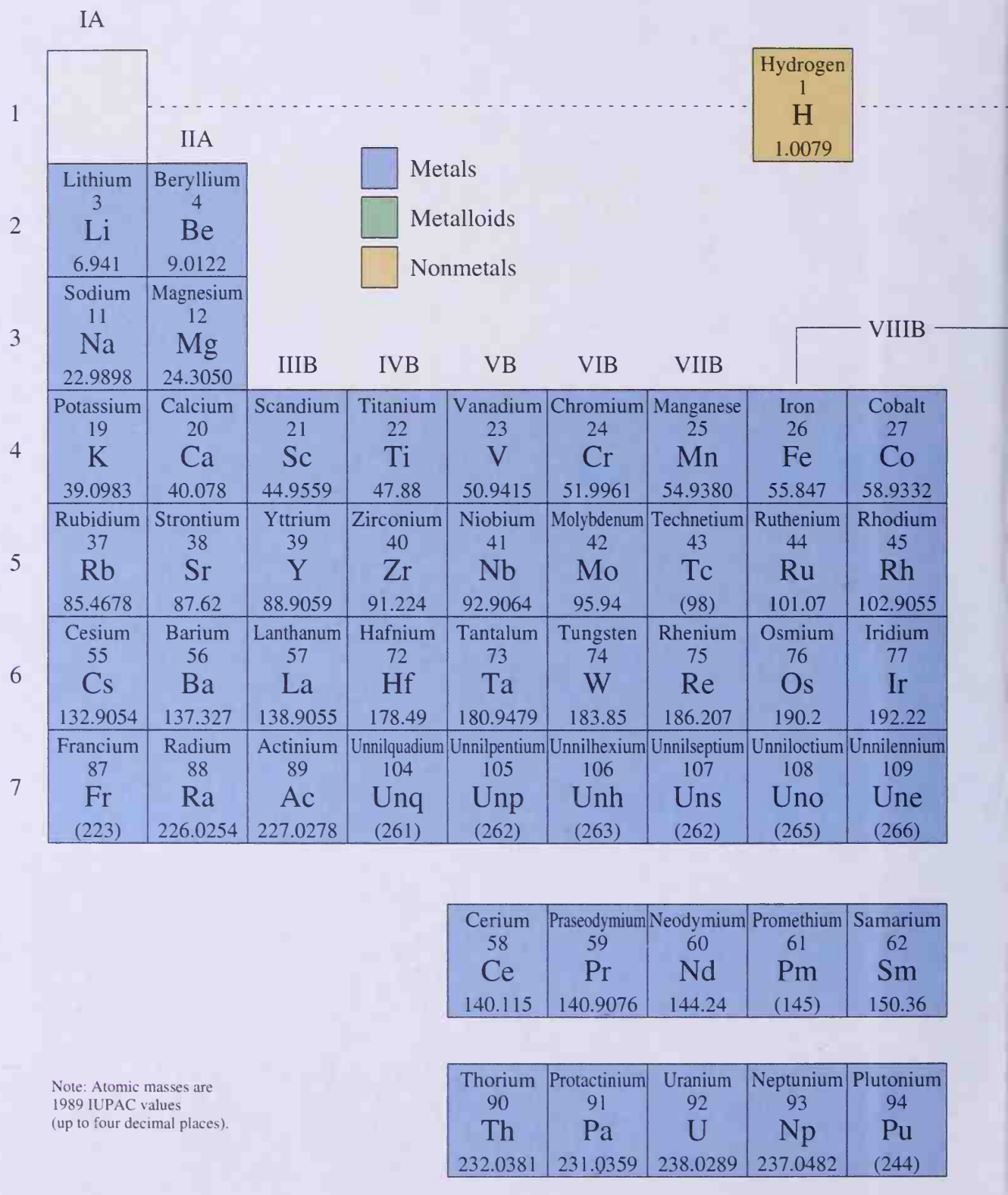
ORGANIC CHEMISTRY

BROWN

Periodic Table of the Elements

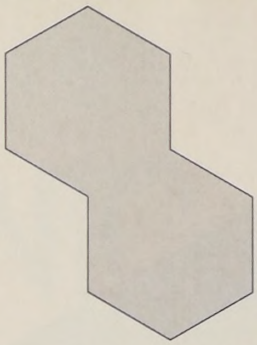


Note: Atomic masses are
1989 IUPAC values
(up to four decimal places).

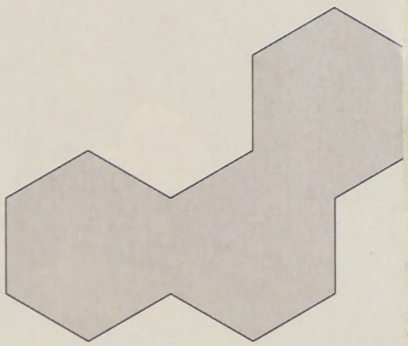
								Noble gases
						VIIA		Helium 2 He 4.0026
			IIIA	IVA	VA	VIA		
			Boron 5 B 10.811	Carbon 6 C 12.011	Nitrogen 7 N 14.0067	Oxygen 8 O 15.9994	Fluorine 9 F 18.9984	Neon 10 Ne 20.1797
			Aluminum 13 Al 26.9815	Silicon 14 Si 28.0855	Phosphorus 15 P 30.9738	Sulfur 16 S 32.066	Chlorine 17 Cl 35.4527	Argon 18 Ar 39.948
Nickel 28 Ni 58.6934	Copper 29 Cu 63.546	Zinc 30 Zn 65.39	Gallium 31 Ga 69.723	Germanium 32 Ge 72.61	Arsenic 33 As 74.9216	Selenium 34 Se 78.96	Bromine 35 Br 79.904	Krypton 36 Kr 83.80
Palladium 46 Pd 106.42	Silver 47 Ag 107.8682	Cadmium 48 Cd 112.411	Indium 49 In 114.82	Tin 50 Sn 118.710	Antimony 51 Sb 121.757	Tellurium 52 Te 127.60	Iodine 53 I 126.9045	Xenon 54 Xe 131.29
Platinum 78 Pt 195.08	Gold 79 Au 196.9665	Mercury 80 Hg 200.59	Thallium 81 Tl 204.3833	Lead 82 Pb 207.2	Bismuth 83 Bi 208.9804	Polonium 84 Po (210)	Astatine 85 At (210)	Radon 86 Rn (220)

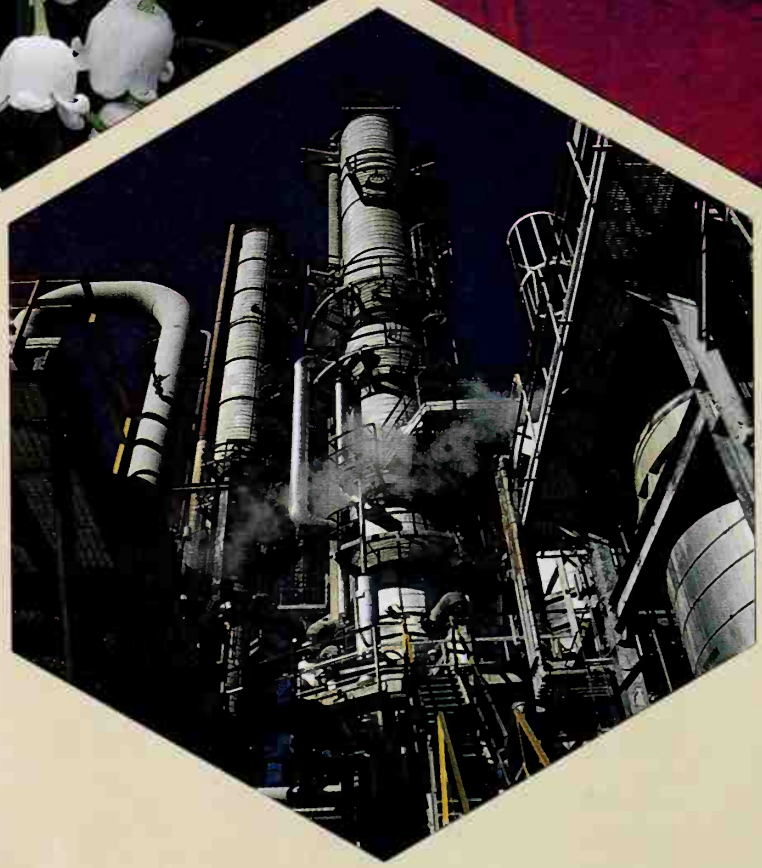
Europium 63 Eu 151.965	Gadolinium 64 Gd 157.25	Terbium 65 Tb 158.9253	Dysprosium 66 Dy 162.50	Holmium 67 Ho 164.9303	Erbium 68 Er 167.26	Thulium 69 Tm 168.9342	Ytterbium 70 Yb 173.04	Lutetium 71 Lu 174.967

Americium 95 Am (243)	Curium 96 Cm (247)	Berkelium 97 Bk (247)	Californium 98 Cf (251)	Einsteinium 99 Es (252)	Fermium 100 Fm (257)	Mendelevium 101 Md (256)	Nobelium 102 No (259)	Lawrencium 103 Lr (262)



ORGANIC CHEMISTRY





ORGANIC CHEMISTRY

William H. Brown
Beloit College

SAUNDERS COLLEGE PUBLISHING
Harcourt Brace College Publishers
Fort Worth Philadelphia San Diego New York Orlando Austin
San Antonio Toronto Montreal London Sydney Tokyo

Text Typeface: Times Roman
Compositor: Progressive Information Technologies
Vice President; Publisher: John Vondeling
Developmental Editor: Sandra Kiselica
Managing Editor: Carol Field
Project Editor: Beth Ahrens
Copy Editor: Linda Davoli
Manager of Art and Design: Carol Bleistine
Senior Art Director: Christine Schueler
Art and Design Coordinator: Sue Kinney
Photo Researchers: Dena Digilio-Betz, Avery Hallowell
Text Designer: Tracy Baldwin
Cover Designer: Lawrence R. Didona
Text Artwork: J/B Woolsey Associates, Brent Iverson
Layout Artist: Claudia Durrell
Director of EDP: Tim Frelick
Production Manager: Charlene Squibb
Vice President, Marketing: Marjorie Waldron

Cover Credit: Crystals of xylitol viewed under polarizing light. © Herb Charles Ohlmeyer/Fran Heyl Associates
Title Page Credits *(clockwise, from top left)*: Barry L. Runk/Grant Heilman Photography, Inc.; © Herb Charles Ohlmeyer/Fran Heyl Associates; Courtesy of BP America

Printed in the United States of America

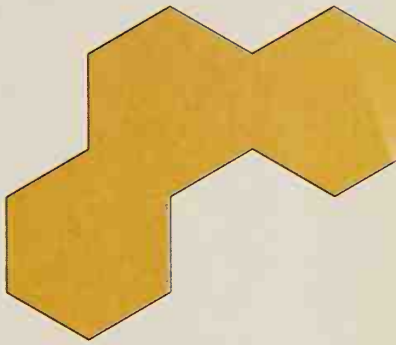
ORGANIC CHEMISTRY
0-03-009618-9

Library of Congress Catalog Card Number: 94-066553

56789 048 6543

To *Carolyn,*
with whom
life is a joy

PREFACE



This book is intended to serve students majoring in the sciences in a one- or two-semester course in organic chemistry. I wrote the book to give students a foundation in the fundamentals of the structure of organic compounds, their reactions, and underlying reaction mechanisms. I also wish to convey to students that organic chemistry is a tool for many other disciplines, such as health and biological studies. My goal is to show students that organic compounds are all around them—in pharmaceuticals, plastics, fibers, dyes and pigments, agrochemicals, surface coatings, toiletry preparations and cosmetics, flavors and fragrances, food additives, adhesives, and elastomers. I make a special effort throughout this text to show the interrelation between organic chemistry and these areas, particularly biology, biochemistry, physiology, pharmacology, health sciences, and polymer science.

Where is the challenge in organic chemistry today? Through this text and their instructors, I hope students will see that organic chemistry is a dynamic and ever-expanding area of science waiting openly for those who are prepared, both by training and inquisitive nature, to ask questions and to explore.

Organization

The main part of this text, consisting of Chapters 1 through 22, presents the major classes of organic functional groups in conjunction with their reactions and their reaction mechanisms. Chapters 12 through 14 within this group present the fundamentals of mass spectrometry, ^{1}H-NMR and ^{13}C-NMR, IR, and UV-visible spectroscopy. The second part of the text, consisting of Chapters 23 through 25 is a brief introduction to the organic chemistry of three major classes of biomolecules, namely lipids, amino acids and proteins, and nucleic acids.

Chapter 1 begins with a review of the electronic structure of atoms and molecules, and use of the VSEPR model to predict shapes of molecules and ions. It is followed by an introduction to some basic organic functional groups: alcohols, ethers, aldehydes, ketones, carboxylic acids, and esters. These particular functional groups are the ones encountered most frequently in Chapters 1 through 14. The theory of resonance is introduced midway through Chapter 1, and with it, the use of curved arrows and electron pushing. The knowledge of resonance theory combined with a facility for moving electrons gives students two powerful tools for writing reaction mechanisms and understanding chemical reactivity. Chapter 1 concludes with an introduction to quantum mechanics and a description of covalent bonding in terms of both the valence bond model and the molecular orbital model.

Chapter 2 describes the structure and shapes of alkanes and cycloalkanes and discusses their nomenclature. Beginning here and continuing throughout the text, a clear distinction is made between IUPAC and common names. Where names are introduced, the IUPAC name is given and the common name or names, where appropriate, follow in parentheses. The IUPAC system is introduced in Section 2.3 through the naming of alkanes, and in Section 2.5 the IUPAC system is presented as a general system of nomenclature.

Chapter 3 contains a general introduction to acid-base chemistry with emphasis on both qualitative and quantitative determination of the position of equilibrium in acid-base reactions. A knowledge of acid-base chemistry gives students another valuable tool for analyzing and understanding chemical reactivity.

Chapters 4 and 5 cover the chemistry of alkenes. Structure and physical properties are presented in Chapter 4 and then chemical reactivity in Chapter 5. Reactions are organized in the order: electrophilic additions, hydroboration, radical addition of HBr, allylic halogenation, oxidation, reduction, and polymerization. Chapter 5 concludes with a consideration of the central role of ethylene, the organic chemical industry's most important building block.

Chapters 6 and 7 continue the theme of reactivity of carbon-carbon pi bonds with the chemistry of alkynes and conjugated dienes.

Chapter 8 begins with a review of isomerism covered in earlier chapters (constitutional, conformational, *cis-trans*/E-Z isomerism) and then introduces the concepts of chirality, enantiomerism, and diastereomerism. Students are then challenged to use these concepts to develop a deeper level of understanding of the stereochemistry of alkene addition, oxidation, and reduction reactions.

Chapter 9 continues the theme of relationships between structure and reactivity by considering the chemistry of alcohols. The concepts of one-step and two-step nucleophilic substitutions are introduced in a preliminary way here with the reactions of alcohols with HX.

Chapter 10 presents what, in my experience, is one of the most formidable and anxiety-producing aspects of introductory organic chemistry, namely S_N1, S_N2, E1, and E2 mechanisms and the attendant concepts of stereochemistry, kinetics, and relationships between structure and chemical reactivity. As I tell students, the difficulty does not lie in any single part of this material; no part of it is any more difficult than material already covered. The difficulty, rather, is in the number of concepts to be assimilated at one time. "Now," I tell students, "you will have to sing, dance, chew gum, snap your fingers, and whistle all at the same time." It is for these reasons that I present nucleophilic substitution after the chemistry of alkenes and alkynes, conjugated dienes, chirality, and alcohols. By this stage in the course, students have a good grounding in the structure of organic molecules, the theory of resonance, electron pushing, and reaction mechanisms. Nucleophilic substitution and β-elimination then become a vehicle for integration of previously covered chemistry into a larger pattern.

Chapter 11 is a logical extension of nucleophilic substitutions as applied to the synthesis of ethers and the reactions of epoxides.

Chapters 12 through 14 examine several instrumental methods for analyzing molecular structure and relate these methods to functional groups that have been studied to this point. First is mass spectrometry (Chapter 12), the instrumental technique by which molecular formulas are determined. Given the placing of this chapter, students are prepared to study the mass spectrometry of alkanes, alkenes, alkynes, alcohols, ethers, and epoxides. The mass spectrometry of other classes of organic compounds is presented in subsequent chapters. Chapter 13 presents the fundamentals of both ^{1}H-NMR and ^{13}C-NMR spectroscopy, while IR and UV-visible spectroscopy are covered in Chapter 14. While this material is presented as a cluster of chapters midway through the text, the chapters are free-standing and can be used in other orders as appropriate to a particular course.

Chapters 15 and 16 present the chemistry of aromatic compounds. The first of these chapters concentrates on structure and nomenclature of aromatic compounds, the concept of aromaticity, and the structure and acid-base properties of phenols. The second of these chapters is devoted to aromatic substitution reactions.

Chapters 17 through 21 concentrate on the chemistry of carbonyl-containing compounds. First is the chemistry of aldehydes and ketones in Chapter 17. Immediately following is the chemistry of carbohydrates in Chapter 18. The reason for this placement is that the chemistry of carbohydrates is built on the chemistry of two functional groups, namely aldehyde and ketone carbonyl groups and alcohol hydroxyl groups.

Chapters 19 and 20 present the chemistry of carboxylic acids and their functional derivatives. Following in Chapter 21 is the chemistry of enolate anions, including the acetoacetic ester and malonic ester syntheses and the Michael reaction.

Chapter 22 completes the introduction to organic functional groups with a presentation of the chemistry of aliphatic and aromatic amines.

Finally, in Chapters 23 through 25, the organic chemistry of lipids, amino acids and proteins, and nucleic acids are presented. Chapter 23 covers the structure of the major classes of lipids: triacylglycerols, fatty acids and prostaglandins, steroids, phospholipids, and the fat-soluble vitamins. Chapter 24 gives considerable attention to the acid-base properties of amino acids and then continues with an introduction to primary, secondary, and tertiary structure of polypeptides. The stereopairs of ribonuclease, hemoglobin, and myoglobin are particularly dramatic and valuable as teaching tools. The concentration in Chapter 25 is on primary, secondary and tertiary structure of DNA and solid-phase synthesis of DNA. An interesting "Chemistry in Action" box discusses the organic compounds used in the treatment of neoplastic diseases.

Special Features

Full-Color Art Program

One of the most distinctive features of this text is its visual impact. The text's extensive full-color art program includes over 250 pieces of art—many never seen before in organic texts—by professional artists John and Bette Woolsey.

Stereopairs

A collection of over 50 stereopairs have been prepared for this text, each chosen to reinforce the concept of organic chemistry as a three-dimensional science. Student reaction to these stereopairs ranges from "cool" to "spectacular." Each copy of the text is equipped with a pair of stereoglasses for easy viewing. Stereoart is indicated by the following icon: 

Chemistry in Action Boxes

These boxes illustrate applications of organic chemistry to everyday settings. Topics range from Drugs that Lower Plasma Levels of Cholesterol, to Carbamate Insecticides, and Chirality and the Search for Extraterrestrial Life.

In-Chapter Examples

There are an abundance of in-chapter examples. Solutions are given in detail so that students can follow the logic behind each step. Following each in-chapter example is a comparable in-chapter problem designed to give students the opportunity to practice solving related problems.

End-of-Chapter Summaries

End-of-chapter summaries highlight all key reactions found in a chapter. Each reaction is annotated and keyed to the section where it is discussed. For those chapters with no new reactions, for example the chapters on spectroscopy and chirality, prose summaries are given.

End-of-Chapter Problems

There are plentiful end-of-chapter problems—more than typically given in organic texts. All problems are categorized by topic. A tetrahedral icon (⏢) is used next to applied problems. A blue number indicates that a problem is more challenging.

Photo Art

Photos, conceived and developed for this text, show organic chemistry as it occurs in the laboratory and in everyday life, and depict the natural sources of many organic compounds.

Color

Color is used to highlight parts of molecules and to follow the course of reactions. The graphic on the next page shows some of the colors used consistently in the artwork in this book.

Interviews

Four interviews with prominent scientists describe how these people became interested in chemistry as a college major, then as an educator and/or research professional. Their enthusiasm for their work is evident, and they invite students to pursue similar interests in the sciences.

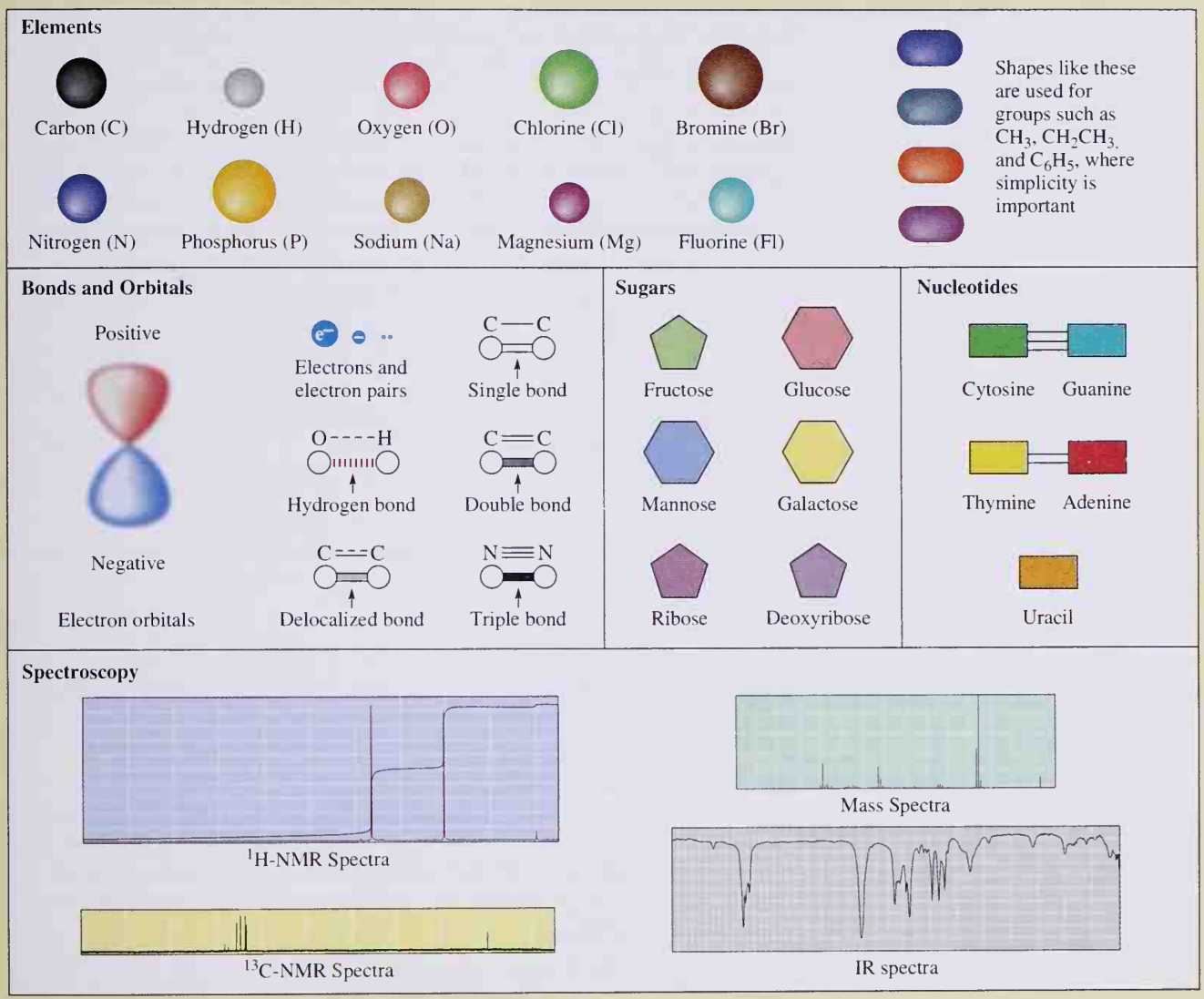
Bio-organic Chemistry

Bio-organic chemistry is emphasized throughout. An invaluable reference for health-related organic chemistry is Goodman and Gilman's *The Pharmacological Basis of Therapeutics,* 8th Edition, A. Goodman Gilman, T. W. Rall, A. S. Nies, and P. Taylor, Editors, (Pergamon Press, New York, 1990).

Glossary of Key Terms

At the end of the book is a section that gives the definitions of important terminology used in this text.

COLOR KEY



Support Package

- Student Study Guide and Problems Book by Brent and Shiela Iverson of the University of Texas, Austin. Contains section-by-section overviews of each chapter and detailed solutions to all text problems. Each reaction chapter includes a "reactions grid," which organizes in a unique way the transformations of each new functional group and the reagent(s) required to bring about each transformation.

- 1001 Ways to Pass Organic Chemistry: A Guide for Helping Students Prepare for Exams by Shelton and Janet Bank, State University of New York, Albany. Contains 1001 problems with answers and tips for problem solving.

- Test Bank by Shelton and Janet Bank, State University of New York, Albany. Contains 25 multiple-choice questions per chapter for instructors to use for tests, quizzes, or homework assignments. Available also in computerized form for IBM-compatible and Macintosh computers.

- Pushing Electrons: A Guide for Students of Organic Chemistry, 2/e (Updated Edition) by Daniel P. Weeks, Northwestern University. A paperback workbook designed to help students learn techniques of electron pushing. Its programmed approach emphasizes repetition and active participation.

- Organic Polymer Chemistry: A Primer by Bruce M. Novak, Polymer Science and Engineering Department, University of Massachusetts. A supplemental chapter in paperback containing an introduction to polymer chemistry: molecular weight distributions, polymer morphology, step-growth and chain polymerizations, ring-opening metathesis polymerizations, and conjugated polymers through ROMP techniques. Also included are a chapter summary, end-of-chapter problems, and three "Chemistry in Action" boxes.

- Overhead Transparency Acetates. A selection of 125 full-color figures from the text.

- Saunders Chemistry of Life Videodisc Multimedia Package. Includes still images from this text, as well as hundreds from other Saunders chemistry texts. The disc can be operated via a computer, a bar code reader, or a hand-controlled keypad.

- Chemoffice Ltd. 2.0 (Chem Draw and Chem 3D) is a software package from Cambridge Scientific that provides students with the capabilities to draw molecular structures, and to manipulate them in three-dimension. A User's Guide and Quick Reference Card, written exclusively for Saunders College Publishing, accompany the software.

The following Organic Chemistry Laboratory Manuals published by Saunders College Publishing can be used along with this text:

- Introduction to Organic Laboratory Techniques, A Microscale Approach, 2/e by Pavia, Lampman, Kriz, and Engel.

- Introduction to Organic Laboratory Techniques, 3/e by Pavia, Lampman, and Kriz.

- Organic Chemistry Laboratory: Standard and Microscale Experiments by Rodig, Bell, and Clark.

- Experimental Organic Chemistry: A Miniscale Approach by Roberts, Gilbert, and Martin.

Acknowledgments

While one or a few persons are listed as "author" of any textbook, the book is in fact the product of collaboration of many individuals, some obvious, others not so obvious. It is with gratitude that I herein acknowledge the contributions of the many. It is only fitting to begin with John Vondeling, Vice President and Publisher of Saunders College Publishing. John's contribution began with the faith that I could do this book and then marshalling the support systems necessary to bring it from rough manuscript to bound book form, assembling the elements of the supplemental materials, and finally bringing to bear his keen sense of the marketplace.

Sandi Kiselica has been a rock of support as Developmental Editor. I so appreciate her ability to set challenging but manageable schedules for me and then her constant encouragement as I worked to meet those deadlines. She was also an invaluable resource person with whom I could discuss everything from pedagogy to details of art work.

Beth Ahrens as Project Editor shouldered with ease the daunting task of coordinating the transformation from manuscript to galleys to pages, including incorporation of the completed art program. Anytime I called Saunders, Beth was at her desk, ready to answer my questions or provide information, and always fully knowledgeable about every phase of the project. I also want to acknowledge others at Saunders who contributed to this project, in particular, Christine Schueler, Art Director; Margie Waldron, Vice President, Marketing; and Charlene Squibb, Production Manager.

E. Paul Papadopoulos of the University of New Mexico, Albuquerque, has been invaluable first as a very involved reviewer and then as a proofer/reviewer without peer. Paul has been deeply involved in all aspects of the final phases of this project and I am deeply indebted to him for his thoroughness and attention to detail.

J. William Suggs of Brown University has provided a unique contribution, the majority of Chemistry in Action boxes. Bill has both industrial and academic background and brings an unusually broad range of professional experience to the writing of these informative pieces.

I also want to acknowledge other colleagues who contributed their comments and suggestions to this book.

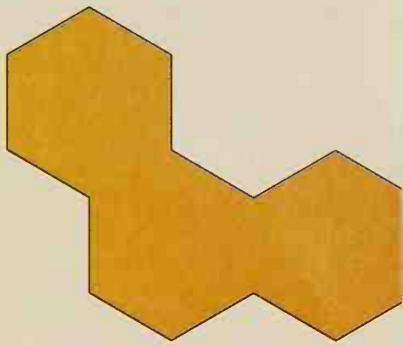
Neil T. Allison, *University of Arkansas*
Rodney Badger, *Southern Oregon State College*
Shelton Bank, *State University of New York, Albany*
Nancy Barta, graduate student, *Michigan State University*
John L. Belletiri, *University of Cincinnati*
Edwin Bryant, graduate student, *Michigan State University*
Edward M. Burgess, *Georgia Institute of Technology*
Robert G. Carlson, *University of Kansas*
Dana S. Chatellier, *University of Delaware*
William D. Closson, *State University of New York, Albany*
David Crich, *University of Illinois, Chicago*
Dennis D. Davis, *New Mexico State University*
James A. Deyrup, *University of Florida*
Thomas A. Dix, *University of California, Irvine*
Paul Dowd, *University of Pittsburgh*

Michael B. East, *Florida Institute of Technology*
Raymond C. Fort, Jr., *University of Maine*
Warren Giering, *Boston University*
Leland Harris, *University of Arizona*
John Helling, *University of Florida*
John L. Hogg, *Texas A&M University*
John W. Huffman, *Clemson University*
Brent Iverson, *University of Texas, Austin*
Ronald Kluger, *University of Toronto*
Joseph B. Lambert, *Northwestern University*
Allan K. Lazarus, *Trenton State University*
Jerry March, *Adelphi University*
Kenneth L. Marsi, *California State University, Long Beach*
David M. McKinnon, *University of Manitoba*
James Mulvaney, *University of Arizona*
Walter Ott, *Emory University*
E. Paul Papadopoulos, *University of New Mexico*
Russell C. Petter, *Sandoz Research Institute*
Joseph M. Prokipcak, *University of Guelph*
William A. Pryor, *Louisiana State University*
Michael Rathke, *Michigan State University*
Charles B. Rose, *University of Nevada, Reno*
James Schreck, *University of Northern Colorado*
Jonathan Sessler, *University of Texas*
Martin Sobczak, graduate student, *Michigan State University*
Steve Steffke, graduate student, *Michigan State University*
John Stille, *Michigan State University*
J. William Suggs, *Brown University*
Peter Trumper, *Bowdoin College*
Ken Turnbull, *Wright State University*
George Wahl, *North Carolina State University*
Michael Waldo, graduate student, *Michigan State University*
Daniel Weeks, *Northwestern University*
Desmond Wheeler, *University of Nebraska*
David F. Wiemer, *University of Iowa*
Darrell J. Woodman, *University of Washington*
Ali Zand, graduate student, *Michigan State University*

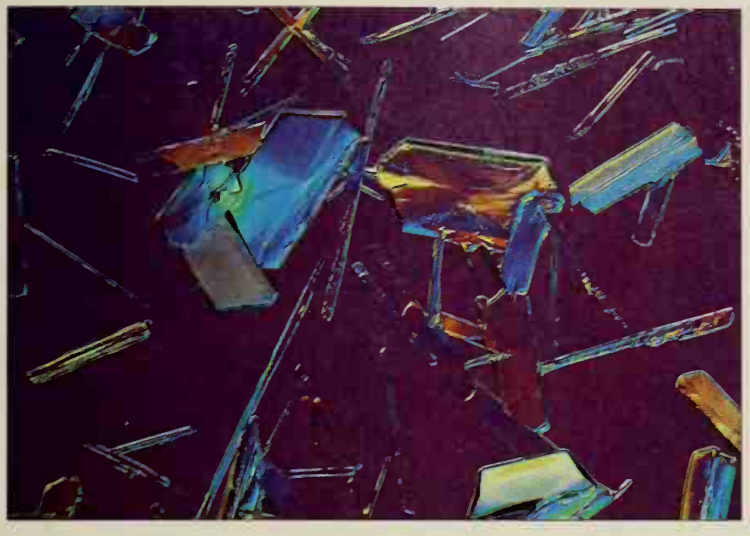
I have enjoyed writing this text, and I hope that instructors and students alike find in it a measure of the excitement I feel for organic chemistry.

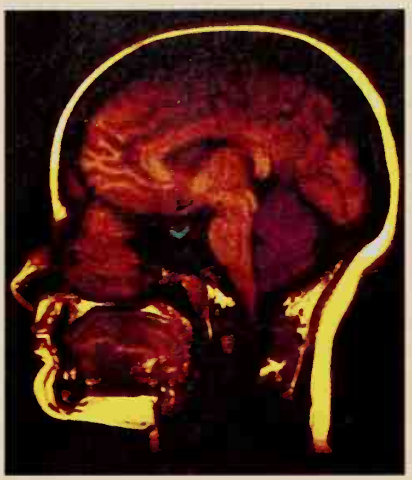
William H. Brown
Beloit College
Beloit, WI
July 1994

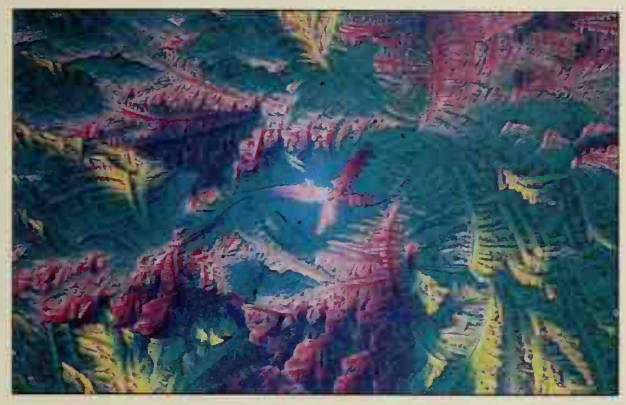
CONTENTS OVERVIEW

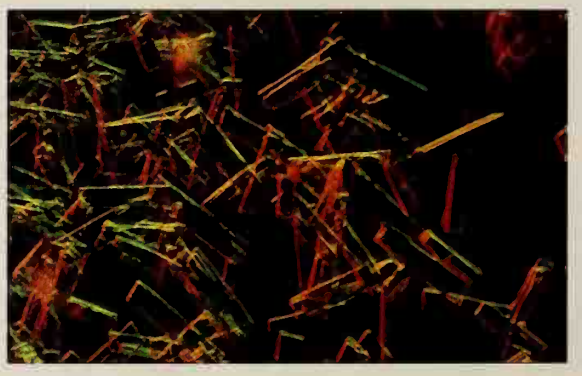


CONTENTS





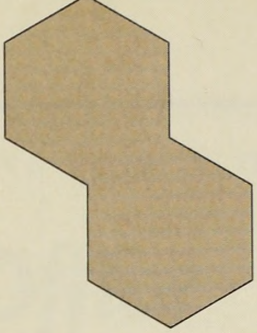




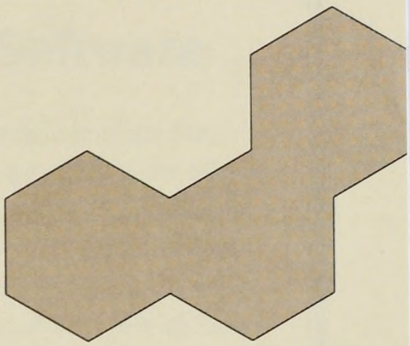
The following chapter is published in a separate paperback supplement entitled **Organic Polymer Chemistry: A Primer**

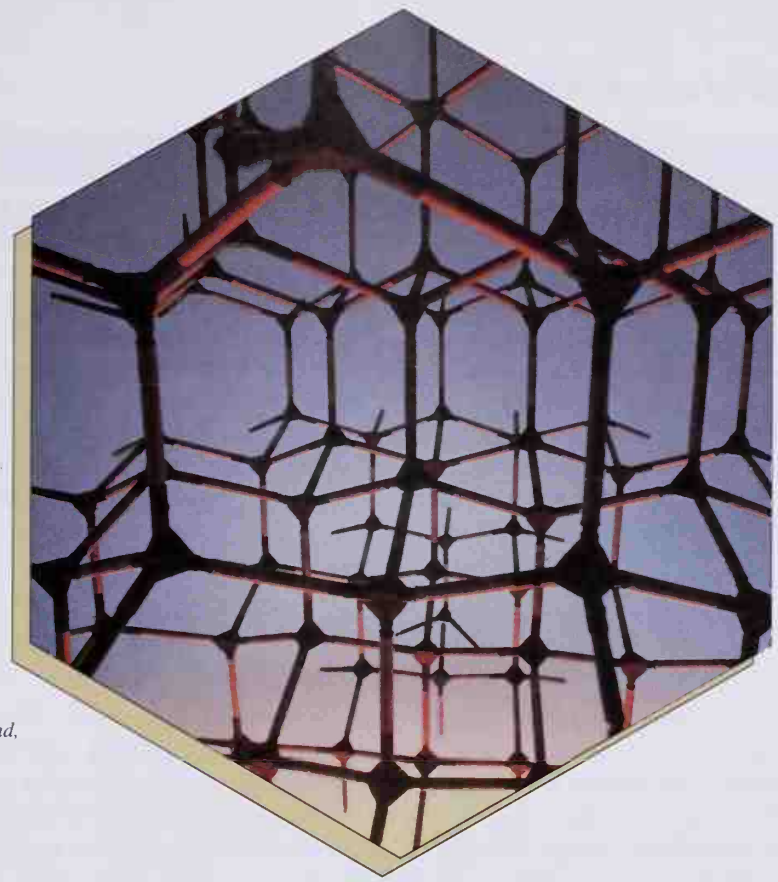
STEREOART

The following figures may be viewed in stereo using the glasses provided with this text:



ORGANIC CHEMISTRY





A model of the structure of diamond, a network solid. (Charles D. Winters)

1

COVALENT BONDS AND SHAPES OF MOLECULES

According to the simplest definition, **organic chemistry** is the study of the compounds of carbon. Perhaps the most remarkable feature of organic chemistry is that it is the chemistry of carbon and only a few other elements—chiefly, hydrogen, oxygen, and nitrogen. There are well over ten million compounds composed of carbon and these three other elements. What unique property of carbon allows it to form so many compounds? The answer lies in its position in the periodic table. As a second-period element, carbon has relatively small atoms allowing it to form double and triple bonds that are rare in the compounds of other Group IV elements such as silicon. In addition, as a Group IV element, carbon can form four bonds to other elements, giving it a wide range of opportunities for bonding. Finally, as an element with intermediate electronegativity, carbon can bond covalently to more electronegative elements, such as oxygen, nitrogen, and the halogens, and with more electropositive elements, such as hydrogen, mercury, and lead.

Key to understanding the physical and chemical properties of organic molecules is an understanding of their structure, and, therefore, we begin with a review of how atoms are bonded together. We study three models of chemical bonding. First is the **Lewis model of bonding,** which accounts in a very simple and straightforward way for the coordination numbers of atoms and for the geometry of chemical bonds. This model, however, gives us little insight into relationships between structure and chemical reactivity. For that, we turn to two models developed using the theory of quantum mechanics, namely, **valence bond theory** and **molecular orbital theory.** Which model should you use and when? The answer depends on what you want to do. If you want to predict a bond angle about a particular atom in a molecule, the Lewis model serves you well. If you wish to understand why a particular bonding pattern imparts a unique set of chemical properties to molecules in which it is found, you need to turn to the valence bond model or the molecular orbital model. And now, let us begin.

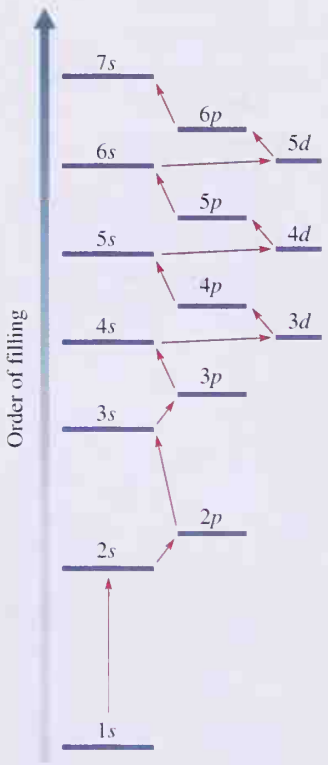
1.1 Electronic Structure of Atoms

You are already familiar with the fundamentals of the electronic structure of atoms. Briefly, an atom contains a small, dense nucleus made of neutrons and positively charged protons. The nucleus is surrounded by a much larger extranuclear space containing negatively charged electrons. Electrons are concentrated about the nucleus in regions of space called **principal energy levels** identified by the **principal quantum numbers** 1, 2, 3, and so on. Each principal energy level can contain up to $2n^2$ **electrons,** where n is the number of the principal energy level. Thus, the first energy level can contain 2 electrons, the second 8 electrons, the third 18 electrons, the fourth 32 electrons, and so on.

Each principal energy level is subdivided into regions of space called **orbitals.** The first principal energy level contains a single orbital called a $1s$ orbital. The second principal energy level contains one s orbital and three p orbitals; these orbitals are designated $2s$, $2p_x$, $2p_y$, and $2p_z$. The third principal energy level contains one $3s$ orbital, three $3p$ orbitals, and five $3d$ orbitals.

Every atom has an infinite number of possible electron configurations. At this stage, we are concerned only with the **ground-state electron configuration**—the electron configuration of lowest energy. The chemical properties of an atom are related primarily to its ground-state electron configuration.

According to the **aufbau principle,** orbitals fill in order of increasing energy from lowest to highest. The first orbital to fill with electrons is the $1s$ orbital. According to the **Pauli exclusion principle,** no more than two electrons may be present in an orbital, one with **spin quantum number** $+\frac{1}{2}$, the other with spin quantum number $-\frac{1}{2}$. Thus, with two electrons, the $1s$ orbital is filled. Next to fill is the $2s$ orbital, followed by the three $2p$ orbitals. The three $2p$ orbitals are said to be **degenerate orbitals,** meaning that electrons in them have equivalent energies. According to **Hund's rule,** when a number of degenerate orbitals are available but not enough electrons are present to fill them completely, then one electron is added to each degenerate orbital before a second electron is added to any one of them. Thus, after the $1s$ and $2s$ orbitals are filled with four electrons, a fifth electron is added to the $2p_x$ orbital, a sixth electron to the $2p_y$ orbital, and a seventh electron to the $2p_z$ orbital. Only after each $2p$ orbital contains one electron is a second electron added to the $2p_x$ orbital. Table 1.1 shows ground-state electron configurations of the first 18 elements of the periodic table.



A representation of the order of filling of subshells for many-electron atoms.

Table 1.1 Ground-state electron configurations for elements 1–18

Element	Atomic Number	Orbital								
		1s	2s	$2p_x$	$2p_y$	$2p_z$	3s	$3p_x$	$3p_y$	$3p_z$
H	1	1								
He	2	2								
Li	3	2	1							
Be	4	2	2							
B	5	2	2	1						
C	6	2	2	1	1					
N	7	2	2	1	1	1				
O	8	2	2	2	1	1				
F	9	2	2	2	2	1				
Ne	10	2	2	2	2	2				
Na	11	2	2	2	2	2	1			
Mg	12	2	2	2	2	2	2			
Al	13	2	2	2	2	2	2	1		
Si	14	2	2	2	2	2	2	1	1	
P	15	2	2	2	2	2	2	1	1	1
S	16	2	2	2	2	2	2	2	1	1
Cl	17	2	2	2	2	2	2	2	2	1
Ar	18	2	2	2	2	2	2	2	2	2

When discussing the physical and chemical properties of an element, chemists often focus on the outermost orbitals of the element because electrons in these orbitals are the ones involved in the formation of chemical bonds and in chemical reactions. To show the outermost electrons of an atom, we commonly use a representation called a **Lewis structure** after the American chemist who devised this notation, G. N. Lewis (1875–1946). A Lewis structure shows the symbol of the element surrounded by a number of dots equal to the number of electrons in the outer shell of that element. In Lewis structures, the atomic symbol represents the "core," that is, the nucleus and all completely filled inner shells. Outer shell electrons are called **valence electrons,** and the energy level in which they are found is called the **valence shell.** Table 1.2 shows Lewis structures for the first 18 elements of the periodic table.

Helium, neon, argon, and krypton are called **noble gases** because of their relative unreactivity. The valence shell of helium is filled with two electrons. Neon, argon, and krypton have in common an electron configuration in which the *s* and *p* orbitals of their outermost, or valence, shell are filled with eight electrons. The valence shells of all other elements shown in Table 1.2 contain fewer than eight electrons.

Compare the Lewis structures given in Table 1.2 with the ground-state electron configurations given in Table 1.1. For example, boron is shown in Table 1.2 with three valence electrons; these are the paired $2s$ electrons and the single $2p_x$ electron shown in Table 1.1. Carbon is shown with four valence electrons; these are the two paired $2s$ electrons and the single $2p_x$ and $2p_y$ electrons shown in Table 1.1.

Gilbert N. Lewis introduced the theory of the shared electron pair bond and revolutionized chemistry. It is in his honor that we often refer to "electron dot" structures as Lewis structures. *(UPI/Bettmann)*

Table 1.2 Lewis structures for elements 1–18 of the periodic table

IA	IIA	IIIA	IVA	VA	VIA	VIIA	VIIIA
H·							He:
Li·	Be:	B:	·C:	·N:	:O:	:F:	:Ne:
Na·	Mg:	Al:	·Si:	·P:	:S:	:Cl:	:Ar:

Notice also from Table 1.2 that for C, N, O, and F in the second row of the periodic table, the valence electrons belong to the principal quantum number 2 shell. With eight electrons, this shell is completely filled. For Si, P, S, and Cl in the third row of the periodic table, the valence electrons belong to the principal quantum number 3 shell. This shell is only partially filled with eight electrons; the $3s$ and $3p$ orbitals are fully occupied, but the five $3d$ orbitals can accommodate an additional ten valence electrons. Because of the differences in number and kind of orbitals in principal energy levels 2 and 3, significant differences exist in the covalent bonding of oxygen and sulfur, and of nitrogen and phosphorus. For example, although oxygen and nitrogen can accommodate no more than 8 electrons in their valence shells, phosphorus can accommodate as many as 10 electrons in its valence shell, and sulfur as many as 12.

1.2 The Lewis Model of Bonding

A. Formation of a Chemical Bond

In 1916, G. N. Lewis devised a beautifully simple model that unified many of the observations about chemical bonding and reactions of the elements. He pointed out that the chemical inertness of the noble gases indicates a high degree of stability of the electron configurations of these elements: helium with a valence shell of two electrons ($1s^2$), neon with a valence shell of eight electrons ($2s^2 2p^6$), and argon with a valence shell of eight electrons ($3s^2 3p^6$). The tendency of atoms to react in ways that achieve an outer shell of eight valence electrons is particularly common among elements of Groups IA–VIIA (the main-group elements) and is given the special name **octet rule.**

EXAMPLE 1.1

Show how calcium in forming Ca^{2+} follows the octet rule.

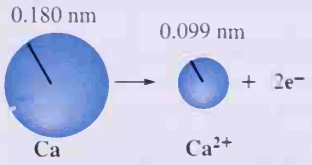
Solution

Following are ground-state electron configurations for Ca and Ca^{2+}:

Ca (20 electrons): $1s^2 2s^2 2p^6 3s^2 3p^6 4s^2$

Ca^{2+} (18 electrons): $1s^2 2s^2 2p^6 3s^2 3p^6$

Thus, Ca^{2+} has a complete octet of electrons in its outermost (valence) shell and has the same electron configuration as argon.



PROBLEM 1.1

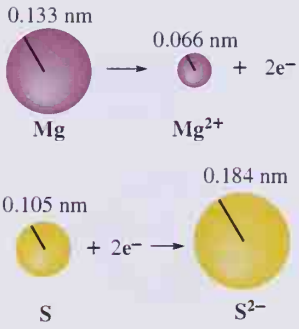
Show that the following obey the octet rule:

(a) Sulfur (atomic number 16) forms sulfide ion, S^{2-}.
(b) Magnesium (atomic number 12) forms Mg^{2+}.

■

According to Lewis' model, atoms bond together in such a way that each atom participating in a chemical bond acquires a completed outer-shell electron configuration resembling that of the noble gas nearest it in the periodic table. Atoms acquire completed outer shells in two ways.

1. An atom may lose or gain enough electrons to acquire a completely filled outer shell. An atom that gains electrons becomes an anion (a negatively charged ion), and an atom that loses electrons becomes a cation (a positively charged ion). A chemical bond between a positively charged ion and a negatively charged ion is called an **ionic bond.**
2. An atom may share electrons with one or more other atoms to complete its outer shell. A chemical bond formed by sharing electrons is called a **covalent bond.**



B. Electronegativity and Chemical Bonds

One way to estimate the degree of ionic or covalent character in a chemical bond is to compare the electronegativities of the atoms involved. **Electronegativity** is a measure of the force of an atom's attraction for electrons that it shares in a chemical bond with another atom. The most widely used scale of electronegativities was devised by Linus Pauling in the 1930s and is based on bond energies. On the Pauling scale, fluorine, the most electronegative element, is assigned an electronegativity of 4.0, and all other elements are assigned values in relation to fluorine. Table 1.3 shows electronegativities of the elements on

Linus Pauling received the Nobel Prize in chemistry in 1954 for his contributions to our understanding of the nature of chemical bonding. He received the Nobel Prize for peace in 1962.

Table 1.3 Electronegativity values for some atoms (Pauling scale)

IA	IIA											IIIA	IVA	VA	VIA	VIIA
								H 2.1								
Li 1.0	Be 1.5											B 2.0	C 2.5	N 3.0	O 3.5	F 4.0
Na 0.9	Mg 1.2	IIIB	IVB	VB	VIB	VIIB	VIIIB				IB	IIB	Al 1.5	Si 1.8	P 2.1	S 2.5	Cl 3.0
K 0.8	Ca 1.0	Sc 1.3	Ti 1.5	V 1.6	Cr 1.6	Mn 1.5	Fe 1.8	Co 1.8	Ni 1.8	Cu 1.9	Zn 1.6	Ga 1.6	Ge 1.8	As 2.0	Se 2.4	Br 2.8
Rb 0.8	Sr 1.0	Y 1.2	Zr 1.4	Nb 1.6	Mo 1.8	Tc 1.9	Ru 2.2	Rh 2.2	Pd 2.2	Ag 1.9	Cd 1.7	In 1.7	Sn 1.8	Sb 1.9	Te 2.1	I 2.5
Cs 0.7	Ba 0.9	La 1.1	Hf 1.3	Ta 1.5	W 1.7	Re 1.9	Os 2.2	Ir 2.2	Pt 2.2	Au 2.4	Hg 1.9	Tl 1.8	Pb 1.8	Bi 1.9	Po 2.0	At 2.2

<1.0 1.0 – 1.4 1.5 – 1.9 2.0 – 2.4 2.5 – 2.9 3.0 – 4.0

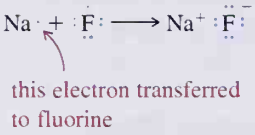
Linus Pauling (1901–) was the first person ever to receive two unshared Nobel Prizes. *(UPI/Bettmann)*

the Pauling scale. Note that because bond energy for a particular bond varies somewhat depending on its chemical environment, electronegativity values in Table 1.3 are actually average values. The main-group elements (Groups IA–VIIA) exhibit the following periodic trends in electronegativity.

1. Electronegativity increases from left to right within a period (horizontal row).
2. Electronegativity decreases from top to bottom within a column (vertical row).

Ionic Bonds

An **ionic bond** is a chemical bond formed by the attractive force between positive and negative ions. As an approximation we say that an ionic bond is formed by the transfer of electrons from the valence shell of an atom of low electronegativity to the valence shell of an atom of high electronegativity. The more electronegative atom gains one or more valence electrons and becomes an anion; the less electronegative atom loses one or more valence electrons and becomes a cation. An example of an ionic bond is that formed between sodium (electronegativity 0.9) and fluorine (electronegativity 4.0).



In forming this bond, the single $3s$ valence electron of sodium is transferred to the partially filled valence shell of fluorine:

$$Na(1s^2 2s^2 2p^6 \mathbf{3s^1}) + F(1s^2 2s^2 \mathbf{2p^5}) \longrightarrow Na(1s^2 2s^2 2p^6) + F(1s^2 2s^2 \mathbf{2p^6})$$

As a result of this transfer of one electron, both sodium and fluorine form ions that arisoelectronic with neon, the noble gas nearest each in the periodic table.

Ions with noble gas configurations are particularly stable, and their formation accounts in part for the stability of ionic solids. A second factor in the stability of ionic solids is the lattice energy released when positive and negative ions become arranged in an ordered array in a crystal lattice. In sodium fluoride, each Na^+ ion is surrounded by six F^- ions, and each F^- ion is in turn surrounded by six Na^+ ions (Figure 1.1).

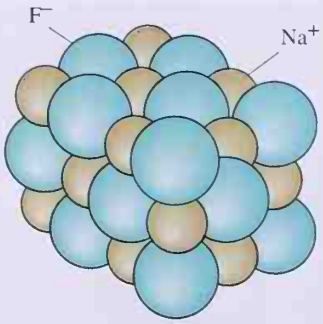


Figure 1.1
Model of the NaF lattice. Each Na^+ ion is surrounded by six F^- ions, and each F^- ion is in turn surrounded by six Na^+ ions.

Covalent Bonds

A **covalent bond** is a chemical bond formed by sharing electron pairs between two atoms. The simplest example of a covalent bond is that in the hydrogen molecule. When two hydrogen atoms combine, the single electrons from each combine to form an electron pair. This shared pair completes the valence shell of each hydrogen. According to the Lewis model, a pair of electrons in a covalent bond functions in two ways simultaneously; it is shared by two atoms and at the same time fills the outer (valence) shell of each.

$$H\cdot + \cdot H \longrightarrow H{-}H \qquad \Delta H = -104 \text{ kcal/mol } (-435 \text{ kJ/mol})$$

The Lewis model accounts for the stability of covalent bonds in the following way. In forming a covalent bond, an electron pair occupies the region between two nuclei and serves to shield one positively charged nucleus from the repulsive force of the other positively charged nucleus. At the same time, the electron pair attracts both nuclei. In other words, an electron pair in the space between two nuclei bonds them together and fixes the internuclear distance to within very narrow limits. The distance between nuclei participat-

ing in a chemical bond is called a **bond length.** The attraction between positively charged nuclei and negatively charged electrons is one factor contributing to the stability of covalent bonds. We discuss a second and more important factor in Section 1.8B.

Percent Ionic Character of Covalent Bonds

Although all covalent bonds involve the sharing of electrons, they differ widely in the degree of sharing. Consider, for example, a covalent bond between carbon and hydrogen. Because these atoms have almost identical electronegativities (C = 2.5; H = 2.1), electrons in a C—H bond are shared almost equally. A **nonpolar covalent bond** is one in which the sharing of electrons is equal or almost equal. Another situation arises when the difference in electronegativity between two atoms joined by a covalent bond is somewhat larger. A **polar covalent bond** is one in which the sharing of electrons is unequal. We also refer to polar covalent bonds as covalent bonds with partial ionic character. For example, on the Pauling scale, the difference in electronegativity between chlorine and hydrogen is 3.0 − 2.1 = 0.9 unit. The H—Cl bond is covalent, but the sharing of electrons is not equal. Electrons of the bond are attracted to chlorine more strongly than to hydrogen. An important consequence of this unequal sharing of electrons is that chlorine has a greater proportion of the shared electrons around it and hence has a partial negative charge, indicated by the symbol $\delta-$. Hydrogen has a lesser proportion of the shared electrons and consequently has a partial positive charge, indicated by the symbol $\delta+$. The respective distributions of electrons in a nonpolar covalent bond, a polar covalent bond, and an ionic bond are illustrated in Figure 1.2.

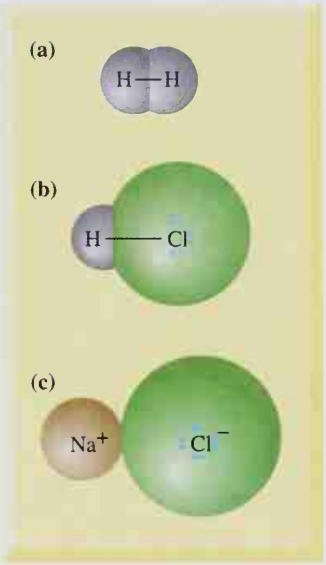


Figure 1.2
Sharing of electrons in (a) nonpolar and (b) polar covalent bonds, and (c) the transfer of electrons in an ionic bond. These drawings show relative sizes of the atoms and ions involved in each bond.

As we shall see throughout this text, the degree of polarity (partial ionic character) of covalent bonds is one of the most important factors in determining both physical and chemical properties of organic molecules. For this reason, chemists have sought ways to calculate the degree of polarity of covalent bonds. Of the various methods developed for this purpose, the simplest and most direct is that based on electronegativity. The **percent ionic character of a covalent bond** can be calculated as follows, where E_a is the electronegativity of the more electronegative atom and E_b that of the less electronegative atom.

$$\% \text{ ionic character} = \frac{E_a - E_b}{E_a} \times 100$$

EXAMPLE 1.2

Calculate the percent ionic character of the following covalent bonds. For each, show which atom bears the partial positive charge and which the partial negative charge.

(a) C—O **(b)** C—H **(c)** H—O

Solution

(a) A C—O bond has 29% ionic character. Oxygen, the more electronegative atom, bears a partial negative charge; and carbon, the less electronegative atom, bears a partial positive charge.

$$\% \text{ ionic character} = \frac{3.5 - 2.5}{3.5} \times 100 = 29\% \qquad \overset{\delta+\ \ \delta-}{\text{C—O}}$$

(b) A C—H bond has approximately 16% ionic character, with carbon, the more

electronegative element, bearing a partial negative charge and hydrogen, the less electronegative element, a partial positive charge.

$$\% \text{ ionic character} = \frac{2.5 - 2.1}{2.5} \times 100 = 16\% \qquad \overset{\delta-\ \ \delta+}{\text{C—H}}$$

(c) An H—O bond has approximately 40% ionic character, with oxygen bearing a partial negative charge and hydrogen a partial positive charge.

$$\% \text{ ionic character} = \frac{3.5 - 2.1}{3.5} \times 100 = 40\% \qquad \overset{\delta+\ \ \delta-}{\text{H—O}}$$

PROBLEM 1.2

Calculate the percent ionic character of the following covalent bonds. For each, show which atom bears the partial negative charge and which atom bears the partial positive charge.

(a) N—H (b) C—Mg (c) B—H

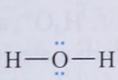
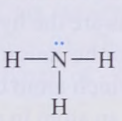
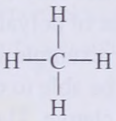
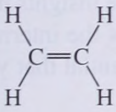
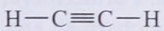
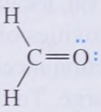
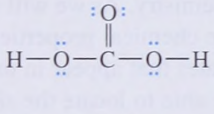
C. Lewis Structures of Covalent Molecules and Ions

The ability to write Lewis structures for covalent molecules and ions is a fundamental skill for the study of organic chemistry. The following guidelines will help you to do this:

1. Determine the number of valence electrons in the molecule or ion. To do this, add the number of valence electrons contributed by each atom. For ions, add one electron for each negative charge on the ion, and subtract one electron for each positive charge on the ion.
2. Determine the arrangement (order of attachment) of atoms in the molecule or ion. Except for the simplest molecules and ions, this arrangement must be determined experimentally. For some molecules and ions given as examples in the text, you are asked to propose an arrangement of atoms. For most, however, you are given the experimentally determined arrangement of atoms.
3. Connect the atoms with single bonds. Then arrange the remaining electrons in pairs so that each atom in the molecule or ion has a complete outer shell. Each hydrogen atom must be surrounded by two electrons. Each atom of carbon, oxygen, nitrogen, and halogen must be surrounded by eight electrons (per the octet rule).
4. A pair of electrons involved in a covalent bond (bonding electrons) is shown as a single bond; an unshared (nonbonding) pair of electrons is shown as a pair of dots.
5. In a **single bond,** two atoms share one pair of electrons. In a **double bond** they share two pairs of electrons, and in a **triple bond** they share three pairs of electrons.

Table 1.4 shows Lewis structures, molecular formulas, and names for several molecules. After the molecular formula of each, the number of valence electrons it contains is given. Notice that in these molecules, each hydrogen atom is surrounded by two valence electrons, and each atom of carbon, nitrogen, oxygen, and chlorine is surrounded by eight valence electrons. Furthermore, each carbon atom has four bonds, the nitrogen atom has three bonds and one unshared pair of electrons, each oxygen atom has two bonds and two unshared pairs of electrons, and the chlorine atom (as is true for other halogens as well) has one bond and three unshared pairs of electrons.

Table 1.4 Lewis structures for several small molecules

			
H_2O (8) Water	NH_3 (8) Ammonia	CH_4 (8) Methane	HCl (8) Hydrogen chloride
			
C_2H_4 (12) Ethene (Ethylene)	C_2H_2 (10) Ethyne (Acetylene)	CH_2O (12) Methanal (Formaldehyde)	H_2CO_3 (24) Carbonic acid

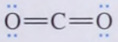
EXAMPLE 1.3

Draw Lewis structures, showing all valence electrons, for the following covalent molecules:

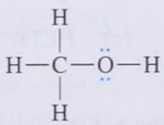
(a) CO_2 **(b)** CH_4O **(c)** CH_3Cl

Solution

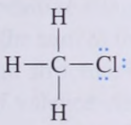
Under each Lewis structure is the number of valence electrons it contains.

(a) 

Carbon dioxide
(16 valence electrons)

(b) 

Methanol
(14 valence electrons)

(c) 

Chloromethane
(14 valence electrons)

PROBLEM 1.3

Draw Lewis structures, showing all valence electrons, for the following covalent molecules:

(a) C_2H_6 **(b)** CS_2 **(c)** HCN

D. Formal Charge

Throughout this course we deal not only with molecules but also with polyatomic cations and polyatomic anions. Examples of polyatomic cations are the hydronium ion, H_3O^+, and the ammonium ion, NH_4^+. An example of a polyatomic anion is the bicarbonate ion, HCO_3^-. It is important that you be able to determine which atom or atoms in a polyatomic ion bear the positive or negative charge. The charge on an atom in an ion or in a molecule is called its **formal charge.** In a sense, formal charge is simply electron bookkeeping. Nonetheless, to be able to calculate formal charge is essential to an understanding of organic chemistry. As we will see very soon, location of formal charge gives valuable insights into the chemical properties and reactivities of molecules. Furthermore, many of the intermediates that appear in organic reaction mechanisms are charged, and it is essential that you be able to locate the site of a charge. To derive formal charge

1. Write a correct Lewis structure for the molecule or ion.
2. Assign to each atom all of its unshared (nonbonding) electrons and one-half of its shared (bonding) electrons.
3. Compare this number with the number of valence electrons in the neutral, unbonded atom. If the number of electrons assigned a bonded atom is less than that assigned to the unbonded atom, then more positive charges are in the nucleus than counterbalancing negative charges, and the atom has a formal positive charge. Conversely, if the number of electrons assigned to a bonded atom is greater than that assigned to the unbonded atom, then the atom has a formal negative charge.

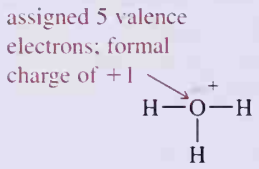
EXAMPLE 1.4

Draw Lewis structures for the following ions, and show which atom in each bears the formal charge:

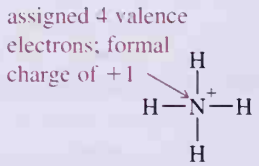
(a) H_3O^+ **(b)** NH_4^+ **(c)** HCO_3^-

Solution

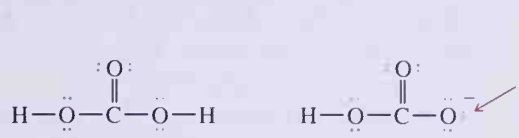
(a) An unbonded oxygen atom has six valence electrons. The oxygen atom in H_3O^+ is assigned five electrons: two nonbonding electrons and one from each shared pair of electrons. Therefore, oxygen has a formal charge of +1 (6 − 5 = +1).



(b) An unbonded nitrogen atom has five valence electrons. Nitrogen is assigned four valence electrons and, therefore, has a formal charge of +1 (5 − 4 = 1).



(c) Loss of a hydrogen ion from carbonic acid (Table 1.4) gives the bicarbonate ion. Carbon is assigned four valence electrons and has no formal charge (4 − 4 = 0). Two oxygens are assigned six valence electrons each and have no formal charges (6 − 6 = 0). The third oxygen is assigned seven valence electrons and has a formal charge of −1 (6 − 7 = −1).



Carbonic acid, H_2CO_3 (an oxyacid)

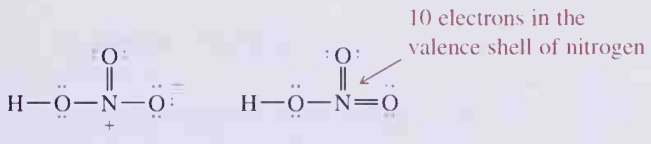
Bicarbonate ion, HCO_3^-

PROBLEM 1.4

Draw Lewis structures for the following ions, and show which atom in each bears the formal charge:

(a) CH_3^+ **(b)** CH_3^- **(c)** OH^-

In writing Lewis structures for molecules and ions, it is essential to remember that elements of the second row, including carbon, nitrogen, and oxygen, can accommodate no more than eight electrons in their valence shells. Following are two Lewis structures for nitric acid, HNO_3, each with the correct number of valence electrons, namely, 24:



An acceptable Lewis structure

Not an acceptable Lewis structure

The first structure is an acceptable Lewis structure. It shows the required 24 valence electrons; each oxygen and nitrogen has a completed valence shell of 8 electrons; it shows a formal positive charge on nitrogen, and a formal negative charge on one of the oxygens. Note that the sum of the formal charges on the acceptable Lewis structure for HNO_3 is zero. The second structure is not an acceptable Lewis structure. Although it shows the correct number of valence electrons, it places ten electrons in the valence shell of nitrogen.

E. Exceptions to the Octet Rule

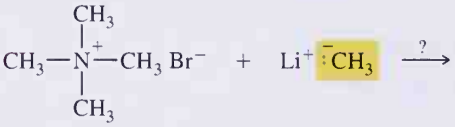
The Lewis model of covalent bonding focuses on valence electrons and the necessity for each atom in a covalent bond to have a completed valence shell of eight electrons. Although most molecules formed by main-group elements (Groups IA–VIIA) have structures that satisfy the octet rule, there are two important exceptions to this rule. In the first group are molecules containing an atom with fewer than eight valence electrons around it. In the second group are molecules containing an atom with more than eight electrons in its valence shell.

CHEMISTRY IN ACTION

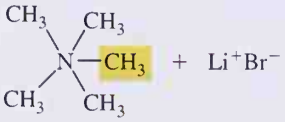
The Octet Rule

The octet rule of G. N. Lewis gives us a powerful and simple model for understanding bonding in organic compounds. Experiments designed to prepare molecules with ten electrons in the valence shell of carbon or nitrogen atoms might seem pointless or absurd. However, because chemistry is an experimental science, the truth of concepts such as the octet rule can be established only by experiment. No matter how many molecules obey the octet rule, a single exception would result in major modifications to the rule, or even its replacement.

In 1949, the German chemist Georg Wittig attempted to prepare pentamethyl nitrogen, a compound with ten electrons in nitrogen's valence shell, by the following reaction:

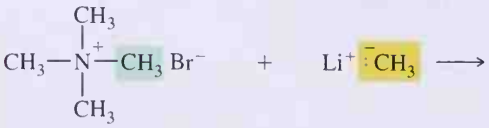


Tetramethylammonium bromide Methyllithium

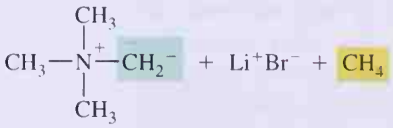


Pentamethylnitrogen

Instead, an acid-base reaction took place with one of the C—H bonds in the tetramethylammonium bromide.



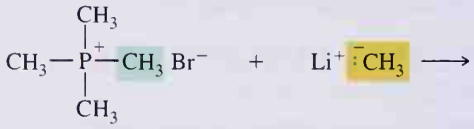
Tetramethylammonium bromide Methyllithium



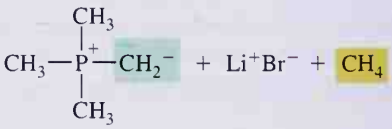
A nitrogen ylide

The product from this reaction, which obeys the Lewis octet rule, has a positively charged nitrogen next to a negatively charged carbon. This novel type of molecule had not been made before. Wittig gave this class of molecules the name "ylide."

Knowing that phosphorus (just below nitrogen in the periodic table) is capable of expanding its octet, Wittig carried out an analogous reaction with phosphorus.



Tetramethylphosphonium bromide Methyllithium



A phosphorus ylide

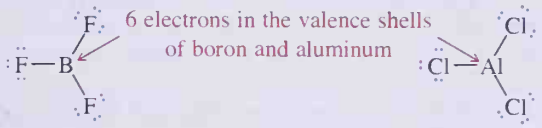
Once again, an acid-base reaction took place, and the product was a phosphorus ylide.

Wittig soon abandoned his attempts to make compounds with five bonds to nitrogen (a goal he later characterized as absurd) and instead studied the chemistry of the newly discovered ylides. He found that phosphorus ylides are extraordinarily useful reagents for preparing complex organic molecules, including such important compounds as vitamin A. In 1979, Professor Wittig was awarded the Nobel Prize in chemistry for his discovery and work with phosphorus ylides.

Today, with our more powerful calculation tools, we can be quite confident that it is not possible to prepare stable compounds that violate the octet rule. Nevertheless, organic chemists continue to test the limits of bonding and reactivity. The results may be even newer kinds of structures and organic reactions, some of which will come as a surprise to everyone.

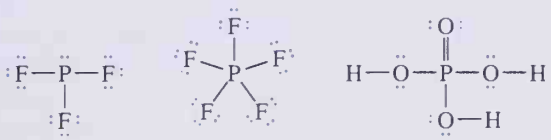
See G. Wittig, *Science*, **210**, 600 (1980).

The most common examples of the first group are molecules containing atoms of Group IIIA elements. Following is a Lewis structure for BF_3. In this uncharged covalent compound, boron is surrounded by only six valence electrons. Aluminum chloride is an example of a compound in which aluminum, the element immediately below boron in Group IIIA, has an incomplete valence shell. Because their valence shell is only partially filled, trivalent compounds of boron and aluminum are highly reactive.



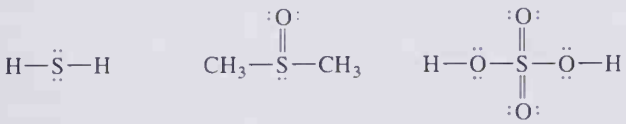
Boron trifluoride Aluminum chloride

A second group of exceptions to the octet rule is made up of molecules and ions that contain an atom with more than eight electrons in its valence shell. Atoms of second-row elements use $2s$ and $2p$ orbitals for bonding, and these orbitals can contain only eight valence electrons, hence the octet rule. Atoms beyond row 2 have *ns*, *np*, and *nd* orbitals and can accommodate more than eight electrons in their valence shells. Following are Lewis structures for phosphorus trifluoride, phosphorus pentafluoride, and phosphoric acid. The first compound has eight electrons in the valence shell of phosphorus, the second and third compounds have ten electrons in the valence shell of phosphorus.



Phosphorus trifluoride Phosphorus pentafluoride Phosphoric acid

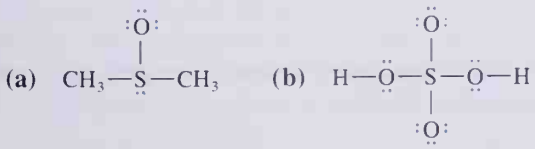
Sulfur, another third-row element, has $3d$ orbitals available for bonding and forms compounds in which its valence shell contains 8, 10, or 12 electrons. Following are Lewis structures for hydrogen sulfide, dimethyl sulfoxide, and sulfuric acid.



Hydrogen sulfide Dimethyl sulfoxide Sulfuric acid

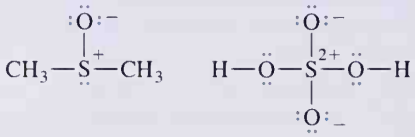
EXAMPLE 1.5

Following are alternative Lewis structures for dimethyl sulfoxide and sulfuric acid that show only eight electrons in the valence shell of sulfur. Assign formal charges in each atom in these Lewis structures.



Solution

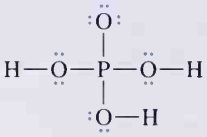
In the alternative Lewis structure for dimethyl sulfoxide, sulfur has a formal charge of +1, and in the alternative Lewis structure for sulfuric acid, sulfur has a formal charge of +2. Each oxygen atom with three unshared pairs of electrons has a formal charge of −1.



Throughout this text, we follow the practice common to organic chemistry of showing sulfur with an expanded valence shell of up to 12 valence electrons and with no formal charge.

PROBLEM 1.5

Assign formal charges in the alternative Lewis structure for phosphoric acid that shows only single bonds to phosphorus and only eight electrons in its valence shell.



1.3 Bond Angles and Shapes of Molecules

In the preceding section, we used a shared pair of electrons as the fundamental unit of a covalent bond and drew Lewis structures for several small molecules and ions containing various combinations of single, double, and triple bonds. We can predict bond angles in these and other covalent molecules in a very straightforward way using the **valence-shell electron-pair repulsion (VSEPR) model.** According to the VSEPR model, an atom is surrounded by an outer shell of valence electrons. These valence electrons may be involved in the formation of single, double, or triple bonds, or they may be unshared. Each of these combinations creates a negatively charged region of space, and because like charges repel each other, the various regions of electron density around an atom spread out so that each is as far away from the others as possible.

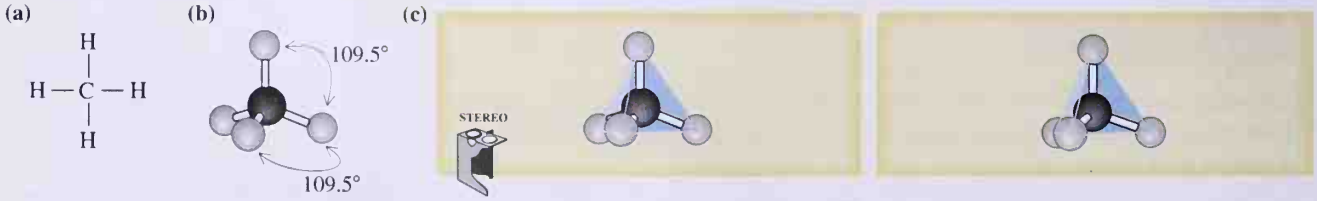


Figure 1.3
The shape of a methane molecule, CH_4: (a) Lewis structure, (b) the three-dimensional shape showing bond angles, and (c) a stereopair.

Let us use the VSEPR model to predict the shape of methane, CH_4. The Lewis structure for CH_4 shows a carbon atom surrounded by four separate regions of electron density, each of which consists of a pair of electrons forming a bond to a hydrogen atom. According to the VSEPR model, the four regions radiate from carbon so that they are as far away from each other as possible. This occurs when the angle between any two pairs of electrons is 109.5°. Therefore, all H—C—H bond angles are predicted to be 109.5°, and the shape of the molecule is predicted to be **tetrahedral.** The H—C—H bond angles in methane have been measured experimentally and found to be 109.5°. Thus, the bond angles and shape of methane predicted by the VSEPR model are identical to those observed. Figure 1.3 shows a Lewis structure for methane, the tetrahedral arrangement of the four regions of electron density around carbon, and a stereopair.

We can predict the shape of the ammonia molecule in exactly the same manner. The Lewis structure of NH_3 shows nitrogen surrounded by four regions of electron density. Three regions contain single pairs of electrons forming covalent bonds with hydrogen atoms. The fourth region contains an unshared pair of electrons. These four regions of electron density are arranged in a tetrahedral manner around the central nitrogen atom as shown in Figure 1.4. The geometry of ammonia is described as **trigonal pyramidal.** Nitrogen is at the apex of a pyramid, and the three hydrogens bonded to it form the triangular base of the pyramid. In trigonal pyramidal geometry, an atom is surrounded by four regions of electron density; three of these are bonding regions, and the fourth is a nonbonding region.

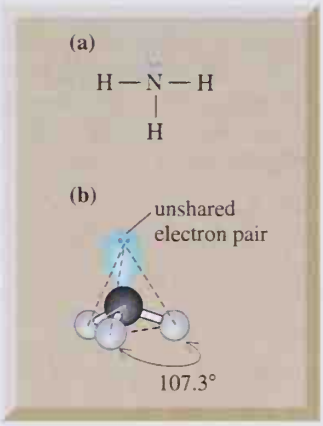


Figure 1.4
The shape of an ammonia molecule, NH_3: (a) Lewis structure and (b) the three-dimensional shape.

According to the VSEPR model, the four regions of electron density around nitrogen are arranged in a tetrahedral manner, and the predicted H—N—H bond angles are 109.5°. The observed bond angles are 107.3°. This small difference between the predicted and observed angles can be explained by proposing that the unshared pair of electrons on nitrogen repels adjacent electron pairs more strongly than do bonding pairs of electrons.

Figure 1.5 shows the Lewis structure and a ball-and-stick model of a water molecule. In H_2O, oxygen is surrounded by four separate regions of electron density. Two of these regions contain pairs of electrons used to form covalent bonds with hydrogen; the remaining two contain unshared electron pairs.

According to the VSEPR model, the four regions of electron density around oxygen are arranged in a tetrahedral manner, and the predicted H—O—H bond angle is 109.5°. Experimental measurements show that the actual bond angle is 104.5°, a value smaller than that predicted. This difference between the predicted and observed bond angles can be explained by proposing, as we did for NH_3, that unshared pairs of electrons repel adjacent pairs more strongly than do bonding pairs. Note that the distortion from 109.5° is greater in H_2O, which has two unshared pairs of electrons, than it is in NH_3, which has only one unshared pair.

A general prediction emerges from this discussion of the shapes of CH_4, NH_3, and H_2O. Any time four separate regions of electron density exist around a central atom, the VSEPR model predicts a tetrahedral distribution of electron density and bond angles of approximately 109.5°.

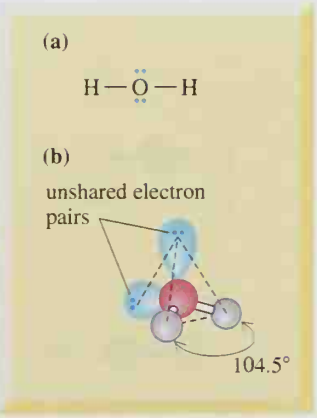


Figure 1.5
The shape of a water molecule, H_2O: (a) Lewis structure and (b) the three-dimensional shape.

In many of the molecules we encounter, an atom is surrounded by three regions of electron density. Shown in Figure 1.6 are Lewis structures for methanal, CH_2O, and ethene, C_2H_4.

According to the VSEPR model, a double bond is treated as a single region of electron density. In methanal, carbon is surrounded by three regions of electron density, two of which contain single pairs of electrons forming single bonds to hydrogen atoms. The third region of electron density contains two pairs of electrons forming a double bond to oxygen.

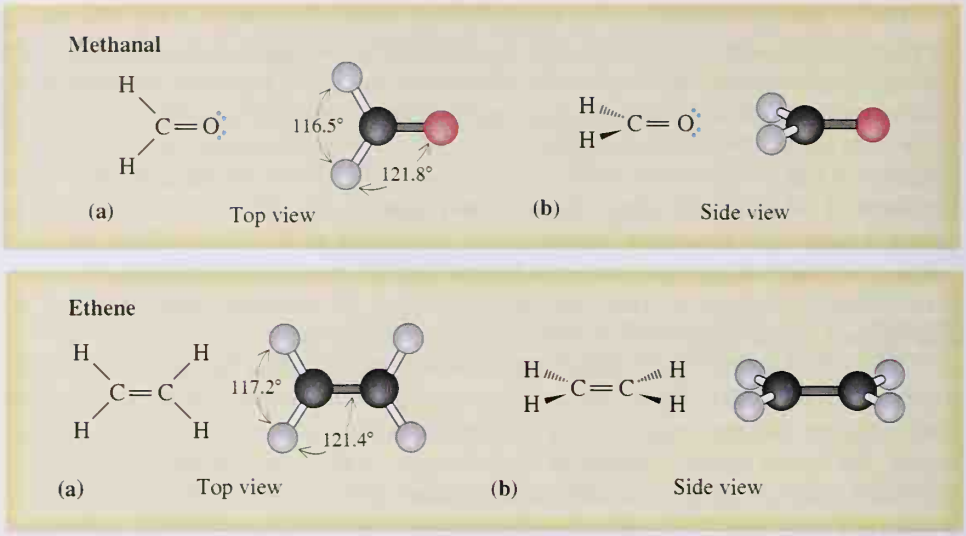


Figure 1.6
Shapes of methanal (formaldehyde) and ethene (ethylene). Lewis structures and three-dimensional shapes shown from (a) top view and (b) side view.

In ethene, each carbon atom is also surrounded by three regions of electron density: two contain single pairs of electrons, and the other contains two pairs of electrons. Three regions of electron density about an atom are farthest apart if they are all in the same plane and make angles of 120° with each other. Thus, the predicted H—C—H and H—C—O bond angles in methanal are 120°; the predicted H—C—H and H—C—C bond angles in ethene are also 120°. Such an arrangement of atoms is described as **trigonal planar.**

In still other types of molecules, a central atom is surrounded by only two regions of electron density. Shown in Figure 1.7 are Lewis structures and ball-and-stick models of carbon dioxide, CO_2, and ethyne, C_2H_2. In carbon dioxide, carbon is surrounded by two regions of electron density: each contains two pairs of electrons and forms a double bond to an oxygen atom. In ethyne, each carbon is also surrounded by two regions of electron density: one contains a single pair of electrons and forms a single bond to a hydrogen atom, and the other contains three pairs of electrons and forms a triple bond to a carbon atom. In each case, the two regions of electron density are farthest apart if they form a straight line through the central atom and create an angle of 180°. Both carbon dioxide and ethyne are linear molecules.

Predictions of the VSEPR model are summarized in Table 1.5.

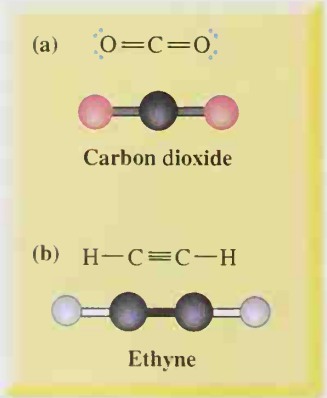


Figure 1.7
Shapes of (a) carbon dioxide and (b) ethyne (acetylene).

EXAMPLE 1.6

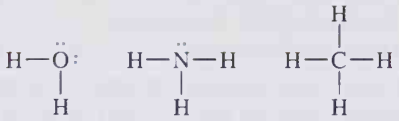
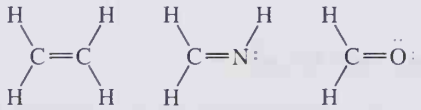
Predict all bond angles in the following molecules:

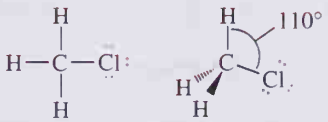
(a) CH_3Cl (b) HCN (c) $CH_2{=}CHCl$

Solution

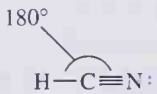
(a) The Lewis structure for chloromethane, CH_3Cl, shows carbon surrounded by four separate regions of electron density. Therefore, predict the distribution of electron pairs to be tetrahedral, all bond angles to be 109.5°, and the shape of CH_3Cl to be tetrahedral. The actual H—C—Cl bond angle is 110°.

Table 1.5 Predicted molecular shapes (VSEPR model)

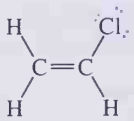
Regions of Electron Density Around Central Atom	Arrangement of Regions of Electron Density in Space	Predicted Bond Angles
4	tetrahedral	109.5°
Examples		
3	trigonal planar	120°
Examples		
2	linear	180°
Examples		



(b) In the Lewis structure of hydrogen cyanide, HCN, carbon is surrounded by two regions of electron density. Therefore, predict 180° for the H—C—N bond angle and the shape of HCN to be linear.



(c) The Lewis structure of chloroethene $CH_2{=}CHCl$, shows each carbon surrounded by three regions of electron density. Therefore, predict all bond angles to be 120°.



PROBLEM 1.6

Predict all bond angles for the following molecules and ions.

(a) CH_3OH **(b)** PF_3 **(c)** CH_2Cl_2 **(d)** CH_3^+

1.4 Functional Groups

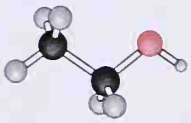
Carbon combines with other atoms (e.g., C, H, N, O, S, halogens) to form characteristic structural units called **functional groups.** Functional groups are important for three reasons. First, they are the units by which we divide organic compounds into classes. Second, they are sites of chemical reaction; a particular functional group, in whatever compound it is found, undergoes the same types of chemical reactions. Third, functional groups serve as a basis for naming organic compounds.

Introduced here are several of the functional groups we encounter early in the course. At this point our concern is nothing more than pattern recognition. We have more to say about the structure and the physical and chemical properties of these functional groups in following chapters.

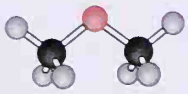
A. Alcohols and Ethers

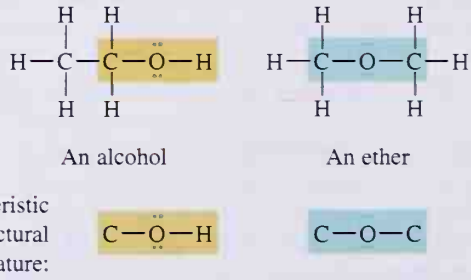
The characteristic structural feature of an **alcohol** is an **—OH (hydroxyl)** group bonded to a carbon atom. The characteristic structural feature of an **ether** is an atom of oxygen bonded to two carbon atoms. Following are Lewis structures for an alcohol and an ether and the characteristic structural feature of each.

CH_3CH_2OH



CH_3OCH_3





We can write formulas for this alcohol and ether in a more abbreviated form using what are called **condensed structural formulas.** In a condensed structural formula, CH_3— indicates a carbon with three attached hydrogens, —CH_2— indicates a carbon with two attached hydrogens, and —CH= indicates a carbon with one attached hydrogen. Unshared pairs of electrons are generally not shown in condensed structural formulas. Following are condensed structural formulas for the alcohol and ether of molecular formula C_2H_6O:

$$CH_3—CH_2—OH \qquad CH_3—O—CH_3$$

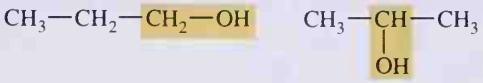
EXAMPLE 1.7

There are two alcohols of molecular formula C_3H_8O. Draw a condensed structural formula for each.

Solution

The molecular formula contains three carbon atoms. These can be bonded together in a chain with the —OH group attached to the end carbon of the chain or attached to the

middle carbon of the chain. Then, add seven hydrogens to satisfy the tetravalence of carbon and give the correct molecular formula.

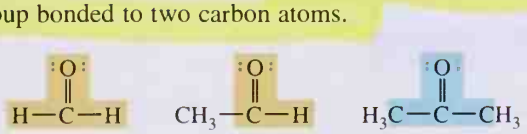


PROBLEM 1.7

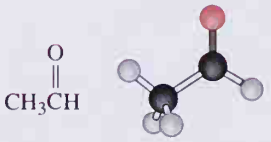
There is one ether of molecular formula C_3H_8O. Draw a condensed structural formula for this compound.

B. Aldehydes and Ketones

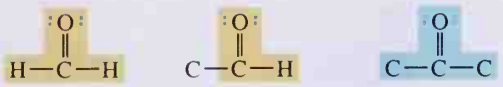
Both aldehydes and ketones contain a **C=O (carbonyl) group.** The characteristic structural feature of an aldehyde is a carbonyl group bonded through carbon to two other atoms—to two hydrogens in the case of methanal, CH_2O, the simplest aldehyde, and to another carbon and a hydrogen in all other aldehydes. The characteristic structural feature of a ketone is a carbonyl group bonded to two carbon atoms.

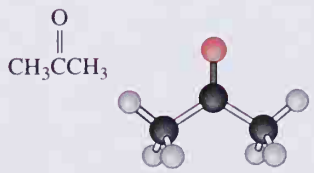


An aldehyde An aldehyde A ketone



Characteristic structural feature:



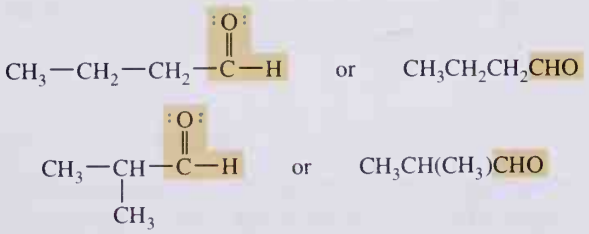


EXAMPLE 1.8

Draw condensed structural formulas for the two aldehydes of molecular formula C_4H_8O.

Solution

First draw the characteristic structural feature of the aldehyde group and then add the remaining carbons. These may be attached in two different ways. Then add seven hydrogens to complete the tetravalence of carbon and give the correct molecular formula. The aldehyde group may be written showing the carbon-oxygen double bond as C=O, or, alternatively, it may be written —CHO.

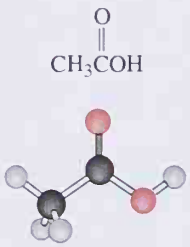


PROBLEM 1.8

Draw condensed structural formulas for the three ketones of molecular formula $C_5H_{10}O$.

C. Carboxylic Acids

The characteristic structural feature of a carboxylic acid is a **$—CO_2H$ (carboxyl:** *carbo*nyl + hydr*oxyl*) group. The carboxyl group may be written in any of the following ways, all of which are equivalent:



Characteristic structural feature: —C(=O)—O—H or —COOH or $—CO_2H$

Examples: $CH_3—C(=O)—O—H$ or CH_3COOH or CH_3CO_2H

EXAMPLE 1.9

Draw a condensed structural formula for the single carboxylic acid of molecular formula $C_3H_6O_2$.

Solution

$CH_3—CH_2—C(=O)—O—H$ or CH_3CH_2COOH or $CH_3CH_2CO_2H$

PROBLEM 1.9

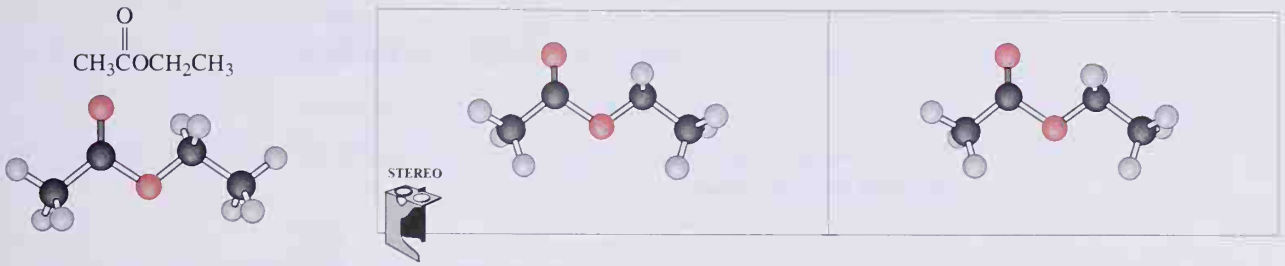
Draw condensed structural formulas for the two carboxylic acids of molecular formula $C_4H_8O_2$.

