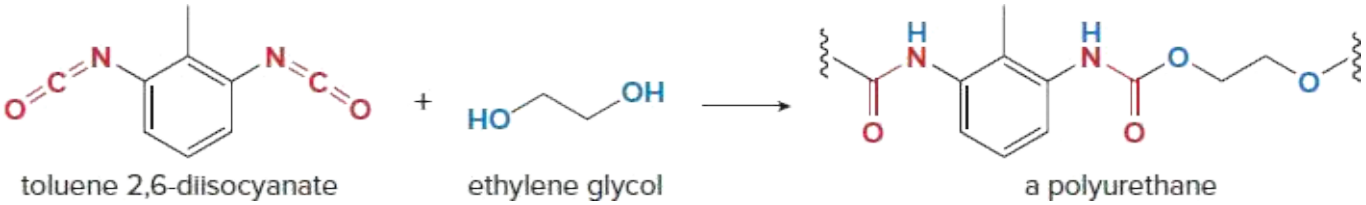


28.6C Polyurethanes

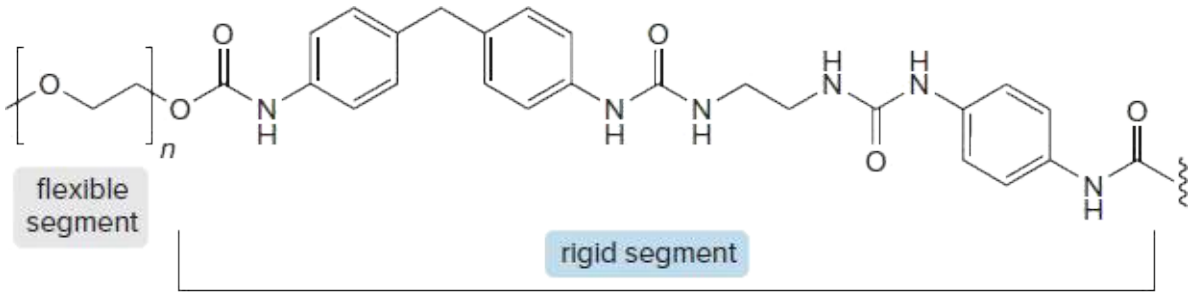
A urethane (also called a carbamate) is a compound that contains a carbonyl group bonded to both an OR group and an NHR (or NR_2) group (Section 27.7). Urethanes are prepared by the nucleophilic addition of an alcohol to the carbonyl group of an isocyanate, RN=C=O.



Polyurethanes are polymers formed by the reaction of a diisocyanate and a diol.



Spandex is a generic term for a strong and flexible polyurethane polymer that illustrates how the macroscopic properties of a polymer depend on its structure at the molecular level. Spandex was first used in women's corsets, girdles, and support hose, but is now routinely used in both men's and women's active wear. Spandex is strong and lends “support” to the wearer, but it also stretches. Spandex is lighter in weight than many other elastic polymers, and it does not break down when exposed to perspiration and detergents. On the molecular level, it has rigid regions that are joined together by soft, flexible segments. The flexible regions allow the polymer to expand and then recover its original shape. The rigid regions strengthen the polymer.



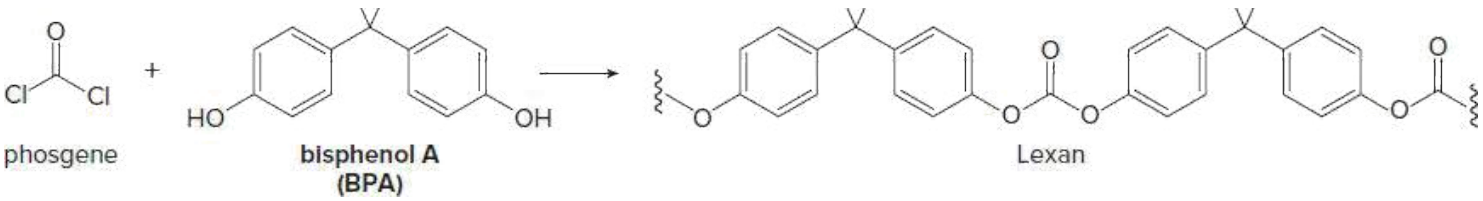
spandex
Trade name **Lycra**

28.6D Polycarbonates

A carbonate is a compound that contains a carbonyl group bonded to two OR groups. Carbonates can be prepared by the reaction of phosgene ($Cl_2C{=}O$) with two equivalents of an alcohol (ROH).

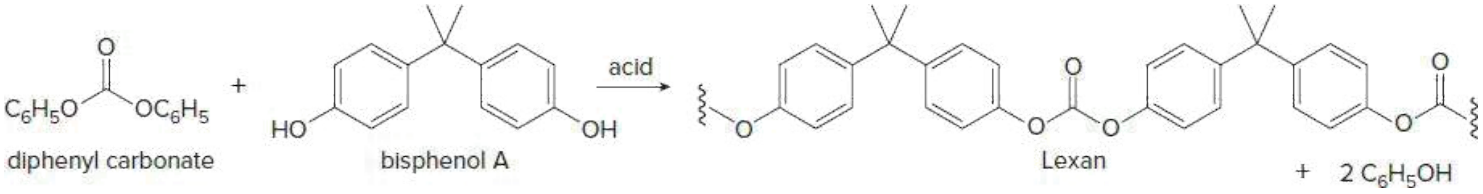
Although it is not acutely toxic, bisphenol A (BPA) mimics the body's own hormones and disrupts normal endocrine functions. Concern over low-dose exposure by infants has led phosgene to a voluntary phase-out of BPA-based polymers in infant formula packaging.

Polycarbonates are formed from phosgene and a diol. The most widely used polycarbonate is Lexan, a lightweight, transparent material that is formed from phosgene and bisphenol A, and used in bike helmets, goggles, catcher's masks, and bulletproof glass.



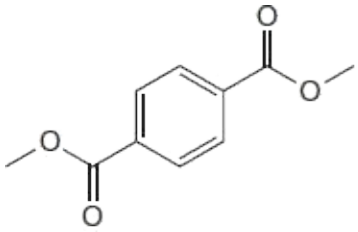
Problem 28.17

Lexan can also be prepared by the acid-catalyzed reaction of diphenyl carbonate with bisphenol A. Draw a stepwise mechanism for this process.

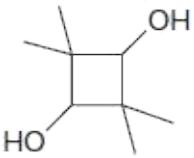


Problem 28.18

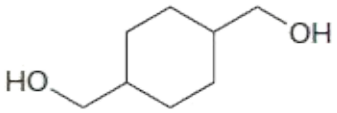
Tritan is a polymer marketed to consumers looking for BPA-free products. Although the detailed structure of Tritan is protected by patent, it is known to be a polyester (not a polycarbonate) composed of three monomers—dimethyl terephthalate, 2,2,4,4-tetramethylcyclobutane-1,3-diol, and 1,4-cyclohexanedimethanol. Propose a possible structure for Tritan from dimethyl terephthalate and the two diols drawn.



dimethyl terephthalate



2,2,4,4-tetramethyl-cyclobutane-1,3-diol

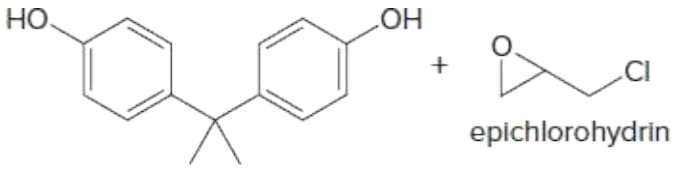


1,4-cyclohexanedimethanol

Nalgene water bottles are made of Tritan (Problem 28.18), a clear and durable copolymer produced by Eastman Chemical Company. ©*Keith Homan/Alamy Stock Photo*

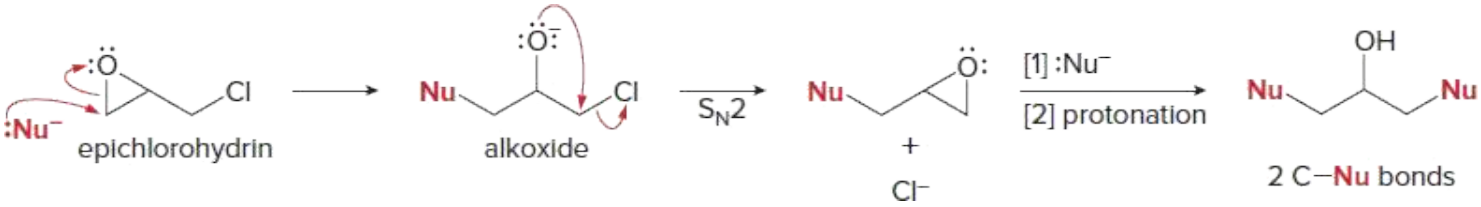
28.6E Epoxy Resins

Epoxy resins represent a class of step-growth polymer familiar to anyone who has used "epoxy" to glue together a broken object. An epoxy resin consists of two components: a fluid prepolymer composed of short polymer chains with reactive epoxides on each end, and a hardener, usually a diamine or triamine that ring opens the epoxides and cross-links the chains together. The prepolymer is formed by reacting two difunctional monomers, bisphenol A and epichlorohydrin.



bisphenol A epichlorohydrin

Bisphenol A has two nucleophilic OH groups, while epichlorohydrin has polar C–O and C–Cl bonds that can react with two different nucleophiles. The general reaction of epichlorohydrin with nucleophiles is given in the accompanying equation. Nucleophilic attack on the strained epoxide ring affords an alkoxide that displaces chloride by an intramolecular SN2 reaction, forming a new epoxide. Ring opening with a second nucleophile gives a 2° alcohol.



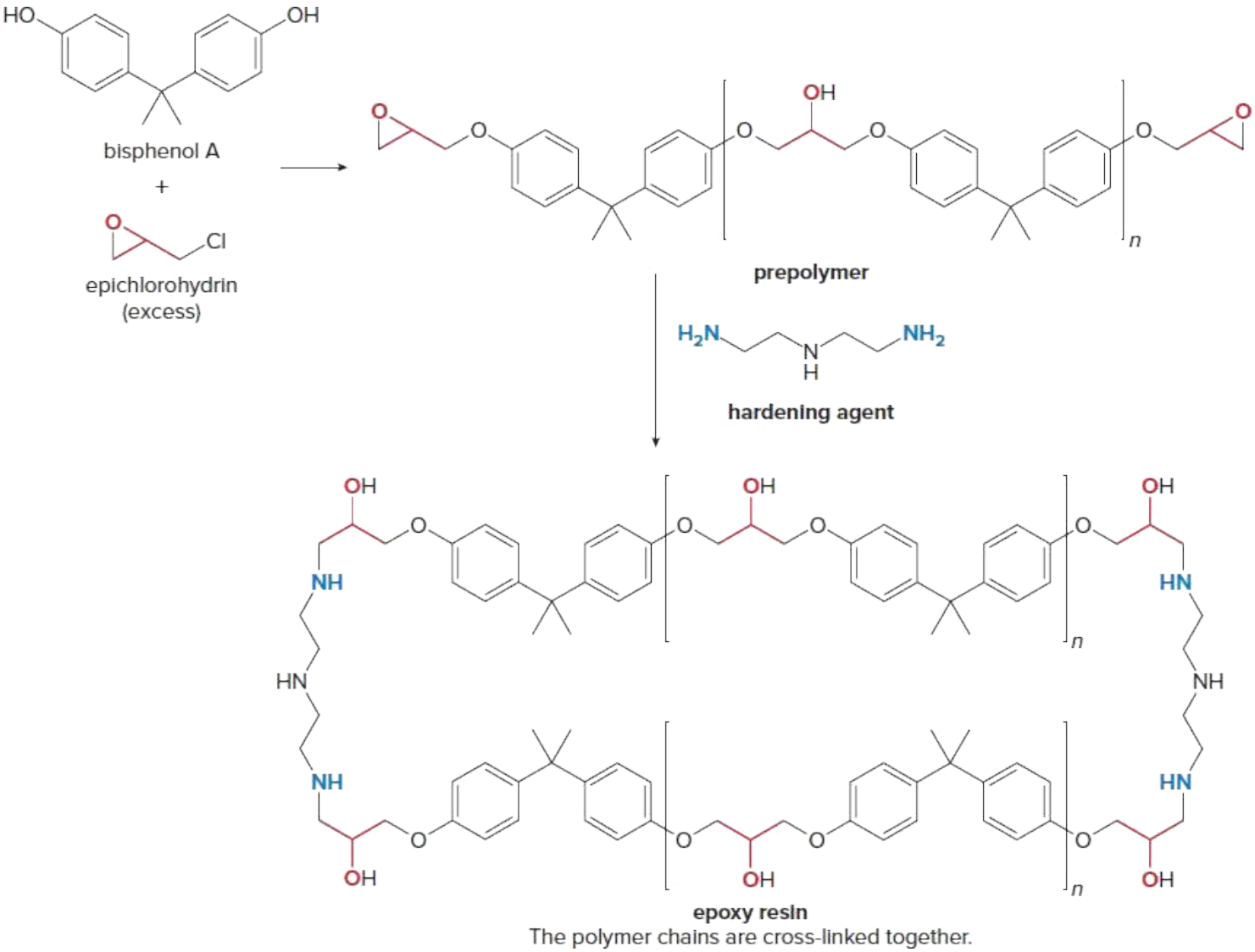


Figure 28.6 **Formation of an epoxy resin from a prepolymer and a hardening agent**

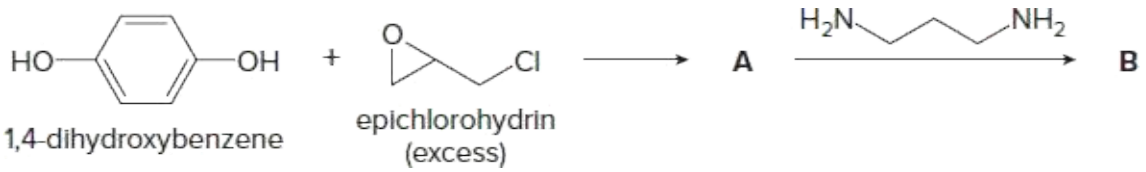
When bisphenol A is treated with excess epichlorohydrin, this stepwise process continues until all the phenolic OH groups have been used in ring-opening reactions, leaving epoxy groups on both ends of the polymer chains. This constitutes the fluid prepolymer, as shown in Figure 28.6.

When the prepolymer is mixed with a diamine or triamine (the hardener), the reactive epoxide rings can be opened by the nucleophilic amino groups to cross-link polymer chains together, causing the polymer to harden. A wide range of epoxy resins is commercially prepared by this process, making them useful for adhesives and coatings. The longer and more extensively cross-linked the polymer chains, the harder the resin.

Problem 28.19

(a) Draw the structure of the prepolymer A formed from 1,4-dihydroxybenzene and excess epichlorohydrin. (b) Draw the structure of the cross-linked polymer B formed

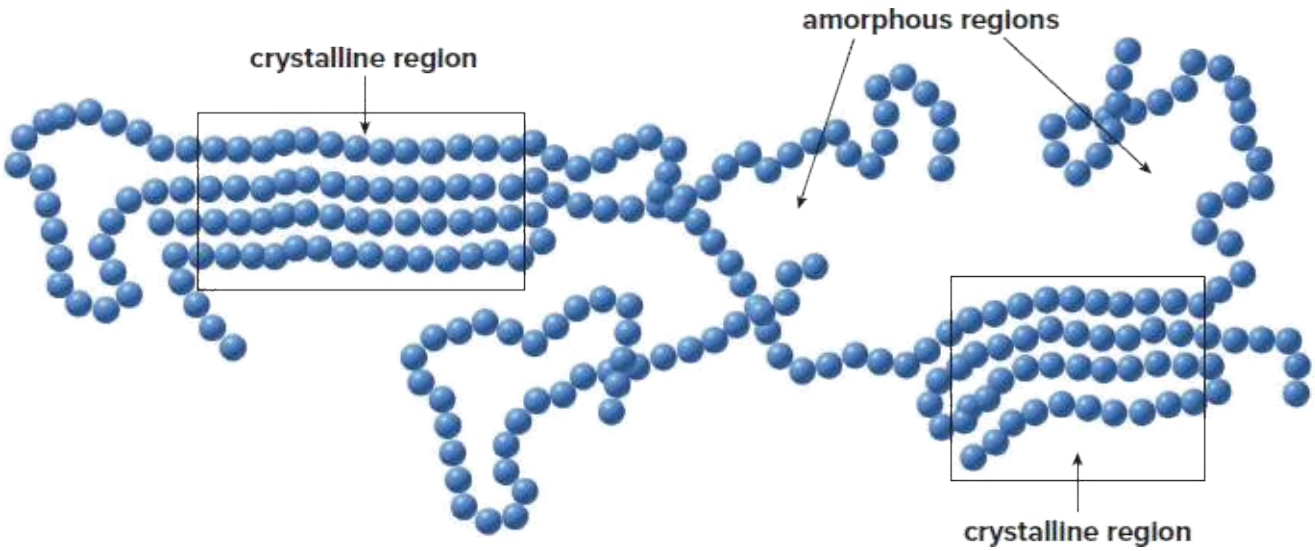
when A is treated with $H_2NCH_2CH_2CH_2NH_2$ as the hardening agent.



28.7 Polymer Structure and Properties

While the chemistry of polymer synthesis can be explained by the usual themes of organic reactions, the large size of polymer molecules gives them some unique physical properties compared to small organic molecules.

Linear and branched polymers do not form crystalline solids because their long chains prevent efficient packing in a crystal lattice. Most polymer chains have crystalline regions and amorphous regions:



- Ordered crystalline regions, called crystallites, are places where sections of the polymer chain lie in close proximity and are held together by intermolecular interactions. Ordered regions of polyethylene, $-[CH_2CH_2]_n-$, are held together by van der Waals interactions, whereas ordered regions of nylon chains are held together by intermolecular hydrogen bonding.
- Amorphous regions are places where the polymer chains are randomly arranged, resulting in weak intermolecular interactions.

Crystalline regions impart toughness to a polymer, whereas amorphous regions impart flexibility. The greater the crystallinity of a polymer—that is, the larger the percentage of ordered regions—the harder the polymer. Branched polymers are generally more amorphous and, because branching prevents chains from packing closely, they are softer, too.

Two temperatures, T_g and T_m, often characterize a polymer's behavior on heating:

- **T_g, the glass transition temperature, is the temperature at which a hard amorphous polymer becomes soft.**
- **T_m, the melt transition temperature, is the temperature at which the crystalline regions of the polymer melt to become amorphous. More-ordered polymers have higher T_m values.**

Thermoplastics are polymers that can be melted and then molded into shapes that are retained when the polymer is cooled. Although they have high T_g values and are hard at room temperature, heating causes individual polymer chains to slip past each other, causing the material to soften. Polyethylene terephthalate and polystyrene are thermoplastic polymers.

Thermosetting polymers are complex networks of cross-linked polymers. Thermosetting polymers are formed by chemical reactions that occur when monomers are heated together to form a network of covalent bonds. Thermosetting polymers *cannot* be re-melted to form a liquid phase, because covalent bonds hold the network together. Bakelite, a thermosetting polymer prepared from phenol (PhOH) and formaldehyde ($H_2C{=}O$) in the presence of a Lewis acid, is formed by electrophilic aromatic substitution reactions. Because formaldehyde is a reactive electrophile and phenol contains a strongly electron-donating OH group, substitution occurs at all ortho and para positions to the OH group, resulting in a highly cross-linked polymer, shown in Figure 28.7.

Problem 28.20

Draw a stepwise mechanism for Step [2] in Figure 28.7 using $AlCl_3$ as the Lewis acid catalyst.

©Anton Balazh/123RF

- Carbons from formaldehyde are labeled in blue.
- Bakelite, the first totally synthetic polymeric material, was patented by Leo Baekeland in 1910. Bowling balls are made of Bakelite.

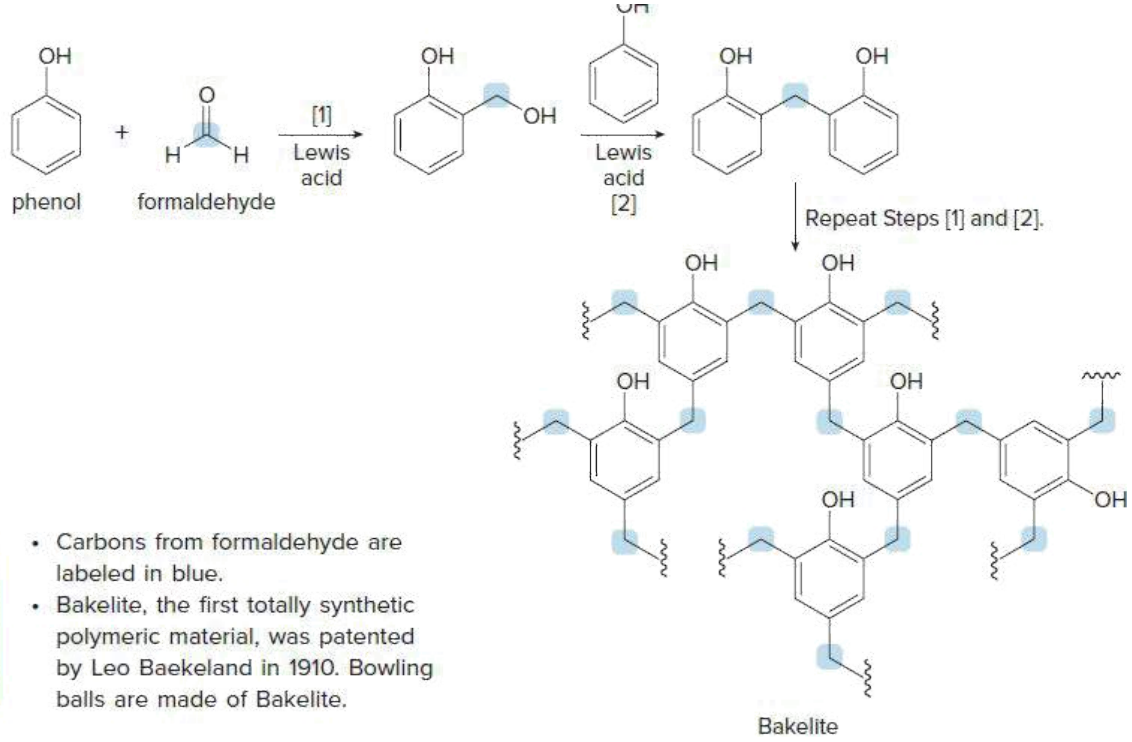
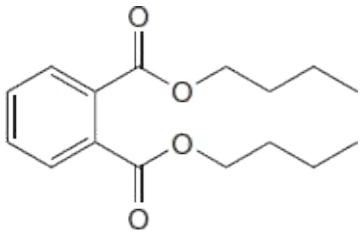


Figure 28.7 **The synthesis of Bakelite from phenol and formaldehyde**

Sometimes a polymer is too stiff and brittle to be useful in many applications. In this case, a low-molecular-weight compound called a plasticizer is added to soften the polymer and give it flexibility. The plasticizer interacts with the polymer chains, replacing some of the intermolecular interactions between the polymer chains. This lowers the crystallinity of the polymer, making it more amorphous and softer.

Dibutyl phthalate is a plasticizer added to the poly(vinyl chloride) used in vinyl upholstery and garden hoses. Because plasticizers are more volatile than the high-molecular-weight polymers, they slowly evaporate with time, making the polymer brittle and easily cracked. Plasticizers like dibutyl phthalate that contain hydrolyzable functional groups are also slowly degraded by chemical reactions.



dibutyl phthalate

28.8 Green Polymer Synthesis

One hundred seventy years ago there were no chemical manufacturing plants and no synthetic polymers, and petroleum had little value. Synthetic polymers have transformed the daily lives of many in the modern world, but not without a hefty price.

Polymer synthesis and disposal have a tremendous impact on the environment, creating two central issues:

- Where do polymers come from? What raw materials are used for polymer synthesis, and what environmental consequences result from their manufacture?
- What happens to polymers once they are used? How does polymer disposal affect the environment, and what can be done to minimize its negative impact?

Recall from Section 4.7 that 3% of a barrel of crude oil is used as the feedstock for chemical synthesis.

28.8A Environmentally Friendly Polymer Synthesis—The Feedstock

In Chapter 12, you were introduced to green chemistry, the use of environmentally benign methods to synthesize compounds. Given the billions of pounds of polymers manufactured worldwide each year, there is an obvious need for methods that minimize the environmental impact.

To date, green polymer synthesis has been approached in a variety of ways:

- Using starting materials that are derived from renewable sources, rather than petroleum. The starting materials for an industrial process are often called the chemical *feedstock*.
- Using safer, less toxic reagents that form fewer by-products.
- Carrying out reactions in the absence of solvent or in aqueous solution (instead of an organic solvent).

Until recently, the feedstock for all polymer synthesis has been petroleum; that is, the monomers for virtually all polymer syntheses are made from crude oil, a nonrenewable raw material. As an example, nylon 6,6 is prepared industrially from adipic acid [$HOOC(CH_2)_4COOH$] and 1,6-diaminohexane [$H_2N(CH_2)_6NH_2$], both of which originate from benzene, a product of petroleum refining (Figure 28.8).

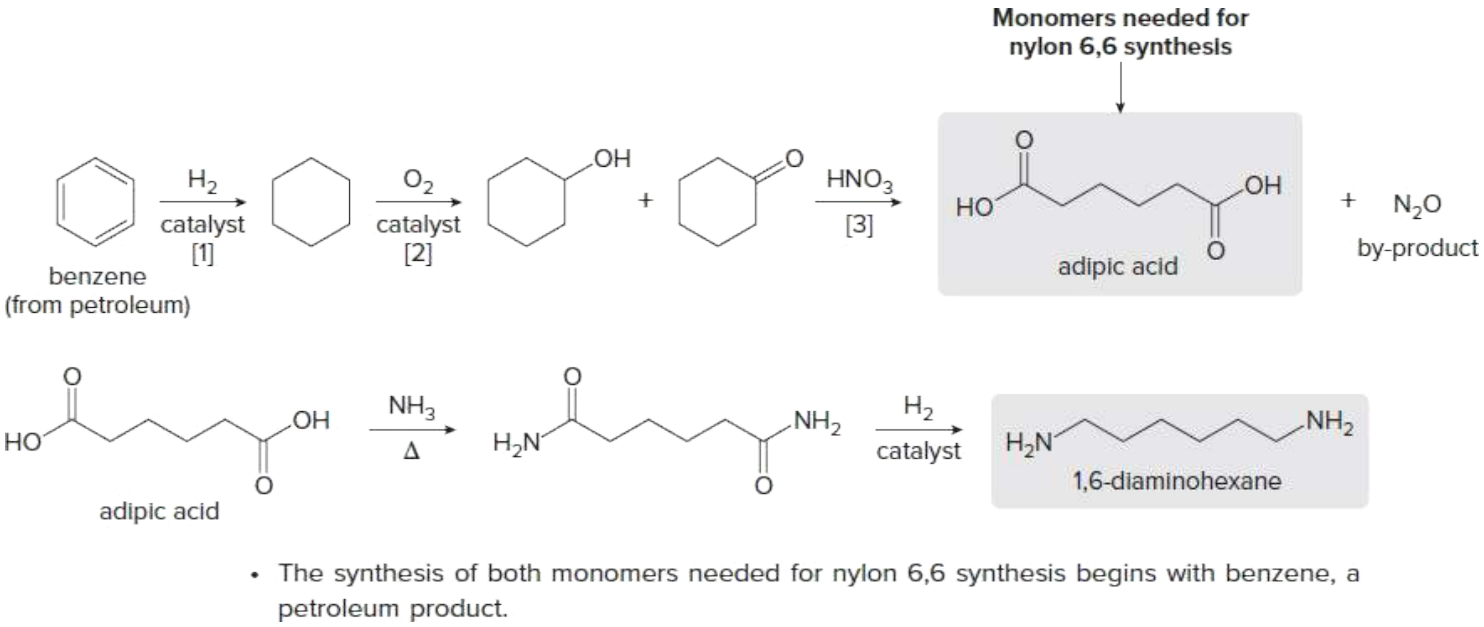
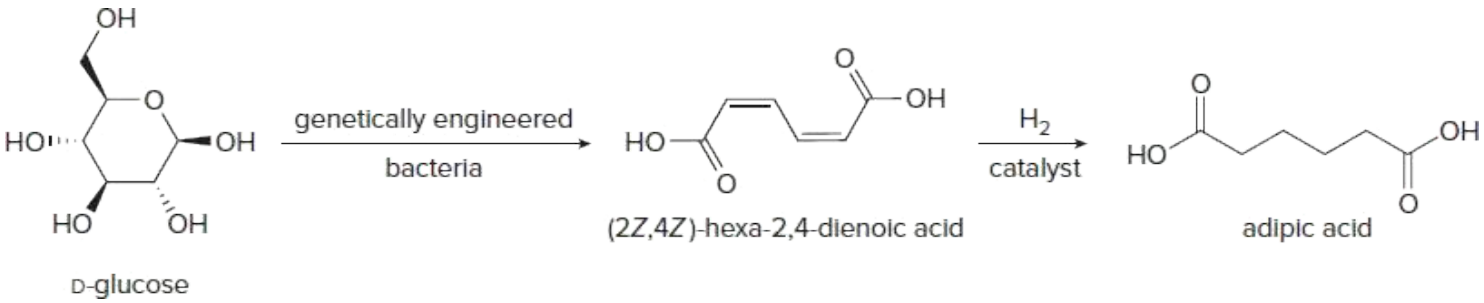


Figure 28.8 **Synthesis of adipic acid and 1,6-diaminohexane for nylon 6,6 synthesis**

Besides beginning with a nonrenewable chemical feedstock, adipic acid synthesis has other problems. The use of benzene, a carcinogen and liver toxin, is undesirable, especially in a large-scale reaction. Moreover, oxidation with HNO_3 in Step [3] produces N_2O as a by-product. N_2O depletes ozone in the stratosphere in much the same way as the CFCs discussed in Chapter 13. In addition, N_2O absorbs thermal energy from the earth's surface like CO_2 and may therefore contribute to global climate change, as discussed in Section 4.14.

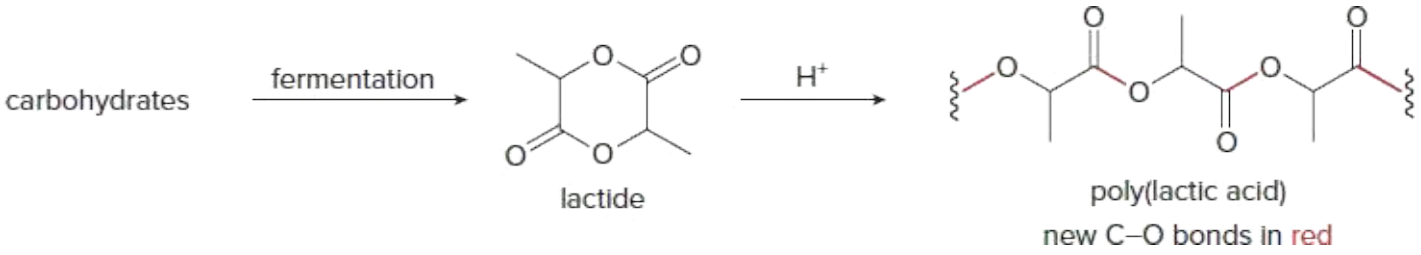
As a result, several research groups are working to develop new methods of monomer synthesis that begin with renewable, more environmentally friendly raw materials and produce fewer hazardous by-products. As an example, chemists at Michigan State University have devised a two-step synthesis of adipic acid from D-glucose, a monosaccharide available from plant sources. The synthesis uses a genetically altered *E. coli* strain (called a biocatalyst) to convert D-glucose to (2Z,4Z)-hexa-2,4-dienoic acid, which is then hydrogenated to adipic acid.

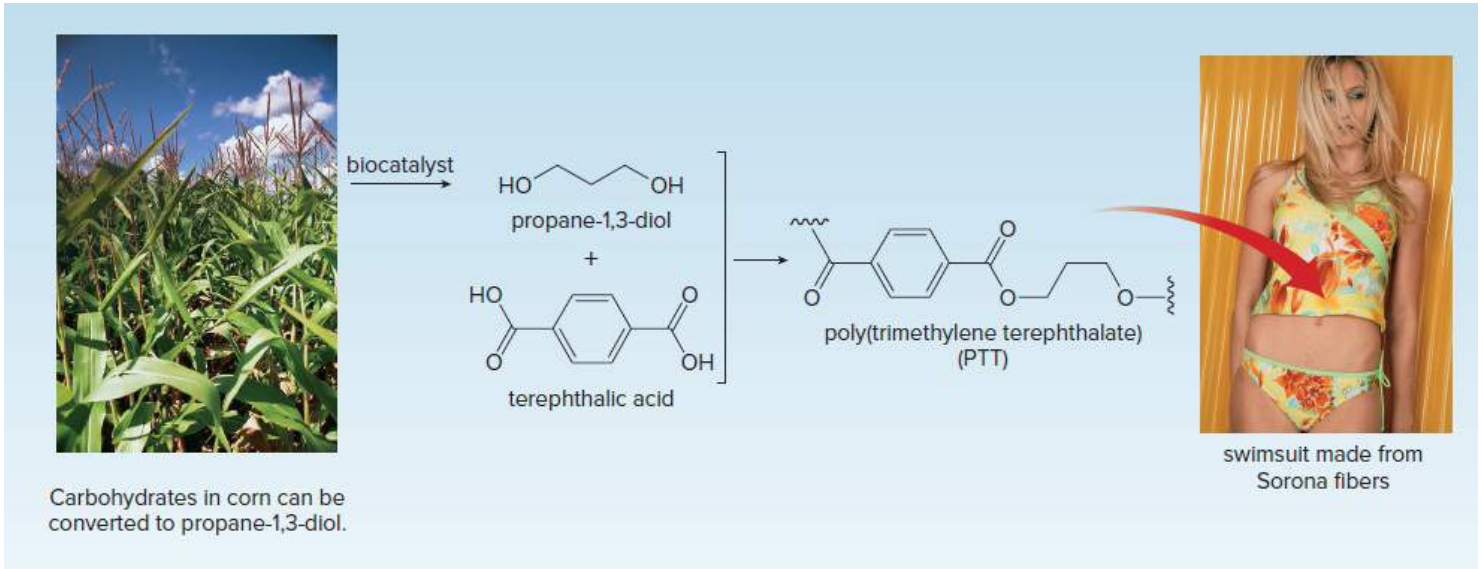
Methods such as this, which avoid starting materials derived from petroleum, are receiving a great deal of attention in the chemical community.



Sorona, DuPont's trade name for poly(trimethylene terephthalate), is a large-volume polymer that can now be made at least in part from glucose derived from a renewable plant source such as corn. A biocatalyst converts D-glucose to propane-1,3-diol, which forms poly(trimethylene terephthalate) (PTT) on reaction with terephthalic acid, as shown in Figure 28.9.

In related chemistry, poly(lactic acid) (PLA) is a polymer used in bottles and packaging, and it can also be made into a synthetic fiber (trade name Ingeo) used in clothing and carpets. Poly(lactic acid) is prepared on a large scale by the fermentation of carbohydrates obtained from corn. Fermentation initially yields a cyclic lactone called lactide, derived from two molecules of lactic acid [$CH_3CH(OH)CO_2H$]. Heating lactide with acid forms poly(lactic acid). PLA is an especially attractive polymer choice, because it readily degrades in a landfill.





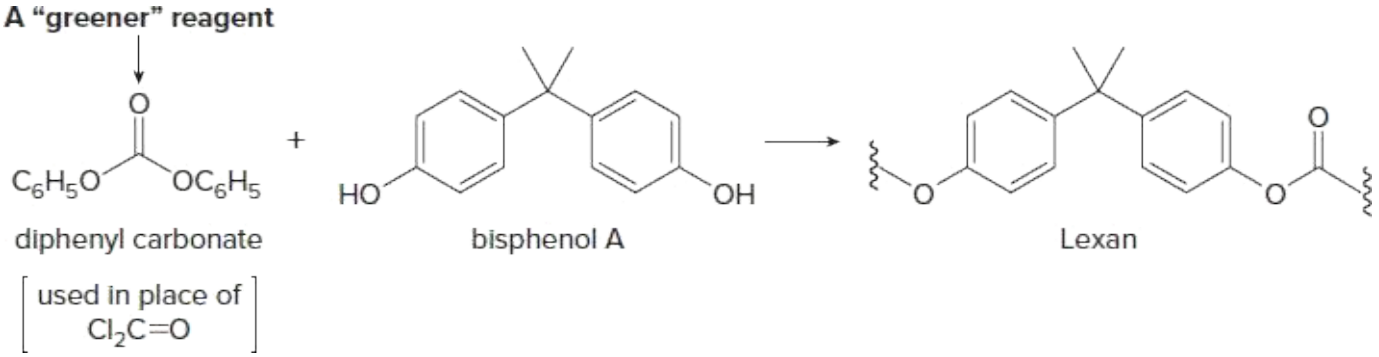
Carbohydrates in corn can be converted to propane-1,3-diol.

- Poly(trimethylene terephthalate), sold as Sorona by the DuPont Corporation, is made into fibers used in clothing and other materials. Although propane-1,3-diol, one of the monomers needed for its synthesis, has been prepared from petroleum feedstocks in the past, it is now available from a renewable plant source such as corn.

Figure 28.9 **A swimsuit made (in part) from corn–The synthesis of poly(trimethylene terephthalate) from propane-1,3-diol derived from corn**

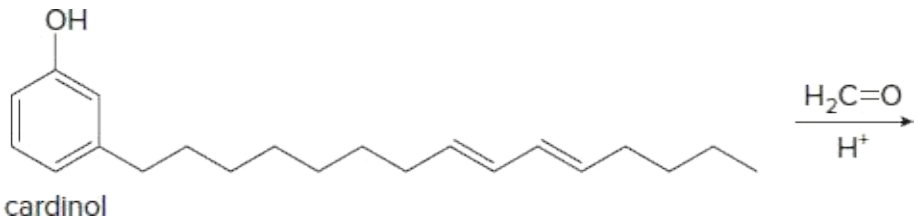
28.8B Polymer Synthesis with Less Hazardous Reagents

Other approaches to green polymer synthesis have concentrated on using less hazardous reagents and avoiding solvents. For example, Lexan can now be prepared by the reaction of bisphenol A with diphenyl carbonate [$(PhO)_2C=O$] in the absence of solvent. This process avoids the use of phosgene ($Cl_2C=O$, Section 28.6D), an acutely toxic reagent that must be handled with extreme care, as well as the large volume of CH2Cl2 typically used as the solvent for the polymerization process.



Problem 28.21

Thermosetting resins similar to Bakelite (Section 28.7) have also been prepared from renewable feedstocks. One method uses cardinol, the major constituent of the liquid obtained from roasted cashew nutshells. What polymer is obtained when cardinol is treated with formaldehyde ($H_2C=O$) in the presence of a proton source?



28.9 Polymer Recycling and Disposal

The same desirable characteristics that make polymers popular materials for consumer products—durability, strength, and lack of reactivity—also contribute to environmental problems. Polymers do not degrade readily, and as a result, billions of pounds of polymers end up in landfills every year.

Two solutions to address the waste problem created by polymers are recycling existing

polymer types to make new materials, and using biodegradable polymers that will decompose in a finite and limited time span.

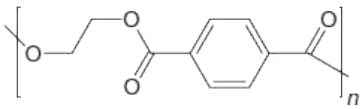
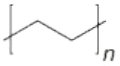
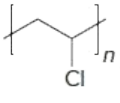
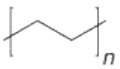
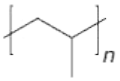
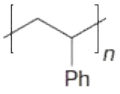
28.9A Polymer Recycling

Although thousands of different synthetic polymers have now been prepared, six compounds account for the bulk of the synthetic polymers produced in the United States each year. Each polymer is assigned a recycling code (1–6) that indicates its ease of recycling; the lower the number, the easier to recycle. Table 28.1 lists these six most common polymers, as well as the type of products made from each recycled polymer.

Recycling begins with sorting plastics by type, shredding the plastics into small chips, and washing the chips to remove adhesives and labels. After the chips are dried and any metal caps or rings are removed, the polymer chips are melted and molded for reuse.

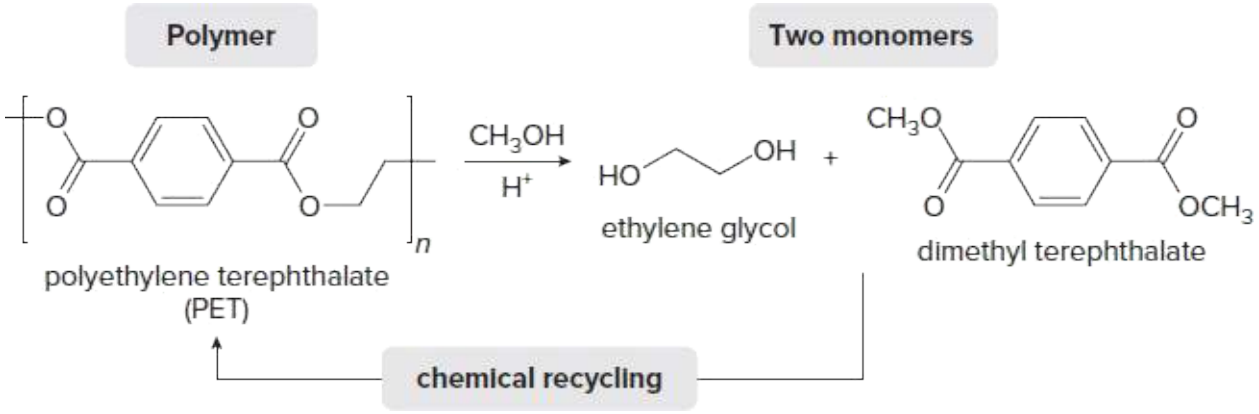
Of the six most common polymers, only the polyethylene terephthalate (PET) in soft drink bottles and the high-density polyethylene (HDPE) in milk jugs and juice bottles are recycled to any great extent. Because recycled polymers are often still contaminated with small amounts of adhesives and other materials, these recycled polymers are generally not used for storing food or drink products. Recycled HDPE is converted to Tyvek, an insulating wrap used in new housing construction, and recycled PET is used to make fibers for fleece clothing and carpeting.

Table 28.1 Recyclable Polymers

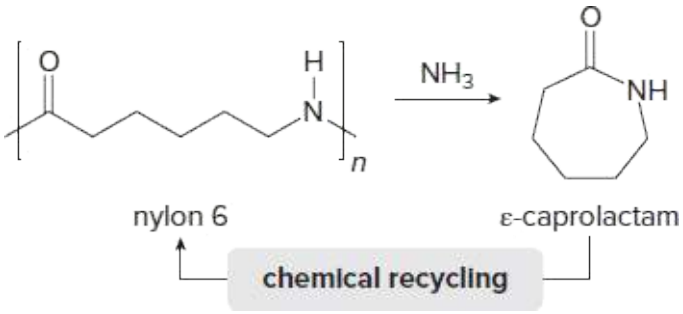
Recycling code	Polymer name	Structure	Recycled product
1	PET Polyethylene terephthalate		fleece jackets carpeting plastic bottles
2	HDPE High-density polyethylene		Tyvek insulation sports clothing
3	PVC Poly(vinyl chloride)		floor mats
4	LDPE Low-density polyethylene		trash bags
5	PP Polypropylene		furniture
6	PS Polystyrene		molded trays trash cans

An alternative recycling process is to re-convert polymers back to the monomers from

which they were made, a process that has been successful with acyl compounds that contain C–O or C–N bonds in the polymer backbone. For example, heating polyethylene terephthalate with CH_3OH cleaves the esters of the polymer chain to give ethylene glycol ($HOCH_2CH_2OH$) and dimethyl terephthalate. These monomers then serve as starting materials for more PET. This chemical recycling process is a transesterification reaction that occurs by nucleophilic acyl substitution, as discussed in Chapter 20.



Similarly, treatment of discarded nylon 6 polymer with NH_3 cleaves the polyamide backbone, forming ε-caprolactam, which can be purified and re-converted to nylon 6.



Problem 28.22

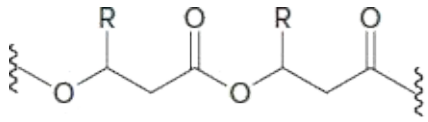
Why can't chemical recycling–that is, the conversion of polymer to monomers and re-conversion of monomers to polymer–be done easily with HDPE and LDPE?

28.9B Biodegradable Polymers

Another solution to the accumulation of waste polymers in landfills is to design and use polymers that are biodegradable.

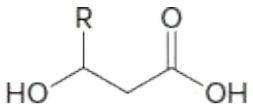
- **Biodegradable polymers are polymers that can be degraded by microorganisms–bacteria, fungi, or algae–naturally present in the environment.**

Several biodegradable polyesters have now been developed. For example, the polyhydroxyal-kanoates (PHAs) are polymers of 3-hydroxy carboxylic acids, such as 3-hydroxybutyric acid or 3-hydroxyvaleric acid.



polyhydroxyalkanoate

PHA

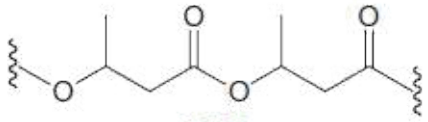


3-hydroxy carboxylic acid

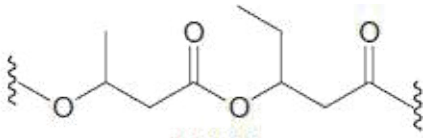
R = CH_3, 3-hydroxybutyric acid
R = CH_2CH_3, 3-hydroxyvaleric acid

monomer

The two most common PHAs are polyhydroxybutyrate (PHB) and a copolymer of polyhydroxybutyrate and polyhydroxyvalerate (PHBV). PHAs can be used as films, fibers, and coatings for hot beverage cups made of paper.



PHB

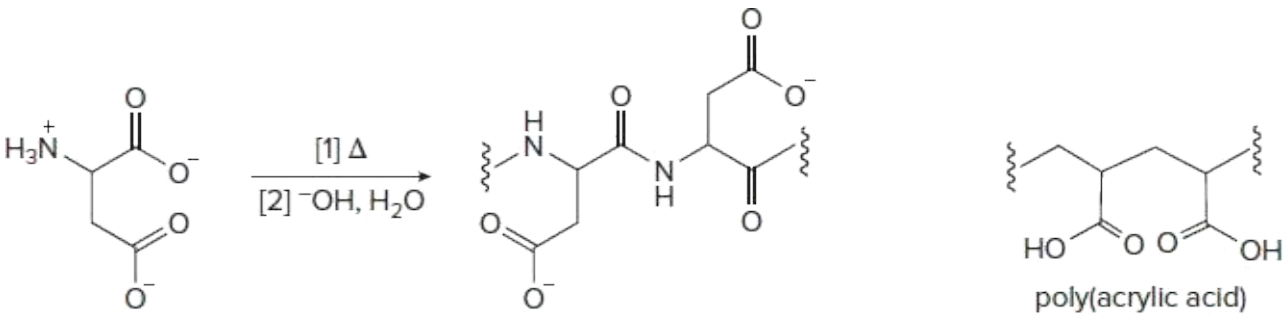


PHBV

Bacteria in the soil readily degrade PHAs, and in the presence of oxygen, the final degradation products are CO_2 and H_2O. The rate of degradation depends on moisture, temperature, and pH. Degradation is slower in enclosed landfills that are lined and covered.

An additional advantage of the polyhydroxyalkanoates is that the polymers can be produced by fermentation. Certain types of bacteria produce PHAs for energy storage when they are grown in glucose solution in the absence of specific nutrients. The polymer forms as discrete granules within the bacterial cell, and it is then removed by extraction to give a white powder that can be melted and modified into a variety of different products.

Biodegradable polyamides have also been prepared from amino acids. For example, aspartic acid can be converted to polyaspartate, abbreviated as TPA (thermal polyaspartate). TPA is commonly used as an alternative to poly(acrylic acid), which is used to line the pumps and boilers of wastewater treatment facilities.



aspartic acid

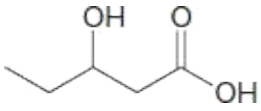
polyaspartate (TPA)

poly(acrylic acid)

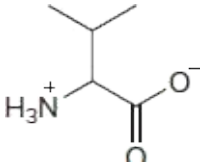
Problem 28.23

What polymers are formed from each monomer?

a.



b.

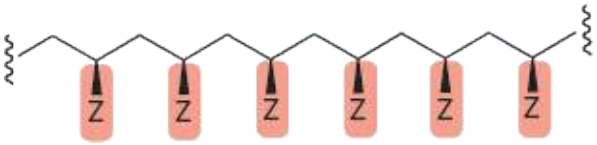


Chapter 28 REVIEW

KEY CONCEPTS

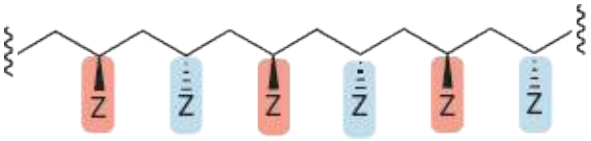
Polymer configurations (28.4)

1 Isotactic polymer



- An *isotactic* polymer has all Z groups on the same side of the carbon backbone.

2 Syndiotactic polymer



- A *syndiotactic* polymer has the Z groups alternating from one side of the carbon chain to the other.

3 A p

- A at p ha gr or ra al

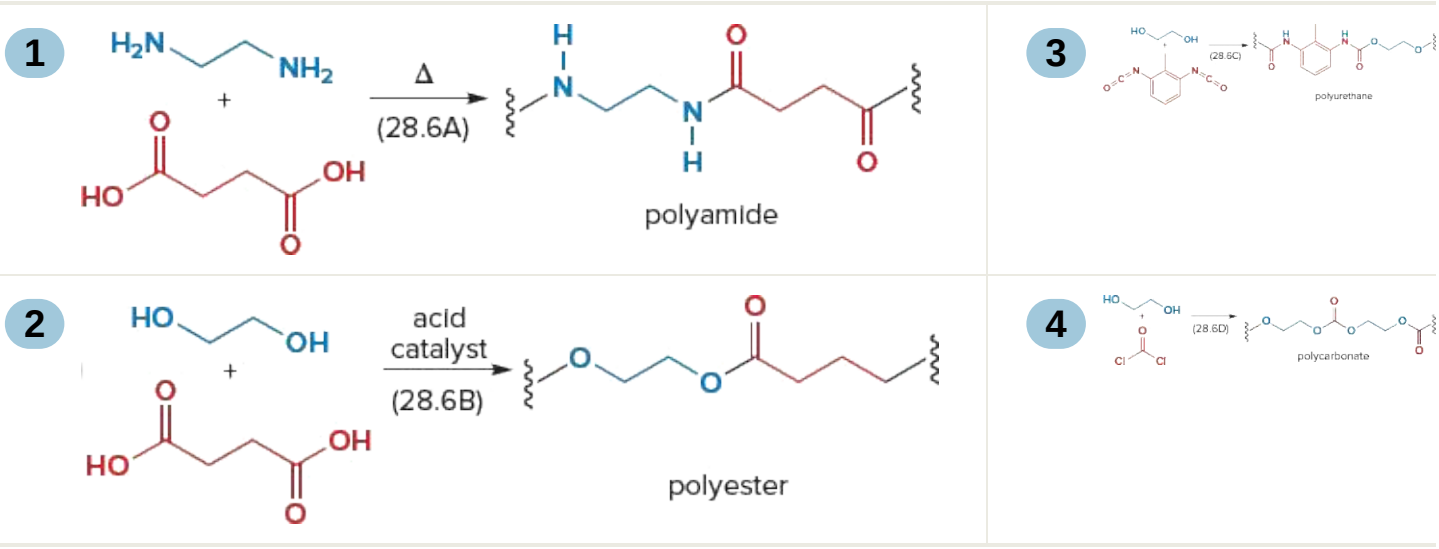
Try Problem 28.32.

KEY REACTIONS

[1] Reactions that form chain-growth polymers

Try Problems 28.24, 28.27, 28.51a–d.

[2] Reactions that form step-growth polymers

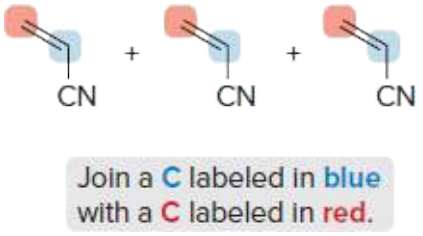


Try Problems 28.26, 28.34, 28.35, 28.38, 28.51e–h, 28.53.

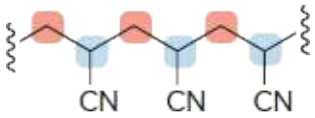
KEY SKILLS

[1] Drawing the product of chain-growth polymerization (28.2); example: polymerization of CH_2=CHCN

1 Draw three (or more) alkene monomers.	**2** Break one bond of each double bond, and join the alkenes with single bonds.
	• Break the π bonds, and join a carbon labeled in blue with a



carbon labeled in red.



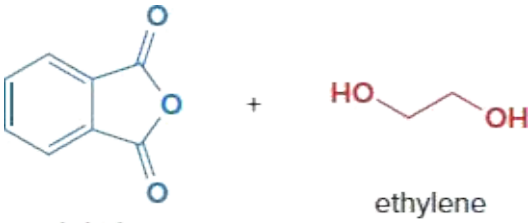
polyacrylonitrile

- With unsymmetrical alkenes, substituents are bonded to every other carbon.

Try Problems 28.24, 28.27, 28.33, 28.51a–c.

[2] Drawing the product of step-growth polymerization (28.6); example: polymerization of phthalic anhydride and ethylene glycol to form a polyester

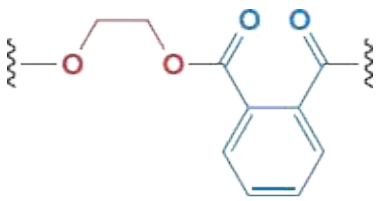
1 Draw the pair of monomers.



phthalic anhydride + ethylene glycol diol

- A dicarboxylic acid could also be used instead of the anhydride.

2 Draw the polymer that forms from the pair of monomers.



polyester

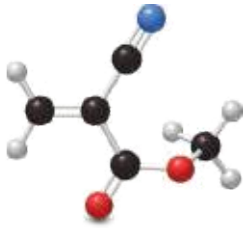
Try Problems 28.26, 28.34, 28.35, 28.38, 28.51e–h, 28.53.

PROBLEMS

Problems Using Three-Dimensional Models

28.24 Draw the structure of the polymer formed by chain-growth polymerization of each monomer.

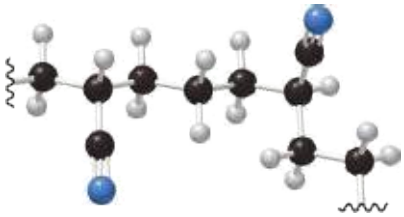
a.



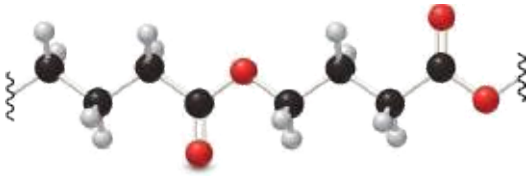
b.

28.25 What monomer(s) are used to prepare each polymer or copolymer?

a.

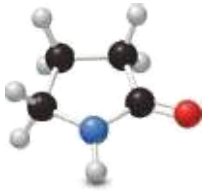


b.

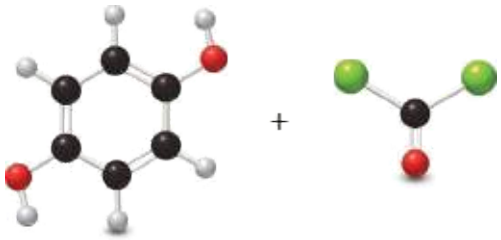


28.26 Draw the structure of the polymer formed by step-growth polymerization of each monomer or pair of monomers.

a.



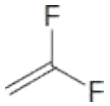
b.



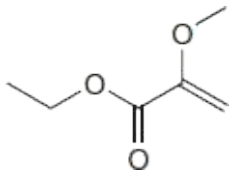
Polymer Structure and Properties

28.27 Draw the structure of the polymer formed by chain-growth polymerization of each monomer.

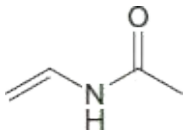
a.



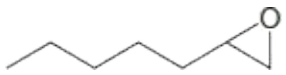
b.



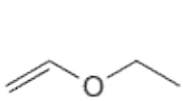
c.



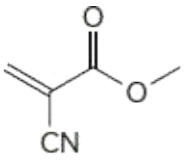
d.



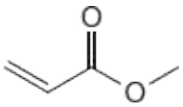
28.28 **Consider monomers A–C. (a) Rank the monomers in order of increasing reactivity in cationic polymerization. (b) Rank the monomers in order of increasing reactivity in anionic polymerization.**



A



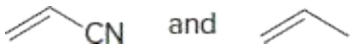
B



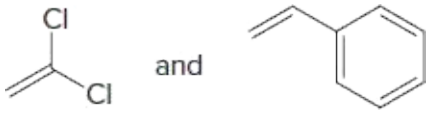
C

28.29 **Draw the structure of the alternating copolymer formed from each pair of monomers.**

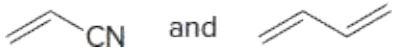
a.



b.



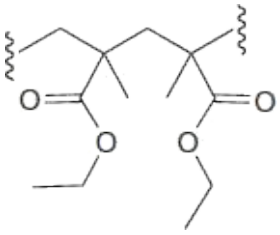
c.



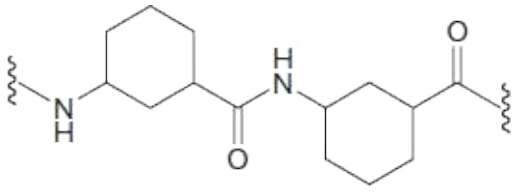
d.

28.30 **What monomer(s) are used to prepare each polymer or copolymer?**

a.



b.



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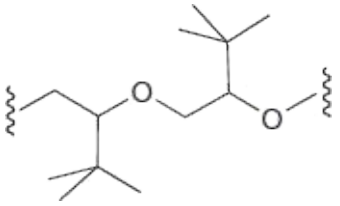

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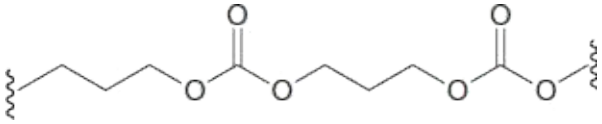
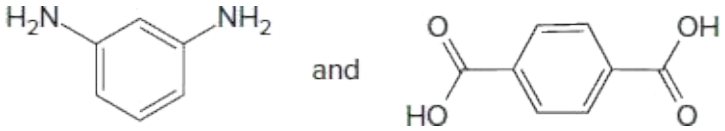


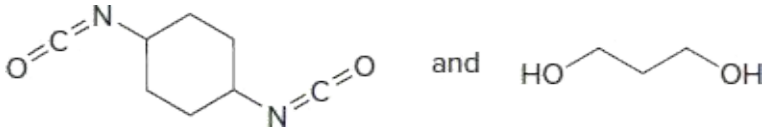
28.31 **Draw each polymer in Problem 28.30 using the shorthand representation shown in Figure 28.2.**

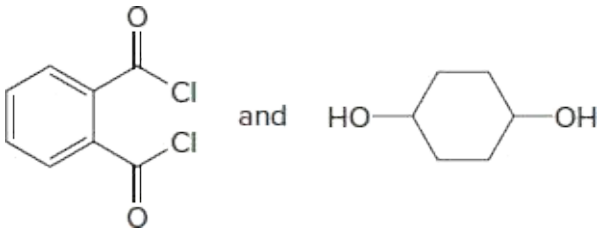
28.32 **Draw a short segment of each polymer: (a) isotactic poly(vinyl chloride); (b) syndiotactic polyacrylonitrile; (c) atactic polystyrene.**

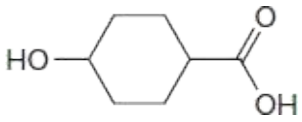
28.33 **Draw the structure of the polymer that results from anionic polymerization of *p*-trichloromethylstyrene ($CCl_3C_6H_4CH{=}CH_2$) using ethylene oxide as the electrophile to terminate the chain.**

28.34 **Draw the structure of the polymer formed by step-growth polymerization of each monomer or pair of monomers.**

a. 

b. 

c. 

d. 

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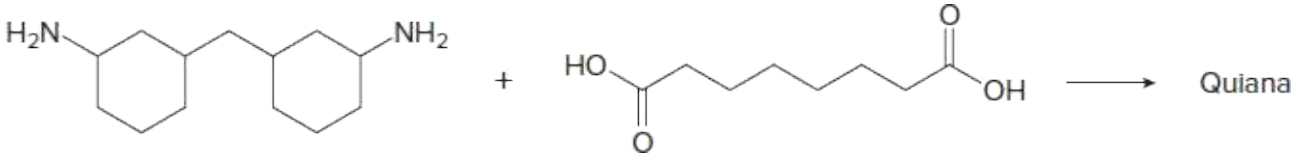
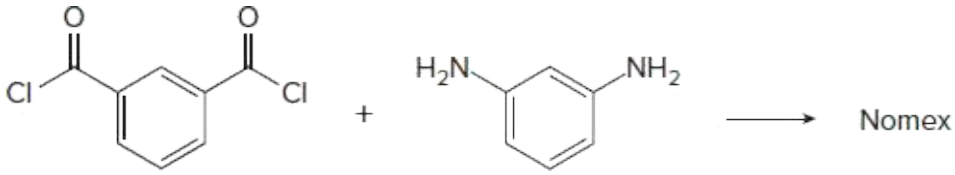
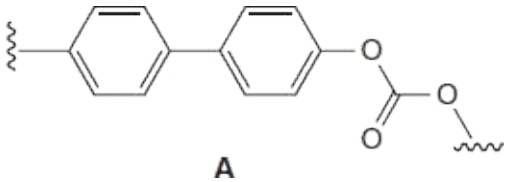
28.35 **Draw the structures of Quiana and Nomex, two commercially available step-growth polymers formed from the given monomers. Nomex is a strong polymer used in aircraft tires and microwave transformers. Quiana has been used to make wrinkle-resistant fabrics.**

a. 

b. 

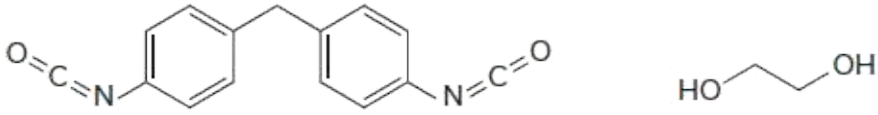
28.36 **Glue guns used in craft projects contain a heating element that melts an adhesive that is a copolymer formed from ethylene and vinyl acetate ($CH_2{=}CHOCOCH_3$). Draw a possible structure of this copolymer, assuming that the copolymer is random and that there are two times as many ethylene monomers as vinyl acetate monomers.**

28.37 **(a) What type of step-growth polymer is represented in A? (b) What monomers are needed to form A?**

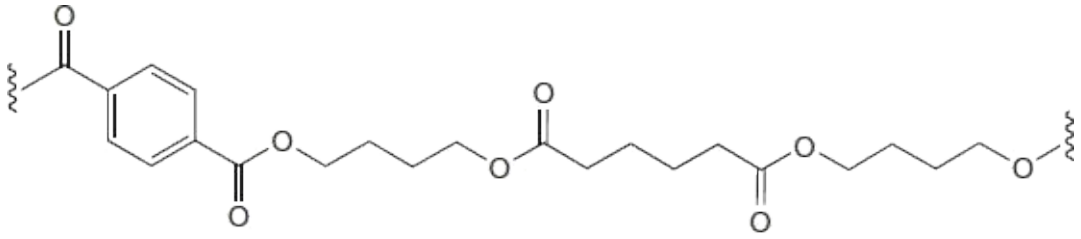


A

28.38 Draw the structure of the polyurethane formed from the given monomers.

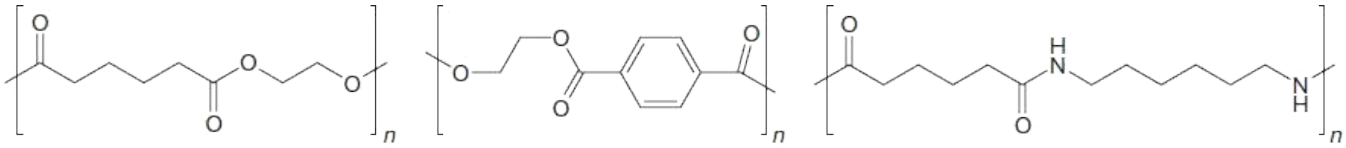


28.39 Draw the structure of the three monomers used to prepare polybutyrate adipate terephthalate (PBAT), a biodegradable copolymer sold under the trade name Ecoflex. Because PBAT has properties similar to low-density polyethylene, it can be used in biodegradable food packaging and plastic bags.



PBAT

28.40 Explain the differences observed in the T_g and T_m values for each pair of polymers: (a) polyester A and PET; (b) polyester A and nylon 6,6. (c) How would you expect the T_m value for Kevlar (Section 28.6A) to compare with the T_m value for nylon 6,6? Explain your prediction.

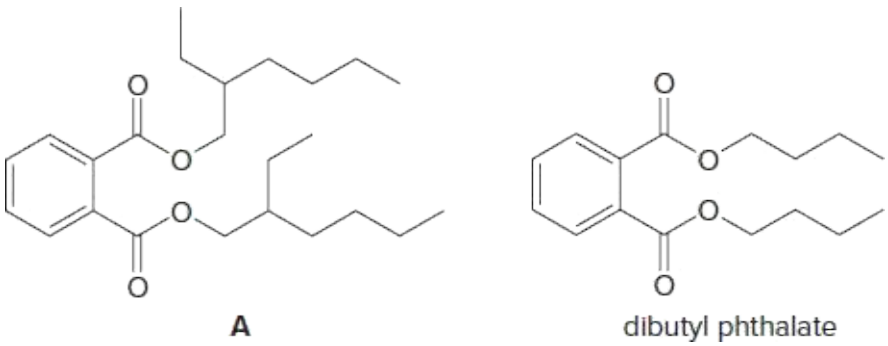


polyester **A**
$T_g < 0$ °C
$T_m = 50$ °C

PET
$T_g = 70$ °C
$T_m = 265$ °C

nylon 6,6
$T_g = 53$ °C
$T_m = 265$ °C

28.41 Explain why diester A is now often used as a plasticizer in place of dibutyl phthalate.

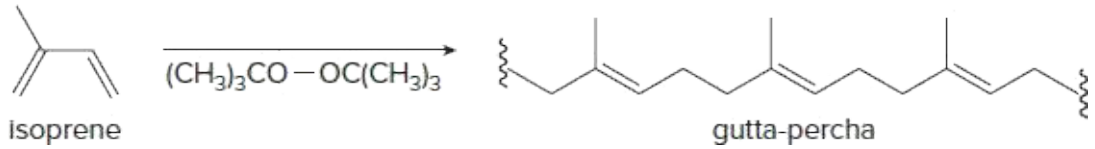


A

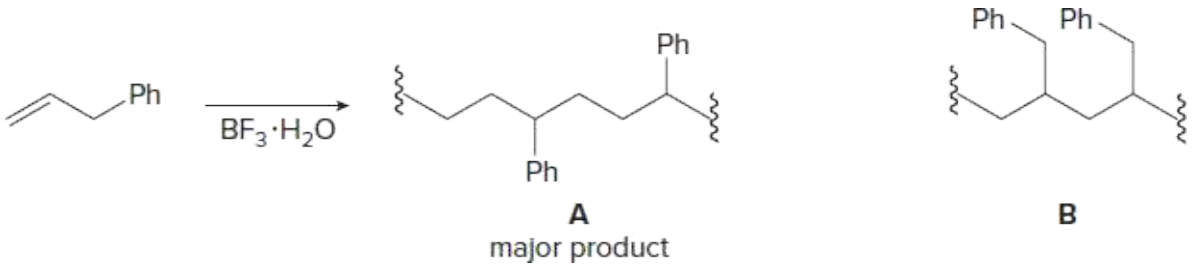
dibutyl phthalate

Mechanism

28.42 **Draw a stepwise mechanism for the polymerization of isoprene to gutta-percha using $(CH_3)_3CO–OC(CH_3)_3$ as the initiator.**



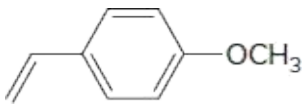
28.43 **Cationic polymerization of 3-phenylpropene (CH_2=$CHCH_2Ph$) affords A as the major product rather than B. Draw a stepwise mechanism to account for this observation.**

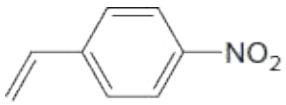


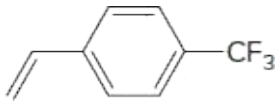
28.44 **Explain why acrylonitrile (CH_2=$CHCN$) undergoes cationic polymerization more slowly than but-3-enenitrile (CH_2=$CHCH_2CN$).**

28.45 **Draw a stepwise mechanism for the anionic polymerization of styrene (CH_2=$CHPh$) to form polystyrene $–[CH_2CHPh]_{n–}$ using BuLi as the initiator. Use CO_2 as the electrophile that terminates the chain mechanism.**

28.46 **Although styrene undergoes both cationic and anionic polymerization equally well, one method is often preferred with substituted styrenes. Which method is preferred with each compound? Explain.**

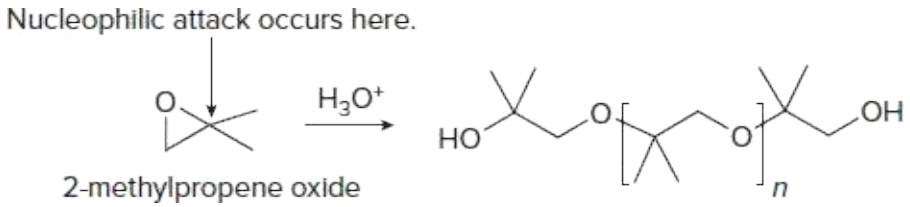
a. 

b. 

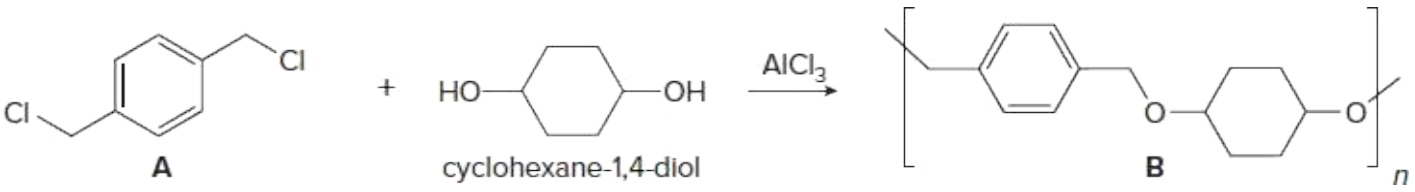
c. 

d.

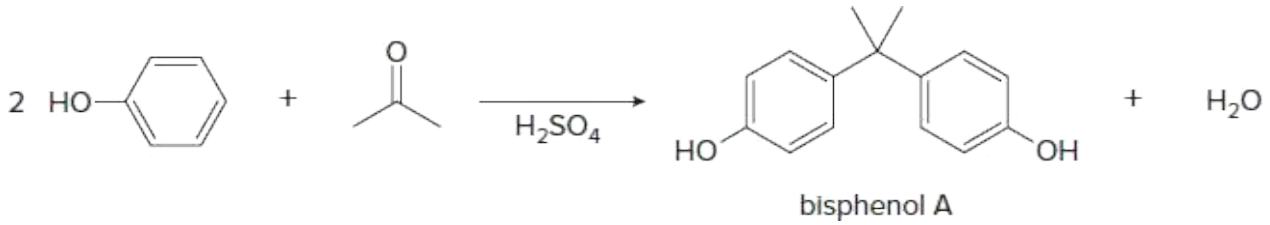
28.47 **In the presence of H_3O^+, 2-methylpropene oxide undergoes chain-growth polymerization such that nucleophilic attack occurs at the more substituted end of the epoxide. Draw a stepwise mechanism for this process, and explain this regioselectivity.**



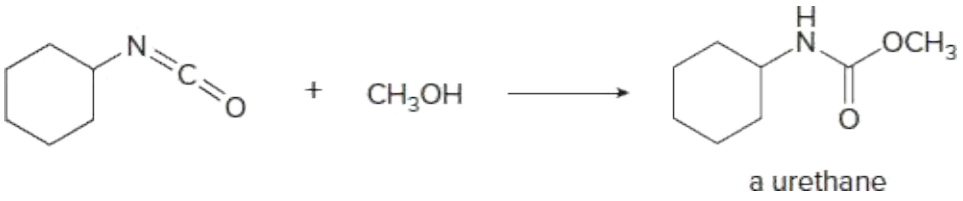
28.48 **Draw a stepwise mechanism for the conversion of dihalide A and cyclohexane-1,4-diol to polyether B in the presence of $AlCl_3$.**



28.49 **Draw a stepwise mechanism for the following reaction, which is used to prepare bisphenol A (BPA), a widely used monomer in polymer synthesis.**



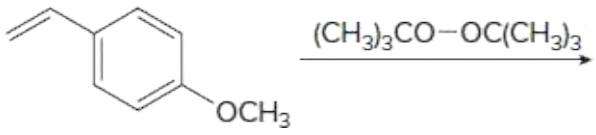
28.50 **Draw a stepwise mechanism for the reaction of an alcohol with an isocyanate to form a urethane.**



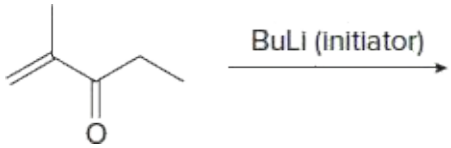
Reactions and Synthesis

28.51 **Draw the products of each reaction.**

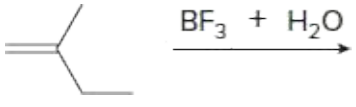
a.



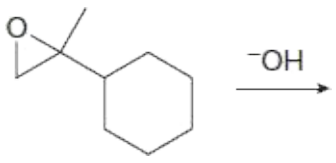
b.



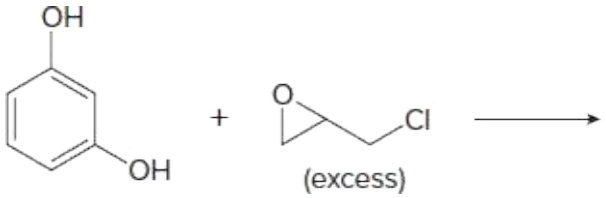
c.



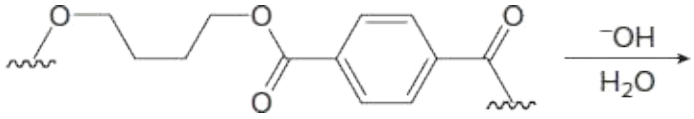
d.



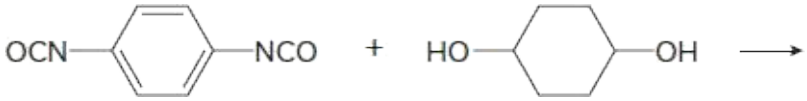
e.



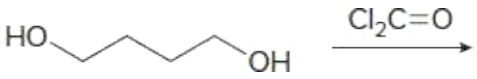
f.



g.

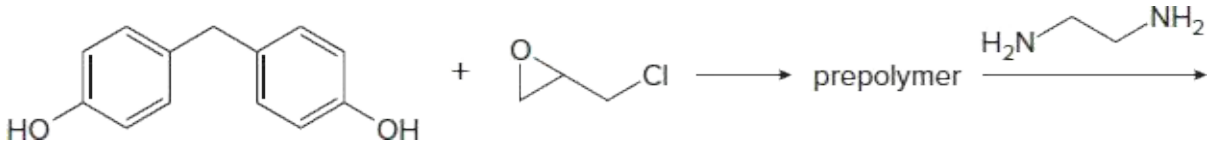


h.

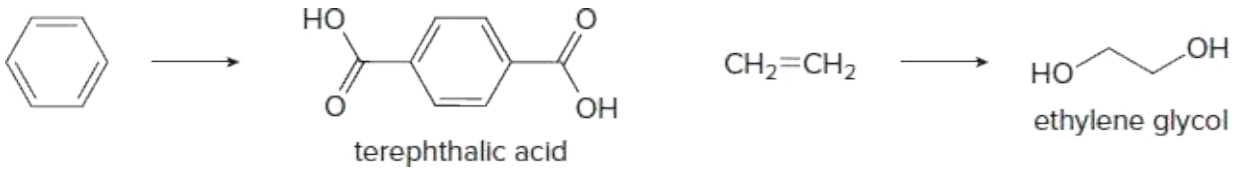


28.52 Explain why aqueous NaOH solution can be stored indefinitely in polyethylene bottles, but spilling aqueous base on a polyester shirt or nylon stockings quickly makes a hole.

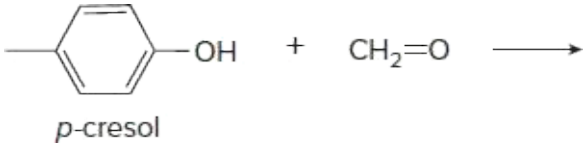
28.53 What epoxy resin is formed by the following reaction sequence?



28.54 Devise a synthesis of terephthalic acid and ethylene glycol, the two monomers needed for polyethylene terephthalate synthesis, from the given starting materials.



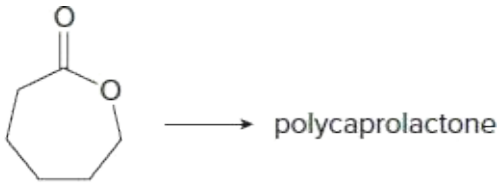
28.55 The reaction of *p*-cresol with CH_2=O resembles the reaction of phenol (PhOH) with CH_2=O, except that the resulting polymer is thermoplastic but not thermosetting. Draw the structure of the polymer formed, and explain why the properties of these two polymers are so different.



Biological Applications

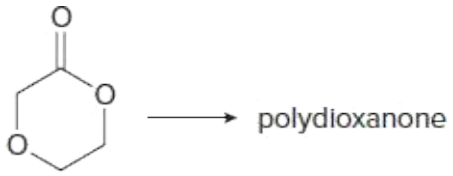
28.56 In addition to glycolic and lactic acids (Section 28.6B), dissolving sutures can also be prepared from each of the following lactone monomers. Draw the structure of the polymer formed from each monomer.

a.



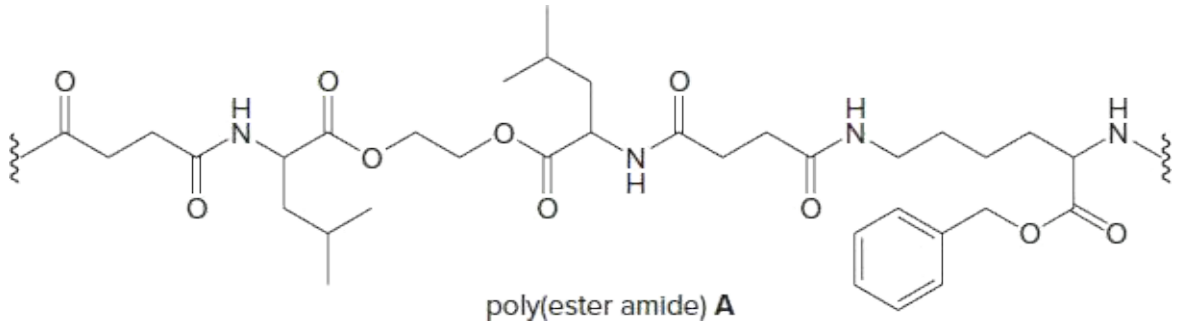
ε-caprolactone

b.



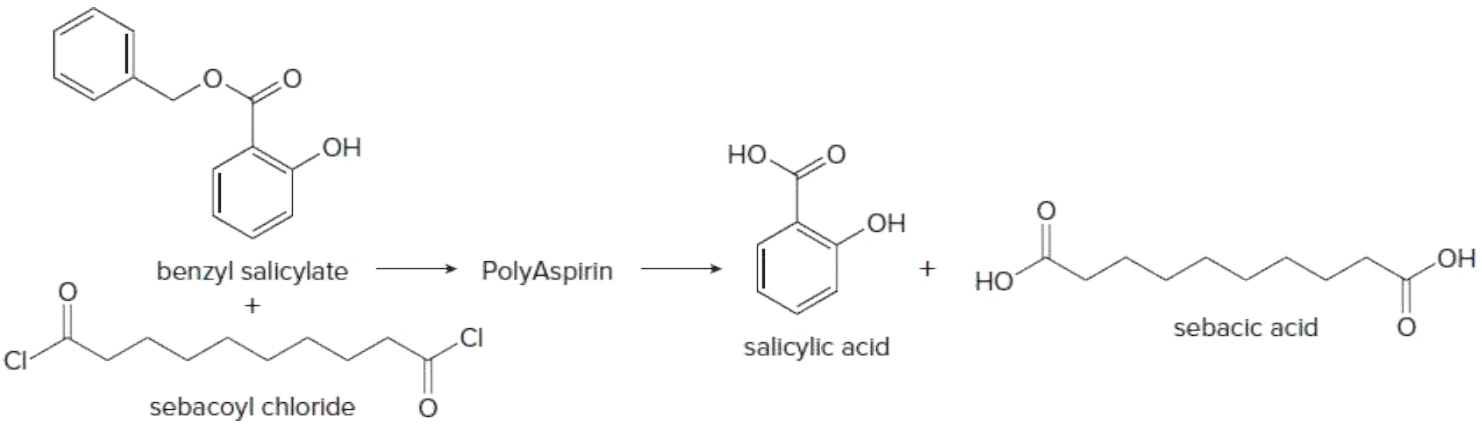
p-dioxanone

28.57 Compound A is a poly(ester amide) copolymer that can be used as a bioabsorbable coating for the controlled release of drugs. A is a copolymer of four monomers, two of which are amino acids or amino acid derivatives. The body's enzymes recognize the naturally occurring amino acids in the polymer backbone, allowing for controlled enzymatic breakdown of the polymer and steady release of an encapsulated drug. Identify the four monomers used to synthesize A; then use Figure 27.2 to name the two amino acids.



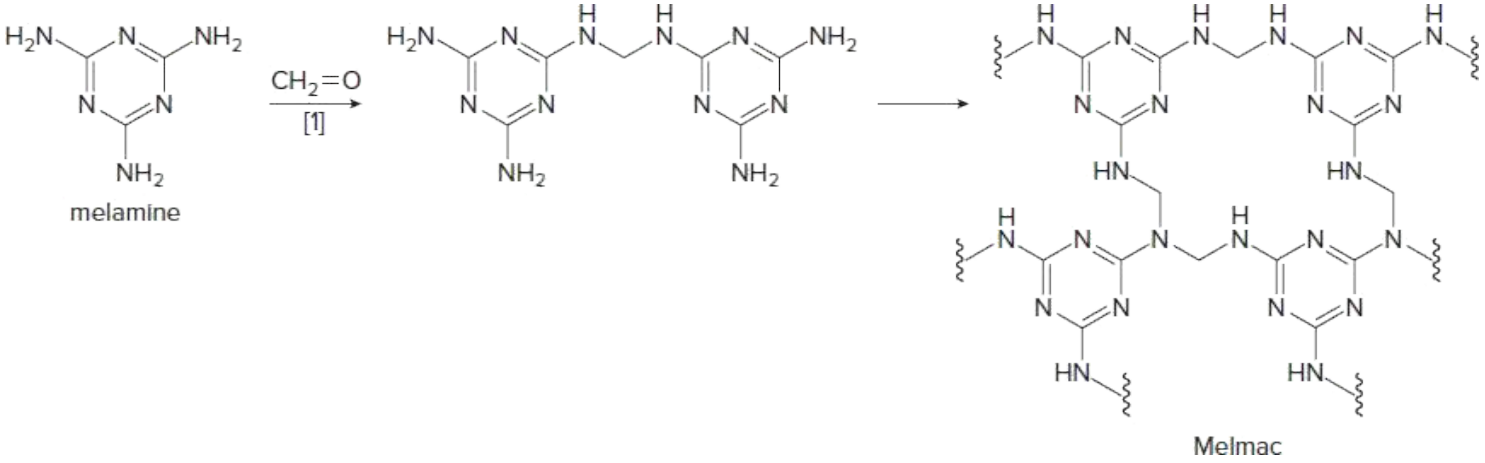
poly(ester amide) **A**

28.58 Researchers at Rutgers University have developed biocompatible polymers that degrade into nonsteroidal anti-inflammatory drugs. For example, the reaction of two equivalents of benzyl salicylate and one equivalent of sebacoyl chloride forms a poly(anhydride ester) called PolyAspirin, which hydrolyzes to salicylic acid (an anti-inflammatory agent) and sebacic acid, which is excreted. This technology can perhaps be used for localized drug delivery at specific sites of injury. What is the structure of PolyAspirin?

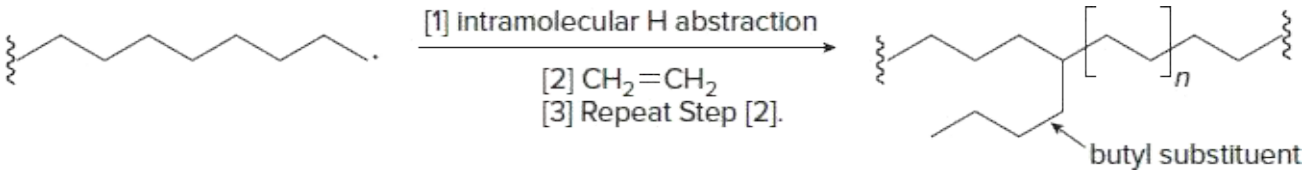


Challenge Problems

28.59 **Melmac, a thermosetting polymer formed from melamine and formaldehyde ($CH_2=O$), is used to make dishes and countertops. Draw a stepwise mechanism for the condensation of one mole of formaldehyde with two moles of melamine, which begins the synthesis of Melmac.**



28.60 **Although chain branching in radical polymerizations can occur by intermolecular H abstraction as shown in Mechanism 28.2, chain branching can also occur by intramolecular H abstraction to form branched polyethylene that contains butyl groups as branches.**



a. Draw a stepwise mechanism that illustrates which H must be intramolecularly abstracted to form butyl substituents.

b. Suggest a reason why the abstraction of this H is more facile than the abstraction of other H's.

28.61 **The reaction of urea [$(NH_2)_2C=O$] and formaldehyde ($CH_2=O$) forms a highly cross-linked polymer used in foams. Suggest a structure for this polymer. [Hint: Examine the structures of Bakelite (Figure 28.7) and Melmac (Problem 28.59).]**

29 Lipids

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29.1 Introduction

29.2 Waxes

29.3 Triacylglycerols

29.4 Phospholipids

29.5 Fat-soluble vitamins

29.6 Eicosanoids

29.7 Terpenes
29.8 Steroids

Stearic acid, a saturated fatty acid first discussed in Chapter 10, is a key component of cocoa butter, a mixture of triacylglycerols obtained from the cocoa bean that is used to make chocolate. Because cocoa butter is high in saturated fatty acid content, cocoa butter is a solid at room temperature, so it is classified as a fat. Triacylglycerols are the most abundant lipids, water-insoluble biomolecules that contain many carbon–carbon and carbon–hydrogen bonds and few functional groups. In Chapter 29, we learn about the many different types of lipids.

Why Study …

Lipids?

We conclude the discussion of the organic molecules in biological systems by turning our attention to lipids, biomolecules that are soluble in organic solvents. Unlike the carbohydrates in Chapter 26 and the amino acids and proteins in Chapter 27, lipids contain many carbon–carbon and carbon–hydrogen bonds and few functional groups.

Lipids are the biomolecules that most closely resemble the hydrocarbons we studied in Chapters 4 and 10, so we have already learned many facts that directly explain their properties. Because there is no one functional group that is present in all lipids, however, the chemistry of lipids draws upon knowledge learned in many prior chapters.

29.1 Introduction

The word *lipid* comes from the Greek word *lipos* for "fat."

- ***Lipids* are biomolecules that are soluble in organic solvents.**

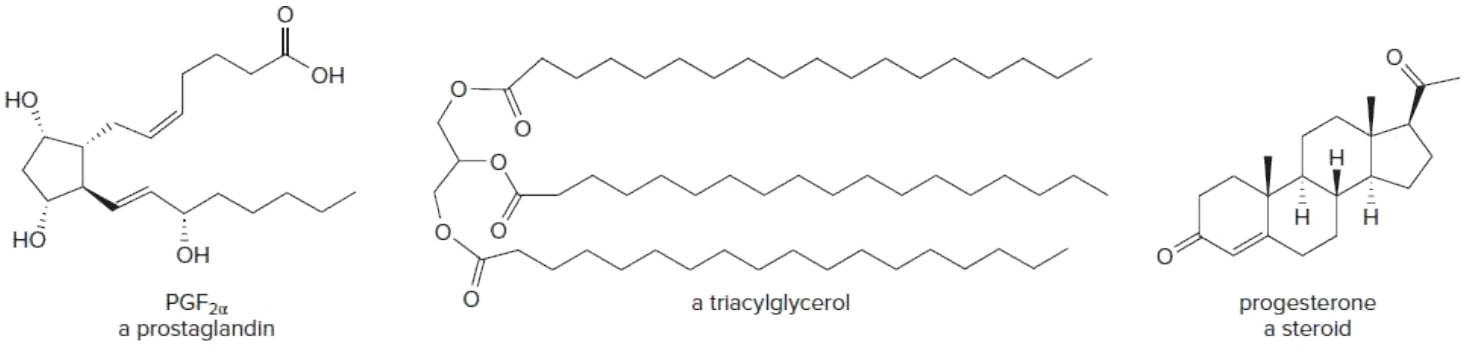
Lipids are unique among organic molecules because their identity is defined on the basis of a *physical property* and not by the presence of a particular functional group.

Because of this, lipids come in a wide variety of structures and they have many different functions in the cell. Three examples are given in Figure 29.1.

The large number of carbon–carbon and carbon–hydrogen σ bonds in lipids makes them very soluble in organic solvents and insoluble in water. Monosaccharides (from which carbohydrates are formed) and amino acids (from which proteins are formed), on the other hand, are very polar, so they tend to be water soluble. Because lipids share many properties with hydrocarbons, several features of lipid structure and properties have already been discussed. Table 29.1 summarizes sections of the text where aspects of lipid chemistry were covered previously.

Table 29.1 Summary of Lipid Chemistry Discussed Prior to Chapter 29

Topic	Section	Topic	Section
• Vitamin A	**3.5**	• Lipid oxidation	**13.11**
• Soap	**3.6**	• Vitamin E	**13.12**
• Phospholipids, the cell membrane	**3.7**	• Steroid synthesis	**14.14**
• Lipids Part 1	**4.15**	• Prostaglandins	**19.5**
• Leukotrienes	**9.17**	• Lipid hydrolysis	**20.11A**
• Fats and oils	**10.6**	• Soap	**20.11B**
• Oral contraceptives	**11.4**	• Cholesteryl esters	**20.16**
• Hydrogenation of oils	**12.4**	• Steroid synthesis	**22.8**

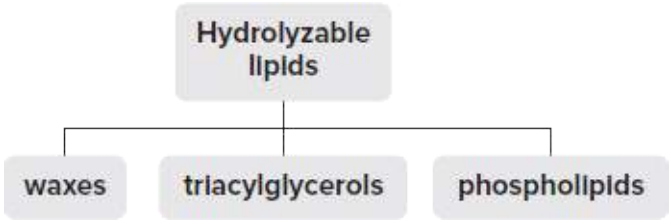


- All lipids have many C–C and C–H bonds, but there is no one functional group common to all lipids.

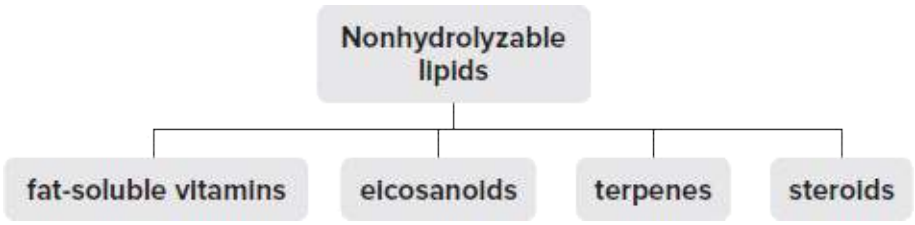
Figure 29.1 **Three examples of lipids**

Lipids can be categorized as hydrolyzable or nonhydrolyzable. Page 1294

[1] ***Hydrolyzable lipids*** can be cleaved into smaller molecules by hydrolysis with water. Most hydrolyzable lipids contain an ester unit. We will examine three subgroups: waxes, triacylglycerols, and phospholipids.



[2] ***Nonhydrolyzable lipids*** cannot be cleaved into smaller units by aqueous hydrolysis. Nonhydrolyzable lipids tend to be more varied in structure. We will examine four different types: fat-soluble vitamins, eicosanoids, terpenes, and steroids.



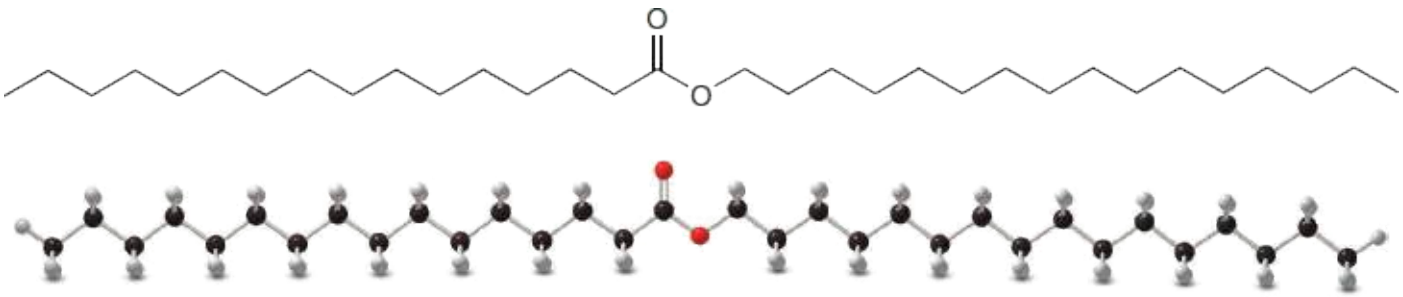
29.2 Waxes

Water beads up on the surface of a leaf because of the leaf's waxy coating. ***©Daniel C. Smith***

The seeds of the jojoba plant grown in the southwestern United States are rich in waxes used in cosmetics and personal care products (Problem 29.1). *Source: USDA, ARS, National Genetic Resources Program*

Waxes are the simplest hydrolyzable lipids. Waxes are esters (RCOOR') formed from a high-molecular-weight alcohol (R'OH) and a fatty acid (RCOOH).

Because of their long hydrocarbon chains, waxes are very hydrophobic. They form a protective coating on the feathers of birds to make them water repellent, and on leaves to prevent water evaporation. Lanolin, a wax composed of a complex mixture of high-molecular-weight esters, coats the wool fibers of sheep. Spermaceti wax, isolated from the heads of sperm whales, is largely $CH_3(CH_2)_{14}COO(CH_2)_{15}CH_3$. The three-dimensional structure of this compound shows how small the ester group is compared to the long hydrocarbon chains.



spermaceti wax (from sperm whales)

Problem 29.1

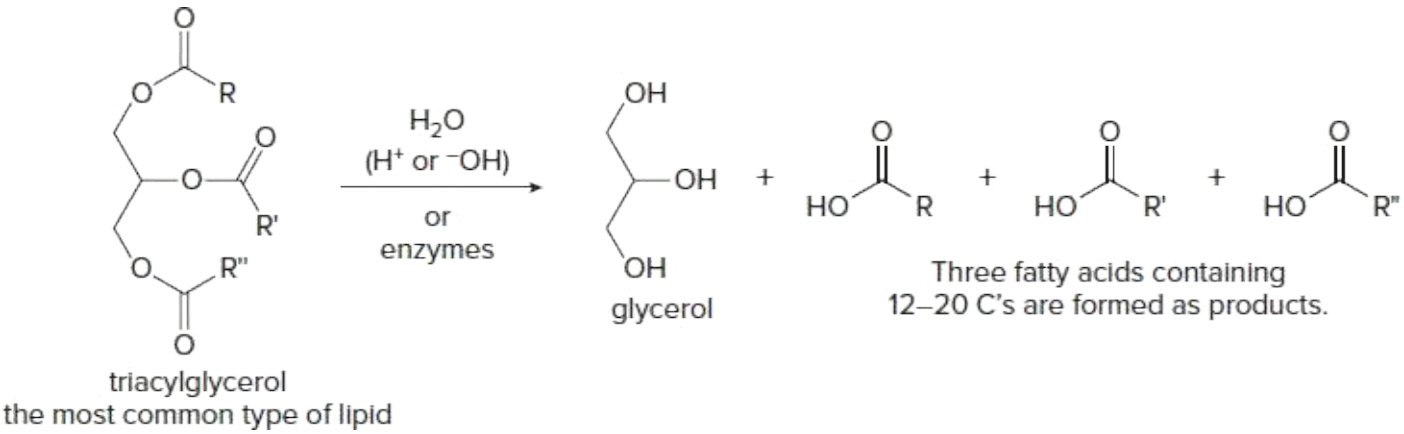
One component of jojoba oil is a wax formed from eicosenoic acid

[$CH_3(CH_2)_7CH{=}CH(CH_2)_9CO_2H$] and $CH_3(CH_2)_7CH{=}CH(CH_2)_8OH$. Draw the structure of the wax, including the cis geometry of both carbon–carbon double bonds.

29.3 Triacylglycerols

Triacylglycerols, or triglycerides, are the most abundant lipids, and for this reason we have already discussed many of their properties in earlier sections of this text.

- **Triacylglycerols are triesters that produce glycerol and three molecules of fatty acid upon hydrolysis.**



triacylglycerol
the most common type of lipid

glycerol

Line structures of stearic, oleic, linoleic, and linolenic acids can be found in Table 10.2. Ball-and-stick models of these fatty acids are shown in Figure 10.5.

Simple triacylglycerols are composed of three identical fatty acid side chains, whereas mixed triacylglycerols have two or three different fatty acids. Table 29.2 lists the most common fatty acids used to form triacylglycerols.

Table 29.2 The Most Common Fatty Acids in Triacylglycerols

Number of C atoms	Number of C=C bonds	Structure	Name
		Saturated fatty acids	
12	0	$CH_3(CH_2)_{10}CO_2H$	lauric acid
14	0	$CH_3(CH_2)_{12}CO_2H$	myristic acid

16	0	$CH_3(CH_2)_{14}CO_2H$	palmitic acid
18	0	$CH_3(CH_2)_{16}CO_2H$	stearic acid
20	0	$CH_3(CH_2)_{18}CO_2H$	arachidic acid
		Unsaturated fatty acids	
16	1	$CH_3(CH_2)_5CH{=}CH(CH_2)_7CO_2H$	palmitoleic acid
18	1	$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H$	oleic acid
18	2	$CH_3(CH_2)_4(CH{=}CHCH_2)_2(CH_2)_6CO_2H$	linoleic acid
18	3	$CH_3CH_2(CH{=}CHCH_2)_3(CH_2)_6CO_2H$	linolenic acid
20	4	$CH_3(CH_2)_4(CH{=}CHCH_2)_4(CH_2)_2CO_2H$	arachidonic acid

The most common saturated fatty acids are palmitic and stearic acids. The most common unsaturated fatty acid is oleic acid.

What are the characteristics of these fatty acids?

- **All fatty acid chains are unbranched, but they may be saturated or unsaturated.**
- **Naturally occurring fatty acids have an even number of carbon atoms.**
- **Double bonds in naturally occurring fatty acids generally have the *Z* configuration.**
- **The melting point of a fatty acid depends on the degree of unsaturation.**

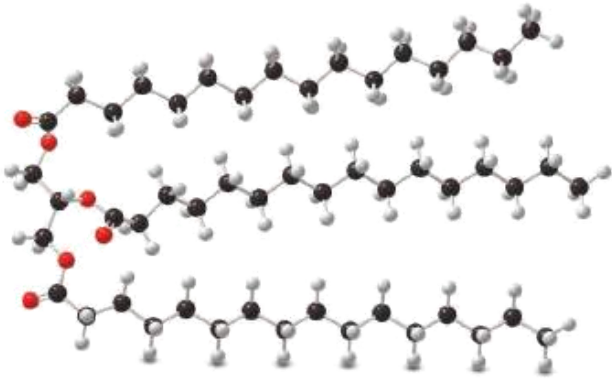
Linoleic and linolenic acids are called essential fatty acids because we cannot synthesize them and must acquire them in our diets.

Fats and oils are triacylglycerols; that is, they are triesters of glycerol and these fatty

acids.

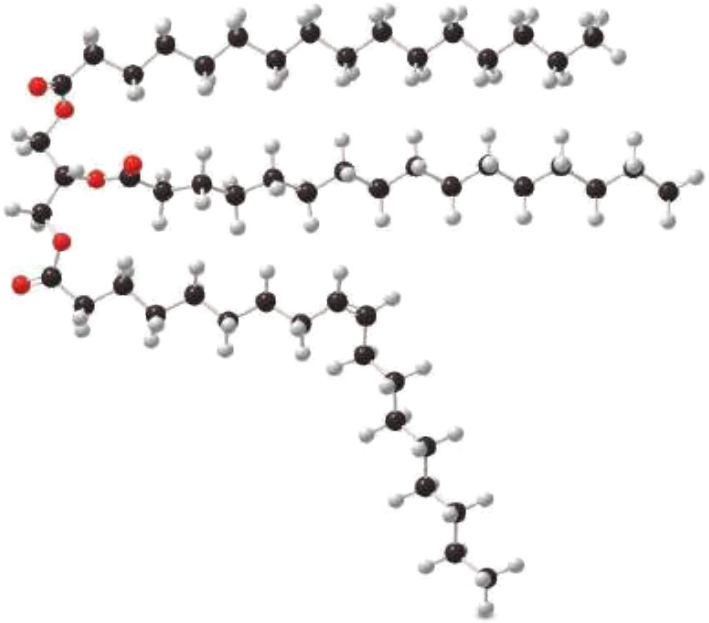
- **Fats have *higher* melting points, making them solids at room temperature.**
- **Oils have *lower* melting points, making them liquids at room temperature.**

a. A saturated triacylglycerol



- Three saturated side chains lie parallel to each other, making a compact lipid.

b. An unsaturated triacylglycerol



- One *Z* double bond in a fatty acid side chain produces a twist so that the lipid is no longer so compact.

Figure 29.2 **Three-dimensional structures of a saturated and unsaturated triacylglycerol**

Unlike other vegetable oils, oils from palm and coconut trees are very high in saturated fats. Considerable evidence currently suggests that diets high in saturated fats lead to a greater risk of heart disease. For this reason, the demand for coconut and palm oils has decreased considerably in recent

years, and many coconut plantations previously farmed in the South Pacific are no longer in commercial operation. top, ©*phiseksit/Shutterstock;* bottom, ©*McGraw-Hill Education/Elite Images*

This melting point difference correlates with the number of degrees of unsaturation present in the fatty acid side chains. As the number of double bonds *increases*, the melting point *decreases*, as it does for the constituent fatty acids as well.

Three-dimensional structures of a saturated and unsaturated triacylglycerol are shown in Figure 29.2. With no double bonds, the three side chains of the saturated lipid lie parallel to each other, making it possible for this compound to pack relatively efficiently in a crystalline lattice, thus leading to a high melting point. In the unsaturated lipid, however, a single *Z* double bond places a kink in the side chain, making it more difficult to pack efficiently in the solid state, thus leading to a lower melting point.

Solid fats have a relatively high percentage of saturated fatty acids and are generally of animal origin. Liquid oils have a higher percentage of unsaturated fatty acids and are generally of vegetable origin. Table 29.3 lists the fatty acid composition of some common fats and oils.

Table 29.3 Fatty Acid Composition of Some Fats and Oils

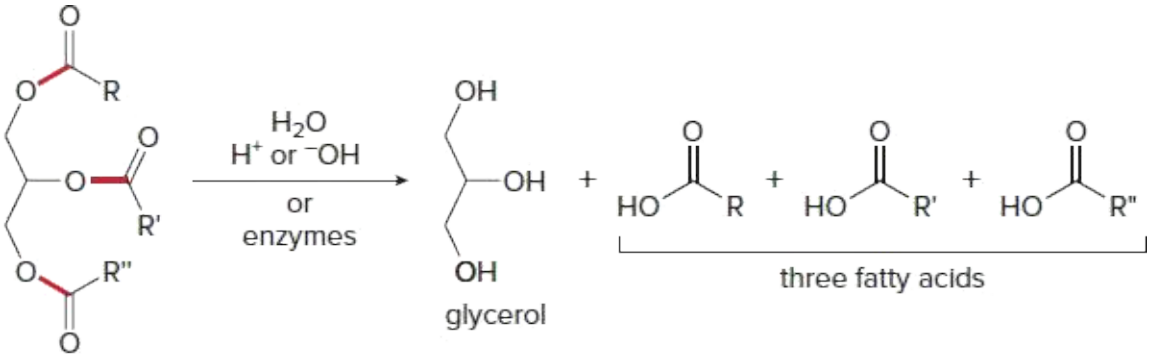
Source	% Saturated fatty acids	% Oleic acid	% Linoleic acid
beef	49–62	37–43	2–3
milk	37	33	3
coconut	86	7	—
corn	11–16	19–49	34–62
olive	11	84	4
palm	43	40	8
saffiower	9	13	78
soybean	15	20	52

Source: Data from *Merck Index*, 10th ed. Rahway, NJ: Merck and Co.; and Wilson et al., 1967, *Principles of Nutrition*, 2nd ed. New York: Wiley.

Fish oils, such as cod liver and herring oils, are very rich in polyunsaturated triacylglycerols. These triacylglycerols pack so poorly that they have very low melting points; thus, they remain liquids even in the cold water inhabited by these fish.
©Pixtal/age fotostock

The hydrolysis, hydrogenation, and oxidation of triacylglycerols—reactions originally discussed in Chapters 12, 13, and 20—are summarized here for your reference.

[1] Hydrolysis of triacylglycerols (Section 20.11A)

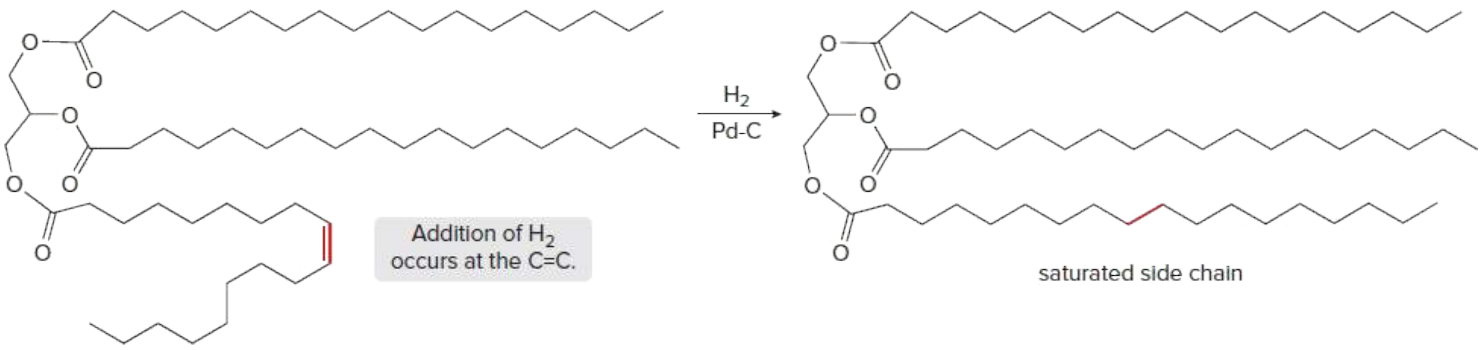


Three ester units are cleaved.

Hydrolysis of a triacylglycerol with water in the presence of either acid, base, or an enzyme yields glycerol and three fatty acids. This cleavage reaction follows the same mechanism as any other ester hydrolysis (Section 20.10). This reaction is the first step

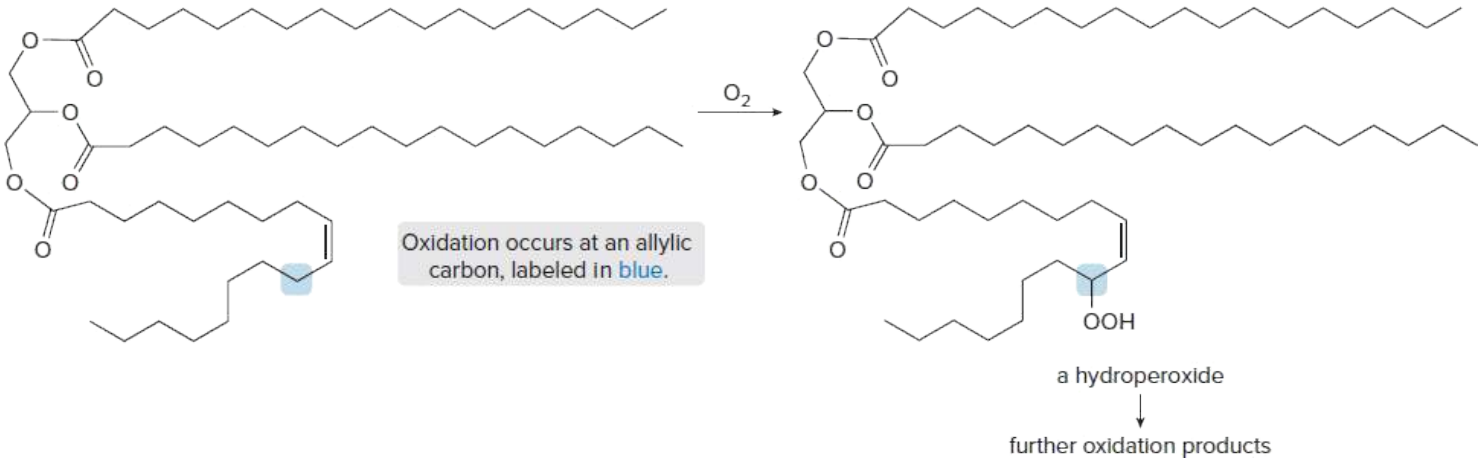
in triacylglycerol metabolism.