D. Esters

An **ester** is a derivative of a carboxylic acid in which the hydrogen of the carboxyl group is replaced by a carbon atom; it contains a **$—CO_2—C$** group.

Characteristic structural feature: —C(=O)—O—C or —COOC or $—CO_2C$

Examples: $CH_3—C(=O)—O—CH_3$ or CH_3COOCH_3 or $CH_3CO_2CH_3$



EXAMPLE 1.10

Draw condensed structural formulas for the four esters of molecular formula $C_4H_8O_2$.

Solution

Unshared pairs of electrons in these structural formulas are omitted.

(a) $HCOCH_2CH_2CH_3$ **(b)** $HCOCH(CH_3)_2$ **(c)** $CH_3COCH_2CH_3$

(d) $CH_3CH_2COCH_3$

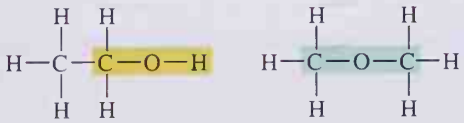
PROBLEM 1.10

Draw condensed structural formulas for

(a) The aldehyde and the ketone of molecular formula C_3H_6O.
(b) The two carboxylic acids of molecular formula $C_4H_8O_2$.
(c) The two esters of molecular formula $C_3H_6O_2$.

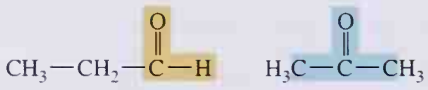
1.5 Constitutional Isomerism

In Section 1.4 we saw that for most molecular formulas it is possible to draw more than one structural formula. For example, the following compounds have the same molecular formula, C_3H_6O, but different structural formulas and different functional groups. The first is an alcohol, the second is an ether.



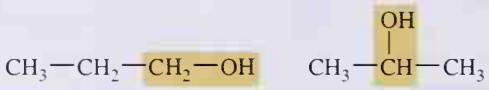
An alcohol An ether

Similarly, the following compounds have the same molecular formula, C_3H_6O, the same functional group (a carbonyl group), but different structural formulas. The first is an aldehyde, the second is a ketone.



An aldehyde A ketone

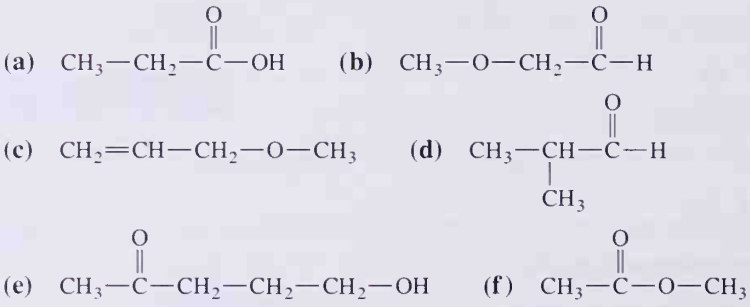
The following alcohols have the same molecular formula, the same functional group, but different structural formulas:



Compounds that have the same molecular formula but different structural formulas (different orders of attachment of atoms) are called **constitutional isomers.**

EXAMPLE 1.11

Divide the following molecules into groups of constitutional isomers:

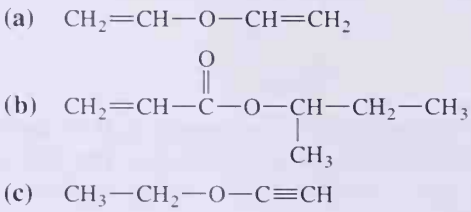


Solution

To determine which are constitutional isomers, compare the molecular formulas of each compound. All compounds that have the same molecular formula but different structural formulas are constitutional isomers. Compounds (a), (b), and (f) have the same molecular formula, $C_3H_6O_2$, but different structural formulas and are, therefore, constitutional isomers. Compounds (c) and (d) have the same molecular formula, C_4H_8O, but different structural formulas and are also constitutional isomers. No constitutional isomers are shown in this problem for compound (e).

PROBLEM 1.11

Divide the following molecules into groups of constitutional isomers:



(d) $CH_3-CH=CH-\overset{\overset{O}{\|}}{C}-H$

(e) $CH_3-CH_2-\overset{\overset{O}{\|}}{C}-O-\underset{\underset{CH_3}{|}}{CH}-C\equiv CH$

(f) $CH_3-\underset{\underset{CH_3}{|}}{C}=CH-\overset{\overset{O}{\|}}{C}-O-CH_2-CH_3$

1.6 Resonance

As the study of organic chemistry unfolded, it became obvious that for a great many molecules and ions, no single Lewis structure provided a truly accurate representation. For example, Figure 1.8 shows three Lewis structures for the carbonate ion, CO_3^{2-}, each of which shows carbon bonded to three oxygen atoms by a combination of one double bond and two single bonds. Each Lewis structure implies that one carbon-oxygen bond is different from the other two. However, this is not the case. It has been shown that all three carbon-oxygen bonds are identical.

To describe molecules and ions for which no single Lewis structure is adequate, it became necessary to refine still further the models for covalent bonding. Chemists commonly use two such approaches. One is the resonance model, the second is the molecular orbital model. In this section, we describe the theory of resonance and its application to the description of the covalent bonding and the stability of certain molecules and ions. We describe the molecular orbital model in Section 1.9.

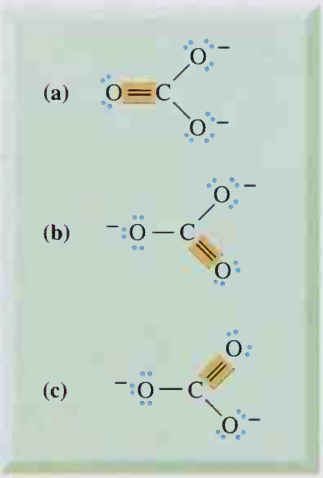


Figure 1.8
Three Lewis structures for the carbonate ion.

A. The Theory of Resonance

The **theory of resonance** was developed primarily by Linus Pauling in the 1930s. According to this theory, many molecules and ions are best described by writing two or more Lewis valence bond structures and considering the real molecule or ion to be a composite of these structures. Individual valence bond structures are called **contributing structures.** Hybridization is the process by which contributing structures are combined into a composite. A **resonance hybrid** is a single structure formed by combination of contributing structures.

We show that the real molecule or ion is a hybrid of the various contributing structures by interconnecting them with *double-headed arrows.* Three contributing structures for the carbonate ion are shown in Figure 1.9. These three contributing structures are said to be equivalent. **Equivalent contributing structures** have identical patterns of covalent bonding and are of equal energy.

The choice of the term "resonance" for this theory of covalent bonding is unfortunate, because it tends to convey the notion of bonds constantly changing back and forth from one position to another over time—that a particular carbon and oxygen in the carbonate ion are

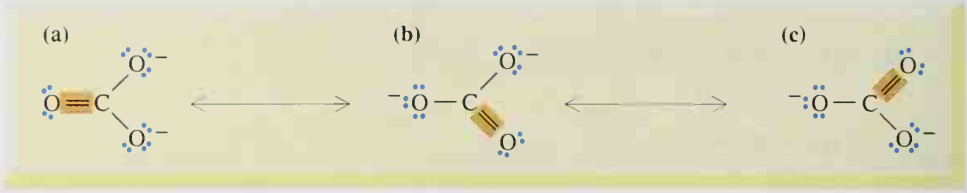


Figure 1.9
The carbonate ion represented as a resonance hybrid of three equivalent contributing structures.

connected by a double bond one instant, a single bond the next instant, and so on. This notion is not at all correct. The carbonate ion has one and only one real structure. The resonance method is an attempt to describe the real structure and at the same time retain Lewis structures with electron-pair bonds. Thus, although we realize that the carbonate ion is not accurately represented by contributing structure (a), (b), or (c) shown in Figure 1.8, we continue to represent it as one of these for convenience. We understand, of course, that what is intended is the resonance hybrid.

B. Curved Arrows to Show Interconversion of Contributing Structures

If you study the first and then the second and third contributing structures for the carbonate ion given in Figure 1.8, you see that each is converted to the next by redistribution of valence electrons. Chemists use *curved arrows* to show how valence electrons are redistributed in interconversion of contributing structures. A curved arrow shows the flow of an electron pair *from where* (the tail of the arrow) *to where* (the head of the arrow). The flow may be only

1. From an atom to an adjacent bond or
2. From a bond to an adjacent atom or
3. From a bond to an adjacent bond.

When a curved arrow is shown on one contributing structure, then the result of that flow of electrons is shown on the contributing structure to the right. Figure 1.10 shows the three contributing structures for the carbonate ion with curved arrows used to show the flow of electrons in conversion of contributing structure (a) to contributing structure (b) and then conversion of contributing structure (b) to contributing structure (c).

In a sense, the curved arrow is nothing more than a bookkeeping symbol favored by organic chemists to show the movement of electron pairs, or, as some call it, "electron pushing." Do not be misled by the seeming simplicity of this symbol. By using the curved arrow properly, you are able to draw contributing structures and thus gain a better understanding of resonance—a powerful tool in understanding the structure and chemical reactivity of organic molecules and ions. Furthermore, by using curved arrows, you are also

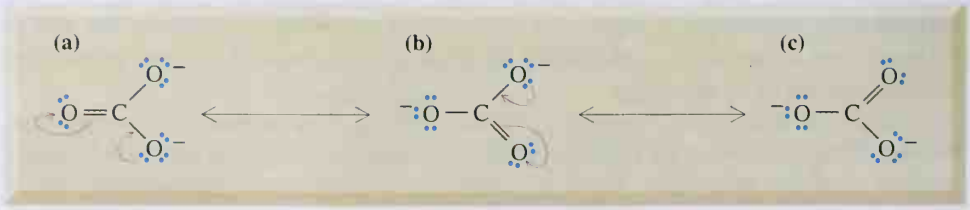
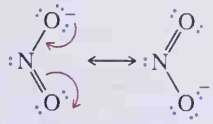


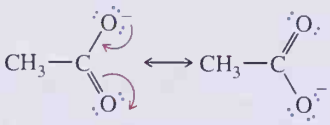
Figure 1.10
The use of curved arrows to show the flow of electrons in conversion of contributing structure (a) to contributing structure (b), and of contributing structure (b) to contributing structure (c).

able to follow bond-breaking and bond-making steps in organic reactions more comfortably.

Equivalent contributing structures have the same pattern of covalent bonding. Following are equivalent contributing structures for the nitrite ion and acetate ion. Curved arrows are used in each case to show how the contributing structure on the left is converted to the equivalent contributing structure on the right.

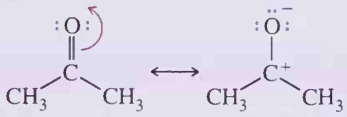


Nitrite ion
(equivalent contributing structures)



Ethanoate ion
(Acetate ion)
(equivalent contributing structures)

Following are contributing structures for the resonance hybrid of propanone (acetone). These contributing structures are nonequivalent; they have different patterns of covalent bonding and different energies.



Propanone
(Acetone)
(nonequivalent contributing structures)

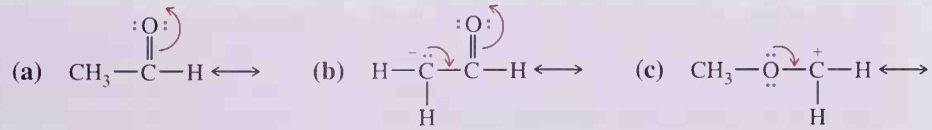
C. Rules for Writing Acceptable Contributing Structures

Certain rules must be followed in drawing acceptable contributing structures.

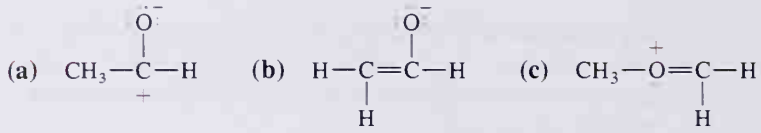
1. All contributing structures must show the correct number of valence electrons.
2. No contributing structure may have more than 8 electrons in the valence shell of a second-row element; third-row elements such as phosphorus and sulfur may have up to 12 electrons in their valence shells.
3. The positions of all nuclei must be the same; that is, contributing structures differ only in the distribution of valence electrons.
4. All contributing structures must show the same number of paired and unpaired electrons.

EXAMPLE 1.12

Draw the contributing structure indicated by the curved arrows. Be certain to show all formal charges.

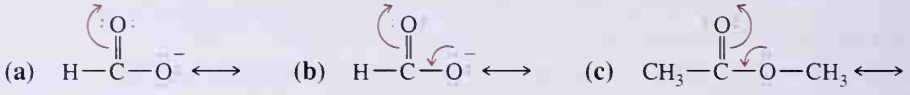


Solution



PROBLEM 1.12

Draw the contributing structure indicated by curved arrows. Be certain to show all formal charges.



D. Estimating the Relative Importance of Contributing Structures

So far, we have seen that certain molecules and ions are best represented as hybrids of two or more contributing structures. Not all structures, however, contribute equally to a hybrid. The following guidelines will help you to estimate the relative importance of various contributing structures:

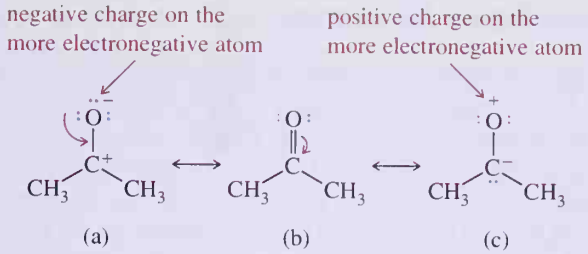
1. Equivalent structures (those that have the same patterns of covalent bonding) contribute equally. Examples of equivalent structures are those already shown for the carbonate, nitrite, and acetate ions.
2. Structures in which all atoms have filled valence shells (completed octets) contribute more than those in which one or more valence shells are unfilled. For example, the following are the contributing structures for Example 1.12(c) and its solution.

Greater contribution; both carbon and oxygen have complete valence shells

Lesser contribution; carbon has only six electrons in its valence shell

Both carbon and oxygen have filled valence shells in the first contributing structure, and therefore, it makes the greater contribution to the resonance hybrid.

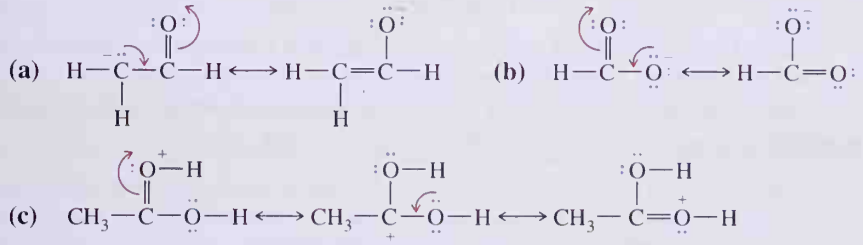
3. Structures involving separation of unlike charges contribute less than those that do not involve charge separation. For example, the second contributing structure for propanone shown earlier in this section involves separation of unlike charges and therefore contributes less to the hybrid than does the first structure.
4. Structures that carry a negative charge on the more electronegative atom contribute more than those with the negative charge on the less electronegative atom. Correspondingly, structures that carry a positive charge on the less electronegative atom contribute more than those that carry a positive charge on the more electronegative atom. Following are three contributing structures for propanone:



Structure (b) makes the largest contribution to the hybrid. Structures (a) and (c) contribute less because they involve separation of unlike charges. Of the structures involving charge separation, (a) makes by far the larger contribution because the negative charge is on the more electronegative atom and the positive charge is on the less electronegative atom. Structures with "reverse polarity" like (c) are rarely drawn as significant contributing structures to a resonance hybrid.

EXAMPLE 1.13

Following are sets of contributing structures. Estimate the relative contribution of each structure to its hybrid.



Solution

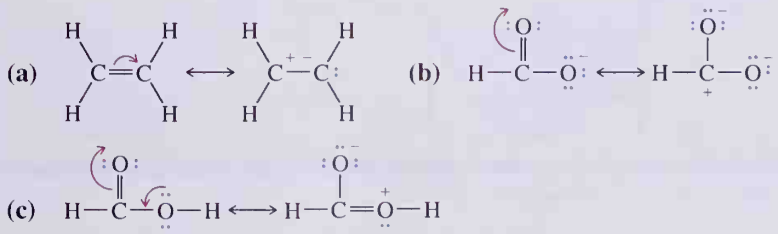
(a) The structures are nonequivalent. The second structure makes a greater contribution to the hybrid because it places the negative charge on the more electronegative oxygen atom.

(b) The structures are equivalent and make equal contributions to the hybrid.

(c) The first and third contributing structures are equivalent and make equal contributions to the hybrid. The second contributing structure makes a lesser contribution because in it carbon has an incomplete valence shell.

PROBLEM 1.13

Following are pairs of contributing structures. Estimate the relative contribution of each structure to its hybrid.



A sine wave displayed on an oscilloscope. *(Courtesy of PASCO Scientific Co.)*

1.7 Quantum, or Wave, Mechanics

Thus far in this chapter, we have concentrated on the Lewis model of bonding and on the VSEPR model. The Lewis model deals primarily with coordination numbers of atoms (the number of bonds a given atom can form), and the VSEPR model deals primarily with bond angles and molecular geometries. Although both models are useful, each in its own way, neither gives us any means of accounting in a quantitative or even semiquantitative way for why atoms combine in the first place to form covalent bonds with the liberation of energy. At this point we need to study an entirely new approach to the theory of covalent bonding, one that provides a means of understanding not only the coordination numbers of atoms and molecular geometries but also the energetics of chemical bonding.

A. A Moving Particle Exhibits the Properties of a Wave

Einstein received a Ph.D. in 1905, and in that same year he published a paper in which he used his photon concept to explain the photoelectric effect. For this work he was awarded the Nobel Prize in physics in 1921.

The beginning of this new approach to the theory of chemical bonding was provided by Albert Einstein (1879–1955), a German-born American physicist. In 1905, Einstein postulated that light consists of photons of electromagnetic radiation. The energy (E) of a photon is proportional to the frequency (ν) of the light. The proportionality constant in this equation is Planck's constant (h).

$$E = h\nu$$

de Broglie received a doctoral degree in physics from the University of Paris in 1924, and for his research on the wave-particle theory of electromagnetic radiation, received the Nobel Prize in physics in 1929.

In 1923, the French physicist Louis de Broglie followed Einstein's lead and advanced the revolutionary idea that if light exhibits properties of a particle in motion, then a particle in motion should exhibit the properties of a wave. He proposed, therefore, that a particle of mass m and speed v has an associated wavelength (λ, the Greek letter lambda), given by the equation

$$\lambda = \frac{h}{mv} \quad \text{(the de Broglie relationship)}$$

Illustrated in Figure 1.11 is a wave such as might result from plucking a guitar string. The mathematical equation that describes this wave is called a **wave equation.** The numerical value of a wave equation may be positive (corresponding to a wave crest), negative (corresponding to a wave trough), or zero. A **node** is any point where the value of a wave

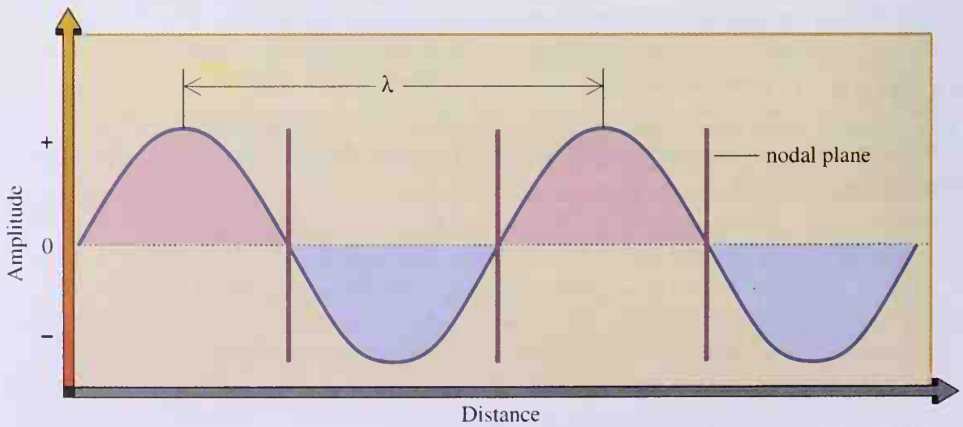


Figure 1.11
Characteristics of a wave associated with a moving particle.

equation is zero. A **nodal plane** is any plane that runs through a node. Shown in Figure 1.11 are three nodal planes, each perpendicular to the plane of the paper.

In 1927, C. Davisson and L. H. Germer in the United States and G. P. Thompson in England demonstrated that a beam of electrons can be diffracted by a crystal, thus providing justification for treating electrons in terms of their associated wave properties.

The de Broglie relationship can be applied only to electrons in free motion; it cannot be applied to electrons in atoms or molecules, where electrons are constrained by the attractive force of a nucleus. Erwin Schrödinger built on the idea of de Broglie and in 1926 proposed an equation that could be used to find the wave properties associated with an electron in an atom or a molecule. **Quantum mechanics (wave mechanics)** is the branch of science that describes particles and their associated waves.

Solving the Schrödinger equation gives a set of wave functions. Each wave function ψ (Greek letter psi) is associated with a unique set of quantum numbers and with a particular atomic orbital. The value of ψ^2 is proportional to the probability of finding an electron at a given point in space; or looked at in another way, the value of ψ^2 at any point in space is proportional to the electron density at that point. One of the commonest ways to visualize the electron density associated with a particular atomic orbital is to draw a boundary surface around the region in space that encompasses 95% of the electron charge associated with the orbital. In this course, we concentrate on wave functions and shapes associated with *s* and *p* atomic orbitals because they are the orbitals most often involved in covalent bonding in organic compounds.

Erwin Schrödinger (1887–1961) wrote the papers that gave the foundations for quantum mechanics. He shared the Nobel Prize for physics in 1933. *(The Bettmann Archive)*

B. Shapes of Atomic *s* and *p* Orbitals

All *s* orbitals are spherical. Shown in Figure 1.12 are cross-sectional plots of probability distributions (electron density) for 1*s* and 2*s* orbitals. In a 1*s* orbital, the probability distribution is a maximum near the nucleus. In a 2*s* orbital, the probability distribution has two maxima: one near the nucleus and another in a spherical shell about the nucleus. A 2*s* orbital contains a spherical **nodal surface** where the value of the probability distribution is zero. An electron in a 2*s* orbital is more likely to be found in the outer spherical shell.

The plus and minus signs in Figure 1.12 specify the sign of the wave function in the different regions of space. The plus sign shown in the 1*s* orbital indicates that the sign of the wave function is positive over the entire orbital. In a 2*s* orbital the sign of the wave function is negative in the inner portion, zero at the nodal surface, and positive in the outer portion.

Shown in Figure 1.13 are three-dimensional shapes of the three 2*p* orbitals, combined in one diagram to illustrate their relative orientations in space. Each 2*p* orbital consists of two lobes arranged in a straight line with the nucleus in the middle. The three 2*p* orbitals

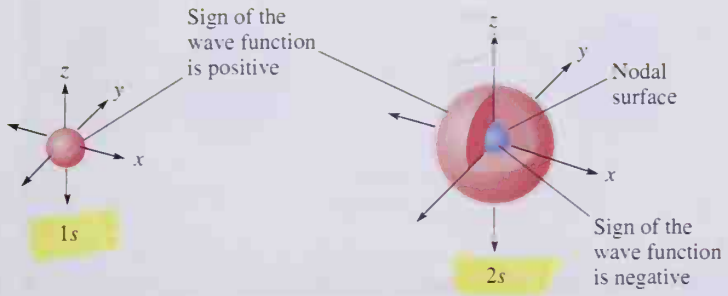


Figure 1.12
Probability distribution for 1*s* and 2*s* orbitals.

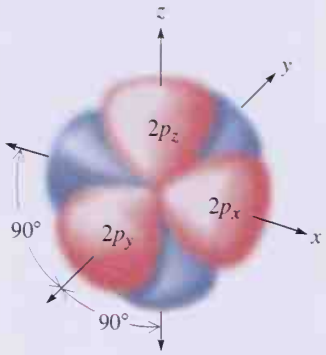


Figure 1.13
The $2p$ orbitals. Three-dimensional shapes of $2p_x$, $2p_y$, and $2p_z$ atomic orbitals and their orientation in space relative to one another. The three $2p$ orbitals are mutually perpendicular.

are mutually perpendicular and are designated $2p_x$, $2p_y$, and $2p_z$. The sign of the wave function of a $2p$ orbital is positive in one lobe, zero at the nucleus, and negative in the other lobe. Because the value of ψ^2 is always positive, the probability of finding an electron in the (+) lobe of a $2p$ orbital is the same as that of finding it in the (−) lobe.

Besides providing a way to determine the shapes of atomic orbitals, the Schrödinger equation also provides a way, at least in principle, to quantify the energetics of covalent bond formation. In practice, such calculations are too difficult for all but the simplest molecules and ions. For other molecules and ions, the equation can be solved only by making approximations. These approximations have taken two forms: (1) the valence bond approach, and (2) the molecular orbital approach. Both approaches to chemical bonding use the methods of quantum mechanics, but each makes different simplifying approximations. Although the valence bond approach was developed first, it has been replaced by the molecular orbital approach for quantitative calculations of molecular properties.

1.8 Valence Bond Approach to Covalent Bonding

The valence bond approach, developed in the 1920s, provides a view of molecular structure that is still very useful. Furthermore, the terminology of the valence bond approach has been incorporated permanently into the language of organic chemistry.

A. Formation of a Covalent Bond by the Overlap of Atomic Orbitals

According to the valence bond approach, a covalent bond is formed when a portion of an atomic orbital of one atom overlaps a portion of an atomic orbital of another atom. Bond strength depends on the degree of orbital overlap; the greater the overlap, the stronger the resulting covalent bond.

Consider the covalent bonding between H and Cl to form HCl. The electron configuration of hydrogen is $1s^1$; that of chlorine is $1s^2 2s^2 2p^6 3s^2 3p^5$. Figure 1.14 shows the overlap resulting from bringing together the $1s$ orbital of hydrogen and the positive lobe of a singly occupied $3p$ orbital of chlorine. For maximum overlap and hence the strongest covalent bonding, overlap must occur along the axis of the singly occupied $3p$ orbital of chlorine. In the covalent bond illustrated in Figure 1.14, the orbital overlap, and therefore the electron density in this covalent bond, is concentrated about the axis joining the two nuclei.

A covalent bond in which orbital overlap is concentrated along the axis joining the two nuclei is called a **sigma (σ) bond.**

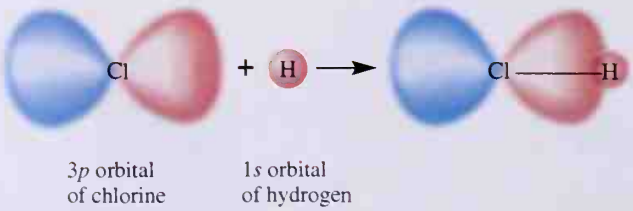


Figure 1.14
Formation of the covalent bond in HCl by overlap of the $1s$ orbital of hydrogen and a singly occupied $3p$ orbital of chlorine.

B. The Hydrogen Molecule

In 1927, W. H. Heitler and Heinz London in Germany used the valence bond approach to calculate the interaction between two hydrogen atoms as a function of internuclear separation (Figure 1.15). At infinite separation no interaction occurs between the two atoms. As they are brought closer together and their atomic orbitals begin to overlap, the potential energy decreases, resulting in a net attraction between hydrogen atoms. From their calculations, Heitler and London predicted that the hydrogen molecule should be most stable at an internuclear distance of 0.074 nm (nanometer), a bond distance that represents a balance between the overlap of atomic orbitals, which draws the atoms closer together, and the electrostatic repulsion between nuclei and between electrons, which forces them apart. At very small internuclear distances, repulsive forces between hydrogen nuclei and between electrons become dominant, and the potential energy curve rises steeply corresponding to net repulsion. Especially significant at the time was that Heitler and London's calculations for the bond length and bond strength of the hydrogen molecule agreed almost exactly with the experimentally measured values.

Besides confirming the essential validity of the valence bond approach, Heitler and London's calculations provided a new insight into the energetics of covalent bond formation. They demonstrated that most of the energy of covalent bond formation occurs because electrons in a covalent bond are free to occupy the atomic orbitals of both atoms participating in formation of the bond. This conclusion arose in the following way. Heitler and London first assumed that each electron originally associated with a particular hydrogen atom in a 1*s* orbital remains associated with the same atom in a hydrogen molecule. Given this assumption, the binding energy calculated for a hydrogen molecule is only a small fraction of the experimentally observed value. If, instead, they assumed that the two electrons associate equally with each hydrogen nucleus, the calculated value for the bond energy was found to agree almost precisely with the observed value. Heitler and London concluded that (1) each electron in a covalent bond is delocalized over two atomic orbitals and (2) the stabilization resulting from formation of a covalent bond is due largely to **electron delocalization.**

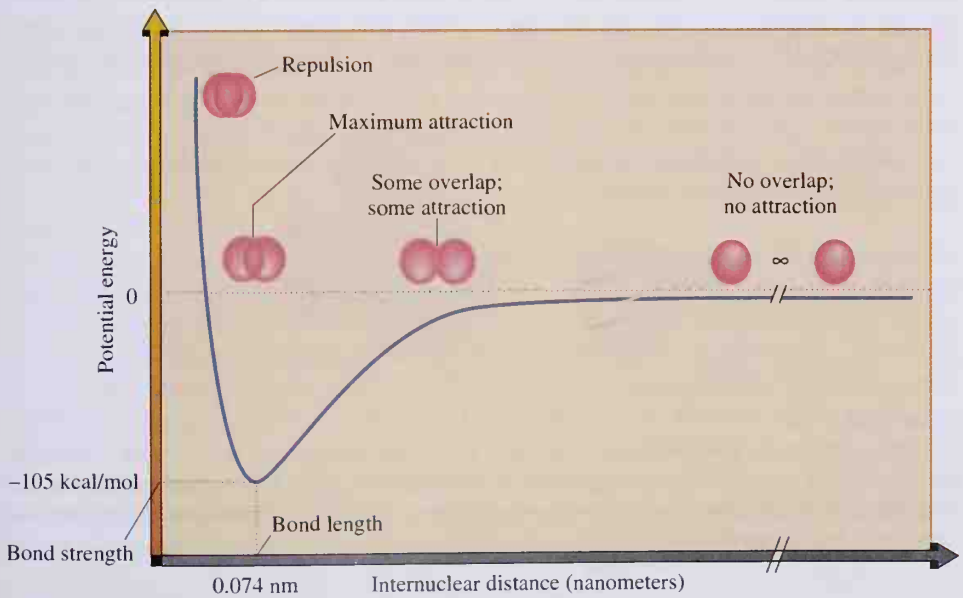


Figure 1.15
Potential energy of a H_2 molecule as a function of internuclear distance.

C. Hybridization of Atomic Orbitals

Soon after the Heitler-London calculations, Linus Pauling proposed the concept of **hybridization of atomic orbitals** in response to the need to account for observed bond angles and molecular geometries. The problem faced at the time was that in forming covalent bonds, atoms of carbon, nitrogen, and oxygen use atomic orbitals of the second principal energy level. The three $2p$ orbitals are at angles of 90° to one another (Figure 1.13), and if atoms of the second principal energy level used these orbitals to form covalent bonds, bond angles around each would be approximately 90°. However, bond angles of 90° are only rarely observed in organic compounds. What are observed instead are bond angles of approximately 109.5°, 120°, and 180°. To account for these observed bond angles, Pauling proposed that atomic orbitals may combine to form new orbitals, which then interact to form bonds with the angles that we do observe. **Hybridization** is the combination of atomic orbitals, and the new atomic orbitals formed are called **hybrid atomic orbitals**, or, more simply, hybrid orbitals. The number of hybrid orbitals formed is the same as the number of atomic orbitals combined, and each hybrid orbital can contain no more than two electrons.

The term "hybridization" has an altogether different meaning in molecular biology. There it is used to mean combination of single strands of DNA to form double-stranded DNA.

sp^3 Hybrid Orbitals

Combination of one $2s$ orbital and three $2p$ orbitals forms four equivalent **sp^3 hybrid orbitals.** Each sp^3 hybrid orbital consists of a larger lobe pointing in one direction and a smaller lobe of opposite sign pointing in the opposite direction. The axes of the four sp^3 hybrid orbitals are directed toward the corners of a regular tetrahedron, and sp^3 hybridization results in bond angles of approximately 109.5° (Figure 1.16).

In Section 1.3, we described the covalent bonding in CH_4, NH_3, and H_2O in terms of the Lewis model. Now let us consider the bonding in these molecules in terms of the overlap of atomic orbitals. To bond with four other atoms, carbon uses sp^3 hybrid orbitals. Carbon has four valence electrons, and one electron is placed in each sp^3 hybrid orbital. Each partially filled sp^3 hybrid orbital then overlaps with a partially filled $1s$ orbital of hydrogen to form a sigma bond, and hydrogen atoms occupy the corners of a regular tetrahedron (Figure 1.17). In bonding with three other atoms, the five valence electrons of nitrogen are distributed so that one sp^3 orbital is filled with a pair of electrons and the other three sp^3 orbitals have one electron each. Overlapping of these partially filled sp^3 hybrid

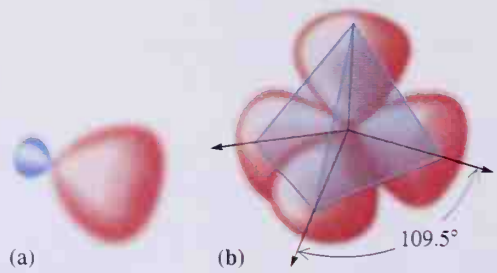


Figure 1.16
sp^3 hybrid orbitals. (a) Representation of a single sp^3 hybrid orbital showing two lobes of unequal size. The sign of the wave function is positive in one lobe, zero at the nucleus, and negative in the other lobe. (b) Three-dimensional representation of four sp^3 hybrid orbitals directed toward the corners of a regular tetrahedron.

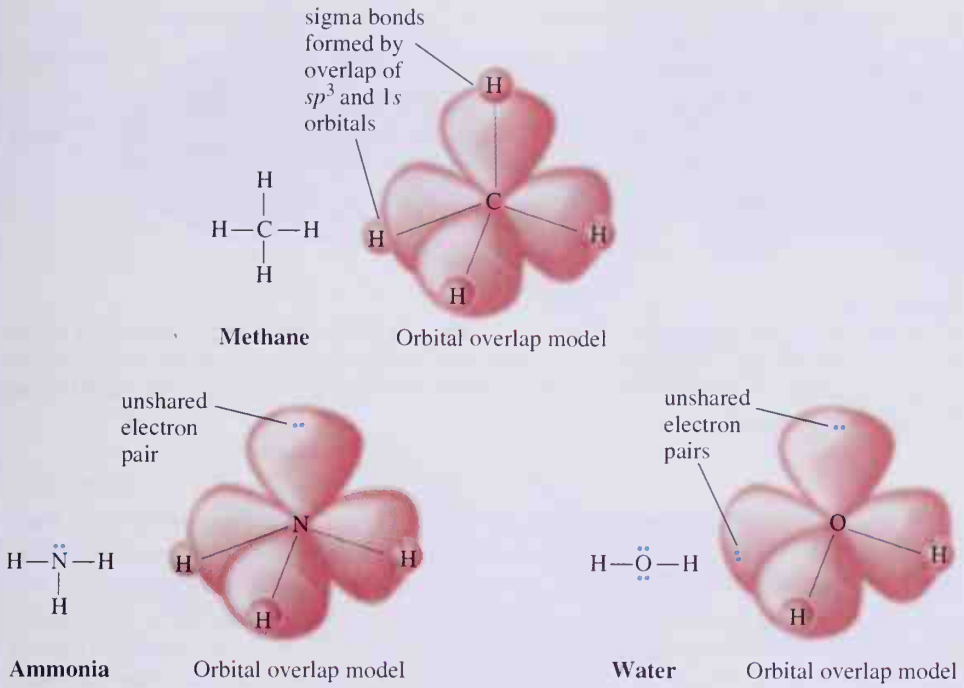


Figure 1.17
Orbital overlap pictures of methane, ammonia, and water.

orbitals with 1*s* orbitals of hydrogen produces the NH_3 molecule (Figure 1.17). In bonding with two other atoms, the six valence electrons of oxygen are distributed so that two sp^3 orbitals are filled and the remaining two have one electron each. Each partially filled sp^3 orbital overlaps with a 1*s* orbital of hydrogen, and hydrogen atoms occupy two corners of a regular tetrahedron. The remaining two corners of the tetrahedron are occupied by unshared pairs of electrons (Figure 1.17).

sp^2 Hybrid Orbitals

Combination of one 2*s* orbital and two 2*p* orbitals forms three equivalent **sp^2 hybrid orbitals.** Each sp^2 hybrid orbital consists of two lobes: one larger than the other and each of opposite sign. The three sp^2 orbitals lie in a plane and are directed toward the corners of an equilateral triangle; the angle between sp^2 orbitals is 120°. The third 2*p* orbital is not involved in hybridization and consists of two lobes lying perpendicular to the plane of the sp^2 orbitals. Figure 1.18 shows three equivalent sp^2 orbitals along with the remaining unhybridized 2*p* orbital.

Second-row elements use sp^2 hybrid orbitals to form double bonds. Consider ethene, C_2H_4, a Lewis structure for which is shown in Figure 1.19(a). A sigma bond between carbons is formed by overlap of sp^2 hybrid orbitals along a common axis; see Figure 1.19(b). Each carbon also forms sigma bonds to two hydrogens. The remaining 2*p* orbitals on adjacent carbon atoms lie parallel to each other and overlap to form a bond in which electron density is concentrated above and below the axis of the two nuclei; see Figure 1.19(c).

A **pi (π) bond** is a covalent bond formed by overlap of parallel *p* orbitals. Because of the lesser degree of overlap of orbitals forming pi bonds compared with those forming sigma bonds, pi bonds are generally weaker than sigma bonds.

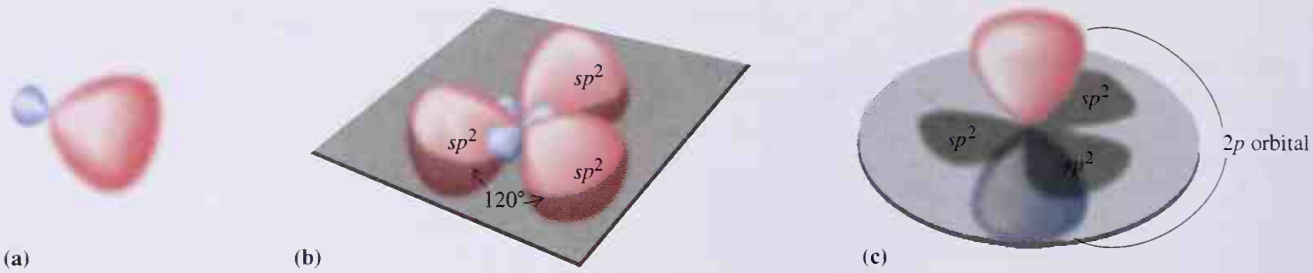


Figure 1.18
sp^2 hybrid orbitals. (a) A single sp^2 hybrid orbital. The sign of the wave function is positive in one lobe, zero at the nucleus, and negative in the other lobe. (b) Three sp^2 hybrid orbitals with their axes in a plane at angles of 120°. (c) The unhybridized $2p$ orbital perpendicular to the plane created by the three sp^2 hybrid orbitals.

The valence bond approach describes all double bonds in the same manner as we have already used to describe carbon-carbon double bonds. In methanal, the simplest organic molecule containing a carbon-oxygen double bond, carbon forms sigma bonds to two hydrogens by overlap of sp^2 orbitals of carbon and $1s$ orbitals of hydrogens. Carbon and oxygen are joined by a sigma bond formed by overlap of sp^2 orbitals and a pi bond formed by overlap of unhybridized $2p$ orbitals. Figure 1.20 shows the Lewis structure for methanal, the sigma bond framework, and the overlap of $2p$ orbitals to form a pi bond. Similarly, carbon-nitrogen double bonds consist of one sigma bond and one pi bond.

sp Hybrid Orbitals

Combination of one $2s$ orbital and one $2p$ orbital forms two equivalent ***sp* hybrid orbitals,** which lie at an angle of 180° with respect to the nucleus. The axes of the unhybridized $2p$ orbitals are perpendicular to each other and to the two *sp* hybrid orbitals. In Figure 1.21, *sp* hybrid orbitals are shown on the x axis and unhybridized $2p$ orbitals on the y axis and z axis.

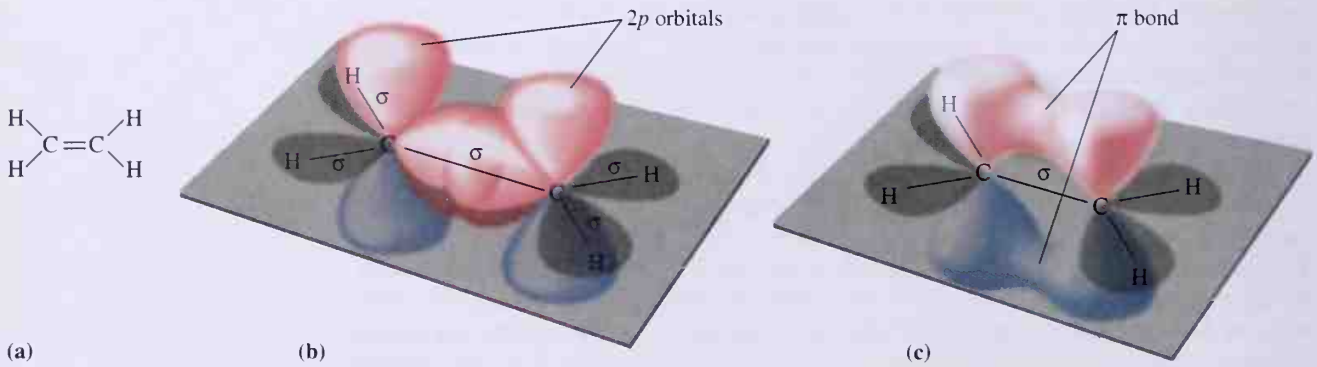


Figure 1.19
Covalent bond formation in ethene (ethylene). (a) Lewis structure. (b) A sigma bond between carbon atoms is formed by overlap of sp^2 hybrid orbitals. (c) Overlap of parallel $2p$ orbitals forms a pi bond.

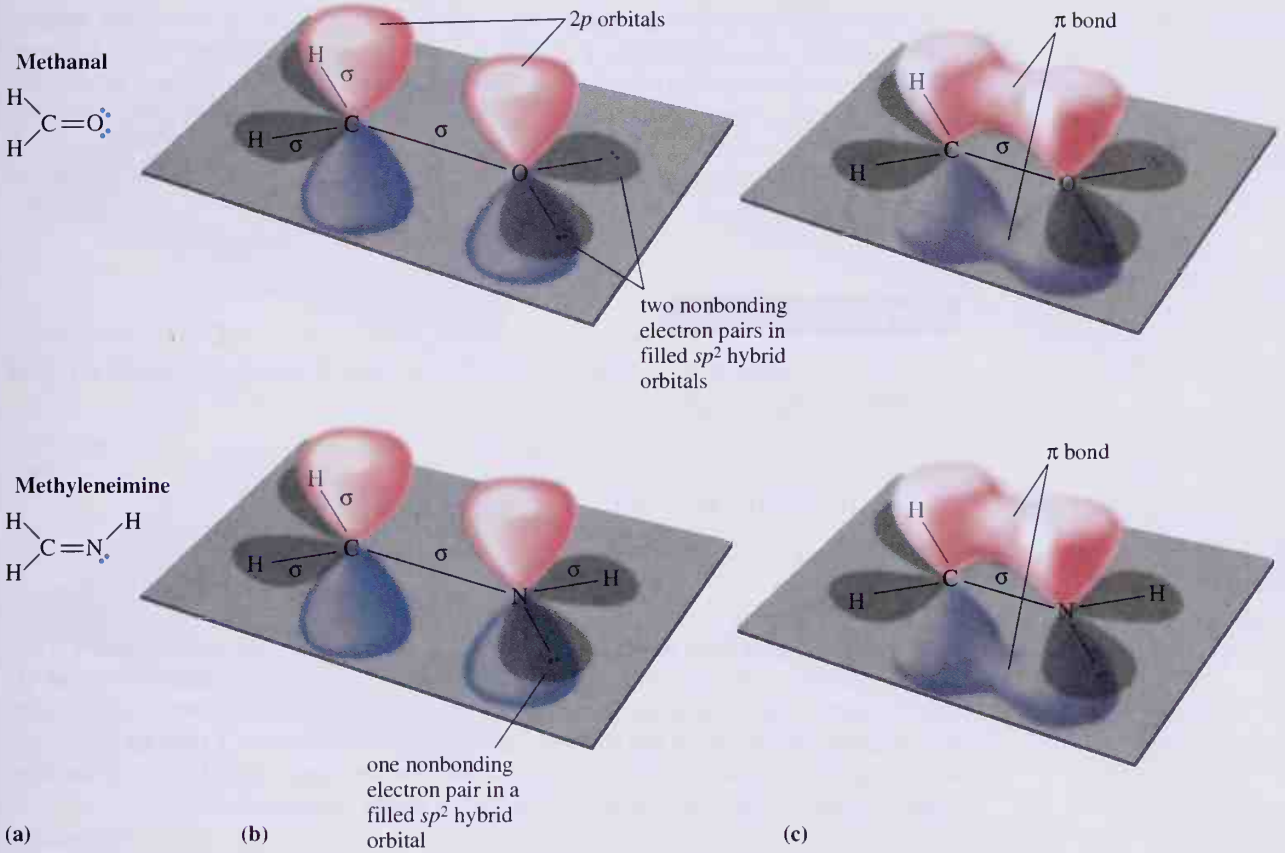


Figure 1.20
Carbon-oxygen and carbon-nitrogen double bonds. (a) Lewis structures of methanal (formaldehyde: $CH_2{=}O$) and methyleneimine ($CH_2{=}NH$), (b) the sigma bond framework and nonoverlapping parallel 2*p* orbitals, and (c) overlap of parallel 2*p* orbitals to form a pi bond.

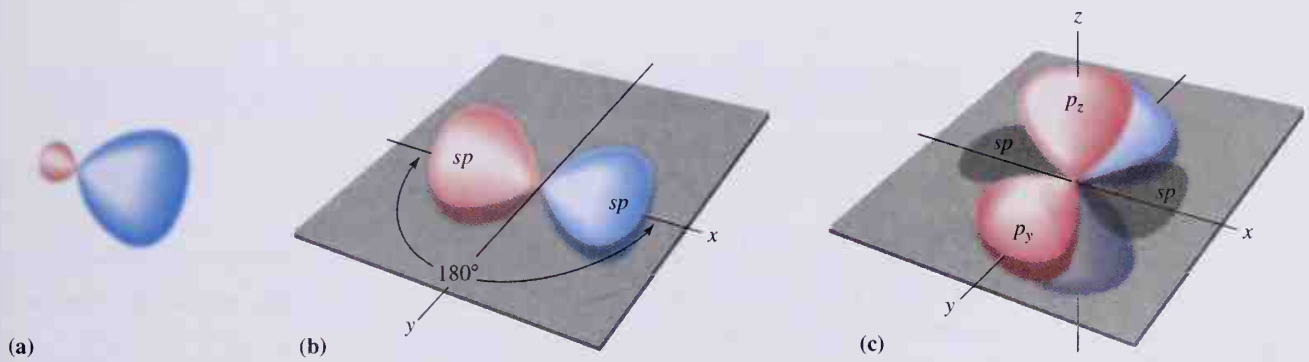
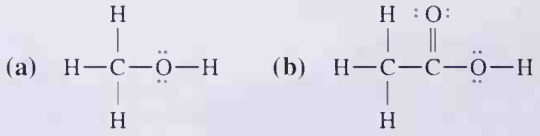


Figure 1.21
sp hybrid orbitals. (a) A single *sp* hybrid orbital consisting of two lobes in a linear arrangement. The sign of the wave function is positive in one lobe, zero at the nucleus, and negative in the other lobe. (b) Two *sp* hybrid orbitals. (c) Unhybridized 2*p* orbitals are perpendicular to the line created by the axes of the two *sp* hybrid orbitals.

Figure 1.22 shows Lewis structures and orbital overlap diagrams for ethyne and hydrogen cyanide. A carbon-carbon triple bond consists of one sigma bond formed by overlap of *sp* hybrid orbitals and two pi bonds. One pi bond is formed by overlap of parallel $2p_y$ orbitals and the second by overlap of parallel $2p_z$ orbitals. Similarly, a carbon-nitrogen triple bond also consists of one sigma bond and two pi bonds. The relationship between the number of groups bonded to carbon, orbital hybridization, and types of bonds involved is summarized in Table 1.6.

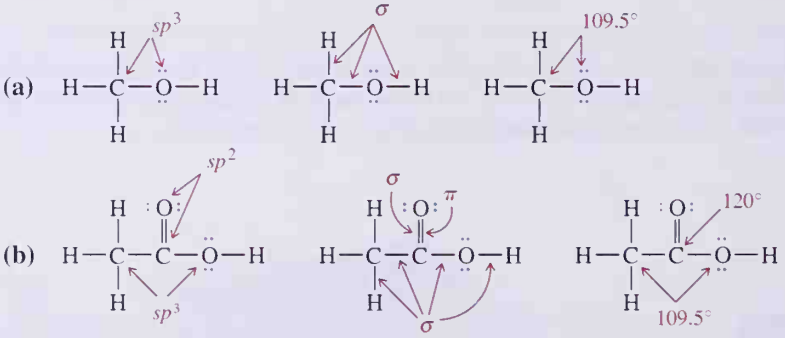
EXAMPLE 1.14

Describe the bonding in the following molecules in terms of the atomic orbitals involved and predict all bond angles:



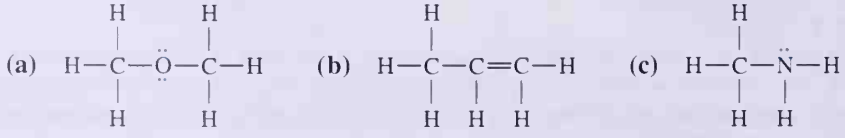
Solution

The problem here is how to show clearly and concisely on a structural formula (1) the hybridization of each atom, (2) the atomic orbitals involved in each covalent bond, and (3) all bond angles. One way to do this is in three separate diagrams as follows. Labels on the first diagram point to atoms and show the hybridization of each atom. Labels on the second diagram point to bonds and show the type of bond, either sigma or pi. Labels on the third diagram point to atoms and show predicted bond angles about each atom.



PROBLEM 1.14

Describe the bonding in the following molecules in terms of atomic orbitals involved, and predict all bond angles:



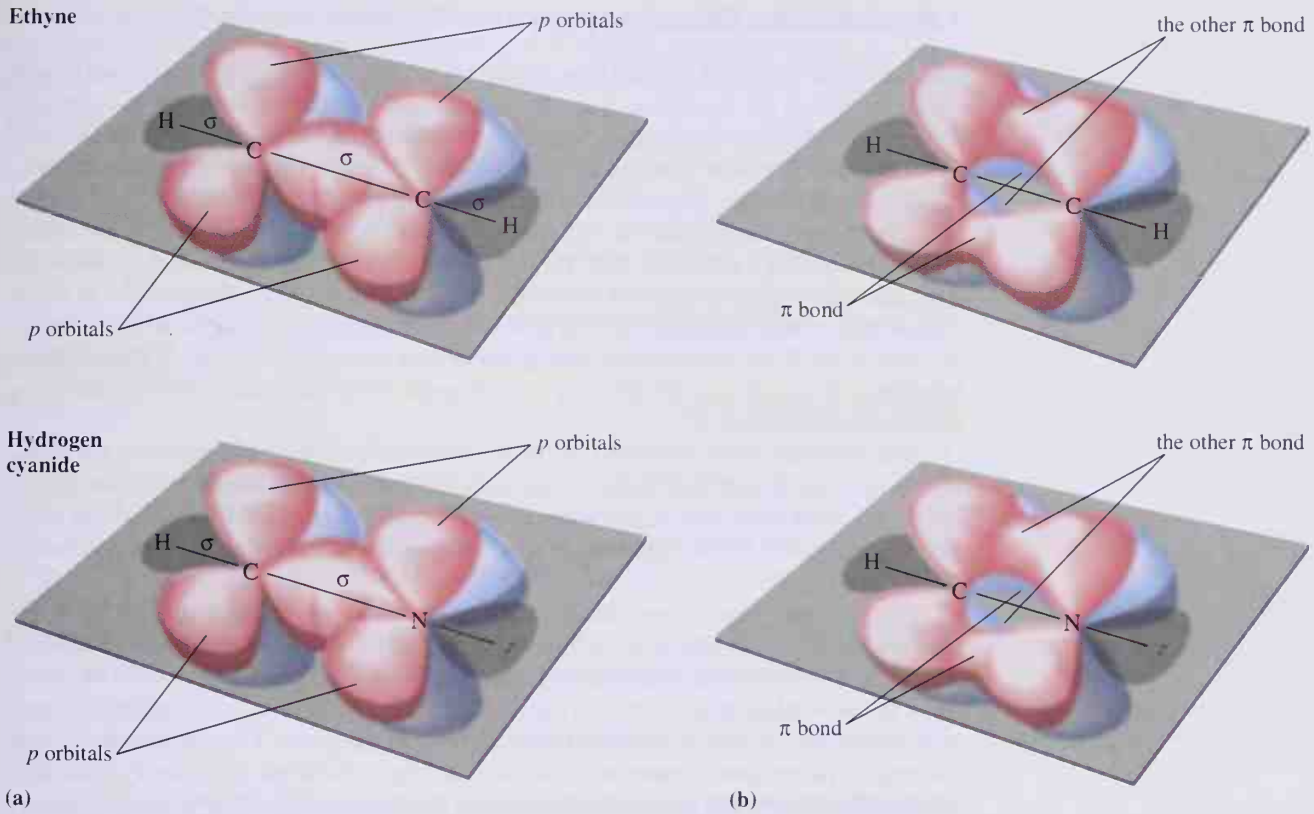
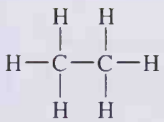
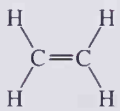
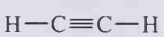


Figure 1.22
Covalent bonding in ethyne (acetylene) and hydrogen cyanide. (a) The sigma bond framework shown along with nonoverlapping $2p$ orbitals. (b) Formation of two pi bonds by overlap of two sets of parallel $2p$ orbitals.

Table 1.6 Covalent bonding of carbon

Number of Groups Bonded to Carbon	Orbital Hybridization	Types of Bonds Involved	Example
4	sp^3	four sigma bonds	
3	sp^2	three sigma bonds and one pi bond	
2	sp	two sigma bonds and two pi bonds	

1.9 Molecular Orbital Approach to Covalent Bonding

The simplified version of valence bond theory we developed in the previous section is very useful in relating the electronic structure of atoms to the electronic structure of molecules and ions and in understanding the energetics of covalent bond formation. It applies to most molecules and ions. For some molecules, however, it does not make correct predictions.

To appreciate one physical basis for testing the predictions of theories of covalent bonding, we need to consider the magnetic properties of molecules and ions. A **paramagnetic substance** is a substance that is weakly attracted to a magnetic field. All substances that have one or more unpaired electrons are paramagnetic. (Paramagnetism is much weaker than ferromagnetism, a special kind of magnetism due to the cooperative alignment of electron spins on atoms of the iron group or rare earths.) In contrast, a **diamagnetic substance** is one that is not attracted to a magnetic field. Substances with all electrons paired are diamagnetic.

Valence bond theory predicts that for any molecule with an even number of electrons, all electrons are paired and, therefore, the molecule should be diamagnetic. Although this is true for most molecules, a few molecules with an even number of electrons are paramagnetic. The best known example of a paramagnetic molecule with an even number of electrons is O_2.

According to valence bond theory, each oxygen is sp^2-hybridized, and the two oxygens are joined by overlap of sp^2 orbitals to form a sigma bond and overlap of parallel $2p$ orbitals to form a pi bond. The unshared electrons on each oxygen are grouped with paired spins in the remaining sp^2 orbitals (Figure 1.23). Thus, according to simplified valence bond theory, the oxygen molecule is predicted to be diamagnetic. The fact that the oxygen molecule is paramagnetic presented a serious challenge for valence bond theory. Although valence bond theory can be extended to account for the paramagnetism of oxygen, molecular orbital theory provides a more straightforward and direct explanation for this phenomenon.

A. Formation of Molecular Orbitals

Molecular orbital (MO) theory begins with the fact that electrons in atoms exist in **atomic orbitals** and assumes that electrons in molecules exist in **molecular orbitals.** Just as the Schrödinger equation can be used to calculate the energies and shapes of atomic orbitals,

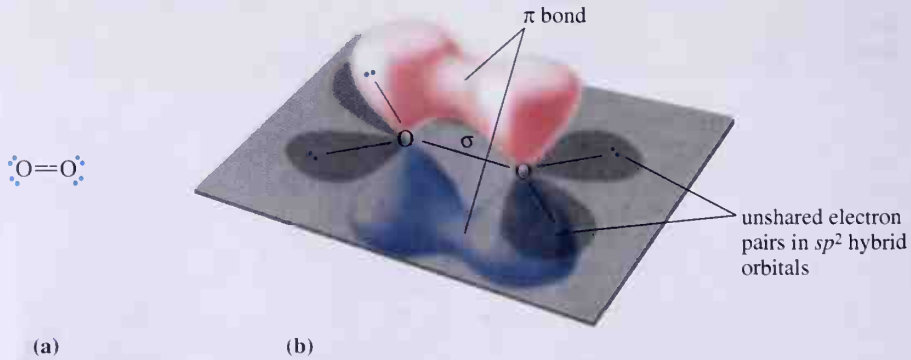


Figure 1.23
The oxygen molecule. (a) Lewis structure and (b) orbital overlap diagram.

molecular orbital theory assumes that the Schrödinger equation can also be used to calculate the energies and shapes of molecular orbitals. Following is a summary of the rules used in applying molecular orbital theory to the formation of covalent bonds:

1. Combination of n atomic orbitals of atoms forms a new set of n molecular orbitals. The number of molecular orbitals formed is equal to the number of atomic orbitals combined because wave functions can be combined by both addition and subtraction.
2. Just like atomic orbitals, molecular orbitals are also arranged in order of increasing energy. In principle, it is possible to calculate the relative energies of a set of molecular orbitals. In practice, however, calculations of this type are possible only for the simplest of molecules. Fortunately, experimental measurements such as those derived from molecular spectroscopy can be used to provide very detailed information about relative energies of molecular orbitals.
3. Filling of molecular orbitals is governed by the same principles as the filling of atomic orbitals. A molecular orbital can accommodate no more than two electrons, and the electrons must have opposite spins (the Pauli exclusion principle). Molecular orbitals are filled beginning with the lowest unoccupied molecular orbital (the aufbau principle, from the German *aufbau,* building). When two or more degenerate molecular orbitals are available, one electron is added to each before any degenerate orbital is filled with two electrons (Hund's rule).
4. **Bond order** is one-half the difference of the number of electrons in bonding molecular orbitals, n_b, minus the number of electrons in antibonding molecular orbitals, n_a:

$$\text{Bond order} = \frac{1}{2}(n_b - n_a)$$

To illustrate the use of these rules, let us consider the shapes and relative energies of several sets of molecular orbitals. Combination of two 1s atomic orbitals gives two **sigma molecular orbitals** (Figure 1.24). One is a sigma **bonding molecular orbital,** designated by the symbol σ_{1s}; the other is a sigma **antibonding molecular orbital,** designated by the symbol σ^*_{1s}. In molecular orbital notation, an asterisk is used to show that a molecular orbital is antibonding. When electrons occupy a bonding MO, electron density is concentrated in the region between the two positively charged nuclei and serves to offset the repulsive interaction between them. If electrons occupy an antibonding MO, electron density is concentrated outside the region between the two nuclei, and consequently there is little or no electron density between nuclei to offset nuclear repulsion. In representations of molecular orbitals, we use blue to indicate the lobe of a particular molecular orbital in which the sign of the wave function is negative and red where it is positive.

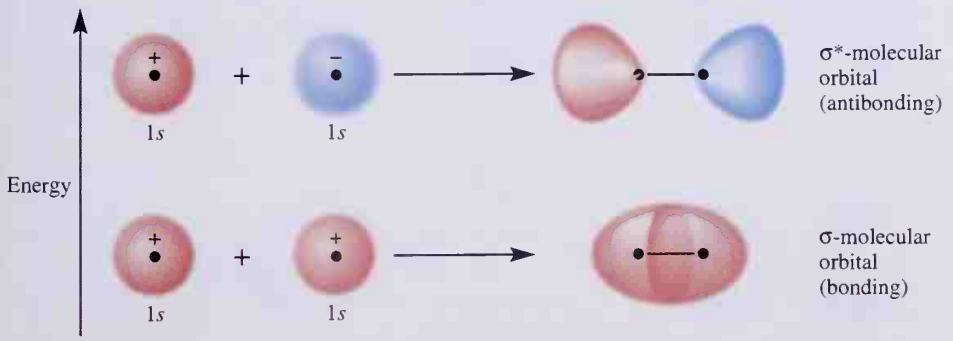


Figure 1.24
Shapes of sigma bonding and antibonding molecular orbitals derived from combination of two 1s atomic orbitals and the relative energies of each.

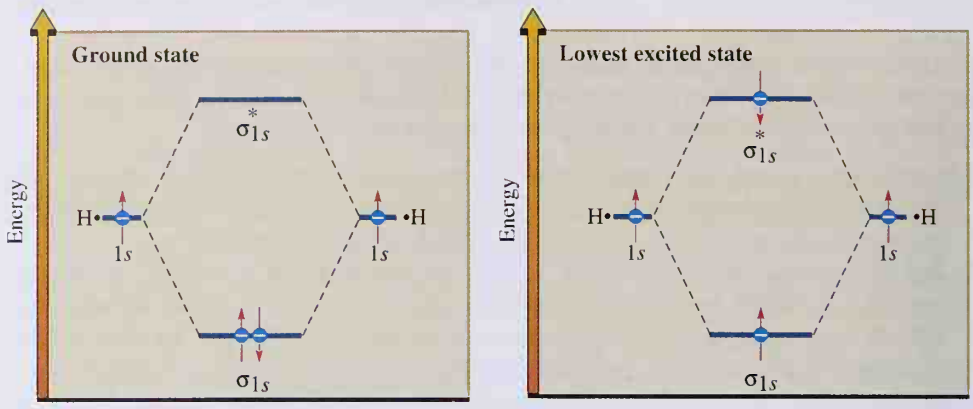


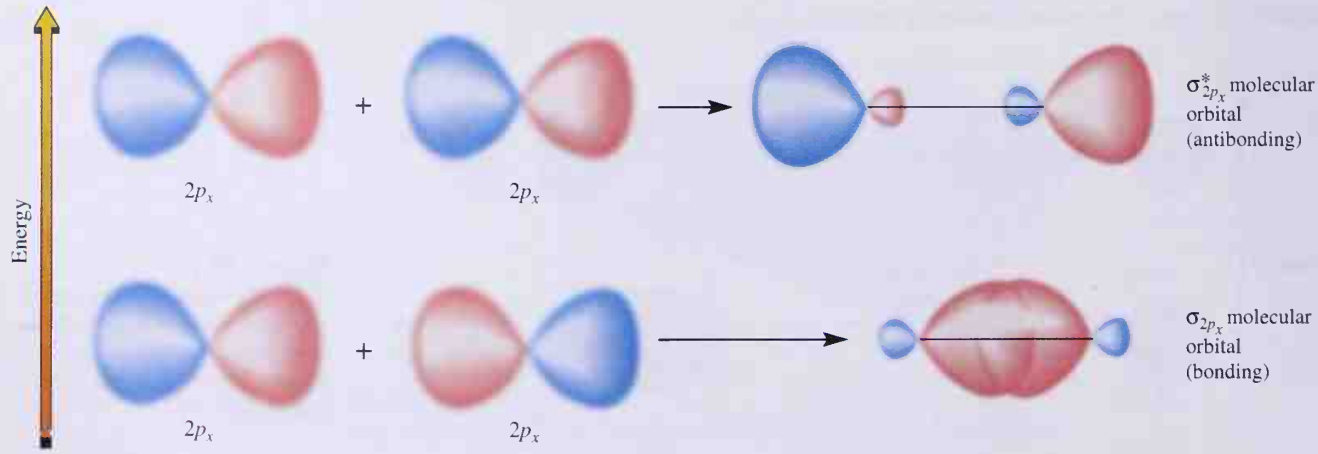
Figure 1.25
Ground state and lowest excited state for H_2.

The energy of the bonding molecular orbital is less than that of the separated atomic orbitals; the energy of the antibonding molecular orbital is greater than that of the separated atomic orbitals. The **ground state** for an atom or molecule is its state of lowest energy. In the ground state of the hydrogen molecule, the two electrons occupy the σ_{1s} molecular orbital with paired spins. An **excited state** is any electronic state other than the ground state. In the lowest excited state of the hydrogen molecule, one electron occupies the σ_{1s} molecular orbital and the other occupies the σ^*_{1s} molecular orbital. Energy-level diagrams for the ground state and the lowest excited state for the hydrogen molecule are shown in Figure 1.25.

Combination of two $2s$ atomic orbitals produces two sigma molecular orbitals, designated σ_{2s} and σ^*_{2s}, that are similar in shape and relative energies to the $1s$ molecular orbitals illustrated in Figure 1.24.

Next let us consider the molecular orbitals formed by the combination of $2p_x$, $2p_y$, and $2p_z$ atomic orbitals. There are two possible ways in which $2p$ atomic orbitals can interact. If we make the arbitrary definition of the x axis as the axis joining the two interacting atoms, then $2p_x$ orbitals combine to form a sigma-bonding molecular orbital (σ_{2p}) and a sigma-antibonding molecular orbital (σ^*_{2p}), as is illustrated in Figure 1.26. Because $2p_y$ orbitals are parallel to each other, they combine to form a pi-bonding MO (π_{2p}) and a pi-antibonding MO (π^*_{2p}). Similarly, $2p_z$ atomic orbitals combine to form a second set of pi-bonding (π_{2p}) and pi-antibonding (π^*_{2p}) MOs. Shapes of these molecular orbitals are shown in Figure 1.27.

Figure 1.26
Combination of $2p_x$ orbitals on a common axis gives a set of sigma MOs.



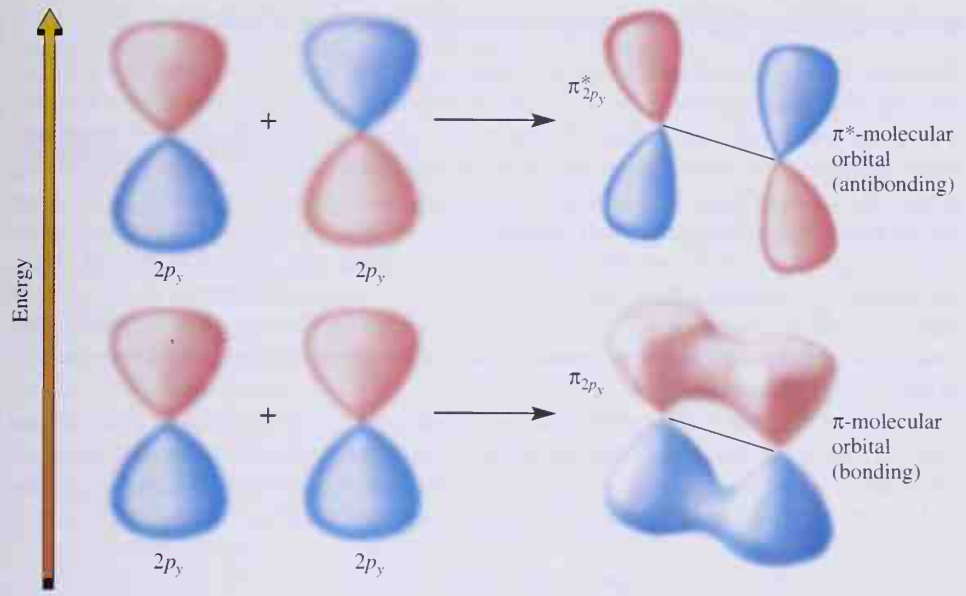


Figure 1.27
Overlap of parallel $2p_y$ orbitals gives one set of pi MOs. Combination of parallel $2p_z$ orbitals (not shown) gives a second set of pi MOs.

An energy-level diagram for the molecular orbitals derived from combinations of $1s$, $2s$, $2p_x$, $2p_y$, and $2p_z$ atomic orbitals is given in Figure 1.28. The most important feature of Figure 1.28 as far as we are concerned is the order of energies of the molecular orbitals themselves.

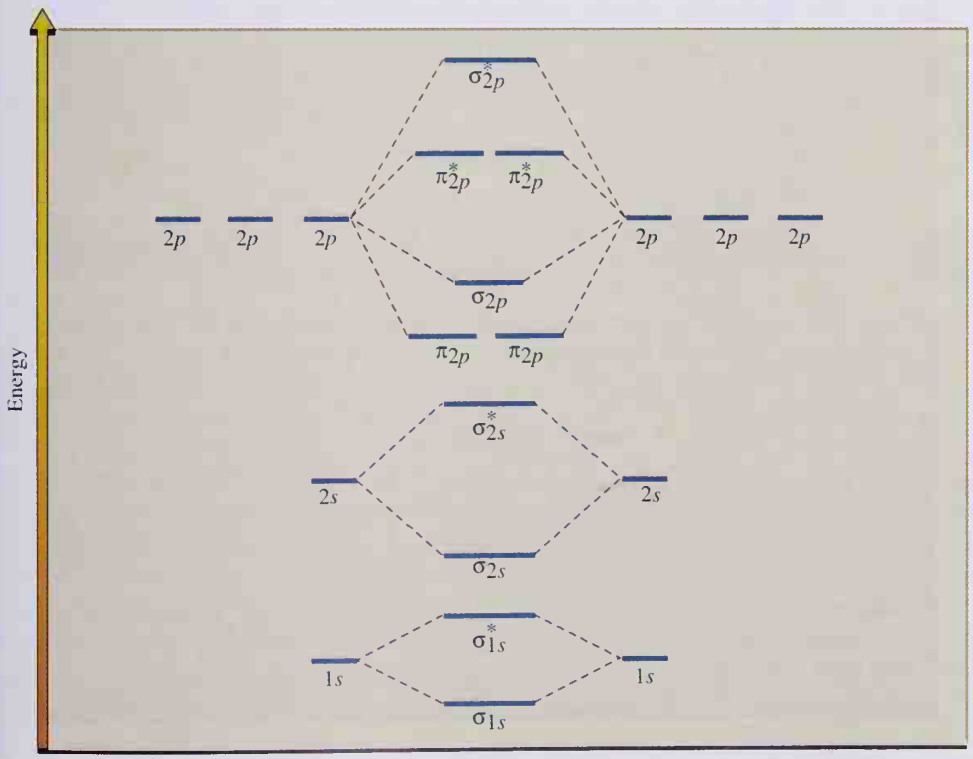


Figure 1.28
Molecular orbital energy diagram for combination of $1s$, $2s$, $2p_x$, $2p_y$, and $2p_z$ atomic orbitals.

B. Homonuclear Diatomic Molecules of Second-Row Elements

Given the energy-level diagram shown in Figure 1.28, we can now describe the bonding in homonuclear diatomic molecules of second-row elements in terms of molecular orbitals. The oxygen molecule, O_2, is derived from two oxygen atoms, each of which contributes eight electrons. The 16 electrons are placed in molecular orbitals in order of increasing energy as shown in Figure 1.29. In the ground state of the oxygen molecule, 14 electrons fill the first seven molecular orbitals through the σ_{2p} molecular orbital. The remaining two electrons are placed with parallel spins in the degenerate π^*_{2p} molecular orbitals. Thus, according to molecular orbital theory, there are two unpaired electrons in the oxygen molecule and the molecule is predicted to be paramagnetic. It was a major triumph that molecular orbital theory could account so easily for the presence of two unpaired electrons in the oxygen molecule.

In calculating the bond order for O_2, we can ignore σ_{1s} and σ^*_{1s} because each is filled with a pair of electrons, and taken together they cancel each other and have no significant effect on bonding. For principal energy level 2, there are eight electrons in bonding MOs and four in antibonding MOs, and therefore the bond order is 2.

$$\text{Bond order} = \frac{1}{2}(8 - 4) = 2$$

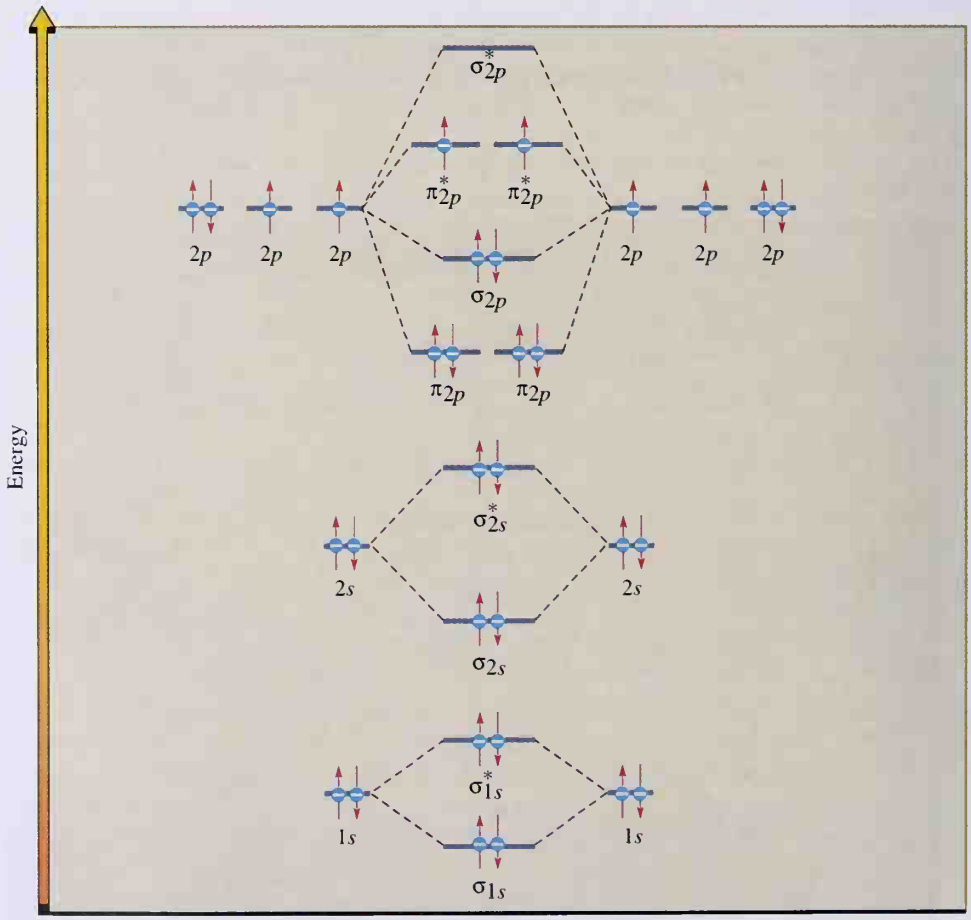


Figure 1.29
Ground-state molecular orbital energy diagram for O_2.

Valence bond theory also predicts a bond order of 2: a double bond, consisting of one sigma bond and one pi bond, between the two oxygen atoms.

EXAMPLE 1.15

Describe the ground-state electron configuration in the fluorine molecule both in terms of valence bond theory and molecular orbital theory. Do you predict this molecule to be paramagnetic or diamagnetic?

Solution

A Lewis structure for F_2 shows a single bond between the atoms and three unshared pairs of electrons on each atom. The sigma bond between the two fluorines may be formed by overlap of $2p$ orbitals, or it may be formed by overlap of hybridized sp^3, sp^2, or sp orbitals. Because no bond angle can be measured in this molecule, there is no experimental way to decide between these alternatives. In any case, valence bond theory predicts one sigma bond, three unshared pairs of electrons on each atom, and no unpaired electrons.

According to molecular orbital theory, the 18 valence electrons (9 from each fluorine atom) are placed in molecular orbitals in order of increasing energy. All bonding molecular orbitals are filled, and all antibonding molecular orbitals except the $\sigma^*_{2p_z}$ are also filled. There are no unpaired electrons. In molecular orbitals of the second principal energy level, there are eight electrons in bonding MOs and six electrons in antibonding MOs; therefore, the bond order in F_2 is $\frac{1}{2}(8 - 6) = 1$. Thus both valence bond theory and molecular orbital theory predict one covalent bond, no unpaired electrons, and diamagnetism.

PROBLEM 1.15

Describe the ground-state electron configuration for the helium molecule, He_2, and show how molecular orbital theory accounts for the fact that He_2 is not stable, that is, that helium instead exists as a monatomic gas, He.

SUMMARY

Atoms consist of a nucleus and electrons concentrated about the nucleus in regions of space called **principal energy levels** (Section 1.1). Each principal energy level n can contain as many as $2n^2$ electrons. Each principal energy level is subdivided into regions of space called **orbitals.** The **Lewis structure** (Section 1.1) of an element shows the symbol of the element surrounded by a number of dots equal to the number of electrons in the outermost, or valence, shell of the atom. According to the **Lewis model of covalent bonding** (Section 1.2), atoms bond together in such a way that each atom participating in a chemical bond acquires a completed valence-shell electron configuration resembling that of the noble gas nearest it in the periodic table. Atoms that lose sufficient electrons to acquire a completed valence shell become **cations;** those that gain sufficient electrons to acquire a completed valence shell become **anions.** An **ionic bond** is a chemical bond formed by the attractive force between an anion and a cation. A **covalent bond** is a chemical bond formed by sharing of electron pairs between atoms. The tendency of main-group elements (those of Groups IA–VIIA) to achieve an outer shell of eight valence electrons is called the **octet rule.**

Electronegativity (Section 1.2B) is a measure of the force of attraction by an atom for electrons it shares in a chemical bond with another atom. On the Pauling scale of electronegativities, fluorine, the most electronegative

element, is assigned a value of 4.0. Electronegativity decreases from right to left and from top to bottom in the periodic table.

A **nonpolar covalent bond** (Section 1.2B) is a covalent bond in which the sharing of electrons is equal or nearly so. A **polar covalent bond** is a covalent bond in which the sharing of electrons is not equal. In a polar covalent bond, the more electronegative atom bears a partial negative charge ($\delta-$), and the less electronegative atom bears a partial positive charge ($\delta+$). Using values of electronegativity of atoms, it is possible to calculate the **percent ionic character of a covalent bond.**

An acceptable Lewis structure (Section 1.2C) for a molecule or an ion must show (1) the correct order of attachment of atoms, (2) the correct number of valence electrons, (3) no more than two electrons in the outer shell of hydrogen and no more than eight electrons in the outer shell of any second-row element, and (4) all **formal charges.** The procedure for calculating formal charge is described in Section 1.2D.

Third-row elements—in particular sulfur and phosphorus—have 3*s*, 3*p*, and 3*d* orbitals available for covalent bond formation and may accommodate more than eight electrons in their valence shells.

Bond angles of covalent molecules and ions can be predicted using the **valence-shell electron-pair repulsion (VSEPR) model** (Section 1.3). For atoms surrounded by four regions of electron density, predict bond angles of 109.5°. For atoms surrounded by three regions of electron density, predict bond angles of 120°, and for atoms surrounded by two regions of electron density, predict bond angles of 180°.

Functional groups (Section 1.4) are characteristic structural units that are (1) a basis for dividing organic compounds into classes, (2) sites of chemical reactions, and (3) the basis for systematic nomenclature of organic compounds. Important functional groups for us at this stage in the course are the **hydroxyl group,** characteristic of alcohols; the **carbonyl group,** characteristic of aldehydes and ketones; and the **carboxyl group,** characteristic of carboxylic acids and esters.

Isomers (Section 1.5) are different compounds that have the same molecular formula. One class of isomers, the **constitutional isomers,** (Section 1.5) have the same molecular formula but a different order of attachment of atoms.

The **theory of resonance** (Section 1.6A), developed by Linus Pauling, is a model to account for the structure of compounds for which no single Lewis structure is adequate. These molecules and ions are best described by writing two or more Lewis structures, called **contributing structures,** and considering the real molecule or ion to be a **hybrid** of the various contributing structures. Contributing structures to the hybrid are interconnected by **double-headed arrows.** The manner in which valence electrons are redistributed from one contributing structure to the next is shown by **curved arrows,** which extend from where the electrons are initially shown (on an atom or in a covalent bond) to their new location (to an adjacent atom or adjacent bond). Rules for writing acceptable contributing structures and for estimating their relative importance are given in Sections 1.6C and 1.6D.

According to the **valence bond model** (Section 1.8A), formation of a covalent bond amounts to overlap of atomic orbitals. The greater the overlap, the stronger the resulting covalent bond. According to the quantum mechanical calculations of Heitler and London in 1927 (Section 1.8B), (1) each electron in a covalent bond is delocalized over the two atomic orbitals overlapping to form the bond and (2) the stabilization due to the formation of a covalent bond arises primarily from electron delocalization.

The combination of atomic orbitals is called **hybridization** (Section 1.8C), and the resulting atomic orbitals are called **hybrid atomic orbitals.** Combination of one 2*s* orbital and three 2*p* orbitals produces four equivalent orbitals called ***sp*³ hybrid orbitals,** each directed toward a corner of a regular tetrahedron at angles of 109.5°. Combination of one 2*s* orbital and two 2*p* orbitals forms three equivalent ***sp*² hybrid orbitals** the axes of which lie at angles of 120°. C=C, C=O, C=N, N=N, and N=O double bonds are a combination of one sigma bond formed by the overlap of sp^2 hybrid orbitals and one pi bond formed by overlap of unhybridized 2*p* orbitals. Combination of one 2*s* orbital and one 2*p* orbital forms two equivalent ***sp* hybrid orbitals** the axes of which form an angle of 180°. C≡C and C≡N triple bonds are a combination of one sigma bond formed by the overlap of *sp* hybrid orbitals and two pi bonds formed by the overlap of two sets of parallel 2*p* orbitals.

According to the **molecular orbital model** (Section 1.9) of covalent bonding, just as atomic orbitals exist for atoms, molecular orbitals exist for molecules. Molecular orbitals are formed by combination of atomic orbitals. Combination of *n* atomic orbitals gives *n* molecular orbitals. Molecular orbitals are divided into sigma- and pi-bonding and antibonding molecular orbitals. These orbitals can be arranged in order of increasing energy, and their order of filling is governed by the same rules as for filling atomic orbitals. One of the major triumphs for the molecular orbital theory of bonding is that it accounts in a very simple way for the fact that the oxygen molecule, O_2, is paramagnetic.

ADDITIONAL PROBLEMS

Lewis Structures

1.16 Write Lewis structures for the following molecules. Be certain to show all valence electrons. For the oxygen acids—that is, parts (l), (n), (r), (s), (t), (v), and (w)—each oxygen is attached directly to the central atom (C, N, P, or S) and each ionizable hydrogen is attached to an oxygen atom. None of these compounds contains a ring of atoms. Under each compound is its name so that you can find the compound within the text.

(a) H_2O_2
Hydrogen peroxide

(b) N_2H_4
Hydrazine

(c) CH_3OH
Methanol

(d) CH_3SH
Methanethiol

(e) CH_3NH_2
Methylamine

(f) CH_3Cl
Chloromethane

(g) CH_3OCH_3
Dimethyl ether

(h) C_2H_6
Ethane

(i) C_2H_4
Ethene

(j) C_2H_2
Ethyne

(k) CO_2
Carbon dioxide

(l) H_2CO_3
Carbonic acid

(m) CH_2O
Methanal

(n) CH_3CO_2H
Ethanoic acid

(o) $CH_3—CO—CH_3$
Propanone

(p) CH_3NNCH_3
Dimethyldiimine

(q) HCN
Hydrogen cyanide

(r) HNO_3
Nitric acid

(s) HNO_2
Nitrous acid

(t) HCO_2H
Methanoic acid

(u) NH_2OH
Hydroxylamine

(v) H_2SO_4
Sulfuric acid

(w) H_3PO_4
Phosphoric acid

1.17 Write Lewis structures for the following ions. Be certain to show all valence electrons and all formal charges. Under each formula is given the name of the ion.

(a) OH^-
Hydroxide ion

(b) H_3O^+
Hydronium ion

(c) NH_4^+
Ammonium ion

(d) NH_2^-
Amide ion

(e) HCO_3^-
Bicarbonate ion

(f) CO_3^{2-}
Carbonate ion

(g) Cl^-
Chloride ion

(h) Cl^+
Chloronium ion

(i) NO_2^-
Nitrite ion

(j) NO_3^-
Nitrate ion

(k) CH_3^-
Methyl anion

(l) CH_3^+
Methyl cation

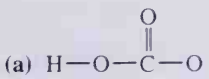
(m) $CH_3CO_2^-$
Ethanoate ion

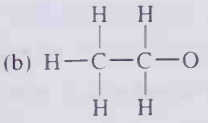
(n) HCO_2^-
Methanoate ion

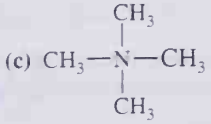
(o) SO_4^{2-}
Sulfate ion

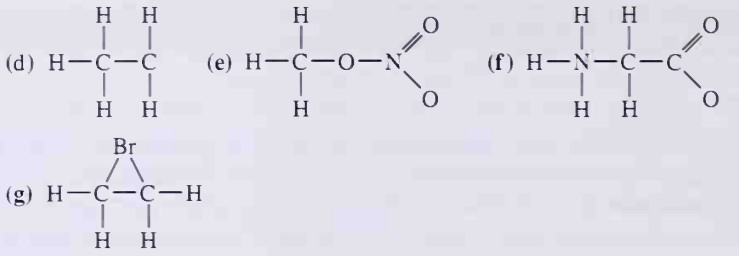
(p) HPO_4^{2-}
Hydrogen phosphate ion

1.18 Following the rule that each atom of carbon, oxygen, nitrogen, and the halogens reacts to achieve a complete outer shell of eight valence electrons, add unshared pairs of electrons as necessary to complete the valence shells of the following molecules and ions. Assign formal charges as appropriate.

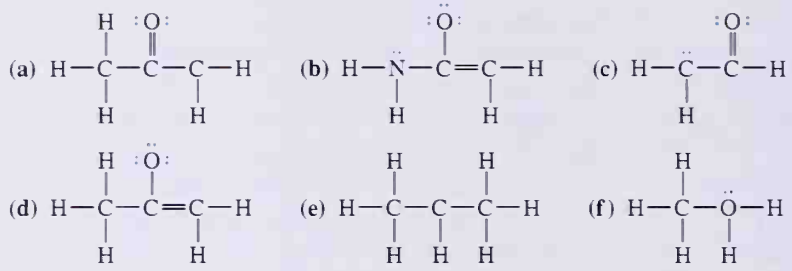
(a) 

(b) 

(c) 



1.19 Following are several Lewis structures showing all valence electrons. Assign formal charges to each structure as appropriate.



1.20 Following are compounds containing ionic and covalent bonds. Draw the Lewis structure for each and show by dashes which are covalent bonds and, by indication of charges, which are ionic bonds.

(a) CH_3ONa
Sodium methoxide

(b) NH_4Cl
Ammonium chloride

(c) $NaHCO_3$
Sodium bicarbonate

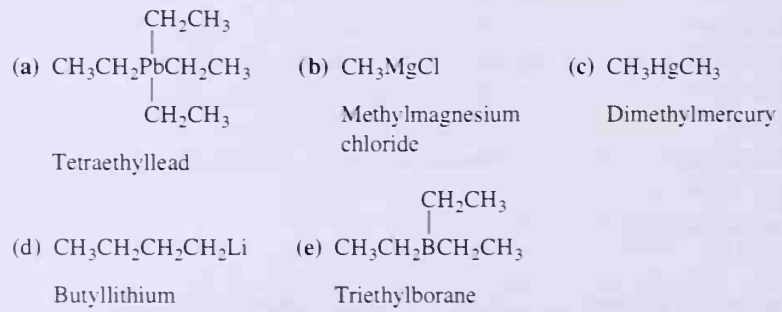
Partial Ionic Character of Covalent Bonds

1.21 Arrange the single covalent bonds within each set in order of increasing partial ionic character.

(a) C—H, O—H, N—H (b) C—H, B—H, O—H (c) C—H, C—Cl, C—I

(d) C—S, C—O, C—N (e) C—Li, C—B, C—Mg

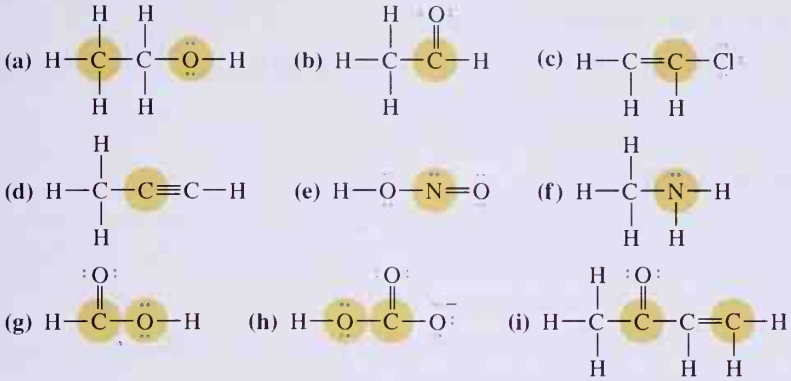
1.22 Following are several organometallic compounds. Calculate the percent ionic character of each carbon-metal bond.



Bond Angles and Shapes of Molecules

1.23 Explain how the VSEPR model is used to predict bond angles.

1.24 Following are Lewis structures for several molecules and ions. Use the VSEPR model to predict bond angles about each highlighted atom.



1.25 Use the VSEPR model to predict bond angles about each atom of carbon, nitrogen, and oxygen in the following molecules. For each molecule that contains atoms of oxygen or nitrogen, be certain that you first show all valence electrons on these atoms.