[2] Hydrogenation of unsaturated fatty acids (Section 12.4)



The double bonds of an unsaturated fatty acid can be hydrogenated by using H_2 in the presence of a transition metal catalyst. Hydrogenation converts a liquid oil to a solid fat. This process, sometimes called hardening, is used to prepare margarine from vegetable oils.

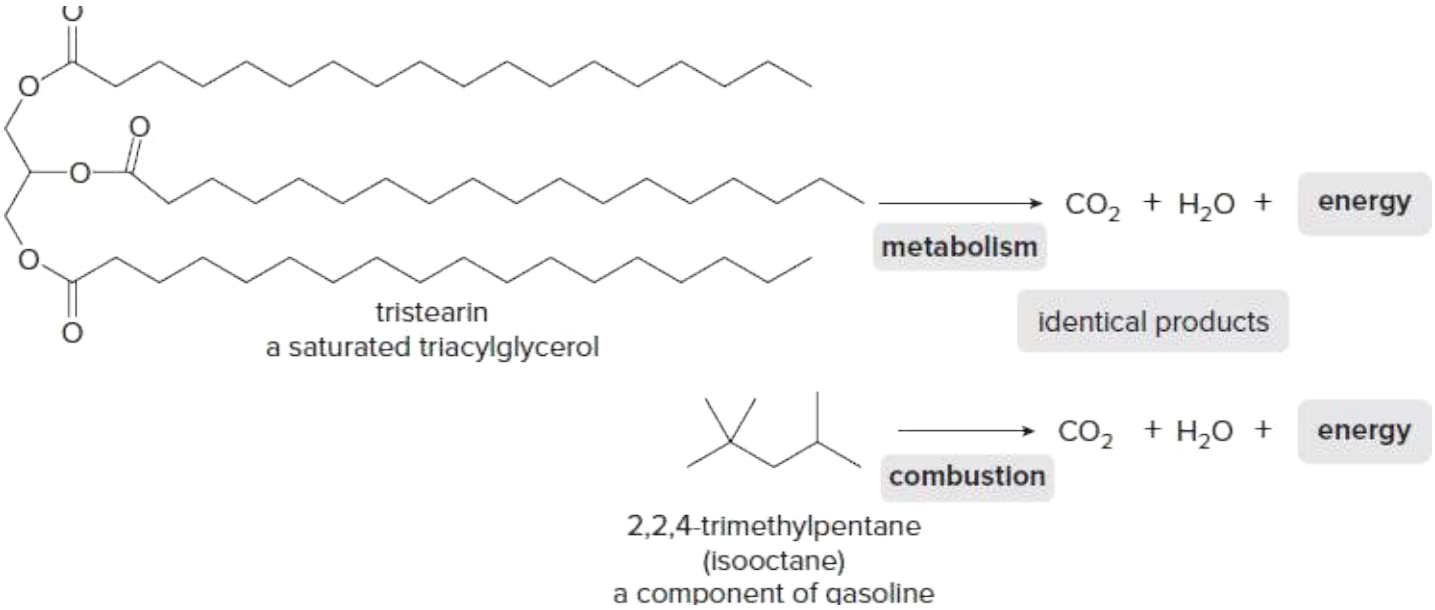
[3] Oxidation of unsaturated fatty acids (Section 13.11)



Allylic C—H bonds are weaker than other C—H bonds and are thus susceptible to oxidation with molecular oxygen by a radical process. The hydroperoxide formed by this process is unstable, and it undergoes further oxidation to products that often have a disagreeable odor. This oxidation process turns an oil rancid.

The average body fat content of men and women is ~20% and ~25%, respectively. (For elite athletes, however, the averages are more like < 10% for men and < 15% for women.) This stored fat can fill the body's energy needs for two or three months.

In the cell, the principal function of triacylglycerols is energy storage. Complete metabolism of a triacylglycerol yields CO_2 and H_2O, and a great deal of energy. This overall reaction is reminiscent of the combustion of alkanes in fossil fuels, a process that also yields CO_2 and H_2O and provides energy to heat homes and power automobiles (Section 4.14B). Fundamentally both processes convert C—C and C—H bonds to C—O bonds, a highly exothermic reaction.



©AP Images

Carbohydrates provide an energy boost, but only for the short term, such as during strenuous exercise. Our long-term energy needs are met by triacylglycerols, because they store ~38 kJ/g, whereas carbohydrates and proteins store only ~16 kJ/g.

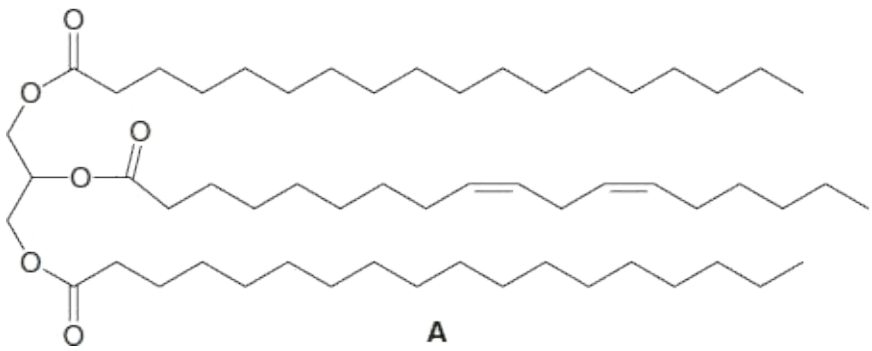
Because triacylglycerols release heat on combustion, they can in principle be used as fuels for vehicles. In fact, coconut oil was used as a fuel during both World War I and World War II, when gasoline and diesel supplies ran short. Coconut oil is more viscous than petroleum products and freezes at 24 °C, so engines must be modified to use it and it can't be used in cold climates. Nonetheless, a limited number of trucks and boats can now use vegetable oils, sometimes blended with diesel, as a fuel source. When the price of crude oil is high, the use of these biofuels becomes economically attractive.

Problem 29.2

How would you expect the melting point of eicosapentaenoic acid [$CH_3CH_2(CH{=}CHCH_2)_5(CH_2)_2COOH$] to compare with the melting points of the fatty acids listed in Table 29.2?

Problem 29.3

Draw the products formed when triacylglycerol A is treated with each reagent. Rank compounds A, B, and C in order of increasing melting point.



A

a. H_2O, H^+
b. H_2 (excess), Pd-C → **B**
c. H_2 (1 equiv), Pd-C → **C**

Problem 29.4

The main fatty acid component of the triacylglycerols in coconut oil is lauric acid, $CH_3(CH_2)_{10}COOH$. Explain why coconut oil is a liquid at room temperature even though it contains a large fraction of this saturated fatty acid.

Problem 29.5

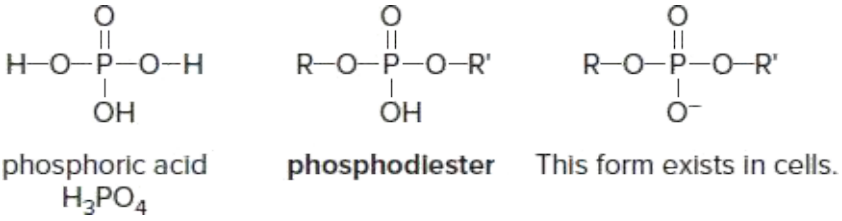
Unlike many fats and oils, the cocoa butter used to make chocolate is remarkably uniform in composition. All triacylglycerols contain oleic acid esterified to the 2° OH group of glycerol, and either palmitic acid or stearic acid esterified to the 1° OH groups. Draw the structures of two possible triacylglycerols that compose cocoa butter.

29.4 Phospholipids

Phospholipids are hydrolyzable lipids that contain a phosphorus atom. There are two common types of phospholipids: phosphoacylglycerols and sphingomyelins. Both classes are found almost exclusively in the cell membranes of plants and animals, as discussed in Section 3.7.

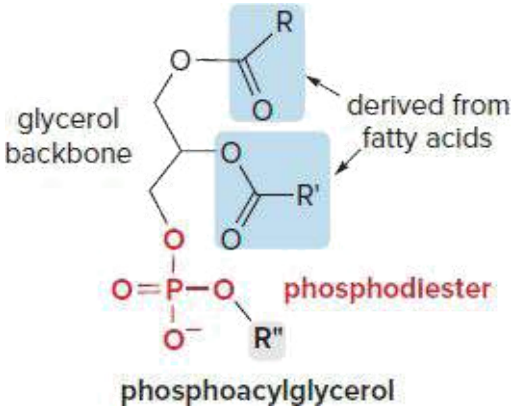
Phospholipids are organic derivatives of phosphoric acid, formed by replacing two of the H atoms by R groups. This type of functional group is called a phosphodiester, or a

phosphoric acid diester. These compounds are phosphorus analogues of carboxylic esters. In cells, the remaining OH group on phosphorus loses its proton, giving the phosphodiester a net negative charge.



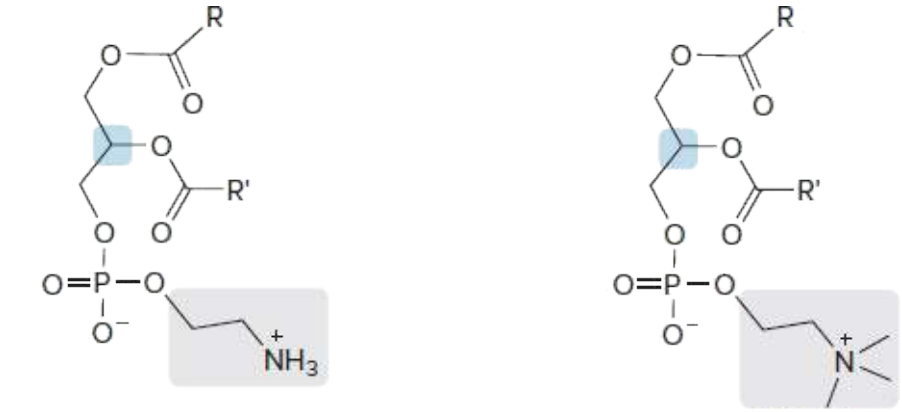
29.4A Phosphoacylglycerols

Phosphoacylglycerols (or phosphoglycerides) are the second most abundant type of lipid. They form the principal lipid component of most cell membranes. Their structure resembles that of the triacylglycerols of Section 29.3 with one important difference. In phosphoacylglycerols, only *two* of the hydroxy groups of glycerol are esterified with fatty acids. The third OH group is part of a phosphodiester, which is also bonded to another low-molecular-weight alcohol.



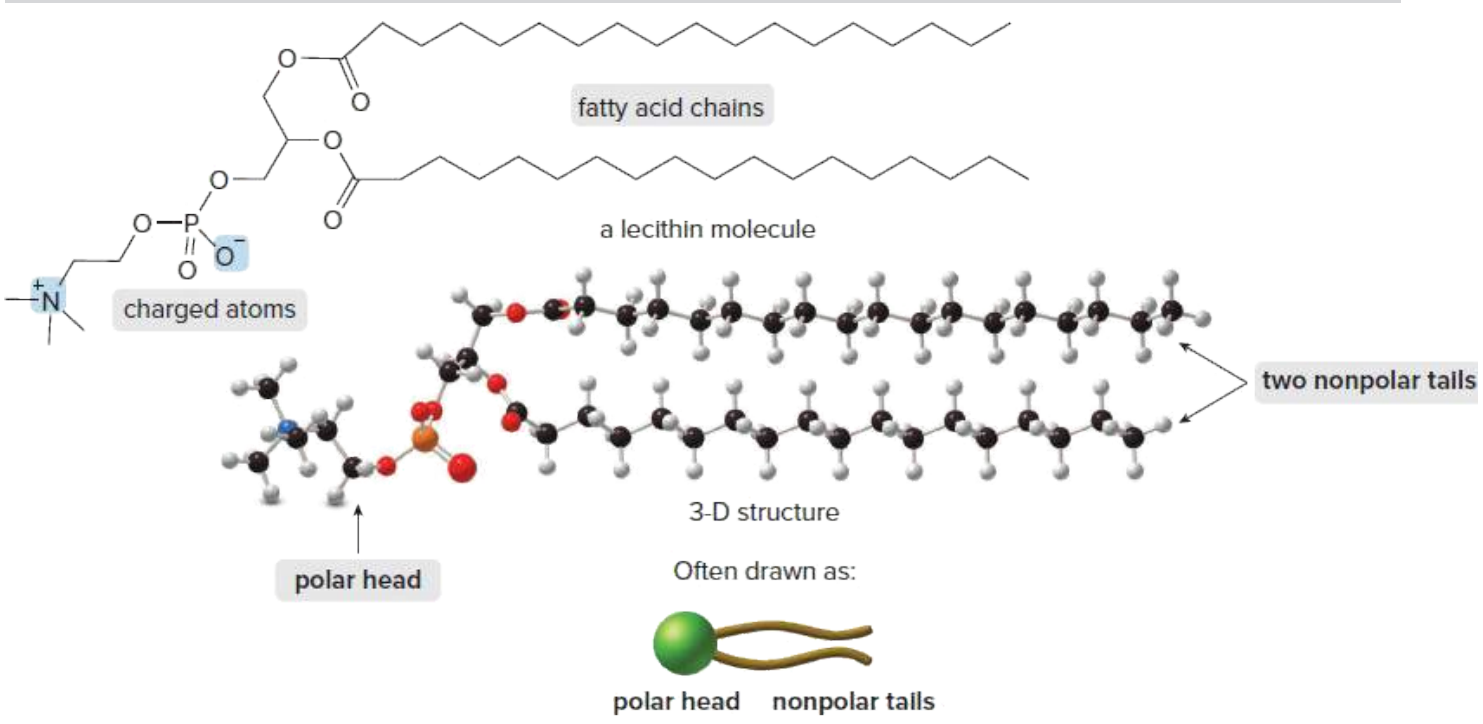
There are two prominent types of phosphoacylglycerols. They differ in the identity of the R" group in the phosphodiester.

- **When R" = $CH_2CH_2NH_3$+, the phosphoacylglycerol is called a phosphatidylethanolamine or cephalin.**
- **When R" = $CH_2CH_2N(CH_3)_3^+$, the phosphoacylglycerol is called a phosphatidylcholine or lecithin.**



The middle carbon of the glycerol backbone of all of these compounds is a stereogenic center (labeled in blue), usually with the *R* configuration.

The phosphorus side chain of a phosphoacylglycerol makes it different from a triacylglycerol. The two fatty acid side chains form two nonpolar "tails" that lie parallel to each other, whereas the phosphodiester end of the molecule is a charged or polar "head." A three-dimensional structure of a phosphoacylglycerol is shown in Figure 29.3.



- A phosphoacylglycerol has two distinct regions: **two nonpolar tails** due to the long-chain fatty acids, and a **very polar head** from the charged phosphodiester.

Figure 29.3 **Three-dimensional structure of a phosphoacylglycerol**

As discussed in Section 3.7, when these phospholipids are mixed with water, they assemble in an arrangement called a lipid bilayer. The ionic heads of the phospholipid

are oriented on the outside and the nonpolar tails on the inside. The identity of the fatty acids in the phospholipid determines the rigidity of this bilayer. When the fatty acids are saturated, they pack well in the interior of the lipid bilayer and the membrane is quite rigid. When there are many unsaturated fatty acids, the nonpolar tails cannot pack as well and the bilayer is more fluid. Thus, important characteristics of this lipid bilayer are determined by the three-dimensional structure of the molecules that comprise it.

Cell membranes are composed of these lipid bilayers (see Figure 3.5). Proteins and cholesterol are embedded in the membranes as well, but the phospholipid bilayer forms the main fabric of the insoluble barrier that protects the cell.

Problem 29.6

Draw the structure of a lecithin containing oleic acid and palmitic acid as the fatty acid side chains.

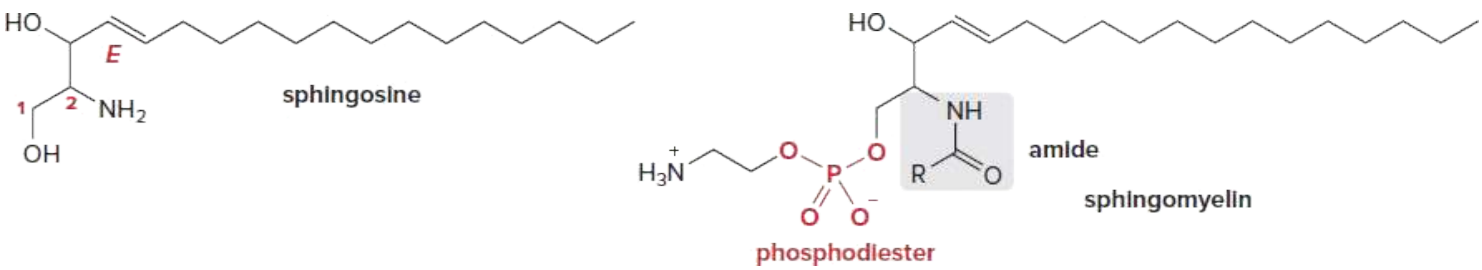
Problem 29.7

Phosphoacylglycerols should remind you of soaps (Section 3.6). In what ways are these compounds similar?

29.4B Sphingomyelins

Sphingomyelins, the second major class of phospholipids, are derivatives of the amino alcohol sphingosine, in much the same way that triacylglycerols and phosphoacylglycerols are derivatives of glycerol. Other notable features of a sphingomyelin include:

- A phosphodiester at C1.
- An amide formed with a fatty acid at C2.



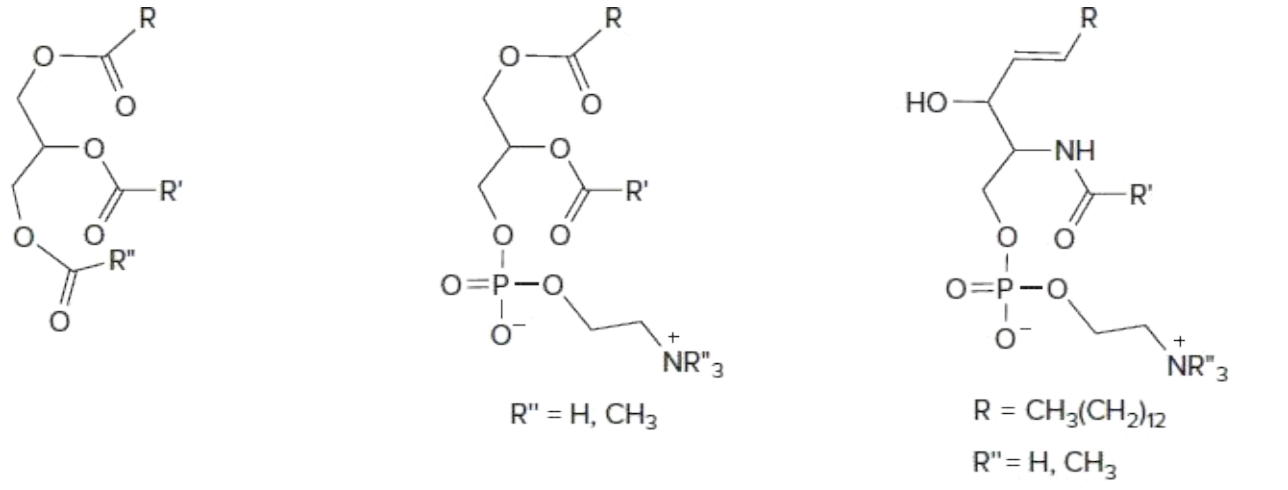
Like phosphoacylglycerols, sphingomyelins are also a component of the lipid bilayer of cell membranes. The coating that surrounds and insulates nerve cells, the myelin sheath, is particularly rich in sphingomyelins and is vital for proper nerve function.

Deterioration of the myelin sheath as seen in multiple sclerosis leads to disabling neurological problems.

Figure 29.4 compares the structural features of the most common hydrolyzable lipids: a triacylglycerol, a phosphoacylglycerol, and a sphingomyelin.

Problem 29.8

Why are phospholipids, but not triacylglycerols, found in cell membranes?



- A **triacylglycerol** has three nonpolar side chains.
- The three OH groups of **glycerol** are esterified with three fatty acids.

- A **phosphoacylglycerol** has two nonpolar side chain tails and one ionic head.
- Two OH groups of **glycerol** are esterified with fatty acids.
- A **phosphodiester** is located on a terminal carbon.

- A **sphingomyelin** has two nonpolar side chain tails and one ionic head.
- A sphingomyelin is formed from **sphingosine,** not glycerol. One of the nonpolar tails is an **amide.**
- A **phosphodiester** is located on a terminal carbon.

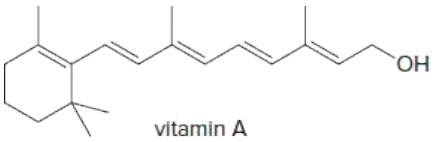
Figure 29.4 **A comparison of a triacylglycerol, a phosphoacylglycerol, and a sphingomyelin**

29.5 Fat-Soluble Vitamins

Vitamins are organic compounds required in small quantities for normal metabolism (Section 3.5). Because our cells cannot synthesize these compounds, they must be obtained in the diet. Vitamins can be categorized as fat soluble or water soluble. The fat-soluble vitamins are lipids.

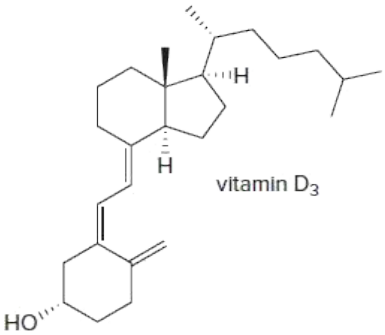
The four fat-soluble vitamins—A, D, E, and K—are found in fruits and vegetables, fish, liver, and dairy products. Although fat-soluble vitamins must be obtained from the

diet, they do not have to be ingested every day. Excess vitamins are stored in fat cells, and then used when needed. Figure 29.5 shows the structure of these vitamins and summarizes their functions.



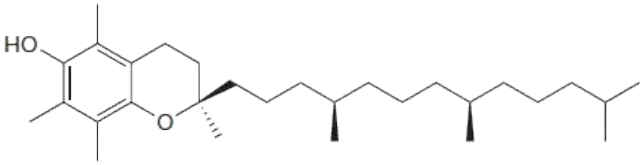
vitamin A

- **Vitamin A** (retinol, Section 3.5) is obtained from fish liver oils and dairy products, and is synthesized from β-carotene, the orange pigment in carrots.
- In the body, vitamin A is converted to 11-*cis*-retinal, the light-sensitive compound responsible for vision in all vertebrates (Section 18.10B). It is also needed for healthy mucous membranes.
- A deficiency of vitamin A causes night blindness, as well as dry eyes and skin.



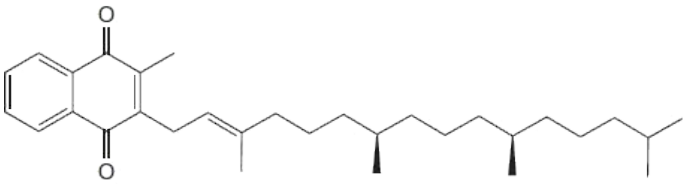
vitamin D_3

- **Vitamin D_3** is the most abundant of the D vitamins. Strictly speaking, it is not a vitamin because it can be synthesized in the body from cholesterol. Nevertheless, it is classified as such, and many foods (particularly milk) are fortified with vitamin D_3 so that we get enough of this vital nutrient.
- Vitamin D helps regulate both calcium and phosphorus metabolism.
- A deficiency of vitamin D causes rickets, a bone disease characterized by knock-knees, spinal curvature, and other deformities.



vitamin E
(α-tocopherol)

- The term **vitamin E** refers to a group of structurally similar compounds, the most potent being α-tocopherol (Section 13.12).
- Vitamin E is an antioxidant, so it protects unsaturated side chains in fatty acids from oxidation.
- A deficiency of vitamin E causes numerous neurologic problems.

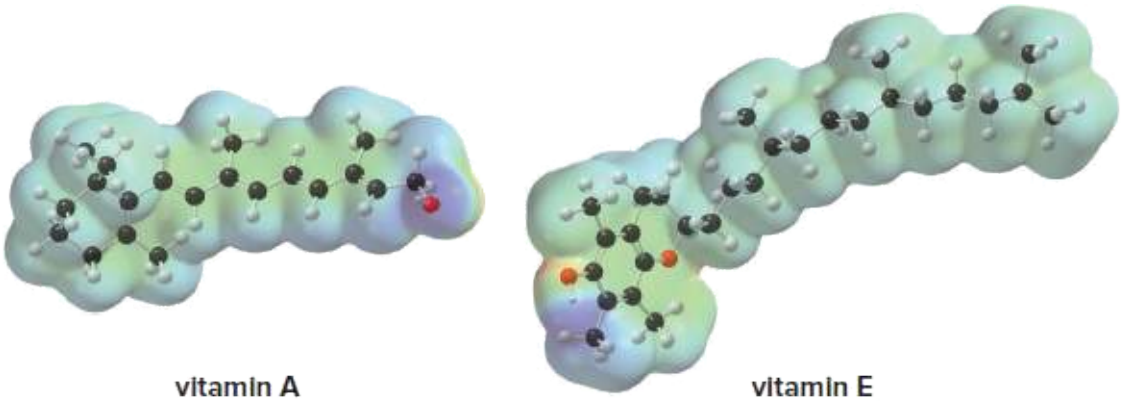


vitamin K

- **Vitamin K** (phylloquinone) regulates the synthesis of prothrombin and other proteins needed for blood to clot.
- A deficiency of vitamin K leads to excessive and sometimes fatal bleeding because of inadequate blood clotting.

Figure 29.5 **The fat-soluble vitamins**

Electrostatic potential plots of vitamins A and E (Figure 29.6) show that the electron density is virtually uniform in these compounds. The large regions of nonpolar C—C and C—H bonds tend to obscure small dipoles that occur in the one or two polar bonds, making these vitamins nonpolar and hydrophobic.



vitamin A vitamin E

- The electron density is distributed fairly evenly among the carbon atoms of these vitamins due to their many nonpolar C—C and C—H bonds.

Figure 29.6 **Electrostatic potential plots of vitamins A and E**

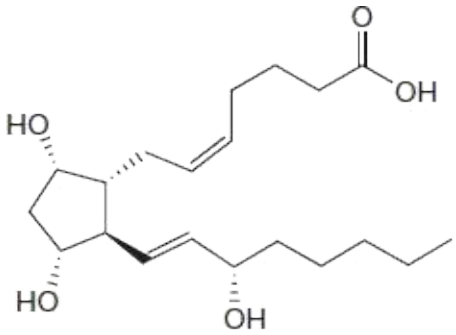
Problem 29.9

Explain why regularly ingesting a large excess of a fat-soluble vitamin can lead to severe health problems, whereas ingesting a large excess of a water-soluble vitamin often causes no major health problems.

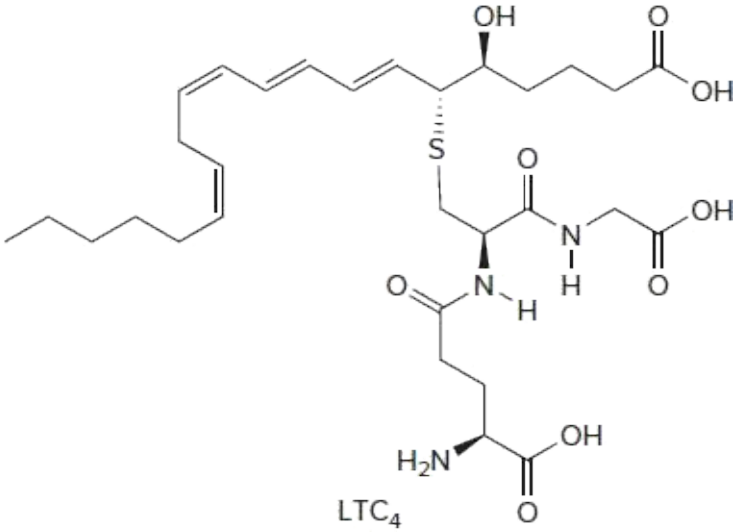
29.6 Eicosanoids

The word *eicosanoid* is derived from the Greek word *eikosi*, meaning "20."

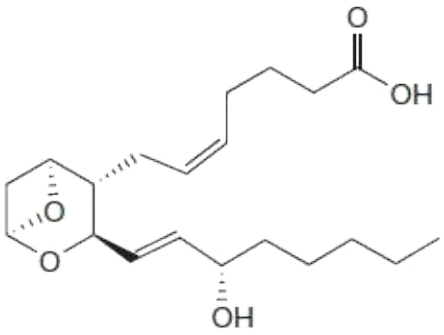
The eicosanoids are a group of biologically active compounds containing 20 carbon atoms derived from arachidonic acid. The prostaglandins (Section 19.5) and the leukotrienes (Section 9.17) are two types of eicosanoids. Two others are the thromboxanes and prostacyclins.



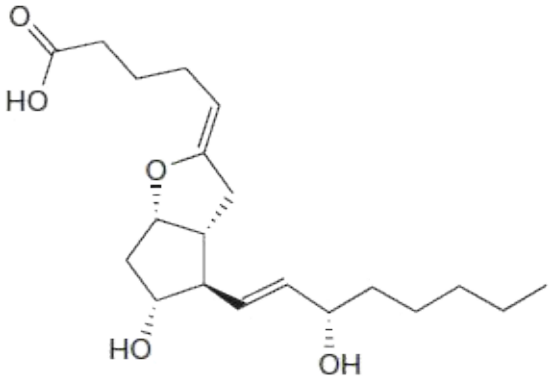
$PGF_{2\alpha}$
a prostaglandin



LTC_4
a leukotriene



TXA_2
a thromboxane



PGI_2
a prostacyclin

All eicosanoids are very potent compounds present in low concentration in cells. They are local mediators, meaning that they perform their function in the environment in which they are synthesized. This distinguishes them from hormones, which are first synthesized and then transported in the bloodstream to their site of action. Eicosanoids are not stored in cells; rather, they are synthesized from arachidonic acid in response to an external stimulus.

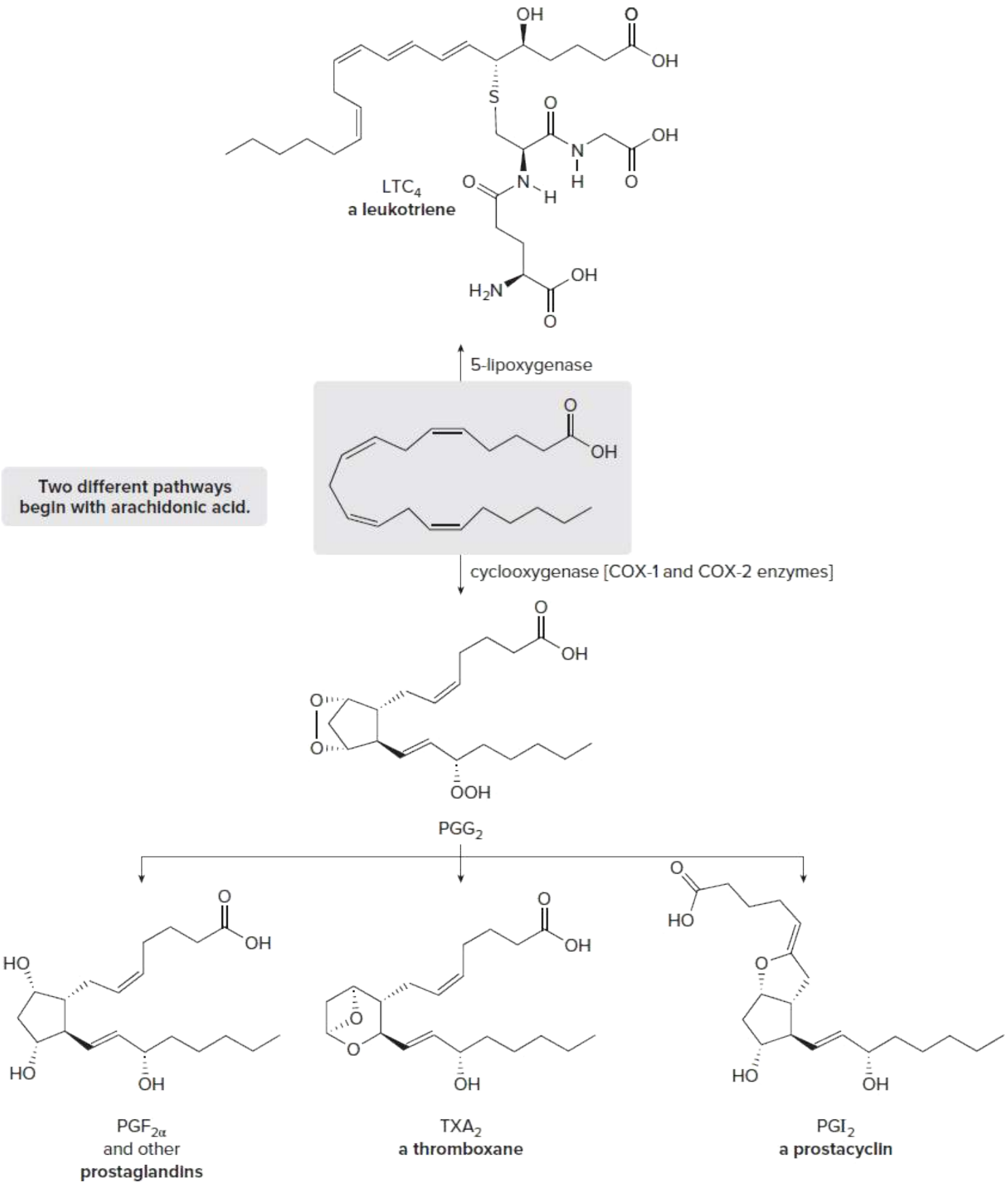


Figure 29.7 **The conversion of arachidonic acid to prostaglandins, thromboxanes, prostacyclins, and leukotrienes**

Other details of the biosynthesis of leukotrienes and prostaglandins were given in Sections 9.17 and 19.5,

respectively.

The synthesis of prostaglandins, thromboxanes, and prostacyclins begins with the oxidation of arachidonic acid with O_2 by a cyclooxygenase enzyme, which forms an unstable cyclic intermediate, PGG_2. PGG_2 is then converted via different pathways to these three classes of compounds. Leukotrienes are formed by a different pathway, using an enzyme called a lipoxygenase. These four paths for arachidonic acid are summarized in Figure 29.7.

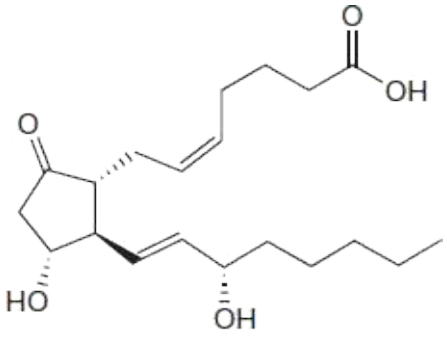
Each eicosanoid is associated with specific types of biological activity (Table 29.4). In some cases, the effects oppose one another. For example, thromboxanes are vasoconstrictors that trigger blood platelet aggregation, whereas prostacyclins are vasodilators that inhibit platelet aggregation. The levels of these two eicosanoids must be in the right balance for cells to function properly.

Table 29.4 Biological Activity of the Eicosanoids

Eicosanoid	Effect	Eicosanoid	Effect
Prostaglandins	• Lower blood pressure • Inhibit blood platelet aggregation • Control inflammation • Lower gastric secretions • Stimulate uterine contractions • Relax smooth muscles of the uterus	**Thromboxanes**	• Constrict blood vessels • Trigger blood platelet aggregation
		Prostacyclins	• Dilate blood vessels • Inhibit blood platelet aggregation
		Leukotrienes	• Constrict smooth muscle, especially

in the lungs

Because of their wide range of biological functions, prostaglandins and their analogues have found several clinical uses. For example, dinoprostone, the generic name for PGE_2, is administered to relax the smooth muscles of the uterus when labor is induced and to terminate pregnancies in the early stages.

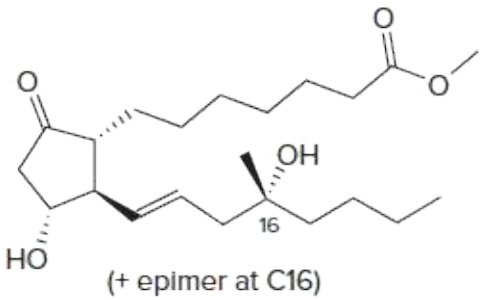


PGE_2
(dinoprostone)

Problem 29.10

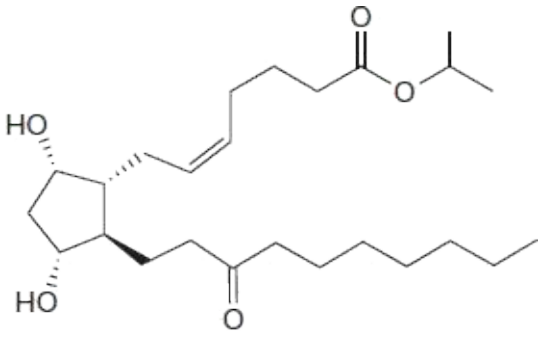
Which carbons of arachidonic acid become the carbons of the five-membered ring in PGE_2?

Because prostaglandins themselves are unstable in the body, often having half-lives of only minutes, more stable analogues have been developed that retain their important biological activity longer. Misoprostol is a prostaglandin analogue administered to prevent gastric ulcers in patients who are at high risk of developing them, and unoprostone isopropyl is used to decrease eye pressure in glaucoma patients.



(+ epimer at C16)

misoprostol

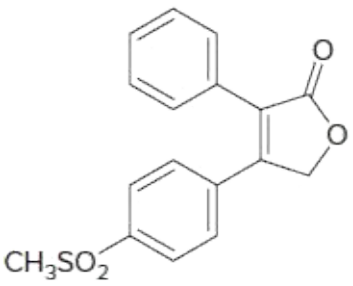


unoprostone isopropyl

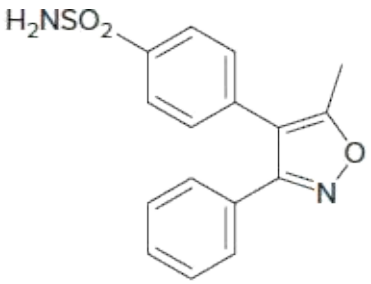
Studying the biosynthesis of eicosanoids has led to other discoveries as well. For example, aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) inactivate the cyclooxygenase enzyme needed for prostaglandin synthesis. In this way, NSAIDs block the synthesis of the prostaglandins that cause inflammation (Section 19.5).

More recently, it has been discovered that two *different* cyclooxygenase enzymes, called COX-1 and COX-2, are responsible for prostaglandin synthesis. COX-1 is involved with the usual production of prostaglandins, but COX-2 is responsible for the synthesis of additional prostaglandins in inflammatory diseases like arthritis. NSAIDs like aspirin and ibuprofen inactivate both the COX-1 and COX-2 enzymes. This activity also results in an increase in gastric secretions, making an individual more susceptible to ulcer formation.

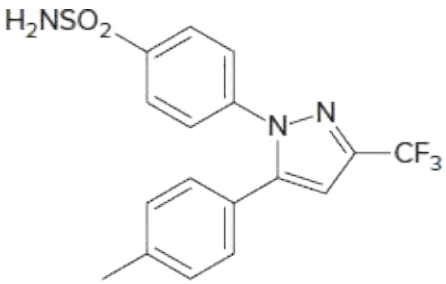
A group of anti-inflammatory drugs that block only the COX-2 enzyme was developed in the 1990s. These drugs—rofecoxib, valdecoxib, and celecoxib—do not cause an increase in gastric secretions, and thus were touted as especially effective NSAIDs for patients with arthritis, who need daily doses of these medications. Unfortunately, both rofecoxib and valdecoxib have now been removed from the market, because their use has been associated with an increased risk of heart attack and stroke.



Generic name rofecoxib
Trade name Vioxx



Generic name valdecoxib
Trade name Bextra

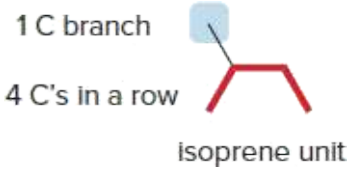


Generic name celecoxib
Trade name Celebrex

The discovery of drugs that block prostaglandin synthesis illustrates how basic research in organic chemistry can lead to important practical applications. Elucidating the structure and biosynthesis of prostaglandins began as a project in basic research. It has now resulted in a number of applications that benefit many individuals with various illnesses.

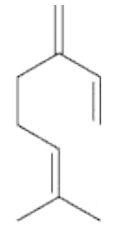
29.7 Terpenes

Terpenes are lipids composed of repeating five-carbon units called isoprene units. An isoprene unit has five carbons: four in a row, with a one-carbon branch on a middle carbon.

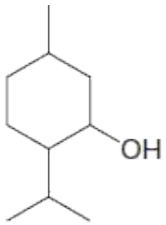


Terpenes are hydrocarbons that may be acyclic or have one or more rings. The term *terpenoid* is used for compounds that contain isoprene units as well as an oxygen heteroatom. Many essential oils, a group of compounds isolated from plant sources by distillation, are terpenes and terpenoids. Examples include myrcene from bayberry and menthol from peppermint.

bayberry plant ©Henriette Kress



myrcene



menthol

peppermint plant ©Cat Act Art/ Shutterstock

29.7A Locating Isoprene Units

How do we identify the isoprene units in these molecules? Start at one end of the molecule near a branch point. Then look for a four-carbon chain with a one-carbon branch. This forms one isoprene unit. Continue along the chain or around the ring until all the carbons are part of an isoprene unit. Keep in mind the following:

- **An isoprene unit may be composed of C—C σ bonds only, or there may be π bonds at any position.**
- **Isoprene units are always connected by one or more carbon–carbon bonds.**
- **Each carbon atom is part of one isoprene unit only.**
- **Every isoprene unit has five carbon atoms. Heteroatoms may be present, but their presence is ignored in locating isoprene units.**

Myrcene and menthol, for example, each have 10 carbon atoms, so they are composed of two isoprene units.

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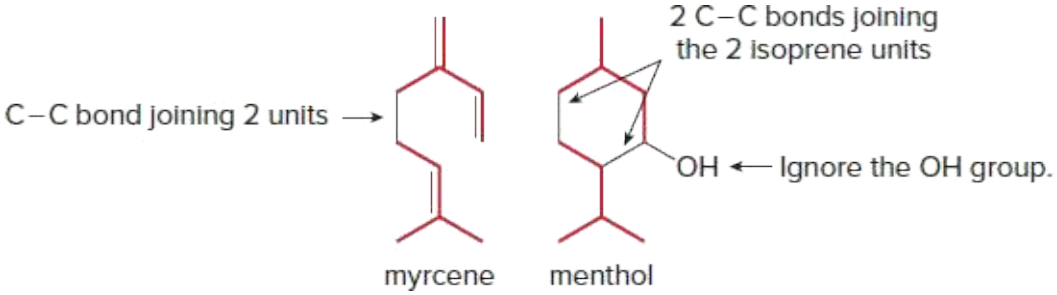
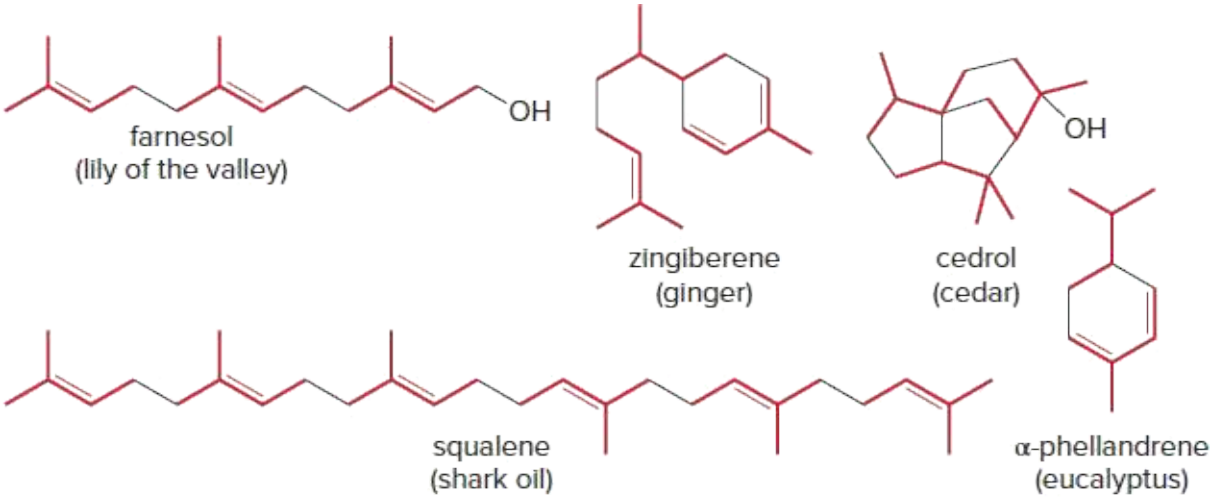


Several examples, with the isoprene units labeled in red, are given in Figure 29.8.



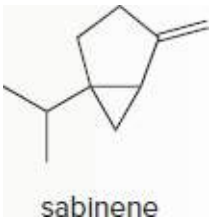
- Isoprene units are labeled in red, with C—C bonds (in black) joining two units.
- The source of each terpene or terpenoid is given in parentheses.

Figure 29.8 **Examples of some common terpenes and terpenoids**

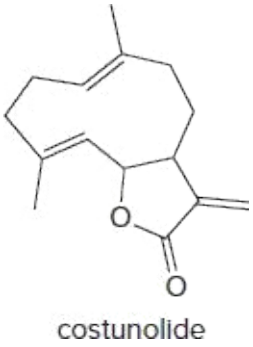
Sample Problem 29.1 Locating Isoprene Units

Locate the isoprene units in each compound.

a.



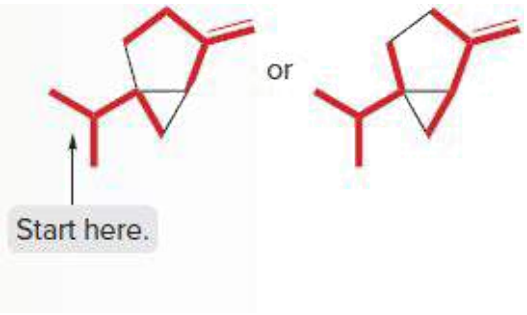
b.



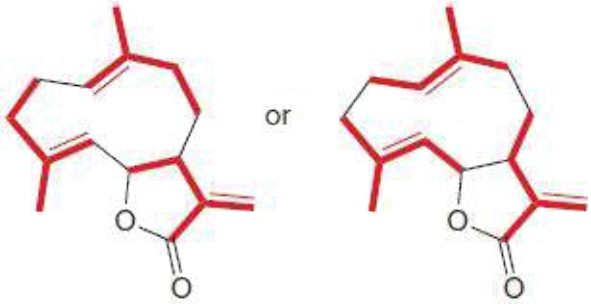
Solution

- **Start looking for isoprene units at a *branch* point. An isoprene unit has four carbons in a row with a one-carbon branch.**
- **Continue along a chain or around a ring until all carbons are part of *one* isoprene unit.**
- **Ignore all heteroatoms.**

a. Sabinene has 10 C's and two isoprene units. Start at the isopropyl group to locate isoprene units. Two possibilities are shown.



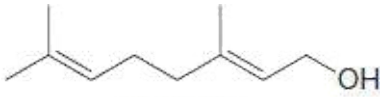
b. Costunolide has 15 C's and three isoprene units. Start at any branch point and ignore the two O's. Two possibilities are shown.



Problem 29.11

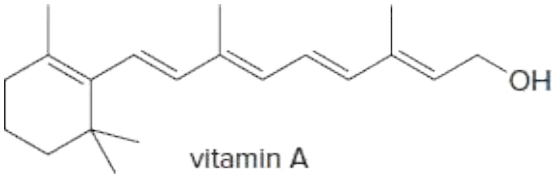
Locate the isoprene units in each compound.

a.



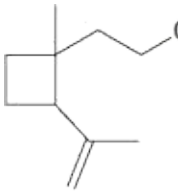
geraniol
(roses and geraniums)

b.



vitamin A

c.



grandisol
(sex pheromone of the male boll weevil)

d.

camphor

More Practice:

Try Problems 29.18, 29.26, 29.28b, 29.29a.

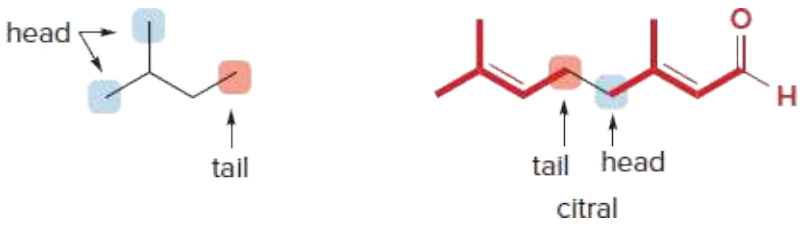
Terpenes and terpenoids are classified by the number of isoprene units they contain. A

monoterpene (or *monoterpenoid*) contains 10 carbons and has two isoprene units, a *sesquiterpene* (or *sesquiterpenoid*) contains 15 carbons and has three isoprene units, and so forth. The different terpene classes are summarized in Table 29.5.

Table 29.5 Classes of Terpenes and Terpenoids

Name	Number of C atoms	Number of isoprene units
Monoterpene (Monoterpenoid)	**10**	**2**
Sesquiterpene (Sesquiterpenoid)	**15**	**3**
Diterpene (Diterpenoid)	**20**	**4**
Sesterterpene (Sesterterpenoid)	**25**	**5**
Triterpene (Triterpenoid)	**30**	**6**
Tetraterpene (Tetraterpenoid)	**40**	**8**

An isoprene unit can be thought of as having a head and a tail. The "head" of the isoprene unit is located at the end of the chain nearest the branch point, and the "tail" is located at the end of the carbon chain farthest from the branch point. Most isoprene units are connected in a "head-to-tail" fashion, as shown for citral, which occurs in lemongrass.



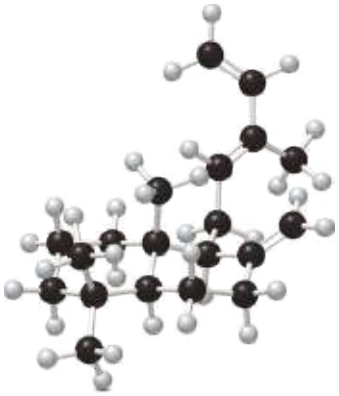
Amber, fossilized resin that oozed from trees long ago,

contains biformene, as well as many other terpenoids called labdanoids (Problem 29.12).

©hjochen/Shutterstock

Problem 29.12

Locate the isoprene units in biformene, a component of amber, and classify biformene as a monoterpene, sesquiterpene, etc.



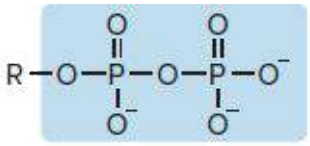
biformene

29.7B The Biosynthesis of Terpenes and Terpenoids

Terpene and terpenoid biosynthesis is an excellent example of how syntheses in nature occur with high efficiency. There are two ways this is accomplished.

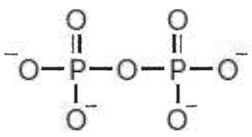
[1] The same reaction is used over and over again to prepare progressively more complex compounds.

[2] Key intermediates along the way serve as the starting materials for a wide variety of other compounds.



organic diphosphate

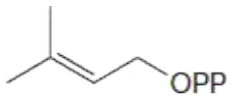
R—OPP



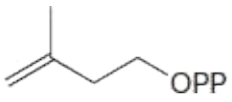
diphosphate leaving group

PP_i

All terpenes and terpenoids are synthesized from dimethylallyl diphosphate and isopentenyl diphosphate. Both of these five-carbon compounds are organic diphosphates (Section 14.2B) with a good leaving group (diphosphate, $P_2O_7^{4-}$, PP_i).



dimethylallyl diphosphate



isopentenyl diphosphate

The overall strategy of biosynthesis from dimethylallyl diphosphate and isopentenyl diphosphate is summarized in Figure 29.9.