(a) $CH_3—CH_2—OH$ **(b)** $CH_3—CH_2—\overset{\overset{O}{\|}}{C}—H$ **(c)** $CH_3—CH=CH_2$

(d) $CH_3—C\equiv CH$ **(e)** $CH_3—NH_2$ **(f)** $CH_3—\overset{\overset{CH_3}{|}}{N}—CH_3$

(g) $CH_3—CH_2—\overset{\overset{O}{\|}}{C}—OH$ **(h)** $CH_3—\overset{\overset{O}{\|}}{C}—O—CH_3$ **(i)** $CH_3—\overset{\overset{O}{\|}}{C}—CH_3$

(j) $CH_2=C=CH_2$ **(k)** $CH_3—CH=N—OH$

1.26 Use the VSEPR theory to predict the geometry of the following molecules:

(a) H_2Se **(b)** CS_2 **(c)** SiH_4 **(d)** PCl_3

1.27 Use the VSEPR theory to predict the geometry of the following ions:

(a) NH_2^- **(b)** NO_2^- **(c)** NO_2^+ **(d)** NO_3^- **(e)** $CH_3CO_2^-$

(f) CH_3^- **(g)** $AlCl_4^-$

Functional Groups

1.28 Draw Lewis structures for the following functional groups. Be certain to show all valence electrons on each.

(a) Carbonyl group **(b)** Carboxyl group **(c)** Hydroxyl group

1.29 Draw condensed structural formulas for all compounds of molecular formula C_4H_8O that contain the following functional groups:

(a) A ketone (there is only one)

(b) An aldehyde (there are two)

(c) A carbon-carbon double bond and an ether (there are four)

(d) A carbon-carbon double bond and an alcohol (there are eight)

1.30 Draw structural formulas for

(a) The eight alcohols of molecular formula $C_5H_{12}O$

(b) The six ethers of molecular formula $C_5H_{12}O$

(c) The eight aldehydes of molecular formula $C_6H_{12}O$

(d) The six ketones of molecular formula $C_6H_{12}O$

(e) The eight carboxylic acids of molecular formula $C_6H_{12}O_2$

(f) The nine esters of molecular formula $C_5H_{10}O_2$

Constitutional Isomers

1.31 Which of the following are true about constitutional isomers?

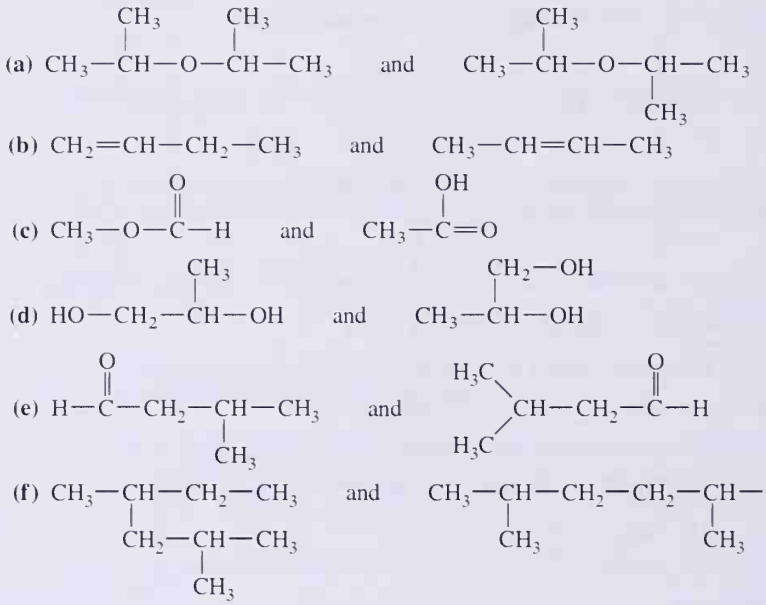
(a) They have the same molecular formula.

(b) They have the same molecular weight.

(c) They have the same order of attachment of atoms.

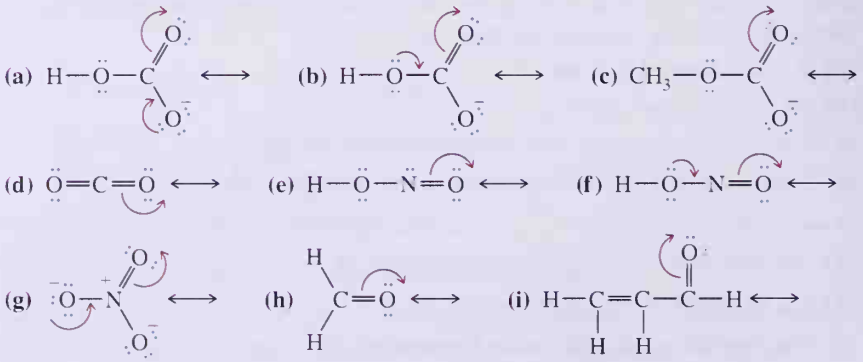
(d) They have the same physical properties.

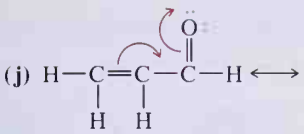
1.32 Do the structural formulas in each set represent constitutional isomers or are they the same compound? Name the functional group(s) in each molecule.



Resonance and Contributing Structures

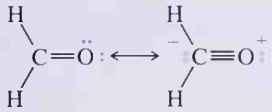
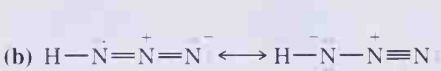
1.33 Draw the contributing structure indicated by the curved arrow(s). Assign formal charges as appropriate.

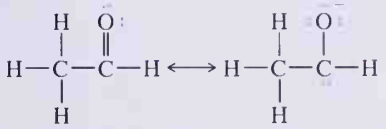
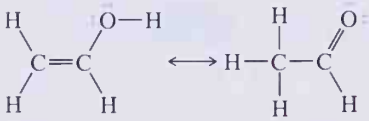


(j) 

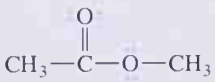
1.34 In the previous problem you were given one contributing structure and asked to draw another. Label pairs of contributing structures that are equivalent. For pairs of contributing structures that are not equivalent, label the more important contributing structure and explain your reasoning.

1.35 Are the structures in each set valid contributing structures? Explain

(a)  (b) 

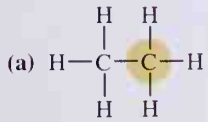
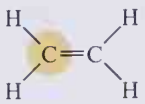
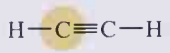
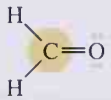
(c)  (d) 

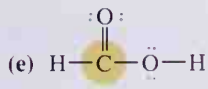
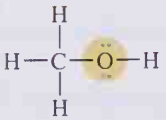
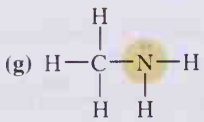
1.36 Following is the structural formula of an ester. It is one contributing structure. Draw two more contributing structures for this hybrid and show by the use of curved arrows how the first is converted to the second and the second to the third. Be certain to assign all formal charges as appropriate.

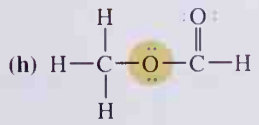
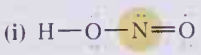
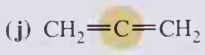


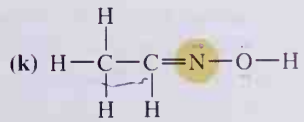
Valence Bond Theory

1.37 Following are Lewis structures for several molecules. State the orbital hybridization of each circled atom.

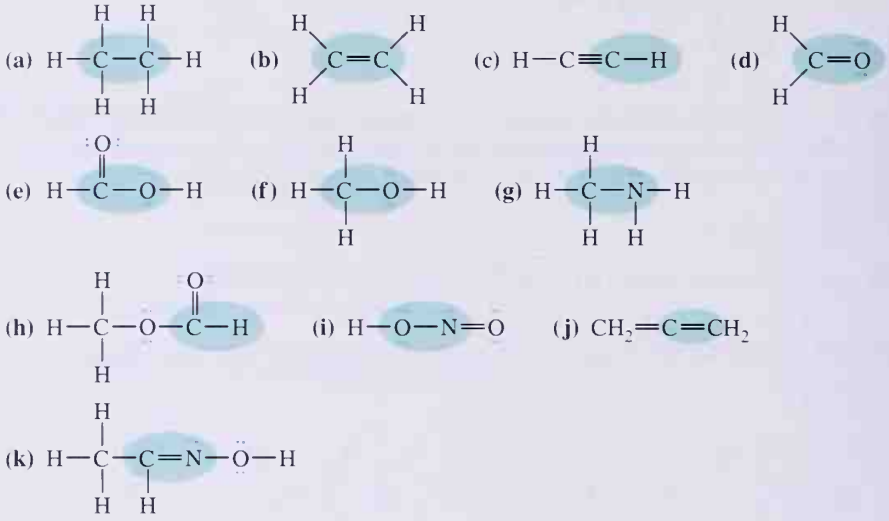
(a)  (b)  (c)  (d) 

(e)  (f)  (g) 

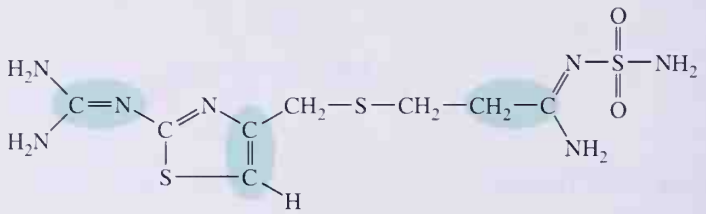
(h)  (i)  (j) 

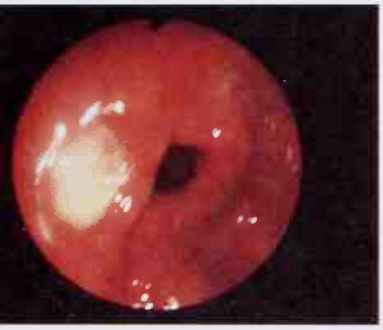
(k) 

1.38 Following are Lewis structures for several molecules. Describe each circled bond in terms of the overlap of atomic orbitals.



1.39 Following is the structural formula of the prescription drug famotidine, which is manufactured by Merck Sharpe & Dohme under the name Pepcid. The primary clinical use of Pepcid is in the treatment of active duodenal ulcers and benign gastric ulcers. Pepcid is a competitive inhibitor of histamine H_2 receptors and reduces both gastric acid concentration and the volume of gastric secretions.





Endoscope image of a superficial stomach (gastric) ulcer. *(Dr. Beer-Gabel/CNRI/Science Photo Library/Photo Researchers, Inc.)*

(a) Complete the Lewis structure of famotidine showing all valence electrons and any formal positive or negative charges.

(b) Describe each circled bond in terms of the overlap of atomic orbitals.

Molecular Orbital Theory

1.40 Figure 1.29 in Section 1.9 shows a molecular orbital energy-level diagram for the ground state of the oxygen molecule, O_2.

(a) Complete a similar molecular orbital energy diagram for the ground state of the nitrogen molecule, N_2.

(b) Do you predict N_2 to be diamagnetic or paramagnetic?

(c) Determine the bond order in N_2 and compare this with the number of bonds in N_2 according to valence bond theory.

1.41 The molecule C_2 exists in the vapor state at high temperature and has been shown to have a bond dissociation energy of 144 kcal/mol (602kJ/mol). For comparison, the bond dissociation energy of O_2 is 118 kcal/mol (494 kJ/mol) and that of N_2 is 225 kcal/mol (942 kJ/mol).

(a) Describe the ground-state electron configuration of C_2.

(b) Do you predict C_2 to be diamagnetic or paramagnetic?

(c) Determine the bond order in C_2.

1.42 Using molecular orbital theory, describe the ground-state electron configuration for the following molecules and ions. Calculate the bond order for each, decide whether each should be stable, and predict whether each is paramagnetic or diamagnetic.

(a) B_2 **(b)** B_2^+ **(c)** Be_2 **(d)** He_2^+ **(e)** O_2^{2-}

2

The planet Neptune. (NASA)

ALKANES AND CYCLOALKANES

A **hydrocarbon** is a compound that contains only carbon and hydrogen. A **saturated hydrocarbon,** or **alkane,** contains only single bonds. An **unsaturated hydrocarbon** contains one or more double or triple bonds. In this chapter we discuss the structure and reactivity of saturated hydrocarbons—the simplest class of organic compounds. We end the chapter with a discussion of sources of alkanes: natural gas, petroleum, and coal.

2.1 Structure of Alkanes

Methane, CH_4, and ethane, C_2H_6, are the first two members of the alkane family. Shown in Figure 2.1 are Lewis structures and stereorepresentations for these molecules. The shape of methane is tetrahedral and all H—C—H bond angles are 109.5°. Each of the carbon atoms in ethane is also tetrahedral and all bond angles are approximately 109.5°.

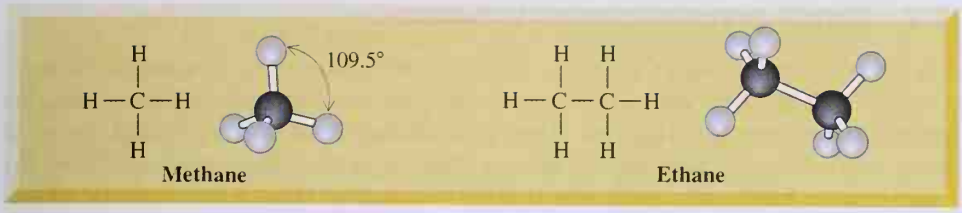


Figure 2.1
Methane and ethane.

Although the three-dimensional shapes of larger alkanes are more complex than those of methane and ethane, each carbon atom is still tetrahedral, and all bond angles are approximately 109.5°.

The next members of the series are propane, butane, and pentane.

$CH_3CH_2CH_3$	$CH_3CH_2CH_2CH_3$	$CH_3CH_2CH_2CH_2CH_3$
Propane	Butane	Pentane

Note that we have omitted the single bonds between successive carbon atoms for the sake of brevity. Consider them to be understood. Henceforward, we provide only double or triple bonds and all bonds in branching structures. Condensed structural formulas for alkanes can be written in an even more abbreviated form. For example, the structural formula of pentane contains three $—CH_2—$ **(methylene)** groups in the middle of the chain. They can be grouped together and the structural formula written $CH_3(CH_2)_3CH_3$. Names, molecular formulas, and condensed structural formulas of the first 20 alkanes are given in Table 2.1.

Alkanes have the general formula $\mathbf{C_nH_{2n+2}}$. Thus, given the number of carbon atoms in an alkane, it is easy to determine the number of hydrogens in the molecule and also its molecular formula. For example, decane with ten carbon atoms must have $(2 \times 10) + 2 = 22$ hydrogens and a molecular formula of $C_{10}H_{22}$.

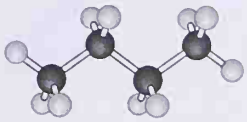
Table 2.1 Names, molecular formulas, and condensed structural formulas for the first 20 unbranched alkanes

Name	Molecular Formula	Condensed Structural Formula	Name	Molecular Formula	Condensed Structural Formula
methane	CH_4	CH_4	undecane	$C_{11}H_{24}$	$CH_3(CH_2)_9CH_3$
ethane	C_2H_6	CH_3CH_3	dodecane	$C_{12}H_{26}$	$CH_3(CH_2)_{10}CH_3$
propane	C_3H_8	$CH_3CH_2CH_3$	tridecane	$C_{13}H_{28}$	$CH_3(CH_2)_{11}CH_3$
butane	C_4H_{10}	$CH_3(CH_2)_2CH_3$	tetradecane	$C_{14}H_{30}$	$CH_3(CH_2)_{12}CH_3$
pentane	C_5H_{12}	$CH_3(CH_2)_3CH_3$	pentadecane	$C_{15}H_{32}$	$CH_3(CH_2)_{13}CH_3$
hexane	C_6H_{14}	$CH_3(CH_2)_4CH_3$	hexadecane	$C_{16}H_{34}$	$CH_3(CH_2)_{14}CH_3$
heptane	C_7H_{16}	$CH_3(CH_2)_5CH_3$	heptadecane	$C_{17}H_{36}$	$CH_3(CH_2)_{15}CH_3$
octane	C_8H_{18}	$CH_3(CH_2)_6CH_3$	octadecane	$C_{18}H_{38}$	$CH_3(CH_2)_{16}CH_3$
nonane	C_9H_{20}	$CH_3(CH_2)_7CH_3$	nonadecane	$C_{19}H_{40}$	$CH_3(CH_2)_{17}CH_3$
decane	$C_{10}H_{22}$	$CH_3(CH_2)_8CH_3$	eicosane	$C_{20}H_{42}$	$CH_3(CH_2)_{18}CH_3$

2.2 Constitutional Isomerism in Alkanes

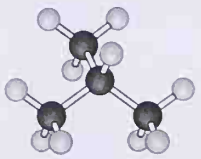
For the molecular formulas CH_4, C_2H_6, and C_3H_8, only one order of attachment of atoms is possible, and, therefore, methane, ethane, and propane have no constitutional isomers. For the molecular formula C_4H_{10}, two orders of attachment of atoms are possible. In one of these, the four carbon atoms are attached in a chain; in the other, they are attached three in a chain with the fourth carbon as a branch on the three-carbon chain. These isomeric alkanes are named butane and 2-methylpropane. We discuss how to name alkanes in the following section.

$CH_3CH_2CH_2CH_3$



Butane

$$\begin{array}{c} CH_3 \\ | \\ CH_3CHCH_3 \end{array}$$



2–Methylpropane

$CH_3CH_2CH_2CH_3$	$\begin{array}{c} CH_3 \\ \vert \\ CH_3CHCH_3 \end{array}$
Butane (bp -0.5°C)	2-Methylpropane (bp -10.2°C)

Butane and 2-methylpropane are constitutional isomers and have different physical and chemical properties. Notice that their boiling points differ by more than 9°C.

There are 3 constitutional isomers of molecular formula C_5H_{12}, 5 constitutional isomers of C_6H_{14}, 18 of C_8H_{18}, and 75 of $C_{10}H_{22}$. It should be obvious that for even a relatively small number of carbon and hydrogen atoms, a very large number of constitutional isomers is possible. In fact, the potential for structural and functional group individuality among organic molecules from just the basic building blocks of carbon, hydrogen, nitrogen, and oxygen is practically limitless.

EXAMPLE 2.1

Identify the members of each pair as formulas of the same compound or as formulas of constitutional isomers.

(a) $CH_3CH_2CH_2CH_2CH_2CH_3$ and $\begin{array}{l} CH_3CH_2CH_2 \\ \quad\quad\vert \\ \quad CH_2CH_2CH_3 \end{array}$

(b) $\begin{array}{l} CH_3CH_2CHCH_2CH_2CH_3 \\ \quad\quad\vert \\ \quad CH_3 \end{array}$ and $\begin{array}{l} CH_3CH_2CH_2CHCH_3 \\ \quad\quad\quad\quad\vert \\ \quad\quad\quad CH_2CH_3 \end{array}$

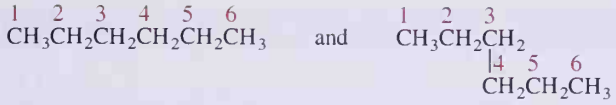
(c) $\begin{array}{l} \quad\quad CH_3 \\ \quad\quad\vert \\ CH_3CHCH_2CH \\ \quad\vert\quad\quad\vert \\ CH_3\quad CH_3 \end{array}$ and $\begin{array}{l} \quad\quad CH_3 \\ \quad\quad\vert \\ CH_3CH_2CHCHCH_3 \\ \quad\quad\quad\vert \\ \quad\quad CH_3 \end{array}$

Butane is used as a fuel in lighters. *(Charles D. Winters)*

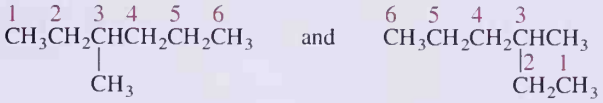
Solution

To determine whether these formulas are identical or represent constitutional isomers, find the longest chain of carbon atoms and number it from the end nearest the first branch. Note that in finding the longest chain, it makes no difference if the chain is drawn straight or bent. As structural formulas are drawn in this problem, there is no attempt to show three-dimensional shapes. After you find the longest carbon chain, number it from the correct end, then compare the lengths of each chain and the size and locations of any branches.

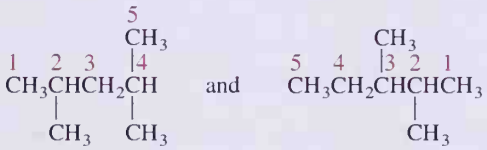
(a) Each formula has an unbranched chain of six carbons; they are identical and represent the same compound.



(b) Each has a chain of six carbons with a CH_3— group on the third carbon atom of the chain; they are identical and represent the same compound.

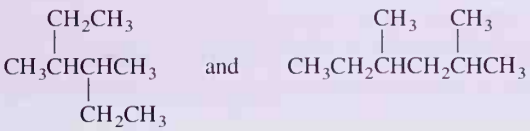


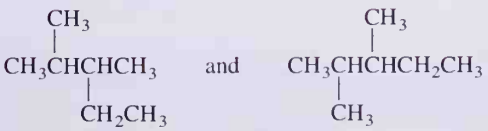
(c) Each has a chain of five carbons with two CH_3— branches. Although the branches are identical, they are at different locations on the chains. Therefore, these formulas represent constitutional isomers.



PROBLEM 2.1

Identify the members of each pair as formulas of identical compounds or as formulas of constitutional isomers.

(a) 

(b) 

EXAMPLE 2.2

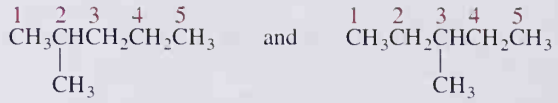
Draw structural formulas for the five constitutional isomers of molecular formula C_6H_{14}.

Solution

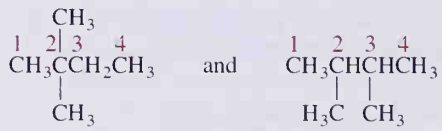
In doing problems of this type, you should devise a strategy and then follow it. One such method for solving this example is the following. First, draw the constitutional isomer with all six carbons in an unbranched chain. Then, draw all constitutional isomers with five carbons in a chain and one carbon as a branch on the chain. Finally, draw all constitutional isomers with four carbons in a chain and two carbons as branches.

Six carbons in an unbranched chain: 

Five carbons in a chain; one carbon as a branch:



Four carbons in a chain; two carbons as branches:



PROBLEM 2.2

Draw structural formulas for the three constitutional isomers of molecular formula C_5H_{12}.

2.3 Nomenclature of Alkanes

Alkanes are named using a systematic set of rules. Many also have common names that are still in use.

A. The IUPAC System

Ideally every organic compound should have a name that clearly describes its structure and from which a structural formula can be drawn. For this purpose, chemists throughout the world have accepted a set of rules established by the **International Union of Pure and Applied Chemistry (IUPAC).** IUPAC names of alkanes with an unbranched chain of carbon atoms consist of two parts: (1) a prefix that indicates the number of carbon atoms in the chain and (2) the suffix **-ane** to show that the compound is a saturated hydrocarbon.

Table 2.2 Prefixes used in the IUPAC system to show the presence of from 1 to 20 carbon atoms in a chain

Prefix	Number of Carbon Atoms	Prefix	Number of Carbon Atoms
meth-	1	undec-	11
eth-	2	dodec-	12
prop-	3	tridec-	13
but-	4	tetradec-	14
pent-	5	pentadec-	15
hex-	6	hexadec-	16
hept-	7	heptadec-	17
oct-	8	octadec-	18
non-	9	nonadec-	19
dec-	10	eicos-	20

CHEMISTRY IN ACTION

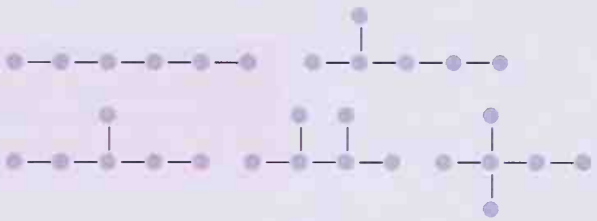
Counting the Number of Constitutional Isomers

The ability of carbon atoms to form strong, stable bonds to other carbon atoms results in a staggering number of constitutional isomers. As shown in the following table, there are three constitutional isomers of molecular formula C_5H_{12}. For molecular formula $C_{15}H_{32}$ there are 4,347 constitutional isomers, and for $C_{25}H_{52}$ there are almost 37 million constitutional isomers possible.

Number of Carbon Atoms	Number of Constitutional Isomers
1	1
5	3
10	75
15	4,347
20	366,319
25	36,797,588
30	4,111,846,763
40	62,419,178,805,831

The number of constitutional isomers becomes even larger for organic compounds with a functional group. For example, although 75 alkanes exist of molecular formula $C_{10}H_{22}$, there are 507 alcohols of molecular formula $C_{10}H_{22}O$.

Obviously, these numbers cannot be obtained by drawing and counting all the possible constitutional isomers. Instead, they are counted using a type of mathematics called **graph theory.*** Mathematically, a graph is a set of points connected by lines. In graph theory, a structure is represented as a graph wherein each carbon is a point and each bond is a line. In addition, for alkanes, no more than four lines can come from a point (a carbon atom), all points must be connected, and there can be no rings. Each constitutional isomer of molecular formula C_6H_{14}, then, is represented as a graph in the following way:



To count the number of constitutional isomers having n carbons, you count the number of graphs with n points. Mathematicians accomplish the counting by constructing something called a **generating function.** For alkanes, the generating function is

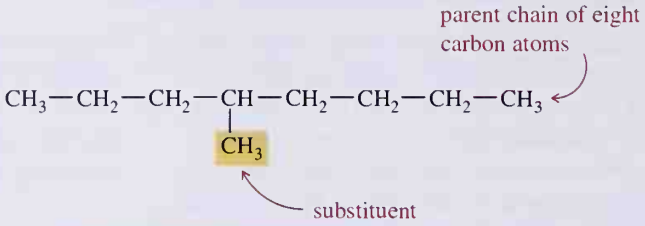
$$x + x^2 + x^3 + 2x^4 + 3x^5 + 5x^6 + 9x^7 + 18x^8 + 35x^9 + 75x^{10} + \cdots$$

The exponent represents the number of carbons, and the coefficient is the number of isomers. Thus, for four carbons, there are two constitutional isomers, and for ten carbons there are 75 constitutional isomers. The English mathematician, Arthur Cayley, was the first person to use these ideas for organic molecules, and his paper of 1874 entitled "On the Mathematical Theory of Isomers" predates many fundamental organic concepts, including the idea that alkane carbons are tetrahedral.

* To read further about the concept of graph theory for counting the number of constitutional isomers, see P. J. Hansen and P. C. Jurs, *J. Chem. Ed.*, **65**, 661, 1988.

Prefixes used to show the presence of from 1 to 20 carbon atoms are given in Table 2.2. The first four prefixes listed in Table 2.2 were chosen by IUPAC because they were well established in the language of organic chemistry. In fact, they were well established even before there were hints of the structural theory underlying the discipline. For example, the prefix *but-* appears in the name butyric acid, a compound of four carbon atoms present in butter fat (Latin: *butyrum,* butter). Roots to show five or more carbons are derived from Greek or Latin roots. Names, molecular formulas, and condensed structural formulas for the first 20 alkanes are given in Table 2.1.

IUPAC names of substituted alkanes consist of a parent or root name that indicates the longest chain of carbon atoms in the compound and substituent names that indicate the groups attached to the parent chain.



A substituent group derived from an alkane by removal of a H atom is called an **alkyl group.** The symbol R- is commonly used to represent an alkyl group. Alkyl groups are named by dropping the -ane from the name of the parent alkane and adding the suffix -yl. For example, the alkyl substituent CH_3CH_2— is named ethyl.

CH_3CH_3	CH_3CH_2—
Ethane (an alkane)	Ethyl group (an alkyl group)

Names and structural formulas for 11 of the most common alkyl groups are given in Table 2.3. Following are the rules of the IUPAC system for naming alkanes:

1. The general name of a saturated hydrocarbon is alkane.
2. For branched-chain alkanes, the hydrocarbon derived from the longest chain of carbon atoms is taken as the parent chain and the root or stem name is that of the parent alkane.

Table 2.3 Names of common alkyl groups

IUPAC Name	Condensed Structural Formula	IUPAC Name	Condensed Structural Formula
methyl	$-CH_3$	*tert*-butyl	$-C(CH_3)_3$
ethyl	$-CH_2CH_3$	pentyl	$-CH_2CH_2CH_2CH_2CH_3$
propyl	$-CH_2CH_2CH_3$	isopentyl	$-CH_2CH_2CH(CH_3)_2$
isopropyl	$-CH(CH_3)_2$	neopentyl	$-CH_2C(CH_3)_3$
butyl	$-CH_2CH_2CH_2CH_3$		
isobutyl	$-CH_2CH(CH_3)_2$		
sec-butyl	$-CH(CH_3)CH_2CH_3$		

3. Groups attached to the parent chain are called substituents. Each substituent is given a name and a number. The number shows the carbon atom of the parent chain to which the substituent is attached.
4. If the same substituent occurs more than once, the number of each carbon of the parent chain on which the substituent occurs is given. In addition, the number of times the substituent group occurs is indicated by a prefix di-, tri-, tetra-, penta-, hexa-, hepta, octa-, nona-, deca-, and so on.
5. If there is one substituent, number the parent chain from the end that gives it the lower number.
6. If there are two or more identical substituents, number the parent chain from the end that gives the lower number to the substituent encountered first.
7. If there are two or more different substituents, list them in alphabetical order and number the chain from the end that gives the lower number to the substituent encountered first. If there are different substituents in equivalent positions on the parent chain, the substituent of lower alphabetical order is given the lower number.
8. Hyphenated prefixes, such as *sec-* and *tert-*, are not considered when alphabetizing. The prefix *iso* is not a hyphenated prefix and, therefore, is included when alphabetizing.

EXAMPLE 2.3

Give IUPAC names for the following alkanes:

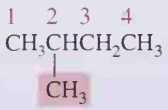
(a) $CH_3CHCH_2CH_3$ (with CH_3 branch)

(b) $CH_3CHCH_2CHCH_2CH_3$ (with CH_3 and CH_2CH_3 branches)

(c) $CH_3CH_2CHCHCH_2CH_3$ (with H_3C and CH_2CH_3 branches)

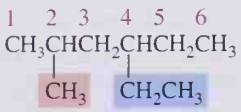
Solution

(a) There are four carbon atoms in the longest chain, and, therefore, the name of the parent chain is butane (rule 2). The butane chain must be numbered so that the single methyl group is on carbon 2 of the chain (rule 5). The correct name of this alkane is 2-methylbutane.



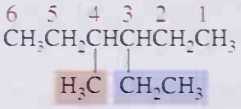
2-Methylbutane

(b) The longest chain contains six carbons, and, therefore, the parent chain is a hexane (rule 2). There are two alkyl substituents: a methyl group and an ethyl group. The hexane chain must be numbered so that the substituent encountered first (the methyl group) is on carbon 2 of the chain (rule 5). The ethyl and methyl substituents are listed in alphabetical order (rule 7) to give the name 4-ethyl-2-methylhexane.



4-Ethyl-2-methylhexane

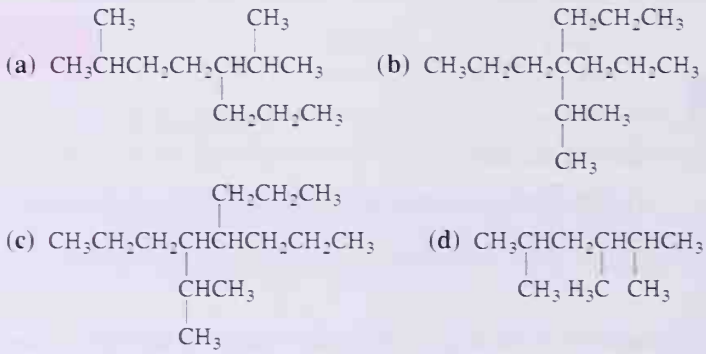
(c) The longest chain contains six carbon atoms, and, therefore, the parent chain is a hexane (rule 2). The two different substituents are in equivalent locations on the parent chain: numbering from the left gives methyl on carbon 3; numbering from the right gives ethyl on carbon 3. When listed in alphabetical order, ethyl comes before methyl. Therefore, number the carbon chain in this molecule to give ethyl the lower number (rule 7).



3-Ethyl-4-methylhexane

PROBLEM 2.3

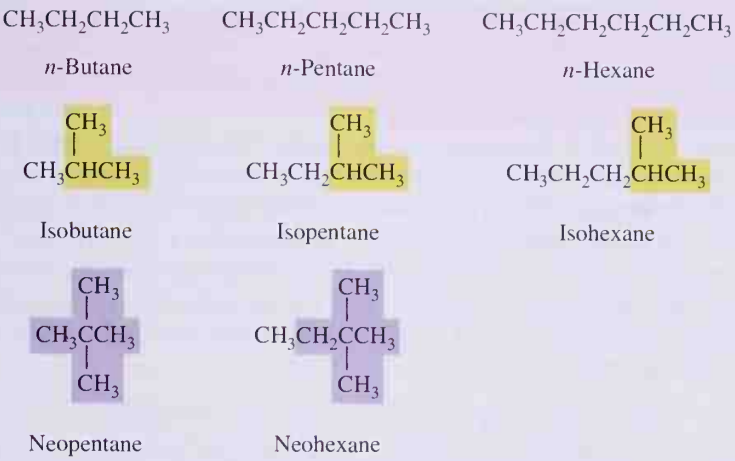
Write IUPAC names for the following alkanes:



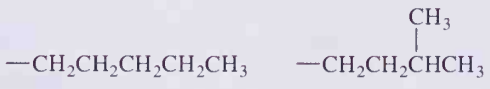
B. Common Names

In spite of the precision of the IUPAC system, routine communication in organic chemistry still relies on a combination of trivial, semisystematic, and systematic names. The reasons for this are rooted in both convenience and historical development.

In the older system of **common nomenclature**, the total number of carbon atoms in an alkane, regardless of their arrangement, determines the name. The first three alkanes are methane, ethane, and propane. All alkanes of formula C_4H_{10} are called butanes, all alkanes of formula C_5H_{12} are called pentanes, and those of formula C_6H_{14} are called hexanes. For alkanes beyond propane, **normal**, or ***n*-**, is used to indicate that all carbons are joined in a continuous chain, and **iso** is used to indicate that one end of an otherwise continuous chain terminates in a $(CH_3)_2CH—$ group. The first compounds of molecular formula C_5H_{12} to be discovered and named were pentane and its isomer, isopentane. Subsequently, another compound of molecular formula C_5H_{12} was discovered and because it was a "new" pentane (at least it was new to those who first discovered it), this isomer was named neopentane (Greek: *neo*, new). The prefix **neo** is used to indicate that one end of an otherwise continuous chain terminates in $(CH_3)_3C—$. Following are examples of common names:



The common names amyl- and isoamyl- are often used in place of the IUPAC names pentyl- and isopentyl-.



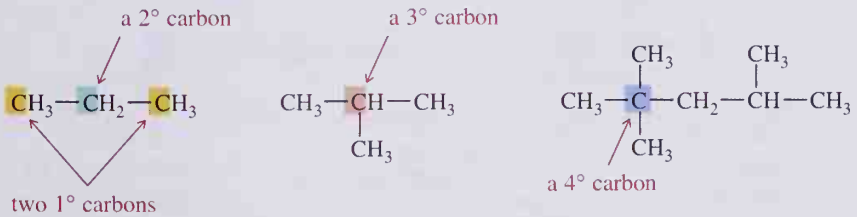
IUPAC name:	Pentyl	Isopentyl
Common name:	(Amyl)	(Isoamyl)

This system of common names has no good way of handling other branching patterns, and for more complex alkanes it is necessary to use the more flexible IUPAC system of nomenclature.

In this text we concentrate on IUPAC names. However, we also use common names, especially when the common name is used almost exclusively in the everyday discussions of chemists. When both IUPAC and common names are given in the text, we always give the IUPAC name first followed by the common name in parentheses. In this way, you should have no doubt about which name is which.

C. Classification of Carbon and Hydrogen Atoms

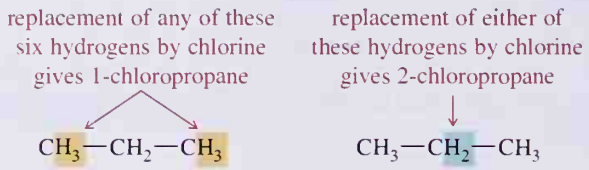
A carbon atom is classified as **primary (1°), secondary (2°), tertiary (3°),** or **quaternary (4°)** depending on the number of carbon atoms bonded to it. A carbon bonded to one carbon atom is a primary carbon; a carbon bonded to two carbon atoms is a secondary carbon, and so forth. For instance, propane contains two primary carbons and one secondary carbon. 2-Methylpropane contains three primary carbons and one tertiary carbon. 2,2,4-Trimethylpentane contains five primary carbons, one secondary carbon, one tertiary carbon, and one quaternary carbon.



A tank of propane fuel. *(Charles D. Winters)*

Similarly, hydrogens are also classified as primary, secondary, or tertiary depending on the type of carbon to which each is bonded. Those attached to primary carbons are classified as primary hydrogens, those on secondary carbons are secondary hydrogens, and those on tertiary carbons are tertiary hydrogens.

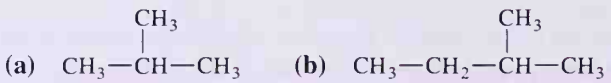
Hydrogen atoms in a compound can be divided into equivalent sets. **Equivalent hydrogens** have the same chemical environment. A direct way to determine which hydrogens in a molecule are equivalent is to replace each in turn by a "test atom," as for example a halogen atom. If replacement of two different hydrogens by a "test halogen" gives the same compound, the hydrogens are equivalent. If replacement gives a different compound, the hydrogens are nonequivalent. Using this test, we can show that propane contains two sets of equivalent hydrogens, a set of six equivalent primary hydrogens, and a set of two equivalent secondary hydrogens.



Propane Propane

EXAMPLE 2.4

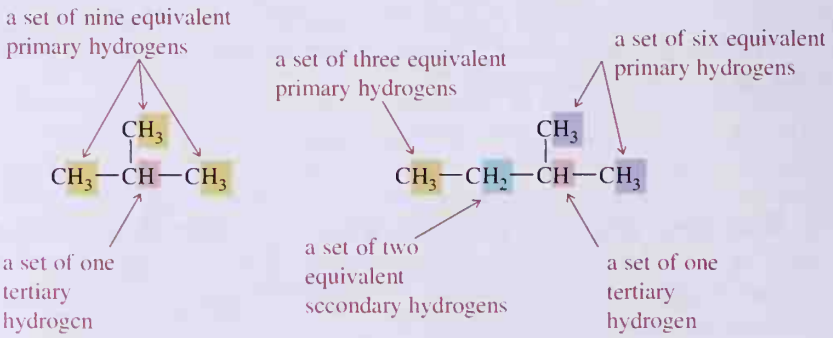
State the number of sets of equivalent hydrogens in each compound and the number of hydrogens in each set.



Solution

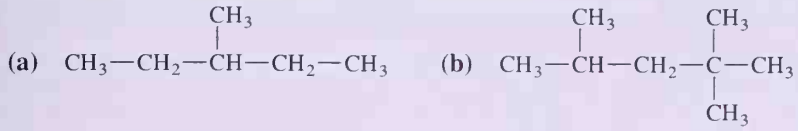
(a) 2-Methylpropane contains two sets of equivalent hydrogens. Replacement of any one of the nine equivalent primary hydrogens gives 1-chloro-2-methylpropane. Replacement of the one tertiary hydrogen gives 2-chloro-2-methylpropane.

(b) 2-Methylbutane contains four sets of equivalent hydrogens. Nine primary hydrogens are in this molecule: three in one set and six in a second set. Replacement of any hydrogen in the set of three gives 1-chloro-3-methylbutane. Replacement of any hydrogen in the set of six gives 1-chloro-2-methylbutane.



PROBLEM 2.4

State the number of sets of equivalent hydrogens in each compound and the number of hydrogens in each set.



2.4 Cycloalkanes

So far we have considered only chains (branched and unbranched) of carbon atoms. A molecule that contains carbon atoms joined together to form a ring is called a **cyclic hydrocarbon.** Furthermore, when all carbons of the ring are saturated, the molecule is called a **cycloalkane.**

A. Structure and Nomenclature

Cycloalkanes of ring sizes ranging from 3 to over 30 are found in nature, and in principle, there is no limit to ring size. Five-member rings (cyclopentanes) and six-member rings (cyclohexanes) are especially abundant in nature and, therefore, have received special attention.

Figure 2.2 shows structural formulas of cyclopropane, cyclobutane, cyclopentane, and cyclohexane. As a matter of convenience, organic chemists often do not show all the carbons and hydrogens when writing out the structural formulas for cycloalkanes. Rather,

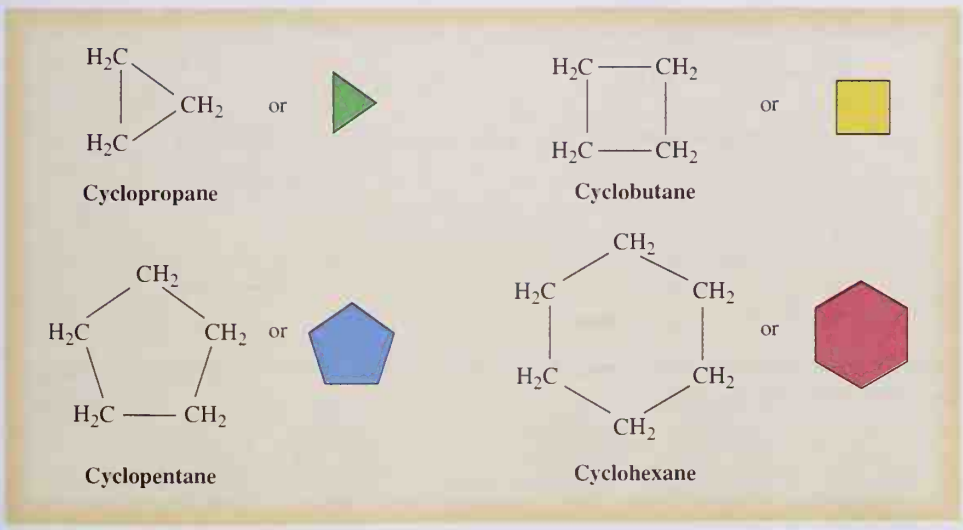


Figure 2.2
Examples of cycloalkanes.

the rings are represented by regular polygons having the same number of sides. For example, cyclopropane is represented by a triangle and cyclohexane by a hexagon.

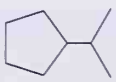
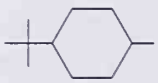
The abbreviated structural formulas shown in Figure 2.2 are called line-angle drawings. In a **line-angle drawing,**

- Each line represents a C—C bond, each double line represents a C=C bond, and each triple line represents a C≡C bond.
- Each angle represents a carbon atom. Thus, only the carbon framework of the molecule is shown and you are left to fill in hydrogen atoms as necessary to complete the tetravalence of carbon.

To name cycloalkanes, prefix the name of the corresponding open-chain hydrocarbon with cyclo-, and name each substituent on the ring. If there is only a single substituent on the cycloalkane ring, there is no need to give it a number. If there are two or more substituents, each substituent must be given a number to indicate its location on the ring.

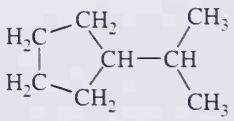
EXAMPLE 2.5

Following are line-angle drawings for two cycloalkanes. Write a structural formula and molecular formula for each.

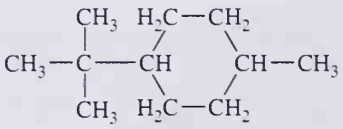
(a)  (b) 

Solution

Because there is only an isopropyl group on the ring in (a), there is no need to number the atoms of the ring. Number the atoms of the cyclohexane ring in (b) beginning with *tert*-butyl, the substituent of lowest alphabetical order.

(a) 

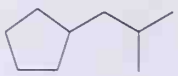
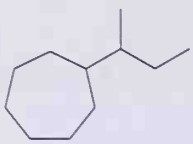
Isopropylcyclopentane
C_8H_{16}

(b) 

1-*tert*-Butyl-4-methylcyclohexane
$C_{11}H_{22}$

PROBLEM 2.5

Following are line-angle drawings for three cycloalkanes. Write a structural formula and molecular formula for each.

(a)  (b)  (c) 

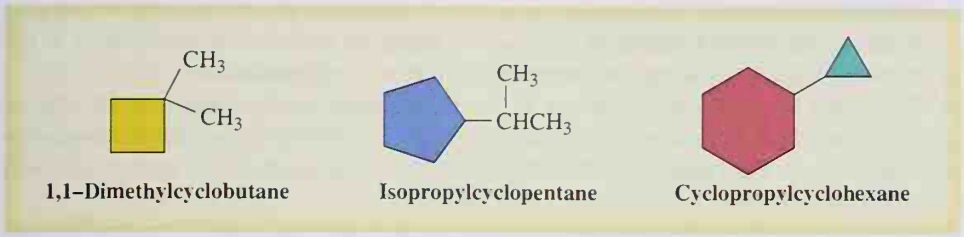


Figure 2.3
Examples of monocyclic ring systems.

The use of carbon bonds to close a ring means that cycloalkanes contain two fewer hydrogen atoms than an alkane of the same number of carbon atoms. For example, compare the molecular formulas of cyclopropane (C_3H_6) and propane (C_3H_8) or those of cyclohexane (C_6H_{12}) and hexane (C_6H_{14}). The general formula of a cycloalkane is $\mathbf{C_nH_{2n}}$.

B. Bicyclic and Spiroalkanes

Any organic compound that contains one ring is classified as monocyclic. Examples of **monocyclic alkanes** are cyclopentane, cyclohexane, and their simple derivatives (Figure 2.3). Compounds that contain two rings but which share no atoms in common are similarly classified as monocyclic.

A hydrocarbon that contains two rings that share two carbon atoms is classified as a **bicycloalkane.** Atoms shared by the two rings in a bicyclic compound are called **bridgehead atoms.** Several examples of bicycloalkanes and bridgehead carbon atoms are given in Figure 2.4. IUPAC names of bicycloalkanes are derived in the following way:

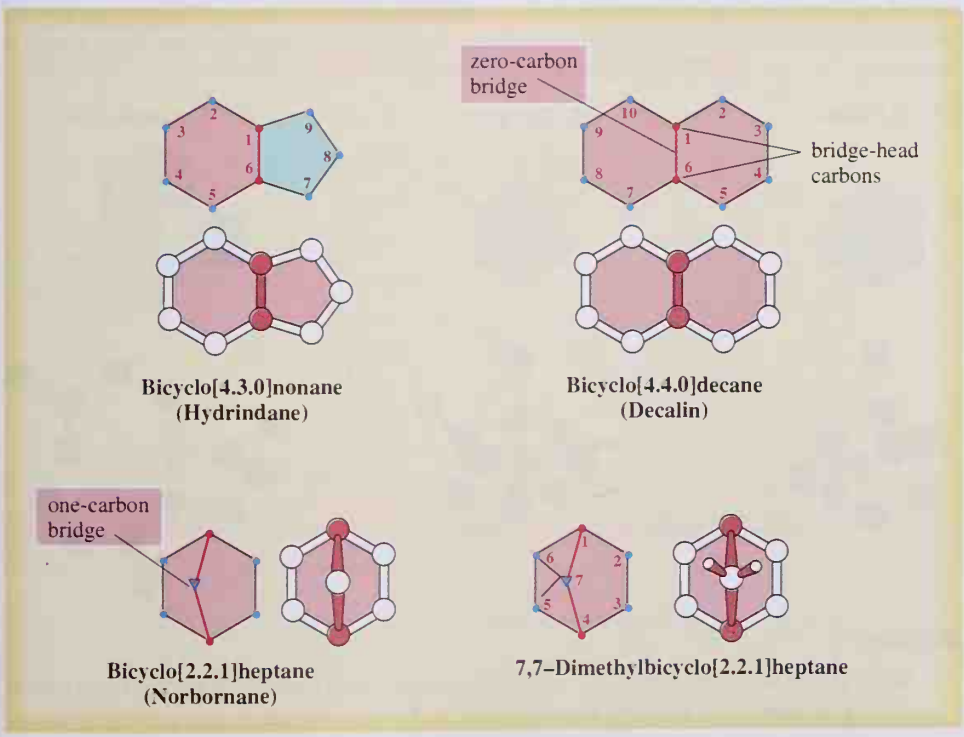
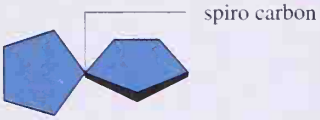


Figure 2.4
Examples of bicycloalkanes.

1. Numbering begins at a one bridgehead carbon atom and proceeds along the longest bridge to the second bridgehead carbon, then along the next longest bridge back to the original bridgehead carbon, and so on until all atoms are numbered.
2. The parent name of a bicycloalkane is that of the hydrocarbon of the same number of carbon atoms as are in the bicyclic ring system. For example, the first compound in Figure 2.4 contains nine carbons and is, therefore, a bicyclononane; the second compound contains ten carbons and is a bicyclodecane.
3. Ring sizes are shown by counting the number of carbon atoms linked to the bridgeheads and placing them in decreasing order in brackets between the prefix bicyclo- and the parent name. For example, the first compound in Figure 2.4 has two bridgehead carbons. There are four carbons in the first bridge, three in the second, and 0 in the third; its name is, therefore, bicyclo[4.3.0]nonane.
4. The name and location of substituents are shown by the rules already described in Section 2.3A as is illustrated by the name 7,7-dimethylbicyclo[2.2.1]heptane.

Spiro[3.3]heptane



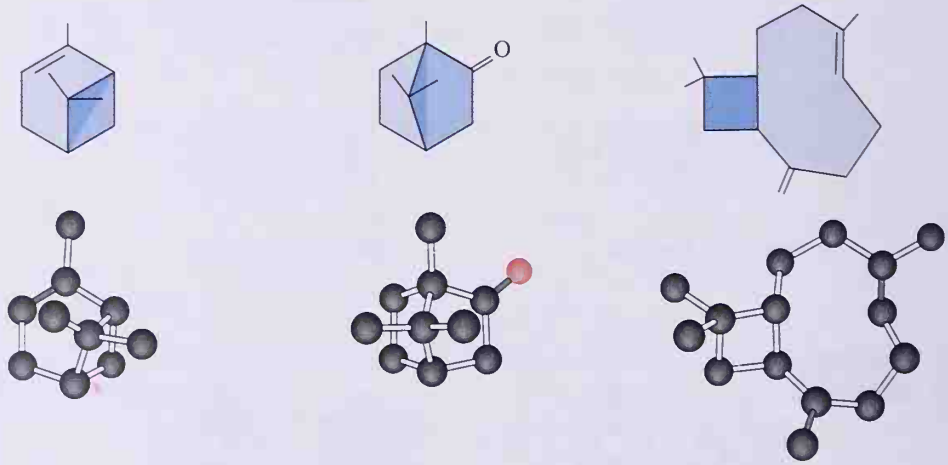
Spiro[4.4]nonane

A cycloalkane in which two rings share only one carbon atom is known as **spiroalkane** (Latin: *spiro,* spiral or coiled), and the single carbon atom shared by the two rings is called a **spiro carbon.** Numbering a spiroalkane begins at the carbon on the shorter bridge nearest the spiro carbon, along the shorter bridge, through the spirocarbon, and along the longer bridge. Following are structural formulas for spiro[3.3]heptane and spiro[4.4]nonane. Note that the four bonds connected to a spiro carbon create two planes at right angles to each other, and, consequently, the two rings thus intersecting lie at right angles to each other.

EXAMPLE 2.6

Following are line-angle formulas and common names for three bicyclic compounds. Write the molecular formula of each compound and name the bicycloalkane from which it is derived.

(a) α-Pinene **(b) Camphor** **(c) Caryophyllene**



Solution

(a) The molecular formula of α-pinene is $C_{10}H_{16}$, and the bicycloalkane from which it is derived is bicyclo[3.1.1]heptane. α-Pinene is a major component, often as high as 65% by volume, of pine oil and turpentine.

(b) The molecular formula of camphor is $C_{10}H_{16}O$, and the bicycloalkane from which it is derived is bicyclo[2.2.1]heptane. Camphor is isolated from the camphor tree. Most camphor sold in the United States today is made synthetically in the laboratory from α-pinene.

(c) The molecular formula of caryophyllene is $C_{15}H_{24}$, and the bicycloalkane from which it is derived is bicyclo[7.2.0]undecane. Caryophyllene is one of the fragrant components of oil of cloves.

PROBLEM 2.6

Draw structural formulas for the following bicycloalkanes and spiroalkanes.

(a) bicyclo[3.1.0]hexane **(b)** bicyclo[2.2.2]octane
(c) bicyclo[4.2.0]octane **(d)** 2,6,6-trimethylbicyclo[3.1.1]heptane
(e) spiro[2.4]heptane **(f)** spiro[2.5]octane

2.5 The IUPAC System—A General System of Nomenclature

The naming of alkanes and cycloalkanes in Sections 2.3 and 2.4 illustrated the application of the IUPAC system of nomenclature to two specific classes of organic compounds. Now, let us describe the general approach of the IUPAC system. The name assigned to any compound with a chain of carbon atoms consists of three parts: a **prefix,** an **infix** (a modifying element inserted into a word), and a **suffix.** Each part provides specific information about the structure of the compound.

1. The prefix tells the number of carbon atoms in the parent chain.

Prefix	Number of Carbon Atoms
meth-	1
eth-	2
prop-	3
but-	4
pent-	5
hex-	6
hept-	7
oct-	8

2. The infix tells the nature of the carbon-carbon bonds in the parent chain.

Infix	Nature of Carbon-Carbon Bonds
-an-	all single bonds
-en-	one or more double bonds
-yn-	one or more triple bonds

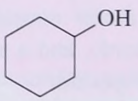
3. The suffix tells the class of compound to which the substance belongs.

Suffix	Class of Compound
-e	hydrocarbon
-ol	alcohol
-al	aldehyde
-one	ketone
-oic acid	carboxylic acid

EXAMPLE 2.7

Following are IUPAC names and structural formulas for several compounds. Divide each name into a prefix, an infix, and a suffix and specify the information about the structural formula that is contained in each part of the name.

(a) $CH_2{=}CHCH_3$ Propene **(b)** CH_3CH_2OH Ethanol **(c)** $CH_3CH_2\overset{\overset{O}{\|}}{C}CH_3$ Butanone

(d) $CH_3CH_2CH_2CH_2\overset{\overset{O}{\|}}{C}OH$ Pentanoic acid **(e)**  Cyclohexanol **(f)** $HC{\equiv}CH$ Ethyne

Solution

(a) prop - en - e
- one carbon-carbon double bond
- a hydrocarbon
- three carbon atoms

(b) eth - an - ol
- only carbon-carbon single bonds
- presence of an —OH (hydroxyl) group
- two carbon atoms

(c) but - an - one
- only carbon-carbon single bonds
- presence of a ketone group
- four carbon atoms

(d) pent - an - oic acid
- only carbon-carbon single bonds
- presence of a $—CO_2H$ (carboxyl) group
- five carbon atoms

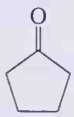
(e) cyclohex - an - ol
- only carbon-carbon single bonds
- presence of an —OH (hydroxyl) group
- six carbon atoms in a ring

(f) eth - yn - e
- one carbon-carbon triple bond
- a hydrocarbon
- two carbon atoms

PROBLEM 2.7

Combine the proper prefix, infix, and suffix and write the IUPAC names for the following:

(a) $CH_2{=}CH_2$ (b) $CH_3C{\equiv}CH$ (c) $CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}CH_3$

(d) $CH_3CH_2CH_2CH_2\overset{\overset{O}{\|}}{C}H$ (e)  (f) 

2.6 Conformations of Alkanes and Cycloalkanes

Structural formulas are useful to show the order of attachment of atoms. However, they usually do not show three-dimensional shapes. As chemists try to understand more and more about the relationships between structure and the chemical and physical properties of molecules, it becomes increasingly important to understand more about the three-dimensional shapes of molecules.

A. Alkanes

Alkanes of two or more carbons can be twisted into a number of different three-dimensional arrangements by rotation about a carbon-carbon bond or bonds. Any three-dimensional arrangement of atoms that results by rotation about single bonds is called a **conformation.** Figure 2.5(a) shows a ball-and-stick model of a **staggered conformation**

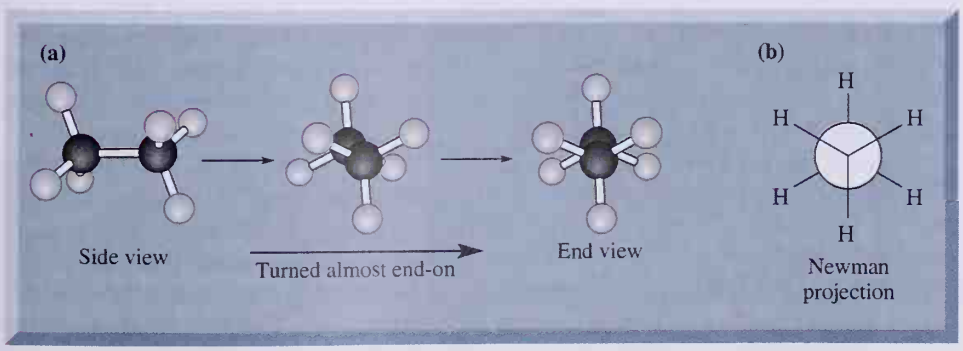


Figure 2.5
A staggered conformation of ethane. (a) Ball-and-stick models and (b) a Newman projection.

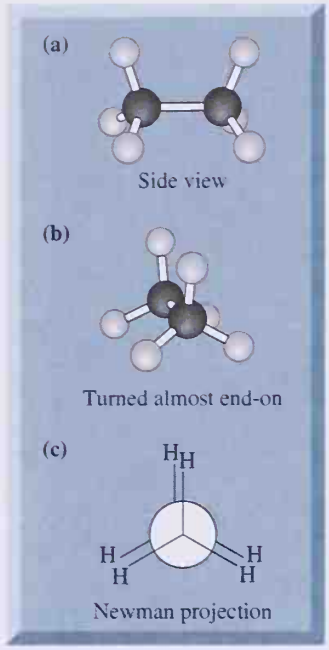


Figure 2.6
An eclipsed conformation of ethane. (a,b) Ball-and-stick models and (c) a Newman projection.

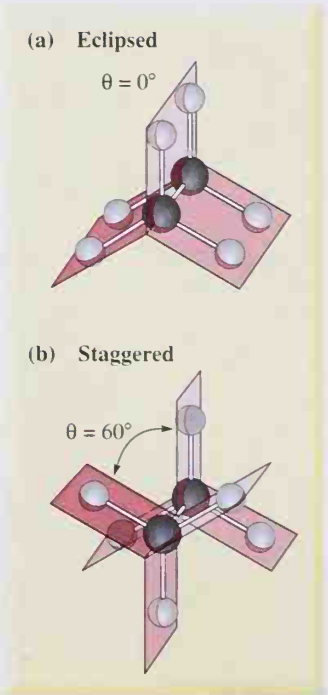


Figure 2.7
Eclipsed and staggered conformations of ethane.

of ethane. Figure 2.5(b) is a **Newman projection** of this conformation of ethane. In the Newman projection shown in Figure 2.5(b), the molecule is viewed along the axis of the C—C bond. The three hydrogens nearer your eye are shown on lines extending from the center of the circle at angles of 120°. The three hydrogens of the carbon farther from your eye are shown on lines extending from the circumference of the circle. Remember that bond angles about each carbon are approximately 109.5° and not 120° as this Newman projection might suggest.

Figures 2.6(a) and 2.6(b) show ball-and-stick models for another conformation of ethane viewed from two different perspectives. In this conformation, C—H bonds on the back carbon are lined up or eclipsed with C—H bonds on the front carbon and for this reason this conformation is called an **eclipsed conformation.**

In principle there are an infinite number of conformations of ethane that differ only in the degree of rotation about the carbon-carbon single bond. At standard conditions of temperature and pressure (STP), ethane is a gas, and under these conditions ethane molecules undergo collision with sufficient energy so that rotation about the carbon-carbon single bond from one conformation to another occurs rapidly. For a long time chemists believed that the rotation about the C—C single bond was completely free. However, studies of ethane and other molecules have shown that a potential energy difference exists between conformations and that rotation is not completely free. In ethane, the potential energy of the eclipsed conformation is a maximum, that of the staggered conformation is a minimum, and a continuum of conformations exists, the potential energies of which lie in between these extremes. To discuss potential energy relationships between conformations, it is convenient to define the term "dihedral angle." A **dihedral angle,** θ (Greek letter theta), is defined as the angle created by two intersecting planes. In the Newman projection of the eclipsed conformation of ethane in Figure 2.7(a), two H—C—C planes are shown. The angle at which these planes intersect (the dihedral angle) is 0°. Illustrated in Figure 2.7(b) is a staggered conformation in which the dihedral angle of the two H—C—C planes is 60°. The relationship between potential energy and dihedral angle for the conformations of ethane is shown in Figure 2.8. The difference in potential energy between the staggered and eclipsed conformations is approximately 3.0 kcal/mol.

Chemists do not yet fully understand the reasons why a staggered conformation of ethane is more stable than an eclipsed conformation. One possible explanation has to do with the repulsion of electron pairs of C—H bonds. In an eclipsed conformation, electron pairs of adjacent C—H bonds are closer to one another than they are in a staggered conformation. Hence, the greater potential energy of an eclipsed conformation is due to repulsive interaction of electron pairs in adjacent C—H bonds.

Next let us look at the staggered and eclipsed conformations of butane with the bond between carbons 2 and 3 taken as the reference point. Because of the methyl groups on these reference carbons, there are two types of staggered conformations for butane and two types of eclipsed conformations. The staggered conformation in which the methyl groups are the maximum distance apart (dihedral angle 180°) is called the **anti conformation;** that in which they are closer together (dihedral angle 60°) is called the **gauche conformation.** There are two eclipsed conformations of butane. In one of these eclipsed conformations (dihedral angle 0°), methyl is eclipsed by methyl and in the other (dihedral angle 120°), methyl is eclipsed by hydrogen. Dihedral angles of 0°, 60°, 120°, and 180° are illustrated in Figure 2.9. The relative potential energies of the conformations of butane along the bond between carbons 2 and 3 reflect the fact that a methyl group occupies a larger volume of space than does a hydrogen atom. Of the two eclipsed conformations, that with methyl eclipsed by methyl is the higher in energy. Of the staggered conformations, the gauche is higher in energy. The energy relationships for rotation from 0° to 360° are illustrated in

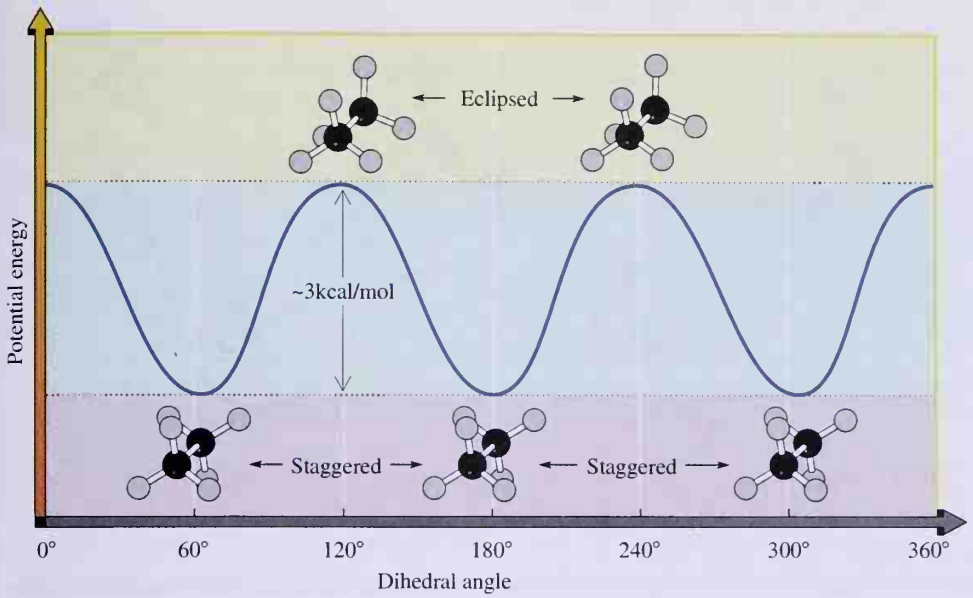
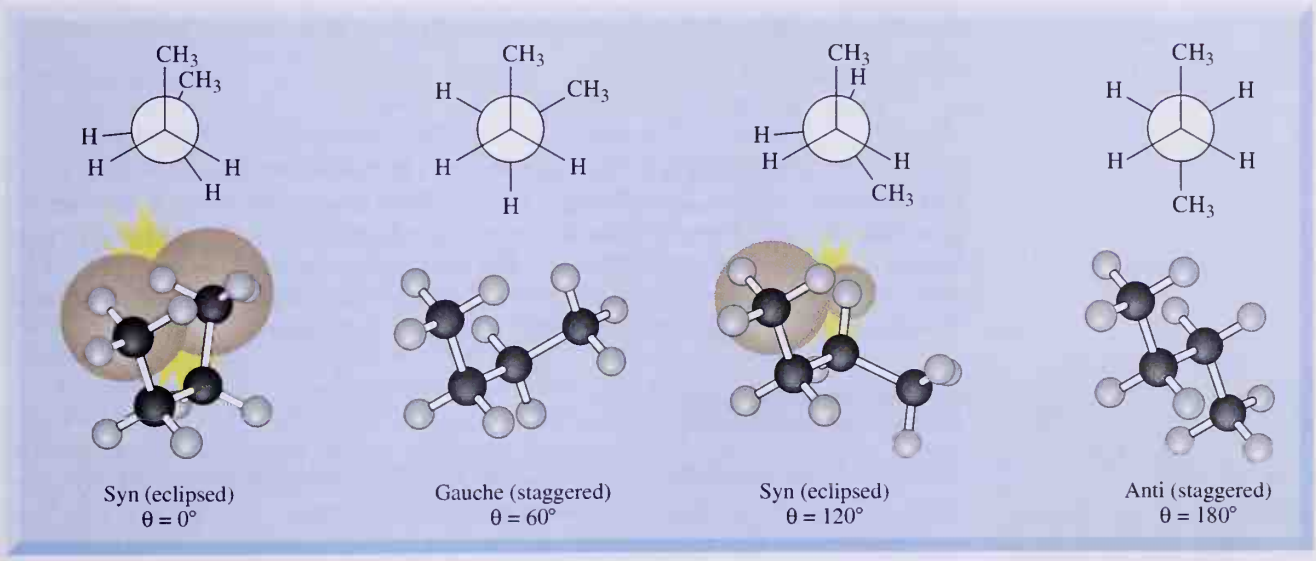


Figure 2.8
Potential energy of ethane as a function of dihedral angle.



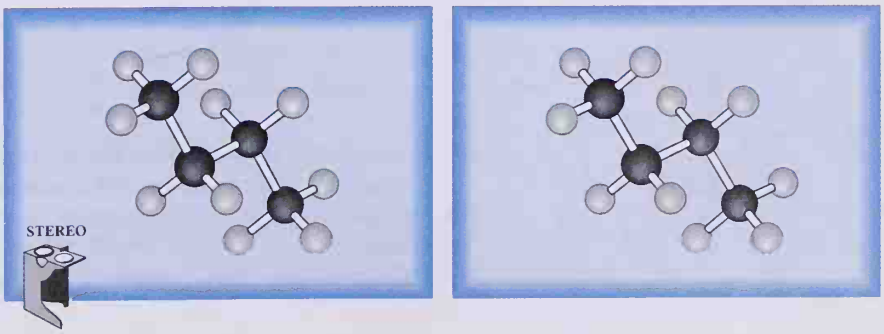


Figure 2.9
Newman projections of eclipsed and staggered conformations of butane. Dihedral angles refer to the intersecting CH_3—C—C planes. The stereopair is the anti (staggered) conformation.

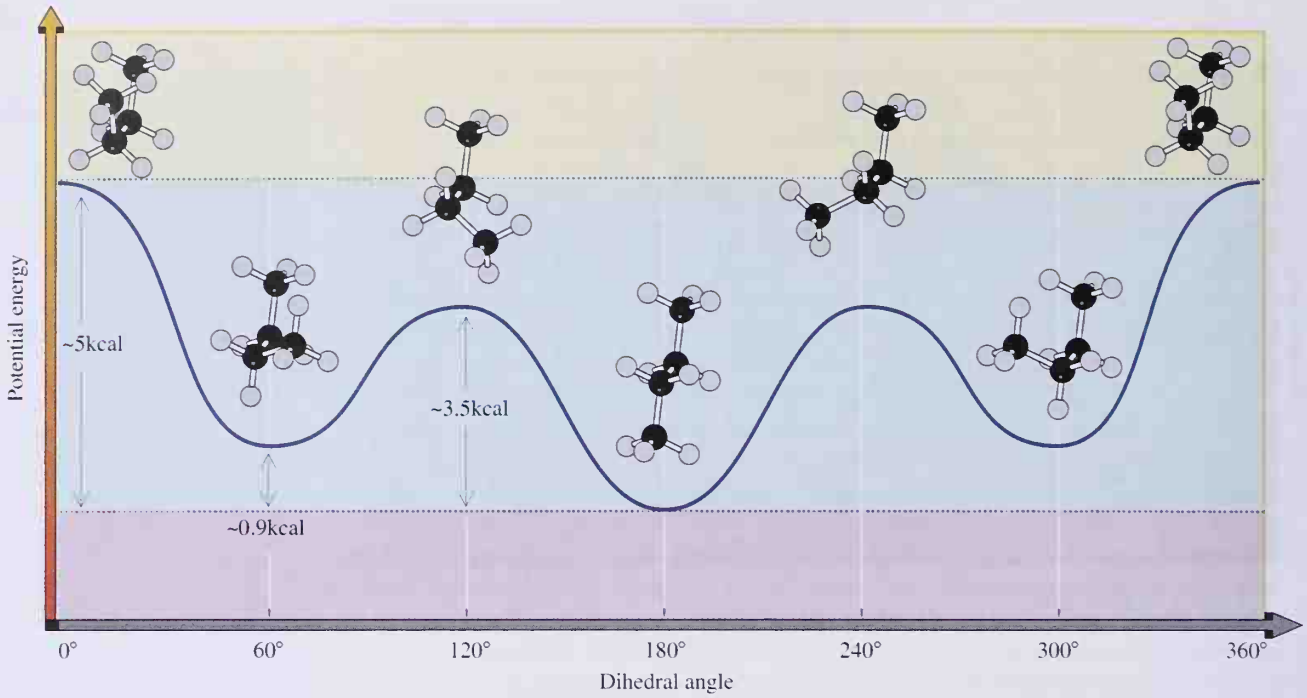
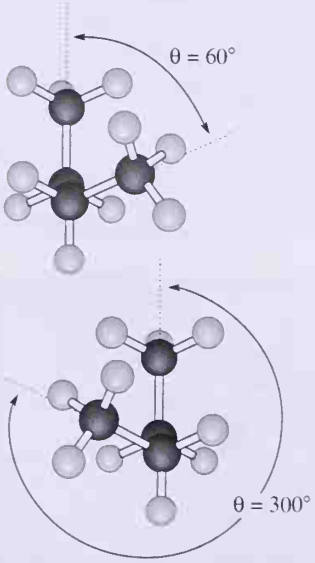


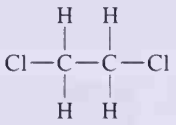
Figure 2.10
Potential energy of butane as a function of the dihedral angle about the bond between carbons 2 and 3.

Figure 2.10. You should note that even though the two staggered conformations with methyl groups gauche (dihedral angles 60° and 300°) have equal energies, they are not identical. They are related by reflection; one is the reflection of the other just as your right hand is the reflection of your left hand. Notice that the conformations with eclipsed —CH_3 and —H groups (dihedral angles of 120° and 240°) are also related by reflection. We have more to say about objects and their mirror reflections in Chapter 8.



EXAMPLE 2.8

Following is the structural formula of 1,2-dichloroethane (ethylene dichloride):



1,2-Dichloroethane
(Ethylene dichloride)

(a) Draw Newman projections for all staggered conformations formed by rotation from 0° to 360° about the carbon-carbon single bond.
(b) Which staggered conformation(s) has the lowest energy; which has the highest energy?
(c) Which, if any, of these conformations are related by reflection?

Solution

(a) If we take as a reference point the dihedral angle when the chlorine atoms are eclipsed, staggered conformations occur at dihedral angles 60°, 180°, and 300°.

Gauche $\theta = 60°$ | Anti $\theta = 180°$ | Gauche $\theta = 300°$

(b) The anti conformation ($\theta = 180°$) has the lowest energy. The two gauche conformations ($\theta = 60°$ and 300°) are of higher but equal energy.

(c) The two gauche conformations are related by reflection.

PROBLEM 2.8

(a) Draw Newman projections for all eclipsed conformations of 1,2-dichloroethane formed by rotation from 0° to 360°.

(b) Arrange the eclipsed conformations in order of increasing energy.

(c) Which, if any, of these eclipsed conformations are related by reflection?

B. Cycloalkanes

We shall discuss the conformations of cycloalkanes containing from three to six carbons in the ring and then introduce some small-ring, highly strained compounds.

Cyclopropane

The three carbons atoms of cyclopropane must lie in a plane (three points determine a plane) with C—C—C bond angles of 60°. Shown in Figure 2.11 is a condensed structural formula and a ball-and-stick model of cyclopropane.

The observed C—C—C bond angles in cyclopropane are 60°, a value considerably smaller than that of the 109.5° predicted for sp^3-hybridized carbon atoms. Furthermore, hydrogen atoms on adjacent carbons are forced into an eclipsed relationship.

Cyclopropane is a strained molecule because of what is called **steric strain.** There are two types of steric strain: **angle strain** and **nonbonded interaction strain,** both of which are present in cyclopropane. Angle strain arises from the creation of abnormal bond angles, in this case compression of C—C—C bond angles from 109.5° to 60°. Nonbonded interaction strain arises because nonbonded atoms are forced into close proximity, in this case eclipsing of hydrogens on adjacent carbons. It is because of this extreme degree of steric strain that cyclopropane and its derivatives undergo several chemical reactions not shown by larger cycloalkanes.

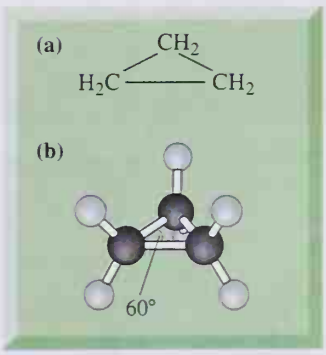


Figure 2.11
Cyclopropane. (a) Structural formula and (b) ball-and-stick model.

Cyclobutane

All cycloalkanes larger than cyclopropane exist in a dynamic equilibrium between planar and **puckered conformations.** Figure 2.12 shows stereorepresentations for one planar and

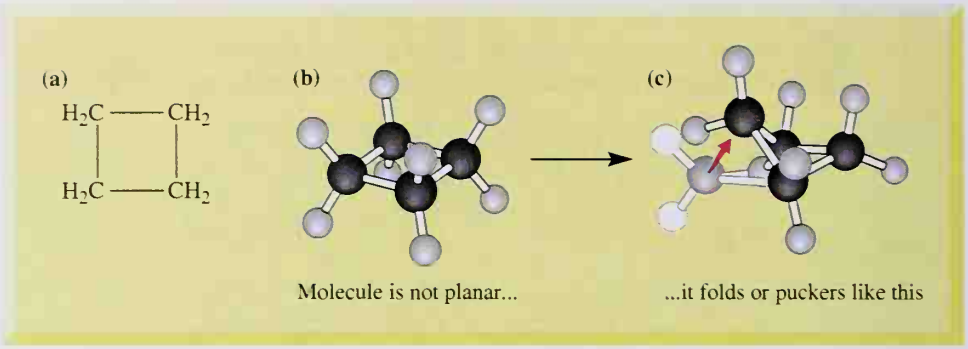


Figure 2.12
Cyclobutane. (a) Structural formula. (b) Planar conformation. All C—C—C bond angles are 90°, and there are eight pairs of eclipsed hydrogens. (c) A puckered "butterfly" conformation in which C—C—C bond angles are approximately 88°. The potential energy of cyclobutane is a minimum in this puckered conformation.

one puckered conformation of cyclobutane. All C—C—C bond angles in the planar conformation of cyclobutane are 90°, and in this conformation there are eight pairs of eclipsed hydrogen interactions. Puckering of the ring alters its potential energy in two ways: (1) it decreases the eclipsed hydrogen interactions, which in turn decreases the potential energy, and (2) it decreases the C—C—C bond angle, which in turn increases the potential energy. The measured bond angle of cyclobutane is 88°, from which we conclude that the conformation of lowest energy has a slight degree of puckering.

Cyclopentane

Cyclopentane is shown as a planar conformation with all C—C—C bond angles equal to 108°. This angle differs only slightly from the tetrahedral angle of 109.5°, and, consequently, little angle strain occurs in the planar conformation of cyclopentane. There are,

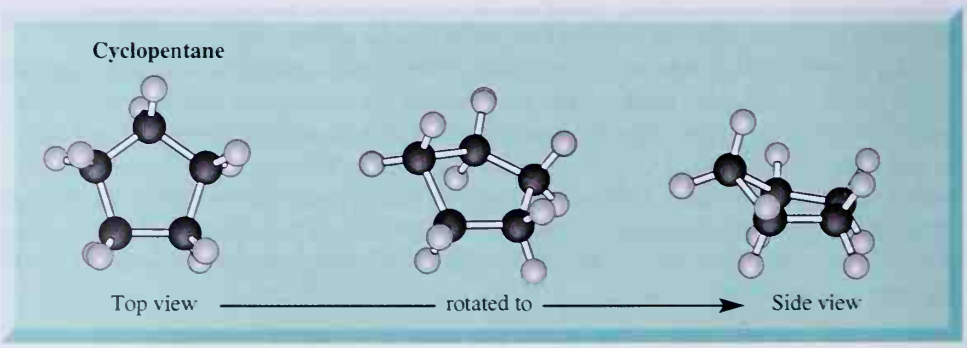


Figure 2.13
Cyclopentane. In the planar conformation on the left, all C—C—C bond angles are 108°, and there are ten pairs of eclipsed hydrogen interactions. On the right is a puckered "envelope" conformation.

however, ten fully eclipsed hydrogen interactions. In the puckered **"envelope" conformation** shown in Figure 2.13, four carbon atoms are in a plane and the fifth is bent out of the plane, rather like an envelope with its flap bent upwards. There are five such puckered conformations of cyclopentane, all of which are in rapid equilibrium. In these puckered conformations, C—C—C bond angles are reduced (increasing the potential energy), but the number of eclipsed hydrogen interactions is also reduced (decreasing the potential energy). The observed C—C—C bond angles in cyclopentane are 105°, indicating that there is a slight puckering in the conformations of lowest energy.

Cyclohexane

All C—C—C bond angles in the planar conformation of cyclohexane are 120°—a value considerably larger than the tetrahedral angle of 109.5°. Cyclohexane can be twisted into a number of nonplanar, or **puckered, conformations,** the most stable of which is the so-called **chair conformation.** In a "chair" conformation, all C—C—C bond angles are 109.5°, and C—H bonds on adjacent carbons are staggered (gauche) with respect to one another (Figure 2.14).

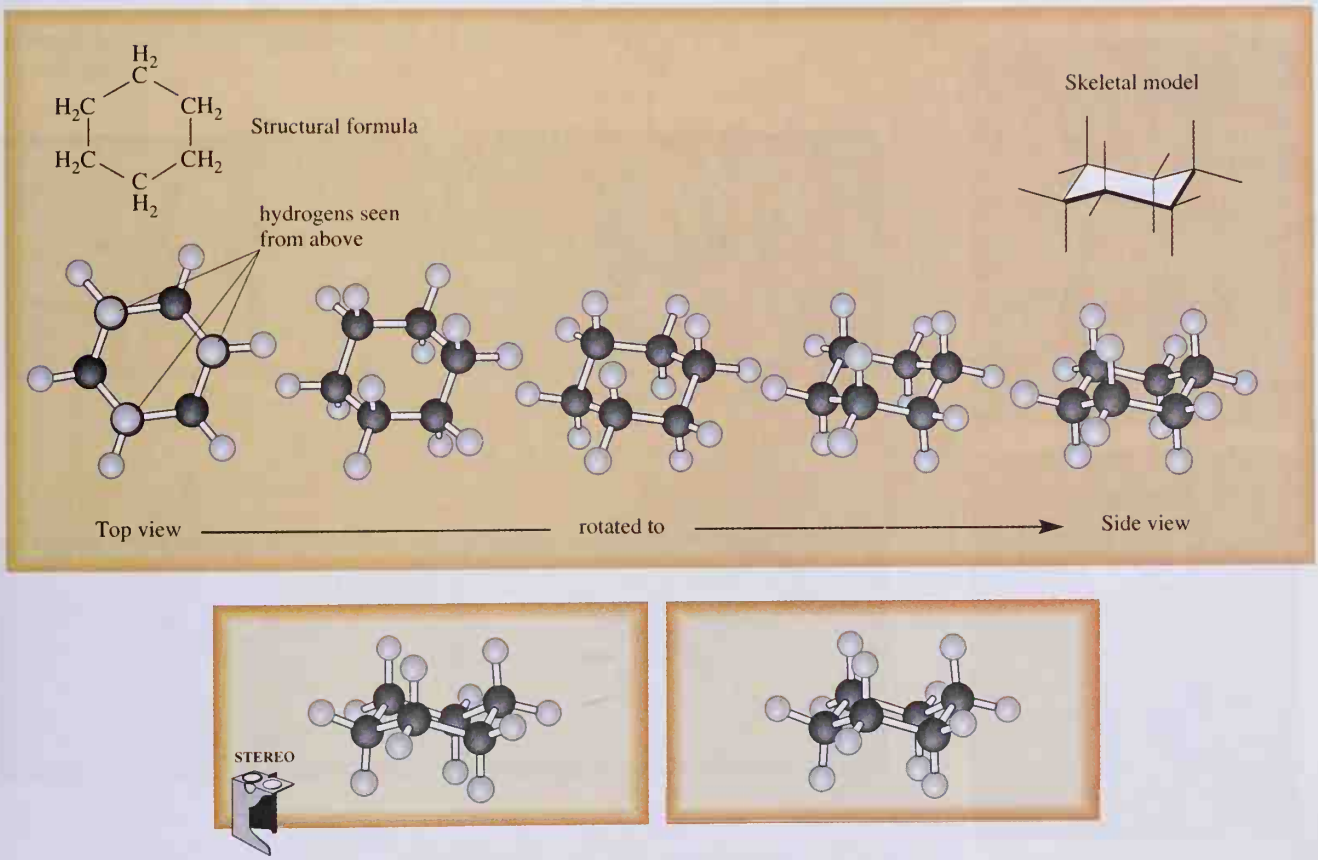


Figure 2.14
Cyclohexane.

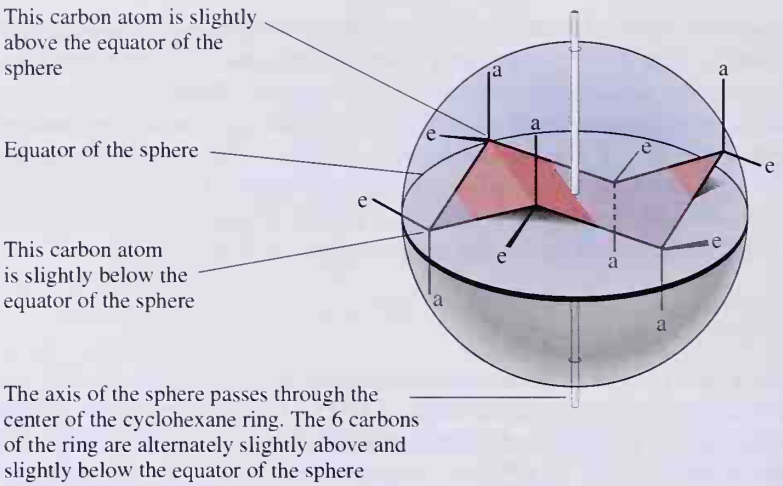


Figure 2.15
Chair conformation of cyclohexane. The six carbon atoms of the ring are alternately slightly above and slightly below the equator of the imaginary sphere in which the ring is centered.

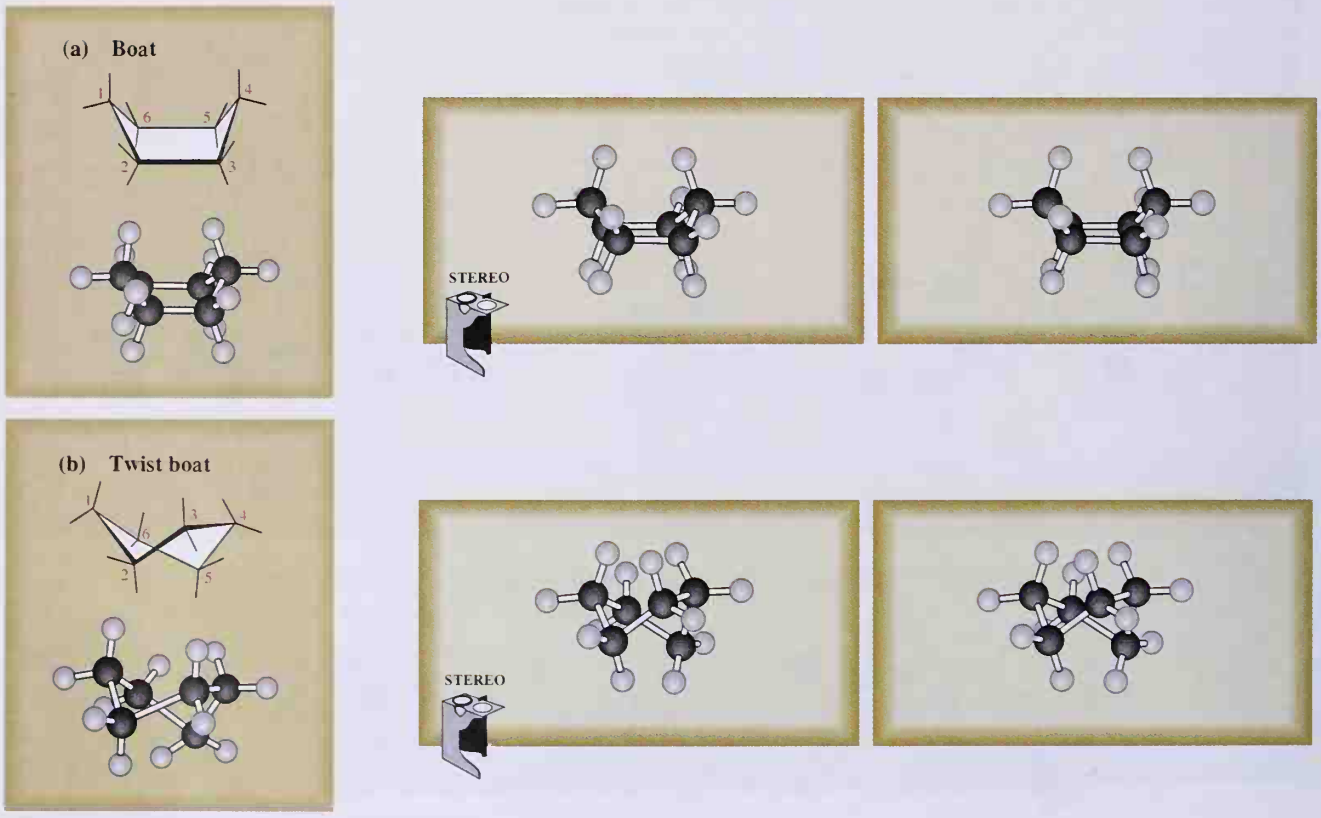


Figure 2.16
Stereorepresentations of (a) boat and (b) twist-boat conformations of cyclohexane.

In a chair conformation, the bonds leading to hydrogen atoms are arranged in two different geometrical situations. Six are called **axial bonds (a),** and the other six are called **equatorial bonds (e).** One way to visualize the difference between these two types of bonds is to imagine a chair conformation of cyclohexane centered in a sphere (Figure 2.15). Axial bonds are parallel to the axis of the imaginary sphere in which the ring is centered. Three axial bonds (those on carbons slightly above the equator) point straight upward; the other three axial bonds (those on carbons slightly below the equator) point straight downward. Notice also that axial bonds alternate, first up and then down as you move from one carbon of the ring to the next. Equatorial bonds are directed more nearly along the equator of the sphere in which the chair is centered. If the axial bond on a carbon points upward, then the equatorial bond on that carbon points downward, slightly below the plane created by the equator of the sphere. Conversely, if the axial bond on a particular carbon points downward, then the equatorial bond on that carbon points slightly upward.

There are many other nonplanar conformations of cyclohexane, two of which, the **twist-boat conformation** and the **boat conformation,** are shown in Figure 2.16. You can visualize interconversion of chair and boat conformations by twisting about a carbon-carbon bond as illustrated in Figure 2.17(a). A boat conformation is considerably less stable than a chair conformation because of two factors: four sets of eclipsed hydrogen interactions in the boat along the C—C bonds labeled 2–3 and 5–6 (Figure 2.17[b]) and one set of **"flagpole" interactions** between hydrogens on carbon 1 and carbon 4. The difference in potential energy between chair and boat conformations is approximately 7 kcal/mol.

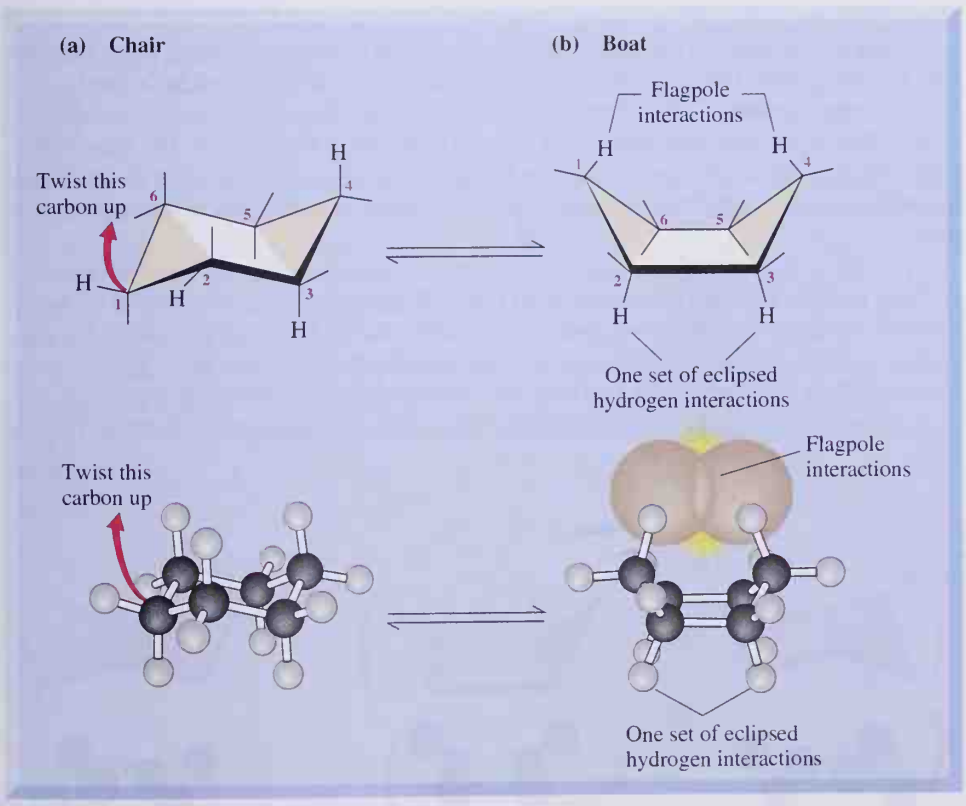


Figure 2.17
Interconversion of (a) a chair conformation to (b) a boat conformation produces one set of "flagpole" interactions and four sets of eclipsed C—H interactions.