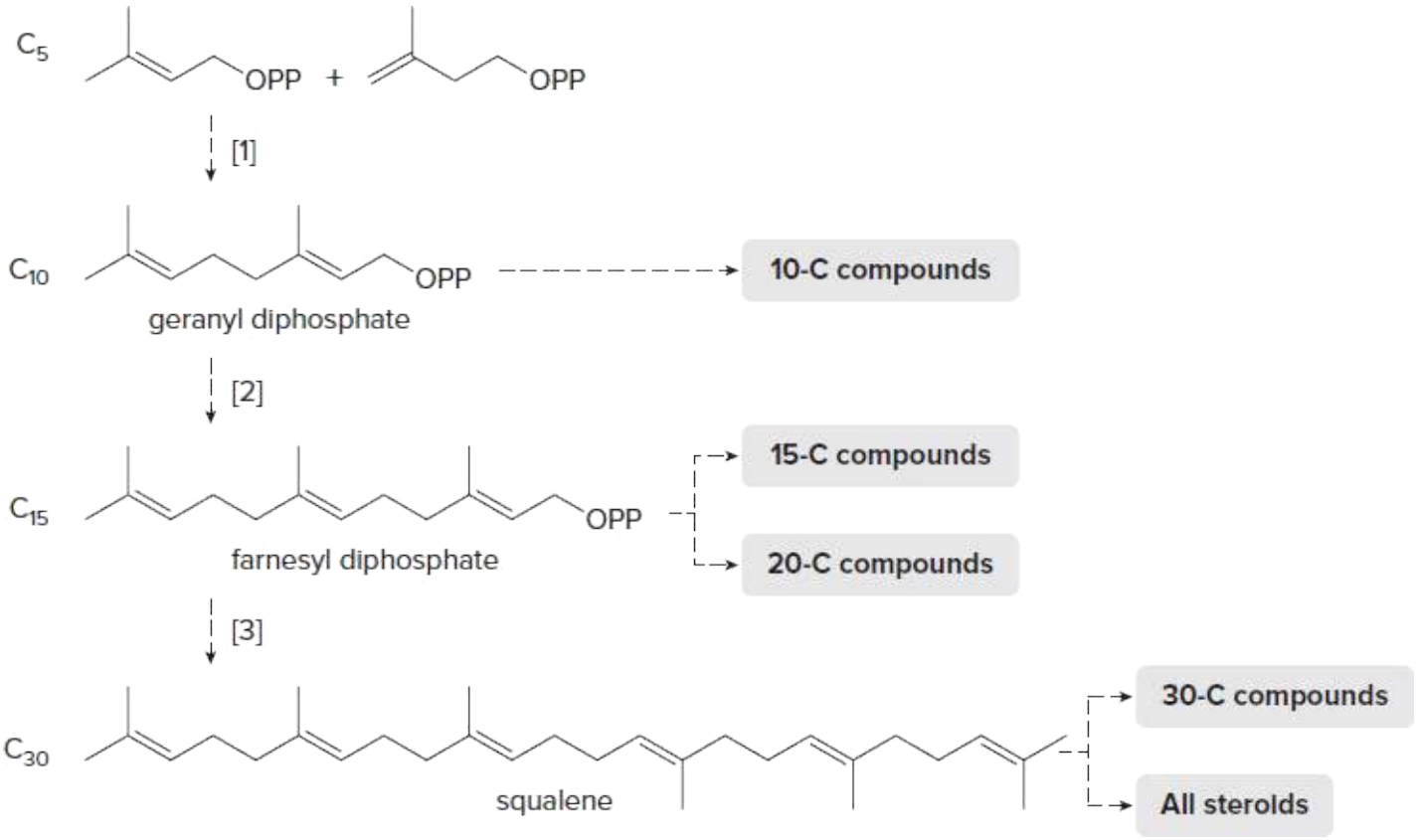


Figure 29.9 **An outline of terpene and terpenoid biosynthesis**

There are three basic parts:

[1] The two C_5 diphosphates are converted to geranyl diphosphate, a C_{10} monoterpenoid. Geranyl diphosphate is the starting material for all other monoterpenes and monoterpenoids.

[2] Geranyl diphosphate is converted to farnesyl diphosphate, a C_{15} sesquiterpenoid, by addition of a five-carbon unit. Farnesyl diphosphate is the starting material for all sesquiterpenes, diterpenes, and related terpenoids.

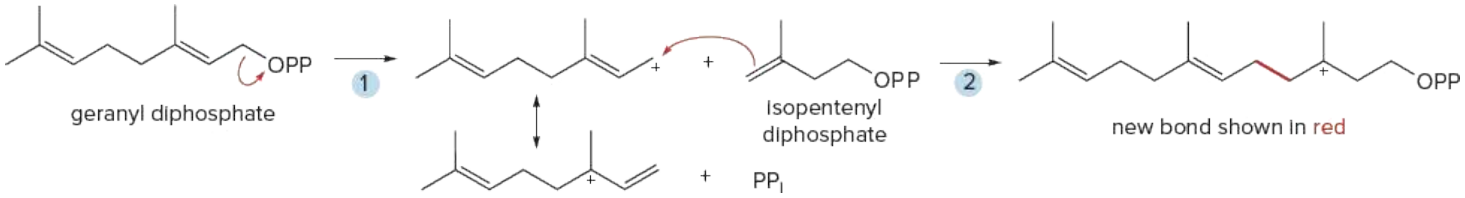
[3] Two molecules of farnesyl diphosphate are converted to squalene, a C_{30} triterpene. Squalene is the starting material for all triterpenes and steroids.

The biological formation of geranyl diphosphate from the two five-carbon

diphosphates was shown in Mechanism 14.1. The biological conversion of geranyl diphosphate to farnesyl diphosphate involves a similar pathway, as shown in Mechanism 29.1.

Mechanism 29.1 Biological Formation of Farnesyl Diphosphate

Part [1] Formation of a new carbon–carbon σ bond



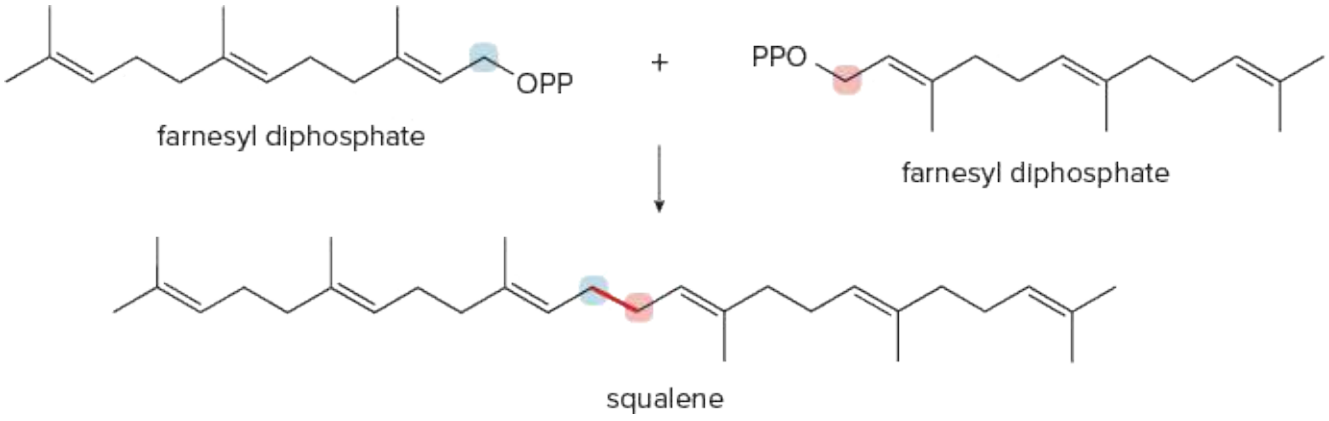
1 **Loss of the diphosphate leaving group forms a resonance-stabilized carbocation.**

2 **Nucleophilic attack of isopentenyl diphosphate on the allylic carbocation forms the new C—C σ bond.**

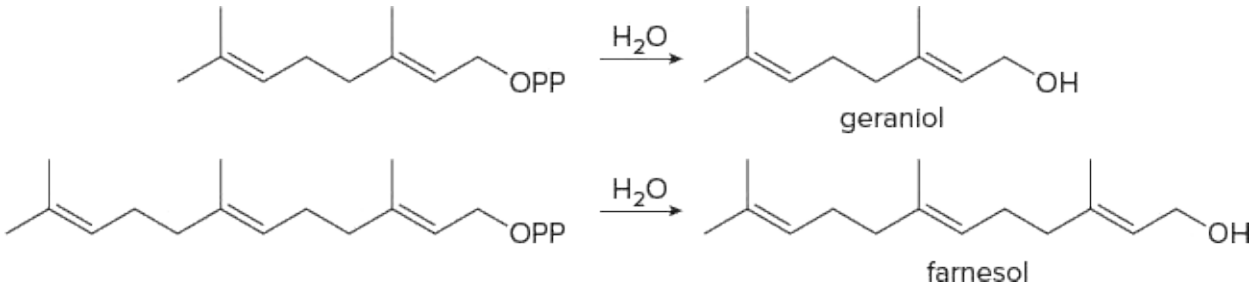
Part [2] Formation of a π bond by loss of a proton

3 **Loss of a proton (shown with the general base B:) forms a new π bond and farnesyl diphosphate.**

Two molecules of farnesyl diphosphate react to form squalene, from which all other triterpenes and steroids are synthesized.



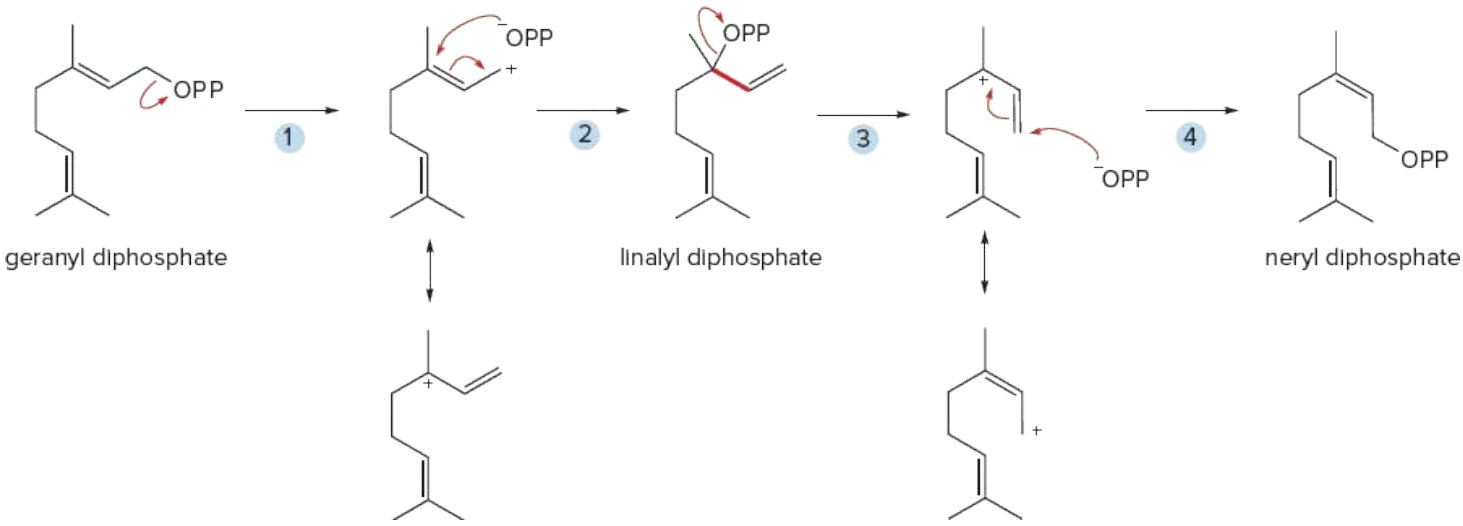
Aqueous hydrolysis of geranyl and farnesyl diphosphates forms the monoterpenoid geraniol and the sesquiterpenoid farnesol, respectively.



All other terpenes and terpenoids are biologically derived from geranyl and farnesyl diphosphates by a series of reactions. Cyclic compounds are formed by intramolecular reactions involving nucleophilic attack of π bonds on intermediate carbocations. To form some cyclic compounds, the *E* double bond in geranyl diphosphate must first isomerize to an isomeric diphosphate with a *Z* double bond, neryl diphosphate, by the process illustrated in Mechanism 29.2. Isomerization forms a substrate with a leaving group and nucleophilic double bond in close proximity so that an intramolecular reaction can occur.

Page 1311

Mechanism 29.2 Isomerization of Geranyl Diphosphate to Neryl Diphosphate



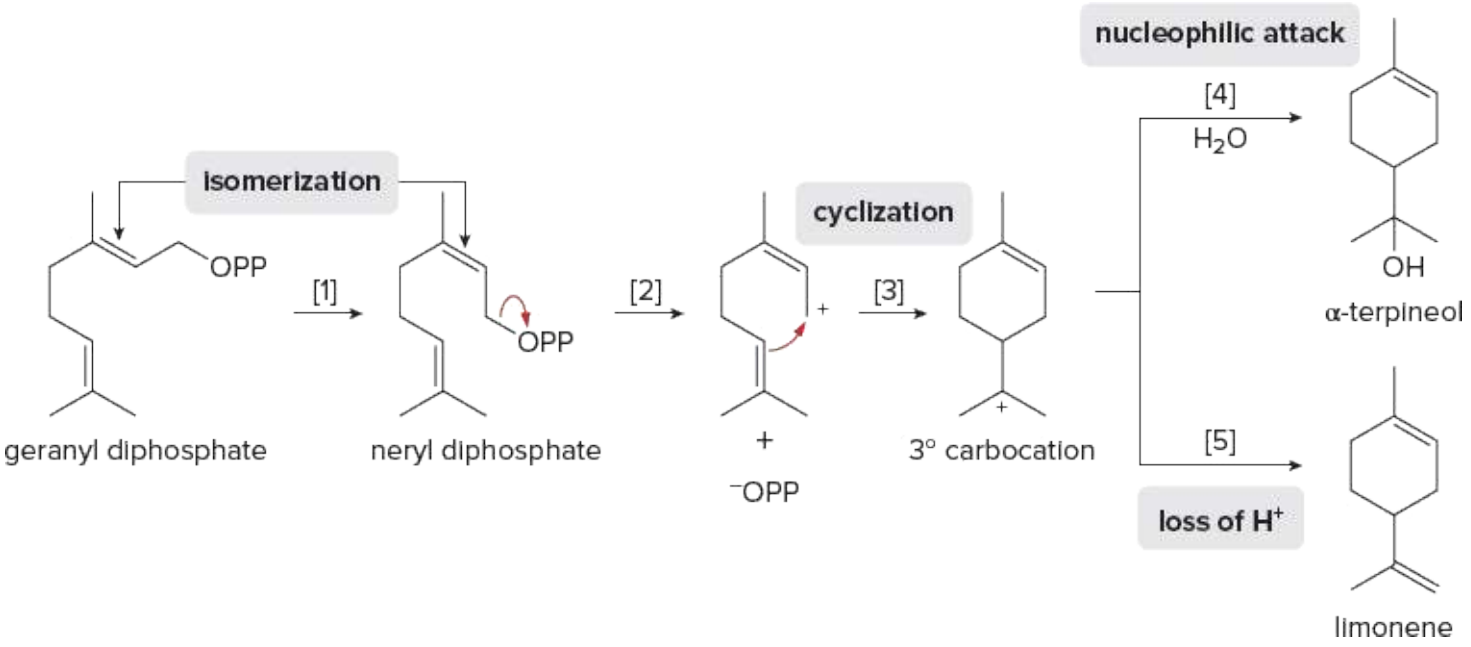
1 – 2 **Loss of diphosphate forms a resonance-stabilized carbocation, which reacts with the diphosphate anion to form linalyl diphosphate.**

3 **Bond rotation of the single bond shown in red and loss of diphosphate forms a resonance-stabilized carbocation.**

4 **Nucleophilic attack with diphosphate forms neryl diphosphate, which has the leaving group and the double bond at the other end of the chain in close proximity for intramolecular cyclization.**

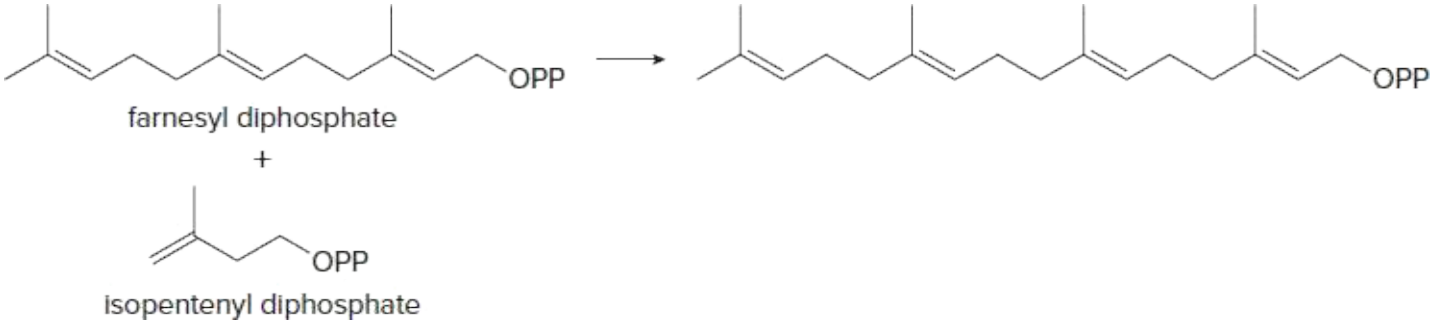
In the synthesis of α-terpineol or limonene, for example, geranyl diphosphate isomerizes to form neryl diphosphate (Step [1] in the following reaction sequence).

Neryl diphosphate then cyclizes to a 3° carbocation by intramolecular attack (Steps [2]–[3]). Nucleophilic attack of water on this carbocation yields the monoterpenoid α-terpineol (Step [4]), or loss of a proton yields the monoterpene limonene (Step [5]).



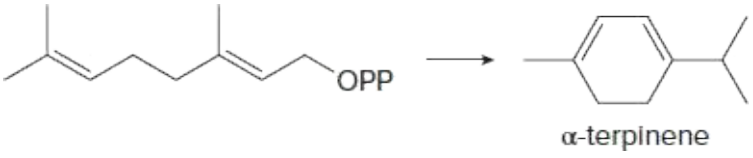
Problem 29.13

Write a stepwise mechanism for the following reaction.



Problem 29.14

Draw a stepwise mechanism for the conversion of geranyl diphosphate to α-terpinene.

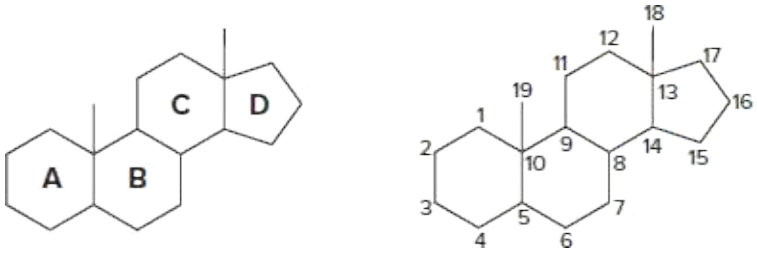


29.8 Steroids

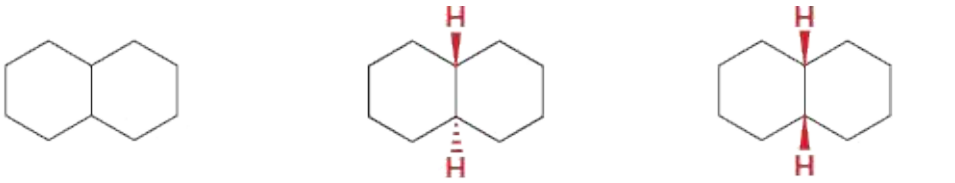
The steroids are a group of tetracyclic lipids, many of which are biologically active.

29.8A Steroid Structure

Steroids are composed of three six-membered rings and one five-membered ring, joined together as drawn. Many steroids also contain two methyl groups, called angular methyl groups, at the two ring junctions indicated. The steroid rings are lettered A, B, C, and D, and the 17 ring carbons are numbered as shown. The two angular methyl groups are numbered C18 and C19.



Whenever two rings are fused together, the substituents at the ring fusion can be arranged cis or trans. To see more easily why this is true, consider decalin, which consists of two six-membered rings fused together. *trans*-Decalin has the two hydrogen atoms at the ring fusion on opposite sides, whereas *cis*-decalin has them on the same side.

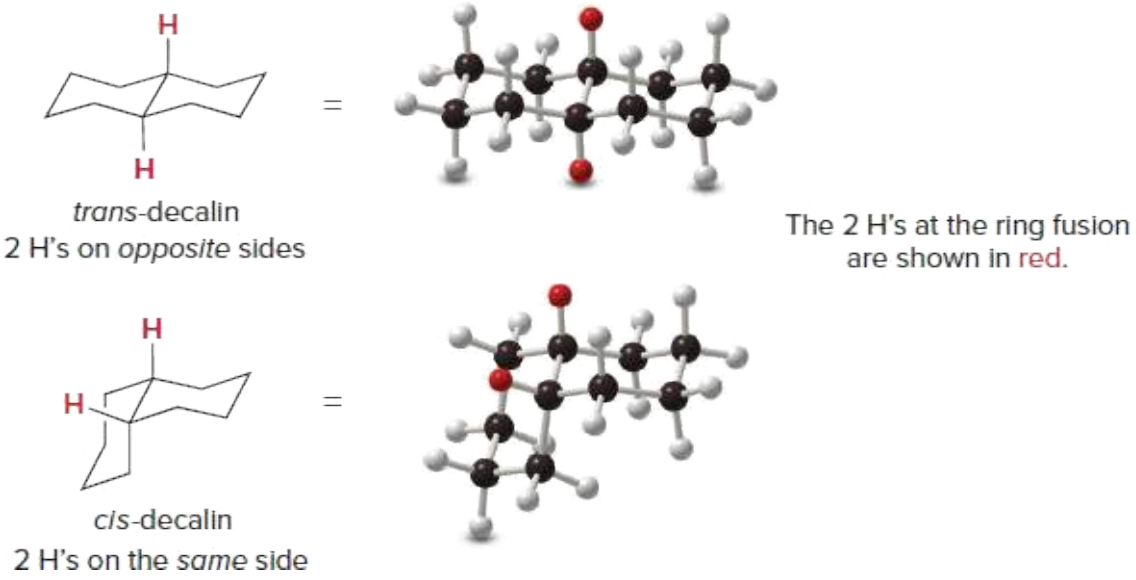


decalin
Two six-membered rings share a C–C bond.

***trans*-decalin**
2 H's on opposite sides

***cis*-decalin**
2 H's on the same side

Three-dimensional structures of these molecules show how different these two possible arrangements actually are. The two rings of *trans*-decalin lie roughly in the same plane, whereas the two rings of *cis*-decalin are almost perpendicular to each other. The trans arrangement is *lower* in energy and therefore more stable.



In steroids, each ring fusion could theoretically have the cis or trans configuration, but by far the most common arrangement is all trans. Because of this, all four rings of the steroid skeleton lie in the same plane, and the ring system is fairly rigid. The two angular methyl groups are oriented perpendicular to the plane of the molecule. These methyl groups make one side of the steroid skeleton significantly more hindered than the other, as shown in Figure 29.10.

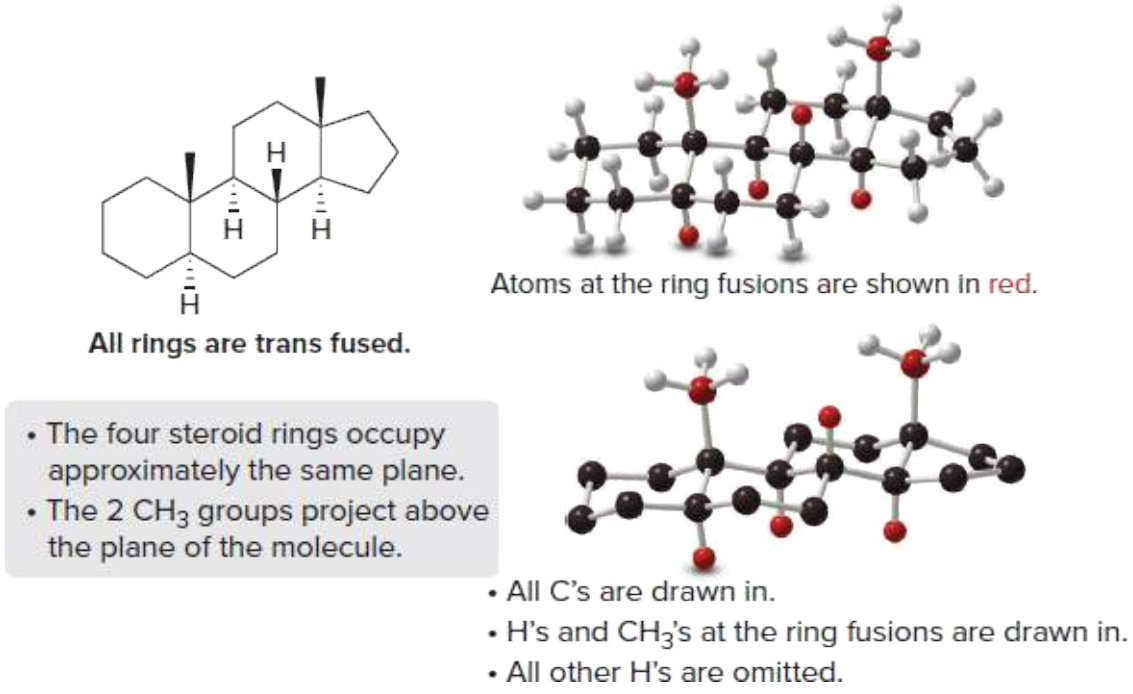


Figure 29.10 **The three-dimensional structure of the steroid nucleus**

Although steroids have the same fused-ring arrangement of carbon atoms, they differ in the identity and location of the substituents attached to that skeleton.

Problem 29.15

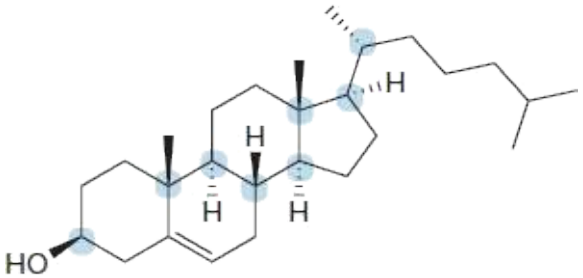
(a) Draw a skeletal structure of the anabolic steroid 4-androstene-3,17-dione, also called "andro," from the following description. Andro contains the tetracyclic steroid skeleton with carbonyl groups at C3 and C17, a double bond between C4 and C5, and methyl groups bonded to C10 and C13.

(b) Add wedges and dashed wedges for all stereogenic centers with the following information: the configuration at C10 is *R*, the configuration at C13 is *S*, and all substituents at ring fusions are trans to each other.

29.8B Cholesterol

Cholesterol has also been discussed in Sections 3.4C and 4.15. The role of cholesterol in plaque formation and atherosclerosis was discussed in Section 20.16.

Cholesterol has the tetracyclic carbon skeleton characteristic of steroids. It also has eight stereogenic carbons (seven on rings and one on a side chain), so there are 2^8 = 256 possible stereoisomers. In nature, however, only the following stereoisomer exists:



cholesterol

Cholesterol is essential to life because it forms an important component of cell membranes and is the starting material for the synthesis of all other steroids. Humans do not have to ingest cholesterol, because it is synthesized in the liver and then transported to other tissues through the bloodstream. Because cholesterol has only one polar OH group and many nonpolar C—C and C—H bonds, it is insoluble in water (and, thus, in the aqueous medium of the blood).

Konrad Bloch and Feodor Lynen shared the 1964 Nobel Prize in Physiology or Medicine for unraveling the complex transformation of squalene to cholesterol.

Cholesterol is synthesized in the body from squalene, a C_{30} triterpene that is itself

prepared from smaller terpenes, as discussed in Section 29.7B. Because the biosynthesis of all terpenes begins with acetyl CoA, every one of the 27 carbon atoms of cholesterol comes from the same two-carbon precursor. The major steps in the conversion of squalene to cholesterol are given in Figure 29.11.

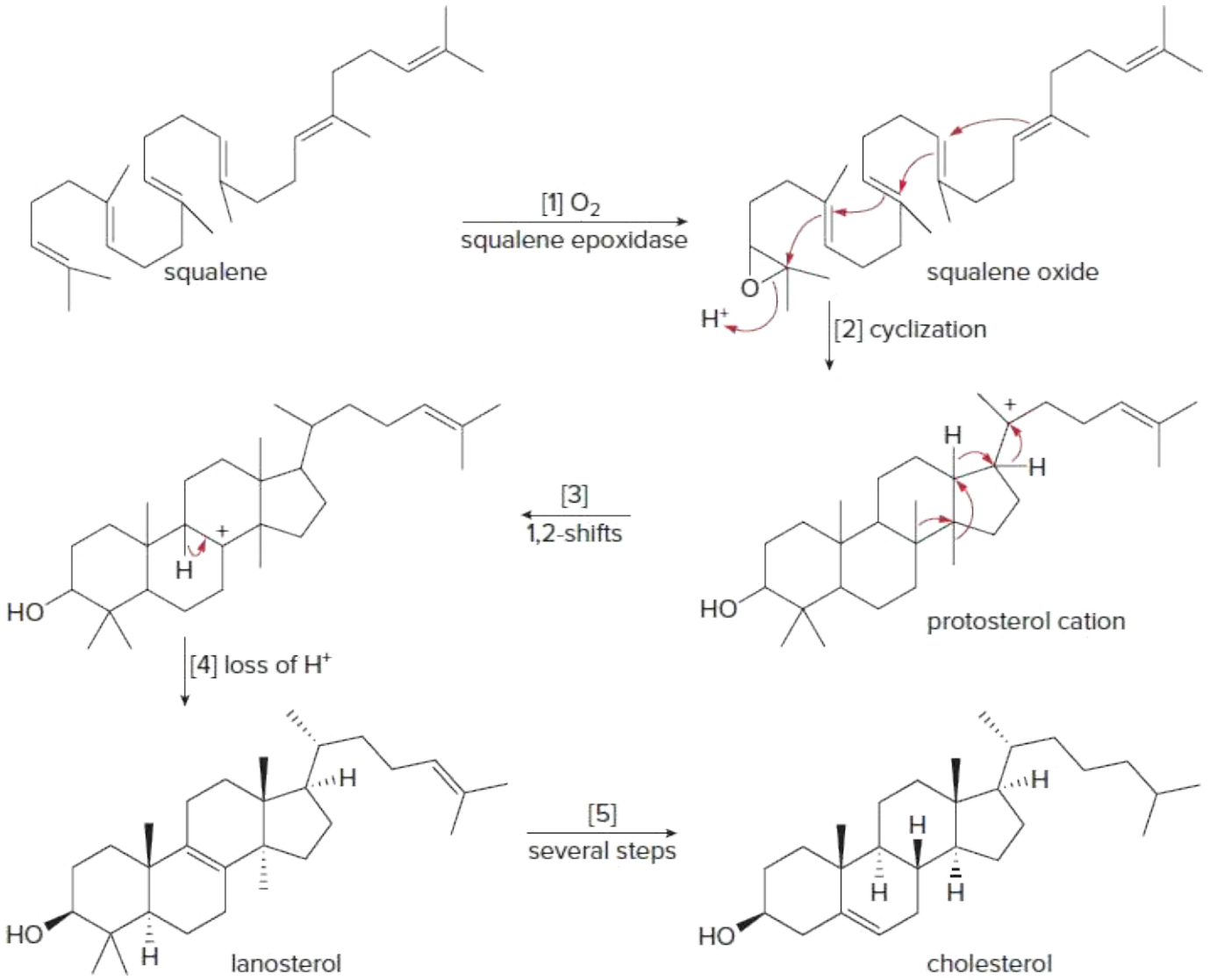


Figure 29.11 **The biosynthesis of cholesterol**

The conversion of squalene to cholesterol consists of five different parts: Page 1315

[1] Epoxidation of squalene with an enzyme, squalene epoxidase, gives squalene oxide, which contains a single epoxide on one of the six double bonds.

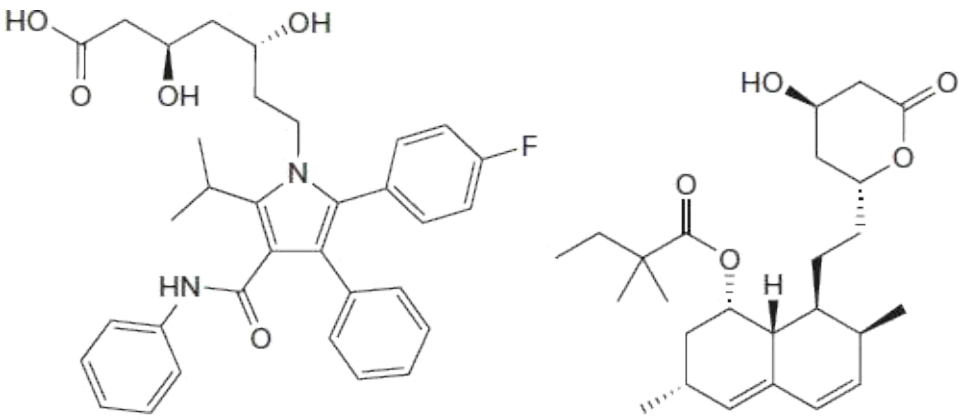
[2] Cyclization of squalene oxide yields a carbocation, called the protosterol cation. This reaction results in the formation of four new C—C bonds and the tetracyclic ring system.

[3] The protosterol carbocation rearranges by a series of 1,2-shifts of either a hydrogen or methyl group to form another 3° carbocation.

[4] Loss of a proton gives an alkene called lanosterol. Although lanosterol has seven stereogenic centers, a single stereoisomer is formed.

[5] Lanosterol is then converted to cholesterol by a multistep process that results in removal of three methyl groups.

Several drugs called statins are now available to reduce the level of cholesterol in the bloodstream. These compounds act by blocking the biosynthesis of cholesterol at its very early stages. Two examples include atorvastatin (Lipitor) and simvastatin (Zocor), whose structures appear in Figure 29.12.



Generic name atorvastatin
Trade name Lipitor

Generic name simvastatin
Trade name Zocor

Figure 29.12 **Two cholesterol-lowering drugs**

Problem 29.16

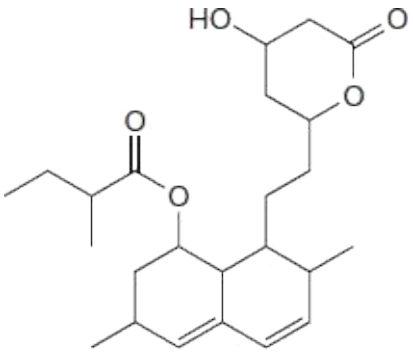
Draw the enantiomer and any two diastereomers of cholesterol. Does the OH group of cholesterol occupy an axial or equatorial position?

Although lovastatin (Problem 29.17) is naturally occurring in oyster mushrooms, the commercial drug is obtained by a fermentation process.

©coxy58/Shutterstock

Problem 29.17

Lovastatin, which occurs naturally in oyster mushrooms, was the first statin to be marketed. What hydrolysis products are formed when lovastatin is treated with aqueous acid?



lovastatin

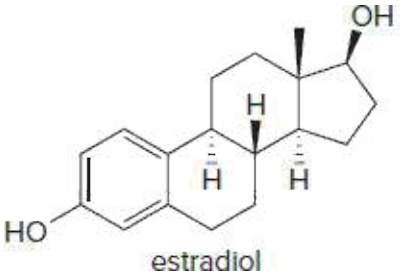
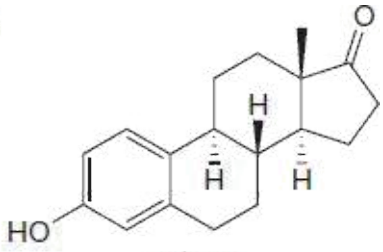
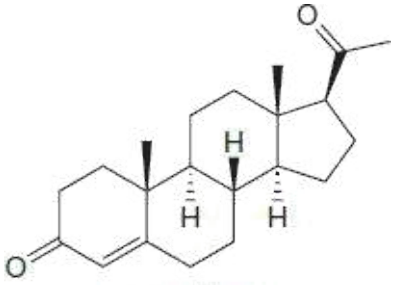
29.8C Other Steroids

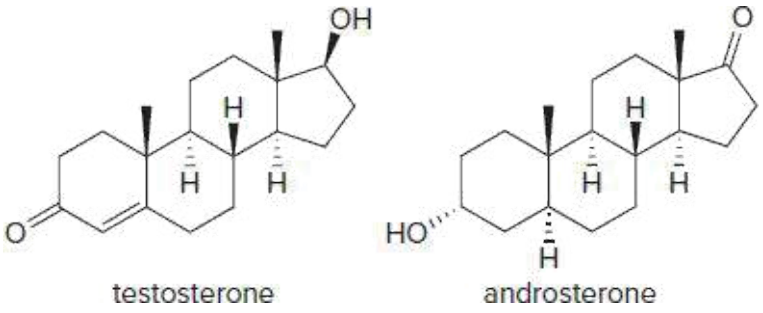
Many other important steroids are hormones secreted by the endocrine glands. Two classes are the sex hormones and the adrenal cortical steroids.

There are two types of female sex hormones, estrogens and progestins. The male sex hormones are called androgens. The most important members of each hormone type are given in Table 29.6.

Page 1316

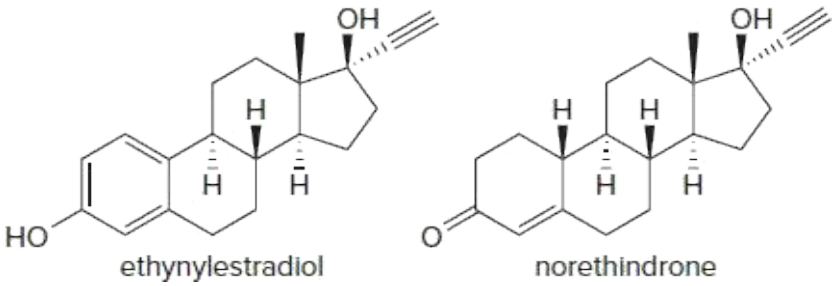
Table 29.6 The Female and Male Sex Hormones

Structure	Properties
 estradiol  estrone	• **Estradiol and estrone are estrogens synthesized in the ovaries. They control the development of secondary sex characteristics in females and regulate the menstrual cycle.**
 progesterone	• **Progesterone is often called the "pregnancy hormone." It is responsible for the preparation of the uterus for implantation of a fertilized egg.**



- **Testosterone and androsterone are androgens synthesized in the testes. They control the development of secondary sex characteristics in males.**

Synthetic analogues of these steroids have found important uses, such as ethynylestradiol and norethindrone in oral contraceptives, first mentioned in Section 11.4.

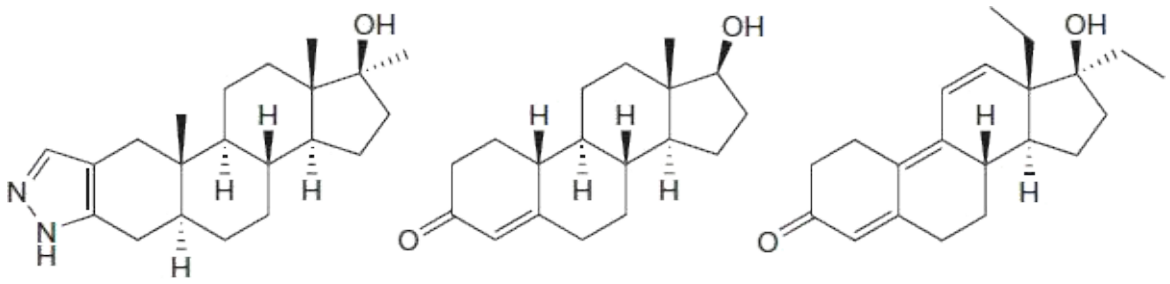


Synthetic androgen analogues, called anabolic steroids, promote muscle growth. They were first developed to help individuals whose muscles had atrophied from lack of use following surgery. They have since come to be used by athletes and body builders, although their use is not permitted in competitive sports. Many physical and psychological problems result from their prolonged use.

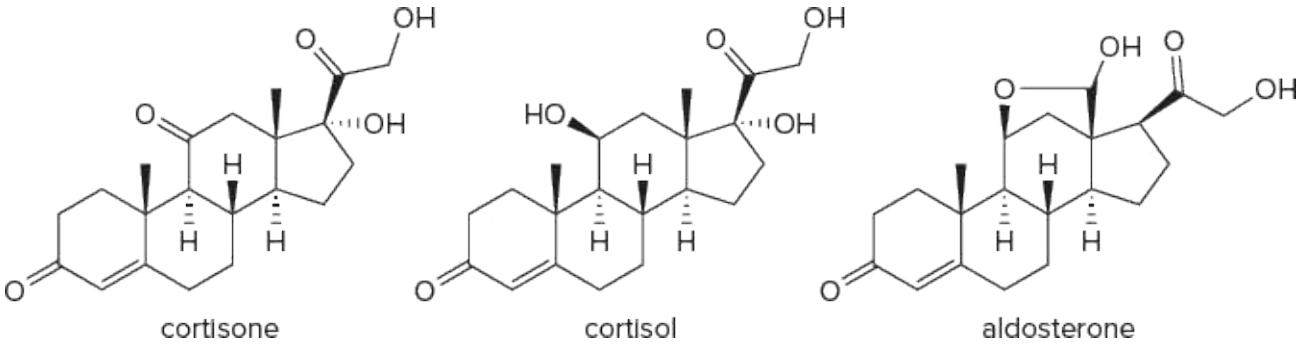
Some body builders use anabolic steroids to increase muscle mass. Long-term or excessive use can cause many health problems, including high blood pressure, liver damage, and cardiovascular disease.

©JupiterImages/Comstock

Anabolic steroids, such as stanozolol, nandrolone, and tetrahydrogestrinone have the same effect on the body as testosterone, but they are more stable, so they are not metabolized as quickly. Tetrahydrogestrinone (also called THG or The Clear), the performance-enhancing drug used by track star Marion Jones during the 2000 Sydney Olympics, was considered a "designer steroid" because it was initially undetected in urine tests for doping. After its chemical structure and properties were determined, it was added to the list of banned anabolic steroids in 2004.



A second group of steroid hormones includes the adrenal cortical steroids. Page 1317
Three examples of these hormones are cortisone, cortisol, and aldosterone.
All of these compounds are synthesized in the outer layer of the adrenal gland. Cortisone and cortisol serve as anti-inflammatory agents, and they also regulate carbohydrate metabolism. Aldosterone regulates blood pressure and volume by controlling the concentration of Na^+ and K^+ in body fluids.

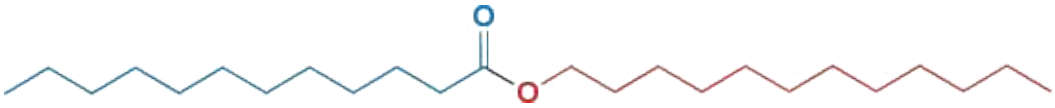


Chapter 29 REVIEW

KEY CONCEPTS

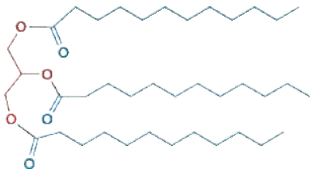
[1] Hydrolyzable lipids

1 Waxes (29.2)



- Esters formed from a long-chain alcohol and a long-chain carboxylic acid

2 Triacylglycer (29.3)

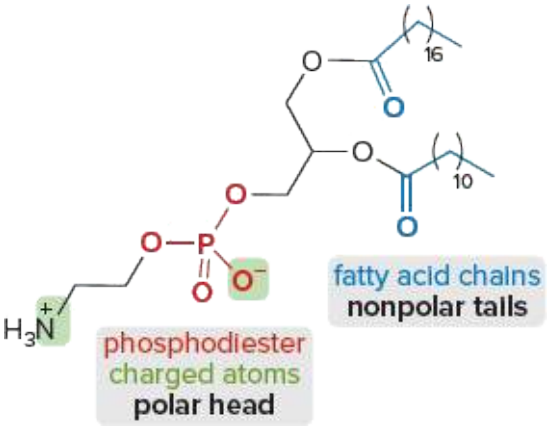


- Triesters of glycerol with three fatty acids

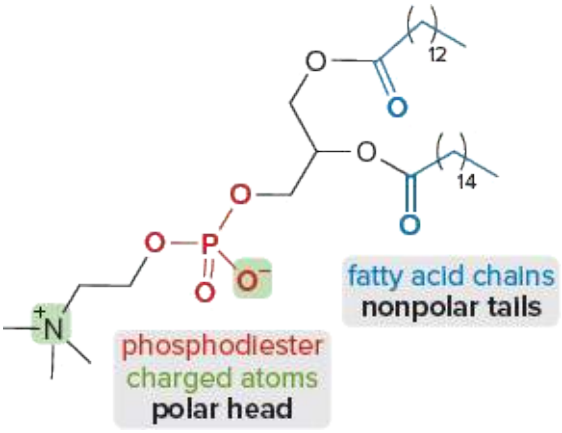
Try Problems 29.21, 29.22.

[2] Hydrolyzable phospholipids (29.4)

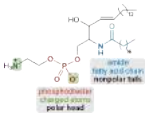
1 Phosphatidylethanolamine



2 Phosphatidylcholine



3 Sph



Try Problem 29.24.

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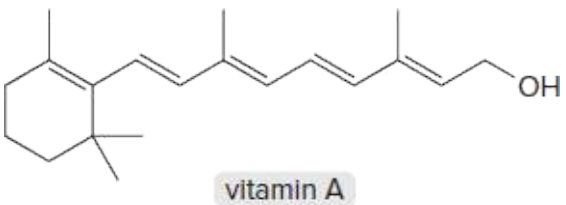
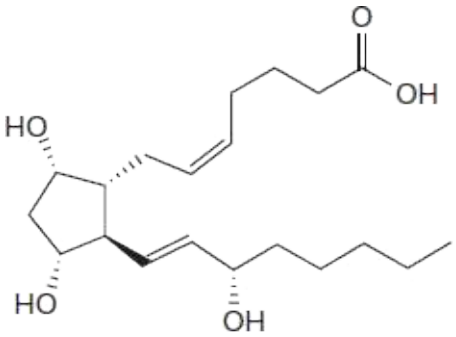
[3] Nonhydrolyzable lipids

1 Fat-soluble vitamins (29.5)



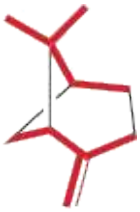
3 Terpenes (29.7)



$PGF_{2\alpha}$
a prostaglandin

- **Lipids composed of repeating 5-C units called isoprene units**

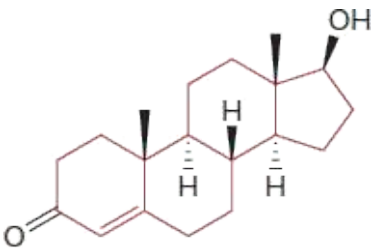
2 Eicosanoids (29.6)



β-pinene

- **Compounds containing 20 C's derived from arachidonic acid**

4 Steroids (29.8)



testosterone

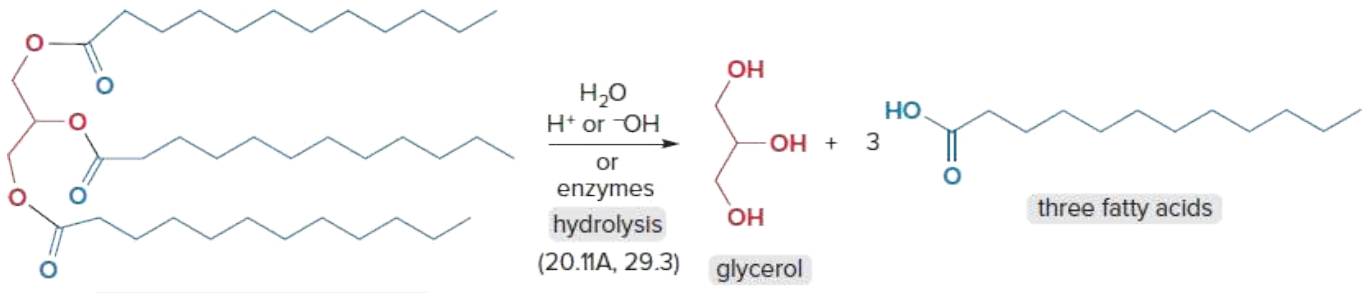
- **Tetracyclic lipids composed of three six-membered and one five-membered ring**

Try Problems 29.20, 29.38, 29.39, 29.40a.

KEY REACTIONS

Reactions of triacylglycerols

1

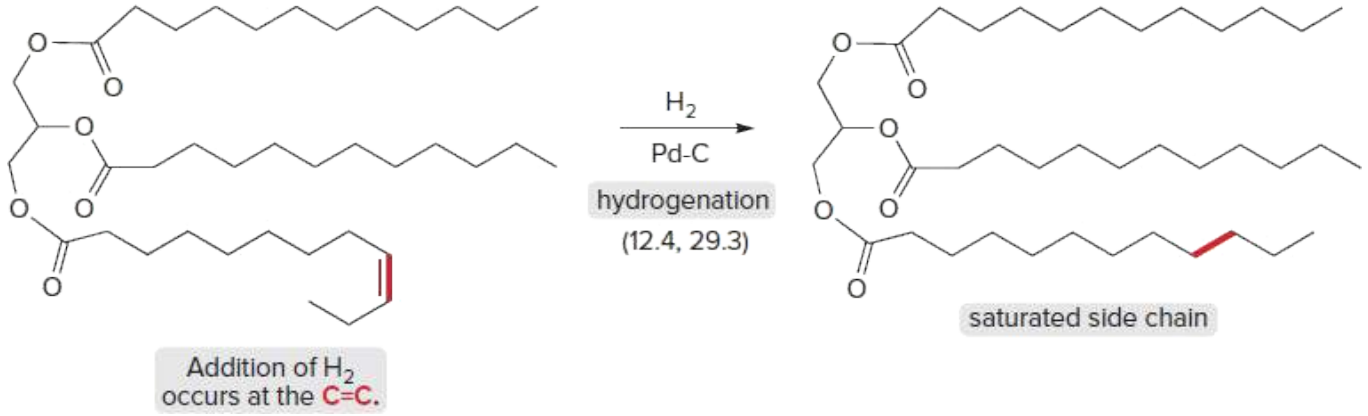


Three ester units are cleaved.

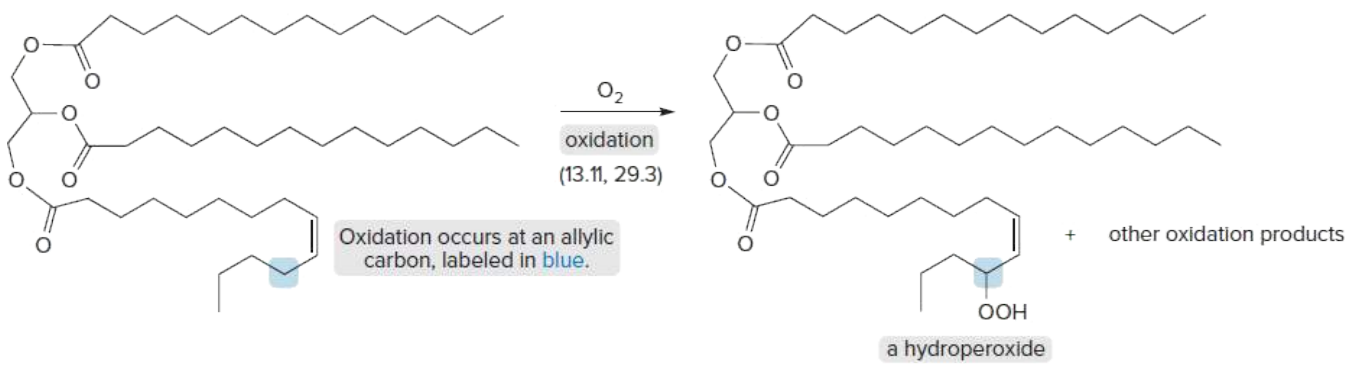
glycerol

three fatty acids

2



3



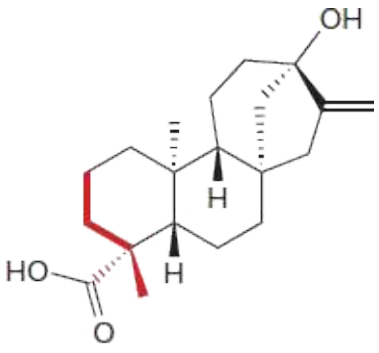
Try Problems 29.22, 29.23.

KEY SKILLS

Locating isoprene units (29.7); example: steviol

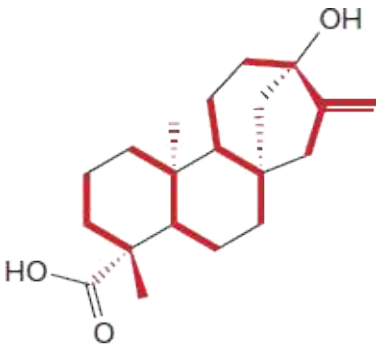
1 **Identify a four-carbon chain with a one-carbon branch.**

2 **Continue along the chain or around the ring until all the carbons are part of an isoprene unit.**



steviol

terpene portion of Stevia, a noncaloric sweetener



diterpene

four isoprene units

- Start at one end of the molecule near the branch point.
- Every isoprene unit has five carbon atoms.
- Heteroatoms may be present, but their presence is ignored in locating isoprene units.

- An isoprene unit may be composed of C—C σ bonds only, or there may be π bonds at any position.
- Isoprene units are always connected by one or more carbon–carbon bonds.
- Each carbon atom is part of only one isoprene unit.

See Sample Problem 29.1. Try Problems 29.18, 29.26, 29.28b, 29.29a.

PROBLEMS

Problems Using Three-Dimensional Models

29.18 **Locate the isoprene units in each compound.**

a.

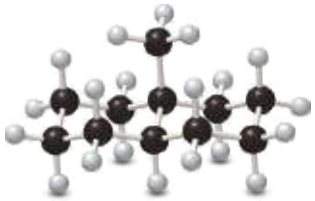
α-pinene

b.

humulene

29.19 **Convert each ball-and-stick model to a skeletal structure that clearly shows the stereochemistry at the ring fusion of these decalin derivatives.**

a.



b.