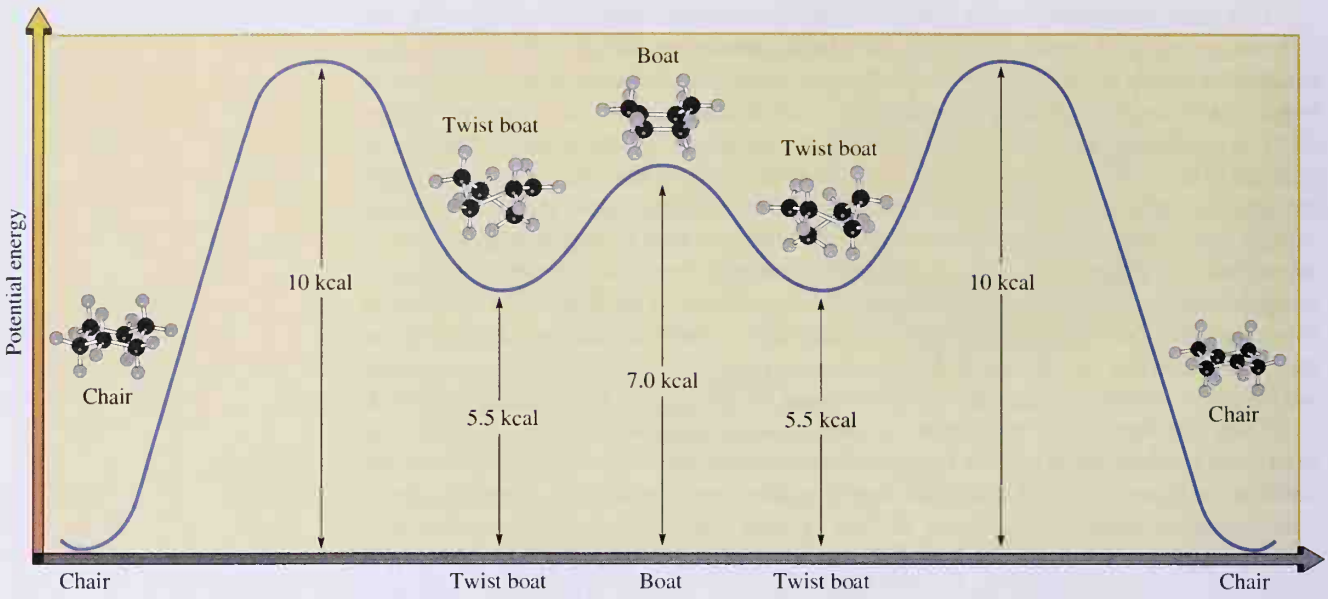
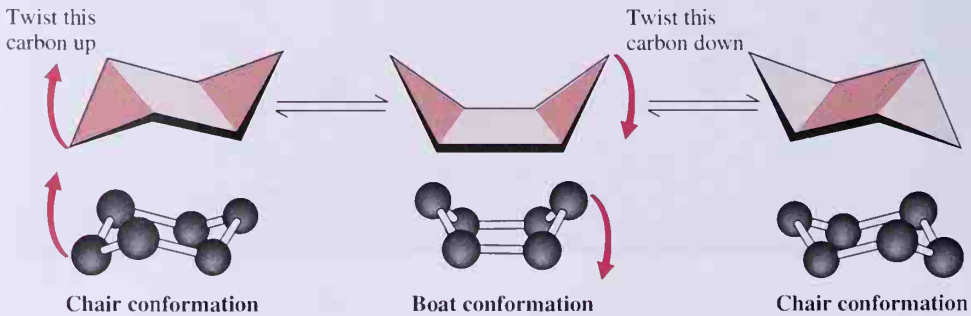


Figure 2.18
Potential energy diagram for interconversion of chair, twist-boat, and boat conformations of cyclohexane.

Some of the strain in the boat conformation can be relieved by a slight twisting of the ring to form a twist-boat conformation. It is estimated that a twist-boat is favored over a boat by approximately 1.5 kcal/mol. A potential energy diagram for interconversion between chair, twist-boat, and boat conformations is shown in Figure 2.18. The large difference in potential energy between chair and boat or twist-boat conformations means that at room temperature, chair conformations make up more than 99.99% of the equilibrium mixture.

For cyclohexane, the two equivalent chair conformations can be interconverted by twisting first to a boat and then to the other chair. When one chair is converted to the other, a change occurs in the relative orientations in space of the hydrogen atoms attached to each carbon. A hydrogen atom axial in one chair becomes equatorial in the other and vice versa. In cyclohexane itself, where the two chairs are readily interconvertible and of equal energy, each hydrogen is axial half of the time and equatorial the other half of the time (Figure 2.19).



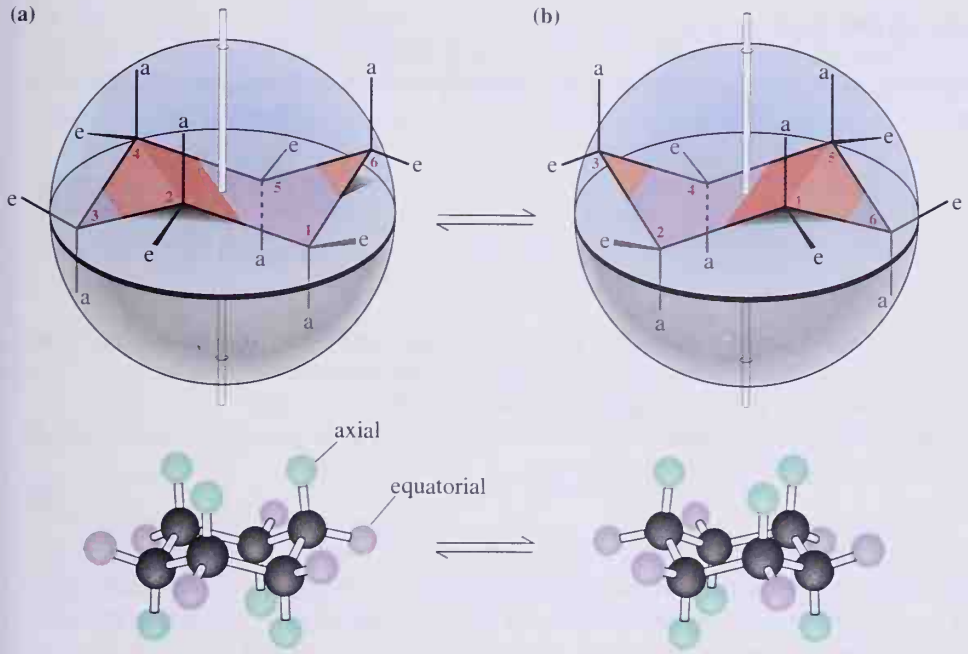
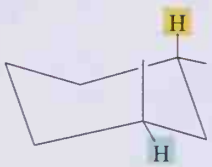


Figure 2.19
Interconversion of chair cyclohexanes. All ring carbons above the equator in (a) are below the equator in (b) and conversely, all ring carbons below the equator in (a) are above the equator in (b). All hydrogens above the equator in (a) remain above it in (b), and conversely, all hydrogens below the equator in (a) remain below it in (b). The letter "a" stands for axial and "e" for equatorial.

EXAMPLE 2.9

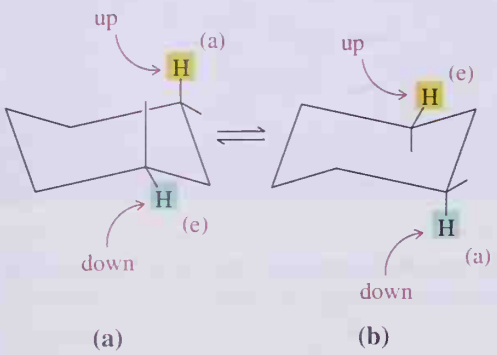
Following is a chair conformation of cyclohexane showing two hydrogen atoms.



(a) Indicate by a label whether each hydrogen is equatorial or axial, that is, whether each is up or down with respect to the equator of the imaginary sphere in which this ring can be made to sit.

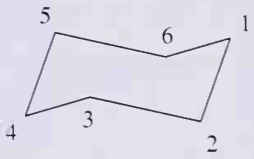
(b) Draw the other chair conformation. Indicate by a label whether each hydrogen is now equatorial or axial, that is, whether each is now up or down.

Solution



PROBLEM 2.9

Following is a chair conformation of cyclohexane with carbon atoms numbered 1 through 6.



(a) Draw hydrogen atoms that are up (above the plane of the ring) on carbons 1 and 2, and down (below the plane of the ring) on carbon 4.

(b) Which of these hydrogens are equatorial; which are axial?

(c) Draw the other chair conformation. Now, which hydrogens are equatorial; which are axial?

If a hydrogen atom of cyclohexane is replaced by a methyl group or other substituent, the group occupies an equatorial position in one chair and an axial position in the other chair. This means that the two chairs are no longer equivalent and no longer of equal stability.

A convenient way to describe the relative stabilities of conformations with equatorial and axial substituents is in terms of **1,3-diaxial interactions.** *Note:* As used here, the numbers in the term "1,3-diaxial interaction" do not refer to the numbering system of the hydrocarbon ring. Rather, they refer to the relationship between an axial substituent and the atom or group on a parallel axial position. Consider methylcyclohexane. When $-CH_3$ is in an equatorial position, it is staggered with respect to all other groups on the ring. When $-CH_3$ is axial, it is parallel to the C—H bond in the axial position on carbon 3 and also parallel to the axial C—H bond on carbon 5. Thus, for axial methylcyclohexane, there are two 1,3-diaxial interactions (Figure 2.20). For methylcyclohexane, the equatorial methyl conformation is favored over the axial methyl conformation by about 1.7 kcal/mol, and equilibrium lies more than 95% toward the equatorial methyl side.

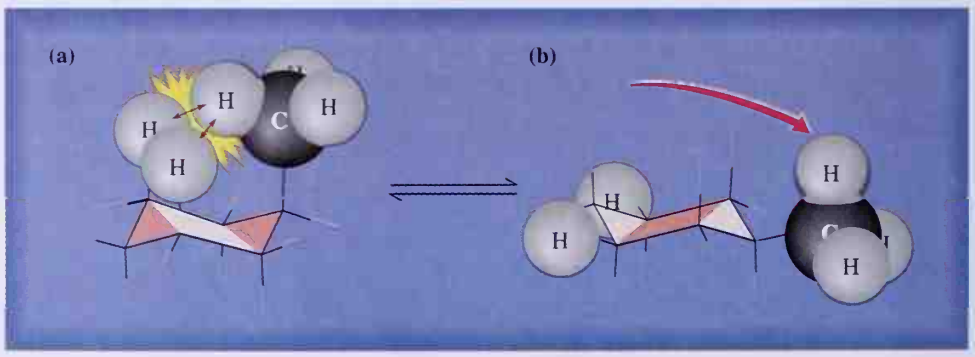
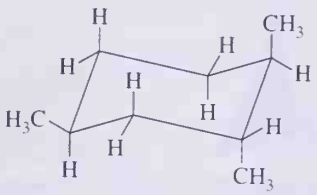


Figure 2.20
Two chair conformations of methylcyclohexane. The two 1,3-diaxial interactions make conformation (a) less stable than conformation (b).

As the size of the substituent increases, preference for conformations with the group equatorial increases. When the group is as large as *tert*-butyl, the equatorial conformation is approximately 10,000 times more abundant at room temperature than the axial, and, in effect, the ring is "locked" into this chair conformation.

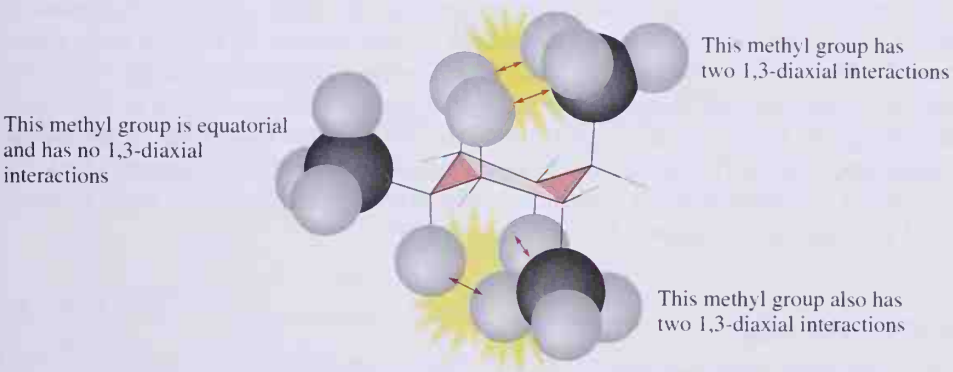
EXAMPLE 2.10

Label all 1,3-diaxial interactions in the following molecule:



Solution

There are four 1,3-diaxial interactions in the molecule shown in this example; each of the axial methyl groups has two sets of 1,3-diaxial interactions with parallel axial hydrogen atoms. The equatorial methyl group has no 1,3-diaxial interactions.



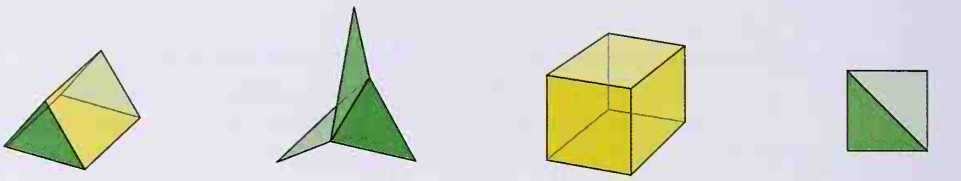
PROBLEM 2.10

The conformational equilibria for methyl-, ethyl-, and isopropylcyclohexane are all about 95% in favor of the equatorial conformation, but that for *tert*-butylcyclohexane is virtually completely on the equatorial side. Explain, by using molecular models and making drawings, why the conformational equilibria for the first three compounds are comparable but the conformational equilibrium for *tert*-butylcyclohexane lies considerably farther toward the equatorial conformation.

Highly Strained Small-Ring Compounds

We have seen that small-ring compounds, such as cyclopropane and cyclobutane, have a high degree of both angle strain and nonbonded interaction strain. It has been a particular challenge to chemists to attempt to synthesize even more highly strained rings, both for the

challenge of devising new reaction sequences to make such molecules and for understanding relationships between molecular strain and chemical reactivity better. Among the fascinating molecules synthesized in recent years are cubane, prismane, and bicyclo[1.1.0]butane. A propellane is a molecule in which two atoms joined by a single bond are also joined by three other bridges. The [1.1.1]propellane shown here is the smallest member of this class of compounds and, surprisingly, is more stable than the larger [2.1.1]propellane and [2.2.1]propellane.



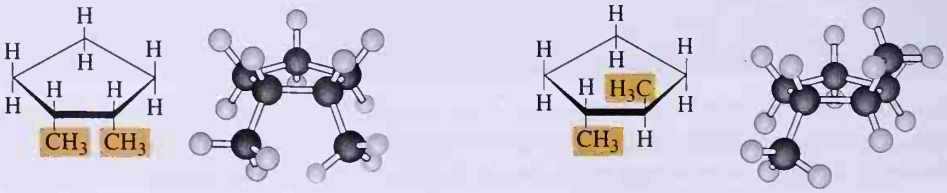
Prismane (C_6H_6) **A propellane** (C_6H_8) **Cubane** (C_8H_8) **Bicyclobutane** (C_4H_6)

2.7 *Cis-Trans* Isomerism in Cycloalkanes and Bicycloalkanes

Cis-trans isomers have the same molecular formula, the same order of attachment of atoms, but an arrangement of atoms that cannot be interchanged by rotation about single bonds under ordinary conditions. By way of comparison, the potential energy difference between conformational isomers is such that they can be interconverted at or near room temperature by rotation about single bonds. The term ***cis-trans* isomerism,** or **geometric isomerism,** is applied to the type of isomerism that depends on the arrangement of substituent atoms or groups, either in a cyclic structure as we see in this chapter, or on a double bond as discussed in Section 4.3.

A. Cycloalkanes

All cycloalkanes with substituents on two or more carbons of the ring show *cis-trans* isomerism. *Cis-trans* isomerism in cyclic structures can be illustrated by models of 1,2-dimethylcyclopentane. In the following drawings, the cyclopentane ring is shown as a planar pentagon viewed through the plane of the ring. Carbon-carbon bonds of the ring projecting forward are shown as heavy lines. When viewed from this perspective, substituents attached to the ring project above and below the plane of the ring. In one isomer of 1,2-dimethylcyclopentane, the methyl groups are on the same side of the ring; in the other, they are on opposite sides of the ring. The prefix ***cis*** (Latin: on the same side) is used to indicate that the substitutents are on the same side of the ring; the prefix ***trans*** (Latin:

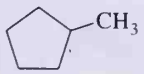


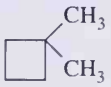
***cis*-1,2-Dimethylcyclopentane** ***trans*-1,2-Dimethylcyclopentane**

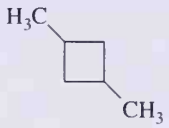
across) is used to indicate that they are on opposite sides of the ring. In each isomer, the configuration of the methyl groups is fixed, and no amount of conformational change can convert the *cis* isomer to the *trans* isomer or vice versa.

EXAMPLE 2.11

Following are several cycloalkanes of molecular formula C_6H_{12}. State which show *cis-trans* isomerism and for each that does, draw the *cis* and *trans* isomers.

(a) 

(b) 

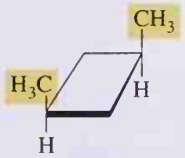
(c) 

Solution

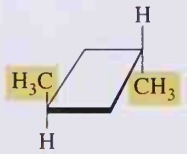
(a) Because it has only one substituent on the ring, methylcyclopentane does not show *cis-trans* isomerism.

(b) 1,1-Dimethylcyclobutane does not show *cis-trans* isomerism because only one possible arrangement exists for the two methyl groups on the ring: they must be across from each other.

(c) 1,3-Dimethylcyclobutane shows *cis-trans* isomerism.



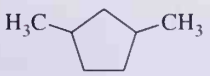
cis-1,3-Dimethylcyclobutane

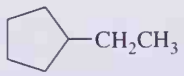


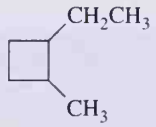
trans-1,3-Dimethylcyclobutane

PROBLEM 2.11

Following are several cycloalkanes of molecular formula C_7H_{14}. State which show *cis-trans* isomerism, and for each that does draw the *cis* and *trans* isomers.

(a) 

(b) 

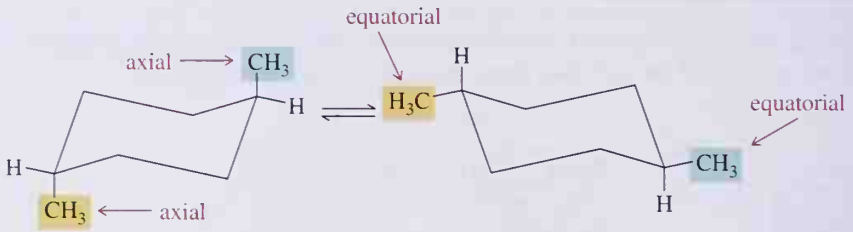
(c) 

For the purposes of determining the number of *cis-trans* isomers in substituted cycloalkanes, it is adequate to draw the cycloalkane ring as a planar polygon as is done in the following structures for cyclohexane. Two *cis-trans* isomers exist for 1,4-dimethylcyclohexane.

trans-1,4-Dimethylcyclohexane

cis-1,4-Dimethylcyclohexane

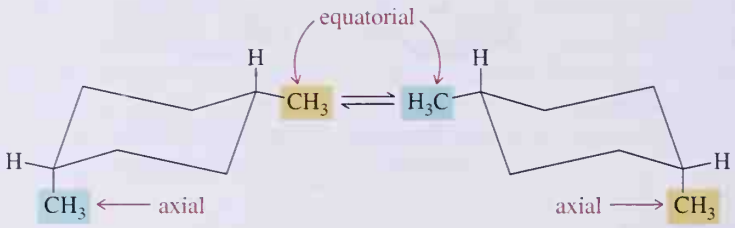
The *cis* and *trans* isomers of 1,4-dimethylcyclohexane can also be drawn as nonplanar chair conformations. In one chair conformation of *trans*-1,4-dimethylcyclohexane the two methyl groups are axial; in the other chair conformation they are equatorial. Of these chair conformations, the one with both methyls equatorial is considerably more stable.



(less stable) (more stable)

trans-1,4-Dimethylcyclohexane

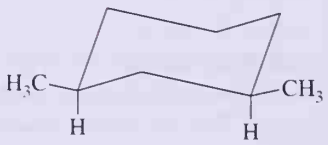
In one chair conformation of *cis*-1,4-dimethylcyclohexane, one methyl group occupies an equatorial position, and the other occupies an axial position. In the other chair, the orientations in space of the $-CH_3$ groups is reversed. The chair conformations of *cis*-1,4-dimethylcyclohexane are of equal energy because in each, one methyl is axial and the other equatorial.



cis-1,4-Dimethylcyclohexane
(these conformations are of equal stability)

EXAMPLE 2.12

Following is a chair conformation of 1,3-dimethylcyclohexane.



(a) Is this a chair conformation of *cis*-1,3-dimethylcyclohexane or of *trans*-1,3-dimethylcyclohexane?

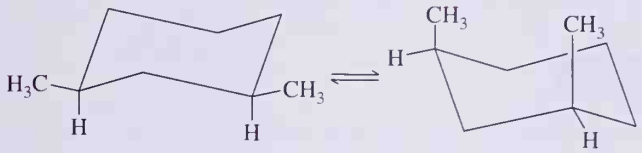
(b) Draw the alternative chair conformation of this isomer. Of the two chair conformations, which is the more stable? Why?

(c) Draw a planar hexagon representation for the isomer shown in this example.

Solution

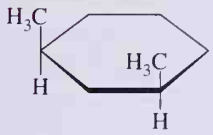
(a) Because the two methyl groups are on the same side of the ring, the isomer shown is *cis*-1,3-dimethylcyclohexane.

(b)



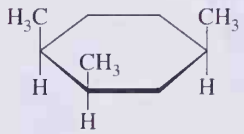
(more stable) (less stable)

(c)



PROBLEM 2.12

Following is a planar hexagon representation for one isomer of 1,2,4-trimethylcyclohexane. Draw alternative chair conformations of this compound, and state which is the more stable.



B. Bicycloalkanes

Bicycloalkanes, particularly those with a carbon skeleton like that of bicyclo[4.4.0]decane (decalin), are particularly abundant in the biological world. Figure 2.21 shows structural formulas for *trans*-decalin and *cis*-decalin. In the *trans* isomer, the two hydrogen atoms on

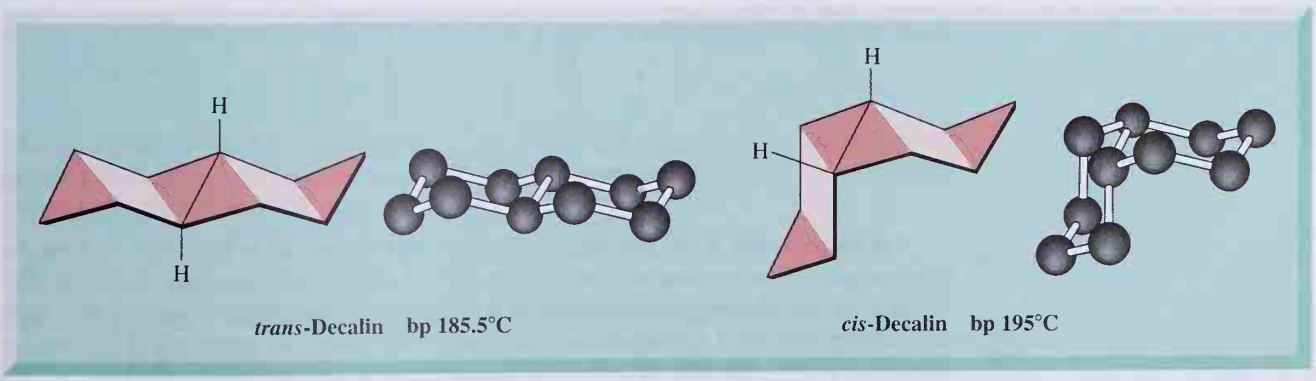


Figure 2.21
Cis-trans isomers of decalin.

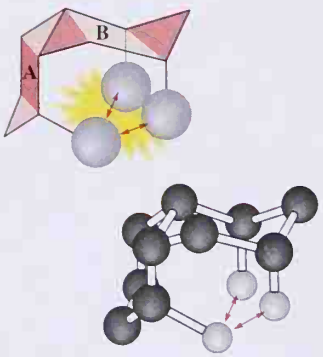
the bridgehead carbons are on opposite sides of the molecule, and in the *cis* isomer, they are on the same side of the molecule. *Trans*-decalin and *cis*-decalin are different compounds and have different physical and chemical properties. The *cis* isomer, for example, has a boiling point of 195°C; the *trans* isomer has a boiling point of 185.5°C.

EXAMPLE 2.13

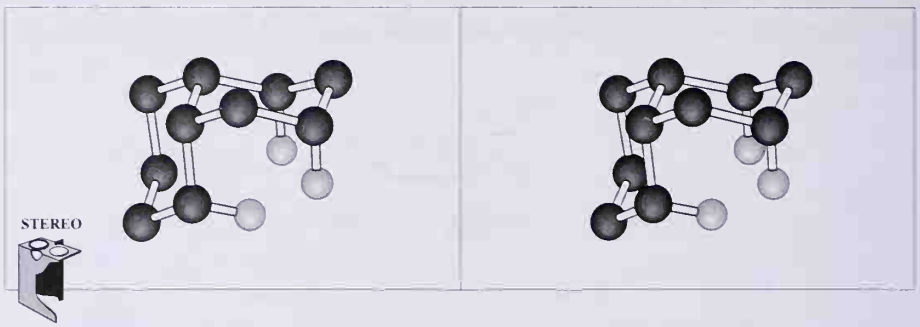
Compare the relative stabilities of *cis*-decalin and *trans*-decalin. Base your answer on the number of 1,3-diaxial interactions in the most stable conformation of each isomer.

Solution

There are no 1,3-diaxial interactions on the all-chair conformation of *trans*-decalin shown in Figure 2.21. In the *cis* isomer, one of the methylene groups of ring A is axial to ring B and, therefore, involved in two 1,3-diaxial interactions with parallel axial hydrogens. Similarly, one CH_2 group of ring B is axial to ring A. Thus, *trans*-decalin is more stable than *cis*-decalin by approximately 3.5 kcal/mol.

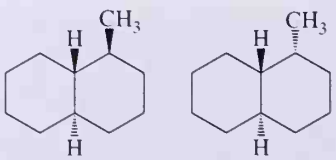


1,3-diaxial interactions

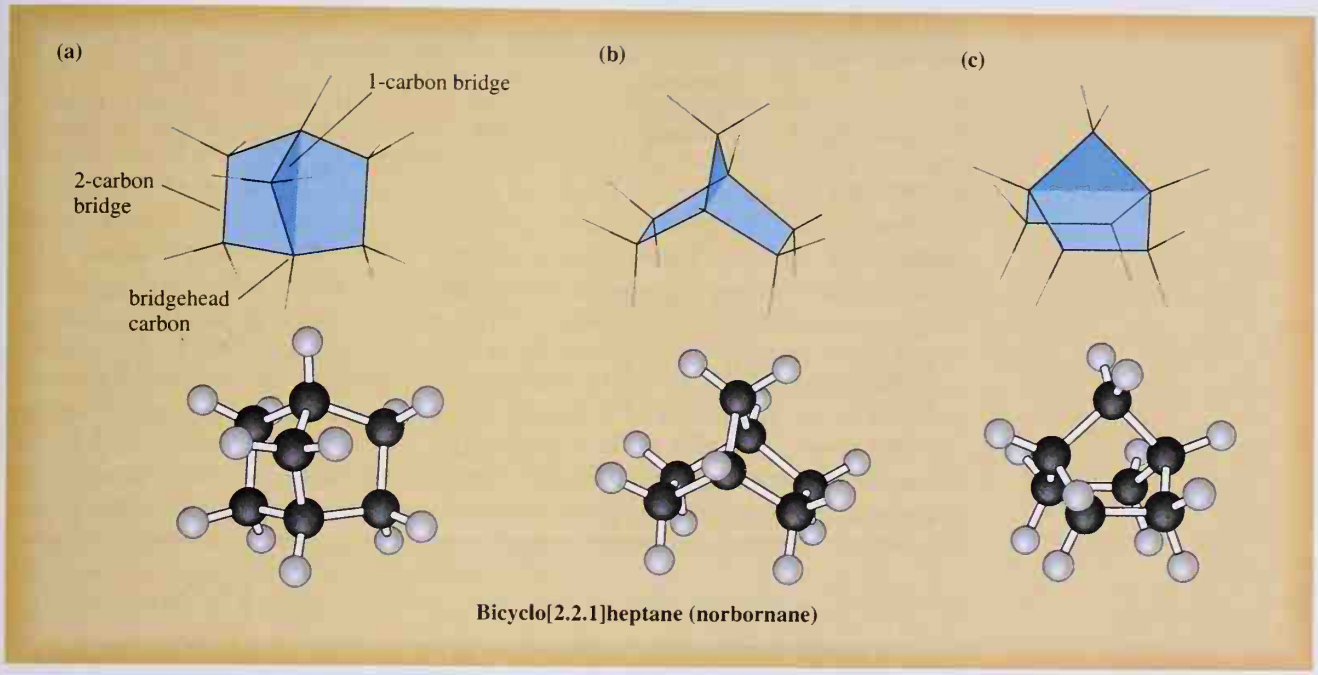


PROBLEM 2.13

Which of the following *cis-trans* isomers is the more stable?



Let us also look at the possibilities for *cis-trans* isomerism in bicyclo[2.2.1]heptane (norbornane). This molecule is drawn in Figure 2.22 in three different ways. Figure 2.22(a) shows a six-member ring with a one-carbon bridge between carbons 1 and 4 of the larger six-member ring. This representation is not intended to show the arrangement of atoms in space and gives little idea of molecular geometry. The representation in Figure 2.22(b) shows that the larger six-member ring is held in a boat conformation by the one-carbon methylene bridge between carbons 1 and 4 of the boat. From this representation of norbor-



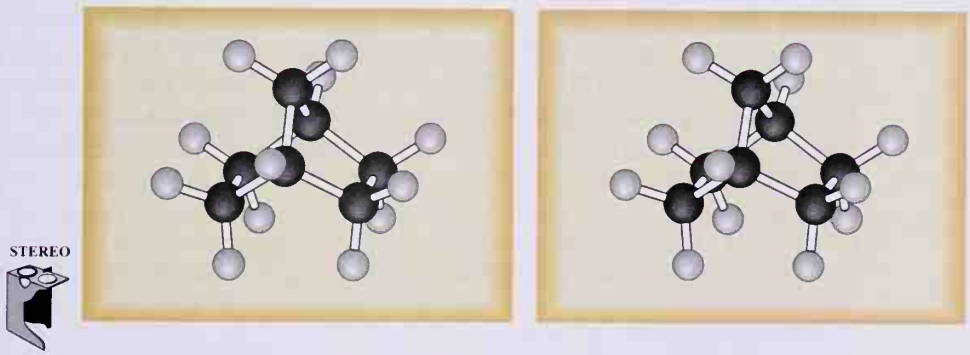


Figure 2.22
Three views of bicyclo[2.2.1]heptane (norbornane). *Cis-trans* isomerism is not possible in this bicycloalkane. The one-carbon methylene bridge must be connected to *cis*-1,4 positions of the larger six-member ring.

nane, it should be obvious that this bicycloalkane does not show *cis-trans* isomerism; the one-carbon methylene bridge can only be connected to carbons 1 and 4 by bonds on the same side of the six-member ring.

2.8 Physical Properties of Alkanes and Cycloalkanes

You are already familiar with the physical properties of some alkanes and cycloalkanes from your everyday experiences. The low-molecular-weight alkanes, such as methane, ethane, propane, and butane, are gases at room temperature and atmospheric pressure.

Table 2.4 Physical properties of some alkanes

Name	Condensed Structural Formula	mp (°C)	bp (°C)	Density of Liquid (g/mL at 0°C)
methane	CH_4	−182	−164	(a gas)
ethane	CH_3CH_3	−183	−88	(a gas)
propane	$CH_3CH_2CH_3$	−190	−42	(a gas)
butane	$CH_3(CH_2)_2CH_3$	−138	0	(a gas)
pentane	$CH_3(CH_2)_3CH_3$	−130	36	0.626
hexane	$CH_3(CH_2)_4CH_3$	−95	69	0.659
heptane	$CH_3(CH_2)_5CH_3$	−90	98	0.684
octane	$CH_3(CH_2)_6CH_3$	−57	126	0.703
nonane	$CH_3(CH_2)_7CH_3$	−51	151	0.718
decane	$CH_3(CH_2)_8CH_3$	−30	174	0.730

Alkanes of higher molecular weight, such as those in gasoline and kerosene, are liquids. Very high molecular weight alkanes, such as those found in paraffin wax, are solids. Melting points, boiling points, and densities of the first ten alkanes are listed in Table 2.4.

Methane can be converted to a liquid if cooled to − 164°C and to a solid if further cooled to − 182°C. The fact that methane (or any other compound, for that matter) can exist as a liquid or solid depends on the existence of **intermolecular forces of attraction** between particles of each pure compound. Although the forces of attraction between particles are all electrostatic in nature, they vary widely in their relative strengths. The strongest attractive forces are those between ions, for example between Na^+ and Cl^- in NaCl (188 kcal/mol). Weaker are dipole-dipole interactions and hydrogen bonding (2–10 kcal/mol). We will have more to say about these intermolecular attractive forces

Methane is a major component of the atmosphere of Neptune. *(NASA)*

in Chapter 9 when we discuss the physical properties of alcohols, compounds containing polar O—H groups.

Dispersion forces (0.02–2 kcal/mol) are the weakest of all intermolecular forces. It is the existence of these forces that accounts for the fact that low-molecular-weight, nonpolar substances, such as hydrogen, neon, and methane, can be liquefied. To visualize the origin of dispersion forces, it is necessary to think in terms of instantaneous distributions of electron density rather than average distributions. Consider, for example, neon. Neon is a gas at room temperature and 1.00 atm. It can be liquefied when cooled to −246°C. From the heat of vaporization, it can be calculated that the neon-neon attractive interaction in the liquid state is approximately 0.07 kcal/mol. We account for this intermolecular attractive interaction in the following way. Over time, the distribution of electron density in a neon atom is symmetrical, and there is no dipole moment. However, at any instant, there is a probability that electron density is polarized (shifted) more toward one part of the atom than toward another. This temporary polarization creates a temporary dipole moment, which in turn induces temporary dipole moments in adjacent atoms. **Dispersion forces** are weak electrostatic interactions that occur between temporary induced dipoles of adjacent atoms or molecules. Creation of temporary dipole moments and the origin of dispersion forces are illustrated schematically in Figure 2.23.

The strength of dispersion forces depends on how easily an electron cloud can be polarized. Electrons in small atoms and molecules tend to be held closer to their nuclei and, therefore, are not easily polarized. Electrons in larger atoms and molecules are more easily polarized. For this reason, the strength of dispersion forces tends to increase with increasing molecular mass and size. Intermolecular interactions between Cl_2 molecules and between Br_2 molecules are estimated to be 0.7 kcal/mol and 1.0 kcal/mol, respectively.

Dispersion forces are inversely proportional to d^6, where d is the distance between particles, and are important only when interacting particles are very close together. For dispersion forces to be important, the interacting particles must be in virtual contact with one another.

Now let us use these concepts of the nature of intermolecular forces to examine the relationships between the physical properties of alkanes and their molecular structure. Alkanes are nonpolar compounds, and the only forces of attraction between them are dispersion forces. Because interactions between molecules are so weak, boiling points of alkanes are lower than those of almost any other type of compound of the same molecular weight. As the number of atoms and molecular weight of an alkane increase, the strength of dispersion forces per molecule also increases. Therefore, the boiling points of alkanes increase as molecular weight increases.

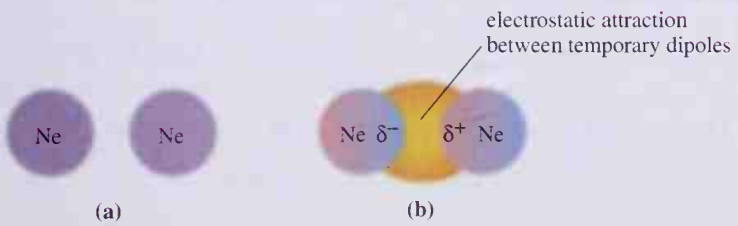


Figure 2.23
Dispersion forces. (a) The average distribution of electron density in a neon atom is symmetrical, and there is no polarity. (b) Temporary polarization in one atom induces temporary polarization in adjacent atoms. Electrostatic interactions between temporary dipoles are called dispersion forces.

Table 2.5 Physical properties of the isomeric alkanes of molecular formula C_6H_{14}

Name	bp (°C)	mp (°C)	Density (g/mL)
hexane	68.7	−95	0.659
2-methylpentane	60.3	−154	0.653
3-methylpentane	63.3	−118	0.664
2,3-dimethylbutane	58.0	−129	0.661
2,2-dimethylbutane	49.7	−98	0.649

Melting points of alkanes also increase with increasing molecular weight. The increase, however, is not as regular as that observed for boiling points because the packing of molecules into ordered patterns changes as molecular size and shape change.

The average density of the alkanes listed in Table 2.4 is about 0.7 g/mL; that of higher molecular weight alkanes is about 0.8 g/mL. All liquid alkanes are less dense than water (1.0 g/mL).

Alkanes that are constitutional isomers of each other are different compounds and have different physical and chemical properties. Listed in Table 2.5 are boiling points, melting points, and densities of the five constitutional isomers of molecular formula C_6H_{14}. The boiling point of each of the branched-chain isomers of C_6H_{14} is lower than that of hexane itself, and the more branching there is, the lower the boiling point. These differences in boiling point are related to molecular shape in the following way. As branching increases, the shape of an alkane molecule becomes more compact and its surface area decreases. As surface area decreases, contact between adjacent molecules decreases, the strength of dispersion forces decreases, and boiling points also decrease. For any group of alkane constitutional isomers, it is usually observed that the least branched isomer has the highest boiling point and the most branched isomer has the lowest boiling point.

EXAMPLE 2.14

Arrange the following in order of increasing boiling point.

(a) $CH_3CH_2CH_2CH_3$ $CH_3CH_2CH_2CH_2CH_2CH_3$ $CH_3(CH_2)_8CH_3$

(b) $CH_3(CH_2)_6CH_3$ $CH_3CCH_2CHCH_3$ (with CH_3 and CH_3 branches) $CH_3CHCH_2CH_2CH_2CH_2CH_3$ (CH_3 branch)

Solution

(a) All the structures in part (a) are unbranched alkanes. As the number of carbon atoms in the chain increases, dispersion forces between molecules increase and boiling points increase. Predict that decane has the highest boiling point and that butane has the lowest boiling point.

$CH_3CH_2CH_2CH_3$	$CH_3CH_2CH_2CH_2CH_2CH_3$	$CH_3(CH_2)_8CH_3$
Butane	Hexane	Decane
bp −0.5°C	bp 69°C	bp 174°C

(b) These three alkanes have the same molecular formula, C_8H_{18}, and are constitutional isomers. Their relative boiling points depend on the degree of branching. 2,2,4-Trimethylpentane, the most highly branched isomer, has the smallest surface area and the lowest boiling point. Octane, the unbranched isomer, has the largest surface area and the highest boiling point.

$CH_3CCH_2CHCH_3$ (with CH_3 on each C)	$CH_3CHCH_2CH_2CH_2CH_2CH_3$ (with CH_3 on 2nd C)	$CH_3(CH_2)_6CH_3$
2,2,4-Trimethylpentane	2-Methylheptane	Octane
bp 99°C	bp 118°C	bp 126°C

PROBLEM 2.14

Arrange the following in order of increasing boiling point.

(a) 2-methylbutane 2,2-dimethylpropane pentane

(b) 3,3-dimethylheptane 2,2,4,4-tetramethylpentane nonane

2.9 Reactions of Alkanes

Alkanes and cycloalkanes are quite unreactive toward most reagents, a behavior consistent with the facts that they are nonpolar compounds and contain only strong sigma bonds. However, saturated hydrocarbons do react under certain conditions with oxygen and with halogens.

A. Oxidation

By far the most economically important reaction of alkanes is their oxidation (combustion) by O_2 to form carbon dioxide and water. Oxidation of saturated hydrocarbons is the basis for their use as energy sources for heat (natural gas, liquefied petroleum gas [LPG], and fuel oil) and power (gasoline, diesel fuel, and aviation fuel). Following are balanced equations for complete oxidation of methane, the major component of natural gas, and 2,2,4-trimethylpentane, a component of gasoline.

$$CH_4 + 2O_2 \longrightarrow CO_2 + 2H_2O$$

Methane

$$CH_3CCH_2CHCH_3 + \frac{25}{2}O_2 \longrightarrow 8CO_2 + 9H_2O$$

2,2,4-Trimethylpentane

Burning natural gas, which is primarily methane with small amounts of ethane, propane, and butane. *(Charles D. Winters)*

B. Halogenation

Halogenation of an alkane is the substitution of an alkane hydrogen by a halogen. The most common halogen substitution reactions involve chlorine and bromine.

Chlorination and Bromination

If a mixture of methane and chlorine gas is kept in the dark at room temperature, no detectable change occurs. If, however, the mixture is heated or exposed to visible or ultraviolet light, a reaction begins almost at once with the evolution of heat. The first products are chloromethane and hydrogen chloride. What occurs is a substitution reaction, in this case substitution of a hydrogen atom in methane by a chlorine atom and the production of an equivalent amount of hydrogen chloride.

$$CH_4 + Cl_2 \xrightarrow[\text{heat}]{\text{light or}} CH_3Cl + HCl$$

Methane — Chloromethane

Substitution is a reaction in which an atom or group of atoms in a compound is replaced by another atom or group of atoms.

Haloalkanes are named according to the rules we have already used for naming alkanes. The parent chain is numbered from the direction that gives the substituent encountered first (be it halogen or an alkyl group) the lowest number. Halogen substituents are indicated by the prefixes fluoro-, chloro-, bromo-, and iodo-.

If chloromethane is allowed to react with more chlorine, further chlorination produces a mixture of dichloromethane (methylene chloride), trichloromethane (chloroform), and tetrachloromethane (carbon tetrachloride).

$$CH_3Cl + Cl_2 \xrightarrow[\text{heat}]{\text{light or}} CH_2Cl_2 + HCl$$

Dichloromethane
(Methylene chloride)

$$CH_2Cl_2 + Cl_2 \xrightarrow[\text{heat}]{\text{light or}} CHCl_3 + HCl$$

Trichloromethane
(Chloroform)

$$CHCl_3 + Cl_2 \xrightarrow[\text{heat}]{\text{light or}} CCl_4 + HCl$$

Tetrachloromethane
(Carbon tetrachloride)

Treatment of ethane with chlorine gives chloroethane (ethyl chloride); treatment with bromine gives bromoethane (ethyl bromide).

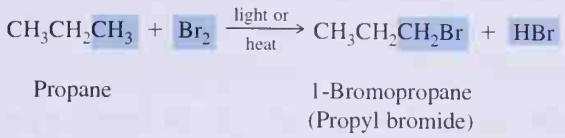
$$CH_3CH_3 + Cl_2 \xrightarrow[\text{heat}]{\text{light or}} CH_3CH_2Cl + HCl$$

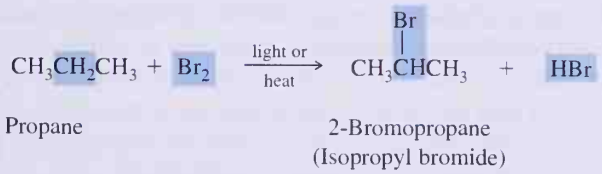
Chloroethane
(Ethyl chloride)

$$CH_3CH_3 + Br_2 \xrightarrow[\text{heat}]{\text{light or}} CH_3CH_2Br + HBr$$

Bromoethane
(Ethyl bromide)

Treatment of propane with bromine gives a pair of constitutional isomers, namely 1-bromopropane (propyl bromide) and 2-bromopropane (isopropyl bromide).



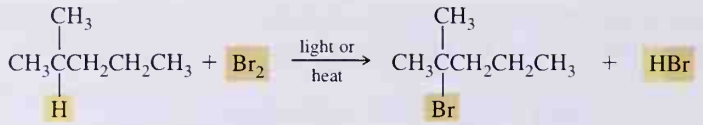


These are different reactions and are written separately. However, it is more common in writing equations for organic reactions to show all products formed in one equation. The following single equation means that treatment of one mole of propane with one mole of bromine produces one mole of HBr and one mole of C_3H_7Br. Of the C_3H_7Br, approximately 8% is 1-bromopropane, and the remaining 92% is 2-bromopropane.

Regioselectivity

Propane contains one set of six equivalent primary hydrogens and one set of two equivalent secondary hydrogens (Section 2.3C). Substitution of bromine for a primary hydrogen gives 1-bromopropane; substitution of bromine for a secondary hydrogen gives 2-bromopropane. On the basis of statistical distribution of hydrogens in propane, we predict the isomeric bromopropanes to be formed in the ratio of 6:2, or 75% 1-bromopropane and 25% 2-bromopropane. In fact, in the bromination of propane, substitution of a secondary hydrogen is favored over a primary hydrogen, and 2-bromopropane is the major product. Other experiments have shown that substitution at a tertiary hydrogen is favored over both secondary and primary hydrogens. For example, monobromination of 2-methylpentane (isohexane) gives almost exclusively 2-bromo-2-methylpentane.

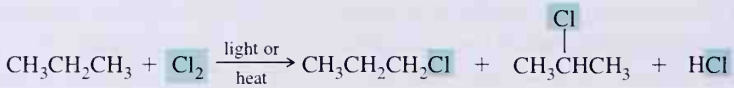
Product Distribution	$CH_3CH_2CH_2Br$ (%)	$CH_3\overset{\overset{Br}{|}}{C}HCH_3$ (%)
Prediction based on ratio of primary hydrogens to secondary hydrogens	75	25
Experimental observation	8	92



2-Methylpentane 2-Bromo-2-methylpentane

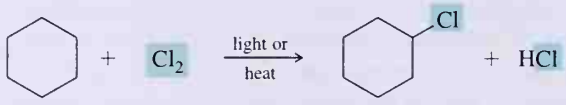
The reaction of bromine with an alkane is selective in that there is a preference for this order of substitution: tertiary, secondary, primary. The extent of discrimination is called selectivity and because it is between various sites or regions within a molecule, it is called regioselectivity. A **regioselective reaction** is a reaction in which one direction of bond making or bond breaking occurs preferentially to all other directions.

Bromination of alkanes occurs with high regioselectivity. Chlorination of alkanes, on the other hand, occurs with much lower regioselectivity. For example, treatment of propane with chlorine gives a mixture consisting of approximately 43% 1-chloropropane and 57% 2-chloropropane.

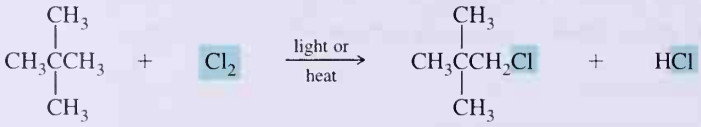


Propane 1-Chloropropane (43%) 2-Chloropropane (57%)

Regioselectivity still favors substitution of a secondary hydrogen over a primary hydrogen, but the extent for chlorination is not nearly as high as it is for bromination. Because of lower regioselectivity and because of the formation of mono-, di-, and polychlorinated products, chlorination of alkanes generally is not a good method for the preparation of pure chloroalkanes. Exceptions do occur, however, to this generalization, namely when all hydrogens on the alkane or cycloalkane are equivalent. Examples of saturated hydrocarbons in which all hydrogens are equivalent are methane, ethane, cyclohexane, and 2,2-dimethylpropane (neopentane). In each of these instances, chlorination can give only one monochlorination product.



Cyclohexane Chlorocyclohexane (Cyclohexyl chloride)



2,2-Dimethylpropane (Neopentane) 1-Chloro-2,2-dimethylpropane (Neopentyl chloride)

Halogenation of alkanes is more common with bromine or chlorine. Fluorine, F_2, is seldom used because its reactions with alkanes are highly exothermic and difficult to control. (There are, however, several methods by which C—H bonds can be converted to C—F bonds). Iodine, I_2, is seldom used because the reaction is endothermic and the position of equilibrium favors alkane and I_2 rather than iodoalkane and HI.

EXAMPLE 2.15

Name and draw structural formulas for all monobromination products formed by reaction of 2-methylpropane with Br_2. In addition, calculate the expected distribution of products based on number and types of hydrogen atoms, and predict the major product based on the known regioselectivity of the reaction of Br_2 with alkanes.

$$\begin{array}{l} \quad\ CH_3 \\ \quad\ | \\ CH_3CHCH_3 \end{array} + Br_2 \xrightarrow[\text{heat}]{\text{light or}} \text{monobromoalkanes} + HBr$$

Solution

In 2-methylpropane, there are nine equivalent primary hydrogens and one tertiary hydrogen. Substitution of bromine for a primary hydrogen gives 1-bromo-2-methylpropane; substitution for the tertiary hydrogen gives 2-bromo-2-methylpropane. The high regioselectivity of Br_2 for tertiary versus primary hydrogens is seen in the fact that the products consist of over 99% 2-bromo-2-methylpropane and only traces of 1-bromo-2-methylpropane. For comparison, percentage yields for the reaction of Cl_2 with 2-methylpropane are also given and, as you can see, although some regioselectivity occurs, it is not as high as that for Br_2.

Production Distribution	$\begin{array}{l} \quad\ CH_3 \\ \quad\ \vert \\ CH_3CHCH_2Br \end{array}$	$\begin{array}{l} \quad\ CH_3 \\ \quad\ \vert \\ CH_3CCH_3 \\ \quad\ \vert \\ \quad\ Br \end{array}$
Based on ratio of primary to tertiary hydrogens	90%	10%
Based on regioselectivity of bromination	considerably less than 90%	considerably more than 10%
Actual yield with Br_2	trace	greater than 99%
Actual yield with Cl_2	64%	36%

PROBLEM 2.15

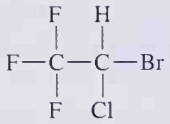
Name and draw structural formulas for all monochlorination products formed by the treatment of butane with Cl_2. Calculate the expected statistical distribution of products, and, given the regioselectivity of Cl_2, predict how the actual product distribution might differ from the calculated statistical distribution.

$$CH_3CH_2CH_2CH_3 + Cl_2 \xrightarrow[\text{heat}]{\text{light or}} \text{monochloroalkanes} + HCl$$

At this point, we have seen experimental evidence that both chlorination and bromination of alkanes are regioselective and furthermore that bromination shows a much higher regioselectivity than does chlorination. How can we account for these experimental obser-

vations? How can we develop insight into why certain molecules react as they do? Or, as we will come to express it, what are the mechanisms of these reactions? We are not in a position in this early stage of the course to take up these questions. Therefore, we leave them for the moment. We return to them in Section 5.6D at which time we take up the study of reaction mechanisms in general and then apply that understanding to an analysis of the halogenation of alkanes and also to the reactions of alkenes.

Because of their physical and chemical properties, many halogenated hydrocarbons have found wide commercial use as solvents, refrigerants, dry-cleaning agents, local and inhalation anesthetics, and insecticides. Of the haloalkanes, the one most widely used as a solvent today is dichloromethane (methylene chloride). Halothane is a widely used inhalation anesthetic.



2-Bromo-2-chloro-1,1,1-trifluoroethane
(Halothane)

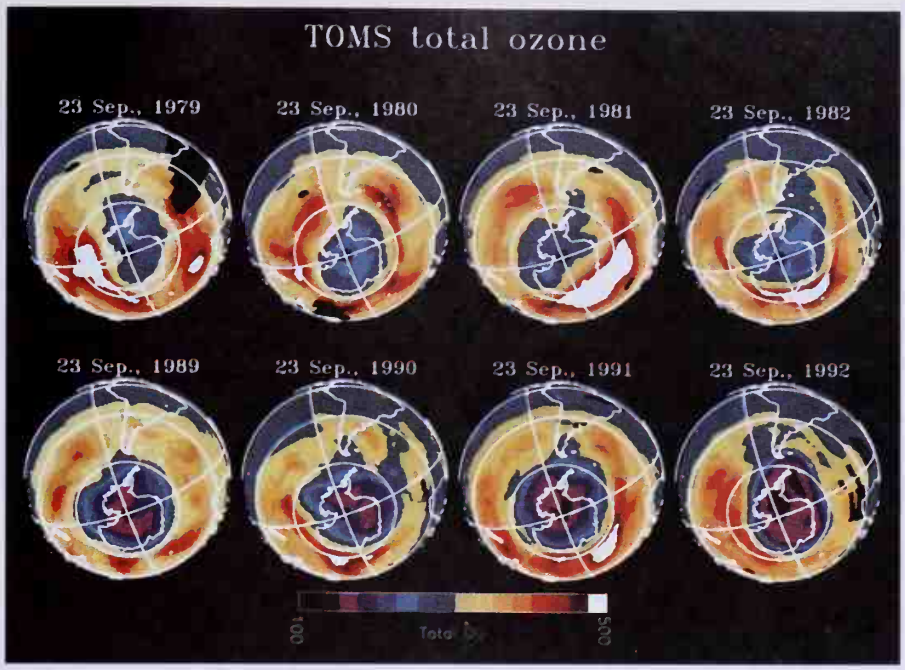
Of all the fluoroalkanes, those manufactured under the trade name **Freons** are the most widely known. The science of fluoroalkanes began in the late 1890s with the discovery that C—F bonds can be formed by treating chloroalkanes with HF in the presence of antimony (V) fluoride, SbF_5, as a catalyst. The resulting **chlorofluorocarbons (CFCs)** were found to be nontoxic, nonflammable, odorless, and noncorrosive. In the late 1920s it was discovered that these compounds were ideal replacements for the hazardous compounds used as heat transfer media in refrigeration systems and by the early 1930s, DuPont had begun production and marketing of trichlorofluoromethane (CFC-11) under the trade name Freon-11. Freons are a class of chlorofluorocarbons derived from methane and ethane. Following are equations for the synthesis of CFC-11 and dichlorodifluoromethane (CFC-12):

$$CCl_4 + HF \xrightarrow{SbF_5} \underset{\substack{\text{Trichlorofluoromethane}\\ \text{CFC-11}}}{CCl_3F} + HCl$$

$$CCl_3F + HF \xrightarrow{SbF_5} \underset{\substack{\text{Dichlorodifluoromethane}\\ \text{CFC-12}}}{CCl_2F_2} + HCl$$

The CFCs along with 1,1,1-trichloroethane (methyl chloroform) and 1,1,2,2-tetrachloroethene (perchloroethylene) also found wide use as industrial solvent cleaners to prepare surfaces for coatings, to remove cutting oils and waxes from millings, and to remove protective coatings, among other uses. CFCs were also used as propellants for aerosol sprays.

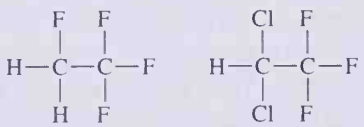
Concern about the environmental impact of chlorofluorocarbons like CFC-11 and CFC-12 arose in the 1970s when it was shown that more than 1 billion pounds per year of CFCs were being emitted into the atmosphere. Then in 1974, Drs. Sherwood Rowland and Mario Molina of the University of California, Irvine, announced their theory of ozone destruction by these compounds. When released into the air, CFCs escape to the lower atmosphere but because of their inertness, they do not decompose there. Slowly, they find



A computer map showing the Antarctic ozone depletion hole. *(NASA)*

their way to the stratosphere where they absorb ultraviolet radiation from the sun and then decompose. As they decompose, they set up a chemical reaction that may also lead to destruction of the stratospheric ozone layer, which acts as a shield for the earth against excess ultraviolet radiation from the sun. An increase in ultraviolet radiation reaching the earth, it is theorized, may lead to destruction of certain crops and agricultural species, and even increased incidence of skin cancer in sensitive individuals.

The results of this concern were two conventions, one in Vienna in 1985 and the other in Montreal in 1987, held by the United Nations Environmental Program. The 1987 meeting produced the "Montreal Protocol" which set limits on the production and use of ozone-depleting CFCs and urged a complete phaseout of their production by the year 1996. The fact that an international agreement on the environment could be reached that set limits on the production of any substance is indeed amazing and bodes well for the health of the planet. The chemical industry is responding by developing nonozone-depleting alternatives to CFCs, among which are the hydrofluorocarbons (HFCs) and hydrochlorofluorocarbons (HCFCs).



HFC-134a HCFC-123

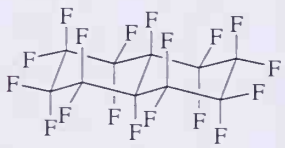
One must not assume, however, that haloalkanes are introduced into the environment from human intervention only. It is estimated, for example, that annual production of bromomethane from natural sources is 300,000 tons, largely from marine algae, giant kelp, and volcanoes. Furthermore, global emission of chloromethane is estimated to be 5 millions tons per year, most of it from terrestrial and marine biomass. Obviously contributions from these natural sources must be taken into account in any plan to limit the concentrations of these substances in the environment.

CHEMISTRY IN ACTION

Artificial Blood

Today, the best known use of fluorocarbons is in nonstick cookware. In the future, this same class of compounds may serve a life-saving role as a substitute for blood. Blood is always in short supply and, even under the best of conditions, can be kept for no more than six or seven weeks. In addition, it can transmit viruses from donor to recipient, as the AIDS epidemic has shown. Furthermore, some patients are unwilling to accept blood transfusions because of their religious beliefs. Because the major short-term function of blood is to deliver oxygen to tissues, a liquid able to mimic this role could provide a stable, noninfectious blood substitute.

Blood picks up oxygen using hemoglobin (an iron-containing protein) in red blood cells. Whole blood can transport approximately 20 mL of oxygen per 100 mL, or 20 vol% oxygen. Fluorinated hydrocarbons, such as perfluorodecalin and perfluorotributylamine are able to dissolve up to 50 vol% oxygen.



Perfluorodecalin (*trans* isomer)

$(CF_3CF_2CF_2CF_2)_3N$

Perfluorotributylamine

The oxygen solubility is so great that mice submerged in oxygen-saturated fluorocarbons are able to breathe the liquid and swim around, uninjured, like furry fish.

Fluorocarbons cannot be used directly in the bloodstream because they are nonpolar and do not mix with water. They can be used as an oxygen-carrying blood substitute, however, as a fluorocarbon-water emulsion. It now appears that mammals can live with a majority of their hemoglobin replaced by fluorocarbons. It has been found, for example, that dogs treated with a 25% perfluorotributylamine-water emulsion replacing 70% of their blood can still live a normal life span.

Studies with humans have been underway for some time, with members of the development team acting as some of the first human volunteers. In 1989, a new drug application was approved in the United States for this type of blood substitute. If results continue to be promising, we can expect that organic chemists will be able to synthesize new perfluorocarbon molecules optimized for use as blood substitutes.

See K. Yamanouchi and C. Heldebrant, *Chem. Tech.*, June 1992, p. 354.

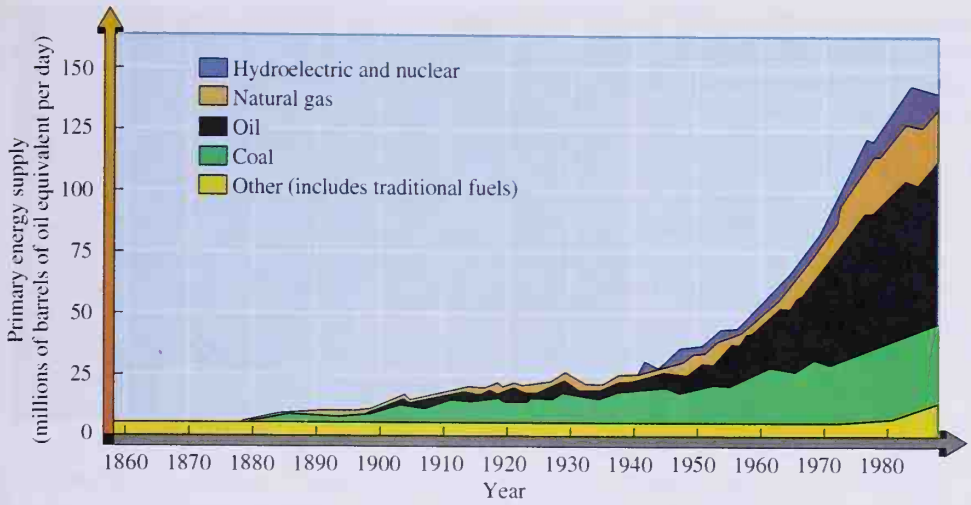
2.10 Sources of Alkanes

The three major sources of alkanes throughout the world are the so-called fossil fuels, namely, natural gas, petroleum, and coal. These fossil fuels account for approximately 90% of the total energy consumed in the United States. Nuclear electric power and hydroelectric power make up most of the remaining 10%. In addition these fossil fuels provide the bulk of raw materials for the organic chemical industry worldwide.

A. Natural Gas

Natural gas consists of approximately 90% to 95% methane, 5% to 10% ethane, and a mixture of other relatively low boiling alkanes; chiefly propane, butane, and 2-methylpropane.

The current widespread use of ethene (ethylene) as the organic chemical industry's most important building block (Section 5.10) is due largely to the ease with which ethane can be separated from natural gas and cracked into ethene. **Cracking** is the process



The rate of use of primary energy from 1860 to the present. (Primary energy exists in a crude form such as fossil fuels.) At the beginning of this period wood was the predominant resource, but coal became more important with the advent of the steam engine and the electric motor. With the invention of the automobile at the end of the 19th century, oil began to contribute. Coal continued to be the most common fuel until the 1920s, when it contributed more than 70% of the world's energy supply. Today coal meets only about 26% of global energy needs, while oil is the major resource. Natural gas and electricity generated by hydro and nuclear power plants have contributed a steady rising portion since the 1940s. For more information see G. R. Davis, *Scientific American,* September 1990, pp. 55–62.

whereby a saturated hydrocarbon is converted into unsaturated hydrocarbons plus H_2. Ethane is cracked by heating it in a furnace at 800° to 900°C for a fraction of a second.

$$\underset{\text{Ethane}}{CH_3CH_3} \xrightarrow[\text{(thermal cracking)}]{800°-900°C} \underset{\text{Ethene}}{CH_2{=}{=}CH_2} + H_2$$

B. Petroleum

Petroleum is a liquid mixture of literally thousands of compounds, most of them hydrocarbons, formed from the decomposition of ancient marine plants and animals. Petroleum and petroleum-derived products fuel automobiles, aircraft, and trains. They provide most of the greases and lubricants required for the machinery of our highly industrialized society. Furthermore, petroleum, along with natural gas, provides close to 90% of the organic raw materials for the synthesis and manufacture of synthetic fibers, plastics, detergents, drugs, dyes, and a multitude of other products.

It is the task of a petroleum refinery to produce usable products, with a minimum of waste, from the thousands of different hydrocarbons in this liquid mixture. The various physical and chemical processes for this purpose fall into two broad categories: separation processes, which separate the complex mixture into various fractions, and conversion processes, which alter the molecular structure of the hydrocarbon components themselves.

The fundamental separation process in refining petroleum is fractional distillation. Practically all crude oil that enters a refinery goes to distillation units where it is heated to

A petroleum refinery. *(Courtesy of Ashland Oil Company.)*

temperatures as high as 370°C to 425°C and separated into fractions. Each fraction contains a mixture of hydrocarbons that boils within a particular range (Figure 2.24). Following are the common names associated with several of these fractions along with the major uses of each.

1. Gases boiling below 20°C are taken off at the top of the distillation column. This fraction is a mixture of low-molecular-weight hydrocarbons, predominantly propane, butane, and 2-methylpropane, substances that can be liquefied under pressure at room temperature. The liquefied mixture, known as liquefied petroleum gas (LPG), can be stored and shipped in metal tanks and is a convenient source of gaseous fuel for home heating and cooking.
2. Naphthas, bp 20° to 200°C, are a mixture of C_5 to C_{12} alkanes and cycloalkanes. The naphthas also contain small amounts benzene, toluene, xylene, and other aromatic hydrocarbons (Chapter 15). The light naphtha fraction, bp 20° to 150°C, is the source of straight-run gasoline and averages approximately 25% of crude petroleum. In a sense, naphthas are the most valuable distillation fractions because they are useful not only as fuel but also as sources of raw materials for the organic chemical industry.
3. Kerosene, bp 175° to 275°C, is a mixture of C_9 to C_{15} hydrocarbons.
4. Fuel oil, bp 250° to 400°C, is a mixture of C_{15} to C_{25} hydrocarbons. It is from this fraction that diesel fuel is obtained.
5. Lubricating oil and heavy fuel oil distill from the column at temperatures above 350°C.
6. Asphalt is the name given to the black, tarry residue remaining after removal of the other volatile fractions.

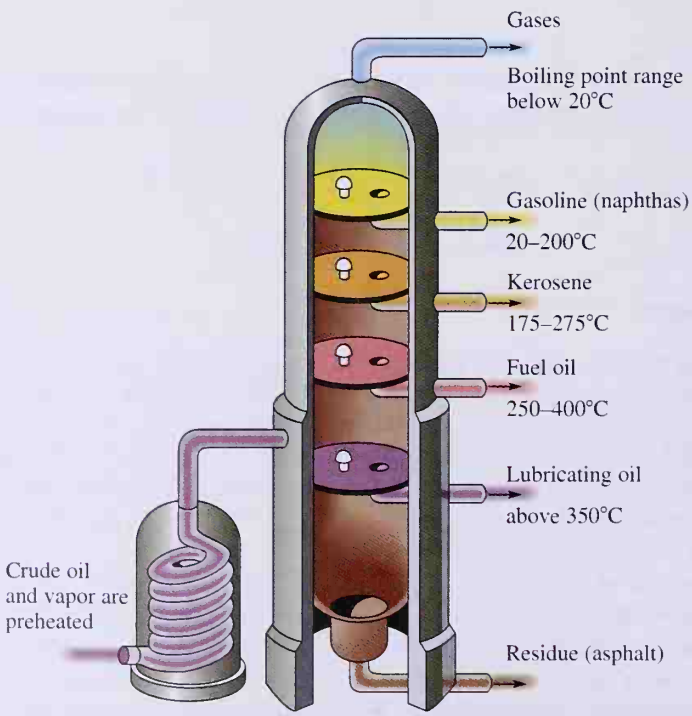


Figure 2.24
The fractional distillation of petroleum. The lighter, more volatile hydrocarbon fractions are removed from higher up the column and the heavier, less volatile fractions from lower down.

A gas pump showing octane rating as (R + M)/2 which is research octane number plus motor octane number divided by 2.
(David R. Frazier Photolibrary)

Gasoline is a complex mixture of C_6 to C_{12} hydrocarbons. The quality of gasoline as a fuel for internal combustion engines is expressed in terms of octane number or antiknock index. When an engine is running normally, the air-fuel mixture is ignited by a spark plug and burns smoothly as the flame moves outward from the plug, building up pressure that forces the piston outward during the power stroke. Engine knocking occurs when a portion of the air-fuel mixture explodes prematurely (usually as a result of heat developed during compression) and independently of ignition by the spark plug. The procedure for measuring the antiknock quality of a gasoline was established in 1929. Two compounds were selected as reference fuels. One of these, 2,2,4-trimethylpentane (isooctane), has very good antiknock properties and was assigned an octane number of 100. (The name "isooctane" as used here is a trivial name; its only relation to the name 2,2,4-trimethylpentane is that both show eight carbon atoms.) Heptane, the other reference compound, has poor antiknock properties and was assigned an octane number of 0. The **octane rating** of a particular gasoline is that percent isooctane in a mixture of isooctane and heptane that has equivalent knock properties. For example, the knock properties of 2-methylhexane are the same as those of a mixture of 42% isooctane and 58% heptane; therefore, the octane rating of 2-methylhexane is 42. Octane itself has an octane rating of -20, which means that it produces even more engine knocking than heptane.

C. Coal

To understand how coal can be used as a raw material for the production of hydrocarbon mixtures, such as those in gasoline and diesel fuel as well as other compounds vital to the organic chemical industry, it is necessary to discuss synthesis gas. **Synthesis gas** is a mixture of carbon monoxide and hydrogen in varying proportions depending on the means by which it is manufactured. For many years in the United States, synthesis gas was manufactured by reaction of methane (derived from natural gas) with steam.

$$CH_4 + H_2O \xrightarrow{\text{catalyst}} CO + 3H_2$$

This reaction amounts to partial oxidation of methane to carbon monoxide and reduction of water to hydrogen. Synthesis gas prepared from the reaction of methane and water has a hydrogen to carbon monoxide ratio of 3 : 1. Synthesis gas is also prepared by reaction of methane with oxygen.

$$CH_4 + \frac{1}{2}O_2 \xrightarrow{\text{catalyst}} CO + 2H_2$$

The most important use of synthesis gas at the present time is as a source of carbon monoxide and hydrogen for the manufacture of methanol and ammonia. In the manufacture of ammonia, H_2 is separated from synthesis gas, mixed with N_2 in a ratio of 3 : 1, and passed over a catalyst at high temperature and pressure.

$$3H_2 + N_2 \xrightarrow{\text{catalyst}} 2NH_3$$

Ammonia

In the production of methanol, the ratio of hydrogen to carbon monoxide is adjusted to 2 : 1 and the mixture passed over a catalyst at elevated temperature and pressure.

$$CO + 2H_2 \xrightarrow{\text{catalyst}} CH_3OH$$

Methanol

Synthesis gas can be made from almost any source of carbon. In the 1950s when the availability of natural gas began to decline and crude oil became available from the Middle East in large quantities and at attractive prices, the chemical industry shifted from natural gas to naphtha as a source of synthesis gas. However, with the rapid increase in the price of petroleum which began in the early 1970s, attention turned to gas oil and other higher boiling, less commercially valuable petroleum fractions as feedstocks from which to manufacture synthesis gas. Attention also turned to the generation of synthesis gas from coal. Because the process for making methanol directly from carbon monoxide is commercially proven, it is likely that the decades ahead will see the development of routes to hydrocarbon fuels and other organic chemicals from coal via methanol.

An ammonia plant using the Haber-Bosch process.
(© Tom Carroll)

SUMMARY OF KEY REACTIONS

1. Chlorination and Bromination (Section 2.9B)

Chlorination and bromination of alkanes are regioselective in the order $3°H > 2°H > 1°H$. Bromination has a higher regioselectivity than chlorination.

$$CH_3CH_2CH_3 + Br_2 \xrightarrow[\text{heat}]{\text{light or}} \underset{\underset{\text{Br}}{|}}{CH_3CHCH_3} + CH_3CH_2CH_2Br + HBr$$

92% 8%

2. Oxidation of Alkanes (Section 2.9A)

Oxidation of alkanes to carbon dioxide and water is the basis for their use as energy sources for heat and power.

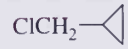
$$CH_3CH_2CH_3 + 5O_2 \longrightarrow 3CO_2 + 4H_2O + \text{energy}$$

ADDITIONAL PROBLEMS

Constitutional Isomerism in Alkanes

2.16 Which of the folowing are identical compounds and which are constitutional isomers?

(a) $CH_3CH_2\underset{\underset{\text{Cl}}{|}}{CH}CH_3$ (b) $CH_3\underset{\underset{\text{Cl}}{|}}{\overset{\overset{\text{CH}_2\text{Cl}}{|}}{C}}CH_3$ (c) $CH_3\overset{\overset{\text{Cl}}{|}}{CH}\underset{\underset{\text{Cl}}{|}}{CH}CH_3$

(d) $\underset{\underset{\text{Cl}}{|}}{CH_2}\underset{\underset{\text{Cl}}{|}}{CH_2}\underset{\underset{\text{Cl}}{|}}{CH}CH_3$ (e)  (f)  (g) $\overset{\overset{\text{CH}_2\text{Cl}}{|}}{CH_3CH}CH_3$

(h) $CH_3CH_2CH_2CH_2CH_2Cl$ (i) $ClCH_2\overset{\overset{\text{CH}_3}{|}}{CH}CH_3$ (j) $CH_3\underset{\underset{\text{Cl}}{|}}{CH}CH_2CH_2Cl$

(k) $CH_3\overset{\overset{\text{CH}_2\text{CH}_3}{|}}{CH}Cl$ (l) $CH_3\underset{\underset{\text{Cl}}{|}}{\overset{\overset{\text{CH}_3}{|}}{C}}CH_3$

2.17 Name and draw structural formulas for all constitutional isomers of molecular formula C_7H_{16}.

Nomenclature of Alkanes and Cycloalkanes

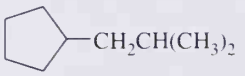
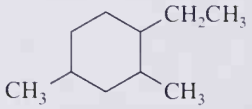
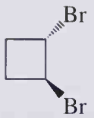
2.18 Write IUPAC names for the following alkanes and cycloalkanes.

(a) $CH_3\underset{\underset{\text{CH}_3}{|}}{CH}CH_2CH_2CH_3$ (b) $CH_3\underset{\underset{\text{CH}_3}{|}}{CH}CH_2CH_2\underset{\underset{\text{CH}_3}{|}}{CH}CH_3$

(c) $CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2\underset{\displaystyle CH_2CH_3}{\underset{|}{C}}HCH_3$ (d) $CH_3(CH_2)_4\underset{\displaystyle CH_2CH_3}{\underset{|}{C}}HCH_2CH_3$

(e) $CH_3CH_2\underset{\displaystyle CH_3CHCH_3}{\underset{|}{C}}HCH_2CH_2CH_2CH_3$ (f) $CH_3CH_2CH_2\underset{\displaystyle CH_2CH(CH_3)_2}{\underset{|}{C}}HCH_2CH_3$

(g) $CH_3(CH_2)_8CH_3$ (h) $(CH_3)_2CHCH_2CH_2C(CH_3)_3$ (i) 

(j)  (k)  (l) 

2.19 Write structural formulas for the following compounds:

(a) 2,2,4-trimethylhexane
(b) 1,1,2-trichlorobutane
(c) 2,2-dimethylpropane
(d) 3-ethyl-2,4,5-trimethyloctane
(e) 2-bromo-2,4,6-trimethyloctane
(f) 5-butyl-2,2-dimethylnonane
(g) 4-isopropyloctane
(h) 3,3-dimethylpentane
(i) 1,1,1-trichloroethane
(j) *trans*-1,3-dimethylcyclopentane
(k) *cis*-1,2-diethylcyclobutane
(l) 1,1-dichlorocycloheptane

2.20 Explain why each of the following is an incorrect IUPAC name. Write a correct IUPAC name for the intended compound.

(a) 1,3-dimethylbutane
(b) 4-methylpentane
(c) 2,2-diethylbutane
(d) 2-ethyl-3-methylpentane
(e) 4,4-dimethylhexane
(f) 2-propylpentane
(g) 2,2-diethylheptane
(h) 5-butyloctane
(i) 2,2-dimethylcyclopropane
(j) 2-*sec*-butyloctane
(k) 4-isopentylheptane
(l) 1,3-dimethyl-6-ethylcyclohexane

2.21 There are 35 constitutional isomers of molecular formula C_9H_{20}. Name and draw structural formulas for the eight that have five carbon atoms in the longest chain.

The IUPAC System of Nomenclature

2.22 For each of the following IUPAC names, draw the corresponding structural formula:

(a) 3-pentanone
(b) 2,2-dimethyl-3-pentanone
(c) 2-butanone
(d) ethanoic acid
(e) hexanoic acid
(f) propanoic acid
(g) propanal
(h) 1-propanol
(i) 2-propanol
(j) cyclopentene
(k) cyclopentanol
(l) cyclopentanone
(m) cyclopropanol
(n) ethene
(o) ethanol
(p) ethanal
(q) decanoic acid
(r) propanone

Conformations of Alkanes and Cycloalkanes

2.23 Consider 1-bromopropane (propyl bromide).

(a) Draw a Newman projection for the conformation in which $-CH_3$ and $-Br$ are anti (staggered, dihedral angle 180°).

(b) Draw Newman projections for the conformations in which $-CH_3$ and $-Br$ are gauche (staggered, dihedral angles 60° and 300°).

(c) Which of these is the lowest energy conformation.

(d) Which of these conformations, if any, are related by reflection?

2.24 Consider 1-bromo-2-methylpropane and draw

(a) The staggered conformation(s) of lowest energy.

(b) The staggered conformation(s) of highest energy.

2.25 In cyclohexane, an equatorial substituent is equidistant from the axial group and the equatorial group on an adjacent carbon. What is the simplest way to demonstrate this fact?

2.26 *trans*-1,4-Di-*tert*-butylcyclohexane exists in a normal chair conformation. *cis*-1,4-Di-*tert*-butylcyclohexane, however, adopts a twist-boat conformation. Draw both isomers and explain why the *cis* isomer is more stable in the twist-boat conformation.

Cis-Trans Isomerism in Cycloalkanes and Bicycloalkanes

2.27 Name and draw structural formulas for the *cis* and *trans* isomers of 1,2-dimethylcyclopropane.

2.28 Name and draw structural formulas for all cycloalkanes of molecular formula C_5H_{10}. Be certain to include *cis-trans* isomers as well as constitutional isomers.

2.29 Using a planar pentagon representation for the cyclopentane ring, draw structural formulas for the *cis* and *trans* isomers of

(a) 1,2-Dimethylcyclopentane **(b)** 1,3-Dimethylcyclopentane

2.30 Draw the alternative chair conformations for the *cis* and *trans* isomers of 1,2-dimethylcyclohexane, 1,3-dimethylcyclohexane, and 1,4-dimethylcyclohexane.

(a) Indicate by a label whether each methyl group is axial or equatorial.

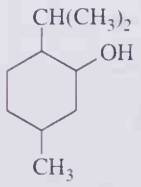
(b) For which isomer(s) are the alternative chair conformations of equal stability?

(c) For which isomer(s) is one chair conformation more stable than the other?

2.31 Complete the following table to show correlations between *cis-trans* and axial-equatorial for the disubstituted derivatives of cyclohexane.

Position of Substitution	*cis*	*trans*
1,4-	a,e or e,a	e,e or a,a
1,3-	_____ or _____	_____ or _____
1,2-	_____ or _____	_____ or _____

2.32 There are four *cis-trans* isomers of 2-isopropyl-5-methylcyclohexanol.



2-Isopropyl-5-methylcyclohexanol

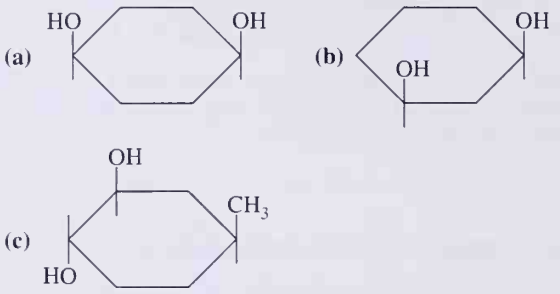
(a) Using a planar hexagon representation for the cyclohexane ring, draw structural formulas for the four *cis-trans* isomers.

Menthol is a component of mint oil, obtained from the plant *Mentha piperita*. *(© Wally Eberhart/ PHOTO/NATS)*

(b) Draw the more stable chair conformation for each of your answers in part (a).

(c) Of the four *cis-trans* isomers, which do you predict to be the most stable? Explain your reasoning. (If you have answered this part correctly, you have picked the isomer found in nature and given the name menthol.)

2.33 Following are planar hexagon representations for several substituted cyclohexanes. Draw alternative chair conformations for each and state which chair is more stable.



2.34 1,2,3,4,5,6-Hexachlorocyclohexane shows *cis-trans* isomerism. At one time a crude mixture of these isomers was sold as the insecticide benzene hexachloride (BHC) under the trade names Kwell and Gammexane. The insecticidal properties of the mixture arise from one isomer known as the γ-isomer (gamma-isomer) which is *cis*-1,2,4,5-*trans*-3,6-hexachlorocyclohexane.

(a) Draw a structural formula for 1,2,3,4,5,6-hexachlorocyclohexane disregarding for the moment the existence of *cis-trans* isomerism. What is the molecular formula of this compound?

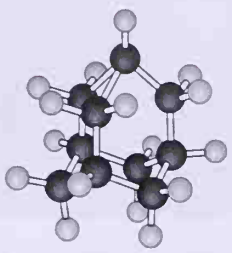
(b) Using a planar hexagon representation for the cyclohexane ring, draw a structural formula for the γ-isomer.

(c) Draw a chair conformation for the γ-isomer and show by labels which chlorine atoms are axial and which are equatorial.

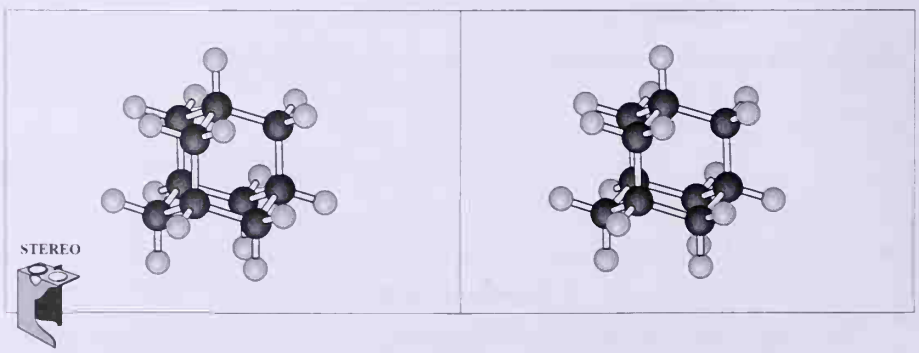
(d) Draw the alternative chair conformation of the γ-isomer and again label which chlorine atoms are axial and which are equatorial.

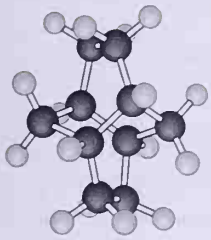
(e) Which of the alternative chair conformations of the γ-isomer is more stable? Explain.

2.35 What kinds of conformations do the six-member rings exhibit in adamantane and twistane? You may find it helpful to build molecular models, particularly of twistane.

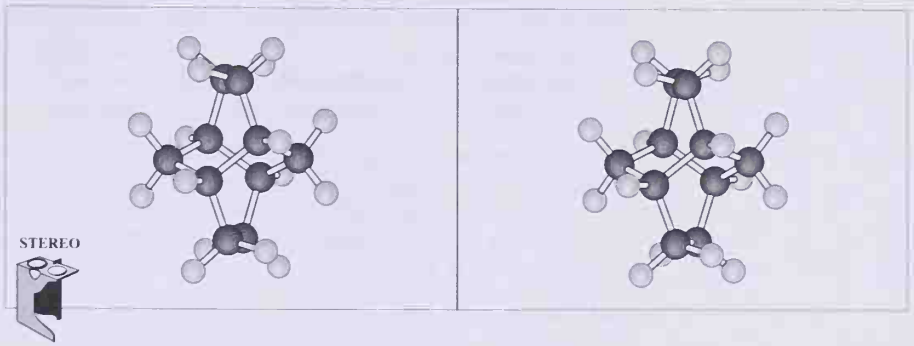


Adamantane





Twistane



2.36 Which of the following bicycloalkanes do you expect to show *cis-trans* isomerism? Explain. For each that does, draw suitable stereorepresentations of both *cis* and *trans* isomers.

(a) bicyclo[2.2.2]octane
(b) bicyclo[4.3.0]nonane
(c) 2-methylbicyclo[2.2.1]heptane
(d) 1-chlorobicyclo[2.2.1]heptane
(e) 7-chlorobicyclo[2.2.1]heptane

Physical Properties

2.37 In Problem 2.17, you drew structural formulas for all isomeric alkanes of molecular formula C_7H_{16}. Predict which isomer has the lowest boiling point; which has the highest boiling point.

2.38 What generalizations can you make about the densities of alkanes relative to that of water?

2.39 What unbranched alkane has about the same boiling point as water? (Refer to Table 2.5 on the physical properties of alkanes.) Calculate the molecular weight of this alkane and compare it with that of water.

Reactions of Alkanes

2.40 Name and draw structural formulas for all possible monohalogenation products that might be formed in the following reactions.

(a)  $+ Cl_2 \xrightarrow{\text{light}}$

(b) $CH_3CHCH_2CH_2CH_3 + Cl_2 \xrightarrow{\text{light}}$ (with CH_3 on the CHCH)

(c) $CH_3CHCHCH_3 + Br_2 \xrightarrow{\text{light}}$ (with CH_3 on the CHCH and CH_3 on the CHCH)

(d)  $+ Br_2 \xrightarrow{\text{light}}$

2.41 Which compounds can be prepared in high yield by regioselective halogenation of an alkane?

(a) 2-chloropentane **(b)** chlorocyclobutane
(c) 3-bromo-3,4-dimethylheptane **(d)** 1-bromo-1-methylcyclohexane
(e) 2-bromo-2,4,4-trimethylpentane **(f)** iodoethane

2.42 There are three constitutional isomers of molecular formula C_5H_{12}. When treated with chlorine gas at 300°C, isomer A gives a mixture of four monochlorination products. Under the same conditions, isomer B gives a mixture of three monochlorination products and isomer C gives only one monochlorination product. From this information, assign structural formulas to isomers A, B, and C.

2.43 Complete and balance the following combustion reactions. Assume that each hydrocarbon is converted completely to carbon dioxide and water.

(a) propane + O_2 ⟶ **(b)** octane + O_2 ⟶
(c) cyclohexane + O_2 ⟶ **(d)** 2-methylpentane + O_2 ⟶

2.44 Following are heats of combustion per mole for methane, propane, and 2,2,4-trimethylpentane. Each is a major source of energy. On a gram-for-gram basis, which of these hydrocarbons is the best source of heat energy?

Hydrocarbon	A Major Component of	ΔH (kcal/mol)
CH_4	natural gas	−212
$CH_3CH_2CH_3$	LPG	−531
$CH_3CCH_2CHCH_3$ (with two CH_3 branches)	gasoline	−1304

2.45 Following are heats of combustion for ethane, propane, and pentane at 25°C.

Hydrocarbon	ΔH (kcal/mol)
ethane(*g*)	−372.8
propane(*g*)	−530.6
pentane(*g*)	−845.2

(a) From these data, calculate the average heat of combustion of a methylene (—CH_2—) group in a gaseous hydrocarbon.

(b) Using the value of the heat of combustion of a methylene group calculated in part (a), estimate the heat of combustion of gaseous cyclopropane.

(c) Compare your estimated value and the experimentally determined value of −499.9 kcal/mol. How might you account for the difference between the two values?

2.46 Using the value of −157.4 kcal/mol as the average heat of combustion of a methylene group,

(a) Calculate the heat of combustion for the following cycloalkanes.

(b) Calculate the total "strain energy" for each cycloalkane.

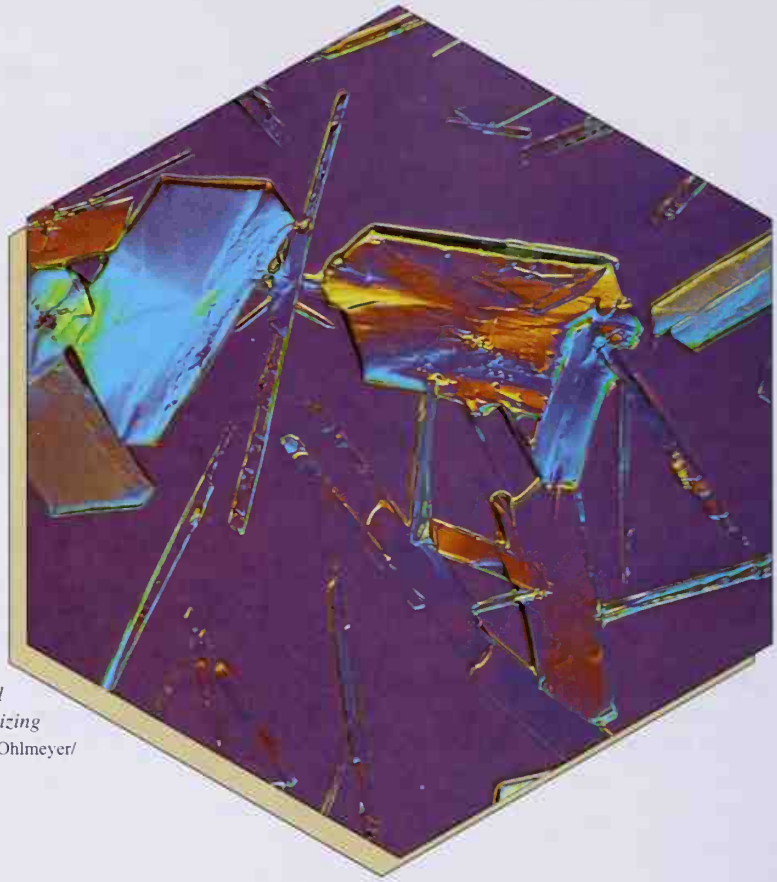
(c) Calculate the strain energy per methylene group.

(d) Rank these cycloalkanes in order of most stable to least stable, based on strain energy per methylene group.

Cycloalkane	Calculated Heat of Combustion (kcal/mol)	Observed Heat of Combustion (kcal/mol)	Calculated Strain Energy (kcal/mol)
cyclopropane	_____	− 499.9	_____
cyclobutane	_____	− 655.9	_____
cyclopentane	_____	− 793.5	_____
cyclohexane	_____	− 944.5	_____
cycloheptane	_____	− 1108.2	_____
cyclooctane	_____	− 1269.0	_____
cyclononane	_____	− 1429.5	_____
cyclodecane	_____	− 1586.0	_____
cycloundecane	_____	− 1742.4	_____
cyclododecane	_____	− 1891.2	_____
cyclotetradecane	_____	− 2203.6	_____

2.47 Hydrocarbons react with strong oxidizing agents. They are quite unreactive, however, toward strong reducing agents such as sodium metal. What do these facts suggest about the energetics of the bonding and antibonding orbitals of hydrocarbons?

3



Crystals of citric acid viewed under a polarizing light. (© Herb Charles Ohlmeyer/ Fran Heyl Associates)

ACIDS AND BASES

A great many organic reactions are acid-base reactions. In this and later chapters, we will study the acid-base properties of the major classes of organic compounds including alkynes, alcohols, phenols, carboxylic acids, α-hydrogens of carbonyl-containing compounds, amines, amino acids and proteins, and finally nucleic acids. Furthermore, a great many organic reactions are catalyzed by proton-donating acids, such as H_3O^+ and $CH_3CH_2OH_2^+$. Other organic reactions are catalyzed by Lewis acids such as BF_3 and $AlCl_3$. It is essential, therefore, that you have a good grasp of the fundamentals of acid-base chemistry.