29.20 **Convert the ball-and-stick model of androsterone to (a) a skeletal structure using wedges and dashed wedges around all stereogenic centers; and (b) a three-dimensional representation using chair cyclohexane rings.**

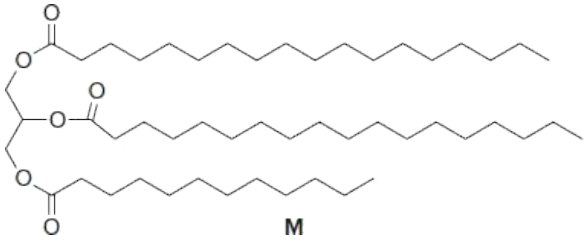
androsterone

Waxes, Triacylglycerols, and Phospholipids

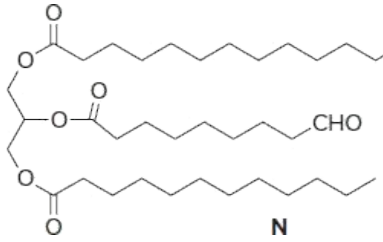
29.21 **One component of lanolin, the wax that coats sheep's wool, is derived from cholesterol and stearic acid. Draw its structure, including the correct stereochemistry at all stereogenic centers.**

29.22 **What is the structure of an optically inactive triacylglycerol that yields two moles of oleic acid and one mole of palmitic acid when hydrolyzed in aqueous acid?**

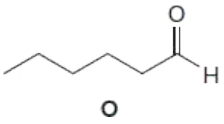
29.23 **Triacylglycerol L yields compound M when treated with excess H_2, Pd-C. Ozonolysis of L ([1] O_3; [2] $(CH_3)_2S$) affords compounds N–P. What is the structure of L?**



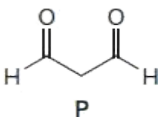
M



N



O



P

29.24 **Draw the structure of these phospholipids:**

a. **a cephalin formed from two molecules of stearic acid**

b. **a sphingomyelin formed from palmitic acid**

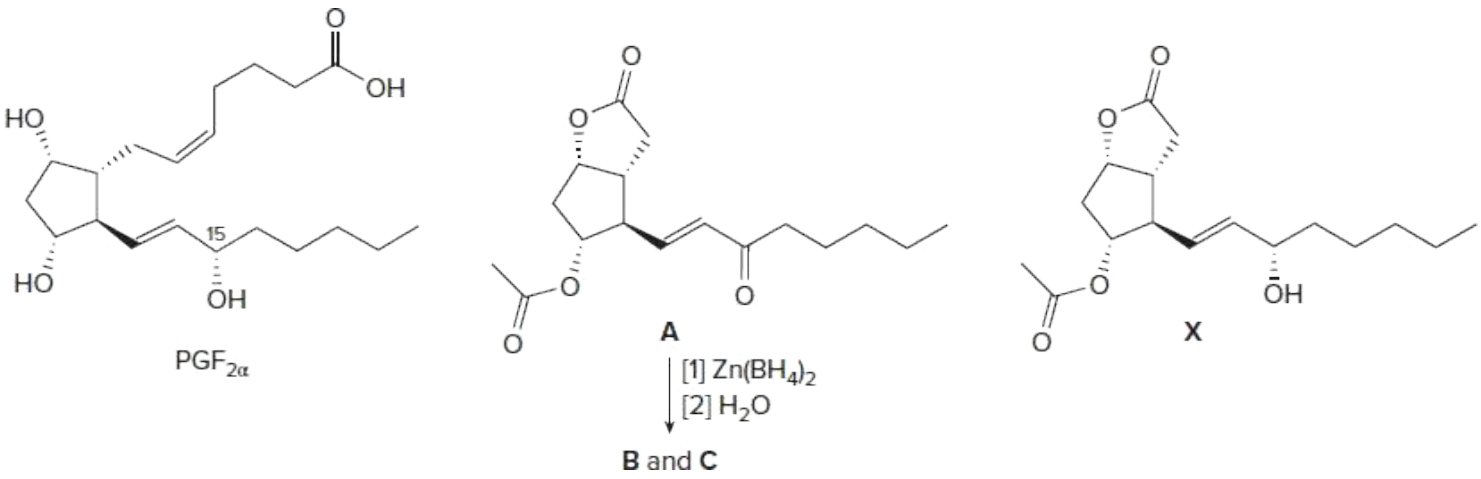
Prostaglandins

29.25 **A difficult problem in the synthesis of $PGF_{2\alpha}$ is the introduction of the OH group at C15 in the desired configuration.**

a. **Label this stereogenic center as *R* or *S.***

b. **A well-known synthesis of $PGF_{2\alpha}$ involves reaction of A with $Zn(BH_4)_2$, a metal hydride reagent similar in reactivity to $NaBH_4$, to form two isomeric products, B and C. Draw their structures and indicate their stereochemical relationship.**

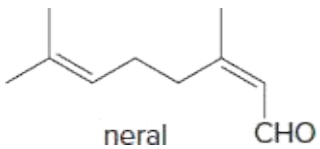
c. **Suggest a reagent to convert A to the single stereoisomer X.**



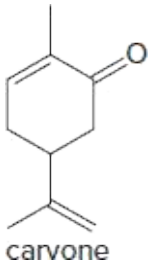
Terpenes and Terpenoids

29.26 **Locate the isoprene units in each compound.**

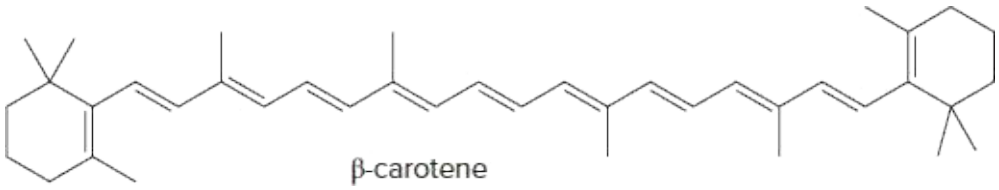
a.



b.

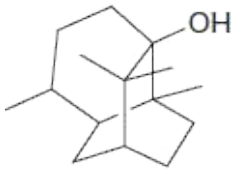


c.



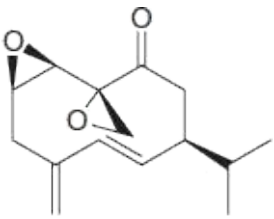
β-carotene

d.



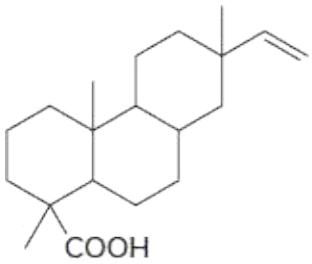
patchouli alcohol

e.



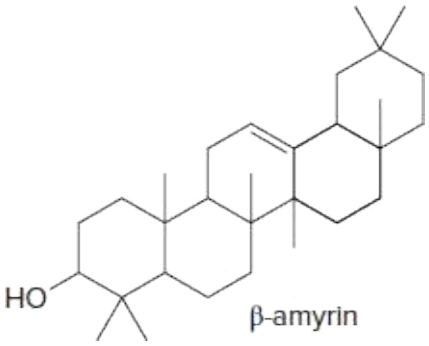
periplanone B

f.



dextropimaric acid

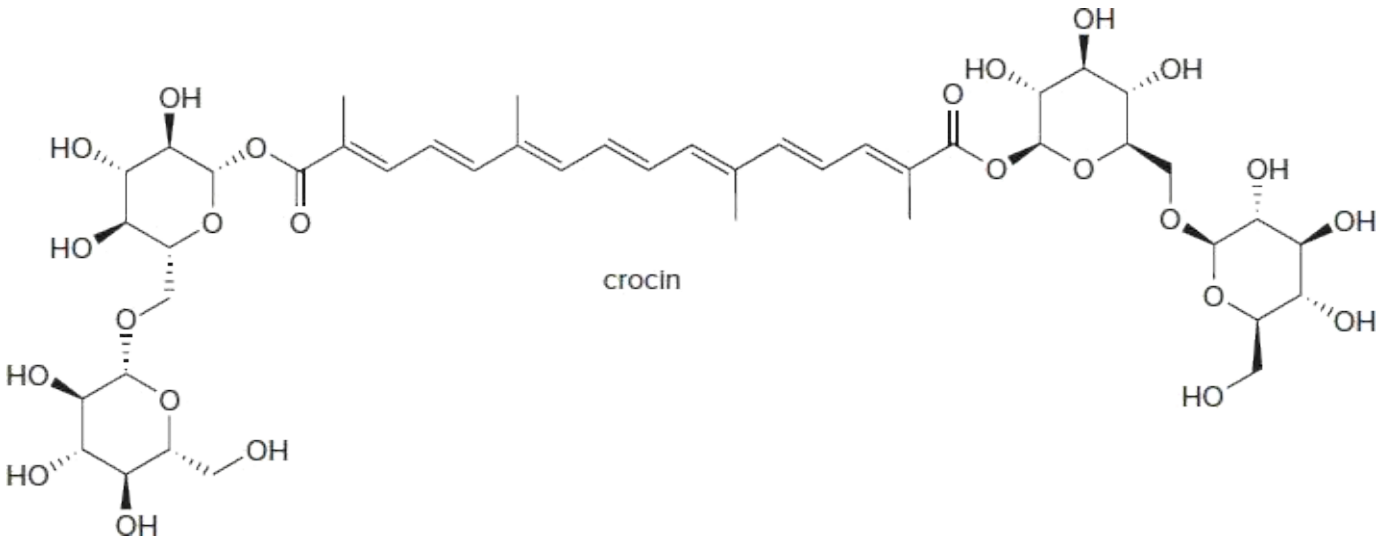
g.



β-amyrin

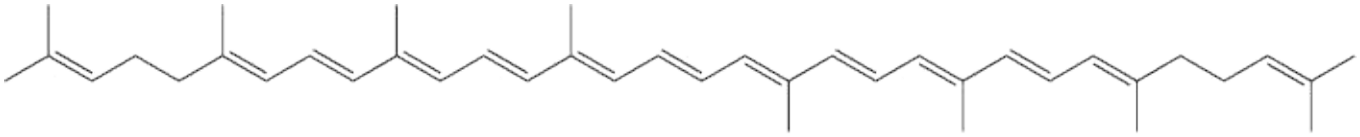
29.27 Classify each terpene and terpenoid in Problem 29.26 (e.g., as a monoterpene, sesquiterpene, etc.).

29.28 Crocin, which occurs naturally in crocus and gardenia flowers, is primarily responsible for the color of saffron. (a) What lipid and monosaccharides are formed by the hydrolysis of crocin? (b) Classify the lipid as a monoterpenoid, diperpenoid, etc., and locate the isoprene units.



crocin

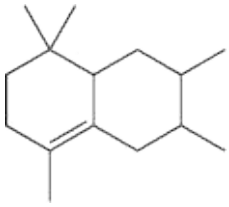
29.29 **(a) Locate the isoprene units in lycopene, the red pigment in tomatoes (Section 14.15). (b) Which isoprene units are connected in a head-to-tail fashion? (c) Label any other isoprene unit as connected in a head-to-head fashion or a tail-to-tail fashion. (d) Classify lycopene as a monoterpene, sesquiterpene, and so on.**



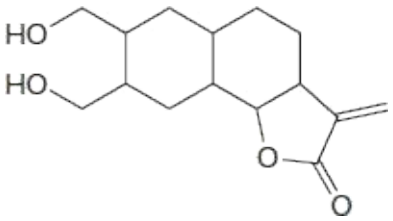
lycopene

29.30 **Which of the following compounds are not composed of isoprene units? Locate the isoprene units in each compound that contains them.**

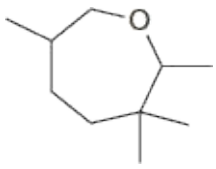
a.



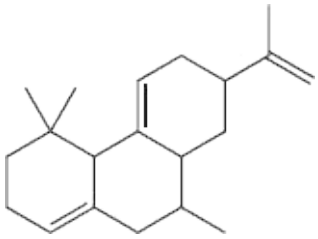
b.



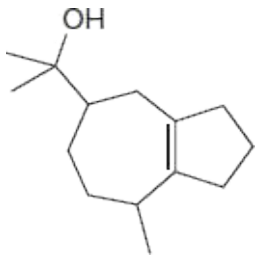
c.



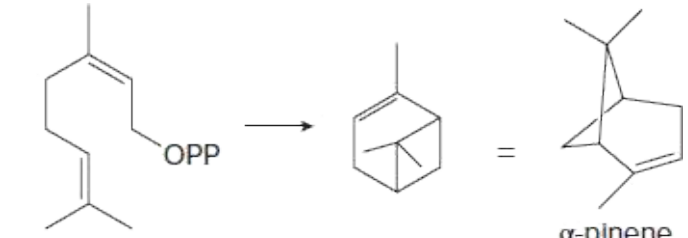
d.



29.31 **Guaiol is a sesquiterpene alcohol found in cannabis and other plants. The structure of guaiol is drawn except for a missing CH_3 group. If the isoprene units are joined in a head-to-tail fashion, draw a possible structure for guaiol that contains the additional CH_3 group.**

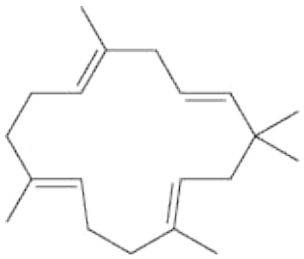


29.32 **Draw a stepwise mechanism for the conversion of neryl diphosphate to α-pinene. α-Pinene is a component of pine oil and rosemary oil.**



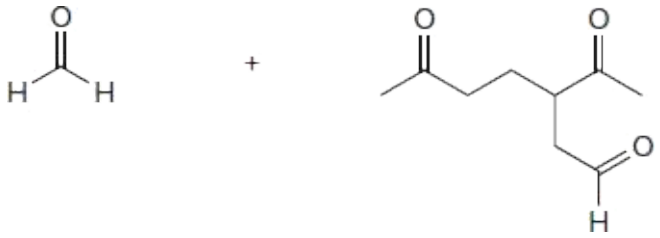
neryl diphosphate

29.33 **Flexibilene is a terpene isolated from *Sinularia flexibilis*, a soft coral found in the Indian Ocean. Draw a stepwise mechanism for the formation of flexibilene from farnesyl diphosphate and isopentenyl diphosphate. What is unusual about the cyclization that forms the 15-membered ring of flexibilene?**



flexibilene

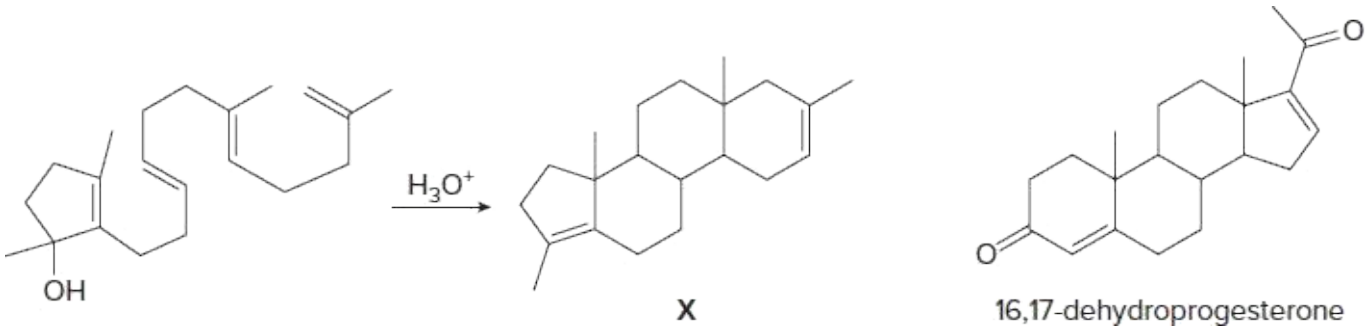
29.34 **Draw the structure of a monoterpene that undergoes ozonolysis to yield the following two products. Show all possibilities.**



29.35 **The biosynthesis of lanosterol from squalene has intrigued chemists since its discovery. It is now possible, for example, to synthesize polycyclic compounds from acyclic or monocyclic precursors by reactions that form several C—C bonds in a single reaction mixture.**

a. Draw a stepwise mechanism for the following reaction.

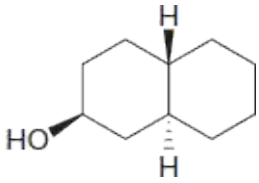
b. Show how X can be converted to 16,17-dehydroprogesterone. (Hint: See Figure 22.5 for a related conversion.)



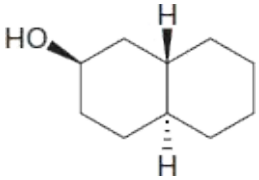
Steroids

29.36 **Draw three-dimensional structures for each alcohol. Label the OH groups as occupying axial or equatorial positions.**

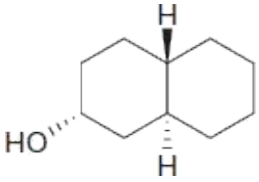
a.



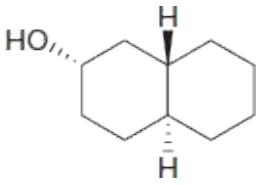
b.



c.

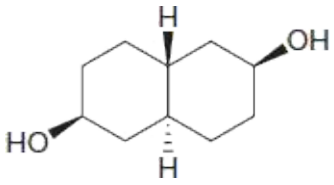


d.

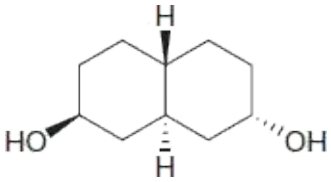


29.37 **Axial alcohols are oxidized faster than equatorial alcohols by PCC and other Cr^{6+} oxidants. Which OH group in each compound is oxidized faster?**

a.



b.

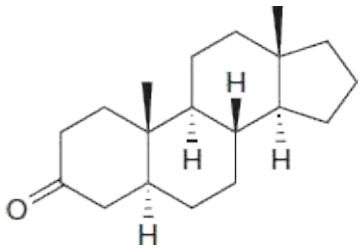


29.38 **(a) Draw a skeletal structure of the anabolic steroid methenolone from the following description. Methenolone contains the tetracyclic steroid skeleton with a carbonyl group at C3, a hydroxyl at C17, a double bond between C1 and C2, and methyl groups bonded to C1, C10, and C13. (b) Add wedges and dashed wedges for all stereogenic centers with the following information: the configuration at C10 is *R*, the configuration at C13 is *S*, the configuration at C17 is S, and all substituents at ring fusions are trans to each other. (c) Draw the structure of Primobolan, the product formed when methenolone is treated with $CH_3(CH_2)_5COCl$ and pyridine. Primobolan is an anabolic steroid that can be taken orally or by injection and has been used illegally by well-known Major League Baseball players.**

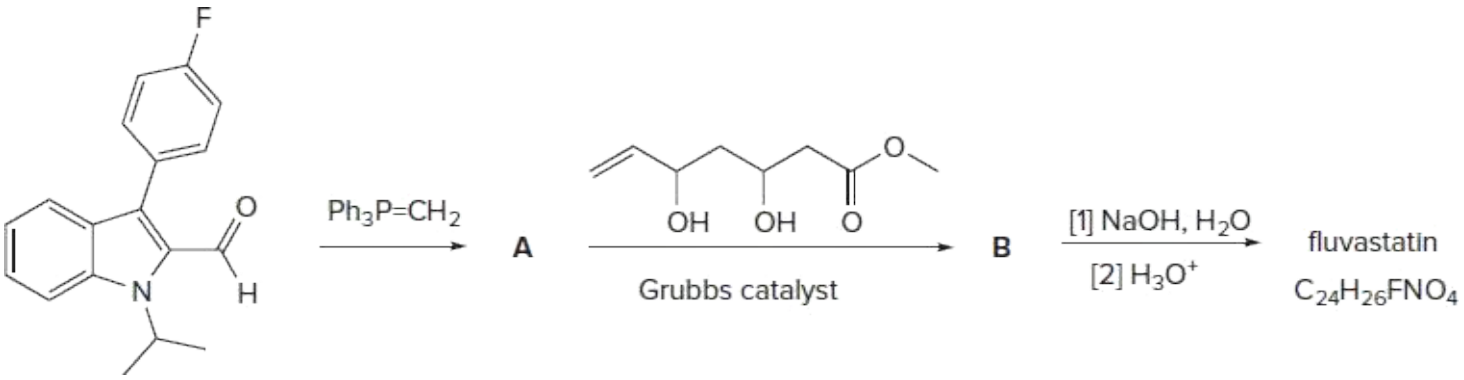
29.39 **Betamethasone is a synthetic anti-inflammatory steroid used as a topical cream for itching. Betamethasone is derived from cortisol, with the following structural additions: a C=C between C1 and C2, a fluorine at C9, and a methyl group at C16. The configuration at C9 is *R*, and the configuration at C16 is *S*. Draw the structure of betamethasone.**

29.40 **a. Draw a three-dimensional structure for the following steroid.**

b. What is the structure of the single stereoisomer formed by reduction of this ketone with H2, Pd-C? Explain why only one stereoisomer is formed.

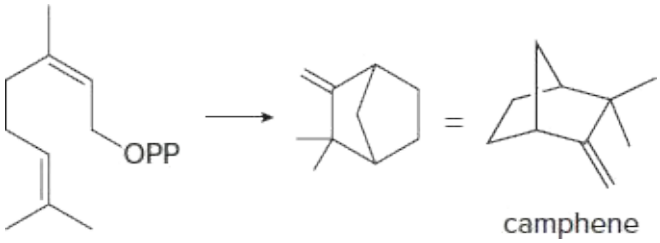


29.41 **Fluvastatin, a cholesterol-lowering drug, can be prepared by the following three-step reaction sequence. Identify intermediates A and B and the final product, fluvastatin.**

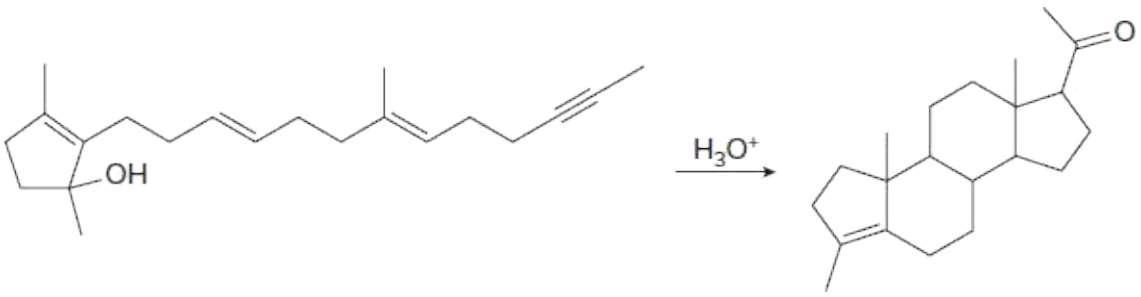


Challenge Problems

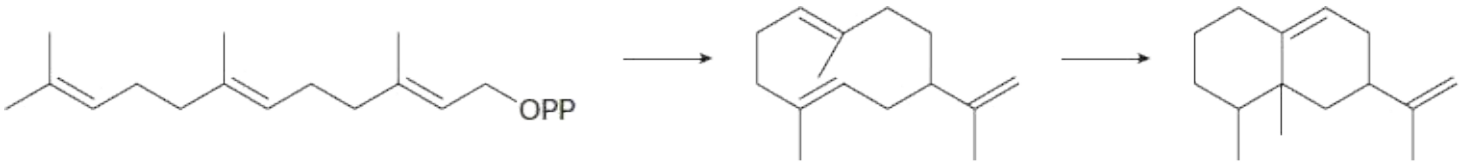
29.42 **Draw a stepwise mechanism for the following conversion, which forms camphene. Camphene is a component of camphor and citronella oils.**



29.43 **Draw a stepwise mechanism for the following reaction.**



29.44 **Farnesyl diphosphate is cyclized to sesquiterpene A, which is then converted to the bicyclic product epi-aristolochene. Write a stepwise mechanism for both reactions.**



farnesyl diphosphate

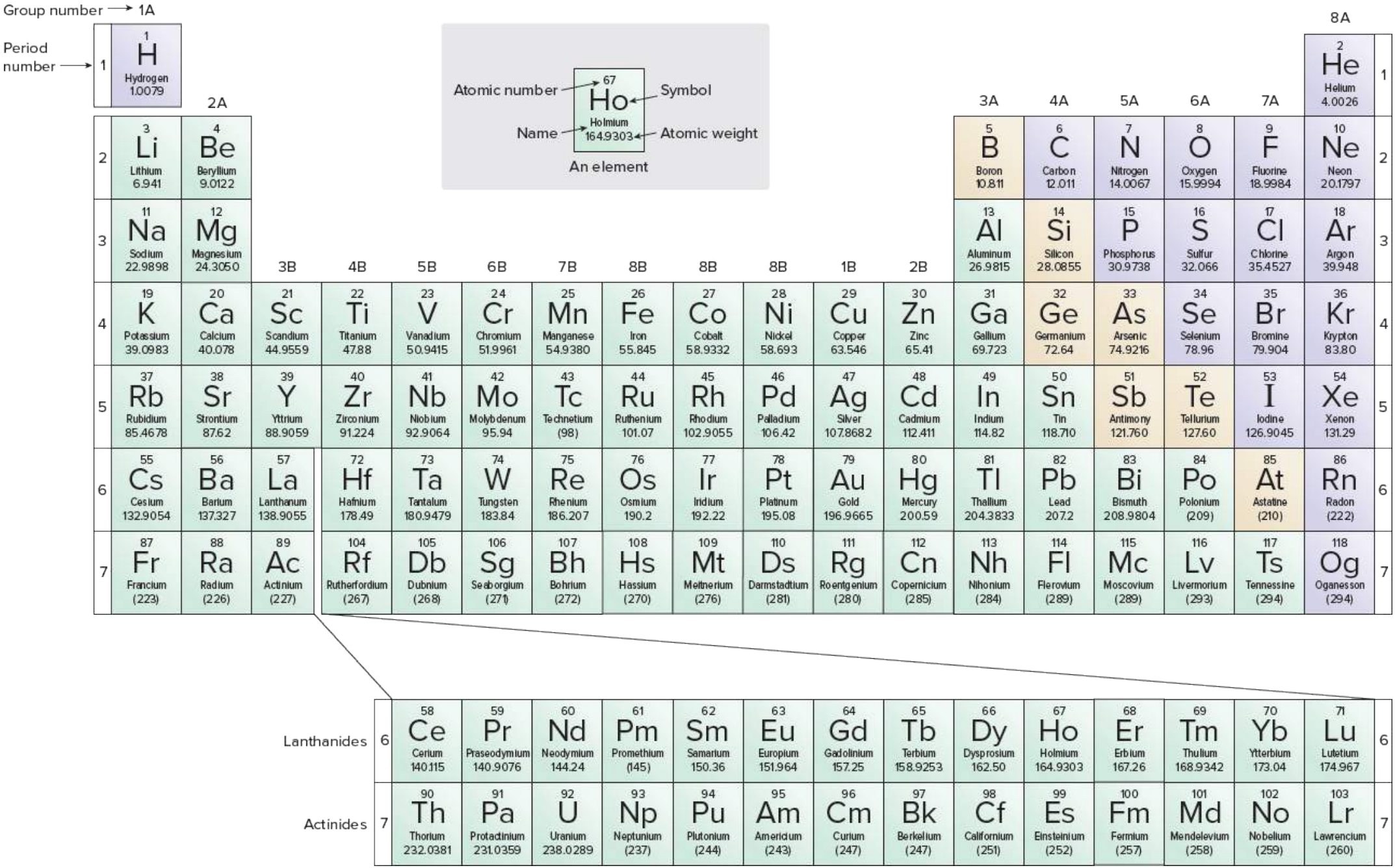
A

epi-aristolochene

APPENDIX

A

Periodic Table of the Elements


Group number → 1A
Period number → 1
8A
Atomic number → 67
Ho ← Symbol
Name → Holmium 164.9303 ← Atomic weight
An element
2A
3A
4A
5A
6A
7A
1 H Hydrogen 1.0079
2 He Helium 4.0026
3 Li Lithium 6.941
4 Be Beryllium 9.0122
5 B Boron 10.811
6 C Carbon 12.011
7 N Nitrogen 14.0067
8 O Oxygen 15.9994
9 F Fluorine 18.9984
10 Ne Neon 20.1797
11 Na Sodium 22.9898
12 Mg Magnesium 24.3050
3B
4B
5B
6B
7B
8B
8B
8B
1B
2B
13 Al Aluminum 26.9815
14 Si Silicon 28.0855
15 P Phosphorus 30.9738
16 S Sulfur 32.066
17 Cl Chlorine 35.4527
18 Ar Argon 39.948
19 K Potassium 39.0983
20 Ca Calcium 40.078
21 Sc Scandium 44.9559
22 Ti Titanium 47.88
23 V Vanadium 50.9415
24 Cr Chromium 51.9961
25 Mn Manganese 54.9380
26 Fe Iron 55.845
27 Co Cobalt 58.9332
28 Ni Nickel 58.693
29 Cu Copper 63.546
30 Zn Zinc 65.41
31 Ga Gallium 69.723
32 Ge Germanium 72.64
33 As Arsenic 74.9216
34 Se Selenium 78.96
35 Br Bromine 79.904
36 Kr Krypton 83.80
37 Rb Rubidium 85.4678
38 Sr Strontium 87.62
39 Y Yttrium 88.9059
40 Zr Zirconium 91.224
41 Nb Niobium 92.9064
42 Mo Molybdenum 95.94
43 Tc Technetium (98)
44 Ru Ruthenium 101.07
45 Rh Rhodium 102.9055
46 Pd Palladium 106.42
47 Ag Silver 107.8682
48 Cd Cadmium 112.411
49 In Indium 114.82
50 Sn Tin 118.710
51 Sb Antimony 121.760
52 Te Tellurium 127.60
53 I Iodine 126.9045
54 Xe Xenon 131.29
55 Cs Cesium 132.9054
56 Ba Barium 137.327
57 La Lanthanum 138.9055
72 Hf Hafnium 178.49
73 Ta Tantalum 180.9479
74 W Tungsten 183.84
75 Re Rhenium 186.207
76 Os Osmium 190.2
77 Ir Iridium 192.22
78 Pt Platinum 195.08
79 Au Gold 196.9665
80 Hg Mercury 200.59
81 Tl Thallium 204.3833
82 Pb Lead 207.2
83 Bi Bismuth 208.9804
84 Po Polonium (209)
85 At Astatine (210)
86 Rn Radon (222)
87 Fr Francium (223)
88 Ra Radium (226)
89 Ac Actinium (227)
104 Rf Rutherfordium (267)
105 Db Dubnium (268)
106 Sg Seaborgium (271)
107 Bh Bohrium (272)
108 Hs Hassium (270)
109 Mt Meitnerium (276)
110 Ds Darmstadtium (281)
111 Rg Roentgenium (280)
112 Cn Copernicium (285)
113 Nh Nihonium (284)
114 Fl Flerovium (289)
115 Mc Moscovium (289)
116 Lv Livermorium (293)
117 Ts Tennessine (294)
118 Og Oganesson (294)
Lanthanides
58 Ce Cerium 140.115
59 Pr Praseodymium 140.9076
60 Nd Neodymium 144.24
61 Pm Promethium (145)
62 Sm Samarium 150.36
63 Eu Europium 151.964
64 Gd Gadolinium 157.25
65 Tb Terbium 158.9253
66 Dy Dysprosium 162.50
67 Ho Holmium 164.9303
68 Er Erbium 167.26
69 Tm Thulium 168.9342
70 Yb Ytterbium 173.04
71 Lu Lutetium 174.967
Actinides
90 Th Thorium 232.0381
91 Pa Protactinium 231.0359
92 U Uranium 238.0289
93 Np Neptunium (237)
94 Pu Plutonium (244)
95 Am Americium (243)
96 Cm Curium (247)
97 Bk Berkelium (247)
98 Cf Californium (251)
99 Es Einsteinium (252)
100 Fm Fermium (257)
101 Md Mendelevium (258)
102 No Nobelium (259)
103 Lr Lawrencium (260)

APPENDIX

B

Common Abbreviations, Arrows, and Symbols

Abbreviations

Ac	acetyl, CH_3CO^-
BBN	9-borabicyclo[3.3.1]nonane
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
Boc	***tert***-butoxycarbonyl, $(CH_3)_3COCO^-$
bp	boiling point
Bu	butyl, $CH_3CH_2CH_2CH_2^-$
CBS reagent	Corey–Bakshi–Shibata reagent
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DET	diethyl tartrate
DIBAL-H	diisobutylaluminum hydride, $[(CH_3)_2CHCH_2]_2AlH$
DMF	dimethylformamide, $HCON(CH_3)_2$
DMSO	dimethyl sulfoxide, $(CH_3)_2S{=}O$
ee	enantiomeric excess
Et	ethyl, $CH_3CH_2^-$
Fmoc	9-fluorenylmethoxycarbonyl
HMPA	hexamethylphosphoramide, $[(CH_3)_2N]_3P{=}O$
HOMO	highest occupied molecular orbital
IR	infrared
LDA	lithium diisopropylamide, $LiN[CH(CH_3)_2]_2$
LUMO	lowest unoccupied molecular orbital
m-	meta
mCPBA	***m***-chloroperoxybenzoic acid
Me	methyl, CH_3^-
MO	molecular orbital

mp	melting point
MS	mass spectrometry
MW	molecular weight
NBS	***N***-bromosuccinimide
NMO	***N***-methylmorpholine ***N***-oxide
NMR	nuclear magnetic resonance
o-	ortho
p-	para
PCC	pyridinium chlorochromate
Ph	phenyl, C_6H_5-
ppm	parts per million
Pr	propyl, $CH_3CH_2CH_2-$
RCM	ring-closing metathesis
ROMP	ring-opening metathesis polymerization
TBDMS	***tert***-butyldimethylsilyl
THF	tetrahydrofuran
TMS	tetramethylsilane, $(CH_3)_4Si$
Ts	tosyl, ***p***-toluenesulfonyl, $CH_3C_6H_4SO_2-$
TsOH	***p***-toluenesulfonic acid, $CH_3C_6H_4SO_3H$
UV	ultraviolet

Arrows

	reaction arrow
	equilibrium arrows
	double-headed arrow, used between resonance structures
	full-headed curved arrow, showing the movement of an electron pair
	half-headed curved arrow (fishhook), showing the movement of an electron
	retrosynthetic arrow
	no reaction

Symbols

	dipole
hν	light
Δ	heat
δ+	partial positive charge
δ−	partial negative charge
λ	wavelength
ν	frequency

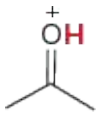
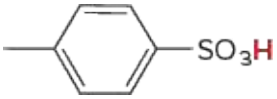
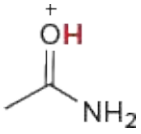
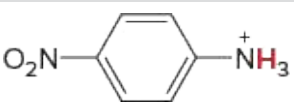
$\tilde{\nu}$	wavenumber
HA	Brønsted–Lowry acid
B:	Brønsted–Lowry base
:Nu$^-$	nucleophile
E$^+$	electrophile
X	halogen
	bond oriented forward
	bond oriented behind
- - -	partial bond
[ ]‡	transition state
[O]	oxidation
[H]	reduction

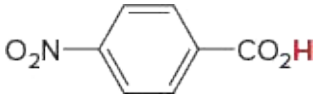
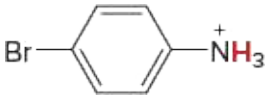
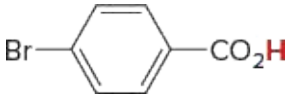
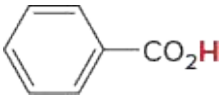
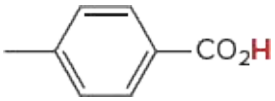
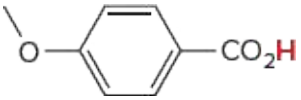
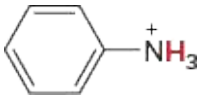
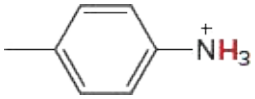
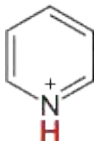
Common Element Colors Used in Molecular Art

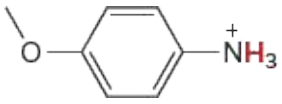
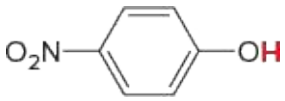
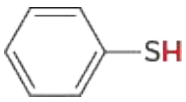
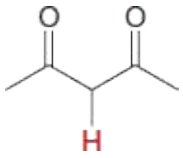
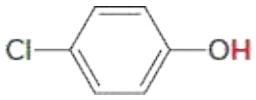
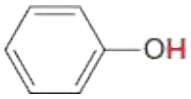
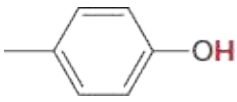
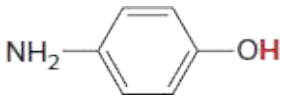
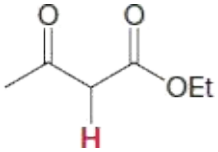
APPENDIX

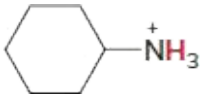
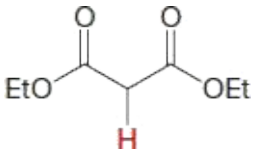
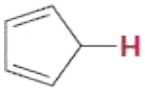
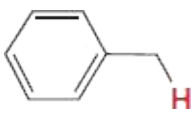
C

pK_a Values for Selected Compounds

Compound	pK_a
HI	−10
HBr	−9
H_2SO_4	−9
	−7.3
	−7
HCl	−7
$[(CH_3)_2OH]^+$	−3.8
$(CH_3OH_2)^+$	−2.5
H_3O+	−1.7
CH_3SO_3H	−1.2
	0.0
CF_3CO_2H	0.2
CCl_3CO_2H	0.6
	1.0

Cl_2CHCO_2H	1.3
H_3PO_4	2.1
FCH_2CO_2H	2.7
$ClCH_2CO_2H$	2.8
$BrCH_2CO_2H$	2.9
ICH_2CO_2H	3.2
HF	3.2
	3.4
HCO_2H	3.8
	3.9
	4.0
	4.2
	4.3
	4.5
	4.6
CH_3CO_2H	4.8
$(CH_3)_3CCO_2H$	5.0
	5.1
	5.3

	5.3
H_2CO_3	6.4
H_2S	7.0
	7.1
	7.8
	8.9
$HC{\equiv}N$	9.1
	9.4
NH_4^+	9.4
$H_3\overset{+}{N}CH_2CO_2^-$	9.8
	10.0
	10.2
HCO_3^-	10.2
CH_3NO_2	10.2
	10.3
CH_3CH_2SH	10.5
$[(CH_3)_3NH]^+$	10.6
	10.7
$(CH_3NH_3)^+$	10.7

	10.7
$[(CH_3)_2NH_2]^+$	10.7
CF_3CH_2OH	12.4
	13.3
	15
CH_3OH	15.5
H_2O	15.7
CH_3CH_2OH	16
CH_3CONH_2	16
CH_3CHO	17
$(CH_3)_3COH$	18
$(CH_3)_2C=O$	19.2
$CH_3CO_2CH_2CH_3$	24.5
$HC\equiv CH$	25
$CH_3C\equiv N$	25
$CHCl_3$	25
$CH_3CON(CH_3)_2$	30
H_2	35
NH_3	38
CH_3NH_2	40
	41
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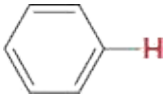
	
$CH_2=CHCH_3$	43
$CH_2=CH_2$	44
	46
CH_4	50
CH_3CH_3	50

APPENDIX

D

Nomenclature

Although the basic principles of nomenclature are presented in the body of this text, additional information is often needed to name many complex organic compounds. Appendix D concentrates on three topics:

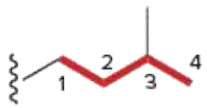
- Naming alkyl substituents that contain branching
- Naming polyfunctional compounds
- Naming bicyclic compounds

Naming Alkyl Substituents That Contain Branching

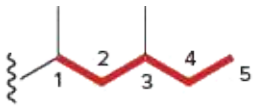
Alkyl groups that contain any number of carbons and no branches are named as described in Section 4.4A: change the *-ane* ending of the parent alkane to the suffix *-yl*. Thus the seven-carbon alkyl group $CH_3CH_2CH_2CH_2CH_2CH_2CH_2–$ is called *heptyl*.

When an alkyl substituent also contains branching, follow a stepwise procedure:

[1] Identify the longest carbon chain of the alkyl group that begins at the point of attachment to the parent. Begin numbering at the point of attachment and use the suffix ***-yl*** to indicate an alkyl group.



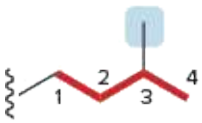
4 C's in the chain ⟶ butyl group



5 C's in the chain ⟶ pentyl group

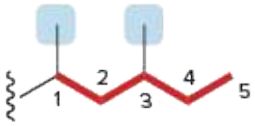
[2] Name all branches off the main alkyl chain and use the numbers from Step [1] to designate their location.

methyl at C3



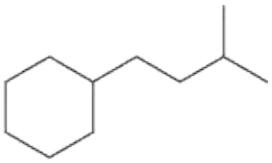
3-methylbutyl

methyls at C1 and C3

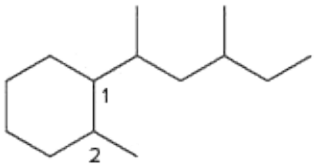


1,3-dimethylpentyl

[3] Set the entire name of the substituent in parentheses, and alphabetize this substituent name by the first letter of the complete name.



(3-methylbutyl)cyclohexane



1-(1,3-dimethylpentyl)-2-methylcyclohexane

- Alphabetize the **d** of **d**imethylpentyl before the **m** of **m**ethyl.
- Number the ring to give the lower number to the first substituent alphabetically: place the dimethylpentyl group at C1.

Naming Polyfunctional Compounds

Many organic compounds contain more than one functional group. When one of those functional groups is halo (X–) or alkoxy (RO–), these groups are named as substituents as described in Sections 7.2 and 9.3B. To name other polyfunctional compounds, we must learn which functional group is assigned a higher priority in the rules of nomenclature. Two steps are usually needed:

[1] Name a compound using the suffix of the highest-priority group, and name other functional groups as *substituents*. Table D.1 lists the common functional groups in order of *decreasing* priority, as well as the prefixes needed when a functional group must be named as a substituent.

[2] Number the carbon chain to give the lower number to the highest-priority functional group that can be named as a suffix, and then follow all other rules of nomenclature. Examples are shown in Figure D.1.

Table D.1 Summary of Functional Group Nomenclature

Functional group	Suffix	Substituent name (prefix)
Carboxylic acid	**-oic acid**	**carboxy**
Ester	**-oate**	**alkoxycarbonyl**
Amide	**-amide**	**amido**
Nitrile	**-nitrile**	**cyano**

Aldehyde	-al	oxo (=O) or formyl (−CHO)
Ketone	-one	oxo
Alcohol	-ol	hydroxy
Amine	-amine	amino
Alkene	-ene	alkenyl
Alkyne	-yne	alkynyl
Alkane	-ane	alkyl
Ether	–	alkoxy
Halide	–	halo

Increasing priority

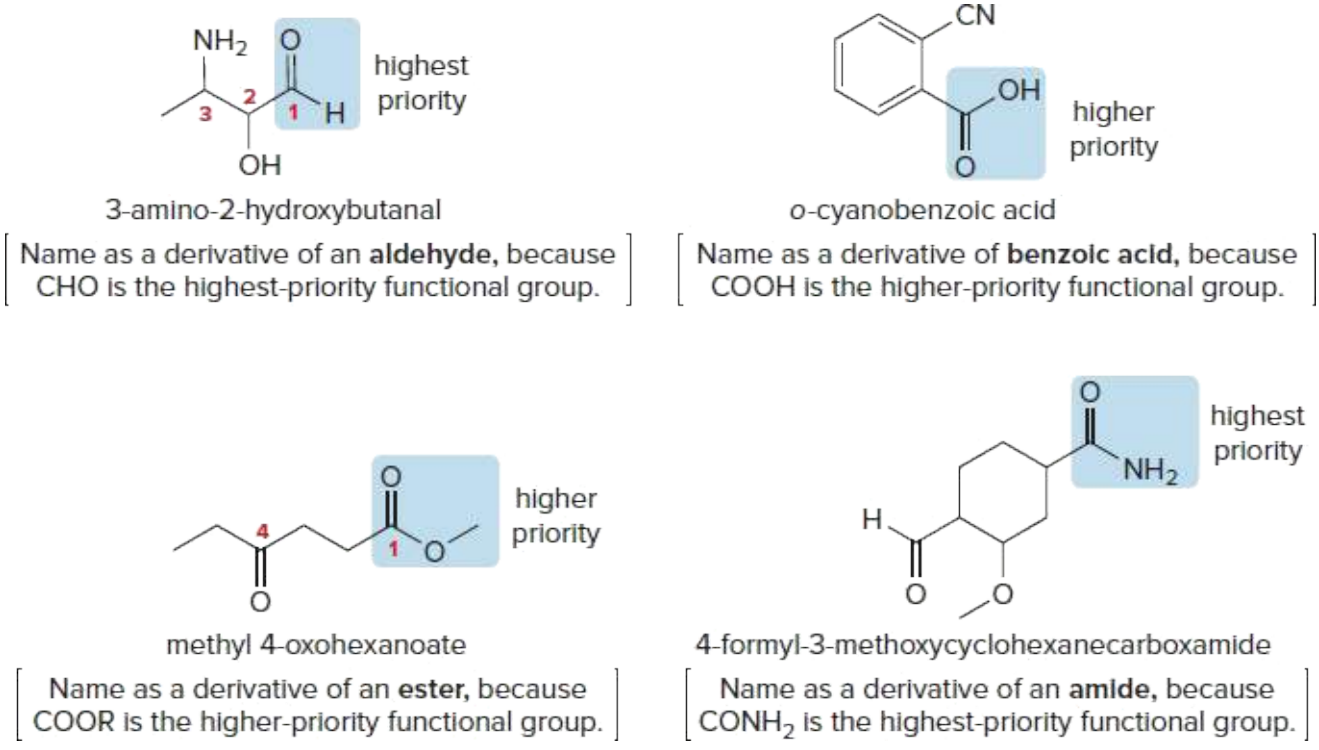


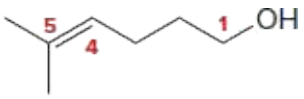
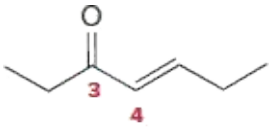
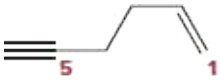
Figure D.1 **Examples of nomenclature of polyfunctional compounds**

Polyfunctional compounds that contain C–C double and triple bonds have characteristic suffixes to identify them, as shown in Table D.2. The higher-priority functional group is assigned the lower number.

Page A-7

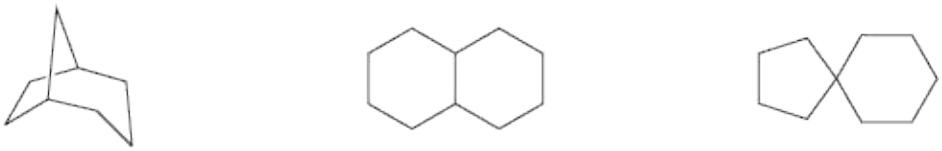
Table D.2 **Naming Polyfunctional Compounds with C–C Double and Triple Bonds**

Functional groups	Suffix	Example
C=C and OH	enol	

		 5-methylhex-4-en-1-ol
C=C + C=O (ketone)	**enone**	 (*E*)-hept-4-en-3-one
C=C + C≡C	**enyne**	 hex-1-en-5-yne

Naming Bicyclic Compounds

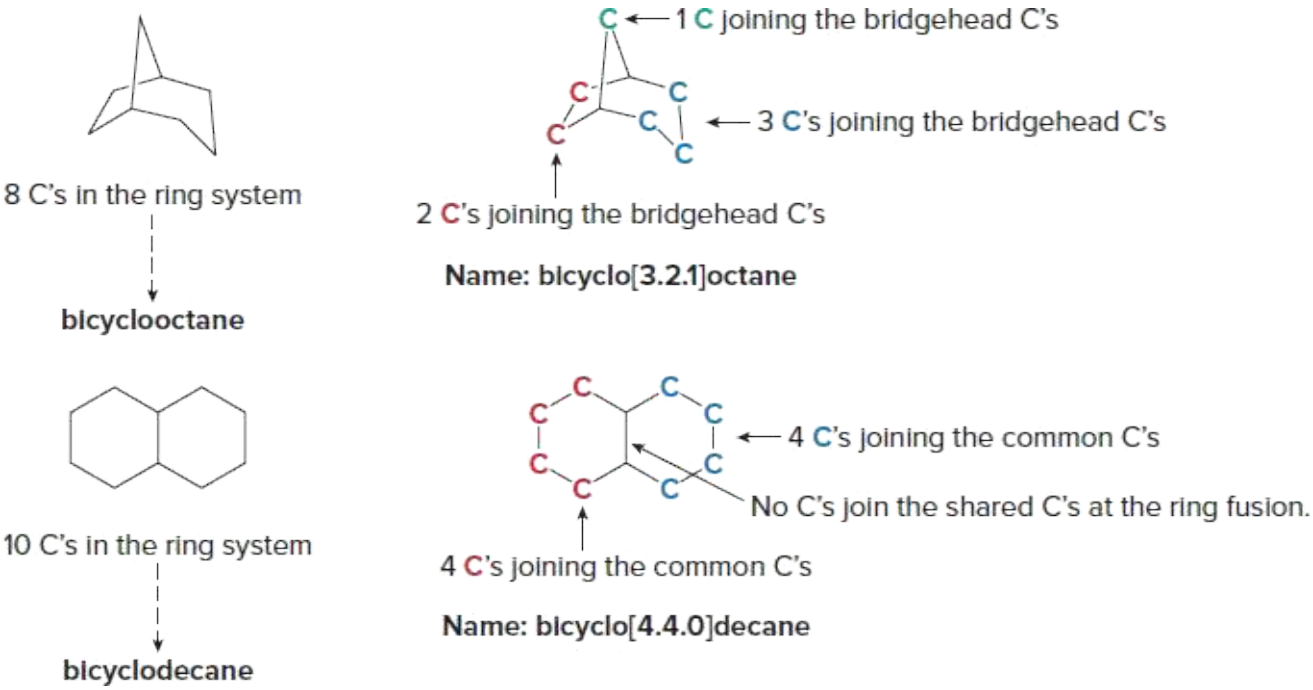
Bicyclic ring systems—compounds that contain two rings that share one or two carbon atoms—can be bridged, fused, or spiro.



bridged ring | fused ring | spiro ring

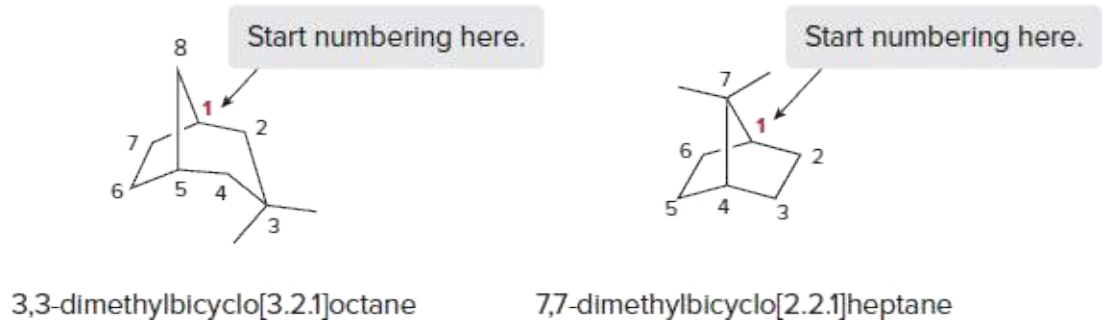
- **A bridged ring system contains two rings that share two *non-adjacent* carbons.**
- **A fused ring system contains two rings that share a *common* carbon–carbon bond.**
- **A spiro ring system contains two rings that share *one carbon atom.***

Fused and bridged ring systems are named as bicyclo[*x*.*y*.*z*]alkanes, where the parent alkane corresponds to the total number of carbons in both rings. The numbers *x*, *y*, and *z* refer to the number of carbons that join the shared carbons together, written in order of *decreasing* size. For a fused ring system, *z* always equals zero, because the two shared carbons are directly joined together. The shared carbons in a bridged ring system are called the bridgehead carbons.

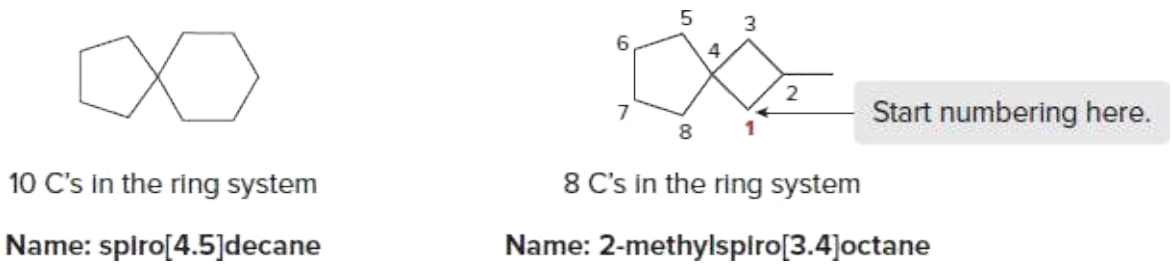


Rings are numbered beginning at a *shared* carbon, and continuing around the *longest* bridge first, then the next longest, and so forth.

Page A-8



Spiro ring systems are named as spiro[*x*.*y*]alkanes where the parent alkane corresponds to the total number of carbons in both rings, and *x* and *y* refer to the number of carbons that join the shared carbon (the spiro carbon), written in order of *increasing* size. When substituents are present, the rings are numbered beginning with a carbon *adjacent* to the spiro carbon in the *smaller* ring.



APPENDIX

E

Bond Dissociation Energies for Some Common Bonds [A−B → A• + •B]

Bond	Δ*H*° kJ/mol	(kcal/mol)
H–Z bonds		
H–F	**569**	**(136)**
H–Cl	**431**	**(103)**
H–Br	**368**	**(88)**
H–I	**297**	**(71)**
H–OH	**498**	**(119)**
Z–Z bonds		
H–H	**435**	**(104)**
F–F	**159**	**(38)**
Cl–Cl	**242**	**(58)**
Br–Br	**192**	**(46)**
I–I	**151**	**(36)**
HO–OH	**213**	**(51)**
R–H bonds		
CH_3–H	**435**	**(104)**

$CH_3CH_2–H$	**410**	**(98)**
$CH_3CH_2CH_2–H$	**410**	**(98)**
$(CH_3)_2CH–H$	**397**	**(95)**
$(CH_3)_3C–H$	**381**	**(91)**
$CH_2=CH–H$	**435**	**(104)**
$HC\equiv C–H$	**523**	**(125)**
$CH_2=CHCH_2–H$	**364**	**(87)**
$C_6H_5–H$	**460**	**(110)**
$C_6H_5CH_2–H$	**356**	**(85)**
R–R bonds		
$CH_3–CH_3$	**368**	**(88)**
$CH_3–CH_2CH_3$	**356**	**(85)**
$CH_3–CH=CH_2$	**385**	**(92)**
$CH_3–C\equiv CH$	**489**	**(117)**
R–X bonds		
$CH_3–F$	**456**	**(109)**
$CH_3–Cl$	**351**	**(84)**
$CH_3–Br$	**293**	**(70)**
$CH_3–I$	**234**	**(56)**
$CH_3CH_2–F$	**448**	**(107)**
$CH_3CH_2–Cl$	**339**	**(81)**
	285	**(68)**

$CH_3CH_2–Br$		
$CH_3CH_2–I$	**222**	**(53)**
$(CH_3)_2CH–F$	**444**	**(106)**
$(CH_3)_2CH–Cl$	**335**	**(80)**
$(CH_3)_2CH–Br$	**285**	**(68)**
$(CH_3)_2CH–I$	**222**	**(53)**
$(CH_3)_3C–F$	**444**	**(106)**
$(CH_3)_3C–Cl$	**331**	**(79)**
$(CH_3)_3C–Br$	**272**	**(65)**
$(CH_3)_3C–I$	**209**	**(50)**
R–OH bonds		
$CH_3–OH$	**389**	**(93)**
$CH_3CH_2–OH$	**393**	**(94)**
$CH_3CH_2CH_2–OH$	**385**	**(92)**
$(CH_3)_2CH–OH$	**401**	**(96)**
$(CH_3)_3C–OH$	**401**	**(96)**
Other bonds		
$CH_2=CH_2$	**635**	**(152)**
$HC\equiv CH$	**837**	**(200)**
$O=C=O$	**535**	**(128)**
O_2	**497**	**(119)**

APPENDIX

F

Reactions That Form Carbon–Carbon Bonds

Section	Reaction
11.11A	S_N2 reaction of an alkyl halide with an acetylide anion, $^-C{\equiv}CR$
11.11B	Opening of an epoxide ring with an acetylide anion, $^-C{\equiv}CR$
13.14	Radical polymerization of an alkene
14.12	Diels–Alder reaction
16.5	Friedel–Crafts alkylation
16.5	Friedel–Crafts acylation
17.10	Reaction of an aldehyde or ketone with a Grignard or organolithium reagent
17.13A	Reaction of an acid chloride with a Grignard or organolithium reagent
17.13A	Reaction of an ester with a Grignard or organolithium reagent
17.13B	Reaction of an acid chloride with an organocuprate reagent
17.14A	Reaction of a Grignard reagent with CO_2
17.14B	Reaction of an epoxide with an organometallic reagent
17.15	Reaction of an α,β-unsaturated carbonyl compound with an organocuprate reagent
18.8	Cyanohydrin formation
18.9	Wittig reaction to form an alkene
19.12	S_N2 reaction of an alkyl halide with NaCN
19.12C	Reaction of a nitrile with a Grignard or organolithium reagent
21.8	Direct enolate alkylation using LDA and an alkyl halide
21.9	Malonic ester synthesis to form a carboxylic acid
21.10	Acetoacetic ester synthesis to form a ketone
22.1	Aldol reaction to form a β-hydroxy carbonyl compound or an α,β-unsaturated carbonyl compound
22.2	Crossed aldol reaction
22.3	Directed aldol reaction
22.5	Claisen reaction to form a β-keto ester
22.6	Crossed Claisen reaction to form a β-dicarbonyl compound
22.7	Dieckmann reaction to form a five- or six-membered ring
22.8	Michael reaction to form a 1,5-dicarbonyl compound

22.9	Robinson annulation to form a cyclohex-2-enone
23.13	Reaction of a diazonium salt with CuCN
24.1	Coupling of an organocuprate reagent (R_2CuLi) with an organic halide (R′X)
24.2	The palladium-catalyzed Suzuki reaction of an organic halide with an organoborane
24.3	The palladium-catalyzed Heck reaction of a vinyl or aryl halide with an alkene
24.4	Addition of a dihalocarbene to an alkene to form a cyclopropane
24.5	Simmons–Smith reaction of an alkene with CH_2I_2 and Zn(Cu) to form a cyclopropane
24.6	Olefin metathesis
25.3	Electrocyclic reactions
25.4	Cycloaddition reactions
25.5	Sigmatropic rearrangements
26.10B	Kiliani–Fischer synthesis of an aldose
27.2B	Alkylation of diethyl acetamidomalonate to form an amino acid
27.2C	Strecker synthesis of an amino acid
28.2	Chain-growth polymerization
28.4	Polymerization using Ziegler–Natta catalysts

APPENDIX

G

Characteristic IR Absorption Frequencies

Bond	Functional group	Wavenumber (cm^{-1})	Comment
O–H			
	• ROH	**3600–3200**	**broad, strong**
	• RCO_2H	**3500–2500**	**very broad, strong**
N–H			
	• RNH_2	**3500–3300**	**two peaks**
	• R_2NH	**3500–3300**	**one peak**
	• $RCONH_2$, RCONHR	**3400–3200**	**one or two peaks; N–H bending also observed at 1640 cm^{-1}**
C–H			
	• $C_{Sp}–H$	**3300**	**sharp, often strong**
	• $C_{sp^2}–H$	**3150–3000**	**medium**
	• $C_{sp^3}–H$	**3000–2850**	**strong**
	• $C_{sp^2}–H$ of RCHO	**2830–2700**	**one or two peaks**
C≡C		**2250**	**medium**
C≡N		**2250**	**medium**
C=O			**strong**

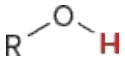
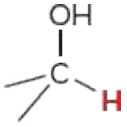
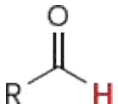
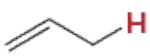
	• $RCOCl$	**1800**	
	• $(RCO)_2O$	**1800, 1760**	**two peaks**
	• RCO_2R	**1745–1735**	**increasing $\tilde{\nu}$ with decreasing ring size**
	• $RCHO$	**1730**	
	• R_2CO	**1715**	**increasing $\tilde{\nu}$ with decreasing ring size**
	• R_2CO, conjugated	**1680**	
	• RCO_2H	**1710**	
	• $RCONH_2$, $RCONHR$, $RCONR_2$	**1680–1630**	**increasing $\tilde{\nu}$ with decreasing ring size**
C=C			
	• Alkene	**1650**	**medium**
	• Arene	**1600, 1500**	**medium**
C=N		**1650**	**medium**

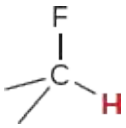
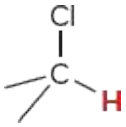
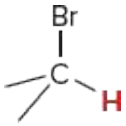
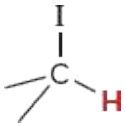
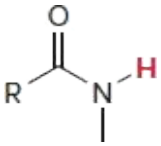
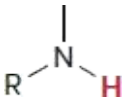
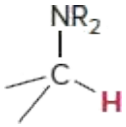
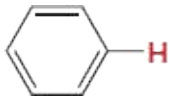
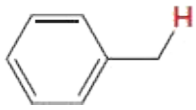
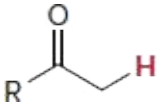
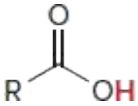
APPENDIX

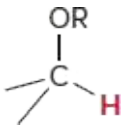
H

Characteristic NMR Absorptions

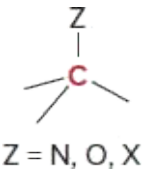
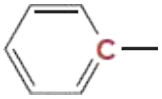
^{1}H NMR Absorptions

Compound type	Chemical shift (ppm)
Alcohol	
	**1–5**
	**3.4–4.0**
Aldehyde	
	**9–10**
Alkane	**0.9–2.0**
RCH_3	**~0.9**
R_2CH_2	**~1.3**
R_3CH	**~1.7**
Alkene	
sp^2 C–H	**4.5–6.0**
 allylic sp^3 C–H	**1.5–2.5**
Alkyl halide	

	**4.0–4.5**
	**3.0–4.0**
	**2.7–4.0**
	**2.2–4.0**
Alkyne	
	~2.5
Amide	**Page A-13**
	**7.5–8.5**
Amine	
	**0.5–5.0**
	**2.3–3.0**
Aromatic compound	
 sp^2 C–H	**6.5–8**
 benzylic sp^3 C–H	**1.5–2.5**
Carbonyl compound	
 sp^3 C–H on the α carbon	**2.0–2.5**
Carboxylic acid	
	**10–12**

Ether		**3.4–4.0**

^{13}C NMR Absorptions

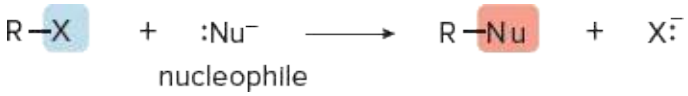
Carbon type	Structure	Chemical shift (ppm)
Alkyl, sp^3 hybridized C		**5–45**
Alkyl, sp^3 hybridized C bonded to N, O, or X		**30–80**
Alkynyl, *sp* hybridized C		**65–100**
Alkenyl, sp^2 hybridized C		**100–140**
Aryl, sp^2 hybridized C		**120–150**
Carbonyl C		**160–210**

APPENDIX

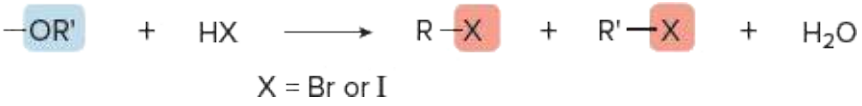
General Types of Organic Reactions

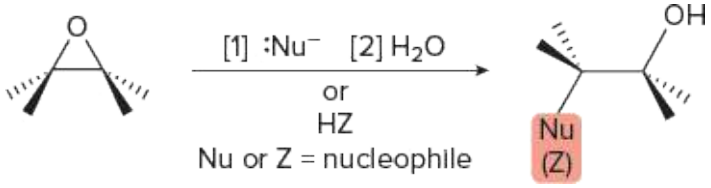
Substitution Reactions

[1] Nucleophilic substitution at an sp^3 hybridized carbon atom

a. Alkyl halides (Chapter 7) 

b. Alcohols (Section 9.11)

c. Ethers (Section 9.14) 

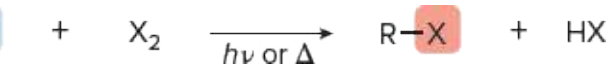
d. Epoxides (Section 9.16) 

[2] Nucleophilic acyl substitution at an sp^2 hybridized carbon atom

Carboxylic acids and their derivatives (Chapter 20)

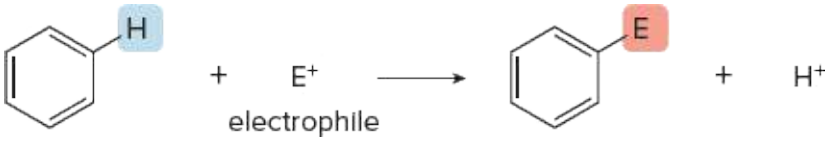
Z = OH, Cl, OCOR, OR', NR'_2

[3] Radical substitution at an sp^3 hybridized C–H bond

Alkanes (Section 13.3) 

[4] Electrophilic aromatic substitution

Aromatic compounds (Chapter 16)



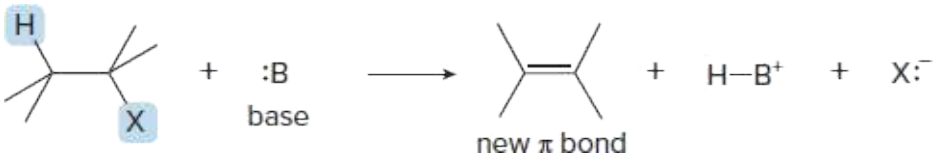
[5] Nucleophilic aromatic substitution

X = F, Cl, Br, I
A = H or electron-withdrawing group

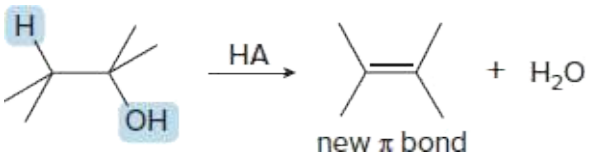
Elimination Reactions

β Elimination at an sp^3 hybridized carbon atom

a. Alkyl halides (Chapter 8)



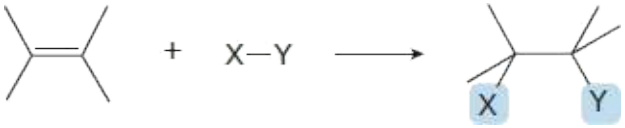
b. Alcohols (Section 9.8)



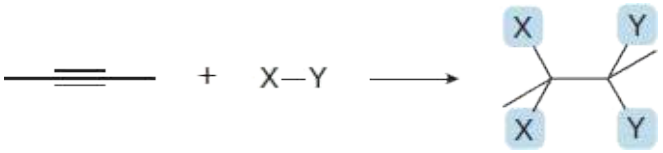
Addition Reactions

[1] Electrophilic addition to carbon–carbon multiple bonds

a. Alkenes (Chapter 10)

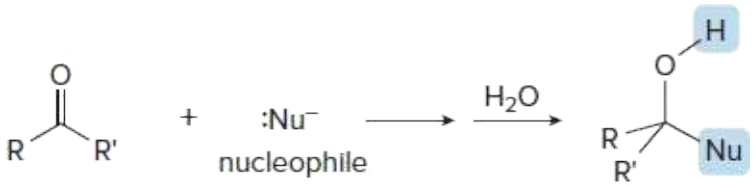


b. Alkynes (Section 11.6)



[2] Nucleophilic addition to carbon–oxygen multiple bonds

Aldehydes and ketones (Chapter 18)



R' = H or alkyl

APPENDIX

How to Synthesize Particular Functional Groups

J

Acetals

- Reaction of an aldehyde or ketone with two equivalents of an alcohol (18.13)

Acid chlorides

- Reaction of a carboxylic acid with thionyl chloride (20.9)

Alcohols

- Nucleophilic substitution of an alkyl halide with ^{-}OH or H_2O (9.6)
- Hydration of an alkene (10.12)
- Hydroboration–oxidation of an alkene (10.16)
- Reduction of an epoxide with $LiAlH_4$ (12.6)
- Reduction of an aldehyde or ketone (17.4)
- Hydrogenation of an α,β-unsaturated carbonyl compound with H_2 + Pd-C (17.4C)
- Enantioselective reduction of an aldehyde or ketone with the chiral CBS reagent (17.6)
- Reduction of an acid chloride with $LiAlH_4$ (17.7)
- Reduction of an ester with $LiAlH_4$ (17.7)
- Reduction of a carboxylic acid with $LiAlH_4$ (17.7)
- Reaction of an aldehyde or ketone with a Grignard or organolithium reagent (17.10)
- Reaction of an acid chloride with a Grignard or organolithium reagent (17.13)
- Reaction of an ester with a Grignard or organolithium reagent (17.13)
- Reaction of an organometallic reagent with an epoxide (17.14B)

Aldehydes

- Hydroboration–oxidation of a terminal alkyne (11.10)

- Oxidative cleavage of an alkene with O_3 followed by Zn or $(CH_3)_2S$ (12.10)
- Oxidation of a 1° alcohol with PCC (12.12)
- Oxidation of a 1° alcohol with $HCrO_4^-$, Amberlyst A-26 resin (12.13)
- Reduction of an acid chloride with $LiAlH[OC(CH_3)_3]_3$ (17.7)
- Reduction of an ester with DIBAL-H (17.7)
- Hydrolysis of an acetal (18.13B)
- Hydrolysis of an imine or enamine (18.11B)
- Reduction of a nitrile (19.12B)

Alkanes

- Catalytic hydrogenation of an alkene with H_2 + Pd-C (12.3)
- Catalytic hydrogenation of an alkyne with two equivalents of H_2 + Pd-C (12.5A)
- Reduction of an alkyl halide with $LiAlH_4$ (12.6)

- Reduction of a ketone to a methylene group (CH_2)—the Wolff–Kishner or Clemmensen reaction (16.15B)
- Protonation of an organometallic reagent with H_2O, ROH, or acid (17.9)
- Coupling of an organocuprate reagent (R_2CuLi) with an alkyl halide, R′X (24.1)
- Simmons–Smith reaction of an alkene with CH_2I_2 and Zn(Cu) to form a cyclopropane (24.5)

Alkenes

- Dehydrohalogenation of an alkyl halide with base (8.3)
- Dehydration of an alcohol with acid (9.8)
- Dehydration of an alcohol using $POCl_3$ and pyridine (9.10)
- β Elimination of an alkyl tosylate with base (9.13)
- Catalytic hydrogenation of an alkyne with H_2 + Lindlar catalyst to form a cis alkene (12.5B)
- Dissolving metal reduction of an alkyne with Na, NH_3 to form a trans alkene (12.5C)
- Wittig reaction (18.9)
- β Elimination of an α-halo carbonyl compound with Li_2CO_3, LiBr, and DMF (21.7C)
- Hofmann elimination of an amine (23.11)
- Coupling of an organocuprate reagent (R_2CuLi) with an organic halide, R′X (24.1)
- The palladium-catalyzed Suzuki reaction of a vinyl or aryl halide with a vinyl- or

arylborane (24.2)
- The palladium-catalyzed Heck reaction of a vinyl or aryl halide with an alkene (24.3)
- Olefin metathesis (24.6)

Alkyl halides
- Reaction of an alcohol with HX (9.11)
- Reaction of an alcohol with $SOCl_2$ or PBr_3 (9.12)
- Cleavage of an ether with HBr or HI (9.14)
- Hydrohalogenation of an alkene with HX (10.9)
- Halogenation of an alkene with X_2 (10.13)
- Hydrohalogenation of an alkyne with two equivalents of HX (11.7)
- Halogenation of an alkyne with two equivalents of X_2 (11.8)
- Radical halogenation of an alkane (13.3)
- Radical halogenation at an allylic carbon (13.10)
- Radical addition of HBr to an alkene (13.13)
- Electrophilic addition of HX to a 1,3-diene (14.10)
- Radical halogenation of an alkyl benzene (16.14)
- Halogenation α to a carbonyl group (21.7)
- Addition of a dihalocarbene to an alkene to form a dihalocyclopropane (24.4)

Alkynes
- Dehydrohalogenation of an alkyl dihalide with base (11.5)
- S_N2 reaction of an alkyl halide with an acetylide anion, $^-C{\equiv}CR$ (11.11)

Amides
- Reaction of an acid chloride with NH_3 or an amine (20.7)
- Reaction of an anhydride with NH_3 or an amine (20.8)
- Reaction of a carboxylic acid with NH_3 or an amine and DCC (20.9)
- Reaction of an ester with NH_3 or an amine (20.10)

Amines
- Nucleophilic aromatic substitution (16.13)
- Reduction of a nitro group (16.15C)
- Reduction of an amide with $LiAlH_4$ (17.7B)
- Reduction of a nitrile (19.12B)
- S_N2 reaction using NH_3 or an amine (23.6A)
- Gabriel synthesis (23.6A)
- Reductive amination of an aldehyde or ketone (23.6C)

Amino acids

- S_N2 reaction of an α-halo carboxylic acid with excess NH_3 (27.2A)
- Alkylation of diethyl acetamidomalonate (27.2B)
- Strecker synthesis (27.2C)
- Enantioselective hydrogenation using a chiral catalyst (27.4)

Anhydrides

- Reaction of an acid chloride with a carboxylate anion (20.7)
- Dehydration of a dicarboxylic acid (20.9)

Aryl halides

- Halogenation of benzene with X_2 + FeX_3 (16.3)
- Reaction of a diazonium salt with CuCl, CuBr, HBF_4, NaI, or KI (23.13A)

Carboxylic acids

- Oxidative cleavage of an alkyne with ozone (12.11)
- Oxidation of a 1° alcohol with CrO_3 (or a similar Cr^{6+} reagent), H_2O, H_2SO_4 (12.12B)
- Oxidation of an alkyl benzene with $KMnO_4$ (16.15A)
- Oxidation of an aldehyde (17.8)
- Reaction of a Grignard reagent with CO_2 (17.14A)
- Hydrolysis of a cyanohydrin (18.8)
- Hydrolysis of a nitrile (19.12A)
- Hydrolysis of an acid chloride (20.7)
- Hydrolysis of an anhydride (20.8)
- Hydrolysis of an ester (20.10)
- Hydrolysis of an amide (20.12)
- Malonic ester synthesis (21.9)

Cyanohydrins

- Addition of HCN to an aldehyde or ketone (18.8)

1,2-Diols

- Anti dihydroxylation of an alkene with a peroxyacid, followed by ring opening with ^-OH or H_2O (12.9A)
- Syn dihydroxylation of an alkene with $KMnO_4$ or OsO_4 (12.9B)

Enamines

- Reaction of an aldehyde or ketone with a 2° amine (18.11)

Epoxides

- Intramolecular S_N2 reaction of a halohydrin using base (9.6)
- Epoxidation of an alkene with mCPBA (12.8)
- Enantioselective epoxidation of an allylic alcohol with the Sharpless reagent (12.15)

Esters

- S_N2 reaction of an alkyl halide with a carboxylate anion, RCO_2^- (7.18)
- Reaction of an acid chloride with an alcohol (20.7)
- Reaction of an anhydride with an alcohol (20.8)
- Fischer esterification of a carboxylic acid with an alcohol (20.9)

Ethers

- Williamson ether synthesis—S_N2 reaction of an alkyl halide with an alkoxide, ^-OR (9.6)
- Reaction of an alkyl tosylate with an alkoxide, ^-OR (9.13)
- Addition of an alcohol to an alkene in the presence of acid (10.12)
- Anionic polymerization of epoxides to form polyethers (28.3)

Halohydrins

- Reaction of an epoxide with HX (9.16)
- Addition of X and OH to an alkene (10.15)

Imine

- Reaction of an aldehyde or ketone with a 1° amine (18.10)

Ketones

- Hydration of an alkyne with H_2O, H_2SO_4, and $HgSO_4$ (11.9)
- Oxidative cleavage of an alkene with O_3 followed by Zn or $(CH_3)_2S$ (12.10)
- Oxidation of a 2° alcohol with any Cr^{6+} reagent (12.12, 12.13)
- Friedel–Crafts acylation (16.5)
- Reaction of an acid chloride with an organocuprate reagent (17.13)
- Hydrolysis of an imine or enamine (18.11B)
- Hydrolysis of an acetal (18.13B)
- Reaction of a nitrile with a Grignard or organolithium reagent (19.12C)
- Acetoacetic ester synthesis (21.10)

Nitriles

- S_N2 reaction of an alkyl halide with NaCN (7.18, 19.12)
- Reaction of an aryl diazonium salt with CuCN (23.13A)

Phenols

- Reaction of an aryl diazonium salt with H_2O (23.13A)
- Nucleophilic aromatic substitution (16.13)

Sulfides

- Reaction of an alkyl halide with ^-SR (9.15)

Thiols

- Reaction of an alkyl halide with ^-SH (9.15)

Glossary

A

Acetal (Section 18.13): A compound having the general structure $R_2C(OR')_2$, where R = H, alkyl, or aryl. Acetals are used as protecting groups for aldehydes and ketones.

Acetoacetic ester synthesis (Section 21.10): A stepwise method that converts ethyl acetoacetate to a ketone having one or two carbons bonded to the α carbon.

Acetylation (Section 20.8): A reaction that transfers an acetyl group ($CH_3CO–$) from one atom to another.

Acetyl coenzyme A (Section 20.16): A biochemical thioester that acts as an acetylating reagent. Acetyl coenzyme A is often referred to as acetyl CoA.

Acetyl group (Section 18.2E): A substituent having the structure $–COCH_3$.

Acetylide anion (Sections 11.11, 17.9B): An anion formed by treating a terminal alkyne with a strong base. Acetylide anions have the general structure $R–C{\equiv}C^-$.

Achiral molecule (Section 5.3): A molecule that is superimposable upon its mirror image. An achiral molecule is not chiral.

Acid chloride (Sections 17.1, 20.1): A compound having the general structure RCOCl.

Acidity constant (Section 2.3): A value symbolized by K_a that represents the strength of an acid (HA). The larger the K_a, the stronger the acid.

$$K_a = \frac{[H_3O^+][A:^-]}{[H{-}A]}$$

Active site (Section 6.11): The region of an enzyme that binds the substrate.

Acyclic alkane (Section 4.1): A compound with the general formula $C_nH_{2n\,+\,2}$. Acyclic alkanes are also called saturated hydrocarbons because they contain the maximum number of hydrogen atoms per carbon.

Acylation (Sections 16.5A, 20.16): A reaction that transfers an acyl group from one atom to another.

Acyl chloride (Section 16.5A): A compound having the general structure RCOCl. Acyl

chlorides are also called acid chlorides.

Acyl group (Section 16.5A): A substituent having the general structure RCO–.

Acylium ion (Section 16.5B): A positively charged electrophile having the general structure $(R–C{\equiv}O)^+$, formed when the Lewis acid $AlCl_3$ ionizes the carbon–halogen bond of an acid chloride.

Acyl transfer reaction (Section 20.16): A reaction that transfers an acyl group from one atom to another.

1,2-Addition (Sections 14.10, 17.15): An addition reaction to a conjugated system that adds groups across two adjacent atoms.

1,4-Addition (Sections 14.10, 17.15): An addition reaction that adds groups to the atoms in the 1 and 4 positions of a conjugated system. 1,4-Addition is also called conjugate addition.

Addition polymer (Section 28.1): A polymer prepared by a chain reaction that adds a monomer to the growing end of a polymer chain. Addition polymers are also called chain-growth polymers.

Addition reaction (Sections 6.2C, 10.8): A reaction in which elements are added to a starting material. In an addition reaction, a π bond is broken and two σ bonds are formed.

Aglycon (Section 26.7C): The alcohol formed from hydrolysis of a glycoside.

Alcohol (Section 9.1): A compound having the general structure ROH. An alcohol contains a hydroxy group (OH group) bonded to an sp^3 hybridized carbon atom.

Aldaric acid (Section 26.9B): The dicarboxylic acid formed by the oxidation of the aldehyde and the primary alcohol of an aldose.

Aldehyde (Section 11.10): A compound having the general structure RCHO, where R = H, alkyl, or aryl.

Alditol (Section 26.9A): A compound formed by the reduction of the aldehyde of an aldose to a primary alcohol.

Aldol condensation (Section 22.1B): An aldol reaction in which the initially formed β-hydroxy carbonyl compound loses water by dehydration.

Aldol reaction (Section 22.1A): A reaction in which two molecules of an aldehyde or ketone react with each other in the presence of base to form a β-hydroxy carbonyl compound.

Aldonic acid (Section 26.9B): A compound formed by the oxidation of the aldehyde of an aldose to a carboxylic acid.

Aldose (Section 26.2): A monosaccharide comprised of a polyhydroxy aldehyde.

Aliphatic (Section 3.2A): A compound or portion of a compound made up of C–C σ and π bonds but not aromatic bonds.

Alkaloid (Section 23.5A): A basic, nitrogen-containing compound isolated from a plant source.

Alkane (Section 4.1): An aliphatic hydrocarbon having only C–C and C–H σ bonds.

Alkene (Section 8.2A): An aliphatic hydrocarbon that contains a carbon–carbon double bond.

Alkoxide (Sections 8.1, 9.6): An anion having the general structure RO^-, formed by deprotonating an alcohol with a base.

Alkoxy group (Section 9.3B): A substituent containing an alkyl group bonded to an oxygen (RO group).

Alkylation (Section 21.8): A reaction that transfers an alkyl group from one atom to another.

Alkyl group (Section 4.4A): A group formed by removing one hydrogen from an alkane. Alkyl groups are named by replacing the suffix *-ane* of the parent alkane with *-yl*.

Alkyl halide (Section 7.1): A compound containing a halogen atom bonded to an sp^3 hybridized carbon atom. Alkyl halides have the general molecular formula $C_nH_{2n + 1}X$.

1,2-Alkyl shift (Section 9.9): The rearrangement of a less stable carbocation to a more stable carbocation by the shift of an alkyl group from one carbon atom to an adjacent carbon atom.

Alkyl tosylate (Section 9.13): A compound having the general structure $ROSO_2C_6H_4CH_3$. Alkyl tosylates are also called tosylates and are abbreviated as ROTs.

Alkyne (Section 8.10): An aliphatic hydrocarbon that contains a carbon–carbon triple bond.

Allyl carbocation (Section 14.1B): A carbocation that has a positive charge on the atom adjacent to a carbon–carbon double bond. An allyl carbocation is resonance stabilized.

Allyl group (Section 10.3C): A substituent having the structure $–CH_2–CH=CH_2$.

Allylic bromination (Section 13.10A): A radical substitution reaction in which bromine replaces a hydrogen atom on the carbon adjacent to a carbon–carbon double bond.

Allylic carbon (Section 13.10): A carbon atom bonded to a carbon–carbon double bond.

Allylic halide (Section 7.1): A molecule containing a halogen atom bonded to the carbon atom adjacent to a carbon–carbon double bond.

Allyl radical (Section 13.10): A radical that has an unpaired electron on the carbon adjacent to a carbon–carbon double bond. An allyl radical is resonance stabilized.

Alpha (α) carbon (Sections 8.1, 18.2B): In an elimination reaction, the carbon that is bonded to the leaving group. In a carbonyl compound, the carbon that is bonded to the carbonyl carbon.

Ambident nucleophile (Section 21.3C): A nucleophile that has two reactive sites.

Amide (Sections 17.1, 20.1): A compound having the general structure $RCONR'_2$, where R′ = H or alkyl.

Amide base (Sections 8.10, 21.3B): A nitrogen-containing base formed by deprotonating an amine or ammonia.

Amine (Sections 18.10, 23.1): A basic organic nitrogen compound having the general structure RNH_2, R_2NH, or R_3N. An amine has a nonbonded pair of electrons on the nitrogen atom.

α-Amino acid (Sections 19.11A, 27.1): A compound having the general structure $RCH(NH_2)COOH$. α-Amino acids are the building blocks of proteins.

Amino acid residue (Section 27.5): The individual amino acids in peptides and proteins.

Amino group (Section 23.3D): A substituent having the structure $–NH_2$.

α-Amino nitrile (Section 27.2C): A compound having the general structure $RCH(NH_2)C{\equiv}N$.

Amino sugar (Section 26.13A): A carbohydrate that contains an NH_2 group instead of a hydroxy group at a non-anomeric carbon.

Ammonium salt (Section 23.1): A compound containing a positively charged nitrogen with four σ bonds; for example, $R_4N^+X^-$.

Angle strain (Section 4.11): An increase in the energy of a molecule resulting when the bond angles of the sp^3 hybridized atoms deviate from the optimum tetrahedral angle of 109.5°.

Angular methyl group (Section 29.8A): A methyl group located at the ring junction of two fused rings of the steroid skeleton.

Anhydride (Section 20.1): A compound having the general structure $(RCO)_2O$.

Aniline (Section 23.3C): A compound having the structure $C_6H_5NH_2$.

Anion (Section 1.2): A negatively charged ion that results from a neutral atom gaining one or more electrons.

Anionic polymerization (Section 28.2C): Chain-growth polymerization of alkenes substituted by electron-withdrawing groups that stabilize intermediate anions.

Annulation (Section 22.9): A reaction that forms a new ring.

Annulene (Section 15.8A): A hydrocarbon containing a single ring with alternating double and single bonds.

α Anomer (Section 26.6): The stereoisomer of a cyclic monosaccharide in which the anomeric OH and the CH_2OH groups are trans. In a D monosaccharide, the hydroxy group on the anomeric carbon is drawn down.

β Anomer (Section 26.6): The stereoisomer of a cyclic monosaccharide in which the anomeric OH and the CH_2OH groups are cis. In a D monosaccharide, the hydroxy group on the anomeric carbon is drawn up.

Anomeric carbon (Section 26.6): The stereogenic center at the hemiacetal carbon of a cyclic monosaccharide.

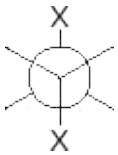
Antarafacial reaction (Section 25.4): A pericyclic reaction that occurs on opposite sides of the two ends of the π electron system.

Anti addition (Section 10.8): An addition reaction in which the two parts of a reagent are added from opposite sides of a double bond.

Antiaromatic compound (Section 15.7): An organic compound that is cyclic, planar, completely conjugated, and has $4n$ π electrons.

Antibonding molecular orbital (Section 15.9A): A high-energy molecular orbital formed when two atomic orbitals of opposite phase overlap.

Anti conformation (Section 4.10): A staggered conformation in which the two larger groups on adjacent carbon atoms have a dihedral angle of 180°.



Anti dihydroxylation (Section 12.9A): The addition of two hydroxy groups to opposite faces of a double bond.

Antioxidant (Section 13.12): A compound that stops an oxidation from occurring.

Anti periplanar (Section 8.8A): In an elimination reaction, a geometry where the β hydrogen and the leaving group are on opposite sides of the molecule.

Aromatic compound (Section 15.1): A planar, cyclic organic compound that has p orbitals on all ring atoms and a total of $4n + 2$ π electrons in the orbitals.

Aryl group (Section 15.3D): A substituent formed by removing one hydrogen atom from an aromatic ring.

Aryl halide (Sections 7.1, 16.3): A molecule such as C_6H_5X, containing a halogen atom X bonded to an aromatic ring.

Asymmetric carbon (Section 5.3): A carbon atom that is bonded to four different groups. An asymmetric carbon is also called a stereogenic center, a chiral center,

or a chirality center.

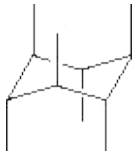
Asymmetric reaction (Sections 12.15, 17.6A, 27.4): A reaction that converts an achiral starting material to predominantly one enantiomer.

Atactic polymer (Section 28.4): A polymer having the substituents randomly oriented along the carbon backbone of an elongated polymer chain.

Atomic number (Section 1.1): The number of protons in the nucleus of an element.

Atomic weight (Section 1.1): The weighted average of the mass of all isotopes of a particular element. The atomic weight is reported in atomic mass units (amu).

Axial bonds (Section 4.12A): Bonds located above or below and perpendicular to the plane of the chair conformation of cyclohexane. Three axial bonds point upwards (on the up carbons) and three axial bonds point downwards (on the down carbons).



Azo compound (Section 23.14): A compound having the general structure RN=NR′.

B

Backside attack (Section 7.11C): Approach of a nucleophile from the side opposite the leaving group.

Barrier to rotation (Section 4.10): The energy difference between the lowest and highest energy conformations of a molecule.

Base peak (Section A.1): The peak in the mass spectrum having the greatest abundance value.

Basicity (Section 7.8): A measure of how readily an atom donates its electron pair to a proton.

Benedict's reagent (Section 26.9B): A reagent for oxidizing aldehydes to carboxylic acids using a Cu^{2+} salt, forming brick-red Cu_2O as a side product.

Benzoyl group (Section 18.2E): A substituent having the structure $-COC_6H_5$.

Benzyl group (Section 15.3D): A substituent having the structure $C_6H_5CH_2-$.

Benzylic halide (Sections 7.1, 16.14): A compound such as $C_6H_5CH_2X$, containing a halogen atom X bonded to a carbon that is bonded to a benzene ring.

Benzyne (Section 16.13B): A reactive intermediate formed by elimination of HX from an aryl halide.

Beta (β) carbon (Sections 8.1, 18.2B): In an elimination reaction, the carbon adjacent

to the carbon with the leaving group. In a carbonyl compound, the carbon located two carbons from the carbonyl carbon.

Bimolecular reaction (Sections 6.9B, 7.10, 7.11A): A reaction in which the concentration of both reactants affects the reaction rate and both terms appear in the rate equation. In a bimolecular reaction, two reactants are involved in the only step or the rate-determining step.

Biodegradable polymer (Section 28.9B): A polymer that can be degraded by microorganisms naturally present in the environment.

Biomolecule (Section 3.9): An organic compound found in a biological system.

Boat conformation of cyclohexane (Section 4.12B): An unstable conformation adopted by cyclohexane that resembles a boat. The instability of the boat conformation results from torsional strain and steric strain. The boat conformation of cyclohexane is 30 kJ/mol less stable than the chair conformation.

Boiling point (Section 3.4A): The temperature at which molecules in the liquid phase are converted to the gas phase. Molecules with stronger intermolecular forces have higher boiling points. Boiling point is abbreviated as bp.

Bond dissociation energy (Section 6.4): The amount of energy needed to homolytically cleave a covalent bond.

Bonding (Section 1.2): The joining of two atoms in a stable arrangement. Bonding is a favorable process that leads to lowered energy and increased stability.

Bonding molecular orbital (Section 15.9A): A low-energy molecular orbital formed when two atomic orbitals of similar phase overlap.

Bond length (Section 1.7A): The average distance between the centers of two bonded nuclei. Bond lengths are reported in picometers (pm).

Branched-chain alkane (Section 4.1A): An acyclic alkane that has alkyl substituents bonded to the parent carbon chain.

Bridged ring system (Section 14.13D): A bicyclic ring system in which the two rings share non-adjacent carbon atoms.

Bromination (Sections 10.13, 13.6, 16.3): The reaction of a compound with bromine.

Bromohydrin (Section 10.15): A compound having a bromine and a hydroxy group on adjacent carbon atoms.

Brønsted–Lowry acid (Section 2.1): A proton donor, symbolized by HA. A Brønsted–Lowry acid must contain a hydrogen atom.

Brønsted–Lowry base (Section 2.1): A proton acceptor, symbolized by :B. A

Brønsted–Lowry base must be able to form a bond to a proton by donating an available electron pair.

C

^{13}C NMR spectroscopy (Section C.1): A form of nuclear magnetic resonance spectroscopy used to determine the type of carbon atoms in a molecule.

Cahn–Ingold–Prelog system of nomenclature (Section 5.6): The system of designating a stereogenic center as either *R* or *S* according to the arrangement of the four groups attached to the center.

Carbamate (Sections 27.7, 28.6): A functional group containing a carbonyl group bonded to both an oxygen and a nitrogen atom. A carbamate is also called a urethane.

Carbanion (Section 2.5D): An ion with a negative charge on a carbon atom.

Carbene (Section 24.4): A neutral reactive intermediate having the general structure $:CR_2$. A carbene contains a divalent carbon surrounded by six electrons, making it a highly reactive electrophile that adds to C–C double bonds.

Carbinolamine (Section 18.6B): An unstable intermediate having a hydroxy group and an amine group on the same carbon. A carbinolamine is formed during the addition of an amine to a carbonyl group.

Carbocation (Section 7.13C): A positively charged carbon atom. A carbocation is sp^2 hybridized and trigonal planar, and contains a vacant *p* orbital.

Carbohydrate (Sections 18.16, 26.1): A polyhydroxy aldehyde or ketone or a compound that can be hydrolyzed to a polyhydroxy aldehyde or ketone.

Carbonate (Section 28.6D): A compound having the general structure $(RO)_2C{=}O$.

Carbon backbone (Section 3.1): The C–C and C–H σ bond framework that makes up the skeleton of an organic molecule.

Carbon NMR spectroscopy (Section C.1): A form of nuclear magnetic resonance spectroscopy used to determine the type of carbon atoms in a molecule.

Carbonyl group (Sections 3.2C, 11.9, 17.1): A functional group that contains a carbon–oxygen double bond (C=O). The polar carbon–oxygen bond makes the carbonyl carbon electrophilic.

Carboxy group (Section 19.1): A functional group having the structure COOH.

Carboxylate anion (Section 19.2C): An anion having the general structure RCO_2^-, formed by deprotonating a carboxylic acid with a Brønsted–Lowry base.

Carboxylation (Section 17.14): The reaction of an organometallic reagent with CO_2 to form a carboxylic acid after protonation.

Carboxylic acid (Section 19.1): A compound having the general structure RCO_2H.

Carboxylic acid derivatives (Section 17.1): Compounds having the general structure RCOZ, which can be synthesized from carboxylic acids. Common carboxylic acid derivatives include acid chlorides, anhydrides, esters, and amides.

Catalyst (Section 6.10): A substance that speeds up the rate of a reaction, but is recovered unchanged at the end of the reaction and does not appear in the product.

Catalytic hydrogenation (Section 12.3): A reduction reaction involving the addition of H_2 to a π bond in the presence of a metal catalyst.

Cation (Section 1.2): A positively charged ion that results from a neutral atom losing one or more electrons.

Cationic polymerization (Section 28.2C): Chain-growth polymerization of alkene monomers involving carbocation intermediates.

CBS reagent (Section 17.6A): A chiral reducing agent formed by reacting an oxazaborolidine with BH_3. CBS reagents predictably give one enantiomer as the major product of ketone reduction.

Cephalin (Section 29.4A): A phosphoacylglycerol in which the phosphodiester alkyl group is $-CH_2CH_2NH_3^+$. Cephalins are also called phosphatidylethanolamines.

Chain-growth polymer (Section 28.1): A polymer prepared by a chain reaction that adds a monomer to the growing end of a polymer chain. Chain-growth polymers are also called addition polymers.

Chain mechanism (Section 13.4A): A reaction mechanism that involves repeating steps.

Chair conformation of cyclohexane (Section 4.12A): A stable conformation adopted by cyclohexane that resembles a chair. The stability of the chair conformation results from the elimination of angle strain (all C–C–C bond angles are 109.5°) and torsional strain (all groups on adjacent carbon atoms are staggered).

Chemical shift (Section C.1B): The position of an absorption signal on the *x* axis in an NMR spectrum relative to the reference signal of tetramethylsilane.

Chirality center (Section 5.3): A carbon atom bonded to four different groups. A chirality center is also called a chiral center, a stereogenic center, and an asymmetric center.

Chiral molecule (Section 5.3): A molecule that is not superimposable upon its mirror image.

Chlorination (Sections 10.14, 13.5, 16.3): The reaction of a compound with chlorine.

Chlorofluorocarbons (Sections 7.4, 13.9): Synthetic alkyl halides having the general molecular formula CF_xCl_{4-x}. Chlorofluorocarbons, abbreviated as CFCs, were used as refrigerants and aerosol propellants and contribute to the destruction of the ozone layer.

Chlorohydrin (Section 10.15): A compound having a chlorine and a hydroxy group on adjacent carbon atoms.

Chromate ester (Section 12.12A): An intermediate in the chromium-mediated oxidation of an alcohol having the general structure $R–O–CrO_3H$.

s-Cis (Sections 14.6, 27.5B): The conformation of a 1,3-diene that has the two double bonds on the same side of the single bond that joins them.

Cis isomer (Sections 4.13B, 8.2B): An isomer of a ring or double bond that has two groups on the same side of the ring or double bond.

Claisen reaction (Section 22.5): A reaction between two molecules of an ester in the presence of base to form a β-keto ester.

Claisen rearrangement (Section 25.5): A [3,3] sigmatropic rearrangement of an unsaturated ether to a γ,δ-unsaturated carbonyl compound.

α Cleavage (Section A.3B): A fragmentation in mass spectrometry that results in cleavage of a carbon–carbon bond. With aldehydes and ketones, α cleavage results in breaking the bond between the carbonyl carbon and the carbon adjacent to it. With alcohols, α cleavage occurs by breaking a bond between an alkyl group and the carbon that bears the OH group.

Clemmensen reduction (Section 16.15B): A method to reduce aryl ketones to alkyl benzenes using Zn(Hg) in the presence of a strong acid.

Coenzyme (Section 12.13): A compound that acts with an enzyme to carry out a biochemical process.

Combustion (Section 4.14B): An oxidation–reduction reaction, in which an alkane or other organic compound reacts with oxygen to form CO_2 and H_2O, releasing energy.

Common name (Section 4.6): The name of a molecule that was adopted prior to and therefore does not follow the IUPAC system of nomenclature.

Compound (Section 1.2): The structure that results when two or more elements are joined together in a stable arrangement.

Concerted reaction (Sections 6.3, 7.11B): A reaction in which all bond forming and bond breaking occurs in one step.

Condensation polymer (Sections 20.15A, 28.1): A polymer formed when monomers

containing two functional groups come together with loss of a small molecule such as water or HCl. Condensation polymers are also called step-growth polymers.

Condensation reaction (Section 22.1B): A reaction in which a small molecule, often water, is eliminated during the reaction process.

Condensed structure (Section 1.8A): A shorthand representation of the structure of a compound in which all atoms are drawn in but bonds and lone pairs are usually omitted. Parentheses are used to denote similar groups bonded to the same atom.

Configuration (Section 5.2): A particular three-dimensional arrangement of atoms.

Conformations (Section 4.9): The different arrangements of atoms that are interconverted by rotation about single bonds.

Conjugate acid (Section 2.2): The compound that results when a base gains a proton in a proton transfer reaction.

Conjugate addition (Sections 14.10, 17.15): An addition reaction that adds groups to the atoms in the 1 and 4 positions of a conjugated system. Conjugate addition is also called 1,4-addition.

Conjugate base (Section 2.2): The compound that results when an acid loses a proton in a proton transfer reaction.

Conjugated diene (Section 14.1A): A compound that contains two carbon–carbon double bonds joined by a single σ bond. Pi (π) electrons are delocalized over both double bonds. Conjugated dienes are also called 1,3-dienes.

Conjugated protein (Section 27.10C): A structure composed of a protein unit and a non-protein molecule.

Conjugation (Section 14.1): The overlap of *p* orbitals on three or more adjacent atoms.

Conrotatory rotation (Section 25.3): Rotation of *p* orbitals in the same direction during electrocyclic ring closure or ring opening.

Constitutional isomers (Sections 1.4, 4.1A, 5.2): Two compounds that have the same molecular formula, but differ in the way the atoms are connected to each other. Constitutional isomers are also called structural isomers.

Coordination polymerization (Section 28.4): A polymerization reaction that uses a homogeneous catalyst that is soluble in the reaction solvents typically used.

Cope rearrangement (Section 25.5): A [3,3] sigmatropic rearrangement of a 1,5-diene to an isomeric 1,5-diene.

Copolymer (Section 28.2D): A polymer prepared by joining two or more different monomers together.

Counterion (Section 2.1): An ion that does not take part in a reaction and is opposite in charge to the ion that does take part in the reaction. A counterion is also called

a spectator ion.

Coupling constant (Section C.6A): The frequency difference, measured in Hz, between the peaks in a split NMR signal.

Coupling reaction (Section 23.15): A reaction that forms a bond between two discrete molecules.

Covalent bond (Section 1.2): A bond that results from the sharing of electrons between two nuclei. A covalent bond is a two-electron bond.

Crossed aldol reaction (Section 22.2): An aldol reaction in which the two reacting carbonyl compounds are different. A crossed aldol reaction is also called a mixed aldol reaction.

Crossed Claisen reaction (Section 22.6): A Claisen reaction in which the two reacting esters are different.

Crown ether (Section 3.7B): A cyclic ether containing multiple oxygen atoms. Crown ethers bind specific cations depending on the size of their central cavity.

Curved arrow notation (Section 1.6A): A convention that shows the movement of an electron pair. The tail of the arrow begins at the electron pair and the head points to where the electron pair moves.

Cyanide anion (Section 18.8A): An anion having the structure $^{-}C{\equiv}N$.

Cyano group (Section 19.1): A functional group consisting of a carbon–nitrogen triple bond (C≡N).

Cyanohydrin (Section 18.8): A compound having the general structure RCH(OH)C≡N. A cyanohydrin results from the addition of HCN across the carbonyl of an aldehyde or a ketone.

Cycloaddition (Section 25.1): A pericyclic reaction between two compounds with π bonds to form a cyclic product with two new σ bonds.

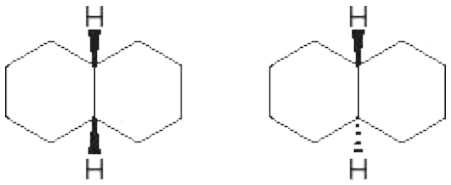
Cycloalkane (Sections 4.1, 4.2): A compound that contains carbons joined in one or more rings. Cycloalkanes with one ring have the general formula C_nH_{2n}.

Cyclopropanation (Section 24.4): An addition reaction to a carbon–carbon double bond that forms a cyclopropane.

D

D-Sugar (Section 26.2C): A sugar with the hydroxy group on the stereogenic center farthest from the carbonyl on the right side in the Fischer projection formula.

Decalin (Section 29.8A): Two fused six-membered rings. *cis*-Decalin has the hydrogen atoms at the ring fusion on the same side of the rings, whereas *trans*-decalin has the hydrogen atoms at the ring fusion on opposite sides of the rings.



Decarboxylation (Section 21.9A): Loss of CO_2 through cleavage of a carbon–carbon bond.

Degenerate orbitals (Section 15.9B): Orbitals (either atomic or molecular) having the same energy.

Degree of unsaturation (Section 10.2): A ring or a π bond in a molecule. The number of degrees of unsaturation compares the number of hydrogens in a compound to that of a saturated hydrocarbon containing the same number of carbons.

Dehydration (Sections 9.8, 20.9B): A reaction that results in the loss of the elements of water from the reaction components.

Dehydrohalogenation (Section 8.1): An elimination reaction in which the elements of hydrogen and halogen are lost from a starting material.

Delta (δ) scale (Section C.1B): A common scale of chemical shifts used in NMR spectroscopy in which the absorption due to tetramethylsilane (TMS) occurs at zero parts per million.

Deoxy (Section 26.13B): A prefix that means without oxygen.

Deoxyribonucleoside (Section 26.13B): An *N*-glycoside formed by the reaction of D-2-deoxyribose with certain amine heterocycles.

Deoxyribonucleotide (Section 26.13B): A DNA building block having a deoxyribose and either a purine or pyrimidine base joined together by an *N*-glycosidic linkage, and a phosphate bonded to a hydroxy group of the sugar nucleus.

Deprotection (Section 17.12): A reaction that removes a protecting group, regenerating a functional group.

Deshielding effects (Section C.3A): An effect in NMR caused by a decrease in electron density, thus increasing the strength of the magnetic field felt by the nucleus. Deshielding shifts an absorption downfield.

Dextrorotatory (Section 5.12A): Rotating plane-polarized light in the clockwise direction. The rotation is labeled *d* or (+).

1,3-Diacid (Section 21.9A): A compound containing two carboxylic acids separated by a single carbon atom. 1,3-Diacids are also called β-diacids.

Dialkylamide (Section 21.3B): An amide base having the general structure R_2N^-.

Diastereomers (Section 5.7): Stereoisomers that are not mirror images of each other. Diastereomers have the same *R*,*S* designation for at least one stereogenic center

and the opposite *R,S* designation for at least one of the other stereogenic centers.

Diastereotopic protons (Section C.2C): Two hydrogen atoms on the same carbon such that substitution of either hydrogen with a group Z forms diastereomers. The two hydrogen atoms are not equivalent and give two NMR signals.

1,3-Diaxial interaction (Section 4.13A): A steric interaction between two axial substituents of the chair form of cyclohexane. Larger axial substituents create unfavorable 1,3-diaxial interactions, destabilizing a cyclohexane conformation.

Diazonium salt (Section 23.12A): An ionic salt having the general structure $(R–N{\equiv}N)^{+}Cl^{-}$.

Diazotization reaction (Section 23.12A): A reaction that converts 1° alkylamines and arylamines to diazonium salts.

1,3-Dicarbonyl compound (Section 21.2): A compound containing two carbonyl groups separated by a single carbon atom.

1,4-Dicarbonyl compound (Section 22.4): A dicarbonyl compound in which the carbonyl groups are separated by three single bonds. 1,4-Dicarbonyl compounds can undergo intramolecular reactions to form five-membered rings.

1,5-Dicarbonyl compound (Section 22.4): A dicarbonyl compound in which the carbonyl groups are separated by four single bonds. 1,5-Dicarbonyl compounds can undergo intramolecular reactions to form six-membered rings.

Dieckmann reaction (Section 22.7): An intramolecular Claisen reaction of a diester to form a ring, typically a five- or six-membered ring.

Diels–Alder reaction (Section 14.12): An addition reaction between a 1,3-diene and a dienophile to form a cyclohexene ring.

1,3-Diene (Section 14.1A): A compound containing two carbon–carbon double bonds joined by a single σ bond. Pi (π) electrons are delocalized over both double bonds. 1,3-Dienes are also called conjugated dienes.

Dienophile (Section 14.12): The alkene component in a Diels–Alder reaction that reacts with a 1,3-diene.

Dihedral angle (Section 4.9): The angle that separates a bond on one atom from a bond on an adjacent atom.

Dihydroxylation (Section 12.9): Addition of two hydroxy groups to a double bond to form a 1,2-diol.

Diol (Section 9.3A): A compound possessing two hydroxy groups. Diols are also called glycols.

Dipeptide (Section 27.5): Two amino acids joined by one amide bond.

Diphosphate (Section 7.16): A good leaving group that is often used in biological systems. Diphosphate ($P_2O_7^{4-}$) is abbreviated as PP_i.

Dipole (Section 1.12): A partial separation of electronic charge.

Dipole–dipole interaction (Section 3.3B): An attractive intermolecular interaction between the permanent dipoles of polar molecules. The dipoles of adjacent molecules align so that the partial positive and partial negative charges are in close proximity.

Directed aldol reaction (Section 22.3): A crossed aldol reaction in which the enolate of one carbonyl compound is formed, followed by addition of the second carbonyl compound.

Disaccharide (Section 26.11): A carbohydrate containing two monosaccharide units joined by a glycosidic linkage.

Disproportionation (Section 28.2): A method of chain termination in radical polymerization involving the transfer of a hydrogen atom from one polymer radical to another, forming a new C–H bond on one polymer chain and a new double bond on the other.

Disrotatory rotation (Section 25.3): Rotation of *p* orbitals in opposite directions during electrocyclic ring closure or ring opening.

Dissolving metal reduction (Section 12.2): A reduction reaction using alkali metals as a source of electrons and liquid ammonia as a source of protons.

Disubstituted alkene (Section 8.2A): An alkene that has two alkyl groups and two hydrogens bonded to the carbons of the double bond ($R_2C{=}CH_2$ or RCH=CHR).

Disulfide (Sections 9.15A, 27.5C): A compound having the general structure RSSR′, often formed between the side chain of two cysteine residues.

Diterpene (Section 29.7A): A terpene that contains 20 carbons and four isoprene units. A diterpenoid contains at least one oxygen atom as well.

Doublet (Section C.6): An NMR signal that is split into two peaks of equal area, caused by one nearby nonequivalent proton.

Doublet of doublets (Section C.8): A splitting pattern of four peaks observed when a signal is split by two different nonequivalent protons.

Downfield shift (Section C.1B): In an NMR spectrum, a term used to describe the relative location of an absorption signal. A downfield shift means the signal is shifted to the left in the spectrum to higher chemical shift on the δ scale.

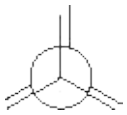
E

E1 mechanism (Sections 8.3, 8.6): An elimination mechanism that goes by a two-step process involving a carbocation intermediate. E1 is an abbreviation for “Elimination Unimolecular.”

E1cB mechanism (Section 22.1B): A two-step elimination mechanism that goes by a carbanion intermediate. E1cB stands for “Elimination Unimolecular, Conjugate Base.”

E2 mechanism (Sections 8.3, 8.4): An elimination mechanism that goes by a one-step concerted process, in which both reactants are involved in the transition state. E2 is an abbreviation for “Elimination Bimolecular.”

Eclipsed conformation (Section 4.9): A conformation of a molecule where the bonds on one carbon are directly aligned with the bonds on the adjacent carbon.



Edman degradation (Section 27.6B): A procedure used in peptide sequencing in which amino acids are cleaved one at a time from the N-terminal end, the identity of the amino acid determined, and the process repeated until the entire sequence is known.

Eicosanoids (Section 29.6): A group of biologically active compounds containing 20 carbon atoms derived from arachidonic acid.

Elastomer (Section 28.5): A polymer that stretches when stressed but then returns to its original shape.

Electrocyclic ring closure (Section 25.1): An intramolecular pericyclic reaction that forms a cyclic product containing one more σ bond and one fewer π bond than the reactant.

Electrocyclic ring-opening reaction (Section 25.1): A pericyclic reaction in which a σ bond of a cyclic reactant is cleaved to form a conjugated product with one more π bond.

Electromagnetic radiation (Section B.1): Radiant energy having dual properties of both waves and particles. The electromagnetic spectrum contains the complete range of electromagnetic radiation, arbitrarily divided into different regions.

Electron-donating inductive effect (Section 7.13A): An inductive effect in which an electropositive atom or polarizable group donates electron density through σ bonds to another atom.

Electronegativity (Section 1.12): A measure of an atom's attraction for electrons in a bond. Electronegativity indicates how much a particular atom “wants” electrons.

Electron-withdrawing inductive effect (Sections 2.5, 7.13A): An inductive effect in which a nearby electronegative atom pulls electron density toward itself through σ bonds.

Electrophile (Section 2.8): An electron-deficient compound, often symbolized by E^+, which can accept a pair of electrons from an electron-rich compound, forming a covalent bond. Lewis acids are electrophiles.

Electrophilic addition reaction (Section 10.9): An addition reaction in which the first step of the mechanism involves addition of the electrophilic end of a reagent to a π bond.