3.1 Arrhenius Acids and Bases

The first useful definition of acids and bases was put forward by Svante Arrhenius in 1884. Arrhenius defined acids and bases in terms of their effect on water. According to the Arrhenius concept, an **acid** is a substance that dissolves in water to increase the concentration of hydrogen ion, H^+. Hydrogen ion is a hydrogen atom stripped of its single electron and containing a single proton in its nucleus; the terms "hydrogen ion" and **"proton"** are

interchangeable. A **base** is a substance that dissolves in water to increase the concentration of hydroxide ion, OH^-. Thus, $HCl(g)$ is an acid because it dissolves in water to increase $[H^+]$ and $NaOH(s)$ is a base because it dissolves in water to increase $[OH^-]$.

$$HCl(g) \xrightarrow{H_2O} H^+(aq) + Cl^-(aq)$$

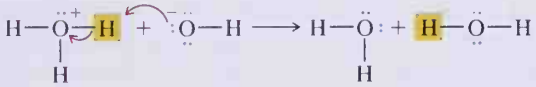
$$NaOH(s) \xrightarrow{H_2O} Na^+(aq) + OH^-(aq)$$

The Arrhenius concept of acids and bases is so intimately tied to water and reactions in water systems that it has no way to deal with acid-base reactions in nonaqueous solutions, as for example the reaction that occurs when HCl gas and NH_3 gas are dissolved in ethanol and react to form solid ammonium chloride.

$$\underset{\text{(In ethanol)}}{HCl} + \underset{\text{(In ethanol)}}{NH_3} \longrightarrow NH_4Cl(s)$$

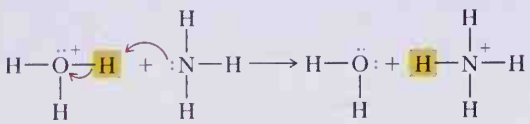
3.2 Brønsted-Lowry Acids and Bases

In 1923, the Danish chemist Johannes Brønsted and the English chemist Thomas Lowry independently proposed these definitions: an acid is a **proton donor,** and a base is a **proton acceptor.** In the neutralization reaction between H_3O^+ and OH^-, a proton is transferred from H_3O^+, a Brønsted acid, to OH^-, a Brønsted base. We use curved arrows to show the flow of electrons in acid-base reactions. The curved arrow on the right in the following equation shows an unshared pair of electrons on oxygen moving to form a new bond with hydrogen; in sharing electrons, this oxygen becomes neutral. The curved arrow on the left shows a shared pair of electrons from an O—H bond moving onto oxygen; this oxygen gains electrons and becomes neutral.



Brønsted acid — Brønsted base

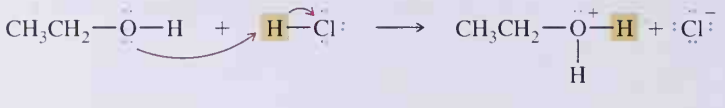
Reaction between $H_3O^+(aq)$ and $NH_3(aq)$ involves transfer of a proton from H_3O^+, a proton donor, to NH_3, a proton acceptor. Note that in this reaction, the base is a neutral molecule.



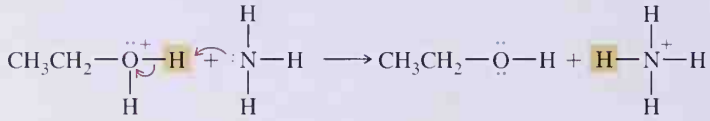
Proton donor — Proton acceptor

The neutralization reaction between solutions of HCl and NH_3 dissolved in ethanol can be written as the sum of two proton-transfer reactions. HCl is a strong acid and when dissolved in ethanol transfers a proton to the oxygen atom of ethanol to give an ethyloxonium ion and chloride ion. When this solution is mixed with a solution of ammonia in ethanol, a proton is transferred from the ethyloxonium ion to ammonia. The sum of these

two **proton-transfer reactions** gives ammonium chloride, which precipitates as white crystals.



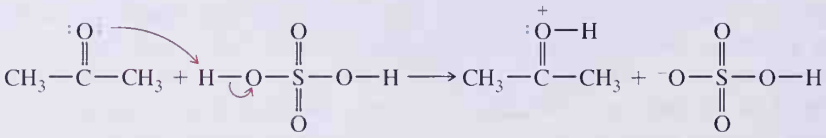
Ethanol (a base) Hydrogen chloride (an acid)



Ethyloxonium ion (an acid) Ammonia (a base)

Net equation: $HCl + NH_3 \longrightarrow NH_4Cl(s)$

Acetone is neutral in aqueous solution, but when it is mixed with sulfuric acid, a strong acid, it acts as a Brønsted base as shown in the following proton-transfer reaction:



Acetone (a base) Sulfuric acid (an acid)

The role of the solvent in proton-transfer reactions cannot be overestimated. Although we often write H^+ as the acid form in solution, H^+ is always associated with a solvent molecule. An acid-base reaction in solution is thus transfer of a proton from a protonated molecule of solvent to a base. In reactions in aqueous solutions, it is transfer of a proton from H_3O^+ to a molecule of base; in ethanol solutions, it is transfer of a proton from $CH_3CH_2OH_2^+$ to a molecule of base.

The reciprocal relationships in proton-transfer reactions are described by the following terminology. When an acid transfers a proton to a base, the acid is converted to its

Table 3.1 Examples of acid-conjugate base pairs and base-conjugate acid pairs

Acid	Conjugate Base	Base	Conjugate Acid
H_3O^+	H_2O	OH^-	H_2O
H_2O	OH^-	H_2O	H_3O^+
NH_4^+	NH_3	NH_2^-	NH_3
NH_3	NH_2^-	NH_3	NH_4^+
$CH_3OH_2^+$	CH_3OH	CH_3O^-	CH_3OH
$CH_3NH_3^+$	CH_3NH_2	CH_3S^-	CH_3SH
HCl	Cl^-	Cl^-	HCl

conjugate base; when a base accepts a proton, the base is converted to its **conjugate acid.** For example, in reaction between hydronium ion and ammonia, H_3O^+ is converted into its conjugate base, H_2O, and NH_3 is converted into its conjugate acid, NH_4^+.

$$\underset{\text{Acid}}{H_3O^+} + \underset{\text{Base}}{NH_3} \longrightarrow \underset{\substack{\text{Conjugate}\\\text{base}}}{H_2O} + \underset{\substack{\text{Conjugate}\\\text{acid}}}{NH_4^+}$$

Several examples of Brønsted-Lowry acid–conjugate base and base–conjugate acid pairs are given in Table 3.1.

EXAMPLE 3.1

Write the following as proton-transfer reactions. Label which reactant is the acid and which the base; which product is the conjugate base and which the conjugate acid. Use curved arrows to show the flow of electrons in each reaction.

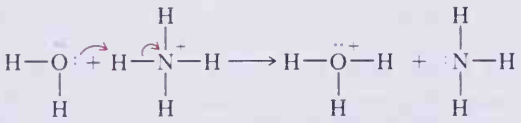
(a) $H_2O + NH_4^+ \longrightarrow H_3O^+ + NH_3$

(b) $CH_3\overset{\displaystyle O}{\overset{\|}{C}}OH + NH_3 \longrightarrow CH_3\overset{\displaystyle O}{\overset{\|}{C}}O^- + NH_4^+$

(c) $CH_3SH + OH^- \longrightarrow CH_3S^- + H_2O$

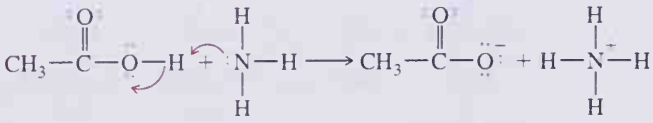
Solution

(a) Water is the base (proton acceptor), and ammonium ion is the acid (proton donor).



Base Acid Conjugate acid Conjugate base

(b) Acetic acid is the acid (proton donor), and ammonia is the base (proton acceptor).



Acid Base Conjugate base Conjugate acid

(c) Methanethiol is the acid (proton donor), and hydroxide ion is the base (proton acceptor).

Acid Base Conjugate base Conjugate acid

PROBLEM 3.1

Write the following as proton-transfer reactions. Label which reactant is the acid and which the base; which product is the conjugate base and which the conjugate acid. Use curved arrows to show the flow of electrons in each reaction.

(a) $CH_3OH + NH_4^+ \longrightarrow CH_3OH_2^+ + NH_3$
(b) $CH_3OH + NH_2^- \longrightarrow CH_3O^- + NH_3$
(c) $CH_3SH + HCl \longrightarrow CH_3SH_2^+ + Cl^-$

3.3 Quantitative Measure of Acid and Base Strength

A **strong acid** is one that is completely ionized in aqueous solution. When HCl is dissolved in water, there is complete transfer of a proton from HCl to H_2O. There is no tendency for the reverse reaction to occur, namely for transfer of a proton from H_3O^+ to Cl^- to form HCl and H_2O. Therefore, when we compare HCl and H_3O^+, we conclude that HCl is the stronger acid and H_3O^+ is the weaker acid. Similarly, H_2O is the stronger base, and Cl^- is the weaker base.

HCl	+	H_2O	$\longrightarrow$	Cl^-	+	H_3O^+
Acid		Base		Conjugate base		Conjugate acid
(stronger acid)		(stronger base)		(weaker base)		(weaker acid)

Examples of other strong acids in aqueous solution are HBr, HI, HNO_3, $HClO_4$, and H_2SO_4. **Strong bases** in aqueous solution are the alkali metal hydroxides (LiOH, NaOH, KOH, RbOH, and CsOH), TlOH, $Ca(OH)_2$, $Ba(OH)_2$, and $Sr(OH)_2$.

A **weak acid** or **weak base** is one that is incompletely ionized in aqueous solution. Most organic acids and bases are weak. Among the most common organic acids we deal with are the carboxylic acids, which contain the functional group $-CO_2H$.

$CH_3\overset{O}{\overset{\|}{C}}OH$	+	H_2O	$\rightleftharpoons$	$CH_3\overset{O}{\overset{\|}{C}}O^-$	+	H_3O^+
Acid		Base		Conjugate base		Conjugate acid
(weaker acid)		(weaker base)		(stronger base)		(stronger acid)

The ionization of a weak acid in water involves transfer of a proton to water. However, such ionizations are commonly written in a more abbreviated way as shown in the following equation:

$$CH_3\overset{O}{\overset{\|}{C}}OH \rightleftharpoons CH_3\overset{O}{\overset{\|}{C}}O^- + H^+$$

Table 3.2 Values of pK_a for some organic and inorganic acids

Acid	Formula	pK_a	Conjugate Base
ethane	CH_3CH_3	48	$CH_3CH_2^-$
hydrogen	H_2	35	H^-
ammonia	NH_3	33	NH_2^-
ethyne (acetylene)	$HC{\equiv}CH$	25	$HC{\equiv}C^-$
ethanol	CH_3CH_2OH	15.9	$CH_3CH_2O^-$
water	H_2O	15.7	HO^-
hydrogen phosphate ion	HPO_4^{2-}	12.32	PO_4^{3-}
bicarbonate ion	HCO_3^-	10.33	CO_3^{2-}
phenol	C_6H_5OH	9.95	$C_6H_5O^-$
methylammonium ion	$CH_3NH_3^+$	9.64	CH_3NH_2
ammonium ion	NH_4^+	9.24	NH_3
dihydrogen phosphate ion	$H_2PO_4^-$	7.20	HPO_4^{2-}
carbonic acid	H_2CO_3	6.36	HCO_3^-
acetic acid	CH_3CO_2H	4.76	$CH_3CO_2^-$
benzoic acid	$C_6H_5CO_2H$	4.19	$C_6H_5CO_2^-$
phosphoric acid	H_3PO_4	2.1	$H_2PO_4^-$
hydrogen sulfate ion	HSO_4^-	1.92	SO_4^{2-}
trichloroacetic acid	CCl_3CO_2H	0.7	$CCl_3CO_2^-$
hydronium ion	H_3O^+	−1.74	H_2O
ethyloxonium ion	$CH_3CH_2OH_2^+$	−3.6	CH_3CH_2OH
sulfuric acid	H_2SO_4	−5.2	HSO_4^-
hydrogen chloride	HCl	−7	Cl^-
hydrogen bromide	HBr	−8	Br^-
hydrogen iodide	HI	−9	I^-

Increasing acid strength

The equation for the ionization of a weak acid, HA, and the acid ionization constant, K_a, for this ionization are

$$HA \rightleftharpoons H^+ + A^-$$

$$K_a = \frac{[H^+][A^-]}{[HA]}$$

Because acid ionization constants for weak acids are numbers with negative exponents, they are often expressed as $\mathbf{p}K_a$, where $pK_a = -\log_{10}K_a$. Given in Table 3.2 are names, molecular formulas, and values of pK_a for some organic and inorganic acids.

EXAMPLE 3.2

For each value of pK_a, calculate the corresponding value of K_a.

(a) ethanol, $pK_a = 15.90$ **(b)** carbonic acid, $pK_a = 6.36$

A pH meter. *(Courtesy of Fisher Scientific.*

Solution

(a) for ethanol, $K_a = 1.3 \times 10^{-16}$ **(b)** for carbonic acid, $K_a = 4.4 \times 10^{-7}$

PROBLEM 3.2

For each value of $[H^+]$, calculate the corresponding value of pH.

(a) blood plasma of $[H^+] = 3.72 \times 10^{-8}$
(b) an acid rain of $[H^+] = 5.89 \times 10^{-5}$

Values of pK_a in aqueous solution in the range pK_a 2–12 can be measured quite precisely. Values of pK_a smaller than 2 are less precise because very strong acids, such as HCl, HBr, and HI, are completely ionized in water and the only acid present in solutions of these acids is H_3O^+. For acids too strong to be measured accurately in water, less basic solvents such as acetic acid or mixtures of water and sulfuric acid are used. Although none of the halogen acids, for example, is completely ionized in acetic acid, HI shows a greater degree of ionization than either HBr or HCl and, therefore, is the strongest acid of the three. Values of pK_a greater than 12 are also less precise. For acids too weak to be measured in aqueous solution, more basic solvents, such as liquid ammonia and dimethyl sulfoxide, are used. Thus, because of the necessity of using different solvent systems to measure relative strengths at either end of the acidity scale, pK_a values smaller than 2 or greater than 12 should be used only in a qualitative way when comparing them with values in the middle of the scale.

3.4 The Position of Equilibrium in Acid-Base Reactions

Let us consider an acid-base reaction represented by the following general equation:

$$HA + B^- \rightleftharpoons A^- + HB$$

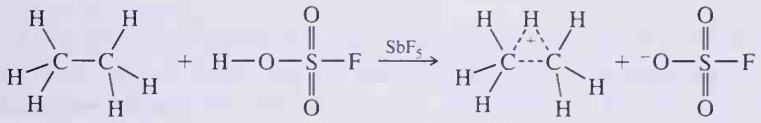
To determine the position of equilibrium for this reaction, we need to know which is the stronger acid, or conversely, which is the stronger base. If HA is the stronger acid, then A^- must be the weaker base, and the position of equilibrium favors A^- and HB.

CHEMISTRY IN ACTION

The Strongest Acid ?

What is the strongest acid? In recent years, organic chemists have prepared mixtures of protic and Lewis acids that have remarkable proton-donating power. Two of the most reactive of these mixtures, termed **superacids,** are HF with SbF_5 and FSO_3H (fluorosulfonic acid) with SbF_5. Either liquid SO_2 or SO_2F_2 are used as solvents for superacids.

Both theoretical and experimental evidence suggests that in superacids, the electron pairs that make up the carbon-carbon and carbon-hydrogen bonds of hydrocarbons act as Lewis bases and become protonated. The resulting cations have unusual structures. In the case of ethane, for example, the ion $C_2H_7^+$ is produced.



Fluorosulfonic acid (Unstable)

The dotted lines in the $C_2H_7^+$ structure indicate the formation of a three-center, two-electron bond. Notice that because the incoming proton has no electrons of its own, the octet rule is not broken.

Even at low temperatures (−78°C), the $C_2H_7^+$ ion is not very stable. One of its decomposition products is methane, CH_4. The observation of methane as a product supports protonation of the carbon-carbon bond electron pair over one of the six carbon-hydrogen electron pairs.

Although the chemistry of alkanes in superacids may seem esoteric, in fact, these reactions provide a model for one of the most important reactions in industrial organic chemistry, namely, the catalytic cracking of petroleum. Highly acidic sites on the solid catalysts used in petroleum refining promote protonation of C—C and C—H bonds. Protonation of C—C bonds leads to fragmentation and isomerization of larger hydrocarbons; protonation of C—H bonds leads to the production of hydrogen and alkenes.

$$\underset{\text{Stronger acid}}{HA} + \underset{\text{Stronger base}}{B^-} \rightleftharpoons \underset{\text{Weaker base}}{A^-} + \underset{\text{Weaker acid}}{HB}$$

Conversely, if HB is the stronger acid, then B^- must be the weaker base, and the position of equilibrium favors HA and B^-.

$$\underset{\text{Weaker acid}}{HA} + \underset{\text{Weaker base}}{B^-} \rightleftharpoons \underset{\text{Stronger base}}{A^-} + \underset{\text{Stronger acid}}{HB}$$

We can determine the position of equilibrium in acid-base reactions of this type using the data in Table 3.2. For example, consider the reaction between aqueous solutions of acetic acid and sodium cyanide. Sodium ion does not appear in the net ionic equation, and, therefore, the equilibrium we must consider is the following:

$$\underset{\substack{\text{Acetic acid}\\ pK_a\ 4.76\\ \text{stronger acid}}}{CH_3CO_2H} + CN^- \rightleftharpoons \underset{\substack{\text{Hydrocyanic acid}\\ pK_a\ 9.31\\ \text{weaker acid}}}{CH_3CO_2^-} + HCN$$

Vinegar (acetic acid) and baking soda (sodium bicarbonate) react to produce sodium acetate, carbon dioxide, and water. *(Charles D. Winters)*

Acetic acid (pK_a 4.76; K_a 1.74×10^{-5}) is a stronger acid than hydrocyanic acid (pK_a 9.31; K_a 4.90×10^{-10}); the position of equilibrium for this reaction, therefore, lies to the right. Using the given values for pK_a for each acid, we can calculate the equilibrium constant, K_{eq}, for this reaction.

$$K_{eq} = \frac{K_a(CH_3CO_2H)}{K_a(HCN)} = \frac{1.74 \times 10^{-5}}{4.90 \times 10^{-10}} = 3.55 \times 10^4$$

Consider the reaction between aqueous solutions of acetic acid and sodium bicarbonate to give sodium acetate and carbonic acid. The net ionic equation for this reaction is

$$\underset{\substack{\text{Acetic acid}\\ pK_a\ 4.76}}{CH_3CO_2H} + \underset{\text{Bicarbonate ion}}{HCO_3^-} \rightleftharpoons \underset{\text{Acetate ion}}{CH_3CO_2^-} + \underset{\substack{\text{Carbonic acid}\\ pK_a\ 6.36}}{H_2CO_3}$$

Acetic acid is the stronger acid, and, therefore, the position of this equilibrium lies to the right. Carbonic acid is formed, which then decomposes to carbon dioxide and water.

EXAMPLE 3.3

Predict the position of equilibrium and calculate the equilibrium constant, K_{eq}, for the following reactions.

(a) $$\underset{\text{Phenol}}{C_6H_5OH} + \underset{\text{Bicarbonate ion}}{HCO_3^-} \rightleftharpoons \underset{\text{Phenoxide ion}}{C_6H_5O^-} + \underset{\text{Carbonic acid}}{H_2CO_3}$$

(b) $$\underset{\text{Ethyne}}{HC{\equiv}CH} + \underset{\text{Amide ion}}{NH_2^-} \rightleftharpoons \underset{\text{Ethynide ion}}{HC{\equiv}C^-} + \underset{\text{Ammonia}}{NH_3}$$

Solution

(a) Carbonic acid is the stronger acid; the position of this equilibrium lies to the left. Phenol does not transfer a proton to bicarbonate ion to form carbonic acid.

$$C_6H_5OH + HCO_3^- \rightleftharpoons C_6H_5O^- + H_2CO_3$$

$$pK_a\ 9.95 \qquad\qquad pK_a\ 6.36$$

$$K_{eq} = \frac{K_a(C_6H_5OH)}{K_a(H_2CO_3)} = \frac{1.12 \times 10^{-10}}{4.37 \times 10^{-7}} = 2.56 \times 10^{-4}$$

(b) Ethyne is the stronger acid; the position of this equilibrium lies to the right.

$$HC{\equiv}CH + NH_2^- \rightleftharpoons HC{\equiv}C^- + NH_3$$

$$pK_a\ 25 \qquad\qquad pK_a\ 33$$

$$K_{eq} = \frac{K_a(HC{\equiv}CH)}{K_a(NH_3)} = \frac{1 \times 10^{-25}}{1 \times 10^{-33}} = 1 \times 10^8$$

PROBLEM 3.3

Predict the position of equilibrium and calculate the equilibrium constant, K_{eq}, for the following reactions:

(a) $CH_3NH_2 + CH_3CO_2H \rightleftharpoons CH_3NH_3^+ + CH_3CO_2^-$

Methylamine; Acetic acid; Methylammonium ion; Acetate ion

(b) $CH_3CH_2O^- + NH_3 \rightleftharpoons CH_3CH_2OH + NH_2^-$

Ethoxide ion; Ammonia; Ethanol; Amide ion

3.5 Lewis Acids and Bases

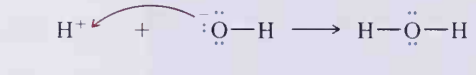
G. N. Lewis, who proposed that covalent bonds are formed by sharing of one or more pairs of electrons (Section 1.2C), further expanded the theory of acids and bases to include a group of reactions not included in the Brønsted-Lowry concept. According to the Lewis definition, a **Lewis acid** is a species that can form a new covalent bond by accepting a pair of electrons; a **Lewis base** is a species that can form a new covalent bond by donating a pair of electrons.

$$A \overset{\frown}{} + :B \longrightarrow A{-}B$$

Lewis acid; Lewis base

Note that although we speak of a Lewis base as "donating" a pair of electrons, the term is not fully accurate. Donating in this case does not mean that the electron pair under consideration is removed completely from the valence shell of the base. Rather, donating means that the electron pair is shared with another atom to form a covalent bond.

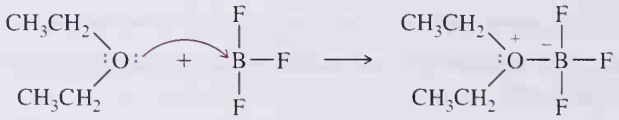
Consider the neutralization of HCl by NaOH in aqueous solution, which consists of transfer of a proton from H_3O^+ to OH^-. The transfer of a proton can be written in the following oversimplified way:



Lewis acid (accepts an electron pair) | Lewis base (donates an electron pair)

In creating the new covalent bond to form a water molecule, the proton accepts a pair of electrons; it is the Lewis acid. In forming the new covalent bond, hydroxide ion donates a pair of electrons; it is the Lewis base.

The Lewis concept of acids and bases includes proton-transfer reactions; all Bronsted bases (proton acceptors) are also Lewis bases, and all Brønsted acids (proton donors) are also Lewis acids. The Lewis model, however, is more general in that it is not restricted to proton-transfer reactions. Consider the reaction that occurs when boron trifluoride gas is dissolved in diethyl ether.



Diethyl ether (a Lewis base) | Boron trifluoride (a Lewis acid) | Diethyloxonium fluoroborate

Diethyl ether is a Lewis base; in forming the O—B bond, its oxygen donates an electron pair. Boron trifluoride is a Lewis acid; in forming the O—B bond, boron accepts an electron pair. The reaction between diethyl ether and boron trifluoride is classified as an acid-base reaction according to the Lewis model, but because there is no proton transfer involved, it is not classified as an acid-base reaction by the Bronsted-Lowry model.

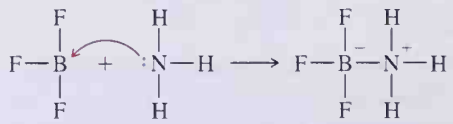
EXAMPLE 3.4

Write the reaction between each Lewis acid-base pair, showing electron flow by means of curved arrows.

(a) $BF_3 + NH_3 \longrightarrow$ **(b)** $CH_3CH_2^+ + Cl^- \longrightarrow$

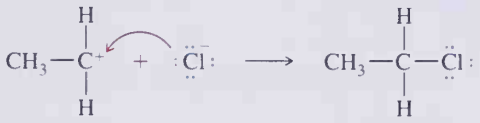
Solution

(a) BF_3 has an empty orbital in the valence shell of boron and is the Lewis acid. NH_3 has an unshared pair of electrons on nitrogen and is the Lewis base. In this example, each atom takes on a formal charge; the resulting structure, however, has no net charge.



Lewis acid Lewis base

(b) The trivalent carbon atom in the ethyl cation has an empty orbital in its valence shell, and, therefore, is the Lewis acid. Chloride ion is the Lewis base.



Lewis acid Lewis base

PROBLEM 3.4

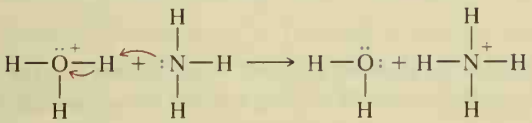
Write the reaction between each Lewis acid-base pair, showing electron flow by means of curved arrows.

(a) $(CH_3CH_2)_3B + OH^- \longrightarrow$ **(b)** $Br^- + AlBr_3 \longrightarrow$

SUMMARY OF KEY REACTIONS

1. Proton-Transfer Reaction (Section 3.2)

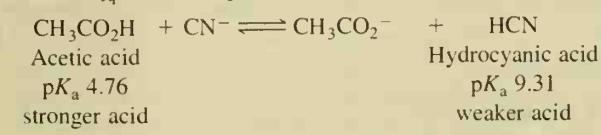
Involves transfer of a proton from a proton donor (a Brønsted acid) to a proton acceptor (a Brønsted base).



Proton donor (Brønsted acid) Proton acceptor (Brønsted base)

2. Position of Equilibrium in an Acid-Base Reaction (Section 3.4)

The stronger acid reacts with the stronger base to give a weaker acid and a weaker base. K_{eq} for this equilibrium can be calculated from pK_a values for the two acids.

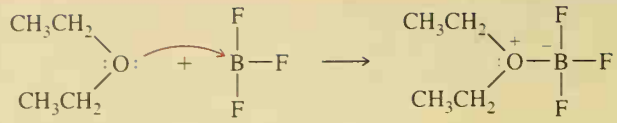


Acetic acid, pK_a 4.76, stronger acid — Hydrocyanic acid, pK_a 9.31, weaker acid

$$K_{eq} = \frac{K_a(CH_3CO_2H)}{K_a(HCN)} = \frac{1.74 \times 10^{-5}}{4.90 \times 10^{-10}} = 3.55 \times 10^4$$

3. Lewis Acid-Base Reaction (Section 3.5)

A Lewis acid-base reaction involves sharing an electron pair between an electron pair donor (a Lewis base) and an electron pair acceptor (a Lewis acid).



Diethyl ether (a Lewis base) Boron trifluoride (a Lewis acid)

ADDITIONAL PROBLEMS

Brønsted-Lowry Acids and Bases

3.5 Complete the following proton-transfer reactions using curved arrows to show the flow of electron pairs in each reaction. In addition, write Lewis structures for all starting materials and products. If you are uncertain about which substance in each equation is the proton donor, refer to Table 3.2 for the relative strengths of proton acids.

(a) $CH_3\overset{\overset{O}{\|}}{C}OH + OH^- \longrightarrow$ (b) $CH_3\overset{\overset{O}{\|}}{C}OH + CH_3O^- \longrightarrow$ (c) $NH_4^+ + OH^- \longrightarrow$

(d) $NH_3 + HCl \longrightarrow$ (e) $CH_3\overset{\overset{O}{\|}}{C}O^- + CH_3NH_3^+ \longrightarrow$

(f) $CH_3CH_2OH + HCl \longrightarrow$ (g) $CH_3CH_2OCH_2CH_3 + HCl \longrightarrow$

(h) $CH_3CH_2^- + H_2O \longrightarrow$

3.6 For each of the proton-transfer reactions in Problem 3.5, label which starting material is the acid and which product is its conjugate base; which starting material is the base and which product is its conjugate acid.

3.7 Each of the following molecules and ions can function as a base. Write the structural formula of the conjugate acid formed by reaction of each with H^+.

(a) CH_3CH_2OH (b) $H\overset{\overset{O}{\|}}{C}H$ (c) $(CH_3)_2NH$ (d) HCO_3^-

3.8 In acetic acid, the O—H proton is more acidic than the H_3C protons. Show how the concept of electronegativity can be used to account for this difference in acidity.

3.9 Using the concepts of resonance and electronegativity as appropriate, offer an explanation for the following observations:

(a) H_3O^+ is a stronger acid than NH_4^+.

(b) Acetic acid is a stronger acid than ethanol.

(c) Ethanol and water have approximately the same acidity.

(d) Hydrocyanic acid is a stronger acid than ethyne (acetylene).

Quantitative Measure of Acid and Base Strength

3.10 In each pair, select the stronger acid:

(a) Pyruvic acid (pK_a 2.49) or lactic acid (pK_a 3.85)

(b) Citric acid (pK_{a1} 3.08) or phosphoric acid (pK_{a1} 2.10)

(c) Nicotinic acid (niacin, K_a 1.4×10^{-5}) or acetylsalicylic acid (aspirin, K_a 3.3×10^{-4})

(d) Phenol (K_a 1.12×10^{-10}) or boric acid (K_a 7.24×10^{-10})

Quantitative Position of Equilibrium in Acid-Base Reactions

3.11 Estimate the value of K_{eq} for the following equilibria and state which lie considerably toward the left; which lie considerably toward the right. The value of pK_a for HCN is 9.31. Values of pK_a for other acids in this problem can be found in Table 3.2.

(a) $CH_3CO_2H + HCO_3^- \rightleftharpoons CH_3CO_2^- + H_2CO_3$

(b) $CH_3CO_2H + NH_3 \rightleftharpoons CH_3CO_2^- + NH_4^+$

(c) $C_6H_5OH + CO_3^{2-} \rightleftharpoons C_6H_5O^- + HCO_3^-$

(d) $CN^- + HCO_3^- \rightleftharpoons HCN + CO_3^{2-}$

(e) $C_6H_5CO_2^- + H_2O \rightleftharpoons C_6H_5CO_2H + OH^-$

3.12 For an acid-base reaction, one way to determine the predominant species at equilibrium is to say that the reaction arrow points to the acid with the higher value of pK_a. For example:

$$\underset{pK_a\ 9.31}{HCN} + H_2O \longleftarrow \underset{pK_a\ -1.74}{CN^-} + H_3O^+$$

$$\underset{pK_a\ 9.31}{HCN} + OH^- \longrightarrow \underset{pK_a\ 15.7}{CN^-} + H_2O$$

Explain why this rule works.

3.13 Using pK_a values given in Table 3.2, predict the position of equilibrium in the following acid-base reactions and calculate the K_{eq} for each reaction:

(a) $PO_4^{3-} + CH_3CO_2H \rightleftharpoons HPO_4^{2-} + CH_3CO_2^-$

(b) $NH_4^+ + HCO_3^- \rightleftharpoons NH_3 + H_2CO_3$

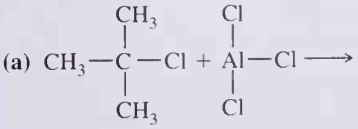
(c) $NH_4^+ + OH^- \rightleftharpoons NH_3 + H_2O$

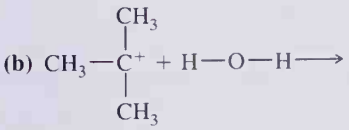
(d) $H_3PO_4 + CH_3CH_2OH \rightleftharpoons H_2PO_4^- + CH_3CH_2OH_2^+$

3.14 Calculate the ratio of acetic acid to sodium acetate concentrations needed to prepare a solution of pH 4.50.

Lewis Acids and Bases

3.15 Complete the following reactions between Lewis acid–Lewis base pairs. Label which starting material is the Lewis acid, which the Lewis base, and use curved arrows to show the flow of electrons in each reaction. In doing these problems, it is essential that you show all valence electrons for all atoms participating directly in each reaction.

(a)


(b)


(c) $CH_3-CH=CH_2 + H^+ \longrightarrow$

(d) $CH_3-\overset{+}{C}H-CH_3 + Br^- \longrightarrow$

(e) $F^- + \begin{array}{c} F \\ | \\ B-F \\ | \\ F \end{array} \longrightarrow$

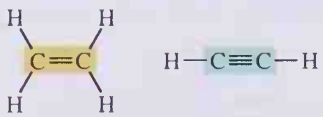
(f) $CH_3-\overset{+}{C}H-CH_3 + CH_3-O-H \longrightarrow$

Lily-of-the-valley, from which farnesol (Section 4.6) is isolated. (Barry L. Runk/Grant Heilman Photography, Inc.)

4

ALKENES I

Unsaturated hydrocarbons are hydrocarbons that contain one or more carbon-carbon double or triple bonds. There are three classes of unsaturated hydrocarbons: alkenes, alkynes, and aromatic hydrocarbons. **Alkenes** contain one or more carbon-carbon double bonds, and **alkynes** contain one or more carbon-carbon triple bonds. The structural formulas of ethene, the simplest alkene, and ethyne, the simplest alkyne, are



Ethene (an alkene)

Ethyne (an alkyne)

In this chapter we study the structure and physical properties of alkenes. Alkynes are discussed separately in Chapter 6.

The third class of unsaturated hydrocarbons are the **aromatic hydrocarbons.** The term "aromatic" is mainly of historical significance. Many fragrant (hence the term "aromatic") compounds were discovered and as the structural formulas of these were

determined, it was found that many were derivatives of benzene and hence the presence of a benzene ring was thought to be a characteristic of many "aromatic" compounds. The Lewis structure of benzene, the simplest aromatic hydrocarbon, is

Benzene
(the simplest aromatic hydrocarbon)

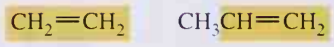
Benzene and other aromatic hydrocarbons are discussed separately in Chapters 15 and 16.

4.1 Nomenclature

Alkenes are named using the IUPAC system, but as we shall see, many alkenes are still referred to by their common names.

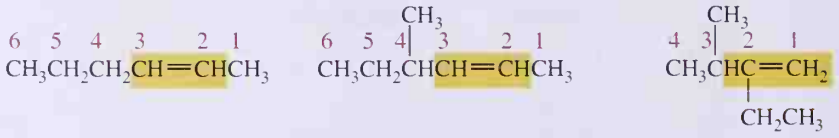
A. IUPAC Names

IUPAC names of alkenes are formed by changing the **-an-** infix of the parent alkane to **-en-** (Section 2.5). Hence, $CH_2{=}CH_2$ is named ethene, and $CH_3CH{=}CH_2$ is named propene.



Ethene Propene

Ethene and propene can contain a double bond in only one position. In higher alkenes where isomers exist that differ in location of the double bond, a numbering system must be used. According to the IUPAC system, the longest carbon chain that contains the double bond is numbered to give the carbon atoms of the double bond the lowest possible numbers. The location of the double bond is indicated by the number of the first carbon of the double bond. Branched or substituted alkenes are named in a manner similar to alkanes. Carbon atoms are numbered, substituent groups are located and named, the double bond is located, and the main chain is named.



2-Hexene 4-Methyl-2-hexene 2-Ethyl-3-methyl-1-butene

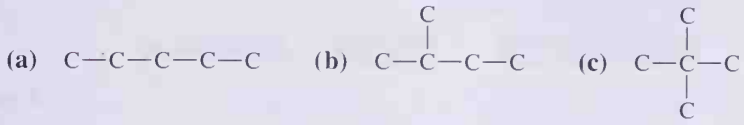
Note that there is a chain of five carbon atoms in 2-ethyl-3-methyl-1-butene. However, because the longest chain that contains the double bond has only four carbons, the parent hydrocarbon is butane and the molecule is named as a disubstituted 1-butene.

EXAMPLE 4.1

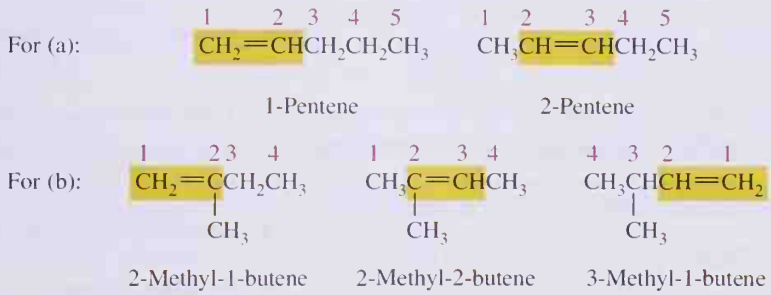
Draw structural formulas for all alkenes of molecular formula C_5H_{10}. Give each an IUPAC name.

Solution

Approach this type of problem systematically. First draw the carbon skeletons possible for molecules of five carbon atoms. There are three such skeletons.

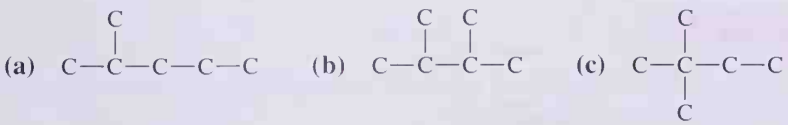


Because skeleton (c) cannot contain a carbon-carbon double bond (the central carbon atom already has four bonds to it), we need consider only skeletons (a) and (b) in answer to this problem. Next, locate the double bond between carbon atoms along the chain. For carbon skeleton (a), there are two possible locations for the double bond, and for carbon skeleton (b), there are three possible locations. Finally, add hydrogens to complete the tetravalence of carbon, and give the correct molecular formula. To name these alkenes, number the carbon chain from the direction that gives the carbons of the double bond the lowest numbers, and then name and give a number to each substituent.



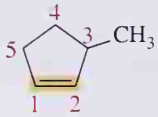
PROBLEM 4.1

Draw structural formulas for all alkenes of molecular formula C_6H_{12} that have the following carbon skeletons. Give each alkene an IUPAC name.

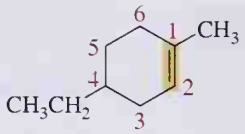


■

In naming **cycloalkenes,** the carbon atoms of the ring multiple bond are numbered 1 and 2 in the direction that gives the substituent encountered first the smallest number.

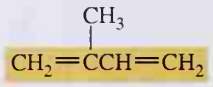


3-Methylcyclopentene



4-Ethyl-1-methylcyclohexene

Alkenes that contain more than one double bond are named as alkadienes, alkatrienes, and so on.

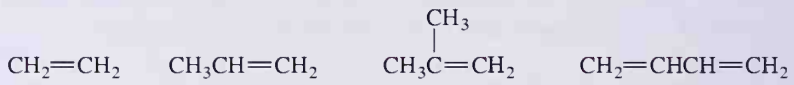


2-Methyl-1,3-butadiene
(Isoprene)

1,4-Pentadiene

B. Common Names

Many alkenes, particularly those of low molecular weight, are known almost exclusively by their common names.



IUPAC name:	Ethene	Propene	2-Methylpropene	1,3-Butadiene
Common name:	Ethylene	Propylene	Isobutylene	Butadiene

Furthermore, the common names **methylene, vinyl,** and **allyl** are often used to show the presence of the alkenyl groups in the following table.

Alkenyl Group	Common Name	Example
$CH_2=$	methylene	CH_2Cl_2 Methylene chloride
$CH_2=CH-$	vinyl	$CH_2=CHCl$ Vinyl chloride
$CH_2=CHCH_2-$	allyl	$CH_2=CHCH_2Cl$ Allyl chloride

4.2 Structure

We will discuss both the valence bond approach and the molecular orbital approach to understanding covalent bonding in alkenes.

A. Valence Bond Approach

In Section 1.8C, we described the formation of carbon-carbon double bonds in terms of the overlap of atomic orbitals. To bind with three other atoms, carbon uses sp^2 hybrid orbitals

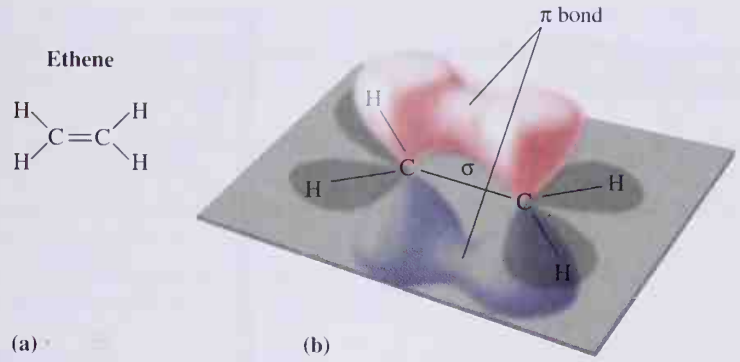
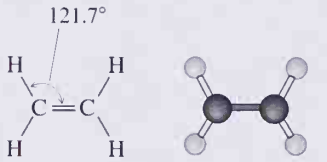
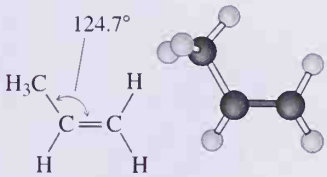


Figure 4.1
Bonding in ethene. (a) Lewis structure and (b) orbital overlap model showing sigma and pi bonds.

formed by combination of one 2*s* orbital and two 2*p* orbitals. The axes of the three sp^2 orbitals lie in a plane at angles of 120° to one another. The remaining 2*p* orbital of carbon is not hybridized and its axis lies perpendicular to the plane created by the three sp^2 orbitals. A carbon-carbon double bond consists of one sigma bond formed by the overlap of sp^2 hybrid orbitals and one pi bond formed by the overlap of two unhybridized 2*p* orbitals (Figure 4.1). Using the valence bond model of a carbon-carbon double bond, we predict a value of 120° for the H—C—C bond angles in ethene. The observed angle is 121.7°, a value close to that predicted. In substituted alkenes, deviations from the predicted angle of 120° may be somewhat larger. The C—C—C bond angle in propene, for example, is 124.7°.



Ethene



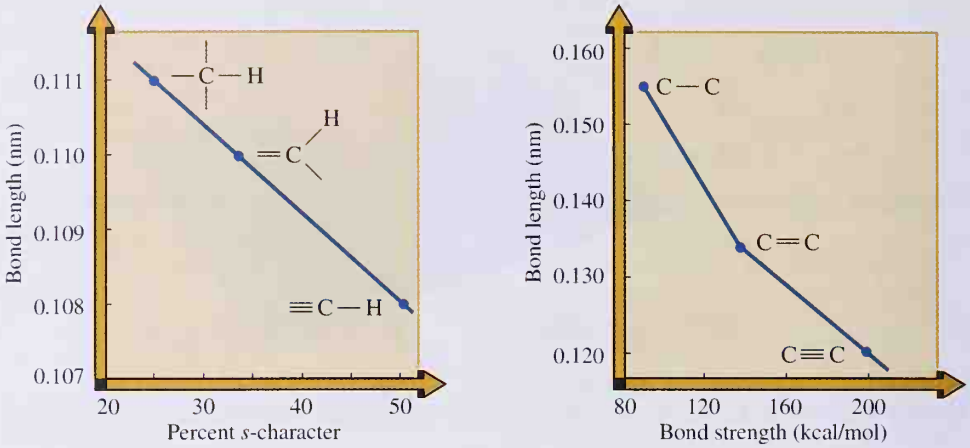
Propene

B. Bond Lengths and Strengths of Alkanes, Alkenes, and Alkynes

Given in Table 4.1 are values of bond lengths and bond strengths (bond dissociation energies) for ethane, ethene, and ethyne.

Table 4.1 Bond lengths and bond dissociation energies for ethane, ethene, and ethyne

Molecule	Bond	Bond Orbital Overlap	Bond Length (nm)	Bond Strength (kcal/mol)
H H H—C—C—H H H	C—C	sp^3–sp^3	0.154	88
	C—H	sp^3–1*s*	0.111	98
H H C=C H H	C=C	sp^2–sp^2, 2*p*–2*p*	0.134	146
	C—H	sp^2–1*s*	0.110	104
H—C≡C—H	C≡C	*sp*–*sp*, two 2*p*–2*p*	0.121	200
	C—H	*sp*–1*s*	0.108	125



As you study Table 4.1, note the following points:

1. Carbon-carbon triple bonds are shorter than carbon-carbon double bonds, which in turn are shorter than carbon-carbon single bonds. This effect is most often explained in terms of orbital hybridization and the percent *s*-character in the orbitals overlapping to form the sigma bond between the two atoms. A 2*s* orbital lies at a lower energy level than a 2*p* orbital, and, therefore, electrons in it are held more tightly than those in a 2*p* orbital. Consequently, the greater the percent *s*-character in an atomic orbital, the more tightly electrons in it are held and the shorter the bond. The relative lengths of carbon-carbon triple, double, and single bonds correlate with the fact that the percent *s*-character in an *sp* orbital is 50%, that in an sp^2 orbital is 33.3%, and that in an sp^3 orbital is 25%.
2. The C—H bond in ethyne is shorter than that in ethene, which in turn is shorter than that in ethane. The relative lengths of these C—H bonds also correlate with the percent *s*-character in the atomic orbital of carbon forming the C—H sigma bond; the greater the percent *s*-character, the shorter the bond.

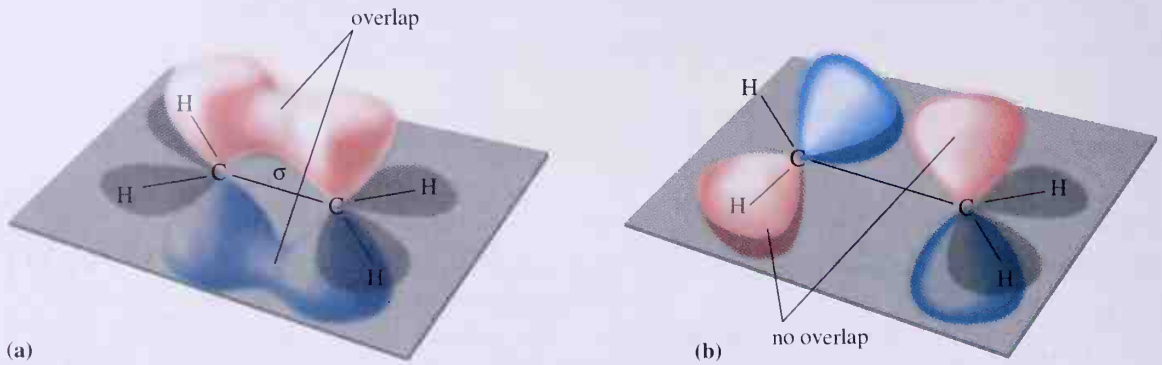


Figure 4.2
Restricted rotation about a carbon-carbon double bond. (a) Orbital overlap model showing the pi bond. (b) The pi bond is broken by rotating the plane of one H—C—H group by 90° with respect to the plane of the other H—C—H group.

3. There is a correlation between bond length and bond strength; the shorter the bond, the stronger the bond. A carbon-carbon triple bond is the shortest carbon-carbon bond; it is also the strongest. The carbon-hydrogen bond in ethyne is the shortest; it is also the strongest.
4. Although a carbon-carbon double bond is stronger than a carbon-carbon single bond, it is not twice as strong. It is estimated that the strength of the pi bond in ethene is approximately 63 kcal/mol, a value which corresponds to the energy necessary to rotate one carbon by 90° with respect to the other, that is, to the point where zero overlap occurs between $2p$ orbitals on adjacent carbons (Figure 4.2). The strength of the sigma bond is approximately 85 kcal/mol.

C. Molecular Orbital Description of a Carbon-Carbon Double Bond

According to molecular orbital theory (Section 1.9), parallel $2p$ atomic orbitals on adjacent carbons combine to form two molecular orbitals: one bonding, the other antibonding (Figure 4.3). The pi bonding MO arises from addition of the wave functions of two $2p$ orbitals (combination of lobes of the same sign) and results in the greatest electron density in two regions between the carbon nuclei: one above the sigma bond framework, the other below it. The pi antibonding MO arises from subtraction of the wave functions of the two $2p$ orbitals (overlap of lobes of opposite signs) and places greatest electron density outside of the region between the two carbon nuclei.

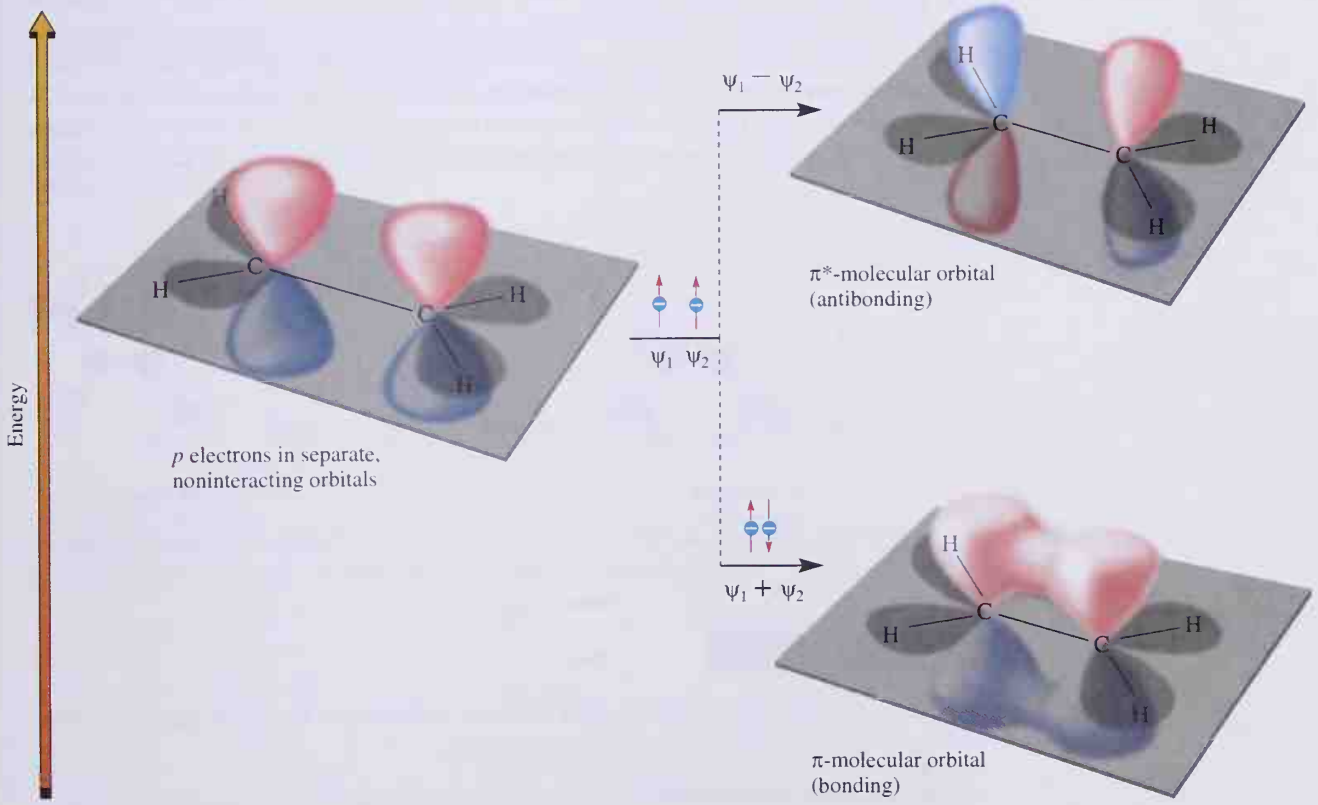


Figure 4.3
Formation of pi bonding and antibonding molecular orbitals in ethene.

The pi bonding MO is lower in energy than the uncombined atomic orbitals, and in the ground state of the ethene molecule, this molecular orbital is filled. The pi antibonding MO is higher in energy than the uncombined atomic orbitals and is unoccupied in the ground state.

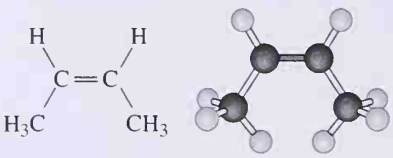
4.3 *Cis-Trans* Isomerism

Stereoisomers have the same molecular formula and the same order of attachment of atoms, but a different arrangement of atoms in space. *Cis-trans* isomerism is one type of stereoisomerism.

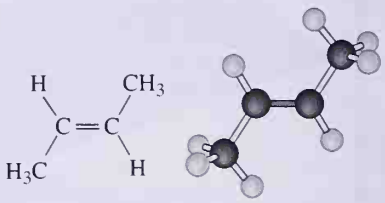
A. The Existence of *Cis-Trans* Isomers

In cycloalkanes, *cis-trans* isomerism depends on the arrangement of substituent groups on a ring (Section 2.7); in alkenes, *cis-trans* isomerism depends on the arrangement of groups on a double bond. The structural feature that makes possible the existence of *cis-trans* isomerism in alkenes is restricted rotation about the double bond (see Figure 4.2).

An alkene shows *cis-trans* isomerism if each carbon of the double bond has two different groups attached to it. Ethene, propene, 1-butene, and 2-methylpropene have only one possible arrangement of groups about the double bond. In 2-butene two possible arrangements exist. In one arrangement, the two methyl groups are on the same side of the double bond; this isomer is called *cis*-2-butene. In the other arrangement, the two methyl groups are on opposite sides of the double bond; this isomer is called *trans*-2-butene. *Cis* and *trans* isomers are different compounds and have different physical and chemical properties. The *cis* and *trans* isomers of 2-butene differ in melting points by 33°C and in boiling points by 3°C.



***cis*-2-Butene**
mp −139°C
bp 4°C



***trans*-2-Butene**
mp −106°C
bp 1°C

EXAMPLE 4.2

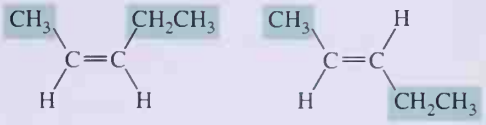
Which of the following alkenes show *cis-trans* isomerism? For each that does, draw structural formulas for both isomers.

(a) $CH_2{=}CHCH_2CH_2CH_3$ (b) $CH_3CH{=}CHCH_2CH_3$

(c) $CH_2{=}C(CH_3)CH_2CH_3$

Solution

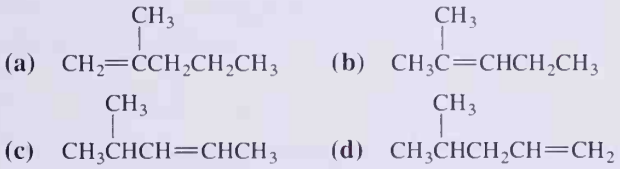
Of the three alkenes, only (b) 2-pentene shows *cis-trans* isomerism. In both (a) 1-pentene and (c) 2-methyl-1-butene, one carbon of the double bond has two identical groups.



cis-2-Pentene *trans*-2-Pentene

PROBLEM 4.2

Which of the following alkenes show *cis-trans* isomerism? For each that does, draw structural formulas for the isomers.

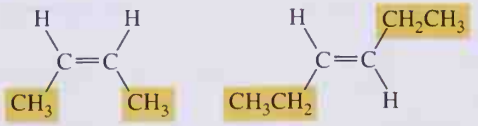


B. Methods for Designating Configurations

To designate the configuration of alkenes, we can use the *cis-trans* system or the E-Z system.

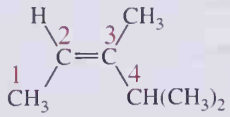
The *Cis-Trans* System

The most common method for specifying configuration in alkenes uses the prefixes *cis-* and *trans-*. There is no doubt whatsoever which isomers are intended by the names *cis*-2-butene and *trans*-3-hexene.



cis-2-Butene *trans*-3-Hexene

For other alkenes, the assignments of *cis* and *trans* are not as obvious. Following is a structural formula for one *cis-trans* isomer of 3,4-dimethyl-2-pentene.



3,4-Dimethyl-2-pentene

Should it be named *cis-* because carbon atoms 1 and 4 of the parent chain are on the same side of the double bond, or should it be named *trans* because the methyl groups on the double bond are on opposite sides? According to IUPAC rules, it should be named *cis* because of the *cis* orientation of the main carbon chain about the double bond.

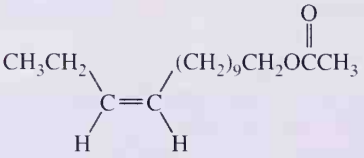
CHEMISTRY IN ACTION

The Case of the Iowa and New York Strains of the European Corn Borer

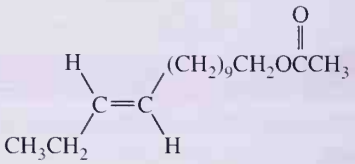
The European corn borer, *Pyrausta nubilalis*. *(Runk/Schoenberger/Grant Heilman Photography, Inc.)*

Although humans communicate largely by sight and sound, chemicals are the primary mode of communication for the vast majority of other species in the animal world. Often communication within a species is specific for one of two configurational isomers. For example, a member of a given species responds to a *cis* isomer of a chemical but not to the *trans* isomer. Or, alternatively, it might respond to a quite precise blend of *cis* and *trans* isomers but not other blends of these same isomers.

Several groups of scientists have studied the components of the sex pheromones of both the Iowa and New York strains of the European corn borer. Females of these closely related species secrete the sex attractant 11-tetradecenyl acetate. Males of the Iowa strain show maximum response to a mixture containing 96% of the *cis* isomer and 4% of the *trans* isomer. When the pure *cis* isomer is used alone, males are only weakly attracted. Males of the New York strain show an entirely different response pattern. They respond maximally to a mixture containing 3% of the *cis* isomer and 97% of the *trans* isomer.



cis-11-Tetradecenyl acetate



trans-11-Tetradecenyl acetate

There is evidence that optimum response to a narrow range of stereoisomers as we see here is widespread in nature and that most insects maintain species isolation, at least for mating and reproduction, by the stereochemistry of their pheromones.

See Klun, J. A., Chapman, O. L. and Beroza, M. *Science*, **181**:661 (1973).

The E-Z System

The configuration about any carbon-carbon double bond can be specified unambiguously using a set of **priority rules** devised in 1964 by R. S. Cahn of England, C. K. Ingold of England, and V. Prelog of Switzerland. These rules have since been incorporated into the IUPAC system of nomenclature and, when applied to naming alkenes, give what is known as the **E-Z system.**

1. Each atom is assigned a priority. Priority is based on atomic number; the higher the atomic number, the higher the priority. Following are several substituents arranged in order of increasing priority. The atomic number of the atom determining priority is shown in parentheses.

(1) (6) (7) (8) (16) (17) (35) (53)
—H, —CH_3, —NH_2, —OH, —SH, —Cl, —Br, —I

Increasing priority

2. For isotopes, the higher the atomic mass, the higher the priority. Deuterium (hydrogen-2), for example, has a higher priority than protium (hydrogen-1).

^{1}H ^{2}H ^{3}H ^{12}C ^{13}C ^{14}C ^{16}O ^{17}O ^{18}O

Increasing priority

3. If priority cannot be assigned on the basis of atomic number or atomic mass considering the first atom of a group, then look at the next set of atoms and continue until a priority can be assigned. Priority is assigned at the first point of difference. Following are a series of groups, arranged in order of increasing priority. Also shown is the atomic number of the atom on which the assignment of priority is based.

1 2 6 7 8 17
—CH_2H —CH_2D —CH_2CH_3 —CH_2NH_2 —CH_2OH —CH_2Cl

Increasing priority

4. In the case of double and triple bonds, atoms participating in the double or triple bond are considered to be bonded to an equivalent number of similar atoms by single bonds, that is, atoms of double and triple bonds are replicated

Example of Double or Triple Bond	Is Treated As
—CH=CH_2	—CH(C)—CH_2(C)
—C(=O)—H	—C(O—C)(—O)—H, replicated atoms
—C≡C—H	—C(C)—C(C)—H

EXAMPLE 4.3

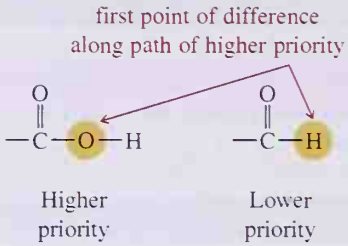
Assign priorities to the following groups and indicate the basis on which assignment is made.

(a) —CO_2H and —CHO **(b)** —CH=CH_2 and —$CH(CH_3)_2$

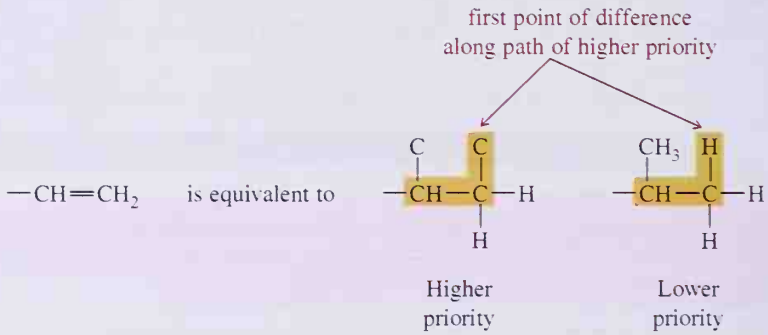
Solution

(a) The first point of difference is —OH on the carboxyl group compared to —H on

the aldehyde group. The carboxyl group, therefore, is higher in priority than the aldehyde group.



(b) The atomic numbers of the atoms along the path of higher priority for the vinyl group are 6,6,6. Comparable atomic numbers for the isopropyl group are 6,6,1. The vinyl group is higher in priority than the isopropyl group.

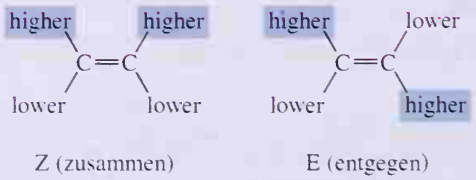


PROBLEM 4.3

Assign priorities to the following groups and explain the basis for the assignment.

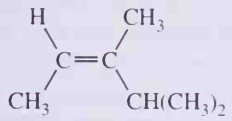
(a) $-CH_2NO_2$ and $-NO_2$ **(b)** $-C{\equiv}CH$ and $-C{\equiv}N$

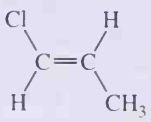
To use the E-Z system, first assign priority to the two atoms or groups of atoms on one carbon of the double bond, and then repeat the process for the two atoms or groups of atoms on the other carbon. If the groups of higher priority are on the same side of the double bond, the alkene is designated **Z** (from the German word *zusammen*, together). If the groups of higher priority are on opposite sides of the double bond, the alkene is designated **E** (from the German word *entgegen*, opposite).

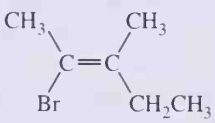


EXAMPLE 4.4

Name each alkene and specify configuration by the E-Z system.

(a) 

(b) 

(c) 

Solution

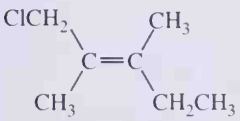
(a) The alkene is 3,4-dimethyl-2-pentene. The group of higher priority on carbon 2 is methyl; that of higher priority on carbon 3 is isopropyl. Because the groups of higher priority are on the same side of the carbon-carbon double bond, the alkene has the Z configuration. Its name is (Z)-3,4-dimethyl-2-pentene. Using the *cis-trans* system, it is named *cis*-3,4-dimethyl-2-pentene.

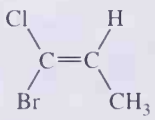
(b) The alkene is 1-chloropropene. Groups of higher priority on carbons 1 and 2 are —Cl and —CH_3. Because these groups are on opposite sides of the double bond, the configuration of this alkene is E and its name is (E)-1-chloropropene.

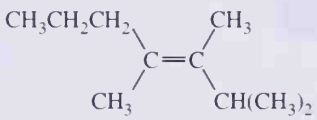
(c) The alkene is 2-bromo-3-methyl-2-pentene. Br and —CH_2CH_3, groups of higher priority, are on the same side, and the alkene has a Z configuration. Its correct name is (Z)-2-bromo-3-methyl-2-pentene. Note that the parent chain of carbon atoms (1-2-3-4-5) extends on opposite sides of the double bond, and in the *cis-trans* system its name is *trans*-2-bromo-3-methyl-2-pentene.

PROBLEM 4.4

Name the following alkenes and specify configuration by the E-Z system.

(a) 

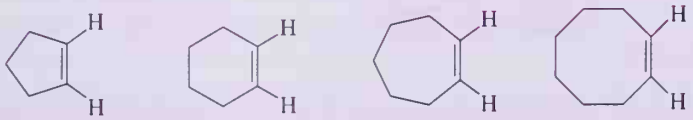
(b) 

(c) 

We use the *cis-trans* system for alkenes in which it is clear which is the main carbon chain. We use the E-Z system in all other cases.

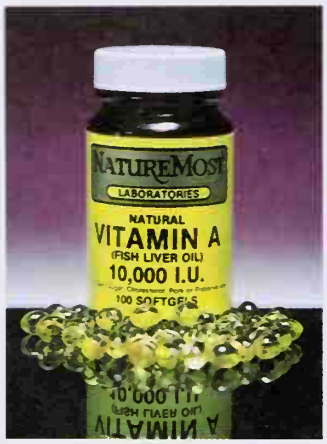
C. *Cis-Trans* Isomerism in Cycloalkenes

Following are structural formulas for four cycloalkenes:



Cyclopentene Cyclohexene Cycloheptene Cyclooctene

In these representations, the configuration about each double bond is clearly *cis*. Is it possible to have a *trans* configuration in these and larger cycloalkenes? To date, *trans*-cyclooctene is the smallest *trans*-cycloalkene that has been prepared in pure form that is stable at room temperature. Yet, even in this *trans*-cycloalkene, there is considerable strain. *cis*-Cyclooctene is more stable than its *trans* isomer by 9.1 kcal/mol. *trans*-Cycloheptene and *trans*-cyclohexene have been detected, but they are so unstable that they have never been isolated in pure form under ordinary conditions. Reasons for the instability of *trans* isomers of cyclohexene and cycloheptene can be appreciated by attempting to make molecular models of these compounds. Formation of these *trans* isomers is possible only if the carbon atoms attached directly to the double bond (carbons 3 and 6 of the cyclohexene ring, carbons 3 and 7 of the cycloheptene ring) are *trans* to each other. Closing the ring between these atoms is possible only by introducing a high degree of angle strain into the completed ring or by rotating the planes of the two carbons of the double bond to such a degree that there is little remaining overlap between the two 2*p* orbitals forming the pi bond or by doing both.

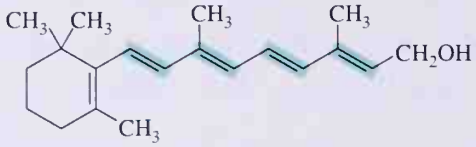


One International Unit (IU) of Vitamin A is 0.30 μg, which is equivalent to 3.3×10^6 IU/g. The Recommended Daily Allowance (RDA) is 5000 IU. *(Charles D. Winters)*

D. *Cis-Trans* Isomerism in Dienes, Trienes, and So Forth

Thus far we have considered *cis-trans* isomerism in compounds containing only one carbon-carbon double bond. For an alkene with one carbon-carbon double bond that can show *cis-trans* isomerism, two *cis-trans* isomers exist. For an alkene with n carbon-carbon double bonds, each of which can show *cis-trans* isomerism, $\mathbf{2^n}$ *cis-trans* isomers are possible.

An example of a biologically important molecule for which a number of *cis-trans* isomers exist is vitamin A. Four carbon-carbon double bonds are present in the chain of atoms attached to the substituted cyclohexene ring, and each has the potential for *cis-trans* isomerism. There are 2^4, or 16, *cis-trans* isomers possible for this structural formula. Vitamin A is the all-trans isomer.

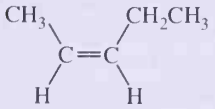
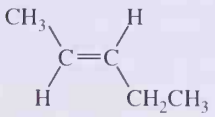
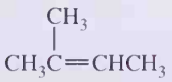


Vitamin A (retinol)
(all-*trans* isomer)

4.4 Physical Properties

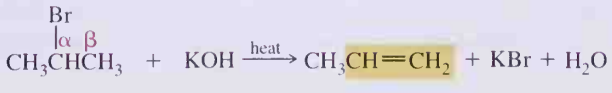
Because alkenes are virtually nonpolar compounds and the only attractive interactions between molecules are dispersion forces, the physical properties of alkenes are similar to those of alkanes (Section 2.8). Alkenes of two, three, and four carbon atoms are gases at room temperature. Those of five or more carbons are colorless liquids less dense than water. Alkenes are insoluble in water but soluble in one another, in other nonpolar organic liquids, and in ethanol. Table 4.2 lists physical properties of some alkenes.

Table 4.2 Physical properties of some alkenes

IUPAC Name	Structural Formula	mp (°C)	bp (°C)
ethene	$CH_2{=}CH_2$	−169	−104
propene	$CH_3CH{=}CH_2$	−185	−47
1-butene	$CH_3CH_2CH{=}CH_2$	−185	−6
1-pentene	$CH_3CH_2CH_2CH{=}CH_2$	−138	30
cis-2-pentene		−151	37
trans-2-pentene		−156	36
2-methyl-2-butene		−134	39

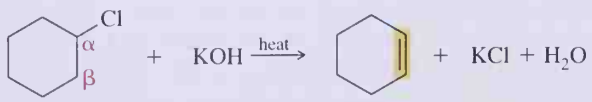
4.5 Preparation: Dehydrohalogenation of Alkyl Halides

Alkenes are often prepared in the laboratory by a process called β-elimination. In **β-elimination,** a small molecule (most commonly HOH, HCl, HBr, or HI) is split out or eliminated from adjacent carbons of a larger molecule. The carbon bearing the halogen or hydroxyl group is designated the α-carbon, and the carbon or carbons immediately adjacent to the α-carbon are called β-carbons. Removal of HCl, HBr, or HI from a haloalkane (alkyl halide) is called **dehydrohalogenation.** Dehydrohalogenation of 2-bromopropane by KOH or another strong base gives propene.



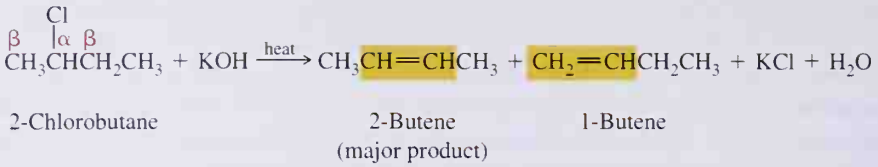
2-Bromopropane Propene

In this reaction, two sigma bonds are broken (C—H and C—Br), and one new pi bond (C=C) and one new sigma bond (H—OH) are formed. Dehydrohalogenation of chlorocyclohexane by a strong base gives cyclohexene.



Chlorocyclohexane Cyclohexene

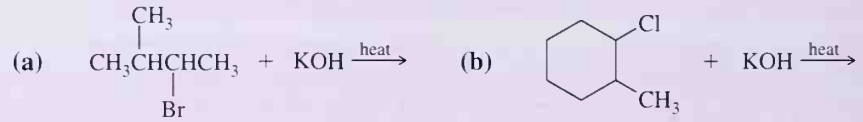
Often, dehydrohalogenation of a haloalkane leads to the formation of alkene constitutional isomers. One such example is base-induced dehydrochlorination of 2-chlorobutane. β-Elimination from carbons 2 and 3 gives 2-butene; alternatively, β-elimination from carbons 1 and 2 gives 1-butene. In practice, both alkenes are formed, but 2-butene is the major product.



The regioselectivity of this type of β-elimination was first set forth in 1875 by Alexander Zaitsev of the University of Kazan (Russia). According to **Zaitsev's rule,** the major product from dehydrohalogenation of a haloalkane is the alkene with the most substituents on the carbon-carbon double bond. We discuss β-elimination reactions in more detail in Chapter 10 and the reasons for the predominance of one product over other possible products. For the moment, however, we are concerned only with identifying all possible alkene products and selecting from among them the most substituted alkene.

EXAMPLE 4.5

Draw structural formulas for the alkenes formed on dehydrohalogenation of the following haloalkanes. Predict which alkene is the major product.

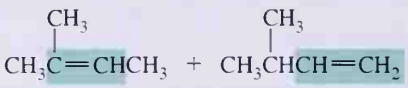


2-Bromo-3-methylbutane

1-Chloro-2-methylcyclohexane

Solution

(a) Elimination of HBr from carbons 1 and 2 of 2-bromo-3-methylbutane gives 3-methyl-1-butene; from carbons 2 and 3 it gives 2-methyl-2-butene.



2-Methyl-2-butene (major product)

3-Methyl-1-butene

The major product, 2-methyl-2-butene, has three alkyl substituents (three methyl groups) on the carbon-carbon double bond. 3-Methyl-1-butene has only one alkyl substituent (an isopropyl group) on the carbon-carbon double bond.

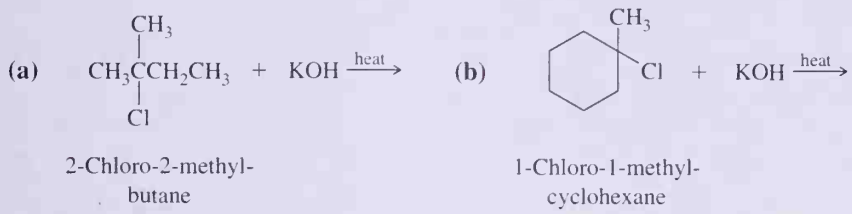
(b) The major product, 1-methylcyclohexene, has three alkyl substituents on the double bond. The minor product, 3-methylcyclohexene, has only two substituents on the double bond.

1-Methylcyclohexene (major product)

3-Methylcyclohexene

PROBLEM 4.5

Draw structural formulas for the alkenes formed on dehydrohalogenation of the following haloalkanes. Where two alkenes are possible, predict which is the major product.



2-Chloro-2-methylbutane

1-Chloro-1-methylcyclohexane

4.6 Naturally Occurring Alkenes: Terpene Hydrocarbons

The characteristic structural feature of a **terpene** is a carbon skeleton that can be divided into two or more units all of which are identical with the carbon skeleton of isoprene. Carbon 1 of an **isoprene unit** is called the tail; carbon 4 is called the head (Figure 4.4).

There are several important reasons for looking at this group of compounds. First, terpenes are among the most widely distributed compounds in the biological world. The number of terpenes found in bacteria, plants, and animals is staggering. Second, terpenes provide a glimpse of the wondrous diversity that nature can generate from a simple carbon skeleton. Third, terpenes illustrate an important principle of the molecular logic of living systems: in building large molecules, small subunits are strung together by an iterative process and then chemically modified by precise enzyme-catalyzed reactions. Chemists use the same principles in the laboratory, but their methods do not have the precision and selectivity of the enzyme-catalyzed reactions of cellular systems.

Probably the terpenes most familiar to you, at least by odor, are components of the so-called essential oils obtained by steam distillation or ether extraction of various parts of

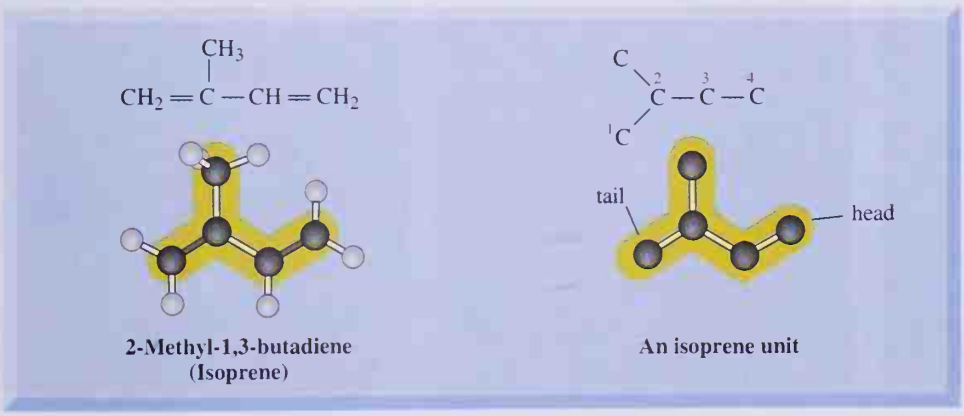


Figure 4.4
Structural formula of 2-methyl-1,3-butadiene (isoprene) and the carbon skeleton of an isoprene unit.

California laurel, *Umbellularia californica*, a source of myrcene. *(© Dan Suzio)*

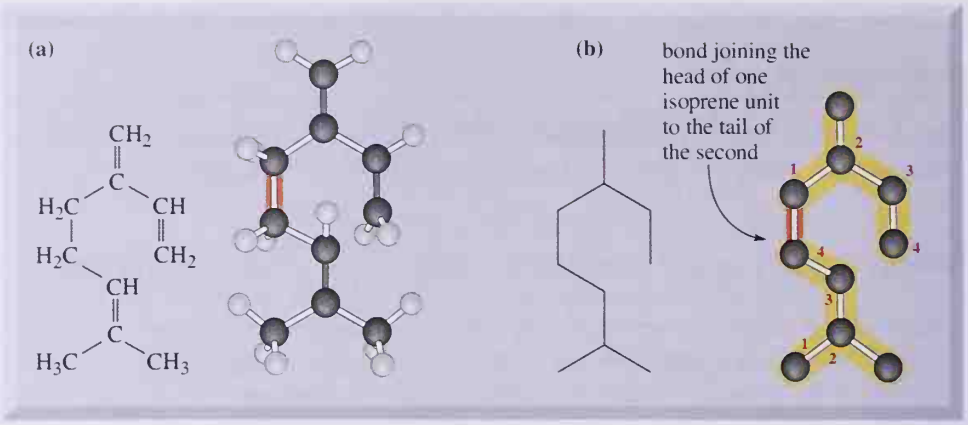


Figure 4.5
Myrcene, a monoterpene. (a) The structural formula of myrcene. (b) The ball-and-stick model of myrcene divided to show two isoprene units joined by a carbon-carbon bond between the head of one unit and the tail of the other.

plants. Essential oils contain the relatively low-molecular-weight substances that are in large part responsible for characteristic plant fragrances (essences). Many essential oils, particularly those from flowers, are used in perfumes.

One example of a terpene obtained from an essential oil is myrcene, $C_{10}H_{16}$, a component of bayberry wax and oils of bay and verbena. Myrcene is a triene with a parent chain of eight carbon atoms and two one-carbon branches (Figure 4.5[a]).

Head-to-tail linkages of isoprene units are vastly more common in nature than are the alternative head-to-head or tail-to-tail patterns. Figure 4.6 shows structural formulas of six more terpenes. Geraniol and the aggregating pheromone of the bark beetle have the same carbon skeleton as myrcene. In addition, each has an —OH (hydroxyl) group. In the last

Lemongrass, a source of geraniol. *(G. Büttner/ Naturbild/Okapia/Photo Researchers, Inc.)*

Orange peel, a source of limonene. *(Charles D. Winters)*

A camphor tree, *Cinnamomum camphora*. *(Peter G. Aitken/Photo Researchers, Inc.)*

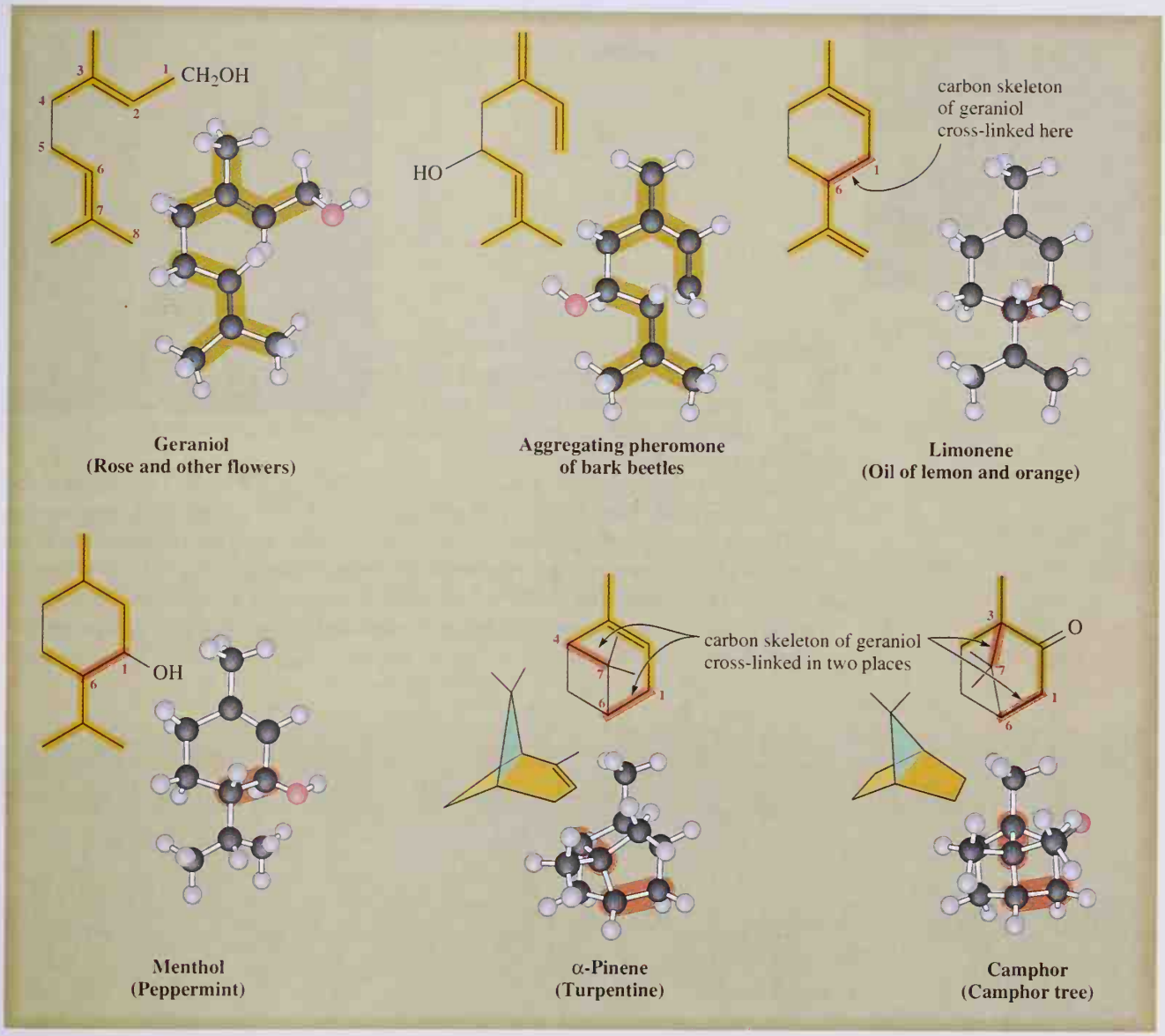


Figure 4.6
Several monoterpenes. Each is divisible into two isoprene units joined by a head-to-tail bond and then cross-linked in one or more places.

four terpenes of Figure 4.6, the framework of carbon atoms present in myrcene, geraniol, and the bark beetle pheromone is cross-linked to give cyclic structures. To help you identify the points of cross linkage and ring formation, the carbon atoms of the geraniol skeleton are numbered 1 through 8. This numbering pattern is used in the remaining terpenes to show points of cross linking. Terpenes are subdivided into subgroups depending on the number of isoprene units as follows:

A bark beetle on a lodgepole pine trunk. *(© William E. Ferguson)*

Subgroup	Number of Isoprene Units	Number of Carbon Atoms
monoterpene	two	10
sesquiterpene	three	15
diterpene	four	20
triterpene	six	30
tetraterpene	eight	40

Shown in Figure 4.7 are structural formulas of three sesquiterpenes (C_{15}). For reference, the carbon atoms of the parent chain of farnesol are numbered 1 through 12. A bond between carbon atoms 1 and 6 of this skeleton gives the carbon skeleton of zingiberene. You should try to discover for yourself what pattern of cross-linking gives the carbon skeleton of caryophyllene.

Vitamin A (Section 4.3D), a diterpene of molecular formula $C_{20}H_{30}O$, consists of four isoprene units linked head to tail and cross-linked at one point to form a six-member ring.

The synthesis of substances in living systems is a fascinating area of research and one of the links between organic and biochemistry. However tempting it might be to propose that nature synthesizes terpenes by joining together molecules of isoprene, this is not the way it is done. A key intermediate in the biosynthesis of terpenes is the pyrophosphate ester of 3-methyl-3-butene-1-ol.

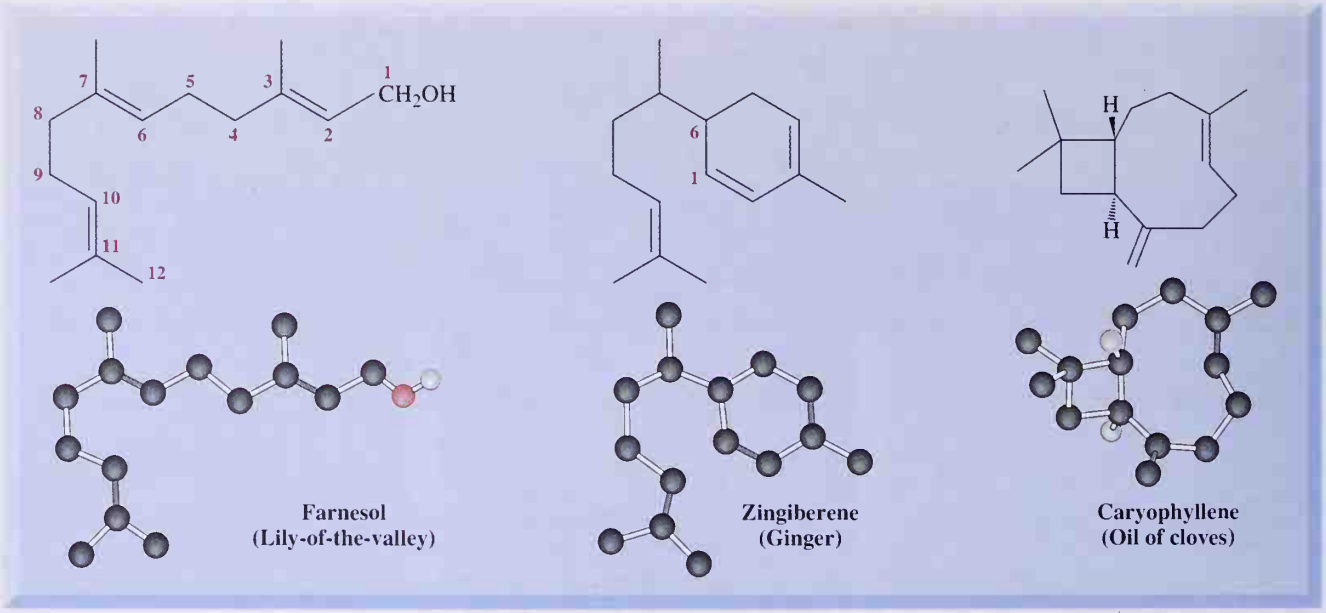
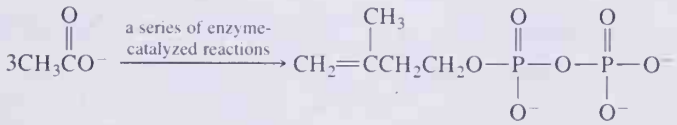


Figure 4.7
Three sesquiterpenes.

Lily-of-the-valley, *Convallaria majalis*. *(Barry L. Runk/Grant Heilman Photography, Inc.)*



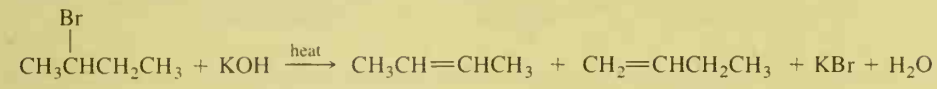
Acetate ion — 3-Methyl-3-butene-1-ol pyrophosphate

We discuss the synthesis of this compound and its transformation into monoterpenes, diterpenes, and so forth in Chapters 20 and 23.

SUMMARY OF KEY REACTIONS

1. Dehydrohalogenation of Alkyl Halides (Section 4.5)

Where it is possible to obtain isomeric alkenes by dehydrohalogenation, the alkene having more substituents on the carbon-carbon double bond usually predominates (Zaitsev's rule).



2-Bromobutane — 2-Butene (major product) — 1-Butene

ADDITIONAL PROBLEMS

Nomenclature

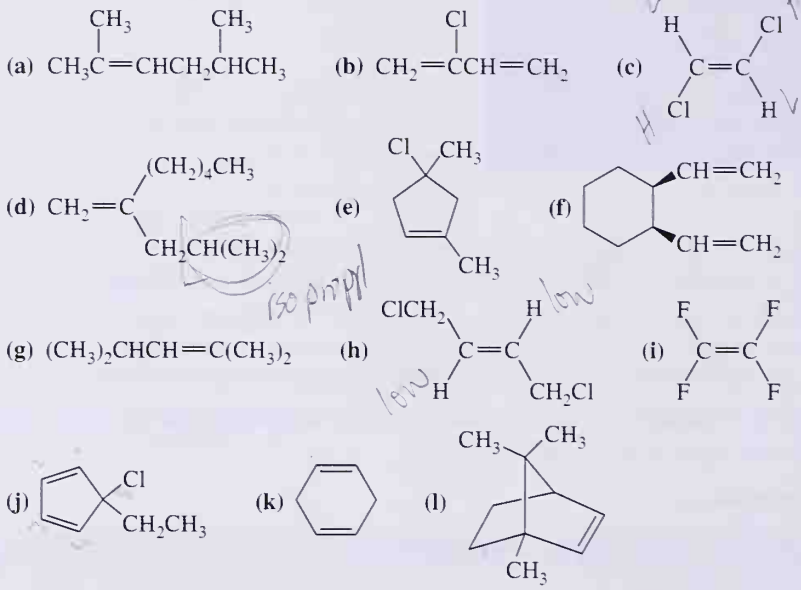
4.6 Draw structural formulas for the following compounds.

(a) 2-Methyl-3-hexene **(b)** 2-Methyl-2-hexene

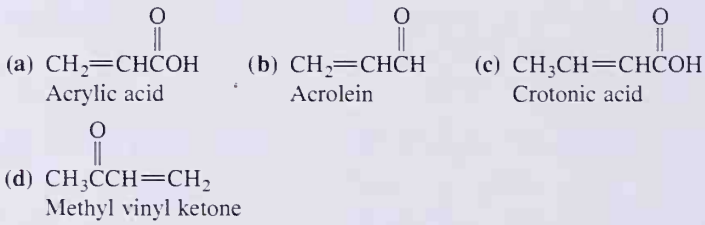
(c) 2-Methyl-1-butene **(d)** 3-Ethyl-3-methyl-1-pentene

(e) 2,3-Dimethyl-2-butene
(f) 1-Pentene
(g) 2-Pentene
(h) 1-Chloropropene
(i) 2-Chloropropene
(j) 3-Methylcyclohexene
(k) 1-Chlorocyclohexene
(l) 1-Isopropyl-4-methylcyclohexene
(m) Tetrachloroethylene
(n) 2,6-Dimethyl-2,6-octadiene
(o) Allylcyclopropane
(p) Vinylcyclopropane
(q) Bicyclo[2.2.1]-2-heptene
(r) Bicyclo[4.4.0]-1-decene

4.7 Name the following compounds.

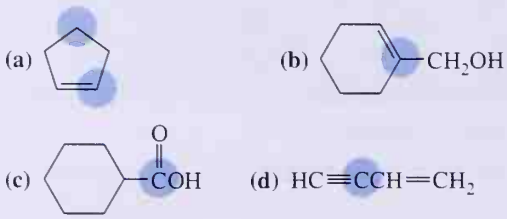


4.8 Following are structural formulas and common names for four molecules that contain both a carbon-carbon double bond and another functional group. Give each an IUPAC name.



Structure: Valence Bond Theory

4.9 Predict all bond angles about each circled carbon atom. To make these predictions, use the valence-shell electron-pair repulsion (VSEPR) model (Section 1.3).



4.10 For each circled carbon atom in the previous problem, identify which atomic orbitals are used to form each sigma bond and which are used to form each pi bond.

4.11 Following is the structural formula of 1,2-propadiene (allene).

$$CH_2{=}C{=}CH_2$$

1,2-Propadiene
(Allene)

(a) State the orbital hybridization of each carbon atom.

(b) Describe each carbon-carbon double bond in terms of the overlap of atomic orbitals.

(c) Predict all bond angles in allene.

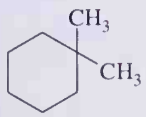
(d) Draw a stereorepresentation showing the shape of this molecule.

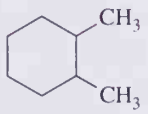
4.12 Following are lengths for a series of C—C single bonds. Propose an explanation for the differences in bond lengths.