Electrophilic aromatic substitution (Section 16.1): A characteristic reaction of benzene in which a hydrogen atom on the ring is replaced by an electrophile.

Electrospray ionization (Section A.4C): A method for ionizing large biomolecules in a mass spectrometer. Electrospray ionization is abbreviated as ESI.

Electrostatic potential map (Section 1.12): A color-coded map that illustrates the distribution of electron density in a molecule. Electron-rich regions are indicated in red, and electron-deficient regions are indicated in blue. Regions of intermediate electron density are shown in orange, yellow, and green.

α Elimination (Section 24.4): An elimination reaction involving the loss of two elements from the same atom.

β Elimination (Section 8.1): An elimination reaction involving the loss of elements from two adjacent atoms.

Elimination reaction (Sections 6.2B, 8.1): A chemical reaction in which elements of the starting material are "lost" and a π bond is formed.

Enamine (Section 18.11): A compound having an amine nitrogen atom bonded to a carbon–carbon double bond [$R_2C{=}CH(NR'_2)$].

Enantiomeric excess (Section 5.12D): A measurement of how much one enantiomer is present in excess of the racemic mixture. Enantiomeric excess (ee) is also called optical purity; *ee* = % of one enantiomer – % of the other enantiomer.

Enantiomers (Section 5.3): Stereoisomers that are mirror images but are not superimposable upon each other. Enantiomers have the exact opposite *R,S* designation at every stereogenic center.

Enantioselective reaction (Sections 12.15, 17.6A, 27.4): A reaction that affords predominantly or exclusively one enantiomer. Enantioselective reactions are also called asymmetric reactions.

Enantiotopic protons (Section C.2C): Two hydrogen atoms on the same carbon such that substitution of either hydrogen with a group Z forms enantiomers. The two hydrogen atoms are equivalent and give a single NMR signal.

Endo position (Section 14.13D): A position of a substituent on a bridged bicyclic compound in which the substituent is closer to the longer bridge that joins the two

carbons common to both rings.

Endothermic reaction (Section 6.4): A reaction in which the energy of the products is higher than the energy of the reactants. In an endothermic reaction, energy is absorbed and the ΔH° is a positive value.

Energy of activation (Section 6.7): The energy difference between the transition state and the starting material. The energy of activation, symbolized by E_a, is the minimum amount of energy needed to break bonds in the reactants.

Energy diagram (Section 6.7): A schematic representation of the energy changes that take place as reactants are converted to products. An energy diagram indicates how readily a reaction proceeds, how many steps are involved, and how the energies of the reactants, products, and intermediates compare.

Enolate (Sections 17.15, 21.3): A resonance-stabilized anion formed when a base removes an α hydrogen from the α carbon to a carbonyl group.

Enol tautomer (Sections 9.1, 11.9, 17.15): A compound having a hydroxy group bonded to a carbon–carbon double bond. An enol tautomer [such as $CH_2{=}C(OH)CH_3$] is in equilibrium with its keto tautomer [$(CH_3)_2C{=}O$].

Enthalpy change (Section 6.4): The energy absorbed or released in a reaction. Enthalpy change is symbolized by ΔH° and is also called the heat of reaction.

Entropy (Section 6.6): A measure of the randomness in a system. The more freedom of motion or the more disorder present, the higher the entropy. Entropy is denoted by the symbol S°.

Entropy change (Section 6.6): The change in the amount of disorder between reactants and products in a reaction. The entropy change is denoted by the symbol ΔS°. $\Delta S^\circ = S^\circ_{\text{products}} - S^\circ_{\text{reactants}}$.

Enzyme (Section 6.11): A biochemical catalyst composed of at least one chain of amino acids held together in a very specific three-dimensional shape.

Enzyme–substrate complex (Section 6.11): A structure having a substrate bonded to the active site of an enzyme.

Epoxidation (Section 12.8): Addition of a single oxygen atom to an alkene to form an epoxide.

Epoxide (Section 9.1): A cyclic ether having the oxygen atom as part of a three-membered ring. Epoxides are also called oxiranes.

Epoxy resin (Section 28.6E): A step-growth polymer formed from a fluid prepolymer and a hardener that cross-links polymer chains together.

Equatorial bonds (Section 4.12A): Bonds located in the plane of the chair conformation of cyclohexane (around the equator). Three equatorial bonds point

slightly upwards (on the down carbons) and three equatorial bonds point slightly downwards (on the up carbons).

Equilibrium constant (Section 6.5A): A mathematical expression, denoted by the symbol K_{eq}, which relates the amount of starting material and product at equilibrium. K_{eq} = [products]/[starting materials].

Essential oil (Section 29.7): A class of terpenes isolated from plant sources by distillation.

Ester (Sections 17.1, 20.1): A compound having the general structure RCOOR′.

Esterification (Section 20.9C): A reaction that converts a carboxylic acid or a derivative of a carboxylic acid to an ester.

Ether (Section 9.1): A functional group having the general structure ROR′.

Ethynyl group (Section 11.2): An alkynyl substituent having the structure –C≡C–H.

Excited state (Sections 1.9B, 14.15A): A high-energy electronic state in which one or more electrons have been promoted to a higher-energy orbital by absorption of energy.

Exo position (Section 14.13D): A position of a substituent on a bridged bicyclic compound in which the substituent is closer to the shorter bridge that joins the two carbons common to both rings.

Exothermic reaction (Section 6.4): A reaction in which the energy of the products is lower than the energy of the reactants. In an exothermic reaction, energy is released and the ΔH° is a negative value.

Extraction (Section 19.10): A laboratory method to separate and purify a mixture of compounds using solubility differences and acid–base principles.

E,Z System of nomenclature (Section 10.3B): A system for unambiguously naming alkene stereoisomers by assigning priorities to the two groups on each carbon of the double bond. The *E* isomer has the two higher-priority groups on opposite sides of the double bond, and the *Z* isomer has them on the same side.

F

Fat (Sections 10.6B, 29.3): A triacylglycerol that is solid at room temperature and composed of fatty acid side chains with a high degree of saturation.

Fatty acid (Sections 10.6A, 19.5): A long-chain carboxylic acid having between 12 and 20 carbon atoms.

Fehling's reagent (Section 26.9B): A reagent for oxidizing aldehydes to carboxylic acids using a Cu^{2+} salt as an oxidizing agent, forming brick-red Cu_2O as a by-product.

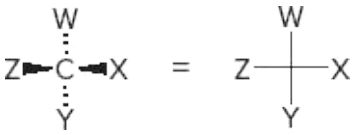
Fibrous proteins (Section 27.10): Long linear polypeptide chains that are bundled together to form rods or sheets.

Fingerprint region (Section B.2B): The region in an IR spectrum at < 1500 cm^{-1}. The region often contains a complex set of peaks and is unique for every compound.

First-order rate equation (Sections 6.9B, 7.10): A rate equation in which the reaction rate depends on the concentration of only one reactant.

Fischer esterification (Section 20.9C): An acid-catalyzed esterification reaction between a carboxylic acid and an alcohol to form an ester.

Fischer projection formula (Section 26.2A): A method for representing stereogenic centers with the stereogenic carbon at the intersection of vertical and horizontal lines. Fischer projections are also called cross formulas.



Fishhook (Section 6.3B): A half-headed curved arrow used in a reaction mechanism to denote the movement of a single electron.

Flagpole hydrogens (Section 4.12B): Hydrogens in the boat conformation of cyclohexane that are on either end of the "boat" and are forced into close proximity to each other.

Formal charge (Section 1.3C): The electronic charge assigned to individual atoms in a Lewis structure. The formal charge is calculated by subtracting an atom's unshared electrons and half of its shared electrons from the number of valence electrons that a neutral atom would possess.

Formyl group (Section 18.2E): A substituent having the structure –CHO.

Four-centered transition state (Section 10.16): A transition state that involves four atoms.

Fragment (Section A.1): Radicals and cations formed by the decomposition of the molecular ion in a mass spectrometer.

Freons (Sections 7.4, 13.9): Chlorofluorocarbons consisting of simple halogen-containing organic compounds that were once commonly used as refrigerants.

Frequency (Section B.1): The number of waves passing a point per unit time. Frequency is reported in cycles per second (s^{-1}), which is also called hertz (Hz).

Frequency is abbreviated with the Greek letter nu (ν).

Friedel–Crafts acylation (Section 16.5A): An electrophilic aromatic substitution reaction in which benzene reacts with an acid chloride in the presence of a Lewis acid to give a ketone.

Friedel–Crafts alkylation (Section 16.5A): An electrophilic aromatic substitution reaction in which benzene reacts with an alkyl halide in the presence of a Lewis acid to give an alkyl benzene.

Frontside attack (Section 7.11C): Approach of a nucleophile from the same side as the leaving group.

Full-headed curved arrow (Section 6.3B): An arrow used in a reaction mechanism to denote the movement of a pair of electrons.

Functional group (Section 3.1): An atom or group of atoms with characteristic chemical and physical properties. The functional group is the reactive part of the molecule.

Functional group interconversion (Section 11.12): A reaction that converts one functional group to another.

Functional group region (Section B.2): The region in an IR spectrum at ≥ 1500 cm^{-1}. Common functional groups show one or two peaks in this region, at a characteristic frequency.

Furanose (Section 26.6): A cyclic five-membered ring of a monosaccharide containing an oxygen atom.

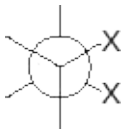
Fused ring system (Section 14.13D): A bicyclic ring system in which the two rings share one bond and two adjacent atoms.

G

Gabriel synthesis (Section 23.6A): A two-step method that converts an alkyl halide to a primary amine using a nucleophile derived from phthalimide.

Gas chromatography (Section A.4B): An analytical technique that separates the components of a mixture based on their boiling points and the rate at which their vapors travel through a column.

Gauche conformation (Section 4.10): A staggered conformation in which the two larger groups on adjacent carbon atoms have a dihedral angle of 60°.



GC–MS (Section A.4B): An analytical instrument that combines a gas

chromatograph (GC) and a mass spectrometer (MS) in sequence.

gem-Diol (Section 18.12): A compound having the general structure $R_2C(OH)_2$. *gem*-Diols are also called hydrates.

Geminal dihalide (Section 8.10): A compound that has two halogen atoms on the same carbon atom.

Gibbs free energy (Section 6.5A): The free energy of a molecule. Gibbs free energy is denoted by the symbol G°.

Gibbs free energy change (Section 6.5A): The overall energy difference between reactants and products. The Gibbs free energy change is denoted by the symbol ΔG°. $\Delta G^\circ = G^\circ_{\text{products}} - G^\circ_{\text{reactants}}$.

Globular proteins (Section 27.10): Polypeptide chains that are coiled into compact shapes with hydrophilic outer surfaces that make them water soluble.

Glycol (Section 9.3A): A compound possessing two hydroxy groups. Glycols are also called diols.

Glycosidase (Section 26.12B): An enzyme that hydrolyzes glycosidic linkages. An α-glycosidase hydrolyzes only α-glycosidic linkages.

Glycoside (Section 26.7A): A monosaccharide with an alkoxy group bonded to the anomeric carbon.

N-Glycoside (Section 26.13B): A monosaccharide containing a nitrogen bonded to the anomeric carbon.

Glycosidic linkage (Section 26.11): An acetal linkage formed between an OH group on one monosaccharide and the anomeric carbon on a second monosaccharide.

Green chemistry (Sections 12.13, 28.8): The use of environmentally benign methods to synthesize compounds.

Grignard reagent (Section 17.9): An organometallic reagent having the general structure RMgX.

Ground state (Sections 1.9B, 14.15A): The lowest-energy arrangement of electrons for an atom.

Group number (Section 1.1): The number above a particular column in the periodic table. Group numbers are represented by either an Arabic (1 to 8) or Roman (I to VIII) numeral followed by the letter A or B. The group number of a second-row element is equal to the number of valence electrons in that element.

Grubbs catalyst (Section 24.6): A widely used ruthenium catalyst for olefin metathesis that has the structure $Cl_2(Cy_3P)_2Ru{=}CHPh$.

Guest molecule (Section 9.5B): A small molecule that can bind to a larger host molecule.

H

^{1}H NMR spectroscopy (Section C.1): A form of nuclear magnetic resonance spectroscopy used to determine the number and type of hydrogen atoms in a molecule. ^{1}H NMR is also called proton NMR spectroscopy.

Half-headed curved arrow (Section 6.3B): An arrow used in a reaction mechanism to denote the movement of a single electron. A half-headed curved arrow is also called a fishhook.

α-Halo aldehyde or ketone (Section 21.7): An aldehyde or ketone with a halogen atom bonded to the α carbon.

Haloform reaction (Section 21.7B): A halogenation reaction of a methyl ketone ($RCOCH_3$) with excess halogen, which results in formation of RCO_2^- and CHX_3 (haloform).

Halogenation (Sections 10.13, 13.3, 16.3): The reaction of a compound with a halogen.

Halohydrin (Sections 9.6, 10.15): A compound that has a hydroxy group and a halogen atom on adjacent carbon atoms.

Halonium ion (Section 10.13): A positively charged halogen atom. A bridged halonium ion contains a three-membered ring and is formed in the addition of a halogen (X_2) to an alkene.

Hammond postulate (Section 7.14): A postulate that states that the transition state of a reaction resembles the structure of the species (reactant or product) to which it is closer in energy.

Haworth projection (Section 26.6A): A representation of the cyclic form of a monosaccharide in which the ring is drawn flat.

Head-to-tail polymerization (Section 13.14B): A mechanism of radical polymerization in which the more substituted radical of the growing polymer chain always adds to the less substituted end of the new monomer.

Heat of hydrogenation (Section 12.3A): The ΔH° of a catalytic hydrogenation reaction equal to the amount of energy released by hydrogenating a π bond.

Heat of reaction (Section 6.4): The energy absorbed or released in a reaction. Heat of reaction is symbolized by ΔH° and is also called the change in enthalpy.

Heck reaction (Section 24.3): The palladium-catalyzed coupling of a vinyl or aryl halide with an alkene to form a more highly substituted alkene with a new carbon–carbon bond.

α-Helix (Section 27.9B): A secondary structure of a protein formed when a peptide chain twists into a right-handed or clockwise spiral.

Heme (Section 27.10C): A complex organic compound containing an Fe^{2+} ion coordinated with a porphyrin.

Hemiacetal (Section 18.13A): A compound that contains an alkoxy group and a hydroxy group bonded to the same carbon atom.

Hertz (Section B.1): A unit of frequency measuring the number of waves passing a point per second.

Heteroatom (Sections 1.6, 3.1): An atom other than carbon or hydrogen. Common heteroatoms in organic chemistry are nitrogen, oxygen, sulfur, phosphorus, and the halogens.

Heterocycle (Section 9.3B): A cyclic compound containing a heteroatom as part of the ring.

Heterolysis (Section 6.3A): The breaking of a covalent bond by unequally dividing the electrons between the two atoms in the bond. Heterolysis generates charged intermediates. Heterolysis is also called heterolytic cleavage.

Hexose (Section 26.2): A monosaccharide containing six carbons.

Highest occupied molecular orbital (Section 15.4B): The molecular orbital with the highest energy that also contains electrons. The highest occupied molecular orbital is abbreviated as HOMO.

High-resolution mass spectrometer (Section A.4A): A mass spectrometer that can measure mass-to-charge ratios to four or more decimal places. High-resolution mass spectra are used to determine the molecular formula of a compound.

Hofmann elimination (Section 23.11): An E2 elimination reaction that converts an amine to a quaternary ammonium salt as the leaving group. The Hofmann elimination gives the less substituted alkene as the major product.

Homologous series (Section 4.1B): A group of compounds that differ by only a CH_2 group in the chain.

Homolysis (Section 6.3A): The breaking of a covalent bond by equally dividing the electrons between the two atoms in the bond. Homolysis generates uncharged radical intermediates. Homolysis is also called homolytic cleavage.

Homopolymer (Section 28.2D): A polymer prepared from a single monomer.

Homotopic protons (Section C.2C): Two equivalent hydrogen atoms such that substitution of either hydrogen with a group Z forms the same product. The two hydrogen atoms give a single NMR signal.

Hooke's law (Section B.3): A physical law that can be used to calculate the frequency of a bond vibration from the strength of the bond and the masses of the atoms attached to it.

Host–guest complex (Section 9.5B): The complex that is formed when a small guest molecule binds to a larger host molecule.

Host molecule (Section 9.5B): A large molecule that can bind a smaller guest molecule.

Hückel's rule (Section 15.7): A principle that states for a compound to be aromatic, it must be cyclic, planar, completely conjugated, and have $4n + 2$ π electrons.

Hybridization (Section 1.9B): The mathematical combination of two or more atomic orbitals (having different shapes) to form the same number of hybrid orbitals (all having the same shape).

Hybrid orbital (Section 1.9B): A new orbital that results from the mathematical combination of two or more atomic orbitals. The hybrid orbital is intermediate in energy compared to the atomic orbitals that were combined to form it.

Hydrate (Sections 12.12B, 18.12): A compound having the general structure $R_2C(OH)_2$. Hydrates are also called *gem*-diols.

Hydration (Sections 10.12, 18.8A): Addition of the elements of water to a molecule.

Hydride (Section 12.2): A negatively charged hydrogen ion ($H:^-$).

1,2-Hydride shift (Section 9.9): Rearrangement of a less stable carbocation to a more stable carbocation by the shift of a hydrogen atom from one carbon atom to an adjacent carbon atom.

Hydroboration (Section 10.16): The addition of the elements of borane (BH_3) to an alkene or alkyne.

Hydrocarbon (Sections 3.2A, 4.1): A compound made up of only the elements of carbon and hydrogen.

Hydrogen bonding (Section 3.3B): An attractive intermolecular interaction that occurs when a hydrogen atom bonded to an O, N, or F atom is electrostatically attracted to a lone pair of electrons on an O, N, or F atom in another molecule.

Hydrogenolysis (Section 27.7): A reaction that cleaves a σ bond using H_2 in the presence of a metal catalyst.

α Hydrogens (Section 21.1): The hydrogen atoms on the carbon bonded to the carbonyl carbon atom (the α carbon).

Hydrohalogenation (Section 10.9): An electrophilic addition of hydrogen halide (HX) to an alkene or alkyne.

Hydrolysis (Section 18.8A): A cleavage reaction with water.

Hydroperoxide (Section 13.11): An organic compound having the general structure ROOH.

Hydrophilic (Section 3.4C): Attracted to water. The polar portion of a molecule that

interacts with polar water molecules is hydrophilic.

Hydrophobic (Section 3.4C): Not attracted to water. The nonpolar portion of a molecule that is not attracted to polar water molecules is hydrophobic.

β-Hydroxy carbonyl compound (Section 22.1A): An organic compound having a hydroxy group on the carbon β to the carbonyl group.

Hydroxy group (Section 9.1): The OH functional group.

Hyperconjugation (Section 7.13B): The overlap of an empty *p* orbital with an adjacent σ bond.

I

Imide (Section 23.6A): A compound having a nitrogen atom between two carbonyl groups.

Imine (Sections 18.6B, 18.10A): A compound with the general structure $R_2C{=}NR'$. Imines are also called Schiff bases.

Iminium ion (Section 18.10A): A resonance-stabilized cation having the general structure $(R_2C{=}NR'_2)^+$, where R′ = H or alkyl.

Inductive effect (Sections 2.5B, 7.13A): The pull of electron density through σ bonds caused by electronegativity differences of atoms.

Infrared (IR) spectroscopy (Section B.2): An analytical technique used to identify the functional groups in a molecule based on their absorption of electromagnetic radiation in the infrared region.

Initiation (Section 13.4A): The initial step in a chain mechanism that forms a reactive intermediate by cleavage of a bond.

Inscribed polygon method (Section 15.10): A method to predict the relative energies of cyclic, completely conjugated compounds to determine which molecular orbitals are filled or empty. The inscribed polygon is also called a Frost circle.

Integration (Section C.5): The area under an NMR signal that is proportional to the number of absorbing nuclei that give rise to the signal.

Intermolecular forces (Section 3.3): The types of interactions that exist between molecules. Functional groups determine the type and strength of these forces. Intermolecular forces are also called noncovalent interactions or nonbonded interactions.

Internal alkene (Section 10.1): An alkene that has at least one carbon atom bonded to each end of the double bond.

Internal alkyne (Section 11.1): An alkyne that has one carbon atom bonded to each end of the triple bond.

Inversion of configuration (Section 7.11C): The opposite relative stereochemistry of a stereogenic center in the starting material and product of a chemical reaction. In a nucleophilic substitution reaction, inversion results when the nucleophile and leaving group are in the opposite position relative to the three other groups on carbon.

Iodoform test (Section 21.7B): A test for the presence of methyl ketones, indicated by the formation of the yellow precipitate, CHI_3, via the haloform reaction.

Ionic bond (Section 1.2): A bond that results from the transfer of electrons from one element to another. Ionic bonds result from strong electrostatic interactions between ions with opposite charges. The transfer of electrons forms stable salts composed of cations and anions.

Ionophore (Section 3.7B): An organic molecule that can form a complex with cations so they may be transported across a cell membrane. Ionophores have a hydrophobic exterior and a hydrophilic central cavity that complexes the cation.

Isocyanate (Section 28.6C): A compound having the general structure RN=C=O.

Isoelectric point (Sections 19.11C, 27.1A): The pH at which an amino acid exists primarily in its neutral zwitterionic form. Isoelectric point is abbreviated as *pI*.

Isolated diene (Section 14.1A): A compound containing two carbon–carbon double bonds joined by more than one σ bond.

Isomers (Sections 1.4A, 4.1A, 5.1): Two different compounds that have the same molecular formula.

Isoprene unit (Section 29.7): A five-carbon unit with four carbons in a row and a one-carbon branch on one of the middle carbons.

Isotactic polymer (Section 28.4): A polymer having all the substituents on the same side of the carbon backbone of an elongated polymer chain.

Isotope (Section 1.1): Two or more atoms of the same element having the same number of protons in the nucleus but a different number of neutrons. Isotopes have the same atomic number but different mass numbers.

IUPAC system of nomenclature (Section 4.3): A systematic method for naming compounds developed by the International Union of Pure and Applied Chemistry.

K

K_a (Section 2.3): The symbol that represents the acidity constant of an acid HA. The larger the K_a, the stronger the acid.

$$K_a = \frac{[H_3O^+][A:^-]}{[H{-}A]}$$

K_{eq} (Section 2.3): The equilibrium constant. K_{eq} = [products]/[starting materials].

Kekulé structures (Section 15.1): Two equilibrating structures for benzene. Each structure contains a six-membered ring and three π bonds alternating with σ bonds around the ring.

Ketal (Section 18.13): A compound having the general structure $R_2C(OR')_2$, where R = alkyl or aryl. Ketals are derived from ketones and constitute a subclass of acetals.

β-Keto ester (Section 21.10): A compound containing a ketone carbonyl on the carbon β to the ester carbonyl group.

Ketone (Section 11.9): A compound with two alkyl groups bonded to the C=O carbon atom, having the general structures $R_2C{=}O$ or RCOR′.

Ketose (Section 26.2): A monosaccharide comprised of a polyhydroxy ketone.

Keto tautomer (Section 11.9): A tautomer of a ketone that has a C=O and a hydrogen bonded to the α carbon. The keto tautomer is in equilibrium with the enol tautomer.

Kiliani–Fischer synthesis (Section 26.10B): A reaction that lengthens the carbon chain of an aldose by adding one carbon to the carbonyl end.

Kinetic enolate (Section 21.4): The enolate that is formed the fastest—generally the less substituted enolate.

Kinetic product (Section 14.11): In a reaction that can give more than one product, the product that is formed the fastest.

Kinetic resolution (Section 27.3B): The separation of two enantiomers by a chemical reaction that selectively occurs for only one of the enantiomers.

Kinetics (Section 6.5): The study of chemical reaction rates.

L

L-Sugar (Section 26.2C): A sugar with the hydroxy group on the stereogenic center farthest from the carbonyl on the left side in the Fischer projection formula.

Lactam (Section 20.1): A cyclic amide in which the carbonyl carbon–nitrogen σ bond is part of a ring. A β-lactam contains the carbon–nitrogen σ bond in a four-membered ring.

Lactol (Section 18.15): A cyclic hemiacetal.

Lactone (Section 20.1): A cyclic ester in which the carbonyl carbon–oxygen σ bond is part of a ring.

Leaving group (Section 7.6): An atom or group of atoms (Z) that is able to accept the electron density of the C–Z bond during a substitution or elimination reaction.

Leaving group ability (Section 7.7): A measure of how readily a leaving group (Z) can accept the electron density of the C–Z bond during a substitution or elimination reaction.

Le Châtelier's principle (Section 9.8D): The principle that a system at equilibrium will react to counteract any disturbance to the equilibrium.

Lecithin (Section 29.4A): A phosphoacylglycerol in which the phosphodiester alkyl group is $-CH_2CH_2N(CH_3)_3^+$. Lecithins are also called phosphatidylcholines.

Leukotriene (Section 9.17): An unstable and potent biomolecule synthesized in cells by the oxidation of arachidonic acid. Leukotrienes are responsible for biological conditions such as asthma.

Levorotatory (Section 5.12A): Rotating plane-polarized light in the counterclockwise direction. The rotation is labeled *l* or (–).

Lewis acid (Section 2.8): An electron pair acceptor.

Lewis acid–base reaction (Section 2.8): A reaction that results when a Lewis base donates an electron pair to a Lewis acid.

Lewis base (Section 2.8): An electron pair donor.

Lewis structure (Section 1.3): A representation of a molecule that shows the position of covalent bonds and nonbonding electrons. In Lewis structures, unshared electrons are represented by dots and a two-electron covalent bond is represented by a solid line. Lewis structures are also called electron dot structures.

Ligand (Section 24.2A): A group coordinated to a metal, which donates electron density to or sometimes withdraws electron density from the metal.

"Like dissolves like" (Section 3.4C): The principle that compounds dissolve in solvents having similar kinds of intermolecular forces; that is, polar compounds dissolve in polar solvents and nonpolar compounds dissolve in nonpolar solvents.

Lindlar catalyst (Section 12.5B): A catalyst for the hydrogenation of an alkyne to a cis alkene. The Lindlar catalyst is Pd adsorbed onto $CaCO_3$ with lead(II) acetate and quinoline.

Lipid (Sections 4.15, 29.1): A biomolecule with a large number of C–C and C–H σ bonds that is soluble in organic solvents and insoluble in water.

Lone pair of electrons (Section 1.2): A pair of valence electrons that is not shared with another atom in a covalent bond. Lone pairs are also called unshared or nonbonded pairs of electrons.

Lowest unoccupied molecular orbital (Section 15.9B): The molecular orbital with the lowest energy that does not contain electrons. The lowest unoccupied molecular orbital is abbreviated as the LUMO.

M

M peak (Section A.1): The peak in the mass spectrum that corresponds to the mass of the molecular ion. The M peak is also called the molecular ion peak or the parent peak.

M + 1 peak (Section A.1): The peak in the mass spectrum that corresponds to the mass of the molecular ion plus one. The M + 1 peak is caused by the presence of isotopes that increase the mass of the molecular ion.

M + 2 peak (Section A.2): The peak in the mass spectrum that corresponds to the mass of the molecular ion plus two. The M + 2 peak is caused by the presence of isotopes, typically of a chlorine or a bromine atom.

Magnetic resonance imaging (MRI) (Section C.12): A form of NMR spectroscopy used in medicine.

Malonic ester synthesis (Section 21.9A): A stepwise method that converts diethyl malonate to a carboxylic acid having one or two carbons bonded to the α carbon.

Markovnikov's rule (Section 10.10): The rule that states in the addition of HX to an unsymmetrical alkene, the H atom bonds to the less substituted carbon atom.

Mass number (Section 1.1): The total number of protons and neutrons in the nucleus of a particular atom.

Mass spectrometry (Section A.1): An analytical technique used for measuring the molecular weight and determining the molecular formula of an organic molecule.

Mass-to-charge ratio (Section A.1): A ratio of the mass to the charge of a molecular ion or fragment. Mass-to-charge ratio is abbreviated as *m/z*.

Megahertz (Section C.1A): A unit used for the frequency of the RF radiation in NMR spectroscopy. Megahertz is abbreviated as MHz; 1 MHz = 10^6 Hz.

Melting point (Section 3.4B): The temperature at which molecules in the solid phase are converted to the liquid phase. Molecules with stronger intermolecular forces and higher symmetry have higher melting points. Melting point is abbreviated as mp.

Merrifield method (Section 27.8): A method for synthesizing polypeptides using insoluble polymer supports.

Meso compound (Section 5.8): An achiral compound that contains two or more tetrahedral stereogenic centers.

Meta director (Section 16.7): A substituent on a benzene ring that directs a new group to the meta position during electrophilic aromatic substitution.

Meta isomer (Section 15.3B): A 1,3-disubstituted benzene ring. Meta substitution is abbreviated as *m*-.

Metal hydride reagent (Section 12.2): A reagent containing a polar metal–hydrogen bond that places a partial negative charge on the hydrogen and acts as a source of hydride ions ($H:^-$).

Metathesis (Section 24.6): A reaction between two alkene molecules that results in the interchange of the carbons of their double bonds.

Methylation (Section 7.16): A reaction in which a CH_3 group is transferred from one compound to another.

Methylene group (Sections 4.1B, 10.3C): A CH_2 group bonded to a carbon chain ($-CH_2-$) or part of a double bond ($CH_2=$).

1,2-Methyl shift (Section 9.9): Rearrangement of a less stable carbocation to a more stable carbocation by the shift of a methyl group from one carbon atom to an adjacent carbon atom.

Micelles (Section 3.6): Spherical droplets formed by soap molecules having the ionic heads on the surface and the nonpolar tails packed together in the interior. Grease and oil dissolve in the interior nonpolar region.

Michael acceptor (Section 22.8): The α,β-unsaturated carbonyl compound in a Michael reaction.

Michael reaction (Section 22.8): A reaction in which a resonance-stabilized carbanion (usually an enolate) adds to the β carbon of an α,β-unsaturated carbonyl compound.

Mixed aldol reaction (Section 22.2): An aldol reaction between two different carbonyl compounds. A mixed aldol reaction is also called a crossed aldol reaction.

Mixed anhydride (Section 20.1): An anhydride with two different alkyl groups bonded to the carbonyl carbon atoms.

Molecular ion (Section A.1): The radical cation having the general structure $M^{+\cdot}$, formed by the removal of an electron from an organic molecule. The molecular ion is also called the parent ion.

Molecular orbital theory (Section 15.9A): A theory that describes bonds as the mathematical combination of atomic orbitals to form a new set of orbitals called molecular orbitals. Molecular orbital theory is also called MO theory.

Molecular recognition (Section 9.5B): The ability of a host molecule to recognize and bind specific guest molecules.

Molecule (Section 1.2): A compound containing two or more atoms bonded together with covalent bonds.

Monomers (Sections 5.1, 13.14): Small organic compounds that can be covalently

bonded to each other (polymerized) in a repeating pattern.

Monosaccharide (Section 26.2): A simple sugar having three to seven carbon atoms.

Monosubstituted alkene (Section 8.2A): An alkene that has one alkyl group and three hydrogens bonded to the carbons of the double bond ($RCH{=}CH_2$).

Monoterpene (Section 29.7A): A terpene that contains 10 carbons and two isoprene units. A monoterpenoid also contains at least one oxygen atom.

Multiplet (Section C.6C): An NMR signal that is split into more than seven peaks.

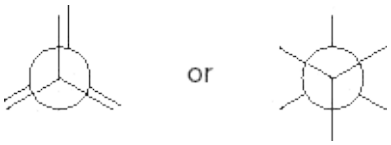
Mutarotation (Section 26.6A): The process by which a pure anomer of a monosaccharide equilibrates to a mixture of both anomers when placed in solution.

N

n + 1 rule (Section C.6C): The rule that an NMR signal for a proton with *n* nearby nonequivalent protons will be split into *n* + 1 peaks.

Natural product (Section 7.18): A compound isolated from a natural source.

Newman projection (Section 4.9): An end-on representation of the conformation of a molecule. The Newman projection shows the three groups bonded to each carbon atom in a particular C–C bond, as well as the dihedral angle that separates the groups on each carbon.



Nitration (Section 16.4): An electrophilic aromatic substitution reaction in which benzene reacts with $^{+}NO_2$ to give nitrobenzene, $C_6H_5NO_2$.

Nitrile (Sections 19.1, 19.12): A compound having the general structure RC≡N.

Nitronium ion (Section 16.4): An electrophile having the structure $^{+}NO_2$.

N-Nitrosamine (Section, 23.12B): A compound having the general structure $R_2N{-}N{=}O$. Nitrosamines are formed by the reaction of a secondary amine with ^{+}NO.

Nitrosonium ion (Section 23.12): An electrophile having the structure ^{+}NO.

NMR peak (Section C.6A): The individual absorptions in a split NMR signal due to nonequivalent nearby protons.

NMR signal (Section C.6A): The entire absorption due to a particular kind of proton in an NMR spectrum.

NMR spectrometer (Section C.1A): An analytical instrument that measures the absorption of RF radiation by certain atomic nuclei when placed in a strong

magnetic field.

Nonbonded pair of electrons (Section 1.2): A pair of valence electrons that is not shared with another atom in a covalent bond. Nonbonded electrons are also called unshared or lone pairs of electrons.

Nonbonding molecular orbital (Section 15.10): A molecular orbital having the same energy as the atomic orbitals that formed it.

Nonnucleophilic base (Section 7.8B): A base that is a poor nucleophile due to steric hindrance resulting from the presence of bulky groups.

Nonpolar bond (Section 1.12): A covalent bond in which the electrons are equally shared between the two atoms.

Nonpolar molecule (Section 1.13): A molecule that has no net dipole. A nonpolar molecule has either no polar bonds or multiple polar bonds whose dipoles cancel.

Nonreducing sugar (Section 26.9B): A carbohydrate that cannot be oxidized by Tollens, Benedict's, or Fehling's reagent.

Normal alkane (Section 4.1A): An acyclic alkane that has all of its carbons in a row. A normal alkane is an "*n*-alkane" or a straight-chain alkane.

Nuclear magnetic resonance spectroscopy (Section C.1): A powerful analytical tool that can help identify the carbon and hydrogen framework of an organic molecule.

Nucleophile (Sections 2.8, 7.6): An electron-rich compound, symbolized by $:Nu^-$, which donates a pair of electrons to an electron-deficient compound, forming a covalent bond. Lewis bases are nucleophiles.

Nucleophilic acyl substitution (Sections 17.2B, 20.1): Substitution of a leaving group by a nucleophile at a carbonyl carbon.

Nucleophilic addition (Section 17.2A): Addition of a nucleophile to the electrophilic carbon of a carbonyl group followed by protonation of the oxygen.

Nucleophilic aromatic substitution (Section 16.13): A substitution reaction of an aryl halide with a strong nucleophile.

Nucleophilicity (Section 7.8A): A measure of how readily an atom donates an electron pair to other atoms.

Nucleophilic substitution (Section 7.6): A reaction in which a nucleophile replaces the leaving group in a molecule.

Nucleoside (Section 26.13B): A biomolecule having a sugar and either a purine or pyrimidine base joined by an *N*-glycosidic linkage.

Nucleotide (Section 26.13B): A biomolecule having a sugar and either a purine or pyrimidine base joined by an *N*-glycosidic linkage, and a phosphate bonded to a hydroxy group of the sugar nucleus.

O

Observed rotation (Section 5.12A): The angle that a sample of an optically active compound rotates plane-polarized light. The angle is denoted by the symbol α and is measured in degrees (°).

Octet rule (Section 1.2): The general rule governing the bonding process for second-row elements. Through bonding, second-row elements attain a complete outer shell of eight valence electrons.

Oil (Sections 10.6B, 29.3): A triacylglycerol that is liquid at room temperature and composed of fatty acid side chains with a high degree of unsaturation.

Olefin (Section 10.1): An alkene; a compound possessing a carbon–carbon double bond.

Oligosaccharide (26.12D): A carbohydrate with a small number of monosaccharides —generally three to ten—joined together.

Optically active (Section 5.12A): Able to rotate the plane of plane-polarized light as it passes through a solution of a compound.

Optically inactive (Section 5.12A): Not able to rotate the plane of plane-polarized light as it passes through a solution of a compound.

Optical purity (Section 5.12D): A measurement of how much one enantiomer is present in excess of the racemic mixture. Optical purity is also called enantiomeric excess (*ee*); *ee* = % of one enantiomer – % of the other enantiomer.

Orbital (Section 1.1): A region of space around the nucleus of an atom that is high in electron density. There are four different kinds of orbitals, called *s, p, d*, and *f*.

Order of a rate equation (Section 6.9B): The sum of the exponents of the concentration terms in the rate equation of a reaction.

Organoborane (Section 10.16): A compound that contains a carbon–boron bond. Organoboranes have the general structure RBH_2, R_2BH, or R_3B.

Organocopper reagent (Section 17.9): An organometallic reagent having the general structure R_2CuLi. Organocopper reagents are also called organocuprates.

Organolithium reagent (Section 17.9): An organometallic reagent having the general structure RLi.

Organomagnesium reagent (Section 17.9): An organometallic reagent having the general structure RMgX. Organomagnesium reagents are also called Grignard reagents.

Organometallic reagent (Section 17.9): A reagent that contains a carbon atom bonded to a metal.

Organopalladium compound (Section 24.2): An organometallic compound that contains a carbon–palladium bond.

Organophosphorus reagent (Section 18.9A): A reagent that contains a carbon–phosphorus bond.

Ortho isomer (Section 15.3B): A 1,2-disubstituted benzene ring. Ortho substitution is abbreviated as *o*-.

Ortho, para director (Section 16.7): A substituent on a benzene ring that directs a new group to the ortho and para positions during electrophilic aromatic substitution.

Oxaphosphetane (Section 18.9B): An intermediate in the Wittig reaction consisting of a four-membered ring containing a phosphorus–oxygen bond.

Oxazaborolidine (Section 17.6A): A heterocycle possessing a boron, a nitrogen, and an oxygen. An oxazaborolidine can be used to form a chiral reducing agent.

Oxidation (Sections 4.14A, 12.1): A process that results in a loss of electrons. For organic compounds, oxidation results in an increase in the number of C–Z bonds or a decrease in the number of C–H bonds; Z = an element more electronegative than carbon.

Oxidative addition (Section 24.2A): The addition of a reagent to a metal, often increasing the number of groups around the metal by two.

Oxidative cleavage (Section 12.10): An oxidation reaction that breaks both the σ and π bonds of a multiple bond to form two oxidized products.

Oxime (Section 26.10A): A compound having the general structure $R_2C{=}NOH$.

Oxirane (Section 9.1): A cyclic ether having the oxygen atom as part of a three-membered ring. Oxiranes are also called epoxides.

Oxy-Cope rearrangement (Section 25.5): A [3,3] sigmatropic rearrangement of a 1,5-dien-3-ol to a δ,ε-unsaturated carbonyl compound.

Ozonolysis (Section 12.10): An oxidative cleavage reaction in which a multiple bond reacts with ozone (O_3) as the oxidant.

P

Para isomer (Section 15.3B): A 1,4-disubstituted benzene ring. Para substitution is abbreviated as *p*-.

Parent ion (Section A.1): The radical cation having the general structure $M^{+\cdot}$, formed by the removal of an electron from an organic molecule. The parent ion is also called the molecular ion.

Parent name (Section 4.4): The portion of the IUPAC name of an organic compound

that indicates the number of carbons in the longest continuous chain in the molecule.

Pentose (Section 26.2): A monosaccharide containing five carbons.

Peptide bond (Section 27.5): The amide bond in peptides and proteins.

Peptides (Sections 20.5B, 27.5): Low-molecular-weight polymers of less than 40 amino acids joined together by amide linkages.

Percent *s*-character (Section 1.11B): The fraction of a hybrid orbital due to the *s* orbital used to form it. As the percent *s*-character increases, a bond becomes shorter and stronger.

Percent transmittance (Section B.2): A measure of how much electromagnetic radiation passes through a sample of a compound and how much is absorbed.

Pericyclic reaction (Section 25.1): A concerted reaction that proceeds through a cyclic transition state.

Peroxide (Section 13.2): A reactive organic compound with the general structure ROOR. Peroxides are used as radical initiators by homolysis of the weak O–O bond.

Peroxyacid (Section 12.7): An oxidizing agent having the general structure RCO_3H.

Peroxy radical (Section 13.11): A radical having the general structure $ROO^{\cdot}$.

Petroleum (Section 4.7): A fossil fuel containing a complex mixture of compounds, primarily hydrocarbons with 1 to 40 carbon atoms.

Phenol (Sections 9.1, 13.12): A compound such as C_6H_5OH, which contains a hydroxy group bonded to a benzene ring.

Phenyl group (Section 15.3D): A group formed by removal of one hydrogen from benzene, abbreviated as $C_6H_5–$ or Ph–.

Pheromone (Section 4.1): A chemical substance used for communication in an animal or insect species.

Phosphate (Section 7.16): A PO_4^{3-} anion.

Phosphatidylcholine (Section 29.4A): A phosphoacylglycerol in which the phosphodiester alkyl group is $–CH_2CH_2N(CH_3)_3^+$. Phosphatidylcholines are also called lecithins.

Phosphatidylethanolamine (Section 29.4A): A phosphoacylglycerol in which the phosphodiester alkyl group is $–CH_2CH_2NH_3^+$. Phosphatidylethanolamines are also called cephalins.

Phosphoacylglycerols (Section 29.4A): A lipid having a glycerol backbone with two of the hydroxy groups esterified with fatty acids and the third hydroxy group as part of a phosphodiester.

Phosphodiester (Section 29.4): A functional group having the general formula $ROPO_2OR'$ formed by replacing two of the H atoms in phosphoric acid (H_3PO_4) with alkyl groups.

Phospholipid (Sections 3.7A, 29.4): A hydrolyzable lipid that contains a phosphorus atom.

Phosphonium salt (Section 18.9A): An organophosphorus reagent with a positively charged phosphorus and a suitable counterion; for example, $R_4P^+X^-$. Phosphonium salts are converted to ylides upon treatment with a strong base.

Phosphorane (Section 18.9A): A phosphorus ylide; for example, $Ph_3P{=}CR_2$.

Photon (Section B.1): A particle of electromagnetic radiation.

Pi (π) bond (Section 1.10B): A bond formed by side-by-side overlap of two *p* orbitals where electron density is not concentrated on the axis joining the two nuclei. Pi (π) bonds are generally weaker than σ bonds.

pK_a (Section 2.3): A logarithmic scale of acid strength. pK_a = –log K_a. The smaller the pK_a, the stronger the acid.

Plane-polarized light (Section 5.12A): Light that has an electric vector that oscillates in a single plane. Plane-polarized light, also called polarized light, arises from passing ordinary light through a polarizer.

Plane of symmetry (Section 5.3): A mirror plane that cuts a molecule in half, so that one half of the molecule is the mirror reflection of the other half.

Plasticizer (Section 28.7): A low-molecular-weight compound added to a polymer to give it flexibility.

β-Pleated sheet (Section 27.9B): A secondary structure of a protein formed when two or more peptide chains line up side by side.

Poisoned catalyst (Section 12.5B): A hydrogenation catalyst with reduced activity that allows selective reactions to occur. The Lindlar catalyst is a poisoned Pd catalyst that converts alkynes to cis alkenes.

Polar aprotic solvent (Section 7.8C): A polar solvent that is incapable of intermolecular hydrogen bonding because it does not contain an O–H or N–H bond.

Polar bond (Section 1.12): A covalent bond in which the electrons are unequally shared between the two atoms. Unequal sharing of electrons results from bonding between atoms of different electronegativity values, usually with a difference of ≥ 0.5 units.

Polarimeter (Section 5.12A): An instrument that measures the degree that a

compound rotates plane-polarized light.

Polarity (Section 1.12): A characteristic that results from a dipole. The polarity of a bond is indicated by an arrow with the head of the arrow pointing toward the negative end of the dipole and the tail with a perpendicular line through it at the positive end of the dipole. The polarity of a bond can also be indicated by the symbols δ+ and δ−.

Polarizability (Section 3.3B): A measure of how the electron cloud around an atom responds to changes in its electronic environment.

Polar molecule (Section 1.13): A molecule that has a net dipole. A polar molecule has either one polar bond or multiple polar bonds whose dipoles reinforce.

Polar protic solvent (Section 7.8C): A polar solvent that is capable of intermolecular hydrogen bonding because it contains an O–H or N–H bond.

Polyamide (Sections 20.15A, 28.6A): A step-growth polymer that contains many amide bonds. Nylon 6,6 and nylon 6 are polyamides.

Polycarbonate (Section 28.6C): A step-growth polymer that contains many –OC(=O)O– bonds in its backbone, often formed by reaction of $Cl_2C{=}O$ with a diol.

Polycyclic aromatic hydrocarbon (Sections 9.18, 15.5): An aromatic hydrocarbon containing two or more benzene rings that share carbon–carbon bonds. Polycyclic aromatic hydrocarbons are abbreviated as PAHs.

Polyene (Section 14.7): A compound that contains three or more double bonds.

Polyester (Sections 20.15B, 28.6B): A step-growth polymer consisting of many ester bonds between diols and dicarboxylic acids.

Polyether (Sections 9.5B, 28.3): A compound that contains two or more ether linkages.

Polymer (Sections 5.1, 13.14): A large molecule composed of smaller monomer units covalently bonded to each other in a repeating pattern.

Polymerization (Section 13.14A): The chemical process that joins together monomers to make polymers.

Polysaccharide (Section 26.12): A carbohydrate containing three or more monosaccharide units joined together by glycosidic linkages.

Polyurethane (Section 28.6C): A step-growth polymer that contains many –NHC(=O)O– bonds in its backbone, formed by reaction of a diisocyanate and a diol.

Porphyrin (Section 27.10C): A nitrogen-containing heterocycle that can complex metal ions.

Primary (1°) alcohol (Section 3.2): An alcohol having the general structure RCH_2OH.

Primary (1°) alkyl halide (Section 3.2): An alkyl halide having the general structure RCH_2X.

Primary (1°) amide (Section 3.2): An amide having the general structure $RCONH_2$.

Primary (1°) amine (Section 3.2): An amine having the general structure RNH_2.

Primary (1°) carbocation (Section 7.13): A carbocation having the general structure RCH_2^+.

Primary (1°) carbon (Section 3.2): A carbon atom that is bonded to one other carbon atom.

Primary (1°) hydrogen (Section 3.2): A hydrogen that is bonded to a 1° carbon.

Primary protein structure (Section 27.9A): The particular sequence of amino acids joined together by peptide bonds.

Primary (1°) radical (Section 13.1): A radical having the general structure $RCH_2\cdot$.

Propagation (Section 13.4A): The middle part of a chain mechanism in which one reactive particle is consumed and another is generated. Propagation repeats until a termination step occurs.

Prostaglandin (Section 4.15): A class of lipids containing 20 carbons, a five-membered ring, and a CO_2H group. Prostaglandins possess a wide range of biological activities.

Prosthetic group (Section 27.10C): The non-protein unit of a conjugated protein.

Protecting group (Section 17.12): A blocking group that renders a reactive functional group unreactive, so that it does not interfere with another reaction.

Protection (Section 17.12): The reaction that blocks a reactive functional group with a protecting group.

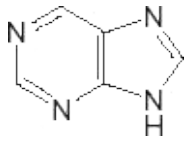
Proteins (Sections 20.5B, 27.5): High-molecular-weight polymers of 40 or more amino acids joined together by amide linkages.

Proton (Section 2.1): A positively charged hydrogen ion (H^+).

Proton NMR spectroscopy (Section C.1): A form of nuclear magnetic resonance spectroscopy used to determine the number and type of hydrogen atoms in a molecule.

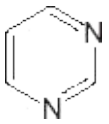
Proton transfer reaction (Section 2.2): A Brønsted–Lowry acid–base reaction; a reaction that results in the transfer of a proton from an acid to a base.

Purine (Sections 23.3, 26.13B): A bicyclic aromatic heterocycle having two nitrogens in each of the rings.



Pyranose (Section 26.6): A cyclic six-membered ring of a monosaccharide containing an oxygen atom.

Pyrimidine (Sections 23.3, 26.13B): A six-membered aromatic heterocycle having two nitrogens in the ring.



Q

Quantum (Section B.1): The discrete amount of energy associated with a particle of electromagnetic radiation (i.e., a photon).

Quartet (Section C.6C): An NMR signal that is split into four peaks having a relative area of 1:3:3:1, caused by three nearby nonequivalent protons.

Quaternary (4°) carbon (Section 3.2): A carbon atom that is bonded to four other carbon atoms.

Quaternary protein structure (Section 27.9C): The shape adopted when two or more folded polypeptide chains aggregate into one protein complex.

Quintet (Section C.6C): An NMR signal that is split into five peaks caused by four nearby nonequivalent protons.

R

Racemic mixture (Section 5.12B): An equal mixture of two enantiomers. A racemic mixture, also called a racemate, is optically inactive.

Racemization (Section 7.12C): The formation of equal amounts of two enantiomers from an enantiomerically pure starting material.

Radical (Sections 6.3B, 13.1): A reactive intermediate with a single unpaired electron, formed by homolysis of a covalent bond.

Radical anion (Section 12.5C): A reactive intermediate containing both a negative charge and an unpaired electron.

Radical cation (Section A.1): A species with an unpaired electron and a positive charge, formed in a mass spectrometer by the bombardment of a molecule with an electron beam.

Radical inhibitor (Section 13.2): A compound that prevents radical reactions from occurring. Radical inhibitors are also called radical scavengers.

Radical initiator (Section 13.2): A compound that contains an especially weak bond that serves as a source of radicals.

Radical polymerization (Section 13.14B): A radical chain reaction involving the polymerization of alkene monomers by adding a radical to a π bond.

Radical scavenger (Section 13.2): A compound that prevents radical reactions from occurring. Radical scavengers are also called radical inhibitors.

Rate constant (Section 6.9B): A constant that is a fundamental characteristic of a reaction. The rate constant, symbolized by *k*, is a complex mathematical term that takes into account the dependence of a reaction rate on temperature and the energy of activation.

Rate-determining step (Section 6.8): In a multistep reaction mechanism, the step with the highest-energy transition state.

Rate equation (Section 6.9B): An equation that shows the relationship between the rate of a reaction and the concentration of the reactants. The rate equation depends on the mechanism of the reaction and is also called the rate law.

Reaction coordinate (Section 6.7): The *x* axis in an energy diagram that represents the progress of a reaction as it proceeds from reactant to product.

Reaction mechanism (Section 6.3): A detailed description of how bonds are broken and formed as a starting material is converted to a product.

Reactive intermediate (Sections 6.3, 10.18): A high-energy unstable intermediate formed during the conversion of a stable starting material to a stable product.

Reciprocal centimeter (Section B.2): The unit for wavenumber, which is used to report frequency in IR spectroscopy.

Reducing sugar (Section 26.9B): A carbohydrate that can be oxidized by Tollens, Benedict's, or Fehling's reagent.

Reduction (Sections 4.14A, 12.1): A process that results in the gain of electrons. For organic compounds, reduction results in a decrease in the number of C–Z bonds or an increase in the number of C–H bonds; Z = an element more electronegative than carbon.

Reductive amination (Section 23.6C): A two-step method that converts aldehydes and ketones into amines.

Reductive elimination (Section 24.2A): The elimination of two groups that surround a metal, often forming new carbon–hydrogen or carbon–carbon bonds.

Regioselective reaction (Section 8.5): A reaction that yields predominantly or exclusively one constitutional isomer when more than one constitutional isomer is possible.

Resolution (Section 27.3): The separation of a racemic mixture into its component

enantiomers.

Resonance (Section C.1A): In NMR spectroscopy, when an atomic nucleus absorbs RF radiation and spin flips to a higher-energy state.

Resonance hybrid (Sections 1.6C, 14.4): A structure that is a weighted composite of all possible resonance structures. The resonance hybrid shows the delocalization of electron density due to the different locations of electrons in individual resonance structures.

Resonance structures (Sections 1.6, 14.2): Two or more structures of a molecule that differ in the placement of π bonds and nonbonded electrons. The placement of atoms and σ bonds stays the same.

Retention of configuration (Section 7.11C): The same relative stereochemistry of a stereogenic center in the reactant and the product of a chemical reaction.

Retention time (Section A.4B): The length of time required for a component of a mixture to travel through a chromatography column.

Retro Diels–Alder reaction (Section 14.14B): The reverse of a Diels–Alder reaction in which a cyclohexene is cleaved to give a 1,3-diene and an alkene.

Retrosynthetic analysis (Section 10.18): Working backwards from a product to determine the starting material from which it is made.

RF radiation (Section C.1A): Radiation in the radiofrequency region of the electromagnetic spectrum, characterized by long wavelength and low frequency and energy.

Ribonucleoside (Section 26.13B): An *N*-glycoside formed by the reaction of D-ribose with certain amine heterocycles.

Ribonucleotide (Section 26.13B): An RNA building block having a ribose and either a purine or pyrimidine base joined by an *N*-glycosidic linkage, and a phosphate bonded to a hydroxy group of the sugar nucleus.

Ring-closing metathesis (Section 24.6): An intramolecular olefin metathesis reaction using a diene starting material, which results in ring closure.

Ring current (Section C.4): A circulation of π electrons in an aromatic ring caused by the presence of an external magnetic field.

Ring-flipping (Section 4.12B): A stepwise process in which one chair conformation of cyclohexane interconverts with a second chair conformation.

Ring-opening metathesis polymerization (Problem 24.38): An olefin metathesis reaction that forms a high-molecular-weight polymer from certain cyclic alkenes.

Robinson annulation (Section 22.9): A ring-forming reaction that combines a Michael reaction with an intramolecular aldol reaction to form a cyclohex-2-

enone.

R,S System of nomenclature (Section 5.6): A system of nomenclature that distinguishes the stereochemistry at a tetrahedral stereogenic center by assigning a priority to each group connected to the stereogenic center. *R* indicates a clockwise orientation of the three highest-priority groups and *S* indicates a counterclockwise orientation of the three highest groups. The system is also called the Cahn–Ingold–Prelog system.

Rule of endo addition (Section 14.13D): The rule that the endo product is preferred in a Diels–Alder reaction.

S

Sandmeyer reaction (Section 23.13A): A reaction between an aryl diazonium salt and a copper(I) halide to form an aryl halide (C_6H_5Cl or C_6H_5Br).

Saponification (Section 20.10B): Basic hydrolysis of an ester to form an alcohol and a carboxylate anion.

Saturated fatty acid (Section 10.6A): A fatty acid having no carbon–carbon double bonds in its long hydrocarbon chain.

Saturated hydrocarbon (Section 4.1): A compound that contains only C–C and C–H σ bonds and no rings, thus having the maximum number of hydrogen atoms per carbon.

Schiff base (Section 20.10A): A compound having the general structure $R_2C{=}NR'$. A Schiff base is also called an imine.

Secondary (2°) alcohol (Section 3.2): An alcohol having the general structure R_2CHOH.

Secondary (2°) alkyl halide (Section 3.2): An alkyl halide having the general structure R_2CHX.