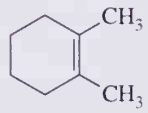
Structure	Length of C—C Single Bond (nm)
CH_3CH_3	0.1537
$CH_2{=}CHCH_3$	0.1510
$CH_2{=}CHCH{=}CH_2$	0.1465
$HC{\equiv}CCH_3$	0.1459

Cis-Trans Isomerism

4.13 Which of the following molecules show *cis-trans* isomerism. For each that does, draw the *cis* isomer.

(a) 

(b) 

(c) 

4.14 Which of the molecules in Problem 4.6 show *cis-trans* isomerism? For each that does, draw the *trans* isomer.

4.15 Which of the molecules in Problem 4.7 show *cis-trans* isomerism? For each that does, draw the *trans* isomer.

4.16 How many *cis-trans* isomers are possible for the following natural products?

(a) Geraniol (Figure 4.6) **(b)** Limonene (Figure 4.6)

(c) α-Pinene (Figure 4.6) **(d)** Farnesol (Figure 4.7)

(e) Zingiberene (Figure 4.7)

4.17 Draw structural formulas for all compounds of molecular formula C_5H_{10} that are

(a) Alkenes that do not show *cis-trans* isomerism.

(b) Alkenes that do show *cis-trans* isomerism.

(c) Cycloalkanes that do not show *cis-trans* isomerism.

(d) Cycloalkanes that do show *cis-trans* isomerism.

4.18 Draw structural formulas for the four isomeric chloropropenes of molecular formula C_3H_5Cl.

4.19 Following are structural formulas and common names for six of the most abundant carboxylic acids found in animal fats, plant oils, and biological membranes. Because many of these carboxylic acids were first isolated from animal fats, they are often referred to as fatty acids.

1. $CH_3(CH_2)_{14}CO_2H$ Palmitic acid
2. $CH_3(CH_2)_{16}CO_2H$ Stearic acid
3. $CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H$ Oleic acid
4. $CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7CO_2H$ Linoleic acid
5. $CH_3CH_2(CH{=}CHCH_2)_3(CH_2)_6CO_2H$ Linolenic acid
6. $CH_3(CH_2)_3(CH_2CH{=}CH)_4(CH_2)_3CO_2H$ Arachidonic acid

(a) How many *cis-trans* isomers are possible for each?

(b) Give each an IUPAC name.

(c) For those that show *cis-trans* isomerism, consult a textbook of biochemistry and try to determine which of the possible configurations is the most prevalent in the biological world.

Nomenclature

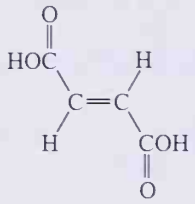
4.20 Arrange the following groups in order of increasing priority:

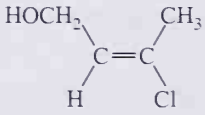
(a) $-CH_3$ $-H$ $-Br$ $-CH_2CH_3$

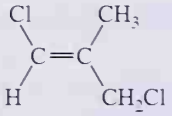
(b) $-OCH_3$ $-CH(CH_3)_2$ $-B(CH_2CH_3)_2$ $-H$

(c) $-CH_3$ $-CH_2OH$ $-CH_2NH_2$ $-CH_2Br$

4.21 Assign E-Z configurations to the C=C in each compound.

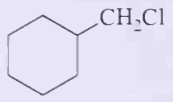
(a) 

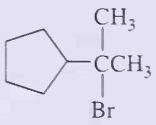
(b) 

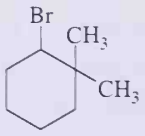
(c) 

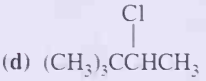
Preparation

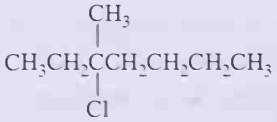
4.22 Draw structural formulas for the alkenes formed on dehydrohalogenation of the following compounds using KOH. Where more than one alkene may be formed, predict which is the major product.

(a) 

(b) 

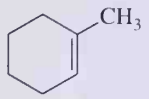
(c) 

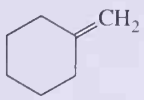
(d) 

(e) 

4.23 Draw the structural formula of all chloroalkanes that undergo dehydrohalogenation in the presence of KOH to give each alkene as the major product. For some parts, only one chloroal-

kane gives the desired alkene as the major product. For other parts, two chloroalkanes may give the desired alkene as the major product.

(a) 

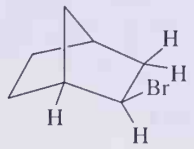
(b) 

(c) $CH_2{=}C(CH_3)CH(CH_3)CH_2CH_3$

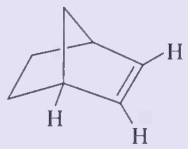
(d) $CH_3C(CH_3){=}CCH_2CH_3$ (CH$_3$ on C)

(e) $CH_3CH(CH_3)C{=}CHCH_3$ (CH$_3$ on C)

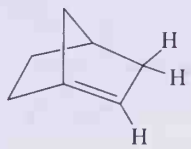
4.24 Elimination of HBr from 2-bromonorbornane gives only 2-norbornene and no 1-norbornene. How do you account for the regioselectivity of this dehydrohalogenation? In answering this question, you may find it helpful to make molecular models of both 1-norbornene and 2-norbornene and analyze the angle strain in each.



2-Bromonorbornane



2-Norbornene



1-Norbornene

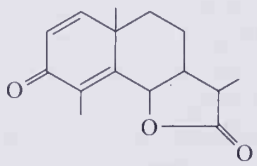
Terpenes

4.25 Show that the carbon skeleton of farnesol can be coiled and then cross-linked to give the carbon skeleton of β-caryophyllene (Figure 4.7).

4.26 Show that the structural formula of vitamin A (Figure 4.8) can be divided into four isoprene units joined by head-to-tail linkages and cross-linked at one point to form the six-member ring.

4.27 Show that the structural formula of β-carotene (Section 23.6A) can be divided into eight isoprene units.

4.28 Santonin, $C_{15}H_{18}O_3$, isolated from the flower heads of certain species of *Artemisia*, is an anthelmintic, that is, a drug used to rid the body of worms (helminths). It has been estimated that over one-third of the world's population is infested with these parasites. Santonin in oral doses of 60 mg is used as an anthelmintic for roundworms *(Ascaris lumbricoides)*.

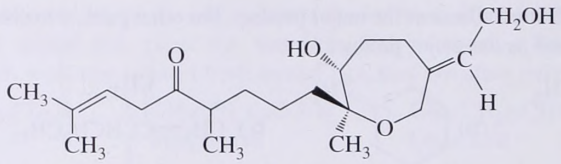


Santonin

Locate the three isoprene units in santonin, show how the carbon skeleton of farnesol might be coiled and then cross-linked to give santonin. Two different coiling patterns of the carbon skeleton of farnesol can lead to santonin. Try to find both.

4.29 In many parts of South America, extracts of the leaves and twigs of *Montanoa tomentosa* are used as a contraceptive, to stimulate menstruation, to facilitate labor, or to terminate early pregnancy. Phytochemical investigations of this plant have resulted in isolation of a very potent fertility-regulating compound called zoapatanol.

Santonin can be isolated from flower heads of wormwood, *Artemisia absinthium*. Principal habitats are Chinese Turkistan and the Southern Urals. *(© E.R. Degginger, © Color-Pic, Inc.)*



Zoapatanol

(a) Show that the carbon skeleton of zoapatanol can be divided into four isoprene units bonded head to tail and then cross-linked in one point along the chain.

(b) Specify the configuration about the carbon-carbon double bond to the seven-member ring according to the E-Z system.

(c) How many *cis-trans* isomers are possible for zoapatanol? Consider the possibilities for *cis-trans* isomerism in both cyclic compounds and in alkenes.

Polyethylene wash bottles. (Charles D. Winters)

5

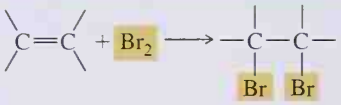
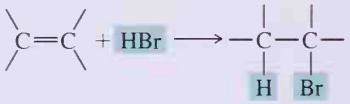
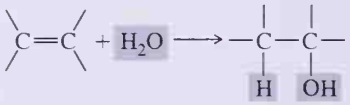
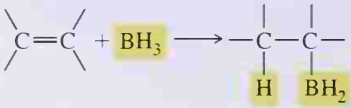
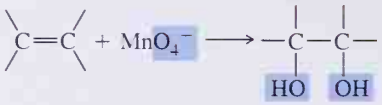
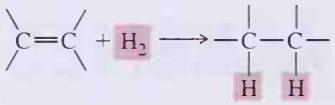
ALKENES II

In this chapter we begin our systematic study of one of the most important unifying themes in organic chemistry, namely the study of how reactions of organic molecules occur or, to use the terminology of chemists, the study of **reaction mechanisms.** By a reaction mechanism we mean how chemical bonds are broken and new ones are formed, the role of catalysts, the effect of solvents and the energetics of chemical reactions. We use the reactions of alkenes as the vehicle by which to introduce these concepts.

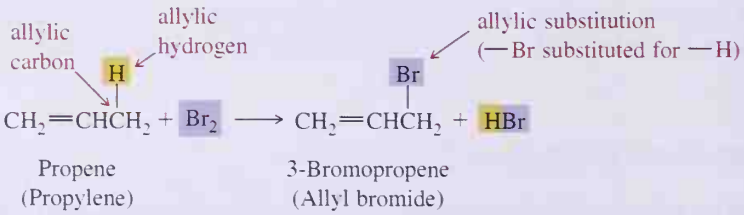
5.1 Reactions of Alkenes: An Overview

In contrast to alkanes, alkenes react with a variety of reagents. The most characteristic reaction of alkenes is **addition to the carbon-carbon double bond** in such a way that the pi bond is broken and in its place sigma bonds are formed to two new atoms or groups of atoms. Several examples of reactions at the carbon-carbon double bond are shown in Table 5.1 along with the descriptive name(s) associated with each.

Table 5.1 Characteristic alkene addition reactions

Reaction	Descriptive Name(s)
	bromination (halogenation)
	hydrobromination (hydrohalogenation)
	hydration
	hydroboration
	hydroxylation (oxidation)
	hydrogenation (reduction)

A second characteristic reaction of alkenes takes place at a carbon adjacent to the carbon-carbon double bond and involves substitution of a new atom or group of atoms for a hydrogen atom. A carbon atom adjacent to a carbon-carbon double bond is called an **allylic carbon** (Section 4.1B), and a hydrogen atom on an allylic carbon is called an **allylic hydrogen. Allylic substitution** is illustrated by reaction of propene with bromine to form 3-bromopropene and hydrogen bromide.



A third characteristic reaction of alkenes is the formation of **addition polymers** (Greek words: *poly*, many and *meros*, part). In the presence of certain catalysts called **initiators,** many alkenes form polymers made by the addition of **monomers** (Greek words: *mono*, one and *meros*, part) to a growing polymer chain as illustrated by the formation of

polyethylene from ethylene. In alkene polymers of industrial and commercial importance, n is a large number, typically several thousand.

$$n\mathrm{CH_2{=}CH_2} \xrightarrow{\text{initiator}} \text{—(}\mathrm{CH_2CH_2}\text{)—}_n$$

Ethylene (A monomer) — Polyethylene (A polymer)

In the following sections, we study these characteristic alkene reactions in considerable detail, including what is known about how each occurs, or in the terminology of organic chemists, we study what is known about the mechanism of each reaction.

5.2 Reaction Mechanisms

A **reaction mechanism** describes how and why a reaction occurs as it does; which bonds are broken and which new ones are formed; the order in which the various bond-breaking and bond-making steps take place and their relative rates; if the reaction takes place in solution, the role of the solvent; and if the reaction involves a catalyst, the role of the catalyst. A complete reaction mechanism describes the position of all atoms during the reaction and the energy of the entire system during the course of the reaction. This ideal can rarely be approached in practice, however.

A. Chemical Energetics

Let us consider a general reaction in which A and B react to give C and D. The **total energy** E of reacting molecules is the sum of their **kinetic energy** (KE) and **potential energy** (PE).

$$\mathrm{A + B \longrightarrow C + D} \qquad E_{\text{total}} = \mathrm{KE + PE}$$

Before reactants collide, they have a certain kinetic energy. As they collide, part of the kinetic energy is absorbed and converted to potential energy in the form of vibration motions of bonds. To understand the relationship between chemical reaction and potential energy, it is helpful to think of a chemical bond as a spring. As a spring is stretched from its resting position, its potential energy is increased. As it returns to its resting position, its potential energy is decreased. Similarly, during a chemical reaction, bond breaking corresponds to an increase in potential energy and bond making corresponds to a decrease in potential energy.

The change in potential energy in going from reactants to products is measured on the vertical coordinate, whereas the corresponding progress of the reaction is on the horizontal axis, the **reaction coordinate.** As reaction between A + B progresses in going from left to right along the reaction coordinate (Figure 5.1), the potential energy of the system increases. If sufficient potential energy becomes concentrated in the proper bonds, then bonds in the reactants break and new bonds form, giving products. The point on the reaction coordinate at which the potential energy is a maximum is called the **transition state.** The difference in potential energy between reactants and the transition state is called the **energy of activation.** A transition state has a definite geometry, a definite arrangement of bonding and nonbonding electrons, and a definite distribution of electron density and charge. Because a transition state is an energy maximum on the reaction coordinate and for

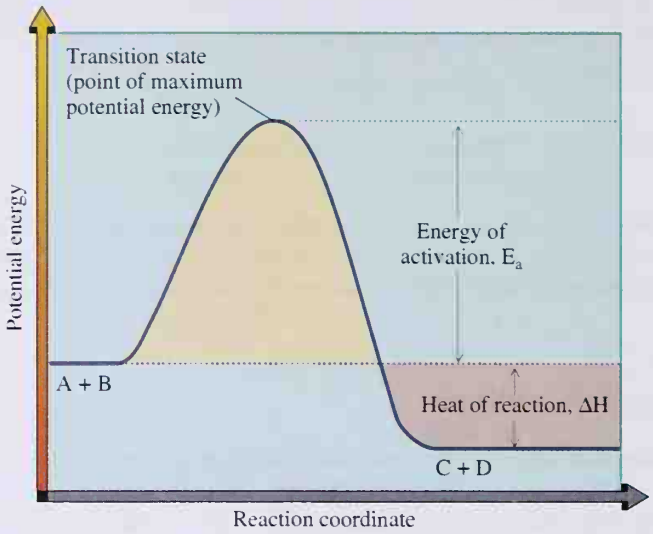


Figure 5.1
Potential energy diagram for a one-step reaction. The energy of the reactants is higher than that of products, and heat energy is released in the conversion of A + B to C + D.

all practical purposes has zero lifetime, it cannot be isolated and its structure cannot be determined experimentally. However, as we shall see soon, even though we cannot observe a transition state directly by any experimental means, we can often infer a great deal about its probable structure from other experimental observations.

In multistep reactions, each step has its own transition state and energy of activation. Shown in Figure 5.2 is a potential energy diagram for conversion of reactants to products in two steps. An **intermediate** corresponds to a potential energy minimum between two transition states, in this case between transition state 1 and transition state 2. Reactive intermediates are never present in appreciable concentration because the energy of activation for their conversion to either reactants or to products is usually very small.

B. Developing a Reaction Mechanism

To develop a reaction mechanism, chemists begin by collecting all available experimental observations about a particular chemical reaction. Next, through a combination of experience, intuition, and guesswork, they propose several sets of steps or mechanisms, each of which might account for the overall chemical transformation. Finally each proposed mechanism is tested against the experimental observations to exclude those mechanisms that are not consistent with the facts. A mechanism becomes generally established by excluding reasonable alternatives and by showing that it is consistent with every test that can be devised. This, of course, does not mean that a generally accepted mechanism is a completely accurate description of the chemical events, but rather that it is the best chemists have been able to devise that is consistent with the mass of experimental evidence available for that particular reaction or type of reaction. It is important to keep in mind that as new experimental evidence is obtained, it may be necessary to modify a generally accepted mechanism or possibly even discard it and start all over again.

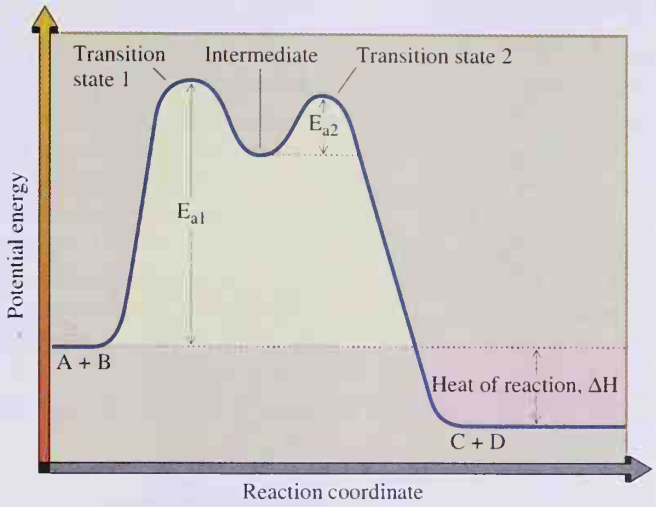


Figure 5.2
Potential energy diagram for a two-step reaction involving formation of an intermediate.

For most of the reactions we study in this introduction to organic chemistry, enough is known so that it is possible to specify (1) the steps in the reaction including the structure(s) of any intermediates, (2) the relative rates of the various steps, (3) the structure(s) of transition states, (4) the role of the solvent, if any, and (5) the role of catalysts, if any.

Before we go on to consider reactions and reaction mechanisms, we might ask why is it worth the trouble to establish them and your time to learn about them. One reason is practical: mechanisms provide a theoretical framework within which to organize a great deal of descriptive chemistry. For example, with insight into how reagents add to particular alkenes, it is possible to make generalizations and then to predict how the same reagents might add to other alkenes. A second reason lies in the intellectual satisfaction derived from constructing models that accurately reflect the behavior of chemical systems. Finally, to a creative scientist, a mechanism is a tool to be used in the search for new information and new understanding. A mechanism consistent with all that is known about a reaction can be used to make predictions about chemical interactions as yet unexplored, and experiments can be designed to test these predictions. Thus, reaction mechanisms provide a way not only to organize knowledge but also to extend it.

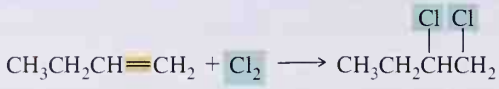
5.3 Electrophilic Additions

We begin our introduction to the chemistry of alkenes with an examination of three types of addition reactions, namely, addition of halogens (Cl_2 and Br_2), addition of hydrogen halides (HCl, HBr, and HI), and addition of water (H_2O). We first study some of the experimental observations about these addition reactions and then discuss mechanisms for them. Then, armed with these insights into addition reactions of alkenes, we examine two further types of addition reactions: addition of mercuric acetate in the presence of water and addition of Cl_2 and Br_2 in the presence of water. Although we study these particular reactions, we wish to develop a more general understanding of how alkenes undergo chemical reaction and why they react as they do.

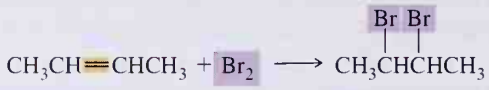
A. Bromination and Chlorination

Reaction of alkenes with Br_2 and Cl_2 is quite different from that of alkanes. Recall from Section 2.9B that chlorine and bromine do not react with alkanes unless the halogen-alkane mixture is exposed to ultraviolet or visible light, or heated to temperatures of 250° to 400°C. The reaction that then occurs is substitution of halogen for hydrogen and formation of a haloalkane and an equivalent amount of HCl or HBr. Halogenation of most alkanes invariably gives a complex mixture of products. In contrast, chlorine and bromine react with alkenes at room temperature by addition of halogen atoms to the two carbon atoms of the double bond with the formation of two new carbon-halogen bonds. Fluorine (F_2) also adds to alkenes, but because its reactions are very fast and difficult to control, addition of fluorine to alkenes is not a general laboratory procedure. Iodine (I_2) is so unreactive that it does not add to alkenes.

Halogenation with bromine or chlorine is generally carried out either with the pure reagents or by mixing them in CCl_4 or some other inert solvent.

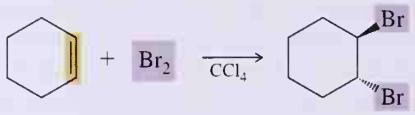


1-Butene 1,2-Dichlorobutane



2-Butene 2,3-Dibromobutane

Addition of bromine or chlorine to an alkene results in anti addition of the halogen to the carbon-carbon double bond. For example, reaction of bromine and cyclohexene gives *trans*-1,2-dibromocyclohexane; the *cis* isomer is not formed. Thus, addition of a halogen to an alkene is stereoselective. A **stereoselective reaction** is one in which one stereoisomer is formed or destroyed in preference to all others that may be formed or destroyed.

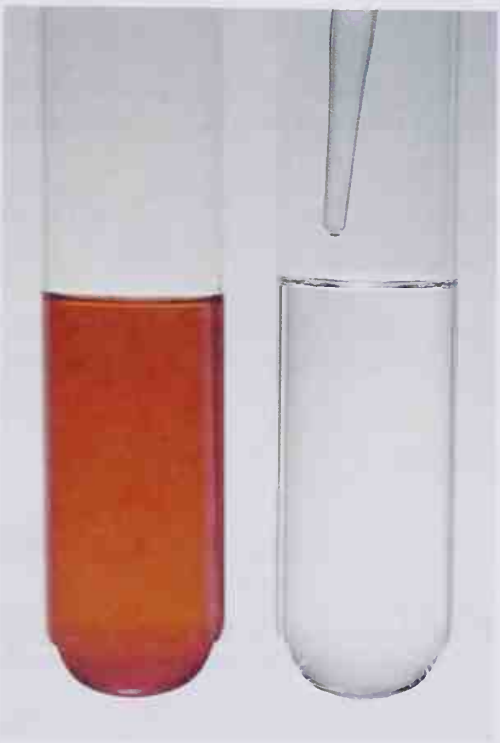


Cyclohexene *trans*-1,2-Dibromo-cyclohexane

Reaction with bromine is a particularly useful qualitative test for the presence of a carbon-carbon double bond. A solution of bromine in carbon tetrachloride is red, whereas alkenes and dibromoalkanes are usually colorless. If a few drops of bromine in carbon tetrachloride is added to an alkene, the red color of the test solution disappears.

B. Addition of Hydrogen Halides

Anhydrous HCl, HBr, and HI add to alkenes to give haloalkanes. These additions may be carried out either with the pure reagents or in the presence of a polar solvent such as acetic acid. Addition of HCl to ethene (ethylene) gives chloroethane.



A solution of bromine in carbon tetrachloride is red. Add a few drops of an alkene and the color disappears. *(Charles D. Winters)*

$$\underset{\text{Ethene}}{CH_2{=}CH_2} + HCl \longrightarrow \underset{\text{Chloroethane}}{CH_3CH_2Cl}$$

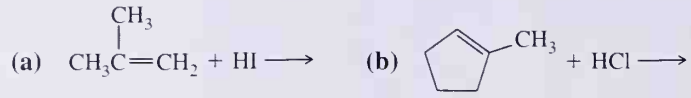
Addition of HCl to propene gives 2-chloropropane as the major product. Thus, in this reaction hydrogen adds to carbon 1 of propene, and chlorine adds to carbon 2. If the orientation of addition is reversed, 1-chloropropane is formed. However, addition of HCl to propene is regioselective; 2-chloropropane is the major product formed.

$$\underset{\text{Propene}}{CH_3CH{=}CH_2} + HCl \longrightarrow \underset{\substack{\text{2-Chloropropane}\\\text{(major product)}}}{CH_3\overset{\overset{Cl}{|}}{C}HCH_3} + \underset{\text{1-Chloropropane}}{CH_3CH_2\overset{\overset{Cl}{|}}{C}H_2}$$

This regioselectivity was noted by Vladimir Markovnikov, who made the generalization known as **Markovnikov's rule,** that in additions of HX to alkenes, hydrogen adds to the double-bonded carbon that has the greater number of hydrogens already attached to it. Remember that although Markovnikov's rule provides a way to predict the major product of an alkene addition reaction, it does not explain why one product predominates over other possible products.

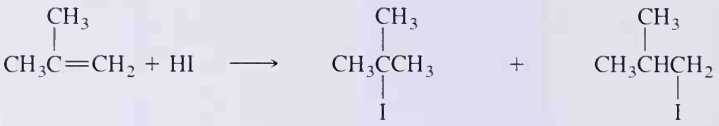
EXAMPLE 5.1

Name and draw structural formulas for the products of the following alkene addition reactions. Use Markovnikov's rule to predict which is the major product.



Solution

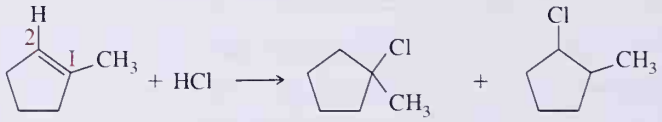
(a) HI adds to 2-methylpropene to form two possible products. Markovnikov's rule predicts that 2-iodo-2-methylpropane is the major product.



2-Iodo-2-methylpropane (major product)

1-Iodo-2-methylpropane

(b) Addition of HCl to 1-methylcyclopentene forms two products. Predict that hydrogen adds to carbon 2 and that 1-chloro-1-methylcyclopentane is the major product.

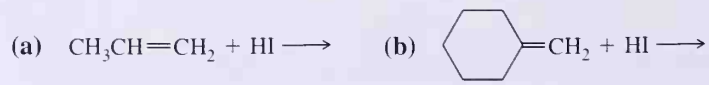


1-Chloro-1-methylcyclopentane (major product)

1-Chloro-2-methylcyclopentane

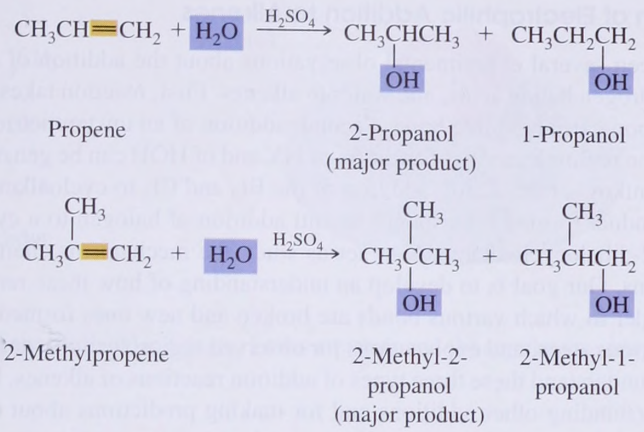
PROBLEM 5.1

Name and draw structural formulas for the two possible products of the following alkene addition reactions. Use Markovnikov's rule to predict which is the major product.



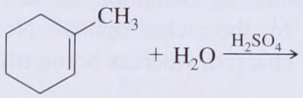
C. Addition of Water: Acid-Catalyzed Hydration of Alkenes

In the presence of an acid catalyst, most commonly sulfuric acid, water adds to alkenes to give alcohols. Addition of water to an alkene is called **hydration.** In the case of simple alkenes, —H adds to the carbon of the double bond with the greater number of hydrogens and —OH adds to the carbon with the fewer hydrogens. Thus, HOH adds to alkenes in accordance with Markovnikov's rule.



EXAMPLE 5.2

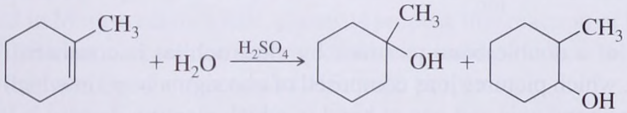
Draw structural formulas for the products of the following hydration reactions. Predict which is the major product.

(a) $CH_3CH_2CH{=}CH_2 + H_2O \xrightarrow{H_2SO_4}$ **(b)**  $+ H_2O \xrightarrow{H_2SO_4}$

Solution

(a) $CH_3CH_2CH{=}CH_2 + H_2O \xrightarrow{H_2SO_4} CH_3CH_2\underset{\displaystyle OH}{C}HCH_3 + CH_3CH_2CH_2\underset{\displaystyle OH}{C}H_2$

1-Butene — 2-Butanol (major product) — 1-Butanol

(b) 

1-Methylcyclohexene — 1-Methylcyclohexanol (major product) — 2-Methylcyclohexanol

PROBLEM 5.2

Draw structural formulas for the products of the following alkene addition reactions. Predict which is the major product.

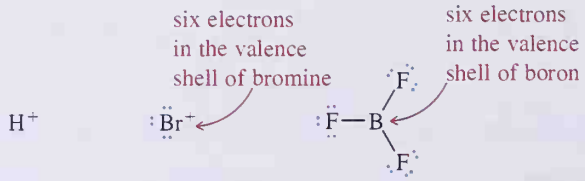
(a) $CH_3C(CH_3){=}CHCH_3 + H_2O \xrightarrow{H_2SO_4}$ **(b)** $CH_2{=}C(CH_3)CH_2CH_3 + H_2O \xrightarrow{H_2SO_4}$

D. Mechanism of Electrophilic Addition to Alkenes

We have now seen several experimental observations about the addition of chlorine and bromine, the hydrogen halide acids, and water to alkenes. First, reaction takes place exclusively at the carbon-carbon double bond. Second, addition of an unsymmetrical reagent is regioselective; the regioselectivity of addition of HX and of HOH can be generalized in the form of Markovnikov's rule. Third, addition of the Br_2 and Cl_2 to cycloalkenes is stereoselective; the product formed corresponds to anti addition of halogen to a cycloalkene to form a *trans*-1,2-dihalocycloalkane. Now let us study the mechanisms chemists propose for these reactions. Our goal is to develop an understanding of how these reactions occur including the order in which various bonds are broken and new ones formed, the relative rates of these various steps, and explanations for observed regioselectivity and stereoselectivity. If we can understand these three types of addition reactions of alkenes, then we have a basis for understanding other additions and for making predictions about new types of addition reactions.

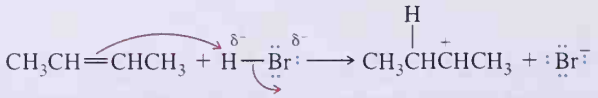
Formation of Carbocation Intermediates

It became apparent to chemists studying the addition of H_2O/H_2SO_4 and HX to alkenes that initial attack on a carbon-carbon double bond is by an electrophile. An **electrophile** is any atom, molecule, or ion that can accept a pair of electrons and in the process form a new covalent bond. By definition, an electrophile is also a Lewis acid. Following are Lewis structures for three electrophiles. Note that both hydrogen ion and bromonium ion are positively charged, whereas boron trifluoride is neutral.



Hydrogen ion | Bromonium ion | Boron trifluoride

The susceptibility of a double bond to attack by electrophiles is consistent with our electronic formulation, which pictures it as composed of one sigma bond in which electron density is located on the bond axis and one pi bond in which electron density is located in two lobes: one above and the other below the plane created by the sigma bond framework. Addition of HX to an alkene can be accounted for by a two-step mechanism. Addition begins by interaction of HX with the electron pair of the pi bond and formation of a new C—H bond as illustrated by the reaction of HBr and 2-butene.



This step leaves one carbon atom with only six electrons in its valence shell and carrying a positive charge. A species containing a positively charged carbon atom is called a carbocation (*carbon* + *cation*). A carbocation has a charge of + 1.

In a carbocation, the carbon bearing the positive charge is bonded to three other atoms, and bond angles about it are approximately 120°. sp^2 Hybrid orbitals of carbon are used to

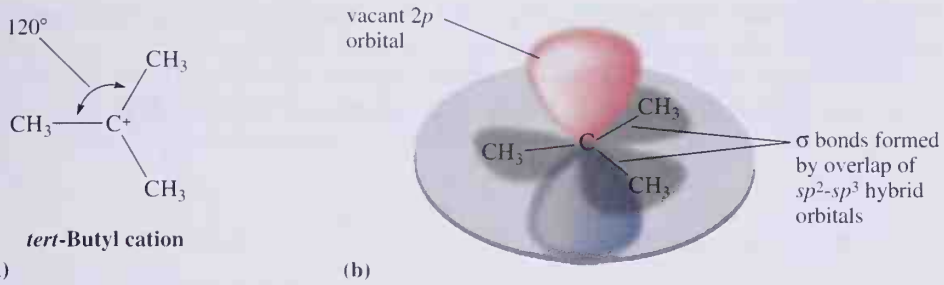
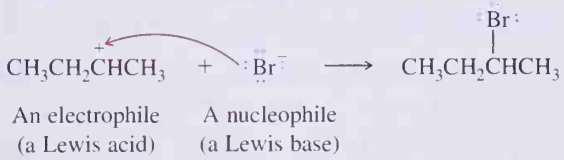


Figure 5.3
The structure of the *tert*-butyl cation. (a) Lewis structure and (b) an orbital overlap picture.

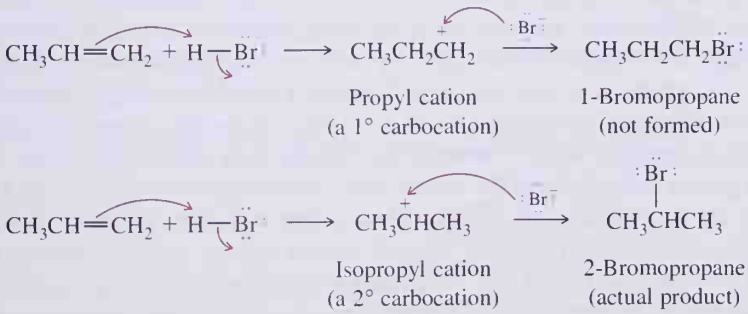
form sigma bonds to the three attached groups. The unhybridized $2p$ orbital lies perpendicular to the sigma bond framework and contains no electrons. A Lewis structure and orbital overlap diagram for the *tert*-butyl cation are shown in Figure 5.3.

Because it contains an electron-deficient, positively charged carbon atom, a carbocation is an unstable intermediate. In reaction of HX with an alkene, the carbocation intermediate (by definition both an electrophile and a Lewis acid) reacts rapidly with halide ion (by definition both a nucleophile and a Lewis base) to form a new C—X bond. Thus, although we might not at first think of it as such, this reaction is but another example of an acid-base reaction according to the Lewis definition of acids and bases.



Regioselectivity and the Relative Stabilities of Carbocations

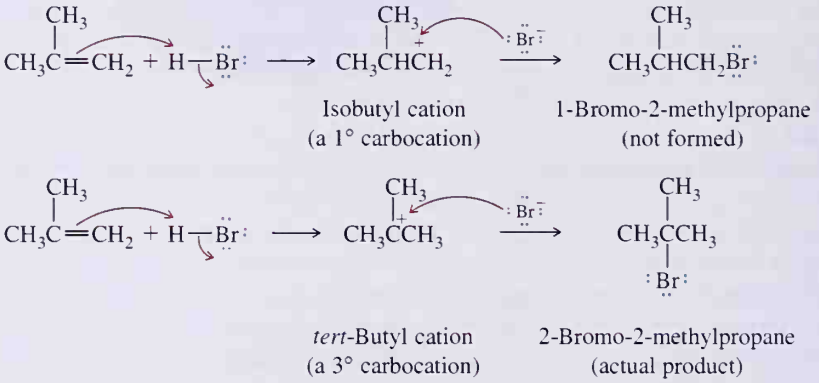
To account for the regioselectivity of the reaction of HX with alkenes and the observations generalized in Markovnikov's rule, chemists propose that reaction of HX and an alkene can give two different carbocation intermediates depending on how H^+ adds to the double bond, as illustrated by the reaction of HBr with propene.



The propyl cation is a primary carbocation (positive charge on a primary carbon) and the isopropyl cation is a secondary carbocation (positive charge on a secondary carbon). The propyl cation reacts with bromide ion to give 1-bromopropane and the isopropyl cation

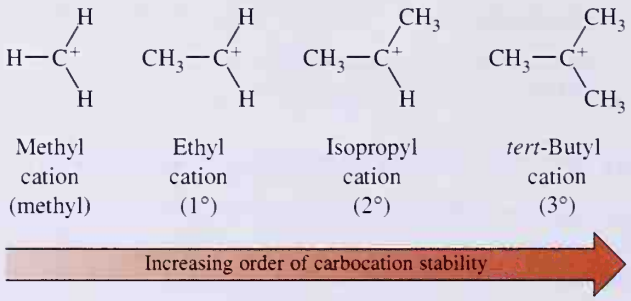
reacts with bromide ion to give 2-bromopropane. The observed product is 2-bromopropane indicating that only the secondary carbocation is actually formed.

Similarly, in reaction of HBr with 2-methylpropene, addition of H^+ to the carbon-carbon double bond gives either an isobutyl cation (a primary carbocation) or a tert-butyl cation (a tertiary carbocation). The observed product is 2-bromo-2-methylpropane.



Reaction of the isobutyl cation with bromide ion gives 1-bromo-2-methylpropane (isobutyl bromide); reaction of the *tert*-butyl cation with bromide ion gives 2-bromo-2-methylpropane (*tert*-butyl bromide). The observed product is 2-bromo-2-methylpropane.

We know from a great deal of experimental evidence that a tertiary carbocation is more stable (requires a lower activation energy for its formation) than a secondary carbocation, which is in turn more stable than a primary carbocation.



The order of stability of carbocations is determined in large part by the polarizability of electrons on alkyl groups. Because of its electron deficiency, a carbon atom bearing a positive charge has a higher electronegativity than an uncharged tetravalent carbon atom. Attraction of electrons from adjacent sigma bonds by a more electronegative atom is called the **inductive effect** and is indicated by an arrowhead on the sigma bond directed toward the more electronegative atom. The larger the volume over which the positive charge is spread, the greater the stability of the cation. Thus, as the number of alkyl groups bonded to the cationic carbon increases, the stability of the cation increases. The electron-withdrawing inductive effect of the positively charged carbon and the resulting delocalization of charge are illustrated in Figure 5.4. According to quantum mechanical calculations, the charge on carbon in the methyl cation is approximately + 0.645, and the charge on each of the hydrogen atoms is + 0.118. Thus, in the methyl cation, the positive charge is not localized on carbon. Rather, it is delocalized over the volume of space occupied by the entire ion. Polarization of electron density and delocalization of charge is even more extensive in the *tert*-butyl cation.

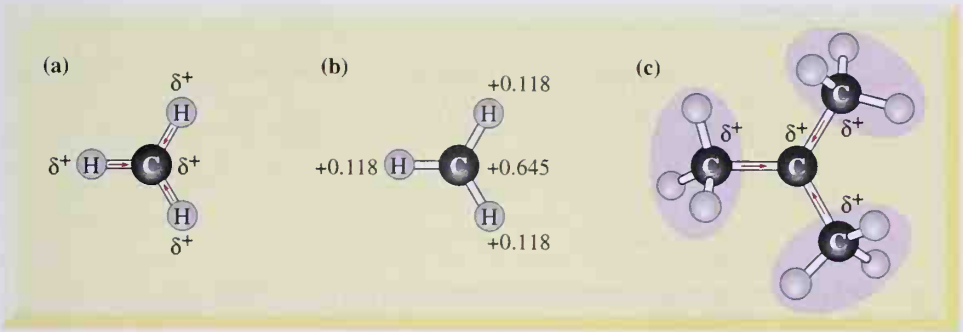
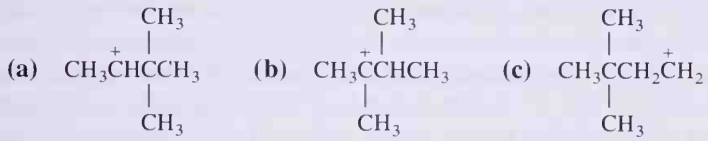


Figure 5.4
Delocalization of charge in carbocations by the inductive effect. (a) The methyl cation, (b) distribution of positive charge in the methyl cation according to molecular orbital calculations, and (c) the *tert*-butyl cation.

EXAMPLE 5.3

Arrange the following carbocations in order of increasing stability:

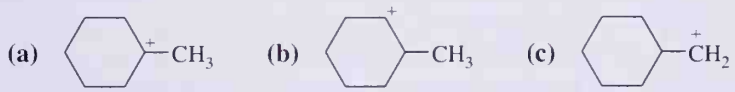


Solution

Carbocation (a) is secondary, (b) is tertiary, and (c) is primary. In order of increasing stability they are c < a < b.

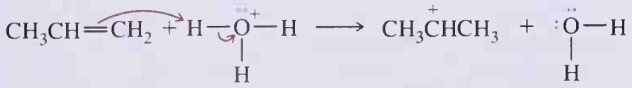
PROBLEM 5.3

Arrange the following carbocations in order of increasing stability:



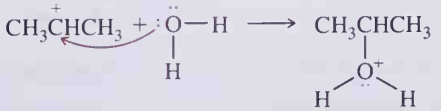
The mechanism for acid-catalyzed hydration of alkenes is quite similar to what we already proposed for addition of HCl, HBr, and HI to a carbon-carbon double bond. In Step 1, proton transfer from H_3O^+ forms a carbocation intermediate. This intermediate then completes its valence shell in Step 2 by forming a new covalent bond with an unshared pair of electrons of the oxygen atom of H_2O. Finally, transfer of a proton to H_2O in Step 3 gives the alcohol and regenerates the acid catalyst. These steps are illustrated for the acid-catalyzed hydration of propene to give 2-propanol.

Step 1:



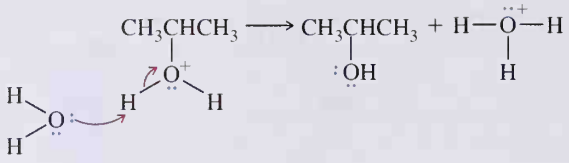
a 2° carbocation intermediate

Step 2:



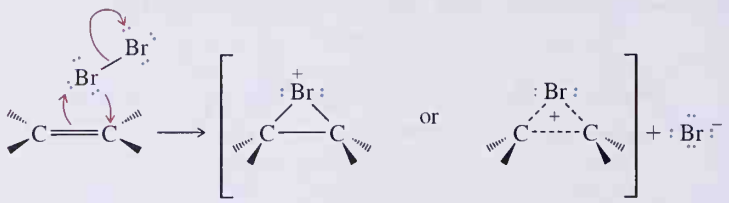
An oxonium ion

Step 3:



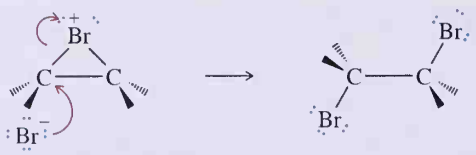
Stereoselectivity and Bridged Halonium Ion Intermediates

The relative stabilities of potential carbocation intermediates can be used to account for the observed regioselectivity of the addition of HX and H_2O to alkenes, but they do not help us to account for stereoselectivity, as for example, anti addition of Br_2 or Cl_2. We can account for this stereoselectivity by proposing that a halogen and an alkene react to form an intermediate containing a **bridged halonium ion.** This sequence of reactions can be illustrated in the following way. Reaction of bromine with an alkene is initiated by interaction of the pi electrons of the alkene with a bromine molecule, and in the transition state at least some degree of partial positive charge exists on the carbon adjacent to that forming the new C—Br bond. Interaction of a pair of valence electrons of bromine with the carbon-carbon double bond forms a three-member ring in which bromine bears a positive charge. A bromine atom bearing a positive charge is called a **bromonium ion,** and the cyclic structure of which it is a part is called a **bridged bromonium ion.** This intermediate may be written showing two C—Br bonds and a positive charge on bromine or, alternatively, with dotted lines for the C—Br bonds to indicate that the positive charge in the intermediate is delocalized with partial positive charges on bromine and the two carbons formerly of the double bond.



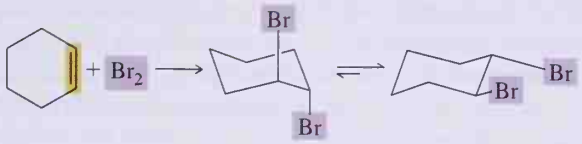
A bridged bromonium ion intermediate

A bromide ion then interacts with this bridged intermediate from the side of the ion opposite that occupied by the bromonium ion to give the dibromoalkane. Addition of new atoms or groups of atoms from opposite sides or faces of the double bond is called **anti addition.** In cyclic systems, anti addition is equivalent to ***trans*** **coplanar addition. Syn addition** is addition of groups to the same side or face of a double bond.



Anti (*trans*-coplanar)
orientation of added bromine atoms

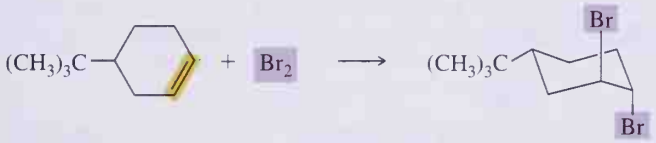
Addition of halogen to cyclohexene and its derivatives gives a *trans*-diaxial product initially because only axial positions on adjacent atoms of a cyclohexane ring are anti and coplanar.



trans-diaxial *trans*-diequatorial (more stable)

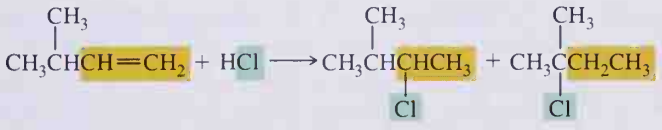
The initial *trans*-diaxial conformation of the product is in equilibrium with the *trans*-diequatorial conformation, and in simple derivatives of cyclohexane, the latter is more stable and predominates.

In derivatives of cyclohexane, however, in which interconversion between one chair conformation and the other is not possible or is severely restricted, the *trans*-diaxial product is isolated. If a cyclohexane ring, for example, contains a bulky alkyl group such as *tert*-butyl, then the molecule exists overwhelmingly in a conformation in which the *tert*-butyl group is equatorial. Bromination of 4-*tert*-butylcyclohexene gives 1-*tert*-butyl-3,4-dibromocyclohexane. In the favored chair conformation, *tert*-butyl is equatorial, and the bromine atoms remain axial.

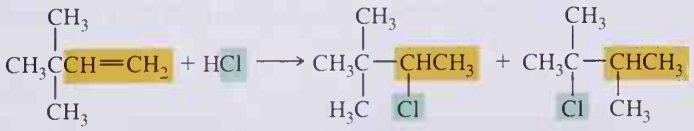


4-*tert*-Butylcyclohexene 1-*tert*-Butyl-3,4-dibromocyclohexane

Whatever the timing of the interactions between alkene, halogen, nucleophile, and the bridged halonium ion, this mechanism proposes that no free carbocation is formed during the reaction. To say that no free carbocation is formed during the addition of Cl_2 or Br_2 to the alkenes we have studied so far leads to the following question. When, if ever, are carbocation intermediates formed in electrophilic addition to alkenes? The answer is that they probably are not present in stereoselective addition reactions. However, they are almost certainly present during nonstereoselective addition reactions (those that give a mixture of syn and anti addition products) or that involve rearrangement of atoms or groups of atoms or both. The following examples illustrate rearrangements:



3-Methyl-1-butene 2-Chloro-3-methylbutane (40%) 2-Chloro-2-methylbutane (60%)

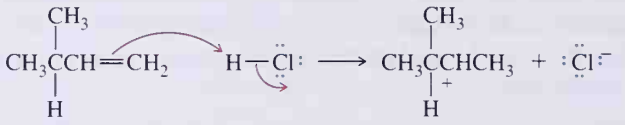


3,3-Dimethyl-1-butene 3-Chloro-2,2-dimethylbutane (17%) 2-Chloro-2,3-dimethylbutane (83%)

The normal product of electrophilic addition to a carbon-carbon double bond involves rupture of the pi bond and formation of two new sigma bonds in its place. In addition of HCl to 3-methyl-1-butene, only 40% of the normal product is formed, and in addition of HCl to 3,3-dimethyl-1-butene, only 17% of the normal product is formed. Formation of the major product in each of these reactions can be accounted for in the following way. Reaction of 3-methyl-1-butene with HX in Step 1 forms a carbocation. In Step 2, migration of a hydrogen atom with its bonding electron pair from an adjacent carbon atom gives a more stable carbocation. This type of rearrangement is called a 1,2-shift. In a **1,2-shift,** an atom or group of atoms with its bonding electrons moves from one atom to an adjacent electron-deficient atom. In the rearrangement shown in Step 2, the migrating group is a hydride ion (a hydrogen nucleus with two valence electrons).

Finally in Step 3, the more stable carbocation reacts with a nucleophile to give the rearrangement product. These steps are illustrated by reaction of 3-methyl-1-butene with HCl to form 2-chloro-2-methylbutane as the major product.

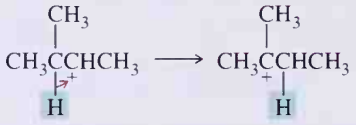
Step 1:



3-Methyl-1-butene

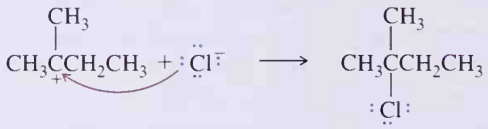
A 2° carbocation intermediate

Step 2:



A 3° carbocation intermediate

Step 3:

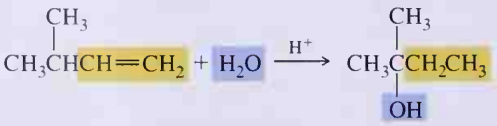


2-Chloro-2-methylbutane

The driving force for this rearrangement is the fact that a secondary carbocation, once formed, undergoes rearrangement to give a more stable tertiary carbocation.

A similar three-step mechanism, this time involving migration of a pair of electrons and the attached $-CH_3$ group from an adjacent carbon to the positively charged carbon atom accounts for the formation of 2-chloro-2,3-dimethylbutane as the major product in the addition of HCl to 3,3-dimethyl-1-butene.

Just as with addition of HX to an alkene, rearrangement often occurs in acid-catalyzed hydration of alkenes, especially when the carbocation formed in the first step can rearrange to a more stable carbocation. For example, acid-catalyzed hydration of 3-methyl-1-butene gives 2-methyl-2-butanol as the major product.



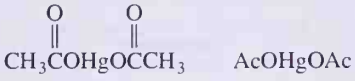
3-Methyl-1-butene

2-Methyl-2-butanol

Other convincing evidence for the relative stabilities of carbocations is that in rearrangements such as those we just studied, 1° carbocations always rearrange to a more stable 2° or 3° carbocation, and 2° carbocations always rearrange to more stable 3° carbocations. They never rearrange in the opposite direction.

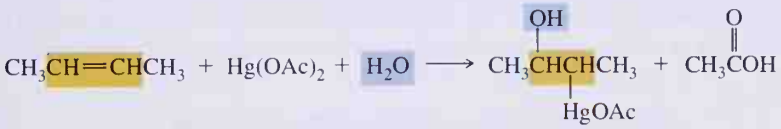
E. Oxymercuration of Alkenes

Hydration of alkenes can also be accomplished by treatment of an alkene with mercury(II) acetate (mercuric acetate) followed by reduction of the resulting carbon-mercury bond with sodium borohydride, $NaBH_4$. In the following structural formulas for mercury(II) acetate, the acetate group is written in full in the first formula. In the second formula, it is abbreviated as AcO—.

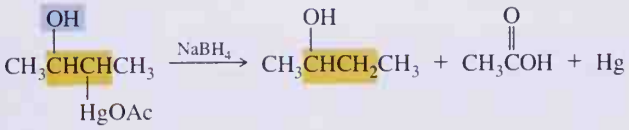


Mercury(II) acetate
(Mercuric acetate)

Oxymercuration, the addition of mercury(II) to one carbon of the double bond and oxygen to the other, is illustrated by the conversion of 2-butene to 2-butanol.

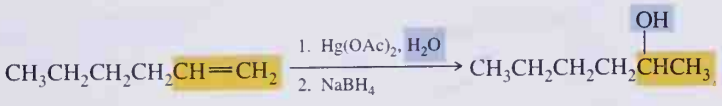


2-Butene | Mercury(II) acetate | An organomercury compound

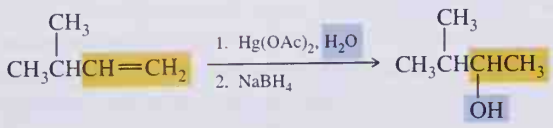


An organomercury compound | 2-Butanol | Acetic acid

Oxymercuration is highly regioselective in that mercury(II), the electrophile, becomes bonded to the less substituted carbon of the alkene and the nucleophile becomes bonded to the more substituted carbon. The result of oxymercuration followed by sodium borohydride reduction is Markovnikov addition of HOH to an alkene.



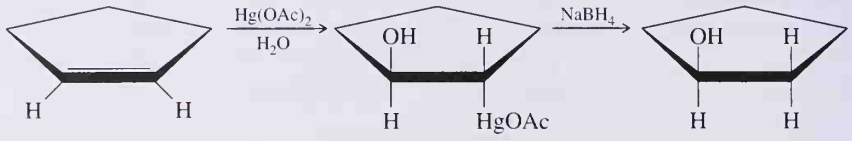
1-Hexene | 2-Hexanol



3-Methyl-1-butene | 3-Methyl-2-butanol

Oxymercuration of 3-methyl-1-butene followed by $NaBH_4$ reduction gives exclusively 3-methyl-2-butanol and illustrates a very important feature of this reaction sequence, namely, it occurs without rearrangement. You might compare the product of oxymercuration-reduction of 3-methyl-1-butene with that formed by acid-catalyzed hydration of the same alkene. In the former, no rearrangement occurs. In the latter, the major product is 2-methyl-2-butanol, a compound formed by rearrangement. The fact that no rearrangement occurs during oxymercuration-reduction indicates that no free carbocation is formed as an intermediate.

The stereoselectivity of oxymercuration is illustrated by the reaction of mercury(II) acetate in the presence of water with cyclopentene.

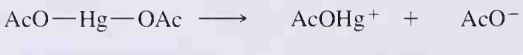


Cyclopentene

(Anti addition of OH and HgOAc)

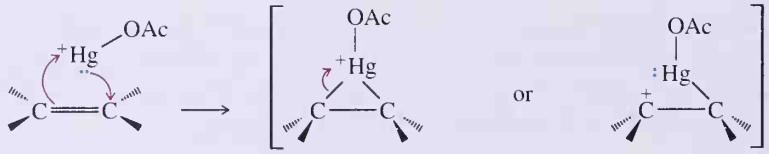
Cyclopentanol

The fact that oxymercuration is both regioselective and stereoselective has led chemists to propose the following mechanism for this reaction. Dissociation of mercury(II) acetate gives acetate ion (a Lewis base) and $AcOHg^+$ (a Lewis acid and an electrophile).



(A Lewis acid and electrophile)

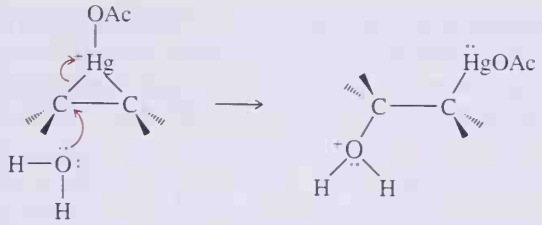
Reaction then proceeds by interaction of the electrophile with the electron pair of the pi bond to give a **bridged mercurinium ion** as the first intermediate. The mercurinium ion can also be written as an open intermediate with the positive charge on the carbon giving the more stable carbocation.



A bridged mercurinium ion intermediate

An open carbocation intermediate

The fact that electrophilic addition occurs without rearrangement indicates that the intermediate is not a true carbocation but has more the character of a bridged or partially bridged intermediate. Furthermore, the bridged structure allows us to account for the fact that this type of electrophilic addition is predominantly anti; the nucleophile attacks the bridged intermediate from the face opposite that occupied by mercury, as shown in the following equation:

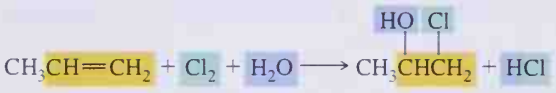


Anti addition of HgOAc and HOH

Yet the fact that the electrophile ($AcOHg^+$) adds to the less substituted carbon and the nucleophile (HOH) adds to the more substituted carbon, that is, addition follows Markovnikov's rule, indicates that the intermediate must have some carbocation character. It is probable that in the actual intermediate, mercury is bonded partially to each carbon, thereby preventing rearrangement. The more substituted carbon has the greater degree of partial positive character and is the one attacked by the nucleophile (H_2O).

F. Addition of HOCl and HOBr

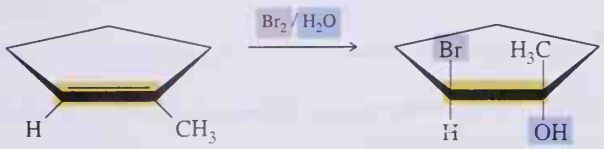
Treatment of an alkene with Br_2 or Cl_2 in the presence of water results in addition of —OH and —Br, or —OH and —Cl to the carbon-carbon double bond as shown in the following example:



Propene (Propylene)

1-Chloro-2-propanol (a chlorohydrin)

A **halohydrin** is a compound containing a halogen atom and a hydroxyl group on adjacent carbon atoms; those containing —Br and —OH are called **bromohydrins,** those containing —Cl and —OH are called **chlorohydrins.** Addition of HOCl and HOBr is both regioselective (halogen usually adds to the less substituted carbon atom) and stereoselective (addition is predominantly anti). Both the regioselectivity and stereoselectivity are illustrated by the addition of HOBr to 1-methylcyclopentene. Bromine and hydroxyl add anti to each other with Br bonding to the less substituted carbon and OH bonding to the more substituted carbon.

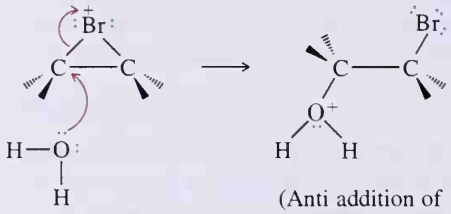


1-Methylcyclopentene

2-Bromo-1-methylcyclopentanol (anti addition of OH and Br)

To account for the regioselectivity and stereoselectivity of these reactions, chemists propose a three-step mechanism. Step 1 involves reaction of halogen with the pi bond of the alkene to form a bridged halonium ion intermediate. This intermediate has some of the character of a carbocation (to account for the regioselectivity) and some of the character of

a halonium ion (to account for the stereoselectivity). Reaction of this halonium ion intermediate with H_2O in Step 2 followed by loss of a proton in Step 3 completes the reaction. The following equation shows the reaction of a bridged bromonium ion with water to illustrate the anti (*trans* and coplanar) addition of —Br and —OH to an alkene.

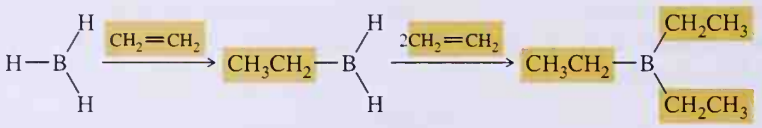


(Anti addition of —Br and HOH)

These discussions of the addition of HX, X_2, H_2O, $Hg(OAc)_2/H_2O$, and X_2/H_2O to alkenes illustrate several significant points about the development of reaction mechanisms. First, it is important to assemble as many facts as possible about the reaction under study. Information about regioselectivity and stereoselectivity is particularly useful. Second, mechanisms are subject to continual refinement as new information is gained about a reaction. Third, even after refinement creating a mechanism that is consistent with all the experimental observations, there is no guarantee that the mechanism is a truly accurate description of the reaction. Finally, there is no guarantee that a mechanism, which is apparently correct for one compound, still operates for another, seemingly closely related compound, or in a different solvent, or even at a different temperature.

5.4 Hydroboration

Hydroboration is the addition of borane, BH_3, to an alkene to form a trialkylborane. The overall reaction occurs in three separate steps. BH_3 reacts with one molecule of alkene, then a second, and finally a third until all three hydrogens of borane have been replaced by alkyl groups.



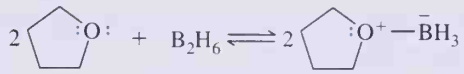
An alkylborane A trialkylborane

Borane cannot be prepared as a pure compound because it dimerizes to diborane, B_2H_6, a toxic gas that ignites spontaneously in air.

$$2BH_3 \rightleftharpoons B_2H_6$$

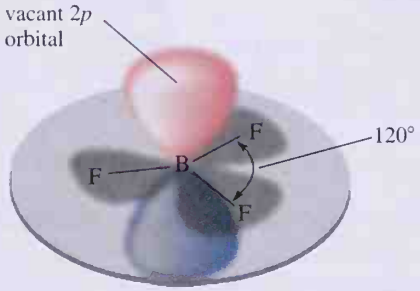
Borane Diborane

However, BH_3 can exist as a stable complex with an ether, such as tetrahydrofuran.



Tetrahydrofuran

Boron, atomic number 5, has three electrons in its valence shell. To bond with three other atoms, boron uses sp^2 hybrid orbitals. The unhybridized $2p$ orbital of boron is perpendicular to the plane created by boron and the three other atoms to which it is bonded. An example of a stable compound in which boron is bonded to three other atoms is boron trifluoride, BF_3, a planar molecule with F—B—F bond angles of 120°. Because of the vacant $2p$ orbital in the valence shell of boron, BH_3, BF_3, and all other compounds of trivalent boron are Lewis acids and act as electron-pair acceptors.

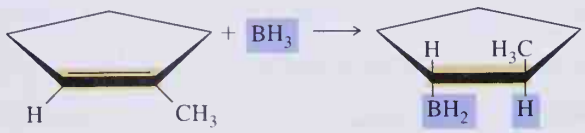


Addition of borane to alkenes is highly regioselective. In addition of borane to an unsymmetrical alkene, boron becomes bonded to the less substituted carbon of the double bond, as illustrated by the hydroboration of 1-hexene.

$$3CH_3CH_2CH_2CH_2CH{=}CH_2 + BH_3 \longrightarrow (CH_3CH_2CH_2CH_2CH_2CH_2)_3B$$

1-Hexene Trihexylborane

Hydroboration is also stereoselective. The major product is that in which hydrogen and boron add from the same side of the double bond, that is, the reaction is **syn stereoselective** as illustrated by hydroboration of 1-methylcyclopentene.

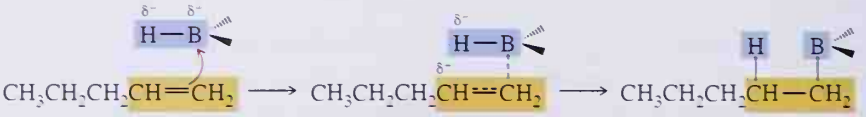


1-Methylcyclopentene (Syn addition of BH_3)

An acceptable mechanism for hydroboration must account for both the regioselectivity and the stereoselectivity. The regioselectivity of hydroboration can be accounted for by a combination of electronic and steric factors. The electronegativity of hydrogen (2.1) is slightly greater than that of boron (2.0), and hence there is a small degree of polarity

(approximately 5%) to each B—H bond, with boron bearing a partial positive charge and hydrogen a partial negative charge.

Addition of borane to an alkene is initiated by coordination of the vacant $2p$ orbital of boron (an electrophile) with the electron pair of the pi bond to form a transition state in which some degree of carbocation character occurs on the more substituted carbon of the double bond. This is followed by a breaking of a B—H sigma bond and the C—C pi bond, and formation of new C—H and C—B sigma bonds. It is thought that this process is concerted (bond making and bond breaking occur simultaneously) and that it involves a cyclic, four-center transition state.



Reaction is initiated with boron acting as the electrophile

Some carbocation character exists in the transition state

Boron adds to the less substituted carbon of the double bond

Thus, the regioselectivity of hydroboration can be accounted for by formation of some degree of carbocation character in the transition state on the carbon of the double bond better able to accommodate a partial positive charge. Alternatively, the regioselectivity can be accounted for by steric effects: boron, the larger part of the reagent, adds to the less hindered carbon of the alkene. It is believed that the observed regioselectivity is largely due to steric effects.

The stereoselectivity of hydroboration is accounted for by the formation of a cyclic, four-center transition state. Boron and hydrogen are added simultaneously and from the same side of the double bond.

Trialkylboranes are rarely isolated. Rather, they are converted directly to other products formed by substitution of another atom (H, O, N, C, or halogen) for boron. One of the most important reactions of trialkylboranes is with hydrogen peroxide in aqueous sodium hydroxide. Hydrogen peroxide is an oxidizing agent and under these conditions reacts with trialkylboranes to form an alcohol and sodium borate, Na_3BO_3. The net reaction from hydroboration and subsequent oxidation is hydration of a carbon-carbon double bond. Because hydrogen is added to the more substituted carbon of the original alkene, we refer to the results of hydroboration and subsequent oxidation as anti-Markovnikov hydration.

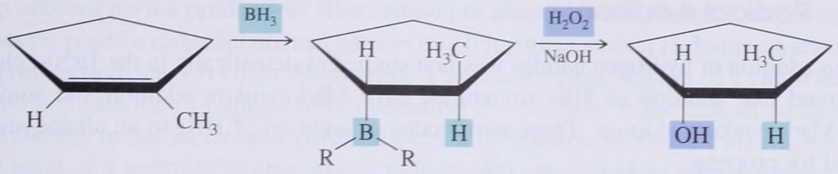
$$(CH_3CH_2CH_2CH_2CH_2CH_2)_3B + 3H_2O_2 + 3NaOH \longrightarrow$$

Trihexylborane

$$3CH_3CH_2CH_2CH_2CH_2CH_2OH + Na_3BO_3 + 3H_2O$$

1-Hexanol — Sodium borate

Hydrogen peroxide oxidation of a trialkylborane is stereoselective in that configuration is retained; whatever the position of boron in relation to other groups in the trialkylborane, the —OH group by which it is replaced occupies the same position.

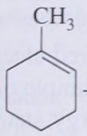


1-Methylcyclopentene | A trialkylborane (R = 2-Methylcyclopentyl) | *trans*-2-Methylcyclopentanol

EXAMPLE 5.4

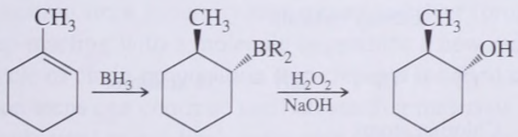
Draw structural formulas for the trialkylborane and alcohol formed in the following reaction sequences:

(a) $CH_3C(CH_3)=CHCH_3 \xrightarrow{BH_3}$ a trialkylborane $\xrightarrow[NaOH]{H_2O_2}$ an alcohol

(b)  $\xrightarrow{BH_3}$ a trialkylborane $\xrightarrow[NaOH]{H_2O_2}$ an alcohol

Solution

(a) $CH_3C(CH_3)=CHCH_3 \xrightarrow{BH_3} [CH_3CH(CH_3)CH_2]_3B \xrightarrow[NaOH]{H_2O_2} CH_3CH(CH_3)CH(OH)CH_3$

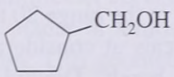
(b) 

(R = 2-Methylcyclohexyl) | *trans*-2-Methylcyclohexanol

PROBLEM 5.4

Draw structural formulas for the trialkylborane and alkene that give the following alcohols under the reaction conditions shown:

(a) an alkene $\xrightarrow{BH_3}$ a trialkylborane $\xrightarrow[NaOH]{H_2O_2}$ $CH_3CH(CH_3)CH_2CH_2OH$

(b) an alkene $\xrightarrow{BH_3}$ a trialkylborane $\xrightarrow[NaOH]{H_2O_2}$ 

5.5 Radical Additions

When addition of hydrogen halides was first studied systematically in the 1920s, chemists observed that addition of HBr sometimes gave Markovnikov addition and sometimes anti-Markovnikov addition. These two modes of addition of HBr to an alkene are illustrated for propene.

Markovnikov addition:

$$CH_3CH{=}CH_2 + HBr \longrightarrow CH_3\overset{\overset{Br}{|}}{C}HCH_3$$

Propene — 2-Bromopropane

Anti-Markovnikov addition:

$$CH_3CH{=}CH_2 + HBr \longrightarrow CH_3CH_2CH_2Br$$

Propene — 1-Bromopropane

The puzzling thing was that these variable additions occurred only for HBr. Both HCl and HI always add to alkenes according to Markovnikov's rule. The puzzle was solved in 1933 when it was discovered that addition of HBr to alkenes gives anti-Markovnikov products only in the presence of peroxides or other sources of radicals; in the absence of radicals, addition of HBr gives only the expected Markovnikov addition products.

A **radical** is any molecule or ion that contains one or more unpaired electrons. Although most radicals are highly reactive species, a few are stable, an example of which is molecular oxygen, O_2. Because the oxygen molecule in its lowest energy state contains two unpaired electrons (Section 1.9B), it is more accurately described as a diradical.

Radicals can be formed from molecules by cleavage of bonds in such a way that each atom or fragment participating in the bond retains one electron. In these equations **"fishhook" arrows** are used to show the change in position of single electrons.

$$CH_3CH_2O{-}OCH_2CH_3 \xrightarrow{80^\circ C} CH_3CH_2O\cdot + \cdot OCH_2CH_3 \qquad \Delta H = +36 \text{ kcal/mol}$$

Diethyl peroxide — Ethoxy radicals

$$Cl{-}Cl \xrightarrow{\text{light}} Cl\cdot + \cdot Cl \qquad \Delta H = +58 \text{ kcal/mol}$$

Chlorine — Chlorine atoms

$$CH_3{-}CH_3 \xrightarrow{700^\circ C} CH_3\cdot + \cdot CH_3 \qquad \Delta H = +88 \text{ kcal/mol}$$

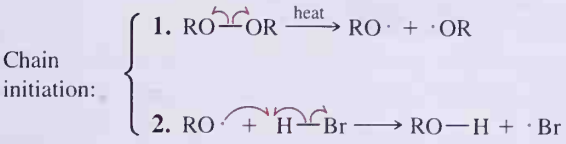
Ethane — Methyl radicals

Energy to cause bond cleavage and generation of radicals can be supplied either by light or heat. The energy of visible and ultraviolet radiation (wavelength from 200–700 nm) falls in the range of 41 to 143 kcal/mol and is of the same order of magnitude as the bond dissociation energies of single covalent bonds. Green light, for example, causes dissociation of chlorine molecules (bond dissociation energy 58 kcal/mol) into chlorine atoms. Alternatively, heating any molecule to a high enough temperature results in cleavage of bonds and generation of radicals.

Oxygen-oxygen single bonds in peroxides (ROOR) and hydroperoxides (ROOH) have dissociation energies in the range 20 to 40 kcal/mol, and compounds containing these bonds are cleaved to radicals at considerably lower temperatures than that required for rupture of carbon-carbon bonds. Diethyl peroxide, for example, dissociates to ethoxy radicals at 80°C.

To account for the products of HBr addition to alkenes in the presence of peroxides, chemists proposed a radical chain mechanism involving three steps: (1) chain initiation, (2) chain propagation, and (3) chain termination. The characteristic feature of a **chain initiation** step is formation of radicals from nonradical compounds. In the case of addition of HBr to alkenes in the presence of peroxides, chain initiation is by thermal cleavage of the O—O bond of a peroxide to give alkoxy radicals and reaction of an alkoxy radical with HBr to give a bromine atom.

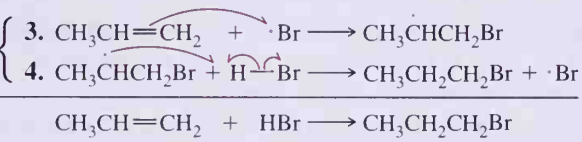
Chain initiation:



Note that the second chain initiation step has more of the character of a chain propagation step (discussed below) but is included under initiation because it produces a bromine atom necessary for the true chain propagation steps.

The characteristic feature of a **chain propagation** step is reaction of a radical and a molecule to give a product or products with an odd number of electrons. The product of a chain propagation step may be a single radical (Step 3) or a molecule and a radical (Step 4).

Chain propagation steps:

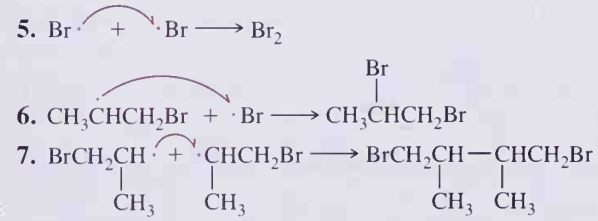


Steps 3 + 4 $CH_3CH{=}CH_2 + HBr \longrightarrow CH_3CH_2CH_2Br$

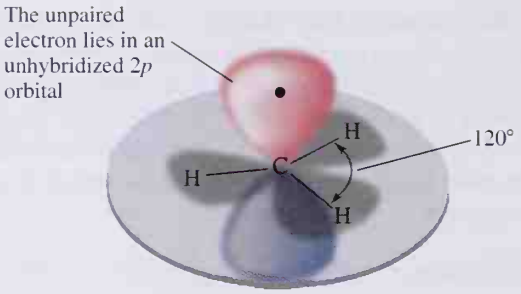
A characteristic feature of chain propagation steps is that when added together, they give the observed stoichiometry of the reaction. Adding Steps 3 and 4 and cancelling structures that appear on both sides of the equation gives the balanced equation for the radical addition of HBr to an alkene.

Propagation steps generally repeat over and over (propagate), with the radical formed in one step reacting with a molecule to produce a new radical, and so on. The number of times a cycle of chain propagation steps repeats is called **chain length.** In principle, chain propagation steps can continue until all starting materials are consumed. In practice, they continue only until two radicals react with each other to terminate the process. The characteristic feature of a **chain termination** step is destruction of radicals. The most important chain termination reactions in the peroxide-catalyzed addition of HBr to alkenes are radical coupling.

Chain termination steps:



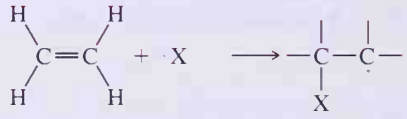
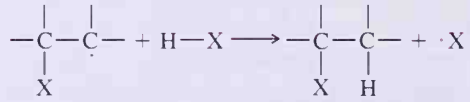
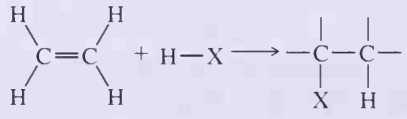
The structures, geometries, and relative stabilities of alkyl radicals are very similar to those of alkyl carbocations. Alkyl radicals are planar or almost so, with bond angles of 120° about the carbon with the unpaired electron. This geometry indicates that carbon is sp^2-hybridized and that the unpaired electron occupies the unhybridized $2p$ orbital. It has



been determined that the order of stability of alkyl radicals is tertiary > secondary > primary > methyl.

Radical addition is observed in the presence of peroxides because the rates of the radical chain propagation steps are much greater than the rate of carbocation formation. Thus, it is possible to control the products of addition of HBr to an alkene by controlling reaction conditions and thereby controlling the mechanism of addition.

The fact that HBr reacts with alkenes by radical addition, whereas HCl and HI do not can be accounted for by looking at the enthalpies and estimated energies of activation for the propagation steps of each process shown in the table. All three additions are exothermic. Using values of ΔH, it is possible to estimate the energy of activation of each propagation step. For radical addition of HBr, the heat of reaction of Step 3 is close to zero, and the energy of activation for this step is estimated to be only a few kcal/mol. It is also estimated to be only a few kcal/mol for Step 4. Radical addition of HCl fails because Step 4 is endothermic by about 5.0 kcal/mol, and the energy of activation is at least that and probably several kcal/mol higher. Given this energy of activation, chain transfer is immeasurably slow, and radical addition of HCl to alkenes is not observed. Radical addition of HI fails because addition of an iodine atom to an alkene is endothermic and the energy of activation for this step of radical addition is at least 10.0 kcal/mol.

		ΔH (kcal/mol)		
		X= Cl	Br	I
Step 3:		−12.0	0.0	+10.0
Step 4:		+5.0	−10.5	−26.7
Net reaction:		−7.0	−10.5	−16.5

5.6 Allylic Halogenation

When an alkene is treated with bromine or chlorine at high temperature, a halogen is substituted for hydrogen at an allylic position (Section 5.1).

A. Conditions for Allylic Halogenation

We already saw in Section 5.3 that propene and higher alkenes react with bromine in carbon tetrachloride at *room temperature* by addition to the carbon-carbon double bond. If, however, bromine and propene are allowed to react at *high temperatures* or under conditions in which the concentration of bromine is very low relative to that of the alkene, an entirely different reaction takes place, namely, **allylic substitution.**

$$CH_2{=}CHCH_3 + Br_2 \xrightarrow{\text{high temp.}} CH_2{=}CHCH_2Br + HBr$$

Propene — 3-Bromopropene

At 400°C, propene and chlorine react similarly.

$$CH_2{=}CHCH_3 + Cl_2 \xrightarrow{\text{high temp.}} CH_2{=}CHCH_2Cl + HCl$$

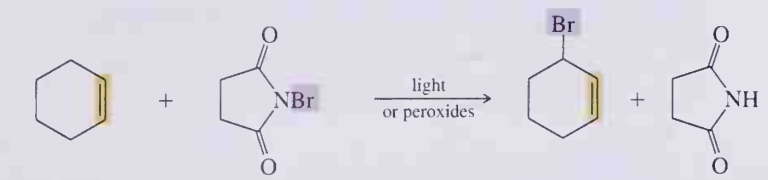
Propene — 3-Chloropropene

Reaction of propene with bromine and chlorine illustrates a very important point about organic reactions: it is often possible to change the product of a reaction by changing reaction conditions and thereby changing the mechanism of the reaction.

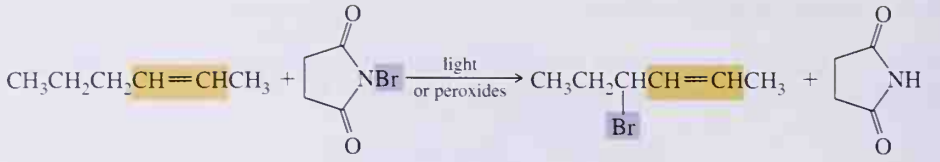
$$CH_2{=}CHCH_3 + Br_2 \xrightarrow{\text{high temp.}} CH_2{=}CHCH_2Br + HBr \qquad \text{(allylic substitution)}$$

$$CH_2{=}CHCH_3 + Br_2 \xrightarrow[CCl_4]{\text{room temp.}} CH_2CHCH_3 \quad (Br, Br) \qquad \text{(electrophilic addition)}$$

Allylic bromination occurs at high temperatures or when the concentration of bromine is very low relative to that of the alkene. One very important way to carry out allylic bromination at or slightly above room temperature is to use the reagent ***N*-bromosuccinimide (NBS)** in carbon tetrachloride. Reaction between an alkene and NBS must be initiated either by light or a peroxide such as dibenzoyl peroxide.



Cyclohexene — *N*-Bromosuccinimide (NBS) — 3-Bromocyclohexene — Succinimide



2-Hexene NBS 4-Bromo-2-hexene (major product) Succinimide

In the NBS reaction, a double substitution occurs: bromine for hydrogen in the alkene and hydrogen for bromine in NBS. Note that in the reaction of NBS (and also for bromine at high temperature) with 2-hexene, allylic substitution is regioselective, that is, bromine is substituted for a secondary allylic hydrogen in preference to a primary allylic hydrogen (4-bromo-2-hexene is the major product, and only trace amounts of the isomeric 1-bromo-2-hexene are formed).

We already encountered another example of this type of regioselectivity in a substitution reaction in Section 2.9 in which we studied the bromination and chlorination of alkanes and cycloalkanes. Recall that reaction of an alkane with bromine or chlorine at elevated temperature shows the following regioselectivity: 3° hydrogen > 2° hydrogen > 1° hydrogen. A similar regioselectivity is shown for allylic halogenation of alkenes. Indeed, as we shall see, the mechanisms for halogenation of alkanes and allylic halogenation of alkenes are remarkably similar.

B. Mechanism of Allylic Halogenation: A Radical Reaction

From detailed studies of allylic substitutions, chemists have concluded that this reaction proceeds by a radical mechanism involving chain initiation, chain propagation, and chain termination steps such as those we just studied for peroxide-catalyzed anti-Markovnikov addition of HBr to alkenes. The purpose of the light or heat is to bring about bond cleavage and initiate reaction. To predict which of the various bonds is most likely to break when a mixture of bromine and propene is heated, we need to look at bond dissociation energies (Table 5.2). From the information in Table 5.2, we see that Br—Br is the weakest bond in a collection of bromine and propene molecules. When heated or exposed to light of an appropriate wavelength, bromine cleaves to two bromine atoms (radicals), thus providing initiation for the ensuing radical chain reaction.

Table 5.2 Selected bond dissociation energies

Bond	Bond Dissociation Energy (kcal/mol)
Br—Br	46
$CH_2{=}CHCH_2{-}H$	89
$CH_2{=}\underset{\displaystyle H}{\overset{\displaystyle |}{C}}CH_3$	108

Chain initiation: $Br{-}Br \xrightarrow[\text{or light}]{\text{heat}} Br\cdot + \cdot Br$

Following are two chain propagation steps. In the first, a bromine atom abstracts an allylic hydrogen (the weakest C—H bond in propene) to produce an allyl radical. The allyl radical in turn reacts with a bromine molecule to form allyl bromide and a new bromine atom. Note that as must be the case, this combination of chain propagation steps adds up to the observed stoichiometry.

Chain propagation:

$$CH_2{=}CHCH_3 + \cdot Br \longrightarrow CH_2{=}CHCH_2\cdot + HBr$$

$$CH_2{=}CHCH_2\cdot + Br_2 \longrightarrow CH_2{=}CHCH_2Br + \cdot Br$$

Sum of chain propagation steps:

$$CH_2{=}CHCH_3 + Br_2 \longrightarrow CH_2{=}CHCH_2Br + HBr$$

Propagation of the chain reaction continues until termination steps produce nonradical products and thus stop further reaction.

Possible chain termination steps:

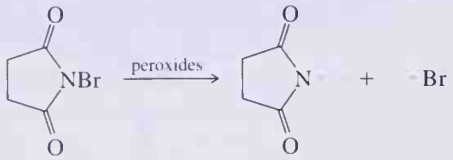
$$Br\cdot + \cdot Br \longrightarrow Br_2$$

$$CH_2{=}CHCH_2\cdot + \cdot Br \longrightarrow CH_2{=}CHCH_2Br$$

$$2CH_2{=}CHCH_2\cdot \longrightarrow CH_2{=}CHCH_2CH_2CH{=}CH_2$$

Allylic bromination brought about by *N*-bromosuccinimide in CCl_4 also proceeds by way of a radical chain reaction. It is thought that the reaction is initiated by formation of a bromine atom made possible by dissociation of NBS.

Possible chain initiation:



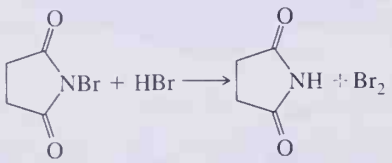
NBS — *N*-Succinimide radical — Bromine atom

The bromine atom then reacts with propene to form HBr and an allyl radical.

Beginning of chain propagation:

$$CH_2{=}CHCH_3 + \cdot Br \longrightarrow CH_2{=}CHCH_2\cdot + HBr$$

Next, reaction of HBr with NBS in a fast, ionic reaction forms bromine, Br_2, and succinimide.



The concentration of Br_2 present at any time in the reaction mixture is very low and is limited by the concentration of HBr from which it must be formed. Bromine formed in this step then reacts with an allyl radical to continue the chain propagation reaction. Thus, in effect, NBS reacts with the HBr formed in the first chain propagation step to yield Br_2,

which then continues the chain reaction. The chain reaction continues until one of the chain termination steps already listed leads to destruction of radicals and termination of the reaction.

The mechanism we described for allylic bromination by NBS poses the following problem. NBS is the direct source of Br_2, which then takes part in chain propagation. But if Br_2 is present in the reaction, why does it not instead react with the carbon-carbon double bond by electrophilic addition? In other words, why is the observed reaction allylic substitution rather than electrophilic addition? The answer is that the rates of the chain propagation steps, once initiated, are much faster than the rate of electrophilic addition of bromine to the alkene.

C. Structure of the Allyl Radical

The allyl radical can be represented as a hybrid of two contributing structures. Here fishhook arrows show the movement of single electrons and how the contributing structure on the left is converted to the one on the right.

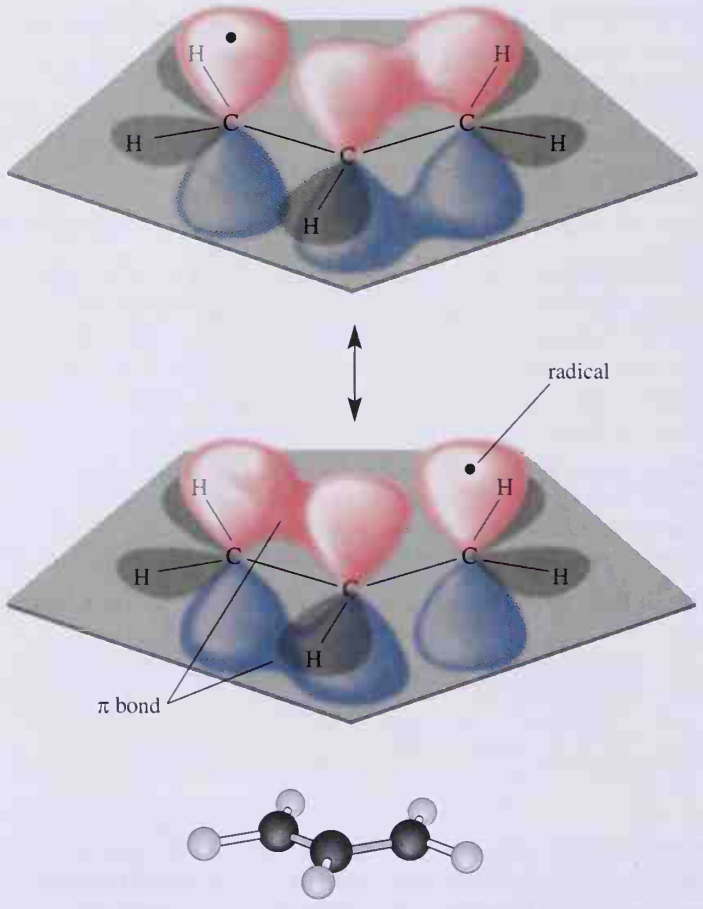
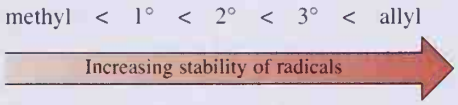


Figure 5.5
Valence bond description of the allyl radical.

Equivalent contributing structures

All eight atoms of the allyl radical lie in a plane, and all bond angles are approximately 120°. Each carbon atom is sp^2-hybridized, and the three $2p$ orbitals participating in resonance stabilization of the radical are parallel to one another as shown in Figure 5.5. Because contributing structures for the allyl radical are equivalent, resonance is important, and the allyl radical is considerably more stable than might be expected by looking at just one contributing structure. Recall from Section 5.5D that tertiary radicals are more stable than secondary radicals, which are in turn more stable than primary radicals. Radicals stabilized by resonance involving equivalent or nearly equivalent structures are even more stable than tertiary radicals. We can, therefore, expand our understanding of the order of stability of radicals to the following:



D. Halogenation of Alkanes Revisited

Armed with the insight we now have into the mechanism of radical addition of HBr to alkenes and allylic bromination and chlorination of alkenes, we are now in a position to reexamine bromination and chlorination of alkanes (Section 2.9B). Each proceeds by a radical chain mechanism initiated by dissociation of halogen into halogen atoms (radicals). The bond dissociation energy of Br_2 is 46 kcal/mol; that for Cl_2 is 56.8 kcal/mol. Each dissociation can be brought about by visible or ultraviolet light or by heating to temperatures above 400°C. We illustrate radical halogenation of alkanes by the reaction of chlorine with ethane.

Chain initiation:

1. $Cl_2 \xrightarrow[\text{or light}]{\text{heat}} Cl\cdot + \cdot Cl$

Chain propagation:

2. $CH_3CH_3 + \cdot Cl \longrightarrow CH_3CH_2\cdot + HCl$

3. $CH_3CH_2\cdot + Cl_2 \longrightarrow CH_3CH_2Cl + \cdot Cl$

Chain termination:

4. $2CH_3CH_2\cdot \longrightarrow CH_3CH_2CH_2CH_3$

5. $CH_3CH_2\cdot + \cdot Cl \longrightarrow CH_3CH_2Cl$

6. $Cl\cdot + \cdot Cl \longrightarrow Cl_2$

Note that as required, combination of the chain propagation Steps (2 + 3) adds up to the observed stoichiometry:

Steps 2 & 3: $CH_3CH_3 + Cl_2 \longrightarrow CH_3CH_2Cl + HCl$

This type of radical chain mechanism allows us to account for the formation of haloalkanes.

From data on product distribution, we can conclude that 3° hydrogens are more easily abstracted than 2° hydrogens, which in turn are more easily abstracted than 1° hydrogens. We also conclude that the order of stability of alkyl radicals is 3° > 2° > 1°. Another obvious conclusion is that although both bromine and chlorine are regioselective in hydro-

gen abstraction in the order $3° > 2° > 1°$, the effect is much greater for bromination (1600 : 80 : 1) than for chlorination (5 : 4 : 1).

The regioselectivity in halogenation of alkanes can be accounted for in terms of the relative stabilities of radicals. But how do we account for the greater regioselectivity in bromination of alkanes compared with chlorination of alkanes? To do so, we need to consider a refinement of transition state theory proposed in 1955 by George Hammond, then of the California Institute of Technology.

Hammond's Postulate

According to what has become known as **Hammond's postulate,** the higher the energy of activation for a process, the later in the course of the reaction the transition state is reached. Shown in Figure 5.6 are reaction energy diagrams for a highly exothermic reaction and a highly endothermic reaction. The structure of the transition state for the exothermic reaction (with a lower energy of activation) looks more like the reactants. Conversely, the structure of the transition state for the endothermic reaction (with a higher energy of activation) looks more like the products. It is important to realize that we cannot observe transition states directly; we can only infer their existence, structure, and so forth. What Hammond's postulate does is give us a reasonable way of deducing something about the structure of the transition state by examining things we can observe: the structure of reactants and products, and heats of reaction and energies of activation.

Now let us apply Hammond's postulate to explain the relative regioselectivities of chlorination versus bromination of alkanes. The rate-determining step in halogenation of alkanes is abstraction of a hydrogen atom by a halogen atom. In the table are heats of reaction and energies of activation for hydrogen abstraction in radical chlorination and bromination of ethane. Also given under the formulas of ethane, HCl, and HBr are bond dissociation energies for the particular bonds broken and formed. Abstraction of hydrogen by chlorine has a lower energy of activation, and, therefore, according to Hammond's postulate, the transition state is reached sooner in the course of the reaction (Figure 5.7[a]).

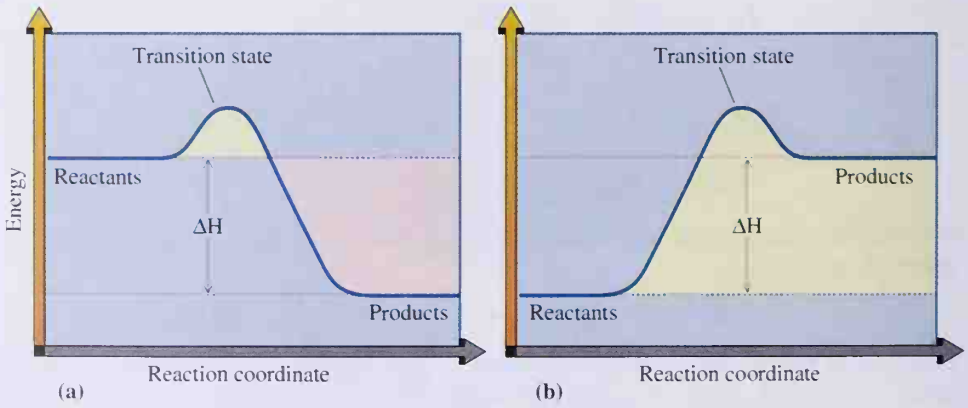


Figure 5.6
The Hammond postulate. Reaction energy diagrams for (a) a highly exothermic reaction and (b) a highly endothermic reaction. In an exothermic reaction, the transition state resembles the reactants. In an endothermic reaction, it resembles the products.

Reaction Step	E_a (kcal/mol)	ΔH (kcal/mol)
$CH_3CH_3 + \cdot Cl \longrightarrow CH_3CH_2\cdot + HCl$ $(\Delta H = +98)$ $(\Delta H = -103)$	+1.0	−5.0
$CH_3CH_3 + \cdot Br \longrightarrow CH_3CH_2\cdot + HBr$ $(\Delta H = +98)$ $(\Delta H = -88)$	+13.2	+10.0

Conversely, abstraction of hydrogen by bromine has a higher energy of activation, and the transition state is reached later in the course of the reaction. (Figure 5.7[b]).

The structure of the transition for hydrogen abstraction in chlorination resembles that of the reactants: ethane and a chlorine atom. In this instance, the type of bond broken has relatively little influence on the course of the reaction, and the products are determined more by whether a chlorine atom collides with a primary, secondary, or tertiary hydrogen. Because tertiary C—H bonds are weaker than secondary C—H bonds, which in turn are weaker than primary C—H bonds, some regioselectivity occurs in chlorination in the order $3° > 2° > 1°$ hydrogens.

The structure of the transition state for hydrogen abstraction by bromine resembles that of the products: an alkyl radical and HBr, and the type of C—H bond broken has a marked influence on the course of the reaction. Given the relative stabilities of radicals ($3° > 2° > 1°$), very high regioselectivity occurs in radical halogenation in the order $3° > 2° > 1°$ hydrogens.

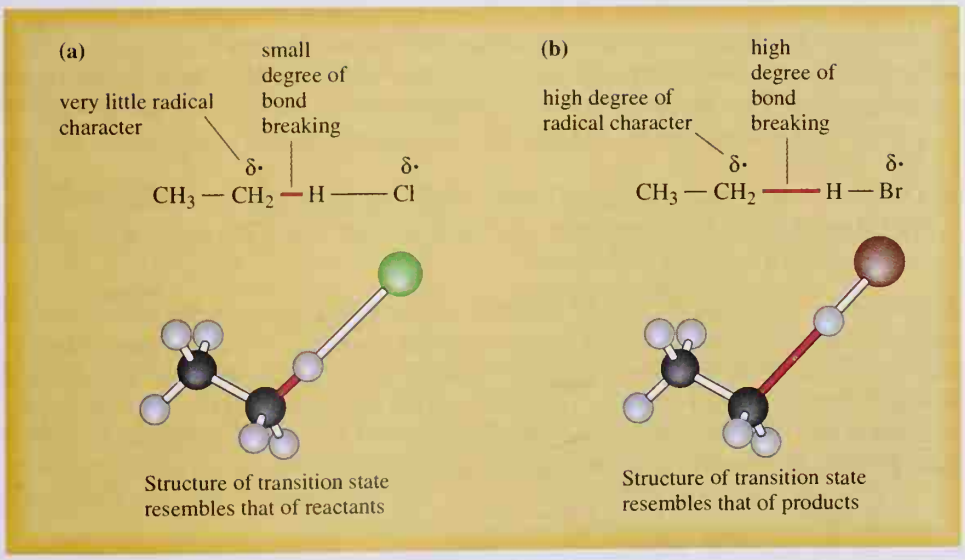


Figure 5.7
Transition states for hydrogen abstraction for radical halogenation of ethane. (a) Chlorination and (b) bromination.

5.7 Oxidation

Because of the importance of oxidation and reduction reactions in chemistry, it is essential to be able to recognize reactions that involve oxidation, those that involve reduction, and those that involve neither oxidation nor reduction.

A. How to Recognize Oxidation-Reduction

In the following reactions, propene is transformed into a variety of compounds by reactions we study in this chapter. One reaction involves reduction, two involve oxidation, and one involves neither oxidation nor reduction. These equations are not complete because they do not specify any reactant other than propene; they do not specify what reagents are necessary to bring about the particular transformation. Each does specify, however, that the carbon atoms of the products are derived from those of propene.

1. $CH_3CH{=}CH_2 \longrightarrow CH_3\underset{\displaystyle H}{\underset{|}{C}}H-\underset{\displaystyle H}{\underset{|}{C}}H_2$ (reduction)

2. $CH_3CH{=}CH_2 \longrightarrow CH_3\underset{\displaystyle HO}{\underset{|}{C}}H-\underset{\displaystyle H}{\underset{|}{C}}H_2$ (neither oxidation nor reduction)

3. $CH_3CH{=}CH_2 \longrightarrow CH_3\underset{\displaystyle HO}{\underset{|}{C}}H-\underset{\displaystyle OH}{\underset{|}{C}}H_2$ (oxidation)

4. $CH_3CH{=}CH_2 \longrightarrow CH_3\overset{\displaystyle O}{\overset{\|}{C}}H + H\overset{\displaystyle O}{\overset{\|}{C}}H$ (oxidation)

It is possible to decide if transformations such as these involve oxidation, reduction, or neither by the use of **balanced half-reactions.** To write a balanced half-reaction

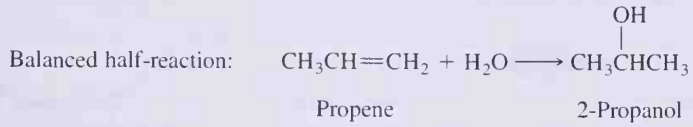
1. Write a half-reaction showing the organic reactant(s) and product(s).
2. Complete a material balance, that is, balance the number of atoms on each side of the half-reaction. To balance the number of oxygens and hydrogens for a reaction taking place in acid solution, use H^+ and H_2O. For a reaction taking place in basic solution, use OH^- and H_2O.
3. Complete a charge balance, that is, balance the charge on both sides of the half-reaction. To balance charge, add electrons, e^-, to one side or the other. The equation completed in this step is a balanced half-reaction.

Oxidation is defined as the loss of electrons. If electrons appear on the right side of a balanced half-reaction, the reactant has given up electrons and has been oxidized. **Reduction** is defined as the gain of electrons. If electrons appear on the left side of a balanced half-reaction, the reactant has gained electrons and has been reduced. If no electrons appear in the balanced half-reaction, then the transformation involves neither oxidation nor reduction. Let us apply these steps to the transformation of propene to propane.

Half-reaction:	**1.** $CH_3CH{=}CH_2 \longrightarrow CH_3CH_2CH_3$
Material balance:	**2.** $CH_3CH{=}CH_2 + 2H^+ \longrightarrow CH_3CH_2CH_3$
Charge and material balance:	**3.** $CH_3CH{=}CH_2 + 2H^+ + 2e^- \longrightarrow CH_3CH_2CH_3$

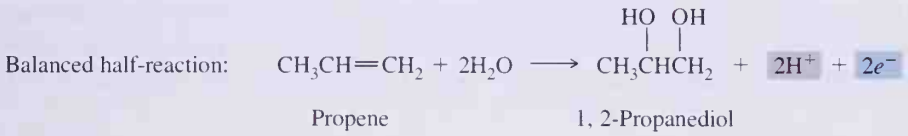
Because two electrons appear on the left side of the balanced half-reaction (Step 3), conversion of propene to propane is a two-electron reduction. To bring it about requires use of a reducing agent.

Following is a balanced half-reaction for the transformation of propene to 2-propanol:



Because no electrons are required to achieve an electrical balance, conversion of propene to 2-propanol is neither oxidation nor reduction. It does involve addition to a carbon-carbon double bond and is given the descriptive name hydration (Table 5.1).

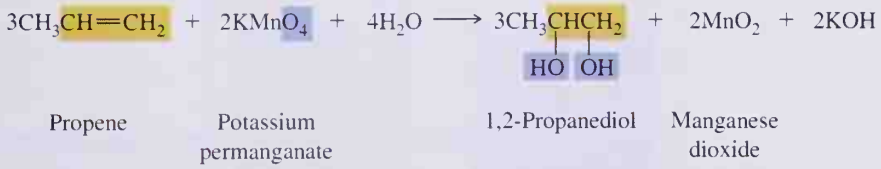
A balanced half-reaction for the transformation of propene to 1,2-propanediol requires two electrons on the right for a charge balance; this transformation is a two-electron oxidation.



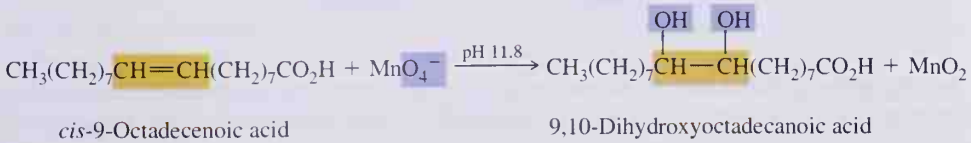
It is important to realize that this strategy for recognizing oxidation and reduction is only that—a strategy. In no way does it give any indication of how a particular oxidation or reduction might be carried out in the laboratory. For example, the balanced half-reaction for the transformation of propene to propane requires $2H^+$ and $2e^-$. Yet by far the most common laboratory procedure for reducing propene does not involve H^+ at all; rather it involves molecular hydrogen, H_2, and a metal catalyst.

B. $KMnO_4$ and OsO_4: Oxidation of Alkenes to Glycols

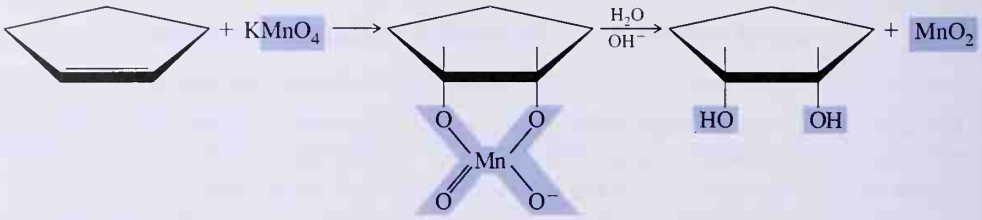
The higher oxidation states of certain transition metals, particularly Mn(VII) and Os(VIII) are effective oxidizing agents for the conversion of an alkene to a **glycol,** a compound with hydroxyl groups on adjacent carbons. In this two-electron oxidation, permanganate is reduced to manganese dioxide, MnO_2, which precipitates as a brown solid.



To form glycols in high yield, it is necessary to control reaction conditions very carefully. Most importantly, the reaction medium must remain quite basic and must be kept cold. For example, it is possible to convert *cis*-9-octadecenoic acid (oleic acid) to 9,10-dihydroxyoctadecanoic acid (9,10-dihydroxystearic acid) in 60% yield at pH 11.8. If however, the pH of the reaction medium is reduced to 9.0, the yield of the desired glycol is only 4%.

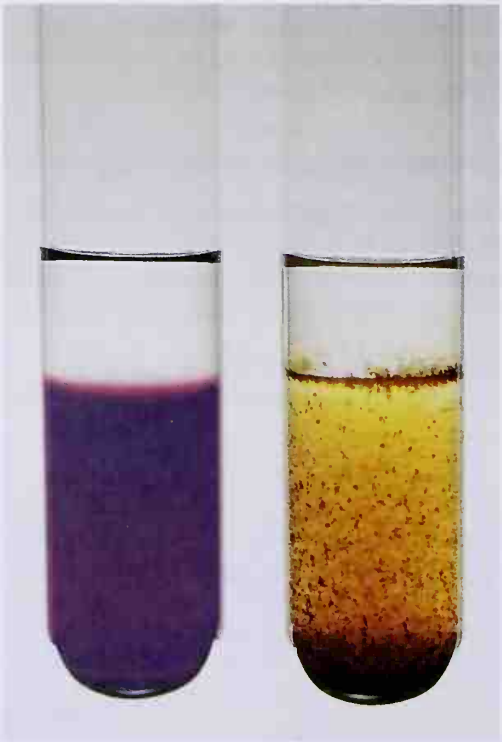


Oxidation of an alkene by potassium permanganate is stereoselective in that it involves syn addition of —OH groups to carbons of the double bond. For example, oxidation of cyclopentene by $KMnO_4$ gives *cis*-1,2-cyclopentanediol, a ***cis*-glycol.** Note that both *cis* and *trans* isomers are possible for this glycol. Because only the *cis*-glycol is formed, this oxidation is said to be stereoselective.



Cyclopentene (A cyclic manganese ester) *cis*-1,2-Cyclopentanediol (a *cis*-glycol)

The stereoselectivity of permanganate oxidation of alkenes is accounted for by the formation of a cyclic manganese ester intermediate in the oxidation. To form this intermediate, oxygen atoms of permanganate ion form new covalent bonds with each carbon of the

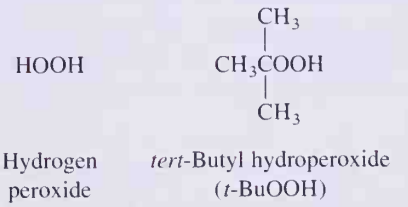


Aqueous $KMnO_4$ shaken with hexane *(left)* retains its purple color. The purple color is removed by reaction with 1-hexene *(right)*, and a brown precipitate of MnO_2 is formed. *(Charles D. Winters)*

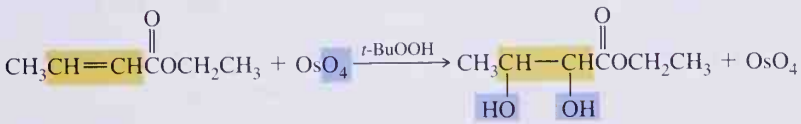
double bond in such a way that the five-member manganese-containing ring is fused in a *cis* configuration to the original alkene. Reaction of this cyclic intermediate with water or hydroxide ion breaks each manganese-oxygen bond and forms manganese dioxide and the *cis*-glycol.

Reaction with permanganate is the basis for a qualitative test for alkenes. An aqueous solution of potassium permanganate is deep purple in color. When permanganate solution reacts with an alkene, the purple color of permanganate disappears and a brown precipitate of MnO_2 appears. Disappearance of the purple color coupled with appearance of a brown precipitate is evidence for the presence of a carbon-carbon double bond. This test is not completely specific for alkenes, however, because several other functional groups also reduce permanganate to manganese dioxide.

Another reagent used to convert alkenes to *cis*-glycols is osmium tetroxide, OsO_4. Like $KMnO_4$, this reagent also forms a cyclic ester intermediate and results in syn addition of —OH groups to an alkene double bond. The chief drawbacks of OsO_4 are that it is both expensive and highly toxic. One strategy to circumvent the high cost of OsO_4 is to develop experimental methods that use it in catalytic amounts along with stoichiometric amounts of another oxidizing agent the function of which is to reoxidize reduced osmium compounds and thus recycle Os(VIII). Oxidizing agents used in conjunction with catalytic amounts of OsO_4 are hydrogen peroxide and *tert*-butyl hydroperoxide, an organic derivative of hydrogen peroxide.

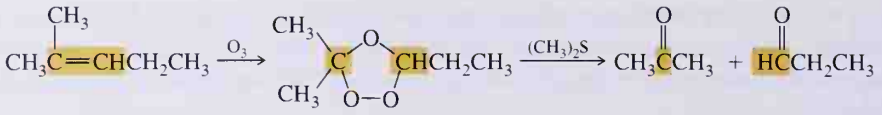


The following example shows oxidation of the ethyl ester of 2-butenoic acid. The only change is syn hydroxylation of the carbon-carbon double bond. Yield of the glycol in this oxidation is 71%.



C. Ozone: Cleavage of Carbon-Carbon Double Bonds

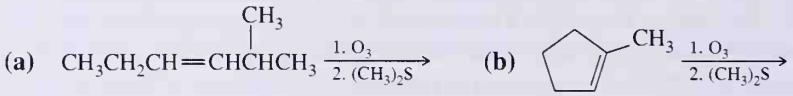
Treatment of an alkene with ozone, O_3, can be used to cleave a carbon-carbon double bond and form two carbonyl (C=O) groups in its place. In practice, the alkene is dissolved in an inert solvent such as CCl_4, and a stream of ozone is bubbled through the solution. A key intermediate in this reaction is an ozonide resulting from addition of ozone to the carbon-carbon double bond. In practice, the products isolated from ozonolysis depend on the reaction conditions. Hydrolysis of an ozonide yields hydrogen peroxide, an oxidizing agent that can bring about further oxidations. To prevent formation of hydrogen peroxide, a weak reducing agent is added during the work-up to reduce hydrogen peroxide to water. The reducing agent most commonly used for this purpose is dimethyl sulfide, $(CH_3)_2S$, as illustrated in the following example:



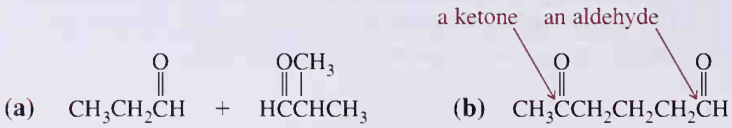
2-Methyl-2-pentene (an ozonide) Propanone (a ketone) Propanal (an aldehyde)

EXAMPLE 5.5

Draw structural formulas for the products of the following ozonolysis reactions. Name the new functional groups formed in each oxidation.



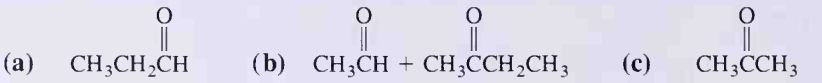
Solution



Propanal (an aldehyde) 2-Methylpropanal (an aldehyde) 5-Oxohexanal (a ketoaldehyde)

PROBLEM 5.5

What alkene of molecular formula C_6H_{12}, when treated with ozone and then dimethyl sulfide, gives the following product(s)?



(only product) (equal moles of each) (only product)

5.8 Catalytic Reduction

Virtually all alkenes, no matter what the nature of the substituents on the double bond, react quantitatively with molecular hydrogen, H_2, in the presence of a transition metal catalyst, the most commonly used of which are platinum, palladium, ruthenium, and nickel.

A. Mechanism of Catalytic Reduction

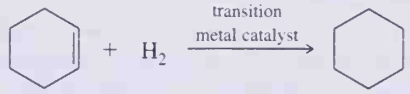
Although addition of hydrogen to an alkene is exothermic (the heat of hydrogenation of ethene is -32.8 kcal/mol and that of cyclohexene is -28.6 kcal/mol), reduction is immeasurably slow in the absence of a catalyst. The metal catalyst is used as a finely powdered solid or may be supported on some inert material such as charcoal or alumina. Reaction is

Parr shaker-type hydrogenation apparatus. *(Parr Instrument Co., Moline, Ill.)*

carried out by dissolving the alkene in ethanol or another nonreacting organic solvent, adding the solid catalyst, and then exposing the mixture to hydrogen gas at pressures from 1 to 50 atm. Alternatively, the metal may be complexed with certain organic molecules and used in the form of a soluble complex ion. The reaction that takes place is one of addition of hydrogen to the double bond, and in the process an alkene is converted into an alkane.

$$CH_2{=}CH_2 + H_2 \xrightarrow[\text{metal catalyst}]{\text{transition}} CH_3CH_3$$

Ethene (ethylene) — Ethane



Cyclohexene — Cyclohexane

Because conversion of an alkene to an alkane involves reduction by hydrogen in the presence of a catalyst, the process is called **catalytic reduction,** or alternatively, **catalytic hydrogenation.**

We know that in catalytic reduction, two hydrogens are added to the carbon-carbon double bond. But what of the stereoselectivity of this reaction? Are hydrogen atoms added from the same side of the double bond, from opposite sides of the double bond, or is the product a mixture of both types of addition? Addition of hydrogen to ethene (ethylene) or to cyclohexene tells us nothing about the stereoselectivity of catalytic reduction, because in these examples, there is no way to determine from what direction hydrogens have been added. We can determine this direction, however, by studying the reduction of properly substituted cycloalkenes. Catalytic reduction of 1,2-dimethylcyclohexene, for example, yields predominantly *cis*-1,2-dimethylcyclohexane; 70% to 85% depending on experimental conditions. Along with the *cis*-isomer are formed lesser amounts of *trans*-1,2-dimethylcyclohexane (30%–15%).

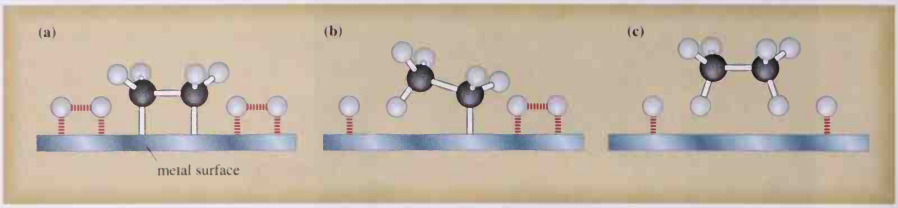
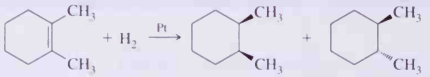


Figure 5.8
Addition of hydrogen to an alkene involving a metal catalyst. (a) Hydrogen and the alkene are adsorbed on the metal surface, and (b) one hydrogen is transferred to the alkene forming a new C—H bond. The other carbon remains adsorbed on the metal surface. (c) A second C—H bond is formed and the alkane is desorbed.



1,2-Dimethylcyclohexene — 70% – 85% *cis*-1,2-Dimethylcyclohexane — 30% – 15% *trans*-1,2-Dimethylcyclohexane

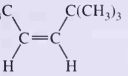
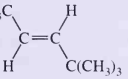
This and other experimental observations show that in most cases of catalytic reduction of alkenes, both hydrogens are added from the same side of the double bond, that is, by **syn addition.** There are often, however, appreciable percentages of product resulting from anti addition. An acceptable mechanism for catalytic reduction must account for the role of the catalyst and for the fact that although addition of hydrogens is most commonly syn, anti addition is also frequently observed.

Chemists have learned that transition metals are able to adsorb large quantities of hydrogen onto their surfaces, probably by forming metal-hydrogen sigma bonds. Similarly, alkenes are also adsorbed on metal surfaces with formation of carbon-metal bonds as shown in Figure 5.8(a). Addition of hydrogens to the alkene most probably occurs in two steps. First, one new C—H bond is formed to give an intermediate in which the alkene remains partially adsorbed to the metal surface (Figure 5.8[b]). If no rotation occurs about the carbon-carbon bond in the intermediate, and the second hydrogen is added from the same side as the first, then addition is syn. If, however, rotation occurs by 180°, and the second hydrogen is subsequently added from the opposite side from the first, then addition of hydrogens is anti.

B. Heats of Hydrogenation and the Relative Stabilities of Alkenes

Heat of hydrogenation is defined as the change in enthalpy, ΔH, for the reaction between an alkene and hydrogen to form an alkane. Table 5.3 lists heats of hydrogenation for several alkenes. Three important points are derived from the information given in Table 5.3.

Table 5.3 Heats of hydrogenation of several alkenes

Name	Structural Formula	ΔH (kcal/mol)
ethene	$CH_2{=}CH_2$	−32.8
propene	$CH_3CH{=}CH_2$	−30.1
1-butene	$CH_3CH_2CH{=}CH_2$	−30.3
cis-2-butene		−28.6
trans-2-butene		−27.6
cis-4,4-dimethyl-2-pentene		−30.8
trans-4,4-dimethyl-2-pentene		−26.5

1. Reduction of an alkene to an alkane is an exothermic process. This observation is consistent with the fact that during hydrogenation, there is net conversion of a pi bond to a sigma bond (i.e., one sigma bond (H—H) and one pi bond (C=C) are broken, and two new sigma bonds (C—H) are formed). For a comparison of the relative strengths of sigma and pi bonds, refer to Section 4.2B.
2. Heats of hydrogenation depend on the degree of substitution; the greater the substitution, the lower the heat of hydrogenation. Compare for example, heats of hydrogenation of ethene (no substituents), propene (one substituent), 1-butene (one substituent), and the *cis-trans* isomers of 2-butene (two substituents).
3. The heat of hydrogenation of a *trans*-alkene is lower than that of the isomeric *cis*-alkene. Compare, for example, the heats of hydrogenation of *cis*-2-butene and *trans*-2-butene. Because reduction of each alkene gives the same compound (namely, butane), any difference in heats of hydrogenation must be due to differences in relative energy between the two alkenes (Figure 5.9). The alkene with the lower (less negative) value of ΔH is the more stable alkene.

The greater stability of *trans*-alkenes relative to *cis*-alkenes can be explained in terms of steric strain and can be visualized by examining space-filling models of the *cis* and *trans* isomers of 2-butene (Figure 5.10). Space-filling models are built to scale and show relative sizes of atoms and groups of atoms in molecules. In *cis*-2-butene, the two $-CH_3$ groups are sufficiently close to each other that a net repulsion exists between the electron clouds of each. This repulsion is reflected in the larger heat of hydrogenation (decreased stability) of

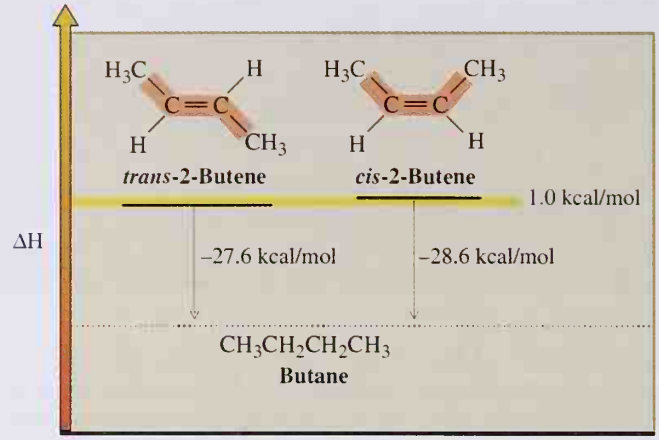
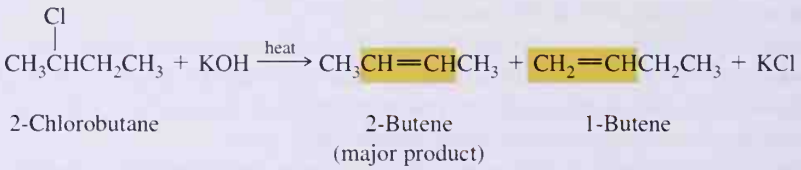


Figure 5.9
Heats of hydrogenation of *cis*-2-butene and *trans*-2-butene.

cis-2-butene compared with *trans*-2-butene. In the case of the *cis* and *trans* isomers of 2-butene, steric strain is between two methyl groups and results in an energy difference of approximately 1.0 kcal/mol. In the *cis* and *trans* isomers of 4,4-dimethyl-2-pentene (Table 5.2), steric strain is between a methyl group and a *tert*-butyl group and results in an energy difference between configurational isomers of approximately 4.3 kcal/mol.

EXAMPLE 5.6

In Section 4.5 we saw that dehydrohalogenation of haloalkanes often leads to formation of isomeric alkenes. For example, dehydrohalogenation of 2-chlorobutane gives 2-butene as the major product and 1-butene as the minor product.



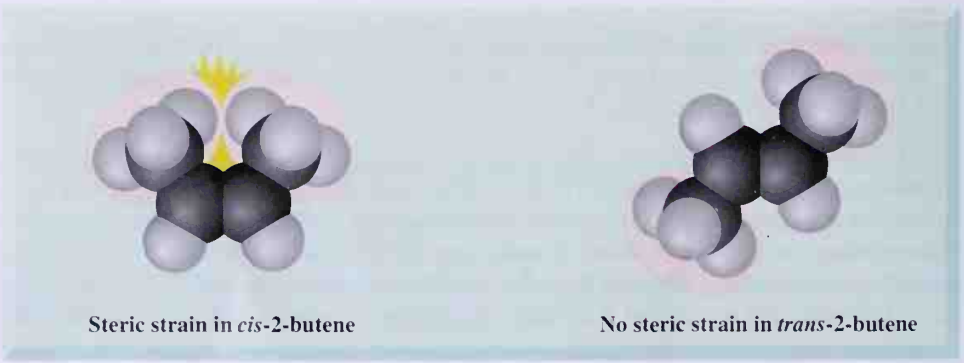


Figure 5.10
Space-filling models of *cis*-2-butene and *trans*-2-butene.

(a) From the discussion of dehydrohalogenation of haloalkanes given in Section 4.5, what generalization can you make about the relationship between major and minor products and the relative stabilities of isomeric alkenes?

(b) In the dehydrohalogenation of 2-chlorobutane, 2-butene is the major product. Which stereoisomer (*cis* or *trans*) of 2-butene do you expect to predominate? Explain.

Solution

(a) According to the examples in Section 4.5, the major product is the alkene with the greater number of substituents on the carbon-carbon double bond. We saw in this section that the greater the number of substituents on the double bond, the more stable the alkene. Therefore, we conclude that in dehydrohalogenation of a haloalkane, the major product is the more stable alkene.

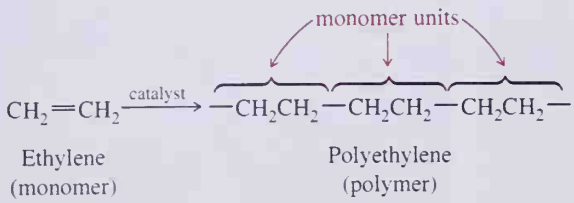
(b) Given the generalization in part (a), predict that more *trans*-2-butene (the more stable configurational isomer) is formed than *cis*-2-butene. Although the generalizations of parts (a) and (b) are good ones at this point, we see in Chapter 10 that the process is not quite that simple. In many instances the less stable alkene is the major product and the less stable configurational isomer is formed in preference to the more stable isomer. It is observations such as these that provide challenge and at the same time open the way to an even more thorough understanding of organic chemistry.

PROBLEM 5.6

Arrange the four *cis-trans* isomers of 2,4-heptadiene in order of decreasing stability.

5.9 Polymerization

From the perspective of the chemical industry, the single most important reaction of alkenes is **polymerization,** the building together of many small monomers (Greek: *mono* + *meros,* single parts) into very large, high-molecular-weight polymers (Greek: *poly* + *meros,* many parts). In addition polymerization, monomer units are joined together without loss of atoms. An example of addition polymerization is the formation of polyethylene from ethene (ethylene).



Polymerization reactions are usually written in the following way, where n is a large number, typically several thousand. Molecular weights of polyethylene molecules produced by polymerization range from 50,000 to over 1,500,000.

repeating monomer unit

$$n\mathrm{CH_2{=}CH_2} \xrightarrow{\text{catalyst}} \mathrm{{-(CH_2CH_2)_n-}}$$

The first commercial polymerizations of ethylene were initiated by radicals formed by thermal decomposition of organic peroxides.

Chain initiation:

1. $\mathrm{RO{-}OR} \xrightarrow{\text{heat}} \mathrm{RO\cdot + \cdot OR}$

Chain propagation:

2. $\mathrm{RO\cdot + CH_2{=}CH_2} \longrightarrow \mathrm{RO{-}CH_2CH_2\cdot}$

3. $\mathrm{RO{-}CH_2CH_2\cdot + CH_2{=}CH_2} \longrightarrow \mathrm{RO{-}CH_2CH_2{-}CH_2CH_2\cdot}$

In polymerization of ethylene, chain-lengthening reactions occur at a very rapid rate, often as fast as thousands of additions per second, depending on experimental conditions.

In principle, polyethylene chains might continue to grow until all monomer units are used up. In practice, chain lengths generally do not exceed 10^4 to 10^5 monomer units and are often far less.

Propene (propylene) and other substituted ethene (ethylene) monomers can also be polymerized under a variety of experimental conditions, including radical chain polymerization. Free radical polymerization of propene involves secondary radical intermediates to give polypropylene, with methyl groups repeating regularly on every other carbon atom of the polymer chain.

$$n\mathrm{CH_3CH{=}CH_2} \xrightarrow{\text{catalyst}} \left(\mathrm{CH(CH_3)CH_2}\right)_n$$

Propylene Polypropylene

Table 5.4 lists several important polymers derived from ethylene and substituted ethylenes along with their common names and most important uses.

Petri dishes made of Plexiglas. *(© Dan McCoy, Rainbow)*

Saran wrap. *(Charles D. Winters)*

Table 5.4 Polymers derived from substituted ethylenes

Monomer Formula	Common Name	Polymer Name(s) and Common Uses
$CH_2{=}CH_2$	ethylene	polyethylene; break-resistant containers and packaging materials
$CH_2{=}CHCH_3$	propylene	polypropylene, Herculon; textile and carpet fibers
$CH_2{=}CHCl$	vinyl chloride	poly(vinyl chloride), PVC; construction tubing
$CH_2{=}CCl_2$	1,1-dichloroethylene	Saran; food packaging
$CH_2{=}CHCN$	acrylonitrile	polyacrylonitrile, Orlon; acrylics and acrylates
$CF_2{=}CF_2$	tetrafluoroethylene	poly(tetrafluoroethylene), Teflon; nonstick coatings
$CH_2{=}CHC_6H_5$	styrene	polystyrene, Styrofoam; insulating materials
$CH_2{=}CHCO_2CH_2CH_3$	ethyl acrylate	poly(ethyl acrylate); latex paints
$CH_2{=}\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}CO_2CH_3$	methyl methacrylate	poly(methyl methacrylate), Lucite, Plexiglas; glass substitutes

The years since the 1930s have seen extensive research and development in polymer chemistry and physics and an almost explosive growth in plastics, coatings, and rubber technology has created a worldwide multibillion-dollar industry. A few basic characteristics account for this phenomenal growth. First, the raw materials for plastics are derived mainly from petroleum. With the development of petroleum refining processes, raw materials for the synthesis of polymers became generally cheap and plentiful. Second, within

The low thermal conductivity of polystyrene makes it a good insulating material. *(Charles D. Winters)*

This plumber is installing pipe fittings made of polyvinyl chloride. *(David R. Frazier Photography)*

broad limits, scientists have learned how to tailor polymers to the requirements of the end use. Third, many plastics can be fabricated more cheaply than competing materials. For example, plastic technology created the water-based (latex) paints that have revolutionized the coatings industry; plastic films and foams have done the same for the packaging industry. The list could go on and on as we think of the manufactured items that are everywhere in our daily lives.

5.10 Alkenes of Industrial Importance: Ethylene

The U.S. chemical industry produces more pounds of ethene (ethylene) than any other organic chemical. In 1993, ethylene production totalled almost 41.3 billion pounds. Next among the organics is propene with a 1993 production of 22.4 billion pounds. The only other alkene produced in quantities even remotely approaching those of ethylene and propene is 1,3-butadiene with a volume of 3.1 billion pounds in 1993.

A. Production by Thermal Cracking of Hydrocarbons

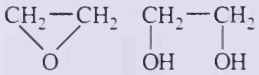
Ethylene, the world over, is produced by thermal cracking of hydrocarbons. In the United States, which has vast reserves of natural gas, the major process for ethylene production has been thermal cracking of the small quantities of ethane, propane, and butane extracted from natural gas. For this reason, most ethylene-generating plants currently in operation in the United States are located on the Gulf Coast of Texas and Louisiana or near other sites of natural gas reserves. Following is the equation for the thermal cracking of ethane:

$$CH_3CH_3 \xrightarrow{\text{thermal cracking}} CH_2{=}CH_2 + H_2$$

B. Ethylene: The Organic Chemical Industry's Most Important Starting Material

Ethylene is the starting material for the synthesis each year of almost 110 billion pounds of organic chemicals and polymers. As you can see from Table 5.5, its most important derivatives are polyethylene, ethylene oxide and ethylene glycol, vinyl chloride, and styrene.

Table 5.5 Major derivatives and end uses of ethylene

Derivative	Structural Formula	1993 Production (billions of pounds)	Major End Uses
polyethylene	$-(CH_2-CH_2)_n-$	20.8	fabricated plastics
ethylene oxide		10.9	antifreeze, polyester textile fibers, solvents
ethylene glycol			
vinyl chloride	$CH_2{=}CHCl$	13.8	fabricated plastics for the construction industry
styrene	$CH_2{=}CHC_6H_5$	10.7	polystyrene, synthetic rubber

C. Synthesis and Fabrication of LDPE and HDPE Plastics

Approximately one-half of the ethylene produced each year by the U. S. chemical industry is converted into polyethylene plastics. The first commercial process for ethylene polymerization used peroxide catalysts at temperatures of 500°C and pressures of 1000 atm and produced a soft, tough polymer known as low-density polyethylene (LDPE). At the molecular level, chains of LDPE are highly branched. LDPE has a density of between 0.91 and 0.94 g/cm^3 and a melting point of about 115°C. Because its melting point is only slightly above 100°C, it cannot be used for products that will be exposed to boiling water.

Approximately 65% of all low-density polyethylene is used for the manufacture of films. Fabrication of LDPE films is done by a blow-molding technique illustrated in Figure 5.11. A tube of LDPE along with a jet of compressed air is forced through an opening and blown into a giant, thin-walled bubble. The film is then cooled and taken up onto a roller. This double-walled film can be slit down the side to give LDPE film or it can be sealed at points along its length to make LDPE bags. LDPE film is cheap, which makes it ideal for packaging such consumer items as baked goods, vegetables, and other produce and for trash bags.

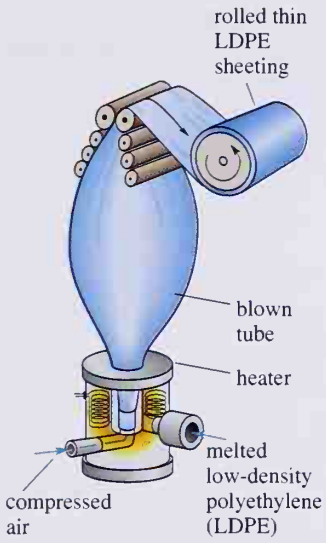


Figure 5.11
Fabrication of an LDPE film.

An alternative method for polymerization of ethylene was developed by Karl Ziegler in the 1940s. He discovered that titanium trichloride, $TiCl_3$, in combination with a trialkylaluminum, as for example triethylaluminum, $Al(CH_2CH_3)_3$, catalyzes polymerization of ethylene at temperatures as low as 60°C and pressures of 20 atm to give a polymer known as high-density polyethylene (HDPE). HDPE has very little chain branching and a higher density (0.96 g/cm^3) and melting point (135°C) than low-density polyethylene. The physical properties and cost of HDPE relative to other packaging materials make it ideal for the production of plastic bottles; bottle caps and other closures; and housewares, such as mixing bowls and refrigerator and freezer containers.

Approximately 45% of all HDPE used in the U.S. is blow-molded. In blow molding, a short length of HDPE tubing is placed in an open die (Figure 5.12[a]), and the die is closed, sealing the bottom of the tube (Figure 5.12[b]). Compressed air is then forced into the warm polyethylene/die assembly, and the tubing is literally blown up to take the shape of the mold (Figure 5.12[c]). The die is opened (Figure 5.12[d]), and there is the container!

A low-density polyethylene (LDPE) bag. *(Charles D. Winters)*

Wash bottles made from high-density polyethylene (HDPE). *(Charles D. Winters)*

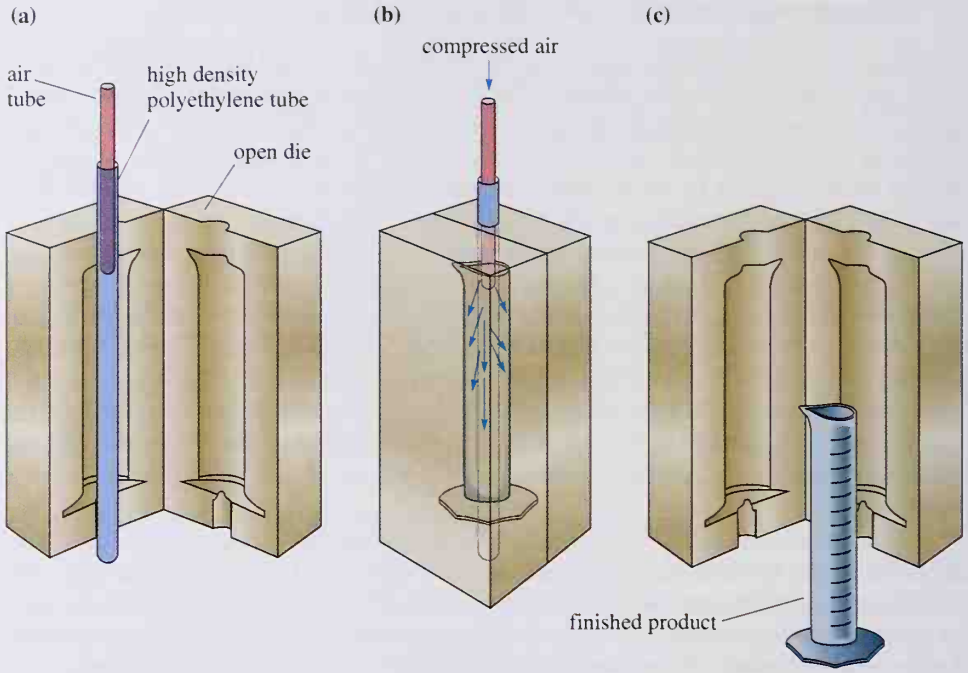
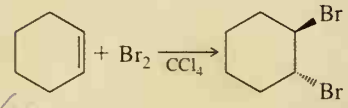


Figure 5.12
Blow molding of an HDPE container.

SUMMARY OF KEY REACTIONS

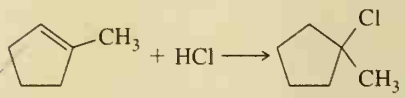
1. Addition of Bromine and Chlorine (Section 5.3A)

Addition is stereoselective; it involves anti addition by way of a bridged halonium ion intermediate.



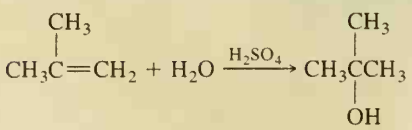
2. Electrophilic Addition of HX (Section 5.3B)

Addition is regioselective and follows Markovnikov's rule. Reaction involves a carbocation intermediate, which may rearrange before it adds the nucleophile.



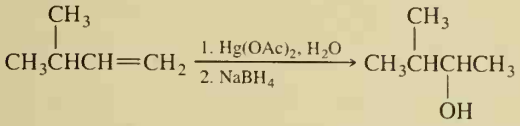
3. Acid-Catalyzed Hydration (Section 5.3C)

Addition is regioselective and follows Markovnikov's rule. Reaction involves a carbocation intermediate, which may rearrange before it adds the nucleophile.



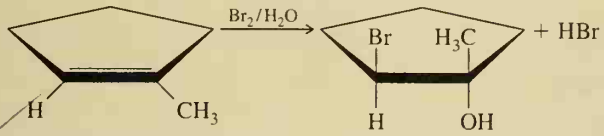
4. Oxymercuration-Reduction (Section 5.3E)

Oxymercuration is regioselective (HgOAc adds to the less substituted carbon and OH to the more substituted carbon) and stereoselective (anti addition). The result of oxymercuration-reduction is Markovnikov hydration. Carbocation rearrangement is rarely observed.



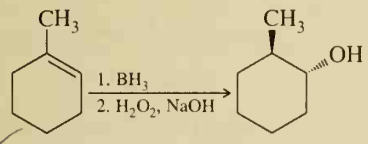
5. Addition of HOCl and HOBr (Section 5.3F)

Addition is regioselective (—X adds to the less substituted carbon) and stereoselective (anti addition).



6. Hydroboration (Section 5.4)

Addition of BH_3 is stereoselective (syn addition) and regioselective (boron adds to the less substituted carbon and hydrogen to the more substituted carbon). Hydroboration-oxidation results in anti-Markovnikov hydration of the alkene.



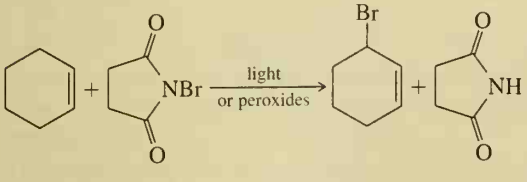
7. Radical Addition (Section 5.5)

Addition of HBr to an alkene in the presence of a radical initiator results in anti-Markovnikov hydrobromination of the alkene.

$$CH_3CH{=}CH_2 + HBr \xrightarrow{\text{peroxide}} CH_3CH_2CH_2Br$$

8. Allylic Bromination or Chlorination (Section 5.6)

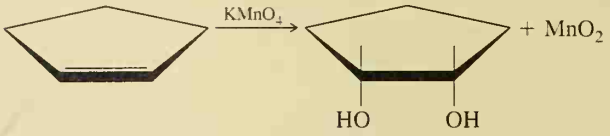
Reaction is by a radical chain reaction and occurs at high temperatures (heat is the radical initiator) using the halogens themselves or at room temperature using *N*-bromosuccinimide, NBS.



NBS

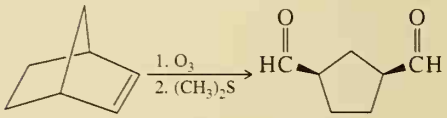
9. Oxidation to a Glycol by $KMnO_4$ or OsO_4 (Section 5.7B)

Oxidation gives a glycol by way of a five-member cyclic intermediate.



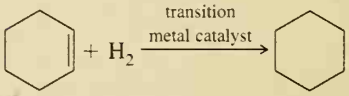
10. Oxidation by Ozone (Section 5.7C)

Treatment with ozone followed by dimethyl sulfide cleaves the double bond and gives two carbonyl groups in its place.



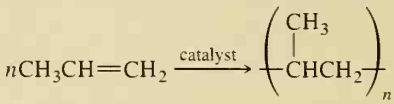
11. Addition of H_2: Catalytic Reduction (Section 5.8)

Catalytic reduction involves predominantly syn addition of hydrogen.



12. Polymerization (Section 5.9)

A chain reaction that may be initiated by radicals, anions, or cations.



ADDITIONAL PROBLEMS

Energetics of Chemical Reactions

5.7 Following are some bond dissociation energies.

Bond	Bond Dissociation Energy (kcal/mol)	Bond	Bond Dissociation Energy (kcal/mol)
H—H	104	C—Si	72
O—H	110.6	C=C	146
C—H	98.7	C=O (aldehyde)	174
N—H	93.4	C=O (CO_2)	192
Si—H	76	C≡O (CO)	257
C—C	82.6	N≡N	227
C—N	73	C≡C	200
C—O	85.5	O=O	119
C—I	51		

If a suitable catalyst could be found, which of the following reactions are energetically favorable?

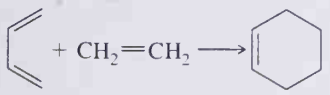
(a) $CH_2{=}CH_2 + 2H_2 + N_2 \longrightarrow H_2NCH_2CH_2NH_2$

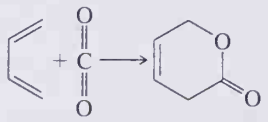
(b) $CH_2{=}CH_2 + CH_4 \longrightarrow CH_3CH_2CH_3$

(c) $CH_2{=}CH_2 + (CH_3)_3SiH \longrightarrow CH_3CH_2Si(CH_3)_3$

(d) $CH_2{=}CH_2 + CHI_3 \longrightarrow CH_3CH_2CI_3$

(e) $CH_2{=}CH_2 + CO + H_2 \longrightarrow CH_3CH_2\overset{\overset{O}{\|}}{C}H$

(f) 

(g) 

(h) $HC{\equiv}CH + O_2 \longrightarrow HC(=O){-}C(=O)H$

(i) $2CH_4 + O_2 \longrightarrow 2CH_3OH$

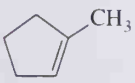
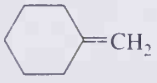
Electrophilic Additions

5.8 Using your knowledge of resonance, predict which doubly bonded carbon atoms in the following molecules are most reactive toward electrophiles (such as H^+):

(a) $CH_2{=}CH{-}\ddot{O}{-}CH_3$ **(b)** $CH_2{=}CH{-}CH{=}CH_2$

5.9 Draw structural formulas for the isomeric carbocations formed by addition of H^+ to the following alkenes. Label each carbocation primary, secondary, or tertiary, and state which of the isomeric carbocations is formed more readily.

(a) $CH_3CH_2\overset{\overset{CH_3}{|}}{C}{=}CHCH_3$ **(b)** $CH_3CH_2CH{=}CHCH_3$

(c)  **(d)** 

5.10 Arrange the following compounds in order of increasing rate of reaction with HI. Draw the structural formula of the major product formed in each case, and explain the basis for your ranking.

(a) $CH_3CH{=}CHCH_3$ **(b)** $CH_3\overset{\overset{CH_3}{|}}{C}{=}CHCH_3$ **(c)** $CH_3CH{=}CH_2$

5.11 Predict the organic product(s) of the reaction of 2-butene with the following reagents:

(a) H_2O (H_2SO_4) **(b)** Br_2 **(c)** Cl_2

(d) Br_2 in H_2O **(e)** HI **(f)** Cl_2 in H_2O

(g) $Hg(OAc)_2$, H_2O **(h)** product (*g*) + $NaBH_4$

5.12 Reaction of 2-methyl-2-pentene with each of the following shows a high regioselectivity. Draw a structural formula for the major product of each reaction, and account for the observed regioselectivity.

(a) HBr (in the absence of peroxides) **(b)** HBr (in the presence of peroxides)

(c) H_2O (in the presence of H_2SO_4) **(d)** Br_2 in H_2O

(e) $Hg(OAc)_2$ in H_2O

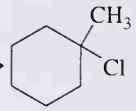
5.13 Reaction of 1-methylcyclopentene with the following reagents shows a high degree of regioselectivity and stereoselectivity. Account for the observed regioselectivity and stereoselectivity.

(a) Br_2 **(b)** Br_2 in H_2O **(c)** $Hg(OAc)_2$ in H_2O

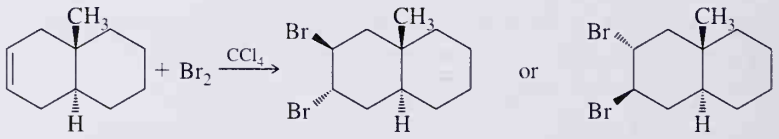
5.14 Draw the structural formula for an alkene or alkenes with the indicated molecular formula that gives the compound shown as the major product. Note that more than one alkene may give the same compound as the major product.

(a) $C_5H_{10} + H_2O \xrightarrow{H_2SO_4} CH_3\overset{\displaystyle CH_3}{\underset{\displaystyle OH}{C}}CH_2CH_3$

(b) $C_5H_{10} + Br_2 \longrightarrow CH_3\overset{\displaystyle CH_3}{C}HCHCH_2$ (Br, Br)

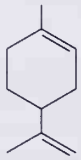
(c) $C_7H_{12} + HCl \longrightarrow$ 

5.15 Reaction of the following bicycloalkene with bromine in carbon tetrachloride gives a *trans*-dibromide. In both (a) and (b), the bromine atoms are *trans* to each other. However, only one of these products is formed. Which *trans*-dibromide is formed, and how do you account for the fact that it is formed to the exclusion of the other *trans*-dibromide?



(a) (b)

5.16 Terpin hydrate is prepared commercially by addition of 2 mol of water to limonene (Figure 4.6) in the presence of dilute sulfuric acid. Terpin hydrate is used medicinally as an expectorant for coughs. It may be given as terpin hydrate and codeine.



$+ 2H_2O \xrightarrow{H_2SO_4} C_{10}H_{20}O_2$

Limonene Terpin hydrate

(a) Propose a structural formula for terpin hydrate, and a mechanism for its formation.

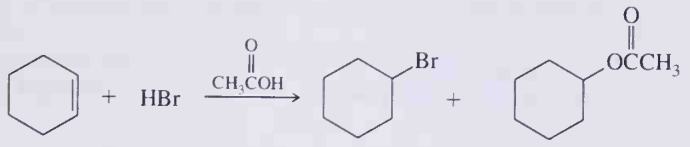
(b) How many *cis-trans* isomers are possible for the structural formula you proposed?

5.17 Treatment of 2-methylpropene with methanol in the presence of sulfuric acid yields a compound of formula $C_5H_{12}O$.

$$CH_3\overset{\displaystyle CH_3}{C}{=}CH_2 + CH_3OH \xrightarrow{H_2SO_4} C_5H_{12}O$$

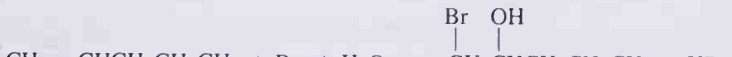
Propose a structural formula for this compound and a mechanism for its formation.

5.18 Treatment of cyclohexene with HBr in the presence of acetic acid gives bromocyclohexane (85%) and cyclohexyl acetate (15%). Propose a mechanism for formation of the latter product.



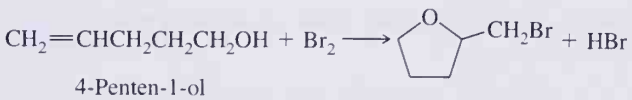
Cyclohexene | Bromocyclohexane (85%) | Cyclohexyl acetate (15%)

5.19 Propose a mechanism for the following reaction:



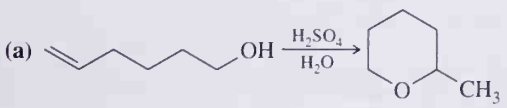
1-Pentene | 1-Bromo-2-pentanol

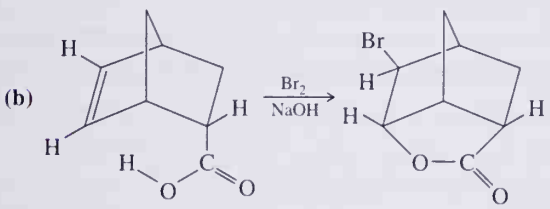
5.20 Treatment of 4-penten-1-ol with bromine in water forms a cyclic bromoether. Account for the formation of this product rather than a simple bromohydrin as was formed in Problem 5.19.



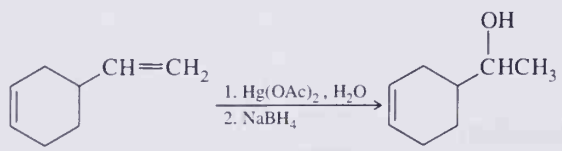
4-Penten-1-ol

5.21 Provide a mechanism for each of the following reactions:



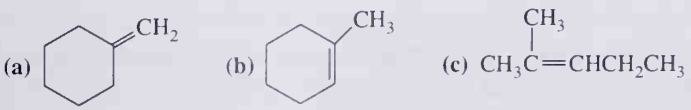


5.22 When 4-vinylcyclohexene is treated with 1 mol of mercuric acetate and then with sodium borohydride, the following unsaturated alcohol is formed. Account for the observation that under these conditions, only the double bond of the vinyl group is hydrated.



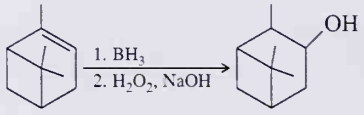
Hydroboration

5.23 Each alkene is treated with diborane in tetrahydrofuran (THF) to form a trialkylborane and then with hydrogen peroxide in aqueous sodium hydroxide. Draw a structural formula of the alcohol formed in each case. Specify stereochemistry where appropriate.



(d) $CH_2{=}CH(CH_2)_5CH_3$ (e) $(CH_3)_3CCH{=}CH_2$

5.24 Reaction of α-pinene with diborane followed by treatment of the resulting trialkylborane with alkaline hydrogen peroxide gives an alcohol with the following structural formula:



α-Pinene

(a) Four *cis-trans* isomers are possible for this bicyclic alcohol. Draw formulas for all four.

(b) Of the four possible *cis-trans* isomers, one is formed in over 85% yield. Which isomer is formed, and how do you account for this stereoselectivity?

Radical Additions

5.25 In the presence of radical initiators, carbon tetrachloride reacts with alkenes as shown in the following example:

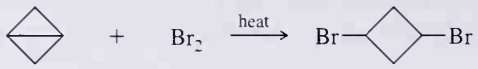
$$CH_3(CH_2)_5CH{=}CH_2 + CCl_4 \xrightarrow[\text{heat}]{\text{peroxide}} CH_3(CH_2)_5\underset{\displaystyle Cl}{\underset{|}{C}}HCH_2CCl_3$$

1-Octene 1,1,1,2-Tetrachlorononane

Propose a radical chain mechanism for the formation of the observed product. In addition, demonstrate that your chain propagation steps add up to the observed reaction.

5.26 Cyclobutane reacts with bromine to give bromocyclobutane, but bicyclo[1.1.0]butane reacts with bromine to give 1,3-dibromocyclobutane. Account for the difference in reaction between the two compounds.

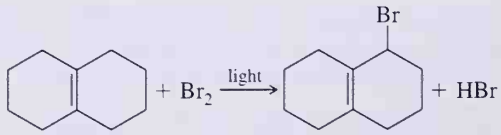
Cyclobutane Bromocyclobutane



Bicyclo[1.1.0]butane 1,3-Dibromocyclobutane

Allylic Halogenation

5.27 Propose a series of chain initiation, propagation, and termination steps for the following reaction:



5.28 Following is a balanced equation for the allylic bromination of propene and relevant bond dissociation energies:

$$CH_2{=}CHCH_3 + Br_2 \longrightarrow CH_2{=}CHCH_2Br + HBr$$

Bond	Bond Dissociation Energy (kcal/mol)
$CH_2{=}CHCH_2{-}H$	87.0
$Br{-}Br$	46.0
$CH_2{=}CHCH_2{-}Br$	55.7
$H{-}Br$	87.5

(a) Calculate the heat of reaction (ΔH) for this conversion.

(b) Propose a pair of chain propagation steps, and show that, taken together, your steps add up to the observed reaction.

(c) Calculate the ΔH for each chain propagation step, and show that they add up to the observed ΔH for the overall reaction.

Halogenation of Alkanes

5.29 Following is a balanced equation for bromination of propane:

$$CH_3CH_2CH_3 + Br_2 \longrightarrow \underset{\displaystyle Br}{\underset{|}{CH_3CHCH_3}} + HBr$$

(a) Using the values for bond dissociation energies given in Appendix A, calculate ΔH for this reaction.

(b) Propose a pair of chain propagation steps, and show that the steps you propose add up to the observed reaction.

(c) Calculate ΔH for each of your chain propagation steps.

(d) Of your chain propagation steps, which is the slower, that is, which has the higher energy of activation?

5.30 Following are balanced equations for fluorination of propane to produce both 1-fluoropropane and 2-fluoropropane.

$$CH_3CH_2CH_3 + F_2 \longrightarrow CH_3CH_2CH_2F + HF$$

$$CH_3CH_2CH_3 + F_2 \longrightarrow \underset{\displaystyle F}{\underset{|}{CH_3CHCH_3}} + HF$$

Assume that each product is formed by a radical chain reaction.

(a) Calculate ΔH for each reaction.

(b) Propose a pair of chain propagation steps for each reaction, and calculate ΔH for each step.

(c) Reasoning from the Hammond postulate, predict the regioselectivity of radical fluorination relative to that of chlorination and bromination.

Oxidation

5.31 Write structural formulas for the major organic product(s) formed by reaction of 1-methylcyclohexene with the following oxidizing agents:

(a) H_2O_2/OsO_4 **(b)** $KMnO_4$ (cold, dilute) **(c)** O_3 (followed by $(CH_3)_2S$)

5.32 Each of the following alkenes is treated with ozone to form an ozonide and then with dimethyl sulfide. Draw the structural formula of the organic product(s) formed from each alkene.

(a) $CH_3C(CH_3)=CHCH_2CH(CH_3)CH_3$ (b) $CH_3C(CH_3)=CHCH_2C(CH_3)=CHCH_2CH_3$

(c) α-Pinene (Figure 4.6) (d) Limonene (Figure 4.6)

(e) Zingiberene (Figure 4.7) (f) Caryophyllene (Figure 4.7)

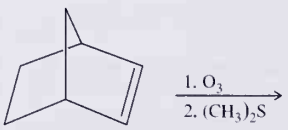
5.33 Draw the structural formula of the alkene that reacts with ozone followed by dimethyl sulfide to give the following products:

(a) $C_7H_{12} \xrightarrow[2.\ (CH_3)_2S]{1.\ O_3} CH_3CCH_2CH_2CH_2CCH_3$ (O, O)

(b) $C_{10}H_{18} \xrightarrow[2.\ (CH_3)_2S]{1.\ O_3} CH_3CCH_3 + CH_3CCH_2CH_3 + HCCH_2CH$ (O, O, O, O)

(c) $C_{10}H_{18} \xrightarrow[2.\ (CH_3)_2S]{1.\ O_3} CH_3CHCH_2CCH_2CH_2CH_2CH_2CH$ (CH_3, O, O)

5.34 Bicyclo[2.2.1]-2-heptene (norbornene) is oxidized by ozone to cyclopentane-1,3-dicarbaldehyde.



Bicyclo[2.2.1]-2-heptene (Norbornene)

Cyclopentane-1,3-dicarbaldehyde

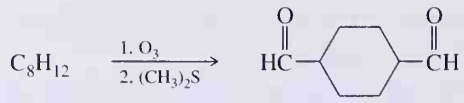
(a) How many *cis-trans* isomers are possible for this dicarbaldehyde?

(b) Which of the possible *cis-trans* isomers is formed by ozonolysis of norbornene?

5.35 (a) Draw a structural formula for the bicycloalkene of molecular formula C_8H_{12} that, on ozonolysis followed by dimethyl sulfide, gives cyclohexane-1,4-dicarbaldehyde.

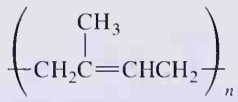
(b) Do you predict the product to be the *cis* isomer, the *trans* isomer, or a mixture of *cis* and *trans* isomers? Explain.

(c) Draw a suitable stereorepresentation for the more stable chair conformation of the dicarbaldehyde formed in this oxidation.



Cyclohexane-1,4-dicarbaldehyde

5.36 Natural rubber is a polymer of 2-methyl-1,3-butadiene (isoprene).



Poly(2-methyl-1,3-butadiene) (Polyisoprene)

(a) Draw the structural formula of a section of natural rubber showing three repeating isoprene units.

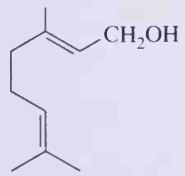
(b) Draw the structural formula of the product of oxidation of natural rubber by ozone followed by a work-up in the presence of $(CH_3)_2S$. Name each functional group present in this product.

(c) The smog prevalent in Los Angeles contains oxidizing agents. Account for the fact that this type of smog attacks natural rubber (automobile tires, etc.) but does not attack polyethylene or polyvinyl chloride.

Reduction

5.37 Predict the major organic product(s) of the following reactions. Show stereochemistry where appropriate.

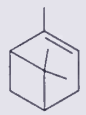
(a)



Geraniol
(rose and
other flowers)

$+ 2H_2 \xrightarrow{Pt}$

(b)

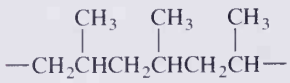


α-Pinene
(Turpentine)

$+ H_2 \xrightarrow{Pt}$

Polymerization

5.38 Following is the structural formula of a section of polypropylene derived from three units of propylene monomer.



Draw structural formulas for comparable sections of

(a) Poly(vinyl chloride)

(b) Polytetrafluoroethylene

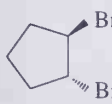
(c) Poly(methyl methacrylate)

(d) Poly(1,1-dichloroethylene)

Synthesis

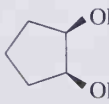
5.39 Show how to convert cyclopentene into these compounds. Following each structural formula is the number of different reactions described in this chapter for bringing about each synthesis.

(a)



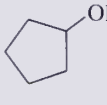
(1)

(b)



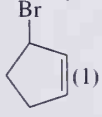
(2)

(c)



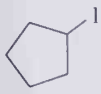
(3)

(d)



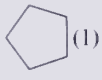
(1)

(e)



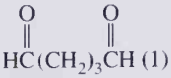
(1)

(f)



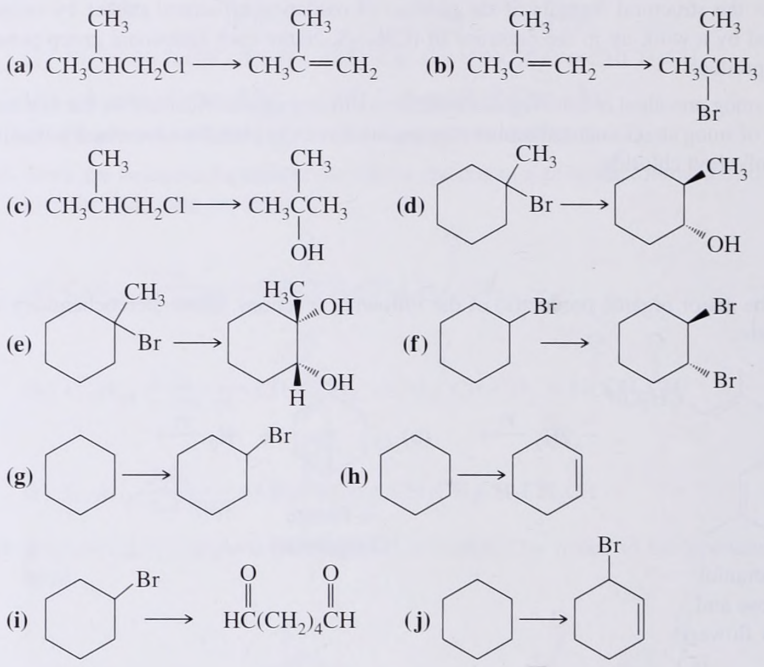
(1)

(g)



(1)

5.40 Show how to convert the given starting material into the desired product. Note that some syntheses require only one step, whereas others require two or more steps.



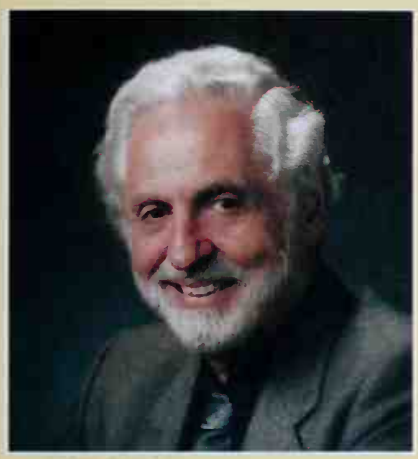
Qualitative Organic Analysis

5.41 Describe how to distinguish between the members of each pair of compounds by a simple chemical test. For each pair, tell what test to perform, what you expect to observe, and write an equation for each positive test. For example, to distinguish between cyclohexane and 1-hexene in part (a), you might consider the reaction of each with Br_2 in CCl_4 or reaction with $KMnO_4$ in basic solution.

(a) cyclohexane and 1-hexene **(b)** 1-hexene and 2-chlorohexane

(c) 1,1-dimethylcyclopentane and 2,3-dimethyl-2-butene

CARL DJERASSI



(Beverly March)

Carl Djerassi, Professor of Chemistry at Stanford University, is a man of many achievements, in science and in letters. Born in Vienna in 1923, Professor Djerassi was forced to leave Europe in 1939 in the face of the Nazi occupation. Although he had not completed high school, he was allowed to enroll at Newark Junior College in New Jersey. He also went to Tarkio College in Missouri and then to Kenyon College where he graduated *summa cum laude* in 1942.

Still short of his nineteenth birthday, he joined the CIBA Corporation, where he and Charles Huttrer synthesized pyribenzamine, one of the first two antihistamines—drugs that act to control allergies. He left CIBA for the University of Wisconsin, where he received his Ph.D. in 1945, at the age of 22. For the next seven years he worked first at CIBA and then at Syntex, S. A., a fledgling pharmaceutical corporation then located in Mexico City. Here he was part of the research team that produced the first synthesis of cortisone, an important hormone, and later synthesized norethindrone, the first oral contraceptive and one that is still widely used all over the world.

In 1952 he moved to Wayne University (now Wayne State) in Detroit, as Associate Professor, and in 1959 accepted a Professorship at Stanford University, where he has remained ever since. Both at Wayne and at Stanford he maintained an association with Syntex, and served as President of Syntex Research from 1968 to 1972. In 1968 he helped to found the Zoecon Corporation, of which he also became president, and which pioneered hormonal methods of insect control that do not rely on conventional insecticides.

Dr. Djerassi has always been involved in steroid chemistry,[1] but his early interest in synthesis turned to the equally important area of the structural determination of naturally occurring steroids, of which there are many thousands. When he began his career, determining the structure of a single naturally occurring steroid was a difficult process that would often take years.

In the 1950s, instrumental methods of structure determination slowly began to replace the laborious, older chemical methods. Dr. Djerassi was one of the pioneers in developing and using techniques such as optical rotatory dispersion, circular dichroism, and mass spectrometry to determine the structures of steroids and other organic compounds. Because of the work of Dr. Djerassi and other pioneers, most unknown structures now can be determined in a few days or less.

Dr. Djerassi has had a prolific career, publishing more than 1000 research papers and seven books dealing with steroids, alkaloids, antibiotics, lipids, and terpenoids, as well as with chemical applications of computer artificial intelligence. His many research awards include the National Medal of Science (1973), the National Medal of Technology (1991), the first Wolf Prize in Chemistry (1978), the Perkin Medal of the Society for Chemical Industry (1975), and the Priestley medal, the highest award given by the American Chemical Society (1992). In 1978 he was inducted into the National Inventor's Hall of Fame.

In recent years Dr. Djerassi, without abandoning his interest in chemistry, has turned to litera-

[1] Steroids are discussed in Section 23.4.

ture. He has published a collection of short stories; two novels: *Cantor's Dilemma* and *The Bourlaxi Gambit;* a collection of poems; and two books of autobiography, one entitled *Steroids Made It Possible,* and the other, intended for a more general audience, called *The Pill, Pygmy Chimps, and Degas's Horse.* Under the auspices of the Djerassi Foundation, he has established an artist's colony near Woodside, California, that provides residences and studio space for visual, literary, choreographic, and musical artists.

Choosing a Career in Chemistry

"I really didn't choose to be an organic chemist; it sort of happened to me. I was the child of two physicians and it was always assumed that I would go to medical school and become a practicing physician. When I arrived in this country at the age of 16 I had taken no chemistry and had not even graduated from high school. Fortunately, I got straight into a Junior College in New Jersey and began a pre-med curriculum that included first-year chemistry. I had a first-rate teacher there, named Nathan Washton, who got me interested in chemistry. After one semester at Tarkio College in Missouri (the alma mater of Wallace Carothers, the inventor of nylon), I went to Kenyon College, a small (at that time) college in Ohio, that had only two faculty members in chemistry. Chemistry classes were very small, but I got a first-class education, and that is where I decided to become a chemist, rather than go to medical school."

Synthesizing Antihistamines

"When I graduated from Kenyon I needed to earn some money, so I got a job as a junior chemist at CIBA Pharmaceutical Corporation, in New Jersey. At that time the company became interested in antihistamines, and I was one of only two chemists working on this project. So despite my youth, I was involved in the synthesis of one of the first two antihistamines produced in this country,

Because of the work of Dr. Djerassi and other pioneers, most unknown structures now can be determined in a few days or less.

pyribenzamine. This compound, which was synthesized during the first year after I graduated from college, turned out to make a significant contribution in the treatment of allergies."

From Antihistamines to Steroids

"While working at CIBA, I began taking classes at NYU and Brooklyn Polytechnic Institute at night, so as to get an advanced degree, but commuting from New Jersey after a day of work was murderous. After a year of night school, I decided I would go to graduate school full time. CIBA was involved in steroid projects, and even though I was working on antihistamines, I started reading books on steroids, especially Louis Fieser's *Natural Products Related to Phenanthrene,* a superb book, which turned me on to steroid chemistry. When I went full time to the University of Wisconsin, I was prepared to work in this field. Fortunately, Wisconsin had two young Assistant Professors in this area, and I did my Ph.D. with one of them, A. L. Wilds, on the conversion of androgens to estrogens, which at that time was a tough problem."

Developing Oral Contraceptives

"We did not set out with the objective of synthesizing oral contraceptives. Our goal was to develop an orally-active progestational hormone, in other words a compound that would mimic the biological properties of progesterone. At that time progesterone was clinically used for menstrual disorders and infertility, but there were ideas about using it as a contraceptive, because it is progesterone that naturally stops further ovulation after an ovum is fertilized. However, progesterone itself is not active by mouth, and daily injections would be needed. By this time I was Associate Director of Chemical Research at Syntex Corporation, located in Mexico City. By combining ideas discovered by previous investigators, we set out to synthesize a steroid that would not only be active by mouth, but would also have enhanced progestational activity. This compound was 19-nor-17α-ethynyltestosterone (norethindrone), whose synthesis we completed on October 15, 1951. It was first tested for menstrual disorders and fertility problems and then as an oral contraceptive. Forty years after its synthesis it is still the active ingredient of about a third of all the oral contraceptives used throughout the world."

The Social Impact of Working on Contraceptives

"If I could do it over again, there is no question that I would work in the area of developing and synthesizing oral contraceptives. By now about 13–14 million women in the U.S. and 50–60 million in the world use the pill, making it the most widely used method of reversible birth control. Population growth is probably the biggest problem facing us in the world, assuming that the possibility of nuclear warfare is now greatly diminished, and the widespread use of oral contraceptives helps in controlling that. I think the development of these contraceptives is one of the most important contributions that chemistry has made to society. New drugs cure diseases of individuals during their lifetimes, but the use of contraceptives has implications for generations, because if you do not control the production of offspring, you do not control future generations. Furthermore, these compounds have had an enormous impact on women, empowering them to be in control of their own fertility."

A Pill for Men?

"I think there will be very little fundamental new research in the area of oral contraceptives over the next couple of decades, and a pill for men is completely out of the question for the next 15 to 20 years. The reason is that the pharmaceutical industry has turned its back on this field for a number of very complex reasons, not only in the U.S., but in other industrialized countries as well. The only really new approach in chemical birth control in the last 25 years is the French 'morning-after pill,' RU486—at present used almost exclusively as an early abortifacient, although it can also be employed as a method of birth control."

From Oral Contraceptives to Insect Control

"Conceptually there was a relationship between our work on oral contraceptives and insect control. In a way, you could say that steroid oral contraceptives were true biorational methods of human birth control, since progesterone—our conceptional lead compound—is really nature's contraceptive. That was a model on which insect control could be based. At this time (the late 1960s) I was in charge of research at Syntex in addition to being Professor at Stanford University. Governments and the public realized that conventional methods of insect control—largely spraying with chlorinated hydrocarbons such as DDT—were damaging the environment. DDT and similar compounds were being banned and a new approach was needed. We formed a new company called Zoecon to try to synthesize insect-controlling steroids. In the 1960s, a juvenile hormone, based on a sesquiterpene skeleton, had been discovered and we decided to focus on it. Insects pass through a juvenile stage controlled by the juvenile hormone, whose production is later shut off by another hormone so that the insect can then mature. Our biorational approach was to synthesize an artificial juvenile hormone which would continue to be applied to immature insects, so that the insect would never reach the stage at which it could reproduce. This turned out to be a new biorational approach to controlling mosquitoes, fleas, cockroaches, and other insects that do their damage as adults, and was approved by the Environmental Protection Agency for public use."

A Leader in Both the Synthetic and Structure Determination Areas of Organic Chemistry

"In my early days—the '50s and '60s—undoubtedly structure determination was more satisfying than synthesis, especially because I was involved in the development of new physical methods for identifying chemical structures. However, these methods have now made structural determination much more routine and automatic. For example, mass spectrometry enables us to identify compounds on a micro scale, which was unheard of before."

Scientists as Advocates for Social or Political Positions

"Scientists should be advocates, as should every intelligent person, provided he or she is well informed. Just because you are a scientist does not mean that you are well informed on any particular issue, but when scientists deal with their own specialties, of course they should. Also, scientists should be interested in the societal implications of their work, just as non-scientists should be informed about certain areas of science, simply because they have such an enormous impact on their daily lives."

Passing the Torch

"I've trained somewhere between three hundred and four hundred

graduate students and post-doctoral fellows in universities and many others in industry as well. Training these students is probably the biggest professional contribution that one makes. These are very intimate relationships, comparable to those between parents and children. The mentor becomes a role model for the student."

The Rewards of Scientific Research

"In my own work, material rewards never played any initial role, because they always came much later. To a large extent it was initially pure intellectual curiosity, but very soon I started to look for the potential benefits to society. My interest has always been in the biological areas and I was never interested in war-related research. I never had the slightest question about the societal appropriateness of the work I was doing."

The Interplay Between Academia and Industry in Developing New Inventions, Including Chemical Inventions

"I have always been connected simultaneously with a university and with chemical companies. This made me a much better Professor, because I became aware of the many steps needed to take a laboratory discovery up to practical realization. Conversely, I was a much better industrial research director because of what I learned in the university. For example, should scientists be concerned with societal implications of their work? Obviously yes, but it is not easy for a scientist who stays only in the ivory tower. You ought to have a responsibility for taking your work a step further. There should however be guidelines to prevent actual or potential conflicts of interest."

Cutting with an oxy-acetylene torch. (© T. J. Florian, Rainbow)

6

ALKYNES

In this chapter we continue our discussion of the chemistry of carbon-carbon pi bonds. We now move from the chemistry of alkenes to the chemistry of alkynes. As we shall see, the chemistry of alkynes is in many ways similar to that of alkenes; in particular, each involves electrophilic addition, hydroboration, oxidation, and reduction. Thus, the principles of organic chemistry you learned in Chapters 4 and 5 serve you well in this chapter also.

6.1 Structure

The characteristic structural feature of an alkyne is the presence of a carbon-carbon triple bond. The simplest alkyne is ethyne, C_2H_2, more commonly named acetylene (Figure 6.1). Ethyne is a linear molecule; all bond angles are 180°. The carbon-carbon bond length in ethyne is 0.121 nm (Table 4.1). By comparison, the length of the carbon-carbon double bond in ethene is 0.134 nm and that of the carbon-carbon single bond in ethane is 0.154 nm. Thus, triple bonds are shorter than double bonds, which, in turn, are shorter than single bonds. The bond dissociation energy of carbon-carbon triple bonds is also considerably larger than that for carbon-carbon double bonds and carbon-carbon single bonds.

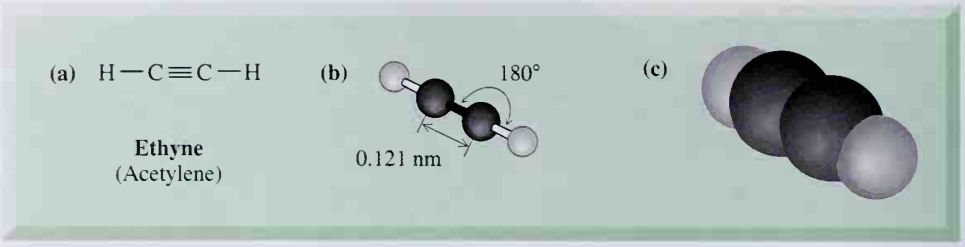


Figure 6.1
Acetylene. (a) Lewis structure, (b) ball-and-stick model, and (c) space-filling model.

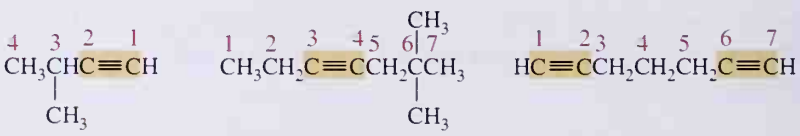
In valence bond theory, a triple bond is described in terms of overlap of *sp* hybrid orbitals of adjacent carbon atoms to form a sigma bond, overlap of parallel $2p_y$ orbitals to form one pi bond, and overlap of parallel $2p_z$ orbitals to form a second pi bond (see Figure 1.22). In acetylene, carbon-hydrogen bonds are formed by overlap of atomic 1*s* orbitals of hydrogen and atomic *sp* orbitals of carbon.

6.2 Nomenclature

Alkynes are named using the IUPAC system, but we shall learn some of the more common names as well.

A. IUPAC Names

According to rules of the IUPAC system, the infix **-yn-** is used to show the presence of a carbon-carbon triple bond (Section 2.5). Thus, HC≡CH is named ethyne, and $CH_3C{\equiv}CH$ is named propyne. The IUPAC system retains the name acetylene, and, therefore, there are two acceptable names for HC≡CH: ethyne and acetylene. Of these two names, acetylene is used much more frequently. For larger molecules, the longest carbon chain that contains the triple bond is numbered from the end that gives the triply bonded carbons the lower numbers. The location of the triple bond is indicated by the number of the first carbon of the triple bond. If a hydrocarbon chain contains more than one triple bond, the infixes **-adiyn-, -atriyn-,** and so forth, are used.



EXAMPLE 6.1

Give each compound an IUPAC name:

(a) $CH_3CH_2C{\equiv}CCH_3$ **(b)** $ClCH_2C{\equiv}CH$ **(c)** $CH_3(CH_2)_2C{\equiv}CCH_2OH$

Solution

(a) 2-pentyne **(b)** 3-chloro-1-propyne

(c) 2-hexyn-1-ol. The hydroxyl group is indicated by the suffix -ol, and its location determines the numbering of the carbon chain.

PROBLEM 6.1

Give each compound an IUPAC name:

(a) $CH_3(CH_2)_5C{\equiv}CH$ (b) $CH_3\overset{\displaystyle OH}{\overset{|}{C}}C{\equiv}CH$ (c) $CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}C{\equiv}CH$

CH_3

B. Common Names

Common names for simple alkynes are derived from that of acetylene by prefixing the names of substituents on the carbon-carbon triple bond to the name acetylene as shown in the following examples:

	$CH_3C{\equiv}CH$	$CH_3C{\equiv}CCH_3$	$CH_2{=}CHC{\equiv}CH$
IUPAC name:	Propyne	2-Butyne	1-Buten-3-yne
Common name:	(Methylacetylene)	(Dimethylacetylene)	(Vinylacetylene)

EXAMPLE 6.2

Give each compound a common name:

(a) $CH_3CHCH_2C{\equiv}CCH_3$ (b) $CH_3CH_2CHC{\equiv}CH$ (c) $HC{\equiv}CCCH_3$

CH_3 CH_3 CH_3

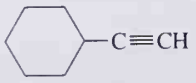
Solution

In answering this problem, it is important to distinguish among three of the four butyl groups, namely isobutyl, *sec*-butyl, and *tert*-butyl.

(a) isobutylmethylacetylene (b) *sec*-butylacetylene
(c) *tert*-butylacetylene

PROBLEM 6.2

Give each compound a common name:

(a) $CH_3CHC{\equiv}CCHCH_3$ (b)  (c) $HC{\equiv}CCH_2CH_2CH_2CH_3$

CH_3 CH_3

Table 6.1 Physical properties of some low-molecular-weight alkynes

Name	Formula	Melting Point (°C)	Boiling Point (°C)	Density at 20°C (g/mL)
acetylene	$HC{\equiv}CH$	−81	−84	(a gas)
propyne	$CH_3C{\equiv}CH$	−102	−23	(a gas)
1-butyne	$CH_3CH_2C{\equiv}CH$	−126	8	(a gas)
2-butyne	$CH_3C{\equiv}CCH_3$	−32	27	0.691
1-pentyne	$CH_3(CH_2)_2C{\equiv}CH$	−90	40	0.690
2-pentyne	$CH_3CH_2C{\equiv}CCH_3$	−101	56	0.711
1-hexyne	$CH_3(CH_2)_3C{\equiv}CH$	−132	71	0.716
2-hexyne	$CH_3(CH_2)_2C{\equiv}CCH_3$	−90	84	0.732
3-hexyne	$CH_3CH_2C{\equiv}CCH_2CH_3$	−103	82	0.723
1-heptyne	$CH_3(CH_2)_4C{\equiv}CH$	−81	100	0.733
1-octyne	$CH_3(CH_2)_5C{\equiv}CH$	−79	125	0.746
1-decyne	$CH_3(CH_2)_7C{\equiv}CH$	−36	174	0.766

6.3 Physical Properties

The physical properties of alkynes are quite similar to those of alkanes and alkenes with similar carbon skeletons. The lower-molecular-weight alkynes are gases at room temperature. Those of five or more carbons are liquids at room temperature, and all have densities less than 1.0 g/mL (they are less dense than water). Listed in Table 6.1 are melting points, boiling points, and densities of several low-molecular-weight alkynes. Because alkynes are essentially nonpolar compounds, they are insoluble in water and other polar liquids. They are soluble in each other and in other nonpolar organic liquids.

6.4 Preparation

There are several important types of reactions by which alkynes can be made. Starting materials include alkyl halides, ketones, alkenes, and other alkynes. At this point in the course, however, we study only the preparation of alkynes from alkenes for the simple reason that alkenes contain the only functional group we have yet studied in any detail.

Alkynes can be synthesized from alkenes by combination of an addition reaction followed by a β-elimination reaction. In the addition reaction, the alkene is treated with bromine or chlorine to form a dibromoalkane or dichloroalkane (Section 5.3A).

$$\underset{\text{An alkene}}{RCH{=}CHR} + Br_2 \xrightarrow[CCl_4]{} \underset{\text{A dibromoalkane}}{RCH(Br){-}CH(Br)R}$$

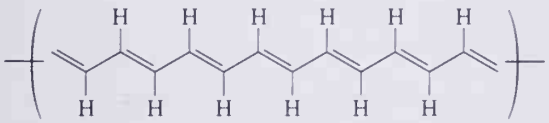
Treatment of a dibromide with 2 mol of strong base, most commonly sodium amide dissolved in liquid ammonia at −33°C (the boiling point of ammonia), results in the elimination of 2 mol of HBr and formation of an alkyne.

CHEMISTRY IN ACTION

Organic Materials that Conduct Electricity

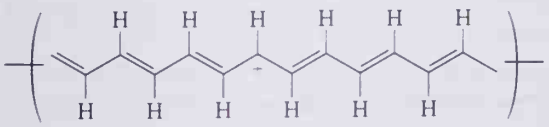
The influence of chemical structure on a molecule's properties is clearly seen in the electric conducting properties of certain organic polymers. Most plastics are insulators. Polytetrafluoroethylene, for example, with the repeating unit $—CF_2CF_2—$ or polyvinyl chloride with the repeating unit $—CH_2CHCl—$ have conductivities of 10^{-18} S/cm. (The unit mho/cm was formerly used to express conductance and is the inverse of resistivity, which has units of Ω-cm. Now the unit S for siemen is used. It is equal to the old mho). On the other end of the scale, the conductivity of copper is almost 10^6 S/cm.

Can organic polymers approach the conductivity of copper? Research carried out over the last 15 years shows that the answer is yes. When acetylene is passed through a solution containing certain transition metal catalysts, it can be polymerized to a shiny film of polyacetylene. The approximate structure of this polymer is as follows:



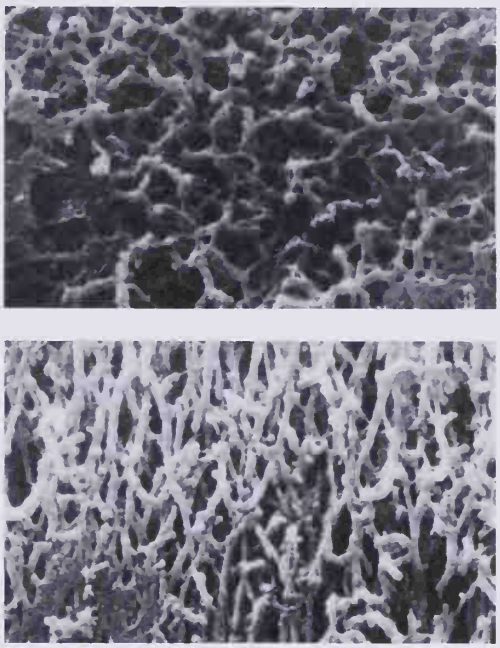
By itself, polyacetylene is not a conductor. However, by a process called **doping,** which involves introducing small amounts of electron-donating or electron-accepting compounds, it is possible to produce a polyacetylene that shows a conductivity of 1.5×10^5 S/cm.

The purpose of the doping agent is either to remove electrons from the pi system (*p*-doping) or add electrons to the pi system (*n*-doping). A *p*-doped polyacetylene can be represented as a polyalkene chain containing positively charged carbons at several points along the chain.



We can think of the positive charge as a defect that can move to the left or to the right along the polymer chain, thus giving rise to conductivity.

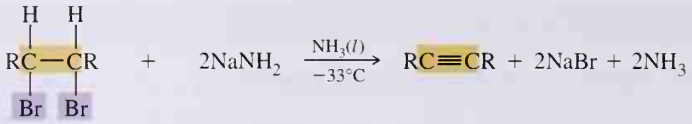
In crude polyacetylene, the polymer chains are jumbled, pointing in all directions. However, by stretching the film, the chains can be made to line up in a more ordered fashion. The conductivity of doped and oriented polyacetylene chains is greater along the direction of the chain than it is perpendicular to the chain. This result suggests that it is much easier for electrons to travel along a chain than to hop from one chain to the next.



Electron micrographs of polyacetylene. The bottom picture shows the material stretched to seven times its original length. *(Richard B. Kaner, UCLA)*

Applications for conducting organic polymers are beginning to be developed. A rechargeable battery with electrodes of *p*-doped and *n*-doped polyacetylene already has been produced. Given the atomic weight of carbon, organic polymer batteries should be lighter than nickel-cadmium or lead-acid batteries. Weight is an important consideration if battery-powered electric cars are ever to be made practical. In addition, many metals used in today's batteries (mercury, nickel, lead) are toxic. If research leads to practical organic batteries, waste-disposal problems could be considerably lessened.

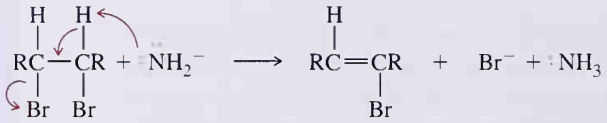
See Kaner, R. B., and A. G. MacDiarmid. *Scientific American,* **258:** 106 (1988).



A dibromoalkane Sodium amide An alkyne

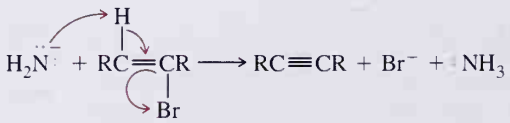
Dehydrohalogenation occurs in two steps: first removal of 1 mol of HBr to form a bromoalkene, and then removal of the second mole of HBr to form the alkyne. In the following mechanism, formation of the bromoalkene is shown as a concerted reaction in which all bond-making and bond-breaking steps occur simultaneously; an amide ion removes a hydrogen ion, the pair of electrons from the C—H bond forms the carbon-carbon double bond, and bromide ion leaves. Conversion of the bromoalkene to an alkyne is also shown as a concerted process.

1. The first dehydrohalogenation:



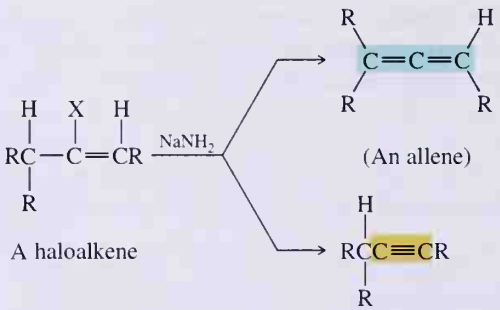
A bromoalkene

2. The second dehydrohalogenation:



With a strong base such as sodium amide, both dehydrohalogenations occur readily. However, with weaker bases, such as sodium hydroxide or potassium hydroxide in ethanol as a solvent, it is often possible to stop the reaction after the first dehydrohalogenation and isolate the haloalkene. In practice, it is much more common to use sodium amide in liquid ammonia and go directly to the alkyne.

In dehydrohalogenation of a haloalkene with at least one hydrogen on each adjacent carbon, a side reaction occurs that must be considered, namely, formation of an allene.