Secondary (2°) amide (Section 3.2): An amide having the general structure RCONHR′.

Secondary (2°) amine (Section 3.2): An amine having the general structure R_2NH.

Secondary (2°) carbocation (Section 7.13): A carbocation having the general structure R_2CH^+.

Secondary (2°) carbon (Section 3.2): A carbon atom that is bonded to two other carbon atoms.

Secondary (2°) hydrogen (Section 3.2): A hydrogen that is attached to a 2° carbon.

Secondary protein structure (Section 27.9B): The three-dimensional conformations of localized regions of a protein.

Secondary (2°) radical (Section 13.1): A radical having the general structure $R_2CH\cdot$.

Second-order rate equation (Sections 6.9B, 7.10): A rate equation in which the reaction rate depends on the concentration of two reactants.

Separatory funnel (Section 19.10): An item of laboratory glassware used for extractions.

Septet (Section C.6C): An NMR signal that is split into seven peaks caused by six nearby nonequivalent protons.

Sesquiterpene (Section 29.7A): A terpene that contains 15 carbons and three isoprene units. A sesquiterpenoid also contains at least one oxygen atom.

Sesterterpene (Section 29.7A): A terpene that contains 25 carbons and five isoprene units. A sesterterpenoid also contains at least one oxygen atom.

Sextet (Section C.6C): An NMR signal that is split into six peaks caused by five nearby nonequivalent protons.

Sharpless asymmetric epoxidation (Section 12.15): An enantioselective oxidation reaction that converts the double bond of an allylic alcohol to a predictable enantiomerically enriched epoxide.

Sharpless reagent (Section 12.15): The reagent used in the Sharpless asymmetric epoxidation. The Sharpless reagent consists of *tert*-butyl hydroperoxide, a titanium catalyst, and one enantiomer of diethyl tartrate.

Shielding effects (Section C.3A): An effect in NMR caused by small induced magnetic fields of electrons in the opposite direction to the applied magnetic field. Shielding decreases the strength of the magnetic field felt by the nucleus and shifts an absorption upfield.

1,2-Shift (Section 9.9): Rearrangement of a less stable carbocation to a more stable carbocation by the shift of a hydrogen atom or an alkyl group from one carbon atom to an adjacent carbon atom.

Sigma (σ) bond (Section 1.9A): A cylindrically symmetrical bond that concentrates the electron density on the axis that joins two nuclei. All single bonds are σ bonds.

Sigmatropic rearrangement (Section 25.1): A pericyclic reaction in which a σ bond is broken in the reactant, the π bonds rearrange, and a σ bond is formed in the product.

Silyl ether (Section 17.12): A common protecting group for an alcohol in which the O–H bond is replaced by an O–Si bond.

Simmons–Smith reaction (Section 24.5): Reaction of an alkene with CH_2I_2 and Zn(Cu) to form a cyclopropane.

Singlet (Section C.6A): An NMR signal that occurs as a single peak.

Skeletal structure (Section 1.8B): A shorthand representation of the structure of an organic compound in which carbon atoms and the hydrogen atoms bonded to them are omitted. All heteroatoms and the hydrogens bonded to them are drawn in. Carbon atoms are assumed to be at the junction of any two lines or at the end of a line.

S_N1 mechanism (Sections 7.10, 7.12): A nucleophilic substitution mechanism that goes by a two-step process involving a carbocation intermediate. S_N1 is an abbreviation for "Substitution Nucleophilic Unimolecular."

S_N2 mechanism (Sections 7.10, 7.11): A nucleophilic substitution mechanism that goes by a one-step concerted process, where both reactants are involved in the transition state. S_N2 is an abbreviation for "Substitution Nucleophilic Bimolecular."

Soap (Sections 3.6, 20.11B): The carboxylate salts of long-chain fatty acids prepared by the basic hydrolysis or saponification of a triacylglycerol.

Solubility (Section 3.4C): A measure of the extent to which a compound dissolves in a liquid.

Solute (Section 3.4C): The compound that is dissolved in a liquid solvent.

Solvent (Section 3.4C): The liquid component into which the solute is dissolved.

Specific rotation (Section 5.12C): A standardized physical constant for the amount that a chiral compound rotates plane-polarized light. Specific rotation is denoted by the symbol [α] and defined using a specific sample tube length (l in dm), concentration (c in g/mL), temperature (25 °C), and wavelength (589 nm). $[\alpha] = \alpha/(l \times c)$

Spectator ion (Section 2.1): An ion that does not take part in a reaction and is opposite in charge to the ion that does take part in a reaction. A spectator ion is also called a counterion.

Spectroscopy (Section A.1): An analytical method using the interaction of electromagnetic radiation with molecules to determine molecular structure.

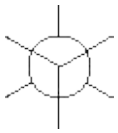
Sphingomyelin (Section 29.4B): A hydrolyzable phospholipid derived from sphingosine.

Spin flip (Section C.1A): In NMR spectroscopy, when an atomic nucleus absorbs RF radiation and its magnetic field flips relative to the external magnetic field.

Spin–spin splitting (Section C.6): Splitting of an NMR signal into peaks caused by nonequivalent protons on the same carbon or adjacent carbons.

Spiro ring system (Appendix D): A compound having two rings that share a single carbon atom.

Staggered conformation (Section 4.9): A conformation of a molecule in which the bonds on one carbon bisect the R–C–R bond angle on the adjacent carbon.



Step-growth polymer (Sections 20.15A, 28.1): A polymer formed when monomers containing two functional groups come together with loss of a small molecule such as water or HCl. Step-growth polymers are also called condensation polymers.

Stereochemistry (Sections 4.9, 5.1): The three-dimensional structure of molecules.

Stereogenic center (Section 5.3): A site in a molecule at which the interchange of two groups forms a stereoisomer. A carbon bonded to four different groups is a tetrahedral stereogenic center. A tetrahedral stereogenic center is also called a chirality center, a chiral center, and an asymmetric center.

Stereoisomers (Sections 4.13B, 5.1): Two isomers that differ only in the way the atoms are oriented in space.

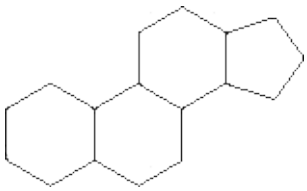
Stereoselective reaction (Section 8.5): A reaction that yields predominantly or exclusively one stereoisomer when two or more stereoisomers are possible.

Stereospecific reaction (Section 10.14): A reaction in which each of two stereoisomers of a starting material yields a particular stereoisomer of a product.

Steric hindrance (Section 7.8B): A decrease in reactivity resulting from the presence of bulky groups at the site of a reaction.

Steric strain (Section 4.10): An increase in energy resulting when atoms in a molecule are forced too close to one another.

Steroid (Sections 14.14C, 29.8): A tetracyclic lipid composed of three six-membered rings and one five-membered ring.



Straight-chain alkane (Section 4.1A): An acyclic alkane that has all of its carbons in a row. Straight-chain alkanes are also called normal alkanes.

Strecker amino acid synthesis (Section 27.2C): A reaction that converts an aldehyde into an α-amino acid by way of an α-amino nitrile.

Structural isomers (Sections 4.1A, 5.2): Two compounds that have the same molecular formula but differ in the way the atoms are connected to each other. Structural isomers are also called constitutional isomers.

Substituent (Section 4.4): A group or branch attached to the longest continuous chain of carbons in an organic molecule.

Substitution reaction (Section 6.2A): A reaction in which an atom or a group of atoms is replaced by another atom or group of atoms. Substitution reactions involve σ bonds: one σ bond breaks and another is formed at the same atom.

Substrate (Section 6.11): An organic molecule that is transformed by the action of an enzyme.

Sulfide (Section 9.15): A compound having the general structure RSR′.

Sulfonation (Section 16.4): An electrophilic aromatic substitution reaction in which benzene reacts with $^{+}SO_3H$ to give a benzenesulfonic acid, $C_6H_5SO_3H$.

Suprafacial reaction (Section 25.4): A pericyclic reaction that occurs on the same side of the two ends of the π electron system.

Suzuki reaction (Section 24.2): The palladium-catalyzed coupling of an organic halide (R′X) with an organoborane (RBY_2) to form a product R–R′.

Symmetrical anhydride (Section 20.1): An anhydride that has two identical alkyl groups bonded to the carbonyl carbon atoms.

Symmetrical ether (Section 9.1): An ether with two identical alkyl groups bonded to the oxygen.

Syn addition (Section 10.8): An addition reaction in which two parts of a reagent are added from the same side of a double bond.

Syn dihydroxylation (Section 12.9B): The addition of two hydroxy groups to the same face of a double bond.

Syndiotactic polymer (Section 28.4): A polymer having the substituents alternating from one side of the backbone of an elongated polymer chain to the other.

Syn periplanar (Section 8.8): In an elimination reaction, a geometry in which the β hydrogen and the leaving group are on the same side of the molecule.

Systematic name (Section 4.3): The name of a molecule indicating the compound's chemical structure. The systematic name is also called the IUPAC name.

T

Target compound (Section 11.12): The final product of a synthetic scheme.

Tautomerization (Sections 11.9, 21.2A): The process of converting one tautomer to another.

Tautomers (Section 11.9): Constitutional isomers that are in equilibrium and differ in the location of a double bond and a hydrogen atom.

Terminal alkene (Section 10.1): An alkene that has the double bond at the end of the

carbon chain.

Terminal alkyne (Section 11.1): An alkyne that has the triple bond at the end of the carbon chain.

C-Terminal amino acid (Section 27.5A): The amino acid at the end of a peptide chain with a free carboxy group.

N-Terminal amino acid (Section 27.5A): The amino acid at the end of a peptide chain with a free amino group.

Termination (Section 13.4A): The final step of a chain reaction. In a radical chain mechanism, two radicals combine to form a stable bond.

Terpene (Section 29.7): A hydrocarbon composed of repeating five-carbon isoprene units.

Terpenoid (Section 29.7): A lipid that contains isoprene units as well as at least one oxygen heteroatom.

Tertiary (3°) alcohol (Section 3.2): An alcohol having the general structure R_3COH.

Tertiary (3°) alkyl halide (Section 3.2): An alkyl halide having the general structure R_3CX.

Tertiary (3°) amide (Section 3.2): An amide having the general structure $RCONR'_2$.

Tertiary (3°) amine (Section 3.2): An amine having the general structure R_3N.

Tertiary (3°) carbocation (Section 7.13): A carbocation having the general structure R_3C^+.

Tertiary (3°) carbon (Section 3.2): A carbon atom that is bonded to three other carbon atoms.

Tertiary (3°) hydrogen (Section 3.2): A hydrogen that is attached to a 3° carbon.

Tertiary protein structure (Section 27.9C): The three-dimensional shape adopted by an entire peptide chain.

Tertiary (3°) radical (Section 13.1): A radical having the general structure $R_3C\cdot$.

Tesla (Section C.1A): A unit used to measure the strength of a magnetic field. Tesla is denoted with the symbol "T."

Tetramethylsilane (Section C.1B): An internal standard used as a reference in NMR spectroscopy. The tetramethylsilane (TMS) reference peak occurs at 0 ppm on the δ scale.

Tetrasubstituted alkene (Section 8.2A): An alkene that has four alkyl groups and no hydrogens bonded to the carbons of the double bond ($R_2C{=}CR_2$).

Tetraterpene (Section 29.7A): A terpene that contains 40 carbons and eight isoprene units. A tetraterpenoid contains at least one oxygen atom as well.

Tetrose (Section 26.2): A monosaccharide containing four carbons.

Thermodynamic enolate (Section 21.4): The enolate that is lower in energy—generally the more substituted enolate.

Thermodynamic product (Section 14.11): In a reaction that can give more than one product, the product that predominates at equilibrium.

Thermodynamics (Section 6.5): A study of the energy and equilibrium of a chemical reaction.

Thermoplastics (Section 28.7): Polymers that can be melted and then molded into shapes that are retained when the polymer is cooled.

Thermosetting polymer (Section 28.7): A complex network of cross-linked polymer chains that cannot be re-melted to form a liquid phase.

Thioester (Section 20.16): A compound with the general structure RCOSR′.

Thiol (Section 9.15): A compound having the general structure RSH.

Tollens reagent (Sections 17.8, 26.9B): A reagent that oxidizes aldehydes, and consists of silver(I) oxide in aqueous ammonium hydroxide. A Tollens test is used to detect the presence of an aldehyde.

p-Toluenesulfonate (Section 9.13): A very good leaving group having the general structure $CH_3C_6H_4SO_3^-$ and abbreviated as TsO^-. Compounds containing a *p*-toluenesulfonate leaving group are called alkyl tosylates and are abbreviated ROTs.

Torsional energy (Section 4.9): The energy difference between the staggered and eclipsed conformations of a molecule.

Torsional strain (Section 4.9): An increase in the energy of a molecule caused by eclipsing interactions between groups attached to adjacent carbon atoms.

Tosylate (Section 9.13): A very good leaving group having the general structure $CH_3C_6H_4SO_3^-$, and abbreviated as TsO^-.

s-Trans (Sections 14.6, 27.5B): The conformation of a 1,3-diene that has the two double bonds on opposite sides of the single bond that joins them.

Trans diaxial (Section 8.8B): In an elimination reaction of a cyclohexane, a geometry in which the β hydrogen and the leaving group are trans with both in the axial position.

Trans isomer (Sections 4.13B, 8.3B): An isomer of a ring or double bond that has two groups on opposite sides of the ring or double bond.

Transition state (Section 6.7): An unstable energy maximum as a chemical reaction proceeds from reactants to products. The transition state is at the top of an energy "hill" and can never be isolated.

Triacylglycerol (Sections 10.6, 20.11A, 29.3): A lipid consisting of the triester of

glycerol with three long-chain fatty acids. Triacylglycerols are the lipids that comprise animal fats and vegetable oils. Triacylglycerols are also called triglycerides.

Triose (Section 26.2): A monosaccharide containing three carbons.

Triphosphate (Section 7.16): A good leaving group used in biological systems. Triphosphate ($P_3O_{10}^{5-}$) is abbreviated as PPP_i.

Triplet (Section C.6): An NMR signal that is split into three peaks having a relative area of 1:2:1, caused by two nearby nonequivalent protons.

Trisubstituted alkene (Section 8.2A): An alkene that has three alkyl groups and one hydrogen bonded to the carbons of the double bond ($R_2C{=}CHR$).

Triterpene (Section 29.7A): A terpene that contains 30 carbons and six isoprene units. A triterpenoid contains at least one oxygen atom as well.

U

Ultraviolet (UV) light (Section 14.15): Electromagnetic radiation with a wavelength from 200 to 400 nm.

Ultraviolet (UV) spectrum (Section 14.15): A plot of the absorbance of ultraviolet light versus wavelength, often recorded for conjugated systems.

Unimolecular reaction (Sections 6.9B, 7.10, 7.12A): A reaction that has only one reactant involved in the rate-determining step, so the concentration of only one reactant appears in the rate equation.

α,β-Unsaturated carbonyl compound (Section 17.15): A conjugated compound containing a carbonyl group and a carbon–carbon double bond separated by a single σ bond.

Unsaturated fatty acid (Section 10.6A): A fatty acid having one or more carbon–carbon double bonds in its hydrocarbon chain. In natural fatty acids, the double bonds generally have the *Z* configuration.

Unsaturated hydrocarbon (Section 10.2): A hydrocarbon that has fewer than the maximum number of hydrogen atoms per carbon atom. Hydrocarbons with π bonds or rings are unsaturated.

Unsymmetrical ether (Section 9.1): An ether in which the two alkyl groups bonded to the oxygen are different.

Upfield shift (Section C.1B): In an NMR spectrum, a term used to describe the relative location of an absorption signal. An upfield shift means a signal is shifted to the right in the spectrum to lower chemical shift.

Urethane (Section 28.6C): A compound that contains a carbonyl group bonded to

both an OR group and an NHR (or NR_2) group. A urethane is also called a carbamate.

V

Valence bond theory (Section 15.9A): A theory that describes covalent bonding as the overlap of two atomic orbitals with the electron pair in the resulting bond being shared by both atoms.

Valence electrons (Section 1.1): The electrons in the outermost shell of orbitals. Valence electrons determine the properties of a given element. Valence electrons are loosely held and participate in chemical reactions.

Van der Waals forces (Section 3.3B): Very weak intermolecular interactions caused by momentary changes in electron density in molecules. The changes in electron density cause temporary dipoles, which are attracted to temporary dipoles in adjacent molecules. Van der Waals forces are also called London forces.

Vicinal dihalide (Section 8.10): A compound that has two halogen atoms on adjacent carbon atoms.

Vinyl group (Section 10.3C): An alkene substituent having the structure $-CH{=}CH_2$.

Vinyl halide (Section 7.1): A molecule containing a halogen atom bonded to the sp^2 hybridized carbon of a carbon–carbon double bond.

Vitamins (Sections 3.5, 29.5): Organic compounds needed in small amounts by biological systems for normal cell function.

VSEPR theory (Section 1.7B): Valence shell electron pair repulsion theory. A theory that determines the three-dimensional shape of a molecule by the number of groups surrounding a central atom. The most stable arrangement keeps the groups as far away from each other as possible.

W

Walden inversion (Section 7.11C): The inversion of a stereogenic center involved in an S_N2 reaction.

Wavelength (Section B.1): The distance from one point of a wave to the same point on the adjacent wave. Wavelength is abbreviated with the Greek letter lambda (λ).

Wavenumber (Section B.2): A unit for the frequency of electromagnetic radiation that is inversely proportional to wavelength. Wave-number, reported in reciprocal centimeters (cm^{-1}), is used for frequency in IR spectroscopy.

Wax (Sections 4.15, 29.2): A hydrolyzable lipid consisting of an ester formed from a high-molecular-weight alcohol and a fatty acid.

Williamson ether synthesis (Section 9.6): A method for preparing ethers by reacting an alkoxide (RO^-) with a methyl or primary alkyl halide.

Wittig reaction (Section 18.9): A reaction of a carbonyl group and an organophosphorus reagent that forms an alkene.

Wittig reagent (Section 18.9A): An organophosphorus reagent having the general structure $Ph_3P{=}CR_2$.

Wohl degradation (Section 26.10A): A reaction that shortens the carbon chain of an aldose by removing one carbon from the aldehyde end.

Wolff–Kishner reduction (Section 16.15B): A method to reduce aryl ketones to alkyl benzenes using hydrazine (NH_2NH_2) and strong base (KOH).

Woodward–Hoffmann rules (Section 25.3): A set of rules based on orbital symmetry used to explain the stereochemical course of pericyclic reactions.

Y

Ylide (Section 18.9A): A chemical species that contains two oppositely charged atoms bonded to each other, and both atoms have octets of electrons.

Z

Zaitsev rule (Section 8.5): In a β elimination reaction, a rule that states that the major product is the alkene with the most substituted double bond.

Ziegler–Natta catalysts (Section 28.4): Polymerization catalysts prepared from an organoaluminum compound and a Lewis acid such as $TiCl_4$, which afford polymer chains without significant branching and with controlled stereochemistry.

Zwitterion (Sections 19.11B, 27.1B): A neutral compound that contains both a positive and negative charge.

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List of Applications

Applications make any subject more relevant and interesting—for nonmajors and majors alike. The following is a list of the biological, medicinal, and environmental applications that have been integrated throughout *Organic Chemistry*. Each chapter opener showcases an interesting and current application relating to the chapter's topic. (Code: G = general; M = medicinal; B = biological; E = environmental)

Prologue

M	Oral contraceptives, antibiotics, plastic syringes, and synthetic heart valves
G	Methane, the main component of natural gas
G	Ethanol, the alcohol in beverages
E	Trichlorofluoromethane, a CFC responsible for destroying the stratospheric ozone layer
M	Amoxicillin, a widely used antibiotic
M	Fluoxetine, the antidepressant Prozac
M	AZT, a drug used to treat HIV
M	Capsaicin, a compound found in topical pain relief creams
E	DDT, a nonspecific pesticide that persists in the environment
M	Marine natural products

Chapter 1 Structure and Bonding

M	Oxybenzone, a component of sunscreens (Chapter opener and Section 1.14)
M	Alendronic acid (Fosamax), a drug used to prevent osteoporosis (Section 1.5)

B	Cicutoxin, a convulsant toxic to livestock and humans (Section 1.7, Problem 1.20)
G	Vanillin, the principal component in the extract of the vanilla bean (Section 1.8B)
M	Structures of active ingredients in common sunscreens (Section 1.8B)
M	Chloroquine (antimalarial drug) and L-dopa (for Parkinson's disease) (Section 1.8B, Problem 1.25)
G	Ethane, a component of natural gas (Section 1.10A)
G	Ethylene, a hydrocarbon used to make the plastic polyethylene (Section 1.10B)
G	Acetylene, a gas used in welding torches (Section 1.10C)
G	Cucumber aldehyde, a compound with the odor of freshly cut cucumbers (Section 1.10C)
G	Santalbic acid, a fatty acid used in cosmetics (Section 1.11B, Problem 1.34)
M	Sinemet, a drug used to treat Parkinson's disease that combines L-dopa and carbidopa (Section 1.14)
B	Vitamin B_6 (Section 1.14)
G, M, B	End-of-chapter problems: 1.40, 1.41, 1.45, 1.46, 1.62, 1.63, 1.64, 1.72, 1.75, 1.77, 1.79, 1.80, and 1.84

Chapter 2 Acids and Bases

G	Quinic acid, which contributes to the acidity of coffee (Chapter opener and Section 2.5)
M	The acid–base chemistry of morphine (Section 2.1)
M	The nasal decongestant pseudoephedrine (Section 2.5, Problem 2.17)
M	Glycolic acid, an α-hydroxy acid used in skin care products (Section 2.5, Problem 2.20)
B, M	THC (active component of marijuana) and ketoprofen (anti-inflammatory agent) (Section 2.5, Problem 2.27)
E	Sulfuric acid, a major contributor to acid rain (Section 2.6)
M	Aspirin, a common analgesic and antipyretic (Section 2.7)

M	Salicin, an analgesic found in willow bark
M, B	End-of-chapter problems: 2.36, 2.37, 2.59, 2.61, 2.63, 2.64, 2.66, 2.75, 2.76, 2.80, and 2.82

Chapter 3 Introduction to Organic Molecules and Functional Groups

B	Vitamin C, a water-soluble vitamin that is important in the formation of collagen (Chapter opener and Section 3.5B)
G	Polyethylene, a plastic used in milk containers, sandwich bags, and plastic wrapping (Section 3.2A)
B	Bilobalide, a compound isolated from the *Ginkgo biloba* extracts used in Chinese medicine (Section 3.2A, Problem 3.3)
M	The local anesthetic chloroethane (Section 3.2B)
E	Hemibrevetoxin B, a neurotoxin produced by algal blooms ("red tides") (Section 3.2B)
M	Diethyl ether, the first common general anesthetic (Section 3.2B)
M	Dexamethasone, a synthetic steroid (Section 3.2B, Problem 3.5)
B	Adrenaline (hormone), dopamine (neurotransmitter), and retronecine (natural product) (Section 3.2B, Problem 3.6)
M	Atenolol, a β blocker used to treat high blood pressure, and donepezil, used to treat Alzheimer's disease (Section 3.2C)

M	Dolastatin, an anticancer compound isolated from the seahare *Dolabella auricularia* (Section 3.2C, Problem 3.8)
M	Tamiflu, an antiviral drug used to treat influenza (Section 3.2C, Problem 3.9)
B	Leukotriene C_4, which contributes to the inflammation associated with asthma (Section 3.2C, Problem 3.11)
G	How geckos use van der Waals forces to stick to walls (Section 3.3B)
B, M	Meperidine (the narcotic Demerol) and aspirin (Section 3.4C)
B	Norethindrone, an oral contraceptive, and arachidonic acid, a fatty acid (Section 3.4C, Problem 3.18)
G	MTBE, a high-octane additive in unleaded gasoline, and 4,4′-dichlorobiphenyl, a PCB (Section 3.4C)

B	Predicting the water solubility of geranyl acetate, citric acid, and tryptophan (Section 3.4C)
B	Predicting the water solubility of eicosapentaenoic acid, cinnamaldehyde, and guanosine (Section 3.4C, Problem 3.20)
B	Vitamin A (retinol), a fat-soluble vitamin found in the vision receptors of the eyes (Section 3.5A)
B	β-Carotene, a precursor to vitamin A (Section 3.5A)
B	Vitamin B_3 and vitamin K_1 (Section 3.5B, Problem 3.21)
B	Avocados as a source of pantothenic acid, vitamin B_5 (Section 3.5B, Problem 3.22)
G	How soap works (Section 3.6)
B	The cell membrane (Section 3.7)
B	The solubilities of nicotine, caffeine, heroin, and sevoflurane (a general anesthetic) (Section 3.7A)
M	Morphine and heroin (Section 3.7A, Problem 3.25)
M	The antibiotics nonactin and valinomycin (Section 3.7B)
B	Biomolecules, such as glucose, oleic acid, alanine, and dAMP (Section 3.9)
B	The artificial sweetener aspartame (Section 3.9, Problem 3.30)
B	Hydrogen bonding in DNA (Section 3.9)
B, M	End-of-chapter problems: 3.31, 3.32, 3.34, 3.36, 3.40, 3.41, 3.45, 3.50, 3.51–3.56, 3.59–3.64, and 3.66

Chapter 4 Alkanes

E	Oil slicks that result from crude petroleum being spilled into the ocean from oil tankers or oil wells (Chapter opener and Section 4.8A)
B	The cockroach pheromone undecane (Section 4.1)
B	Cyclohexane, one component of mangoes (Section 4.1)
B	Long-chain alkanes in olives and olive leaves (Section 4.1, Problem 4.1)
B	Allicin, a compound responsible for the odor of garlic (Section 4.3)
M	Systematic names, generic names, and trade names in over-the-counter drugs like Motrin (Section 4.3)

G	Fossil fuels such as natural gas and petroleum (Section 4.7)
E	The combustion of alkanes and how it contributes to global warming (Section 4.14B)
B	Lipids such as fat-soluble vitamins, phospholipids, waxes, prostaglandins, and steroids (Section 4.15)
B	The solubility of beeswax (Section 4.15, Problem 4.33)
B	End-of-chapter problems: 4.59, 4.69, 4.71, and 4.72

Chapter 5 Stereochemistry

M, B	Paclitaxel (Taxol), a drug used to treat ovarian, breast, and other cancers (Chapter opener)
B	How differences in the three-dimensional structure of starch and cellulose affect their shape and function (Section 5.1)
B	Naturally occurring objects that possess handedness, such as shells (Section 5.3 and Problem 5.5)
M, B	Identifying stereogenic centers in Darvon (an analgesic), ephedrine (a decongestant), and fructose (a simple sugar) (Section 5.4A)
M	Locating stereogenic centers in albuterol (a bronchodilator), chloramphenicol (an antibiotic), and aliskiren (an antihypertensive drug) (Section 5.4A and Problem 5.7)
M	The three-dimensional structure of thalidomide, an anti-nausea drug that caused catastrophic birth defects (Section 5.5)
M, B	Identifying stereogenic centers in paclitaxel (anticancer agent), sucrose, and zanamivir (influenza treatment) (Section 5.5)
M	Identifying stereogenic centers in exemestane (a drug used to treat breast cancer), gabapentin enacarbil, cholesterol, and Zocor (cholesterol-lowering drug) (Section 5.5, Problems 5.10–5.12)
M	Assigning *R* and *S* configurations in the drugs Plavix and Zestril (Section 5.6, Problems 5.17 and 5.18)
B	The sweetener sorbitol (Section 5.9, Problem 5.27)
B	The specific rotation of MSG, a common flavor enhancer (Section 5.12D, Problem 5.35)
M	Chiral drugs and how mirror image isomers can have drastically different properties—the analgesic ibuprofen, the antidepressant

	fluoxetine, and the anti-inflammatory agent naproxen (Section 5.13A)
B	The sense of smell and how mirror image isomers (e.g., carvone and celery ketone) can smell different (Section 5.13B and Problem 5.38)
M, B	End-of-chapter problems: 5.39, 5.46, 5.47, 5.52, 5.55, 5.57, 5.60, 5.68–5.73
Chapter 6	**Understanding Organic Reactions**
B	Energy changes in the metabolism of glucose (Chapter opener and Section 6.4)
B	The synthesis of capsaicin by a substitution reaction (Section 6.2)

B	Precursors to the female sex hormone estrone (Section 6.2C, Problem 6.2)
G	The reaction of gasoline with O_2 (Sections 6.4 and 6.9A)
G	Refrigeration and spoilage (Section 6.9A)
B	Enzymes, biological catalysts (Section 6.11)
B	End-of-chapter problems: 6.34 and 6.56
Chapter 7	**Alkyl Halides and Nucleophilic Substitution**
B	Chloromethane, which is produced by giant kelp, evergreen trees, and volcanic eruptions (Chapter opener)
B, M	Telfairine (insecticide) and halomon (antitumor agent), halogenated compounds isolated from red algae (Section 7.1, Problem 7.1)
B, M	Simple alkyl halides—bromomethane (an ozone-depleting soil fumigant), dichloromethane (once used to decaffeinate coffee), and halothane (a general anesthetic) (Section 7.4)
G	Teflon and PVC—synthetic organic halides used as insulating materials, plastic wrap, and coatings (Section 7.4)
E	CFCs and DDT, two polyhalogenated compounds once widely used, now discontinued because of adverse environmental effects (Section 7.4)
B, M	Ma‘ilione and plocoralide B, halogenated compounds isolated

	from red algae (Section 7.4)
B	Chondrocole A, a marine natural product isolated from red seaweed (Section 7.4, Problem 7.5)
M	The antiseptic CPC and the antiplatelet drug ticlopidine (Section 7.6, Problems 7.8 and 7.9)
M	Nucleophilic substitutions in the syntheses of Myambutol (used to treat tuberculosis) and Prozac (an antidepressant) (Section 7.11)
M	The synthesis of raloxifene, a drug used to reduce the risk of breast cancer in postmenopausal women (Section 7.11)
M	The synthesis of rizatriptan, a drug for the treatment of migraines, by a nucleophilic substitution reaction (Section 7.11, Problem 7.22)
B, M	Biological nucleophilic substitution reactions: phosphate leaving groups and *S*-adenosylmethionine (SAM) (Section 7.16)
B	Adrenaline, a hormone synthesized in the adrenal glands (Section 7.16)
B	The biological synthesis of adrenaline using SAM (Section 7.16)
B	The synthesis of nicotine using SAM (Section 7.16, Problem 7.35)
M	The importance of organic synthesis in preparing useful drugs such as aspirin (Section 7.18)
B, M	End-of-chapter problems: 7.54–7.56, 7.62, 7.65, 7.70, and 7.76
Chapter 8	**Alkyl Halides and Elimination Reactions**
B, M	The antipyretic quinine, originally isolated from the cinchona tree, but now synthesized in the lab (Chapter opener)
E	DDE, a degradation product of the pesticide DDT (Section 8.1)
B	Ethylene, a hormone that regulates plant growth and fruit ripening (Section 8.2)
B	Classifying alkenes using vitamins A and D (Section 8.2, Problem 8.2)
B	Identifying stereoisomerism in alkenes using (*E*)-ocimene, found in lilacs (Section 8.2, Problem 8.4)
B, M	Elimination reactions in the syntheses of a prostaglandin and quinine (Section 8.4)

B, M	End-of-chapter problems: 8.29 and 8.65
Chapter 9	**Alcohols, Ethers, and Related Compounds**
B	Linalool, an alcohol used in scented soaps and lotions and as an insecticide for controlling fleas and cockroaches (Chapter opener)
B	Classifying alcohols using cortisol (Section 9.1)
B	Classifying ethers and alcohols using brevenal, a marine natural product formed in red tides (Section 9.1, Problem 9.1)
G, E	Ethanol, a gasoline additive and renewable fuel source that can be produced from the fermentation of carbohydrates in grains (Section 9.5A)
G	Useful simple alcohols: methanol (wood alcohol), isopropanol (rubbing alcohol), and ethylene glycol (antifreeze) (Section 9.5A)
M	Diethyl ether, a general anesthetic (Section 9.5B)
M	Sevoflurane, a halogenated ether currently used as a general anesthetic (Section 9.5B)
M	Medicinal epoxides: eplerenone (a drug that reduces cardiovascular risk in patients who have already had a heart attack) and tiotropium bromide (a bronchodilator) (Section 9.5C)
M	A Williamson ether synthesis in the preparation of paroxetine (antidepressant) (Section 9.6, Problem 9.9)
G	The syntheses of vitamin A and patchouli alcohol (used in perfumery) using a dehydration reaction (Section 9.10)
G, B	The unpleasant odors related to skunks, onions, and human sweat (Section 9.15A)
B	The oxidation of a thiol to a disulfide using grapefruit mercaptan (Section 9.15A, Problem 9.30C)
B	The synthesis of SAM from methionine and ATP by an S_N2 reaction (Section 9.15B)
M	The syntheses of salmeterol and albuterol (two bronchodilators) by the opening of an epoxide ring (Section 9.16)

G, M	The design of asthma drugs that block the synthesis of leukotrienes, highly potent molecules that contribute to the asthmatic response (Section 9.17)

G, B	The metabolism of polycyclic aromatic hydrocarbons (PAHs) to carcinogens that disrupt normal cell function, resulting in cancer or cell death (Section 9.18)
M	End-of-chapter problems: 9.63, 9.67, 9.68, and 9.79

Chapter 10 Alkenes and Addition Reactions

M	Artemisinin, the active component of qing-hao, a Chinese herbal remedy used to treat malaria (Chapter opener)
M	Degrees of unsaturation in the drugs Ambien and mefloquine (Section 10.2, Problem 10.4)
B	Determining the *E/Z* stereochemistry of the double bonds in a toxin produced by the seaweed *Chlorodesmis fastigiata* (Section 10.3B, Problem 10.8)
G	Ethylene, the starting material for preparing polyethylene and a variety of other polymers (Section 10.5)
B	The naturally occurring alkenes β-carotene and zingiberene (Section 10.5)
B	Triacylglycerols, fatty acids, fats, and oils (Section 10.6)
B	The unsaturated fatty acids found in kukui nuts (Section 10.6A)
B	Omega-3 fatty acids (Section 10.6, Problem 10.11)
B	The synthesis of the female sex hormone estrone (Section 10.15B)
M	The synthesis of artemisinin, an antimalarial drug, by a hydroboration–oxidation step (Section 10.16B)
B, M	End-of-chapter problems: 10.37, 10.44, 10.45, 10.67, and 10.68

Chapter 11 Alkynes and Synthesis

M	Oral contraceptives (Chapter opener and Section 11.4)
B	Nepheliosyne B, a novel acetylenic fatty acid (Section 11.1, Problem 11.1)
G	Acetylene, an alkyne used in welding torches (Section 11.4)
M	Synthetic hormones mifepristone and Plan B, drugs that prevent pregnancy (Section 11.4)
B	Histrionicotoxin, a diyne isolated from the skin of a frog, used as a poison on arrow tips by the Choco tribe of South America (Section 11.4)

B	Acetylide anion reactions in the synthesis of two marine natural products (Section 11.11)
M, B	End-of-chapter problems: 11.26 and 11.43
Chapter 12	**Oxidation and Reduction**
B	Oleic and linoleic acids, two unsaturated fatty acids found in soybean oil (Chapter opener)
B	The partial hydrogenation of vegetable oils and the formation of "trans fats" (Section 12.4)
B	The reduction of an alkyne to form *cis*-jasmone, a component of perfume (Section 12.5B, Problem 12.10)
B	The use of disparlure, a sex hormone, in controlling the spread of gypsy moths (Section 12.8B)
G	The production of ozone from O_2 during electrical storms (Section 12.10)
B	Cembrene A, a natural product isolated from soft corals (Section 12.10, Problem 12.21)
G	Blood alcohol screening (Section 12.12)
E	Green chemistry—environmentally benign oxidation reactions (Section 12.13)
B	Biological oxidations (Section 12.14)
B	The synthesis of insect pheromones using asymmetric epoxidation (Section 12.15)
B	The asymmetric epoxidation of geraniol, a major component of rose oil and citronella oil (Section 12.15, Problem 12.27)
B, M	End-of-chapter problems: 12.34, 12.39, 12.48, 12.50–12.52, 12.57, 12.58, and 12.61
Spectroscopy A	**Mass Spectrometry**
M	Tetrahydrocannabinol (THC), an anti-nausea agent for chemotherapy patients and an appetite stimulant for AIDS-related anorexia (Chapter opener and Section A.5B)
M	Applying the nitrogen rule to 3-methylfentanyl and MPPP, two drugs that mimic the effects of heroin (Section A.1B)
B	Determining the molecular formula of nootkatone (found in

	grapefruit) (Section A.1B)
B	Determining the molecular formula of cedrol, an alcohol found in cedar oil (Section A.1B, Problem A.4)
M	Determining the molecular ion for the antihistamine chlorpheniramine (Section A.2s, Problem A.5)
G, E	Using GC–MS to analyze mixtures containing environmental pollutants, and urine and hair samples for the presence of illegal drugs or performance-enhancing substances (Section A.5B)
G	Using GC–MS to analyze mixtures of gasoline additives designed to boost octane ratings (Section A.5B, Problem A.14)
B	Mass spectra of high-molecular-weight biomolecules (Section A.5C)
B	End-of-chapter problems: A.20 and A.25

Spectroscopy B	**Infrared Spectroscopy**
M	Infrared spectroscopy and the structure determination of penicillin (Chapter opener and Section B.5)
G, B	Electromagnetic radiation—cooking with microwaves and sunburns from UV rays (Section B.1)
B	Major IR absorptions of capsaicin (the spicy component of peppers) and oleic acid (an unsaturated fatty acid) (Section B.4D, Problems B.12 and B.13)

B	Using IR spectroscopy to monitor the formation of periplanone B, the sex pheromone of the female American cockroach (Section B.5)
B	End-of-chapter problems: B.20, B.22, and B.42

Spectroscopy C	**Nuclear Magnetic Resonance Spectroscopy**
B	Modern spectroscopic methods and the structure of palau'amine, a complex natural product isolated from a sea sponge (Chapter opener and Problem C.24)
E	The high-octane gasoline additive MTBE, which has contaminated water supplies (Section C.1B)
G	Vinyl acetate, which is polymerized to PVA, a polymer used in

	paints, glues, and adhesives (Section C.8)
B	Esters of chrysanthemic acid (from chrysanthemum flowers) as insecticides (Section C.11, Problem C.31)
M	Magnetic resonance imaging (Section C.12)
B	End-of-chapter problems: C.39 and C.55
Chapter 13	**Radical Reactions**
G, M	PVC, a synthetic polymer used in medical, industrial, and home products (Chapter opener and Section 13.14)
E	Ozone destruction and CFCs (Section 13.9)
B	The oxidation of unsaturated lipids by radical reactions (Section 13.11)
M	Antioxidants in anti-aging formulations (Section 13.12)
M, B	Two antioxidants—naturally occurring vitamin E and synthetic BHT (Section 13.12)
B	The antioxidant rosmarinic acid (Section 13.12, Problem 13.21)
G	The formation of useful polymers from monomers by radical reactions (Section 13.14)
G	Polystyrene, a common synthetic polymer used in packaging materials and beverage cups (Section 13.14B)
B, G, M	End-of-chapter problems: 13.64, 13.66–13.70, and 13.79
Chapter 14	**Conjugation, Resonance, and Dienes**
M	The laboratory synthesis of morphine by a Diels–Alder reaction (Chapter opener)
B	Allylic carbocations in biological reactions, such as the formation of geranyl diphosphate (Section 14.2B)
B	Neuroprotectin D1, a natural anti-inflammatory agent (Section 14.6, Problem 14.12)
B	Isoprene, a conjugated compound that helps plants tolerate heat stress (Section 14.7)
M	The antioxidant lycopene (Sections 14.7 and 14.15A)
M	Simvastatin (Zocor) and calcitriol (Rocaltrol), two drugs with conjugated double bonds (Section 14.7)
B	The synthesis of tetrodotoxin (found in Japanese puffer fish) by a

	Diels–Alder reaction (Section 14.12)
B	The trienes zingiberene and β-sesquiphellandrene found in ginger root (Section 14.13A, Problem 14.22)
B	The Diels–Alder reaction in the synthesis of steroids (Section 14.14C)
G	Why lycopene and other highly conjugated compounds are colored (Section 14.15A)
G	How sunscreens work (Section 14.15B)
B, M	End-of-chapter problems: 14.62, 14.69, 14.73, and 14.75
Chapter 15	**Benzene and Aromatic Compounds**
B	Histamine and scombroid fish poisoning (Chapter opener and Section 15.8)
M	Drawing resonance structures of the antihistamine diphenhydramine (found in Benadryl) (Section 15.2, Problem 15.1)
G	Polycyclic aromatic hydrocarbons (PAHs), constituents of cigarette smoke and diesel exhaust (Section 15.5)
M	Examples of common drugs that contain an aromatic ring—Zoloft, Novocain, and Viracept (Section 15.5)
B	Pilocarpine, a naturally occurring glaucoma medication that contains an aromatic heterocycle (Section 15.8)
M	Januvia, a drug used to treat type 2 diabetes (Section 15.8, Problem 15.10)
G	Diamond, graphite, and buckminsterfullerene (Section 15.11)
M, B	End-of-chapter problems: 15.33, 15.34, 15.36, 15.57–15.60, and 15.65
Chapter 16	**Reactions of Aromatic Compounds**
B	Vitamin K_1, a fat-soluble vitamin that regulates the synthesis of proteins needed for blood to clot (Chapter opener and Section 16.5E)
M, E	Biologically active aryl chlorides: the drugs bupropion and chlorpheniramine, and 2,4-D and 2,4,5-T, herbicide components of the defoliant Agent Orange (Section 16.3)
M	Intramolecular Friedel–Crafts acylation in the synthesis of LSD

	(Section 16.5D)
M	The synthesis of sertraline (Zoloft), an SSRI antidepressant (Section 16.5D, Problem 16.11)
B	A biological Friedel–Crafts reaction (Section 16.5E)
M	Nucleophilic aromatic substitution by addition–elimination in the synthesis of Prozac (Section 16.13A, Problem 16.28)
M	Benzocaine, the active ingredient in the over-the-counter topical anesthetic Orajel (Section 16.15C)
M, G, B	End-of-chapter problems: 16.45–16.48, 16.60, 16.62, 16.65, 16.70, 16.71, 16.75, 16.76, and 16.80

Chapter 17 Introduction to Carbonyl Chemistry; Organometallic Reagents; Oxidation and Reduction

M, B	Resiniferatoxin, a compound that desensitizes neurons to pain (Chapter opener)
B	The aldehyde α-sinensal, a component of mandarin oil (Section 17.1, Problem 17.1)
M	The anticancer drug Taxol and nucleophilic substitution (Section 17.2, Problem 17.2)

B, M	Reduction reactions in the synthesis of the analgesic ibuprofen and the perfume component muscone (Section 17.4)
M	The synthesis of the long-acting bronchodilator salmeterol (Section 17.6A)
M	The use of CBS reagents in the synthesis of cholesterol-lowering drugs (Section 17.6A, Problem 17.8)
B	Biological oxidation–reduction reactions with the coenzymes NADH and NAD+ (Section 17.6B)
B	The synthesis of NAD+ from the vitamin niacin (Section 17.6B)
B	The use of a reduction reaction to synthesize the marine neurotoxin ciguatoxin CTX3C (Section 17.7A)
M	The use of organometallic reagents to synthesize the oral contraceptive ethynylestradiol (Section 17.10C)
B	The use of Grignard reagents in the synthesis of C_{18} juvenile hormones and the use of juvenile hormone mimics to regulate the

	life cycle of insects (Section 17.10C)
B	The use of organolithium reagents in the synthesis of two components of lavender oil (Section 17.11, Problem 17.22)
M	The use of a Grignard reagent to prepare the antidepressant Effexor (Section 17.11, Problem 17.23)
M	The use of protecting groups in the conversion of estrone to ethynylestradiol (Section 17.12, Problem 17.24)
M, B	End-of-chapter problems: 17.44, 17.50, 17.54, 17.58, 17.68, 17.74, and 17.76

Chapter 18 Aldehydes and Ketones—Nucleophilic Addition

M	Oleandrin, a compound from the oleander plant, which has been used to treat congestive heart failure (Chapter opener and Problem 18.31)
B	Determining the IUPAC names of neral (from lemon grass) and cucumber aldehyde (Section 18.2E, Problem 18.7)
G	Formaldehyde and acetone, an industrially useful aldehyde and ketone (Section 18.4)
B	Examples of naturally occurring compounds that contain aldehydes or ketones—vanillin and cinnamaldehyde (Section 18.4)
M	Cortisone and prednisone, steroids that contain ketones (Section 18.4)
B	Naturally occurring cyanohydrin derivatives: linamarin, from cassava root; amygdalin, from apricot, peach, and wild cherry pits; and laetrile (Section 18.8B)
B	The use of the Wittig reaction in the synthesis of β-carotene, the orange pigment in carrots (Section 18.9B)
B	The role of rhodopsin in the chemistry of vision (Section 18.10B)
M	The sedative chloral hydrate (Section 18.12A)
B	The acid-catalyzed hydrolysis of safrole, a carcinogen once used in root beer (Section 18.13B, Problem 18.30)
B, M	The acid-catalyzed hydrolysis of the acetal in oleandrin (Section 18.13B, Problem 18.31)
G, M	Monensin (an additive in cattle feed) and digoxin (a cardiac drug), compounds that contain stable cyclic hemiacetals and acetals

	(Section 18.15B, Problem 18.34)
B	The carbohydrates glucose and lactose (Section 18.16)
M	The role of carbohydrates in diabetes (Section 18.16)
B	The carbohydrate galactose (Section 18.16, Problem 18.36)
M, B	End-of-chapter problems: 18.50, 18.52, 18.66, 18.69, 18.70, 18.80, and 18.82–18.84

Chapter 19	Carboxylic Acids and Nitriles
B	The essential amino acid lysine (Chapter opener)
B	Biologically significant diacids: oxalic acid, malonic acid, and succinic acid (Section 19.2B)
M	Depakote (used to treat seizures) (Section 19.2B, Problem 19.5)
B	Biologically significant carboxylic acids: formic acid (ant stings), acetic acid (vinegar), hexanoic acid (odor of dirty socks and ginkgo seeds), oxalic acid (spinach), and lactic acid (sour milk) (Section 19.5)
G	Sodium benzoate and potassium sorbate, salts of carboxylic acids that are used as preservatives (Section 19.4)
M	Drugs that contain a nitrile: anastrozole (breast cancer), escitalopram (depression), and verapamil (high blood pressure) (Section 19.4)
M, B	How NSAIDs block the synthesis of prostaglandins to prevent inflammation (Section 19.5)
B	Mandelic acid, a naturally occurring carboxylic acid in plums and peaches (Section 19.7, Problem 19.14)
M	The irritant urushiol in poison ivy (Section 19.9, Problem 19.18)
B	An introduction to amino acids, the building blocks of proteins; why vegetarians must have a balanced diet (Section 19.11)
B, M	End-of-chapter problems: 19.40, 19.42, 19.59–19.64, 19.75, and 19.76

Chapter 20	Carboxylic Acids and Their Derivatives—Nucleophilic Acyl Substitution
M, B	Cocaine, a widely abused recreational drug (Chapter opener)
M	Oxytocin, a naturally occurring hormone used to induce labor

	(Section 20.1, Problem 20.1)
B, M	Ginkgolide B, a major constituent of the extracts of the ginkgo tree, *Ginkgo biloba* (Sections 20.5A and 20.10, Problem 20.21)
B	The esters responsible for the odors of banana, mango, and pineapple (Section 20.5A)
M, B	Vitamin C, a water-soluble vitamin that contains a lactone (Section 20.5A)

M, B	Useful amides: proteins, met-enkephalin, the penicillin antibiotics, and the cephalosporin antibiotics (Section 20.5B)
G	The synthesis of the insect repellant DEET (Section 20.7)
B	Mechanism for the synthesis of blattellaquinone, the sex pheromone of the female German cockroach (Section 20.7, Problem 20.12)
M	Acylation in the syntheses of aspirin, acetaminophen, and heroin (Section 20.8)
M	The cholesterol-lowering drug fenofibrate (Section 20.10B, Problem 20.20)
B	Lipid hydrolysis (Section 20.11)
G	Olestra, a fake fat (Section 20.11A)
G	The synthesis of soap (Section 20.11B)
M	The mechanism of action of β-lactam antibiotics like penicillin (Section 20.13)
G	Natural and synthetic fibers: nylon and polyesters (Section 20.15)
B	Biological acylation reactions (Section 20.16)
M	Cholesteryl esters in plaque, the deposits that form on the inside walls of arteries (Section 20.16)
B	The acylation of glucosamine to form NAG, the monomer in chitin (Section 20.16, Problem 20.30)
B, M	End-of-chapter problems: 20.41, 20.45–20.49, 20.51–20.53, 20.55, 20.58, 20.61, 20.62, 20.66 20.69, 20.73, and 20.74

Chapter 21 Substitution Reactions of Carbonyl Compounds at the α Carbon

M	Stemoamide, an amide used in traditional Chinese medicine to

	treat respiratory illnesses (Chapter opener)
B	Leptospermone, an herbicide produced by the bottlebrush plant (Section 21.2, Problem 21.2)
M	The synthesis of the antimalarial drug quinine by an intramolecular substitution reaction (Section 21.7C, Problem 21.15)
M	Using enolate alkylation to synthesize the analgesic naproxen (Section 21.8A, Problem 21.18)
M	The synthesis of the anticancer drug tamoxifen (Section 21.8C)
M	The heterocyclic ring system in some antitumor agents (Section 21.8C, Problem 21.20)
M	The use of the acetoacetic ester synthesis in the synthesis of illudin-S, an antitumor agent (Section 21.10, Problem 21.28)
M	Retrosynthesis of the pain reliever nabumetone (Section 21.10, Problem 21.29)
B, M	End-of-chapter problems: 21.38, 21.40, 21.44, 21.51, 21.52, 21.54–21.57, 21.64, 21.65, 21.67, 21.71, and 21.73

Chapter 22 Carbonyl Condensation Reactions

M	The synthesis of ibuprofen (Chapter opener and Problem 22.21)
B	The perfume component flosal, an α,β-unsaturated aldehyde (Section 22.2B, Problem 22.6)
M	The reaction of a β-keto ester in the synthesis of azelnidipine, a calcium channel blocker (Section 22.2B, Problem 22.9)
B	The synthesis of periplanone B, sex pheromone of the female American cockroach (Section 22.3)
B	The synthesis of *ar*-turmerone, a component of turmeric, a principal ingredient in curry powder (Section 22.3)
M	A directed aldol reaction in the synthesis of the drug donepezil (for treating dementia) (Section 22.3, Problem 22.13)
B	The synthesis of the steroid progesterone by an intramolecular aldol reaction (Section 22.4)
M	Avobenzone, a common ingredient in commercial sunscreens (Section 22.6A, Problem 22.19)
B	The synthesis of the female sex hormone estrone by a Michael

	reaction (Section 22.8)
M, B	End-of-chapter problems: 22.35, 22.45, 22.50, 22.53–22.56, 22.58, 22.65, 22.67, 22.68, 22.73, and 22.74
Chapter 23	**Amines**
M	Sparteine, an alkaloid that acts as an antiarrhythmic agent (Chapter opener)
M	The stereogenic centers in dobutamine, an amine used in stress tests (Section 23.2, Problem 23.1)
B	Poisonous diamines with putrid odors: putrescine and cadaverine (Section 23.5A)
B	Naturally occurring alkaloids: atropine, nicotine, and scopolamine (Section 23.5A)
M	Histamine, antihistamines, and antiulcer drugs like Tagamet (cimetidine) (Section 23.5B)
B, M	Biologically active derivatives of 2-phenylethanamine: adrenaline, noradrenaline, methamphetamine, mescaline, and dopamine (Section 23.5C)
B, M	The neurotransmitter serotonin and SSRI antidepressants (Section 23.5C)
B	Bufotenin and psilocin (hallucinogens) (Section 23.5C)
M	LSD and codeine (Section 23.5C, Problem 23.5)
M	The synthesis of methamphetamine by reductive amination (Section 23.6C)
M	The synthesis of maraviroc, a drug to treat HIV, by reductive amination (Section 23.6C, Problem 23.13)
M	The synthesis of the drugs rimantadine and pseudoephedrine by reductive amination (Section 23.6C, Problem 23.14)
M	The systematic name of a component of the diet drug fen–phen (Section 23.6C, Problem 23.15)
M	Drugs, such as the antihistamine diphenhydramine, sold as water-soluble ammonium salts (Section 23.8)

M	Acid–base properties of chloroquine, matrine, and quinine (Section 23.9F and Problem 23.22)

G	Azo dyes (Section 23.14)
G	Perkin's mauveine and synthetic dyes (Section 23.15A)
M	Sulfa drugs (Section 23.15B)
M	End-of-chapter problems: 23.36, 23.41, 23.42, 23.44, 23.50, 23.54, 23.55, 23.58, 23.59, 23.64, 23.69, 23.71, 23.78, and 23.79
Chapter 24	**Carbon–Carbon Bond-Forming Reactions in Organic Synthesis**
M	Ingenol mebutate, used to treat the skin condition actinic keratosis (Chapter opener and Section 24.6, Problem 24.18)
B	The synthesis of C_{18} juvenile hormone (Section 24.1A, Problem 24.2)
B, E	Use of the Suzuki reaction to prepare bombykol, the sex pheromone of the female silkworm moth, and humulene, a lipid isolated from hops (Section 24.2B)
E	Pyrethin I, a biodegradable insecticide isolated from chrysanthemums, and decamethrin, a synthetic analogue (Section 24.4)
M	Ring-closing metathesis and the synthesis of epothilone A, an anticancer drug (Section 24.6)
M, B, G	End-of-chapter problems: 24.27, 24.29, 24.45, and 24.48
Chapter 25	**Pericyclic Reactions**
B	One synthesis of periplanone B (sex pheromone of the female American cockroach) using pericyclic reactions (Chapter opener and Section 25.5B, Problem 25.20)
B	The role of photochemical electrocyclic ring opening and sigmatropic rearrangements in the formation of vitamin D_3 from 7-dehydrocholesterol (Section 25.3C, Problem 25.8)
M	Garsubellin A and the synthesis of the neurotransmitter acetylcholine (Section 25.5B, Problem 25.23)
B	End-of-chapter problems: 25.41, 25.48, and 25.65
Chapter 26	**Carbohydrates**
B	Sucrose, the carbohydrate commonly called table sugar (Chapter opener)

B	The use of fructose in “lite” foods (Section 26.2)
B	Dihydroxyacetone, the active ingredient in many artificial tanning agents (Section 26.2)
B	Glucose, the most common simple sugar (Section 26.6)
G	Honey, a mixture of D-fructose and D-glucose (Section 26.6D)
B, M	The naturally occurring glycosides salicin and solanine (Section 26.7C)
G	Rebaudioside A, a sweet glycoside from the stevia plant (Section 26.7C, Problem 26.18)
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