A haloalkene

The characteristic structural feature of an **allene** is adjacent carbon-carbon double bonds, that is, C=C=C. The simplest allene is 1,2-propadiene, commonly named allene. For a description of the bonding in allene in terms of the overlap of atomic orbitals, see your answer to Problem 4.11.

$$CH_2{=}C{=}CH_2$$

1,2-Propadiene
(Allene)

Most allenes are less stable than their isomeric alkynes. For example, allene is less stable by 1.6 kcal/mol than its isomer, propyne, and 1,2-butadiene is less stable by 4.0 kcal/mol than its isomer, 2-butyne.

$$CH_2{=}C{=}CH_2 \longrightarrow CH_3C{\equiv}CH \qquad \Delta H = -1.6 \text{ kcal/mol}$$

$$CH_2{=}C{=}CHCH_3 \longrightarrow CH_3C{\equiv}CCH_3 \qquad \Delta H = -4.0 \text{ kcal/mol}$$

Because of their lower stability relative to isomeric alkynes, allenes are generally only minor products of alkyne-forming dehydrohalogenation reactions.

EXAMPLE 6.3

Show how you might prepare 2-butyne from each starting material:

(a) $CH_3CH{=}CHCH_3$ **(b)** $CH_3CH_2\underset{\displaystyle Cl}{\underset{|}{C}}HCH_3$

Solution

(a) This synthesis can be done in two steps: treatment of 2-butene with 1 mol of chlorine followed by dehydrohalogenation with 2 mol of sodium amide.

$$CH_3CH{=}CHCH_3 + Cl_2 \longrightarrow CH_3\underset{\displaystyle Cl}{\underset{|}{C}}H{-}\underset{\displaystyle Cl}{\underset{|}{C}}HCH_3$$

$$CH_3\underset{\displaystyle Cl}{\underset{|}{C}}H{-}\underset{\displaystyle Cl}{\underset{|}{C}}HCH_3 + 2NaNH_2 \longrightarrow CH_3C{\equiv}CCH_3 + 2NaCl + 2NH_3$$

(b) This synthesis requires three steps. First, dehydrohalogenation of 2-chlorobutane with sodium hydroxide (Section 4.5), followed by addition of chlorine, and then a double dehydrohalogenation as in part (a) of this problem.

$$CH_3CH_2\underset{\displaystyle Cl}{\underset{|}{C}}HCH_3 + NaOH \longrightarrow CH_3CH{=}CHCH_3 + NaCl + H_2O$$

$$CH_3CH{=}CHCH_3 \xrightarrow{Cl_2} CH_3\underset{\displaystyle Cl}{\underset{|}{C}}H{-}\underset{\displaystyle Cl}{\underset{|}{C}}HCH_3 \xrightarrow{2NaNH_2} CH_3C{\equiv}CCH_3$$

PROBLEM 6.3

Draw a structural formula for an alkene and dichloroalkane of given molecular formula that yields the indicated alkyne from each reaction sequence:

(a) $C_6H_{12} \xrightarrow{Cl_2} C_6H_{12}Cl_2 \xrightarrow{2NaNH_2} CH_3CH_2C{\equiv}CCH_2CH_3$

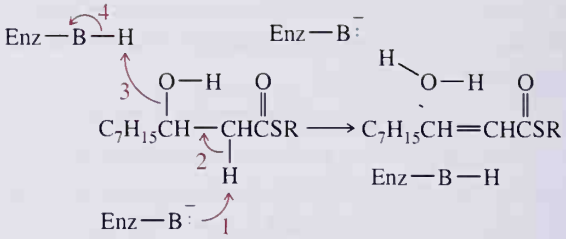
(b) $C_7H_{14} \xrightarrow{Cl_2} C_7H_{14}Cl_2 \xrightarrow{2NaNH_2} CH_3C{\equiv}C\underset{\displaystyle CH_3}{\underset{|}{C}}CH_3$

CHEMISTRY IN ACTION

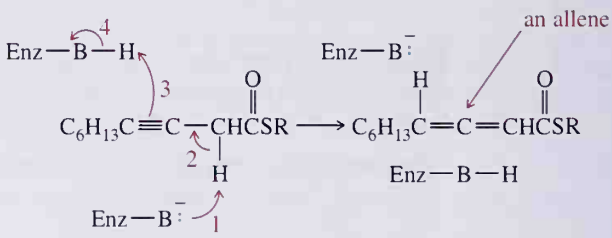
Mechanism-Based Synthesis of Enzyme Inhibitors

Knowing the mechanism of a chemical reaction gives chemists power to predict which molecules will be reactive or unreactive, what regiochemistry and stereochemistry to expect in a reaction, and which molecules can give unusual products. Enzymes, the compounds that catalyze reactions in living systems, use the same kinds of reaction mechanisms found for simple organic molecules. Once chemists understand the mechanism for a particular enzyme-catalyzed reaction, they can design compounds that can irreversibly inactivate that enzyme. These inactivators, sometimes referred to as mechanism-based enzyme inhibitors, also have been given the colorful, if somewhat inaccurate name, of "suicide substrates."

The first example of the use of a suicide substrate was against a key enzyme in the bacterial synthesis of certain fatty acids. The enzyme catalyzes the dehydration of a secondary alcohol to form a carbon-carbon double bond. In the following equation, bond breaking and bond making are shown as a series of four concerted (simultaneous) steps. As a base (the conjugate base of a carboxylic acid) on the surface of the enzyme (1) removes a hydrogen, (2) the pair of electrons from the C—H bond forms the carbon-carbon double bond, (3) the pair of electrons of the —OH bond removes a proton from an acid (a carboxylic acid) on the surface of the enzyme and (4) forms the conjugate base of the acid. That such steps can be made to occur simultaneously, or nearly so, and with complete regioselectivity and stereoselectivity, is one of the remarkable features of enzyme catalysis.



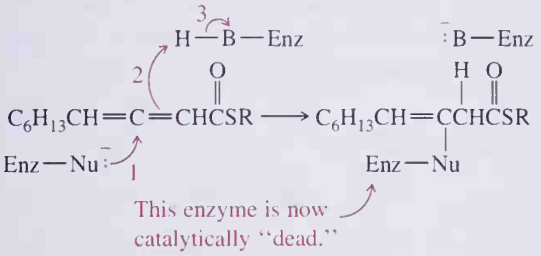
Bloch and coworkers (*J. Biol Chem*, **243:** 3229 (1968)) found that an analog of the alcohol substrate, which contains a carbon-carbon triple bond instead of an alcohol, inactivates the enzyme. The shape of the alkyne molecule, they concluded, must be sufficiently close to the normal substrate of the enzyme so as to fool the enzyme into accepting it. The ensuing inactivation of the enzyme occurs in two stages. In the first stage, (1) a base on the surface of the enzyme removes a proton, (2) the pair of electrons from the C—H bond forms a carbon-carbon double bond, (3) a pair of electrons from the carbon-carbon triple bond removes a proton from an acid on the surface of the enzyme, (4) leaving the acid in its conjugate base form.

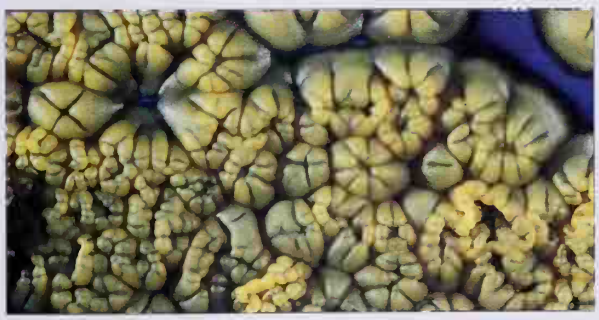


6.5 Reactions

Just as alkynes and alkenes are similar in that each multiple bond is a combination of sigma and pi bonds, so also do these two classes of compounds show similarities in the types of chemical reactions they undergo. One of the most important reactions of alkynes is addition. As we shall see, it is often possible to stop after addition to just one of the two pi bonds; that is, we can convert an alkyne to a substituted alkene and then in a separate step, convert the substituted alkene into a substituted alkane.

The intermediate generated in stage 1 is an allene, a functional group highly reactive toward nucleophilic addition. Then, in the second stage, (1) a nucleophile on the surface of the enzyme adds to the middle carbon of the allene, (2) a pair of electrons from the carbon-carbon double bond removes a proton from an acid on the surface of the enzyme, (3) leaving the acid in its conjugate base form.

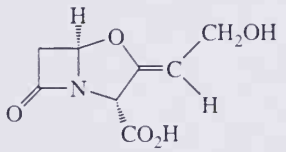




The mold *Streptomyces clavuligerus*. *(Carolina Biological Supply/ Phototake)*

The enzyme in now bonded very firmly to the "suicide substrate" with the result that no new substrates can make their way into the active catalytic site of the enzyme. The enzyme is inactivated, or catalytically "dead."

An example of this strategy is Augmentin, a drug used to treat diseases caused by penicillin-resistant strains of bacteria. Augmentin is a combination of amoxicillin (a member of the penicillin family) and potassium clavulinate (a suicide substrate, isolated from *Streptomyces clavuligerus*).



Clavulinic acid
(a β-lactamase inhibitor)

Potassium clavulinate inhibits the bacterial enzyme (β-lactamase) that breaks down penicillins and thus leaves amoxicillin free to do its work. As the mechanisms of action of more and more enzymes become known, it is hoped that even more drugs or combinations of drugs can be designed to inhibit specific enzymes involved in disease states.

See Ator, M. A., and P. R. Ortiz de Montellano, in D. S. Sigman, and P. D. Boyer (eds.), *The Enzymes*, 3d ed., vol. XIX, pp. 214–282 (Academic Press, San Diego, CA, 1990).

A. Reduction-Addition of Hydrogen

Two types of reactions are used to convert alkynes to alkenes and to alkanes, namely, catalytic reduction and chemical reduction.

Catalytic Reduction

Treatment of an alkyne with hydrogen in the presence of a transition metal catalyst, most commonly palladium, platinum, or nickel, results in addition of 2 mol of hydrogen to the

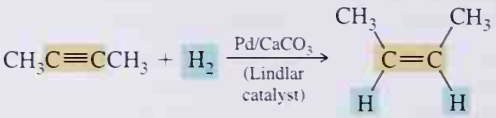
alkyne and its conversion to an alkane. **Catalytic reduction** of an alkyne can be brought about at or slightly above room temperature and with moderate pressures of hydrogen gas.

$$CH_3C{\equiv}CCH_3 + 2H_2 \xrightarrow{\text{Pd, Pt, or Ni}} CH_3CH_2CH_2CH_3$$

2-Butyne Butane

Reduction of an alkyne occurs in two stages: first addition of 1 mol of hydrogen to form an alkene and then addition of the second mole of hydrogen to the alkene to form the alkane.

By careful choice of catalyst, it is possible to stop the reduction after the addition of 1 mol of hydrogen. The catalyst most commonly used for this purpose consists of finely powdered palladium metal deposited on solid calcium carbonate that has been specially modified with lead salts. This combination is known as the **Lindlar catalyst.** Reduction (hydrogenation) of alkynes over a Lindlar catalyst is stereoselective: syn addition of two hydrogen atoms to the carbon-carbon triple bond of an alkyne gives a *cis* alkene, as illustrated by reduction of 2-butyne to give *cis*-2-butene.

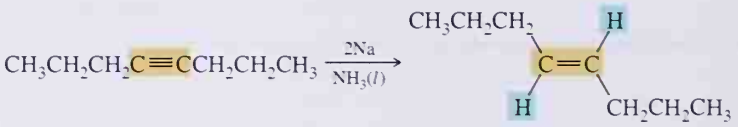


2-Butyne *cis*-2-Butene

Because addition of hydrogen in the presence of the Lindlar catalyst is stereoselective for syn addition, it has been proposed that reduction proceeds by simultaneous or nearly simultaneous transfer of two hydrogen atoms from the surface of the metal catalyst to the alkyne. We presented a similar mechanism in Section 5.8 for the catalytic reduction of an alkene to an alkane.

Chemical Reduction

Alkynes can also be reduced to alkenes by using either sodium or lithium metal dissolved in liquid ammonia or in low-molecular-weight primary or secondary amines. The alkali metal is the reducing agent and in the process is oxidized to M^+. Reduction of alkynes to alkenes by lithium or sodium is stereoselective; it involves anti addition of two hydrogen atoms to the triple bond, as illustrated by the reduction of 4-octyne to *trans*-4-octene.

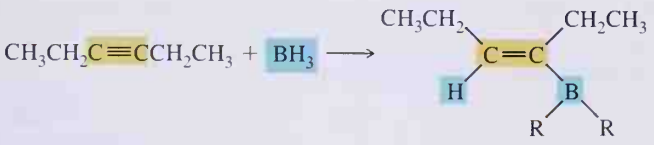


4-Octyne *trans*-4-Octene

Catalytic and alkali metal reduction of alkynes are complementary reactions; by the proper choice of reagents and reaction conditions, it is possible to reduce an alkyne to either a *cis*-alkene or a *trans*-alkene.

B. Addition of Diborane: Hydroboration

Borane adds readily to an internal alkyne as illustrated by the reaction of borane and 3-hexyne. The product of hydroboration of an alkyne is a trialkenylborane (the infix **-enyl-** shows the presence of the carbon-carbon double bond on the carbon attached to boron).

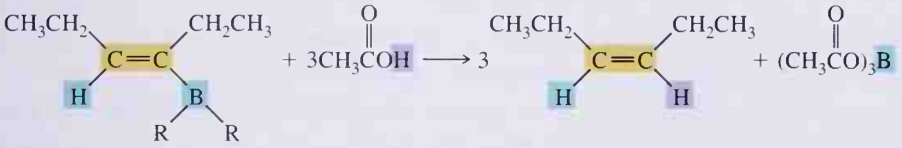


3-Hexyne

A trialkenylborane
(R = *cis*-3-Hexenyl group)

As with hydroboration of alkenes, hydroboration of alkynes is also stereoselective; it involves syn addition of hydrogen and boron.

Treatment of a trialkenylborane with a carboxylic acid such as acetic acid results in stereoselective replacement of boron by hydrogen; a *cis*-alkenylborane is converted to a *cis*-alkene.

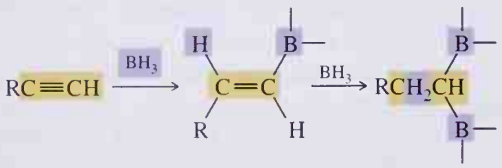


A trialkenylborane

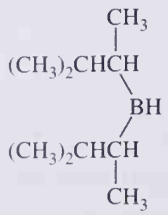
cis-3-Hexene

The net effect of hydroboration of an alkyne followed by treatment with acetic acid is reduction of the alkyne to a *cis*-alkene. Thus, hydroboration-protonation and catalytic reduction over a Lindlar catalyst provide alternative schemes for conversion of an alkyne to a *cis*-alkene.

Terminal alkynes also react with borane to form trialkenylboranes. In practice, however, the reaction is difficult to stop at this stage because the alkenylborane reacts further with borane to form a dihydroborated alkane.

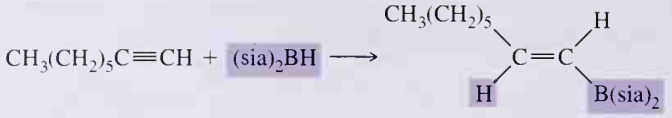


It is possible to prevent the second hydroboration step and in effect stop at an alkenylborane by using a sterically hindered disubstituted borane. One of the most widely used of these is disiamylborane [$(sia)_2BH$], prepared by treatment of borane with two equivalents of 2-methyl-2-butene.



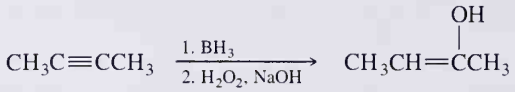
Di-*sec*-isoamylborane
$(sia)_2BH$

Reaction of this hindered dialkylborane with a terminal alkyne results in a single addition and formation of an alkenylborane.



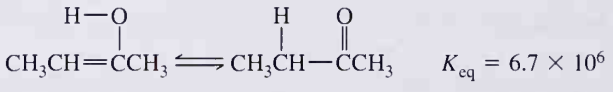
1-Octyne An alkenylborane

Treatment of an alkenylborane with hydrogen peroxide in aqueous sodium hydroxide gives a product that corresponds to hydration of an alkyne, that is, addition of —H to one carbon of the triple bond and —OH to the other as illustrated by the hydroboration-oxidation of 2-butyne.



2-Butyne 2-Buten-2-ol (An enol)

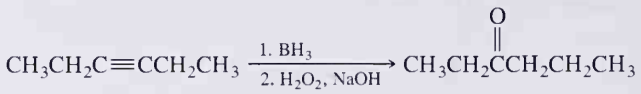
The initial product of hydration is an **enol,** a compound containing a hydroxyl group attached to a carbon-carbon double bond. The name enol is derived from the IUPAC designation of it as both an alkene (-en-) and an alcohol (-ol). Enols are in equilibrium with an isomer formed by migration of a hydrogen atom from oxygen to carbon and rearrangement of the carbon-carbon double bond to form a carbon-oxygen double bond.



2-Buten-2-ol (an enol) 2-Butanone (a ketone)

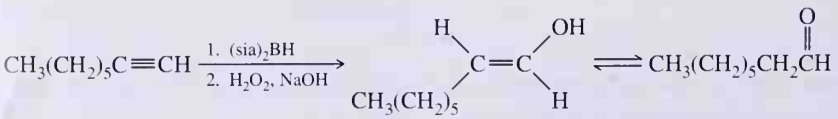
The keto and enol forms of 2-butanone are tautomers. **Tautomers** are constitutional isomers which differ in the location of a hydrogen atom and a double bond relative to a heteroatom, most commonly O, S, or N. This type of isomerism is called **tautomerism.** Because the type of tautomerism we are dealing with in this section involves keto (from ketone) and enol forms, it is commonly called **keto-enol tautomerism.** As can be seen from the value of K_{eq}, 2-butanone (the keto form) is much more stable than its enol.

Thus, the product isolated after hydroboration-oxidation of 2-butyne is 2-butanone and that from hydroboration-oxidation of 3-hexyne is 3-hexanone.



3-Hexyne 3-Hexanone

Hydroboration of a terminal alkyne using disiamylborane followed by oxidation in alkaline hydrogen peroxide gives an enol that is in equilibrium with the more stable aldehyde. Thus, hydroboration-oxidation of a terminal alkyne under these conditions gives an aldehyde.



1-Octyne An enol 1-Octanal

To summarize, a terminal (monosubstituted) alkyne undergoes hydroboration-oxidation to give an aldehyde; an internal (disubstituted) alkyne undergoes hydroboration-oxidation to give a ketone.

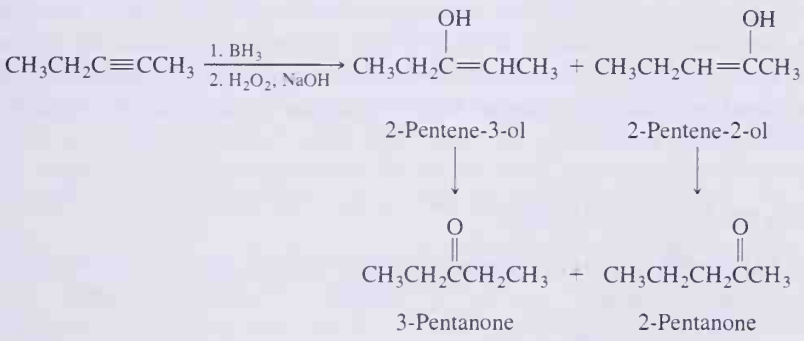
EXAMPLE 6.4

Hydroboration-oxidation of 2-pentyne gives a mixture of two ketones, each of molecular formula $C_5H_{10}O$. Propose structural formulas for these two ketones and for the enol from which each is derived.

$$CH_3CH_2C{\equiv}CCH_3 \xrightarrow[2.\ H_2O_2,\ NaOH]{1.\ BH_3} C_5H_{10}O$$

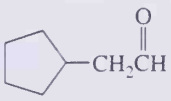
Solution

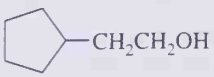
Because each carbon of the triple bond in 2-pentyne has the same degree of substitution, very little regiospecificity occurs during hydroboration. Two enols are formed, and from them isomeric ketones are formed.



PROBLEM 6.4

Draw the structural formula for a hydrocarbon of given molecular formula that undergoes hydroboration-oxidation to give the following compounds:

(a) $C_7H_{10} \xrightarrow[2.\ H_2O_2,\ NaOH]{1.\ (sia)_2BH}$ 

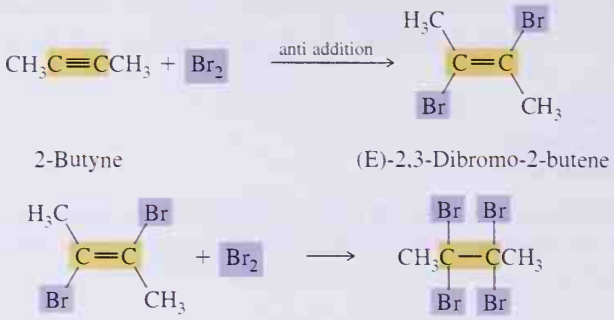
(b) $C_7H_{12} \xrightarrow[2.\ H_2O_2,\ NaOH]{1.\ BH_3}$ 

C. Electrophilic Additions

Alkynes undergo many of the same electrophilic additions as alkenes. In this section, we study addition of bromine and chlorine, of the hydrogen halides, and of water to alkynes.

Addition of Bromine and Chlorine

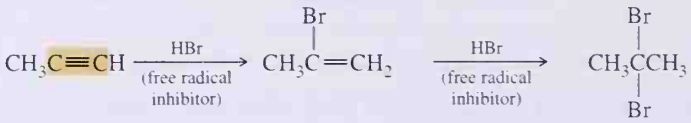
Addition of 1 mol of Br_2 to an alkyne gives a dibromoalkene; addition of a second mole of Br_2 gives a tetrabromoalkane.



As illustrated by the reaction of 2-butyne with 1 mol of Br_2, addition of bromine to a triple bond is stereoselective; the major product corresponds to anti addition of the two bromine atoms. The preference for anti addition can be increased significantly by carrying out bromination in acetic acid in which is dissolved a source of bromide ion, for example LiBr. From this and other experimental evidence, chemists have proposed that addition of bromine to alkynes follows much the same type of mechanism as it does for addition to alkenes (Section 5.3D), namely, formation of a bridged bromonium ion intermediate, which is then attacked by bromide ion from the face opposite that occupied by the positively-charged bromine atom. Alkynes similarly undergo addition of Cl_2, although considerably more slowly than Br_2.

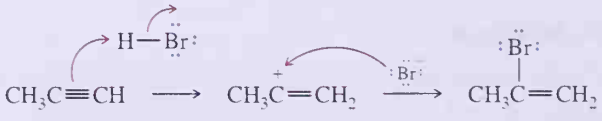
Addition of Hydrogen Halides

Alkynes add either 1 or 2 mol of HBr and HCl depending on the ratios in which the alkyne and halogen acid are mixed.



As shown in this equation, additions of both the first and second moles of HBr are regioselective. They follow Markovnikov's rule (Section 5.3B): hydrogen adds to the carbon that bears the greater number of hydrogens.

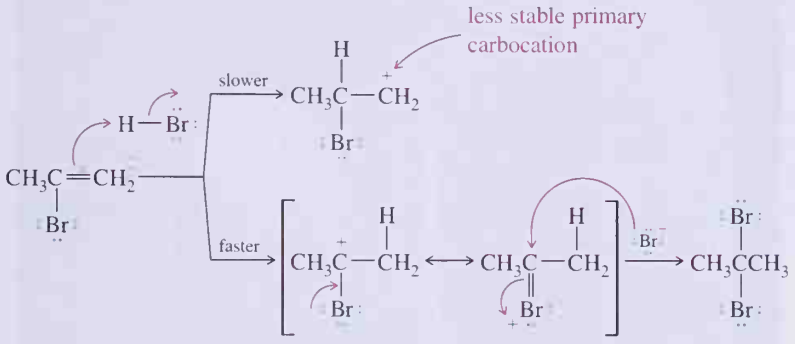
We can account for this regioselectivity of addition of HX by proposing a two-step mechanism for each. In Step 1, reaction of a pi bond of the alkyne (a Lewis base and nucleophile) with HBr forms a **vinylic carbocation,** which then reacts with bromide ion to give the observed product.



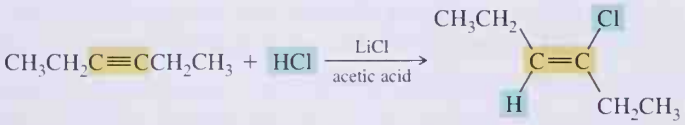
(A vinylic carbocation)

Alkynes are considerably less reactive toward most electrophilic additions than are alkenes. The major reason for this difference is the instability of the vinylic carbocation intermediate formed from an alkyne compared with the alkyl carbocation formed from an alkene.

In the case of addition of the second mole of HX, Step 1 is again reaction with HBr to form a carbocation. Of the two possible carbocations, the one with the positive charge on the carbon bearing the halogen is secondary and, therefore, favored over the primary carbocation. The secondary carbocation is also favored because of resonance stabilization by the adjacent halogen atom.

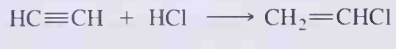


Addition of HCl or HBr to an alkyne is stereoselective and involves anti addition as shown by the reaction of 3-hexyne with HCl. Note that because the groups of higher priority (chlorine on one carbon and ethyl on the other) are on the same side of the double bond, the resulting alkene has the Z configuration. In the *cis-trans* nomenclature, it is designated *trans* because the atoms of the main carbon chain are *trans* to each other.



3-Hexyne (Z)-3-Chloro-3-hexene

Addition of 1 mol of HCl to acetylene gives chloroethylene, a compound of considerable industrial importance.



Ethyne (Acetylene) Chloroethene (Vinyl chloride)

In 1993, the U. S. chemical industry produced 13.8 billion pounds of this substance for use as a monomer in the production of polyvinyl chloride (PVC, Table 5.5).

Chloroethylene (Vinyl chloride) Poly(vinyl chloride) (PVC)

Just as polyethylene dominates the packaging market (Section 5.9C), polyvinyl chloride dominates much of the plumbing and construction market for plastics. Approximately 67% of all pipe, fittings, and conduit along with 42% of all plastics used in construction at the present time are fabricated from vinyl chloride. At one time, hydrochlorination of acetylene was the major source of vinyl chloride. As the cost of production of acetylene

A vinyl chloride plant in Texas. *(Courtesy of Occidental Petroleum Corporation.)*

increased, however, manufacturers of vinyl chloride sought other routes to this material. The starting material chosen was ethylene. What was sought was a way to convert ethylene to vinyl chloride.

$$CH_2{=}CH_2 \xrightarrow{???} CH_2{=}CHCl$$

Ethylene Vinyl chloride

One answer to this problem was to treat ethylene with chlorine gas to form 1,2-dichloroethane. When heated in the presence of charcoal or another catalyst, 1,2-dichloroethane loses a molecule of HCl to form vinyl chloride.

$$CH_2{=}CH_2 \xrightarrow{Cl_2} \underset{\displaystyle Cl\ \ Cl}{CH_2CH_2} \xrightarrow[\text{heat}]{} CH_2{=}CHCl + HCl$$

Ethylene 1,2-Dichloroethane Vinyl chloride

This reaction sequence gives vinyl chloride. However, the byproduct, HCl, is corrosive and presents problems in handling and disposal. Although the problem of how to process this HCl was new, the solution had been discovered many years ago. In 1868 Henry Deacon discovered that HCl can be oxidized to Cl_2 by air (actually, the oxygen in air) over a copper(II) catalyst.

$$4HCl + O_2 \xrightarrow{CuCl_2} 2H_2O + 2Cl_2 \qquad \text{(Deacon process)}$$

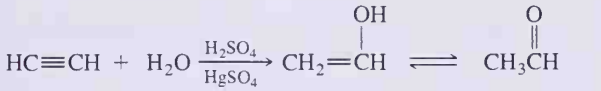
This process has been improved by the use of new technology, and today vinyl chloride is made by passing ethylene, hydrogen chloride, and air over a copper(II) chloride–potassium chloride catalyst to give 1,2-dichloroethane, which is then thermally cracked to vinyl chloride and HCl. HCl is then recycled. The three reactions in this scheme and the net result are shown as follows:

$$\begin{aligned} 4HCl + O_2 &\longrightarrow 2H_2O + 2Cl_2 \\ 2CH_2{=}CH_2 + 2Cl_2 &\longrightarrow 2ClCH_2CH_2Cl \\ 2ClCH_2CH_2Cl &\longrightarrow 2CH_2{=}CHCl + 2HCl \\ \hline \text{Net reaction: } 2CH_2{=}CH_2 + 2HCl + O_2 &\longrightarrow 2CH_2{=}CHCl + 2H_2O \end{aligned}$$

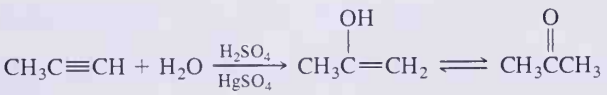
We described the production of vinyl chloride first from acetylene and then ethylene to illustrate an important point about industrial organic chemistry. The aim is to produce a desired chemical from readily available and inexpensive starting materials by a direct scheme of reactions in which byproducts can be recycled in some useful way. Very often, as we already saw for the production of ethylene and now for the production of vinyl chloride, this involves passing reactants "down a hot tube over a suitable catalyst."

Addition of Water: Hydration

In the presence of concentrated acid and Hg(II) salts as catalysts, alkynes undergo the addition of water. The catalysts most often used for this purpose are concentrated sulfuric acid and mercury(II) sulfate or mercury(II) acetate. Addition of water follows Markovnikov's rule; hydrogen adds to the carbon atom of the triple bond bearing the greater number of hydrogens. The resulting enol is in equilibrium with a keto form (Section 6.5B), and the product isolated is a ketone (an aldehyde in the case of acetylene itself).

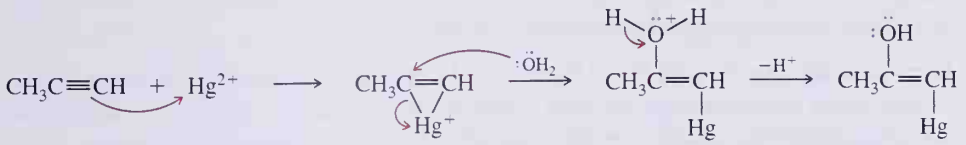


Ethyne (Acetylene) — Ethenol (an enol) — Ethanal (Acetaldehyde)



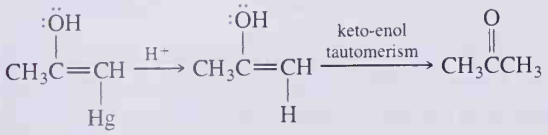
Propyne — 1-Propen-2-ol (an enol) — Propanone (Acetone)

The mechanism for hydration of an alkyne is illustrated by the hydration of propyne to give propanone (acetone). The first step in this Hg^{2+}-catalyzed hydration is formation of an organomercurinium ion intermediate in a reaction similar to that between mercury(II) acetate and an alkene (Section 5.3E). Reaction of this mercurinium ion intermediate with water followed by loss of H^+ gives an organomercury enol. Note that this addition follows Markovnikov's rule: the electrophile, Hg^{2+}, adds to the less substituted carbon, and the nucleophile, H_2O, adds to the more substituted carbon.



Propyne — A bridged mercurinium ion intermediate — An organomercury enol

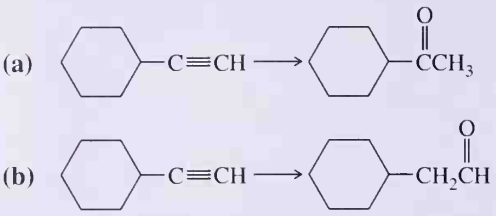
In the presence of acid, the carbon-mercury bond is cleaved and the metal replaced by hydrogen to give an enol that undergoes keto-enol tautomerism to give acetone.



Acetone

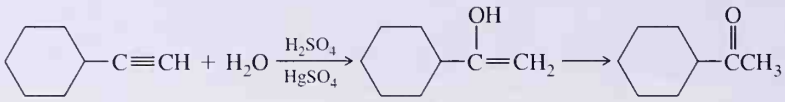
EXAMPLE 6.5

Show how to bring about the following conversions:



Solution

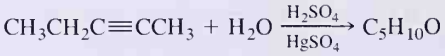
(a) Acid-catalyzed hydration of ethynylcyclohexane gives an enol that is in equilibrium with the keto form.



(b) Hydroboration using disiamylborane followed by oxidation gives an enol that is in equilibrium with the desired aldehyde.

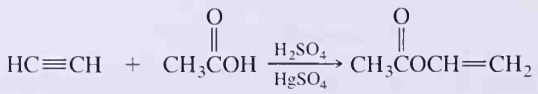
PROBLEM 6.5

Acid-catalyzed hydration of 2-pentyne gives a mixture of two ketones, each of molecular formula $C_5H_{10}O$. Propose structural formulas for these two ketones and for the enol from which each is derived.



Addition of Acetic Acid: Formation of Vinyl Esters

In the presence of sulfuric acid and Hg(II) salts as catalysts, carboxylic acids add to alkynes to form vinyl esters. Perhaps the most important example of this reaction is that between acetylene and acetic acid to form the ester with the common name vinyl acetate.



Ethyne (Acetylene)	Ethanoic acid (Acetic acid)	Ethenyl ethanoate (Vinyl acetate)

Annual production of vinyl acetate, the monomer for the production of polyvinyl acetate, in the United States in 1993 was 2.8 billion pounds. The major use of polyvinyl acetate is as an adhesive in the construction and packaging industries and in the paint and coatings industry.

Until 1967, the bulk of vinyl acetate manufactured in the United States was produced by addition of acetic acid to acetylene using sulfuric acid–mercury(II) sulfate as a catalyst. However, as the price of acetylene rose, manufacturers turned to ethylene as a starting material for the production of vinyl acetate. Using a modification of technology originally developed by Wacker-Chemie in 1959 and known as the **Wacker process,** ethylene, acetic acid, and molecular oxygen are allowed to react at elevated temperatures in the presence of a palladium(II) chloride–copper(II) chloride catalyst to produce vinyl acetate.

$$2CH_2{=}CH_2 + 2CH_3\overset{\overset{O}{\|}}{C}OH + O_2 \xrightarrow[\text{(Wacker process)}]{PdCl_2 \cdot CuCl_2} 2CH_3\overset{\overset{O}{\|}}{C}OCH{=}CH_2 + 2H_2O$$

Ethene (Ethylene) | Ethanoic acid (Acetic acid) | Ethenyl ethanoate (Vinyl acetate)

D. Acidity of Alkynes

One of the major differences between the chemistry of alkynes and alkenes is that a hydrogen attached to a carbon-carbon triple bond is sufficiently acidic that it can be removed by a strong base. For example, treatment of propyne with sodium amide, $NaNH_2$, forms ammonia and the sodium salt of propyne.

$$CH_3C{\equiv}C{-}H + Na^+ :\ddot{N}H_2^- \rightleftharpoons CH_3C{\equiv}C^-\ Na^+ + :NH_3$$

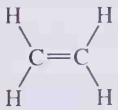
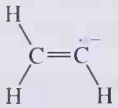
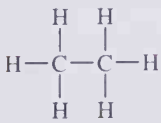
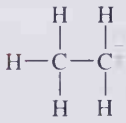
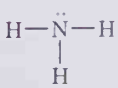
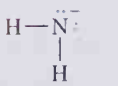
Other strong bases commonly used for this purpose are sodium hydride and lithium diisopropylamide (LDA).

$Na^+\ :\ddot{H}^-$ — Sodium hydride

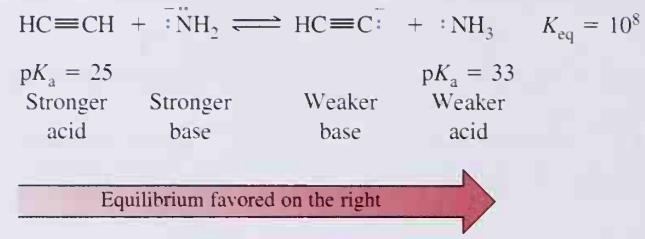
$[(CH_3)_2CH]_2\ddot{N}^-\ Li^+$ — Lithium diisopropylamide (LDA)

We can analyze this reaction in a more quantitative way like we did for other acid-base reactions in Section 3.3. Shown in Table 6.2 are pK_a values for acetylene, ethylene, and ethane. Also shown for comparison are values for ammonia and water.

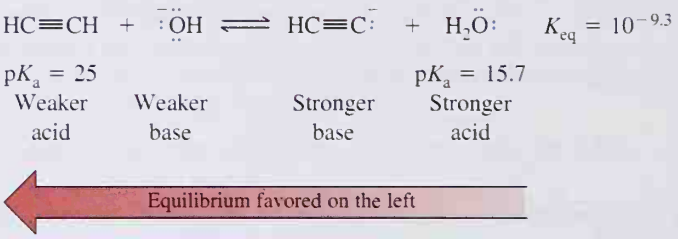
Table 6.2 Acidity of alkanes, alkenes, and alkynes

Weak Acid	Example	Conjugate Base	K_a	pK_a
alkyne	$H{-}C{\equiv}C{-}H$	$H{-}C{\equiv}C^-$	10^{-25}	25
alkene			10^{-44}	44 (approx.)
alkane			10^{-48}	48 (approx.)
ammonia			10^{-33}	33
water			$10^{-15.7}$	15.7

Of the three classes of hydrocarbons shown in Table 6.2, terminal alkynes are by far the most acidic. Note also that acetylene is a stronger acid than ammonia but a weaker acid than water. From this information, we can determine that acetylene (a stronger acid) reacts with amide ion (a stronger base) to form the anion of acetylene (a weaker base) and ammonia (a weaker acid) and that the position of the equilibrium for this reaction lies very much toward the right.



Hydroxide ion is not a strong enough base to remove a hydrogen from acetylene.



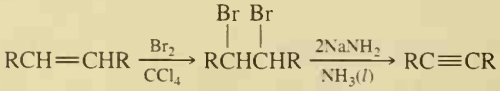
The pK_a values for alkene and alkane hydrogens are so large (they are so weakly acidic) that neither the commonly used alkali metal hydroxides nor sodium hydride, sodium amide, or lithium diisopropylamide are strong enough to remove a hydrogen from alkanes or alkenes.

We account for the greater acidity of alkyne hydrogens compared with those of alkenes and alkanes by considering the hybridization of the orbital bearing the unshared pair of electrons in the conjugate base. For any principal energy level, an *s* orbital lies at a lower energy level than do *p* orbitals, and, therefore, electrons in *s* orbitals are more stable (lower in energy) than those in *p* orbitals. It follows then that the greater the percent *s* character of a hybrid orbital, the greater the stability of electrons in that orbital. The lone pair of the anion from an alkyne lies in an *sp* hybrid orbital that has 50% *s* character; consequently, acetylene anion is the most stable and, therefore, the least basic. Conversely, the lone pair of an anion derived from an alkane lies in an sp^3 orbital that has only 25% *s* character; thus, the anion derived from an alkane is the least stable and, therefore, the most basic.

SUMMARY OF KEY REACTIONS

1. Synthesis of an Alkyne from an Alkene (Section 6.4)

Addition of Br_2 or Cl_2 to an alkene followed by a double hydrohalogenation using $NaNH_2$ or other strong base gives an alkyne.



2. Catalytic Reduction (Section 6.5A)

Reaction with 2 mol of H_2 under moderate pressure in the presence of a transition metal catalyst at room temperature gives an alkane.

$$CH_3C{\equiv}CCH_3 + 2H_2 \xrightarrow{\text{Pd, Pt, or Ni}} CH_3CH_2CH_2CH_3$$

Reaction in the presence of the Lindlar catalyst is stereoselective; syn addition of 1 mol of H_2 gives a *cis*-alkene.

$$CH_3C{\equiv}CCH_3 + H_2 \xrightarrow[\text{(Lindlar catalyst)}]{Pd/CaCO_3} \begin{matrix} H_3C & & CH_3 \\ & C{=}C & \\ H & & H \end{matrix}$$

3. Reduction Using Na or Li Metal in $NH_3(l)$ (Section 6.5A)

Alkali metal reduction is stereoselective: anti addition of hydrogen gives a *trans*-alkene.

$$CH_3CH_2CH_2C{\equiv}CCH_2CH_2CH_3 \xrightarrow[NH_3(l)]{2Na} \begin{matrix} CH_3CH_2CH_2 & & H \\ & C{=}C & \\ H & & CH_2CH_2CH_3 \end{matrix}$$

4. Hydroboration-Oxidation (Section 6.5B)

Hydroboration of an internal alkyne is stereoselective; syn addition of BH_3. Oxidation using H_2O_2/NaOH gives an enol that is in equilibrium by keto-enol tautomerism with a ketone.

$$CH_3CH_2C{\equiv}CCH_2CH_3 \xrightarrow[2.\ H_2O_2,\ NaOH]{1.\ BH_3} CH_3CH_2\overset{\overset{O}{\|}}{C}CH_2CH_2CH_3$$

Hydroboration of a terminal alkyne using a hindered dialkylborane followed by oxidation using H_2O_2/NaOH and then keto-enol tautomerism gives an aldehyde.

$$CH_3(CH_2)_5C{\equiv}CH \xrightarrow[2.\ H_2O_2,\ NaOH]{1.\ (sia)_2BH} CH_3(CH_2)_5CH_2\overset{\overset{O}{\|}}{C}H$$

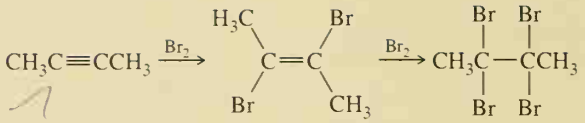
5. Keto-Enol Tautomerism (Section 6.5B)

In an equilibrium betweeen a keto form and an enol form, the keto form generally predominates.

$$\underset{\text{Enol form}}{CH_3CH{=}\overset{\overset{OH}{|}}{C}CH_3} \rightleftharpoons \underset{\text{Keto form}}{CH_3\overset{\overset{H}{|}}{C}H\overset{\overset{O}{\|}}{C}CH_3}$$

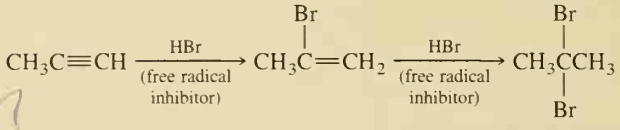
6. Addition of Br_2 and Cl_2 (Section 6.5C)

Electrophilic addition of 1 mol of Br_2 or Cl_2 is stereoselective; anti addition gives an (E)-dihaloalkene. Electrophilic addition of 2 mol of Br_2 or Cl_2 gives a tetrahaloalkane.



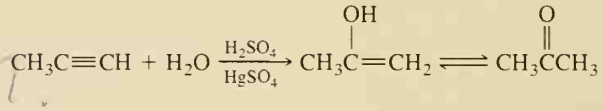
7. Addition of HX (Section 6.5C)

Electrophilic addition of HX is regioselective. Reaction by way of a vinyl carbocation intermediate follows Markovnikov's rule. Electrophilic addition of 2HX gives a 1,1-dihaloalkane.



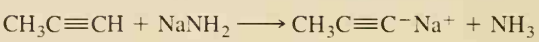
8. Acid-Catalyzed Hydration (Section 6.5C)

Acid-catalyzed addition of water, in the presence of Hg(II) salts, is regioselective. Keto-enol tautomerism of the resulting enol gives a ketone.



9. Acidity of Alkynes (Section 6.5D)

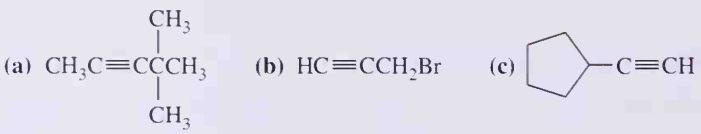
Terminal alkynes react with strong bases, most commonly $NaNH_2$ or NaH, to give salts.



ADDITIONAL PROBLEMS

Structure and Nomenclature

6.6 Write IUPAC names for the following compounds:



(d) $HC{\equiv}CCH_2CH_2CH_2C{\equiv}CH$ **(e)** $CH_3(CH_2)_5C{\equiv}CCH_2OH$

(f) $CH_3(CH_2)_6C{\equiv}CH$ **(g)** $CH_3C{\equiv}CCH_2OH$ **(h)** $CH_3(CH_2)_7C{\equiv}C(CH_2)_7CO_2H$

6.7 Draw structural formulas for the following compounds:

(a) 3-hexyne **(b)** vinylacetylene

(c) 3-chloro-1-butyne **(d)** 5-isopropyl-3-octyne

(e) 3-pentyn-2-ol **(f)** 2-butyne-1,4-diol

(g) diisopropylacetylene **(h)** *tert*-butylmethylacetylene

(i) cyclodecyne

6.8 Predict all bond angles about each circled atom.

(a) $CH_3C{\equiv}CCH_3$ **(b)** $CH_2{=}CHC{\equiv}CH$ **(c)** $CH_2{=}C{=}CHCH_3$

(d) $O{=}C{=}O$

6.9 Following are Lewis structures for several small molecules. State the orbital hybridization of each circled atom.

(a) $CH_3C{\equiv}CCH_3$ **(b)** $CH_2{=}CHC{\equiv}CH$ **(c)** $CH_2{=}C{=}CHCH_3$

(d) $O{=}C{=}O$

6.10 Describe each circled carbon-carbon bond in terms of the overlap of atomic orbitals.

(a) $CH_3C{\equiv}C{-}CH_3$ **(b)** $CH_2{=}CH{-}C{\equiv}CH$ **(c)** $CH_2{=}C{=}CHCH_3$

(d) $CH_2{=}CH{-}CH{=}CH_2$

Preparation of Alkynes

6.11 Show how to prepare each alkyne from the given starting material.

(a) $CH_3CH_2CH_2CH{=}CH_2 \longrightarrow CH_3CH_2CH_2C{\equiv}CH$

(b) $CH_3(CH_2)_5\underset{\displaystyle Cl}{\underset{|}{C}}HCH_3 \longrightarrow CH_3(CH_2)_4C{\equiv}CCH_3$

(c) $CH_3CH_2CH_2C{\equiv}CH \longrightarrow CH_3CH_2CH_2C{\equiv}CD$

Reactions of Alkynes

6.12 Draw structural formulas for the major product(s) formed by reaction of 3-hexyne with each of the following reagents. Where you predict no reaction, write NR.

(a) H_2(excess)/Pt **(b)** H_2(excess)/Lindlar catalyst

(c) Na in NH_3(liquid) **(d)** BH_3 followed by H_2O_2/NaOH

(e) BH_3 followed by CH_3CO_2H **(f)** BH_3 followed by CH_3CO_2D

(g) HCl (1 mol)/LiCl in CH_3CO_2H **(h)** $NaNH_2$ in NH_3 (liquid)

(i) HBr (1 mol) **(j)** HBr (2 mol)

(k) H_2O in $H_2SO_4/HgSO_4$ **(l)** CH_3CO_2H in $H_2SO_4/HgSO_4$

6.13 Draw the structural formula of the bracketed enol formed in each alkyne hydration reaction and then draw the structural formula of the carbonyl compound with which each enol is in equilibrium.

(a) $CH_3(CH_2)_5C{\equiv}CH + H_2O \xrightarrow[H_2SO_4]{HgSO_4}$ (an enol) $\longrightarrow$

(b) $CH_3(CH_2)_5C{\equiv}CH \xrightarrow[NaOH/H_2O_2]{(sia)_2BH}$ (an enol) $\longrightarrow$

Syntheses

6.14 Show how you might convert 9-octadecynoic acid to the following:

$$CH_3(CH_2)_7C{\equiv}C(CH_2)_7CO_2H$$

9-Octadecynoic acid

(a) (E)-9-octadecenoic acid (eliadic acid)

(b) (Z)-9-octadecenoic acid (oleic acid)

(c) 9,10-dihydroxyoctadecanoic acid

(d) 9,10-dibromooctadecanoic acid

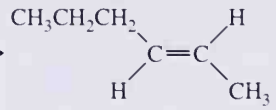
(e) octadecanoic acid

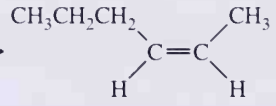
6.15 For small-scale and consumer welding applications, many hardware stores sell cylinders of MAAP gas, which is a mixture of propyne (methyl acetylene) and 1,2-propadiene (allene) gases, with other hydrocarbons. How would you prepare this gas mixture in the laboratory?

6.16 Show reagents and experimental conditions you might use to convert propyne into each product. Some of these syntheses can be done in one step. Others require two or more steps.

(a) $CH_3C(Br)(Br)CH(Br)Br$ **(b)** CH_3CBrCH_3 **(c)** CH_3CCH_3 (O) **(d)** CH_3CH_2CH (O)

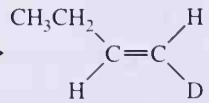
6.17 Show reagents and experimental conditions you might use to convert each starting material into the desired product. Some of these syntheses can be done in one step. Others require two or more steps.

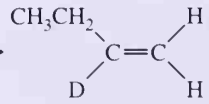
(a) $CH_3CH_2CH_2C{\equiv}CCH_3 \longrightarrow$ 

(b) $CH_3CH_2CH_2C{\equiv}CCH_3 \longrightarrow$ 

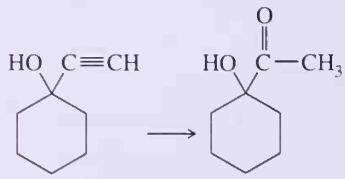
(c) $CH_3(CH_2)_4C{\equiv}CH \longrightarrow CH_3(CH_2)_4C{\equiv}C^-\ Na^+$

(d) $CH_3CH_2C{\equiv}CH \longrightarrow CH_3CH_2C{\equiv}CD$

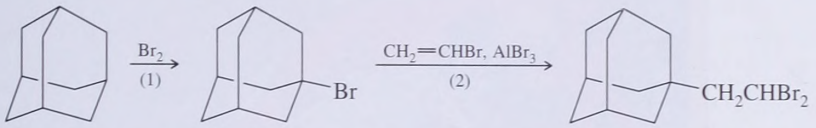
(e) $CH_3CH_2C{\equiv}CH \longrightarrow$ 

(f) $CH_3CH_2C{\equiv}CH \longrightarrow$ 

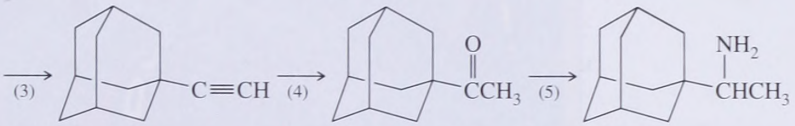
(g) $HOCH_2CH{=}CHCH_2OH \longrightarrow HOCH_2CH_2CH_2CH_2OH$

(h) 

6.18 Rimantadine is effective in preventing naturally occurring infections caused by the influenza A virus and in treating established illness. It is thought to exert its antiviral effect by blocking a late stage in the assembly of the virus. Rimantadine is synthesized from adamantane in the following sequence. We covered the types of chemistry involved in Steps 1–4. We discuss the chemistry of Step 5 in Chapter 17.



Adamantane 1-Bromoadamantane



Rimantadine
(an antiviral agent)

(a) Describe experimental conditions to bring about Step 1. By what type of mechanism does this reaction occur? Account for the regioselectivity of bromination in Step 1.

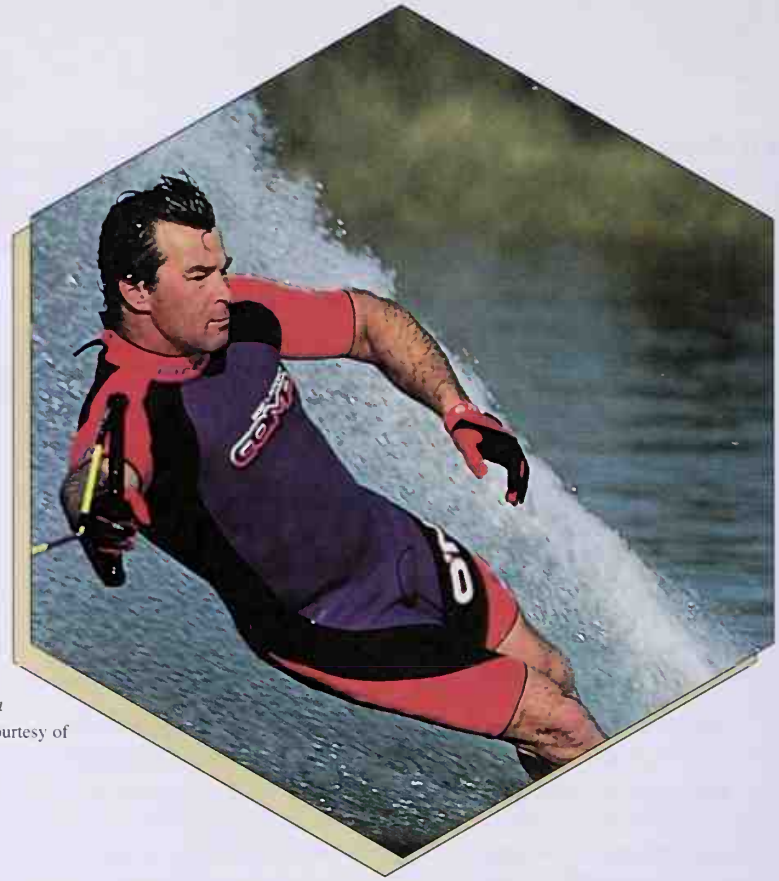
(b) Propose a mechanism for Step 2. *Hint:* As we shall see in Chapter 16, reaction of a bromoalkane such as 1-bromoadamantane with aluminum bromide (a Lewis acid, Section 3.4) results in formation of a carbocation and $AlBr_4^-$. Assume that adamantyl cation is formed in Step 2 and proceed from there to describe a mechanism.

(c) Account for the regioselectivity of carbon-carbon bond formation in Step 2.

(d) Describe experimental conditions to bring about Step 3.

(e) Describe experimental conditions to bring about Step 4.

7



A wet suit made from neoprene rubber. (Courtesy of O'Neill, Inc.)

CONJUGATED DIENES

In Chapters 4 and 5, we discussed the structure and characteristic reactions of alkenes. We limited this discussion to molecules containing one double bond. In this chapter, we extend our study of alkenes to include molecules that contain two or more conjugated double bonds. As we shall see, although conjugated dienes undergo many of the same reactions characteristic of unconjugated alkenes, they also undergo their own unique set of characteristic reactions.

7.1 Nomenclature

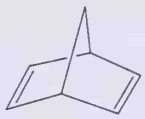
Dienes are compounds that contain two carbon-carbon double bonds. Dienes can be divided into three groups: unconjugated, conjugated, and cumulated. An **unconjugated diene** is one in which the double bonds are separated by one or more atoms. A **conjugated diene** is a diene in which the double bonds are between adjacent pairs of atoms. A **cumulated diene** is one in which two double bonds share a carbon atom. Following are examples of each type of diene. We do not discuss cumulated dienes in this chapter.

$CH_2{=}CHCH_2CH{=}CH_2$ $CH_2{=}CHCH{=}CHCH_3$ $CH_2{=}C{=}CHCH_2CH_3$

1,4-Pentadiene (an unconjugated diene) | 1,3-Pentadiene (a conjugated diene) | 1,2-Pentadiene (a cumulated diene)

EXAMPLE 7.1

Which of these molecules contain conjugated double bonds?

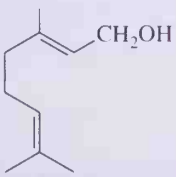
(a)  (b)  (c)  (d) 

Solution

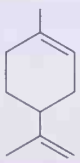
Compounds (b) and (c) contain conjugated double bonds. The double bonds in compounds (a) and (d) are unconjugated.

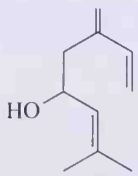
PROBLEM 7.1

Which of these terpenes (Figure 4.6) contains conjugated double bonds?

(a) 

Geraniol

(b) 
Limonene

(c) 

An aggregating pheromone of bark beetles

7.2 Stability

Several types of experimental observations can be used to estimate the effects of conjugation of double bonds on the relative stabilities of molecules. We use heats of hydrogenation data. Recall from Section 5.8 that catalytic hydrogenation (reduction) of an alkene is an exothermic reaction with a heat of hydrogenation of approximately 28 to 30 kcal/mol. The heat of hydrogenation of a particular double bond depends on several factors, including its degree of substitution and whether it has an E or Z configuration. Given in Table 7.1 are heats of hydrogenation for several alkenes and dienes.

By using the data in Table 7.1, we can compare the relative stabilities of conjugated and unconjugated dienes. The simplest conjugated diene is 1,3-butadiene, but because this molecule has only four carbon atoms, it has no unconjugated constitutional isomer. Nonetheless, we can estimate the effect of conjugation of two double bonds in this molecule in the following way. The heat of hydrogenation of 1-butene is −30.3 kcal/mol. The molecule 1,3-butadiene has two terminal double bonds, each with the same degree of substitution as the one double bond in 1-butene, and, therefore, we can estimate that the heat of

Table 7.1 Heats of hydrogenation of some alkenes and alkadienes

Name	Structural Formula	$\Delta H°$ (kcal/mol)
1-butene	$CH_2{=}CHCH_2CH_3$	−30.3
1-pentene	$CH_2{=}CHCH_2CH_2CH_3$	−30.1
1-hexene	$CH_2{=}CHCH_2CH_2CH_2CH_3$	−30.0
cis-2-butene	$CH_3CH{=}CHCH_3$	−28.6
trans-2-butene	$CH_3CH{=}CHCH_3$	−27.6
trans-2-pentene	$CH_3CH{=}CHCH_2CH_3$	−27.6
1,3-butadiene	$CH_2{=}CHCH{=}CH_2$	−56.5
trans-1,3-pentadiene	$CH_2{=}CHCH{=}CHCH_3$	−54.1
1,4-pentadiene	$CH_2{=}CHCH_2CH{=}CH_2$	−60.8

hydrogenation of 1,3-butadiene should be 2(−30.3 kcal/mol) or −60.6 kcal/mol. The observed heat of hydrogenation of 1,3-butadiene is −56.5 kcal/mol, a value 4.1 kcal/mol less than estimated.

$$2CH_2{=}CHCH_2CH_3 + 2H_2 \xrightarrow[\text{metal catalyst}]{\text{transition}} 2CH_3CH_2CH_2CH_3 \qquad \Delta H = 2(-30.3 \text{ kcal/mol}) = -60.6 \text{ kcal/mol})$$

$$CH_2{=}CHCH{=}CH_2 + 2H_2 \xrightarrow[\text{metal catalyst}]{\text{transition}} CH_3CH_2CH_2CH_3 \qquad \Delta H = -56.5 \text{ kcal/mol}$$

The conclusion from this calculation is that conjugation of two double bonds in 1,3-butadiene gives an extra stability to the molecule of approximately 4.1 kcal/mol. These energy relationships are displayed graphically in Figure 7.1.

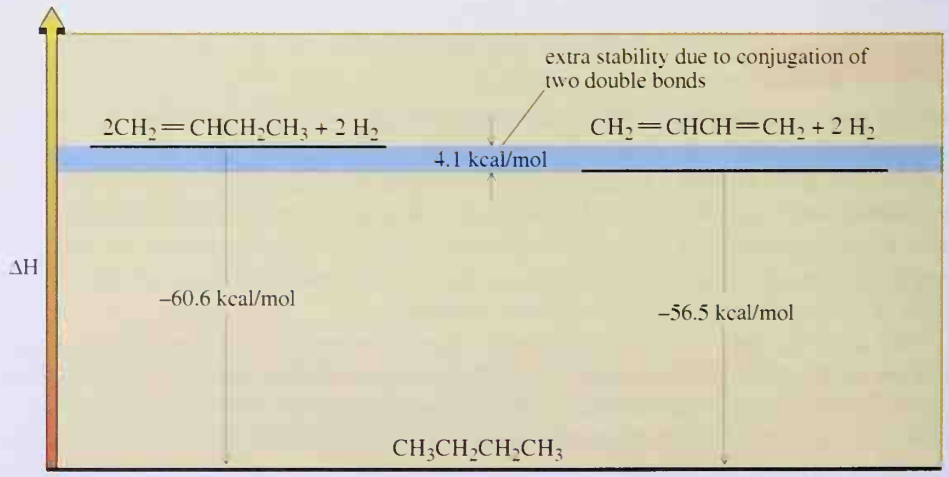


Figure 7.1
Conjugation of double bonds in butadiene gives the molecule an additional stability of approximately 4.1 kcal/mol.

Calculations of this type for other conjugated and unconjugated dienes give similar results: conjugated dienes are more stable than isomeric unconjugated dienes by approximately 3.5 to 4.0 kcal/mol. The effects of conjugation on stability are even more general. Compounds containing conjugated double bonds, not just those in dienes, are more stable than isomeric compounds containing unconjugated double bonds. For example, 2-cyclohexenone is more stable than its isomer 3-cyclohexenone.

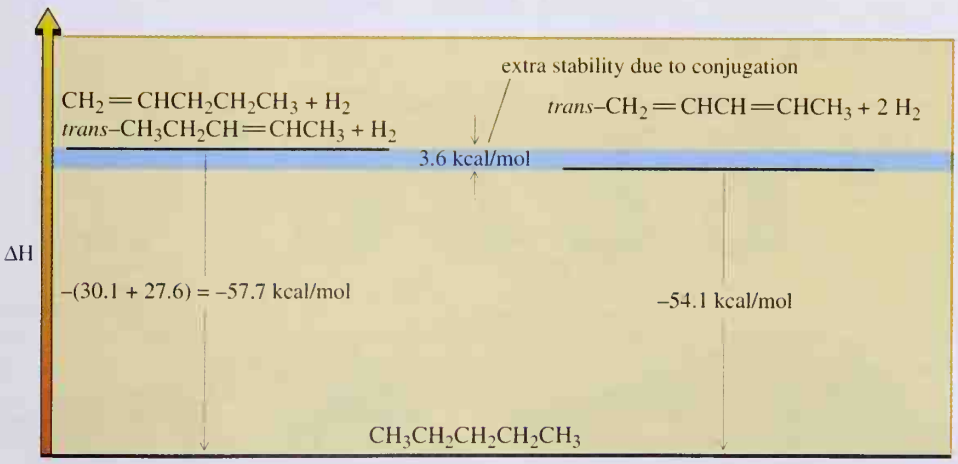
2-Cyclohexenone (more stable) 3-Cyclohexenone (less stable)

EXAMPLE 7.2

Using data from Table 7.1, estimate the extra stability due to the conjugation of double bonds in *trans*-1,3-pentadiene. Display the results of your calculations in graphical form.

Solution

Compare the sum of heats of hydrogenation of 1-pentene and *trans*-2-pentene with the heat of hydrogenation of *trans*-1,3-pentadiene. Conjugation of double bonds in *trans*-1,3-pentadiene imparts an added stability of approximately 3.6 kcal/mol.



PROBLEM 7.2

Estimate the stabilization gained due to conjugation when 1,4-pentadiene is converted to *trans*-1,3-pentadiene. Note that the answer is not as simple as comparing the heats of hydrogenation of 1,4-pentadiene and *trans*-1,3-pentadiene because, although the double bonds are moved from unconjugated to conjugated, the degree of substitution of one of the double bonds is also changed, in this case from a monosubstituted double bond to a disubstituted double bond. To answer this question you must separate the effect due to conjugation from that due to change in degree of substitution.

7.3 Structure

In this section, we use both the valence bond model and the molecular orbital model to describe the structure of conjugated dienes.

A. Valence Bond Model

According to the valence bond model, the additional stability of 1,3-butadiene and other conjugated dienes relative to unconjugated dienes arises because overlap of 2*p* orbitals on C-2 and C-3 creates a continuous set of four interacting 2*p* orbitals, thus allowing for greater electron delocalization (Figure 7.2). We saw in Section 1.8B that delocalization of electron density is a major factor contributing to the stability of covalent bonding in the hydrogen molecule. Similarly, delocalization of electron density over the four parallel 2*p* orbitals of a conjugated diene is a major factor contributing to the additional stability of conjugated dienes compared with unconjugated dienes.

B. Molecular Orbital Model

According to the molecular orbital model, the conjugated system of a diene is described as a set of four pi molecular orbitals arising from combination of four 2*p* atomic orbitals. These MOs have zero, one, two, and three nodes, respectively, as illustrated in Figure 7.3. In the ground state, all four pi electrons lie in pi bonding MOs.

7.4 Electrophilic Addition

Conjugated dienes undergo two-step electrophilic addition reactions just as simple alkenes do (Section 5.3). However, certain features are unique to these reactions compared with those of unconjugated dienes.

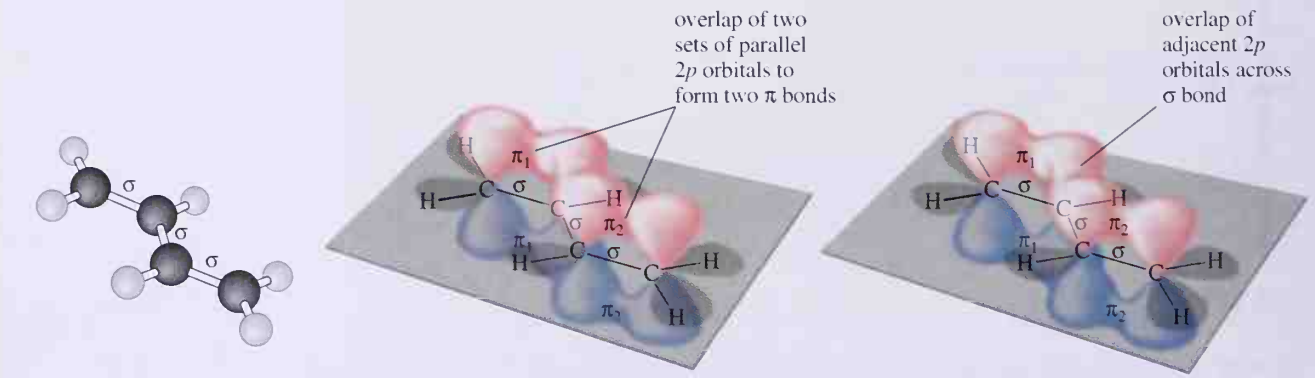


Figure 7.2
Structure of 1,3-butadiene–valence bond model. (a) The skeletal framework: all bond angles are approximately 120°, and all atoms lie in the same plane or nearly so. (b) Overlap of pairs of parallel 2*p* orbitals on C-1 and C-2 and on C-3 and C-4 forms two pi bonds. (c) Further delocalization of electrons by overlap of parallel 2*p* orbitals on C-2 and C-3 gives some double-bond character to that bond.

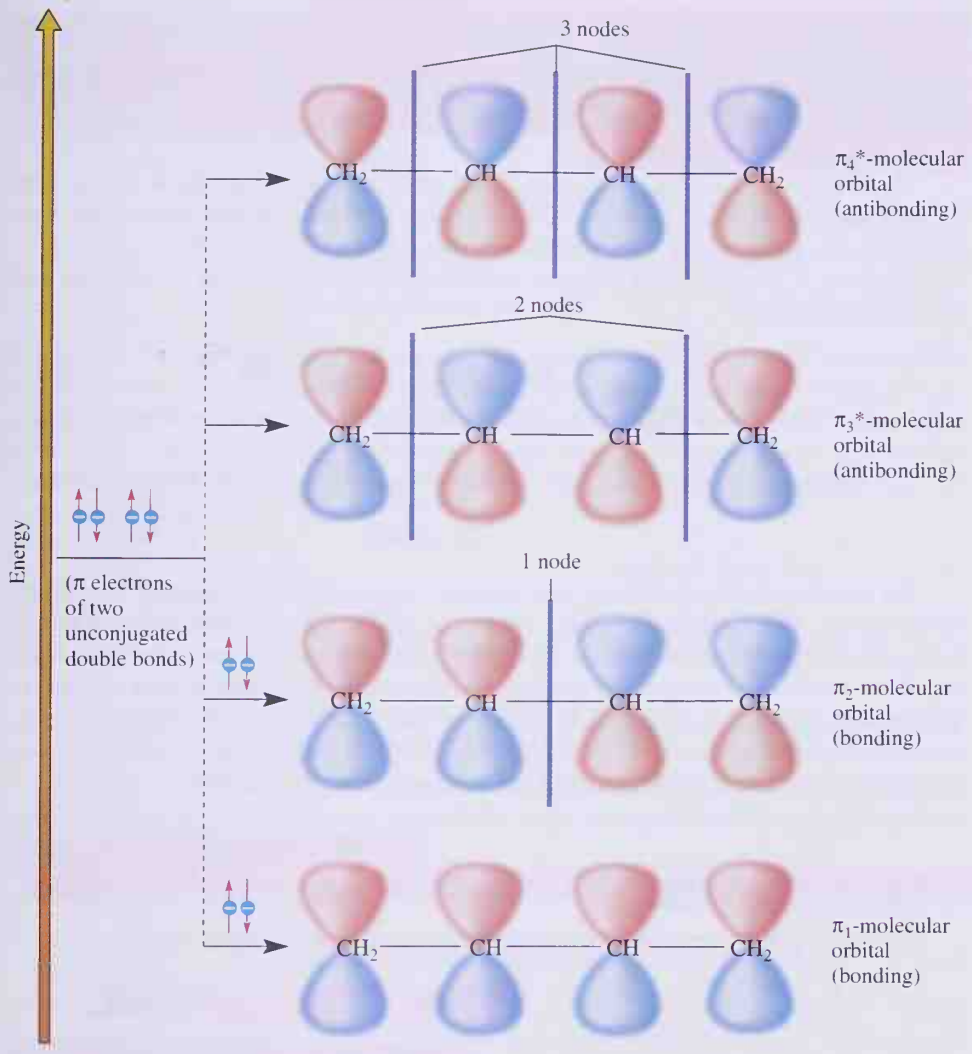
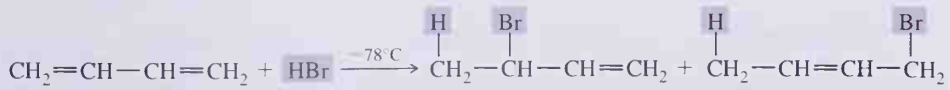


Figure 7.3
Structure of 1,3-butadiene–molecular orbital model. Combination of four parallel 2*p* atomic orbitals gives four pi molecular orbitals: two pi-bonding MOs and two pi-antibonding MOs. In the ground state, each pi-bonding MO is filled with two spin-paired electrons. The pi-antibonding MOs are unoccupied.

A. Conjugate Addition: 1,2-Addition and 1,4-Addition

Addition of one equivalent of HBr to 1,3-butadiene, for example, gives a mixture of two constitutional isomers: 3-bromo-1-butene and 1-bromo-2-butene.



1,3-Butadiene

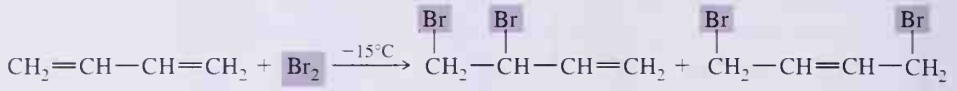
3-Bromo-1-butene (90%) (1,2-addition)

1-Bromo-2-butene (10%) (1,4-addition)

The designations "1,2-" and "1,4-" used here to describe additions to conjugated dienes do not refer to IUPAC nomenclature. Rather, they refer to the four atoms of a system of two conjugated double bonds and indicate that addition takes place at either carbons 1 and 2 of the four-atom system or at atoms 1 and 4. Addition to atoms 1 and 4 of a conjugated diene is said to be **conjugate addition.**

The bromobutenes formed by addition of 1 mol of HBr to butadiene can in turn undergo addition of a second mole of HBr to give a mixture of dibromobutanes. Our concern at this point is only with the products of a single addition of HBr.

Addition of one equivalent of Br_2 at $-15°C$ also gives a mixture of 1,2-addition and 1,4-addition products.

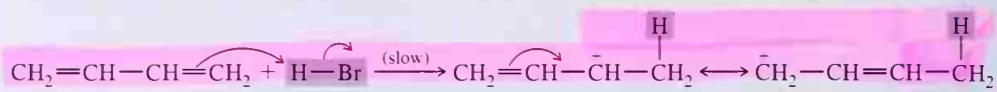


1,3-Butadiene

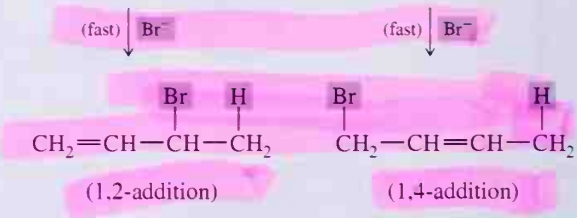
3,4-Dibromo-1-butene (54%) (1,2-addition)

1,4-Dibromo-2-butene (46%) (1,4-addition)

We can account for the formation of isomeric products in the addition of HBr in the following way. Electrophilic addition is initiated by reaction of a terminal carbon of one of the double bonds with HBr to form an allylic carbocation intermediate best represented as a resonance hybrid of two contributing structures. Formation of this cation is the rate-determining step. Addition is completed by rapid reaction of the allylic carbocation with bromide ion. Reaction at one carbon bearing partial positive charge gives 1,2-addition; reaction at the other carbon bearing partial positive charge gives 1,4-addition.

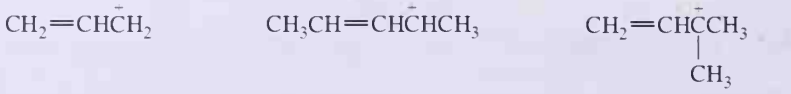


A resonance-stabilized allylic carbocation



(1,2-addition) (1,4-addition)

A word about the terms "allyl cation" and "allylic carbocation." An **allylic carbocation** is any carbocation that has a vinyl (CH_2=CH—) group or substituted vinyl group bonded to the carbon bearing the positive charge. The **allyl cation** is the simplest allylic carbocation. Because the allyl cation has only one substituent on the carbon bearing the positive charge, it is said to be a primary allylic carbocation. Following are examples of a secondary allylic carbocation and a tertiary allylic carbocation.

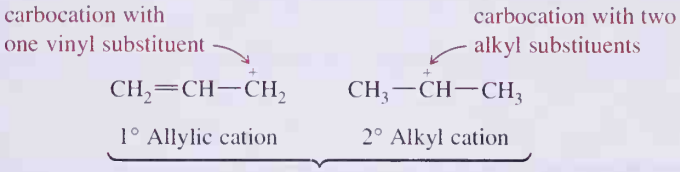


(A 1° allylic carbocation) (A 2° allylic carbocation) (A 3° allylic carbocation)

Allylic carbocations are considerably more stable than comparably substituted alkyl carbocations because of resonance interaction between the positively charged carbon and the vinyl group. The allyl cation, for example, can be represented as a hybrid of two equivalent contributing structures.

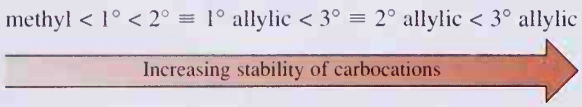
Allyl cation
(hybrid of two equivalent contributing structures)

Because of this resonance interaction, both the pi electrons of the double bond and the positive charge are delocalized. It is this delocalization that gives added stability to an allylic carbocation compared with a similarly substituted alkyl carbocation. It has been determined experimentally that the presence of one vinyl group provides approximately as much stabilization as two alkyl groups. Thus, the allyl cation and isopropyl cation are of comparable stability.



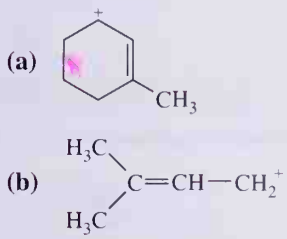
These cations are of comparable stability

In Section 5.3D we presented the order of stability of methyl, primary, secondary, and tertiary carbocations. We can now expand this order to include primary, secondary, and tertiary allylic carbocations as well.



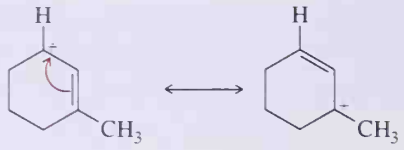
EXAMPLE 7.3

Write an additional contributing structure for each carbocation, and state which of the two makes the greater contribution to the resonance hybrid.

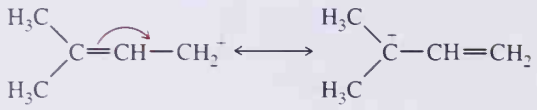


Solution

Both cations (a) and (b) are allylic carbocations. The contributing structure having the greater degree of substitution on the positively charged carbon makes the greater contribution to the hybrid.

(a) 

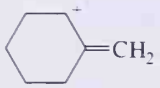
Greater contribution

(b) 

Greater contribution

PROBLEM 7.3

Write an additional contributing structure for each carbocation, and state which of the two makes the greater contribution to the resonance hybrid.

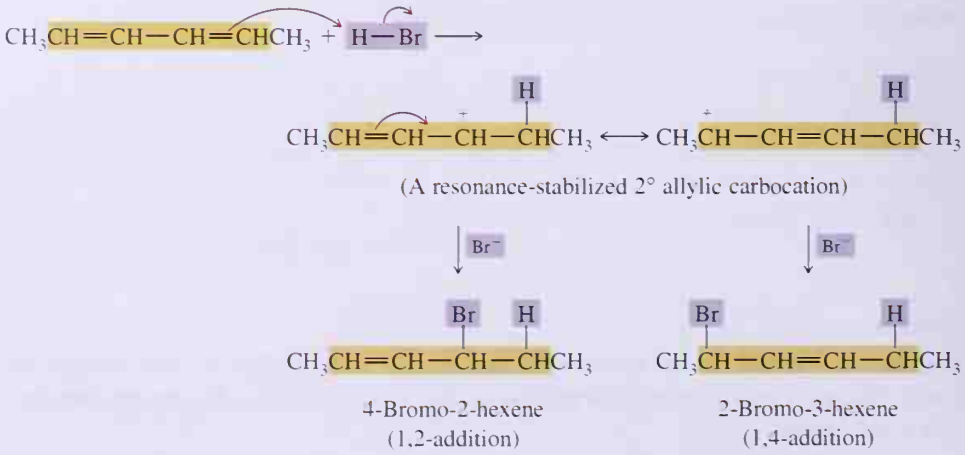
(a)  (b) 

EXAMPLE 7.4

Addition of 1 mol of HBr to 2,4-hexadiene gives a mixture of 4-bromo-2-hexene and 2-bromo-3-hexene. No 5-bromo-2-hexene is formed. Account for the formation of the first two bromoalkenes and for the fact that the third bromoalkene is not formed.

Solution

2,4-Hexadiene is a conjugated diene, and you can expect products from both 1,2-addition and 1,4-addition. Reaction of the diene with HBr in Step 1, the rate-determining step, forms a resonance-stabilized 2° allylic carbocation intermediate. Reaction of this intermediate in Step 2 at one of the carbons bearing partial positive charge gives 4-bromo-2-hexene, a 1,2-addition product; reaction at the other carbon bearing partial positive charge gives 2-bromo-3-hexene, a 1,4-addition product.

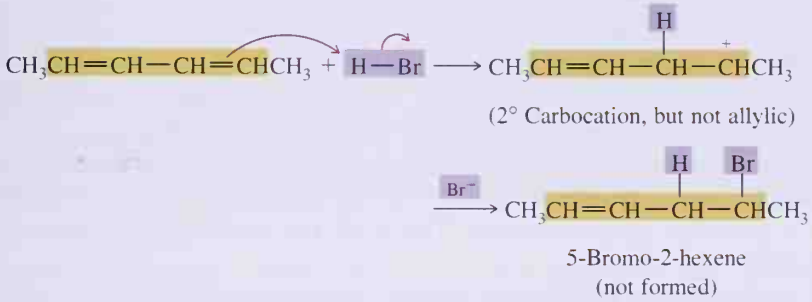


(A resonance-stabilized 2° allylic carbocation)

4-Bromo-2-hexene (1,2-addition)

2-Bromo-3-hexene (1,4-addition)

Formation of 5-bromo-2-hexene requires reaction of the diene with HBr to give a secondary, nonallylic carbocation. The energy of activation for formation of this less stable 2° carbocation is considerably greater than that for formation of the resonance-stabilized allylic carbocation, and, therefore, formation of this carbocation and thus 5-bromo-2-hexene does not compete effectively with formation of the observed products.

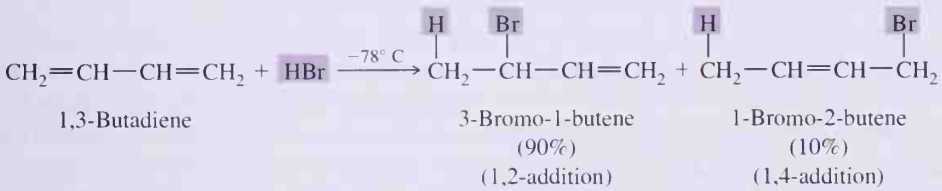


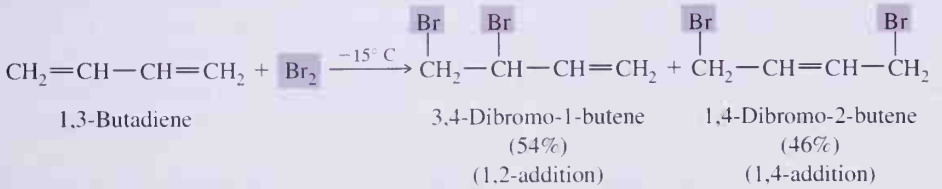
PROBLEM 7.4

Predict the product(s) formed by addition of 1 mol of Br_2 to 2,4-hexadiene.

B. Kinetic versus Thermodynamic Control of Addition to Conjugated Dienes

We saw in the previous section that electrophilic addition to conjugated dienes gives a mixture of 1,2-addition and 1,4-addition products.





Following are some additional experimental observations about the products of electrophilic additions to 1,3-butadiene.

1. For addition of HBr at −78°C and addition of Br_2 at −15°C, the 1,2-addition product predominates over the 1,4-addition product. Generally at lower temperatures, 1,2-addition products predominate over 1,4-addition products.
2. For addition of HBr and Br_2 at higher temperatures (generally 40° to 60°C), 1,4-addition products predominate.
3. If the products of low-temperature addition are warmed to a higher temperature and allowed to remain in solution, the composition of the product changes over time and

becomes identical in composition to that obtained when the reaction is carried out at higher temperature. The same result can be accomplished at the higher temperature in a far shorter time by adding a Lewis acid catalyst, such as $FeCl_3$ or $ZnCl_2$, to the mixture of low-temperature addition products. Thus, under these higher temperature conditions, an equilibrium is established between 1,2- and 1,4-addition products, and 1,4-addition products predominate.

4. If either pure 1,2-addition product or pure 1,4-addition product is dissolved in an inert solvent at the higher temperature and a Lewis acid catalyst added, an equilibrium mixture of 1,2- and 1,4-addition product forms. The same equilibrium mixture is obtained regardless of which isomer is used as the starting material.

Chemists interpret these experimental results using the twin concepts of kinetic control and equilibrium control of reactions. First we state the principle of kinetic control and then apply it to addition to conjugated dienes. Then we do the same for the principle of equilibrium control.

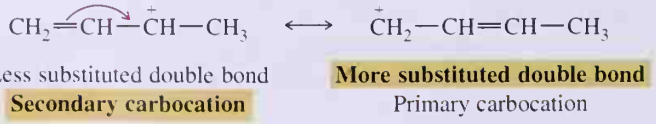
For reactions under **kinetic (rate) control,** the distribution of products is determined by the relative rates of formation of each. We see the operation of kinetic control in conjugate addition in the following way. At lower temperatures, the reaction is essentially irreversible and no equilibrium is established between 1,2-and 1,4-addition products. The 1,2-addition product predominates under these conditions because the rate of 1,2-addition is greater than the rate of 1,4-addition.

For reactions under **thermodynamic (equilibrium) control,** the distribution of products is determined by the relative stability of each. We see the operation of equilibrium control in the following way. At higher temperatures, the reaction is reversible and an equilibrium is established between 1,2- and 1,4-addition products. The percentage of each product present at equilibrium is in direct relation to the relative thermodynamic stability of that product. The fact that 1,4-addition products predominate at equilibrium means that they are thermodynamically more stable than 1,2-addition products.

Relationships between kinetic control and thermodynamic control for electrophilic addition of HBr to 1,3-butadiene are illustrated graphically in Figure 7.4. Step 1 is proton transfer from HBr to 1,3-butadiene to form a resonance-stabilized allylic carbocation intermediate, here shown lying in the potential energy well in the center of the figure. The figure then displays a plot of potential energy versus reaction coordinate for Step 2, namely, reaction of the resonance-stabilized allylic carbocation intermediate with bromide ion to give 1,2- and 1,4-addition products. The energy of activation to form the 1,2-addition product is less than that to form the 1,4-addition product, and, therefore, under experimental conditions of kinetic control, the 1,2-addition product is the major product. The 1,4-addition product is the more stable, and under experimental conditions of thermodynamic control, it is the major product.

To complete our discussion of electrophilic addition to conjugated dienes and of kinetic versus thermodynamic control, we need to ask the following questions:

1. Why is the 1,2-addition product (the less stable product) formed more rapidly at lower temperatures? First, we need to look at the resonance-stabilized allylic carbocation intermediate and determine which Lewis structure makes the greater contribution to the hybrid. We must consider both the degree of substitution of the positive carbon and the degree of substitution of the carbon-carbon double bond in each contributing structure.



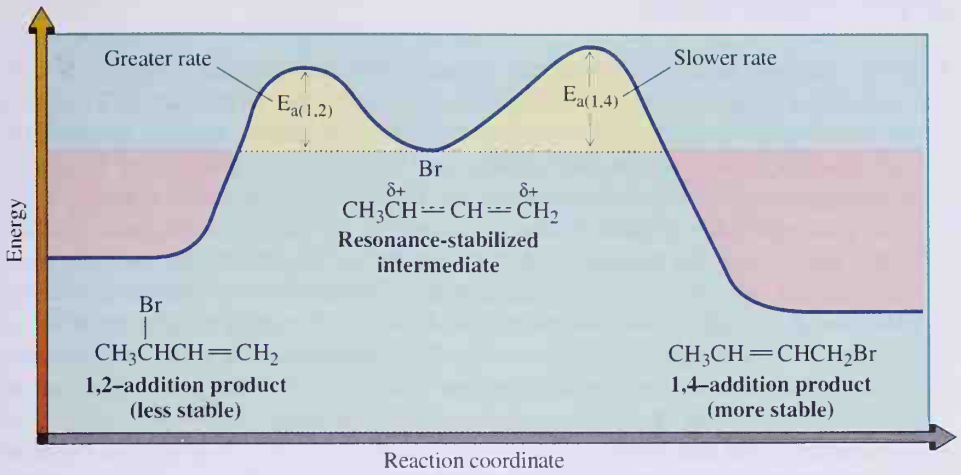
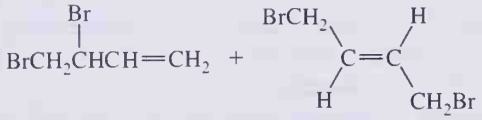


Figure 7.4
Kinetic versus thermodynamic control. A plot of potential energy versus reaction coordinate for Step 2 in the electrophilic addition of HBr to 1,3-butadiene. By way of one transition state, the resonance-stabilized allylic carbocation intermediate reacts with bromide ion to give the 1,2-addition product. By way of an alternative transition state, it reacts with bromide ion to give the 1,4-addition product.

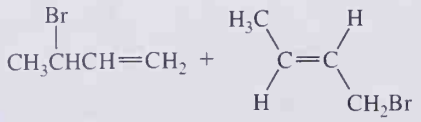
A secondary carbocation is more stable than a primary carbocation, and if the degree of substitution of the carbon bearing the positive charge were the more important factor, then the Lewis structure on the left would make the greater contribution to the hybrid. A more substituted double bond is more stable than a less substituted double bond (Section 5.8B), and if the degree of substitution of the carbon-carbon double bond were the more important factor, then the Lewis structure on the right would make the greater contribution to the hybrid.

We know from other experimental evidence that the location of the positive charge in the allylic carbocation is more important than the location of the double bond. Therefore, in the hybrid, the greater fraction of positive charge is on the secondary carbon. Reaction with bromide ion occurs more rapidly at this carbon, giving 1,2-addition, simply because it has a greater concentration of positive charge.

2. Is the 1,2-addition product also formed more rapidly at higher temperatures, even though it is the 1,4-addition product that predominates under these conditions? The answer is yes. The factors affecting the structure of a resonance-stabilized allylic carbocation intermediate and the reaction of this intermediate with a nucleophile are not greatly affected by changes in temperature.
3. Why is the 1,4-addition product the more thermodynamically stable product? The answer to this question has to do with the relative degree of substitution of the double bonds: in general, the greater the degree of substitution of the carbon-carbon double bond, the greater the stability of the molecule or ion containing it (Section 5.8B). Following are pairs of 1,2- and 1,4-addition products. In each case, the more stable alkene is the 1,4-addition product.



3,4-Dibromo-1-butene (less stable alkene) (E)-1,4-Dibromo-2-butene (more stable alkene)



3-Bromo-1-butene (less stable alkene) (E)-1-Bromo-2-butene (more stable alkene)

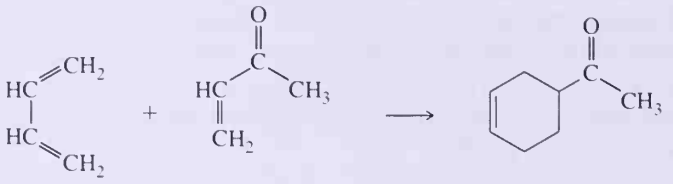
4. What is the mechanism by which the thermodynamically less stable product is converted to the thermodynamically more stable product at higher temperatures? To answer this question, we must look at the relationships between kinetic energy, potential energy, and energy of activation. On collision, some kinetic energy (the energy of motion) may be transformed into potential energy, and if the increase in potential energy is equal to or greater than the activation energy for reaction, then reaction may occur. At the higher temperatures for conjugate addition of HBr and Br_2, collisions are sufficiently energetic that ionization of the 1,2-addition product occurs to re-form the resonance-stabilized allylic carbocation intermediate and then for it to react with bromide ion to form the thermodynamically more stable 1,4-addition product. At lower temperatures, however, the increase in potential energy on collision is insufficient to overcome the potential energy barrier and to bring about this isomerization.
5. Is it a general rule that where two or more products are formed from a common intermediate, the thermodynamically less stable product is formed at a greater rate? The answer is no. Whether the thermodynamically more or less stable product is formed at a greater rate from a common intermediate depends very much on the particular reaction and the reaction conditions.

We return to these concepts of kinetic control versus thermodynamic control in several following chapters. For example, in Chapter 21 we see that it is often possible to form alternative carbanions (*carbon anions*), depending on whether experimental conditions are chosen for kinetic control or thermodynamic control.

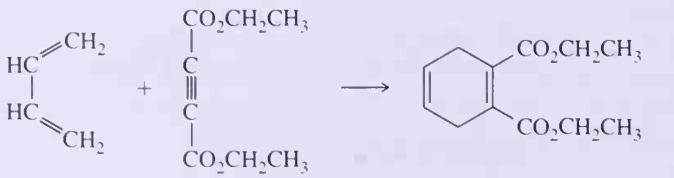
7.5 The Diels-Alder Reaction

In 1928, Otto Diels and Kurt Alder in Germany discovered a second unique reaction of conjugated dienes, namely, that they undergo cycloaddition reactions with certain types of alkenes and alkynes. For their discovery and subsequent studies of this reaction, Diels and Alder were jointly awarded the Nobel Prize in Chemistry in 1950.

Following are two examples of Diels-Alder reactions: one with a compound containing a carbon-carbon double bond, the other with a compound containing a carbon-carbon triple bond.



1,3-Butadiene (a diene) + 3-Buten-2-one (Methyl vinyl ketone; a dienophile) → 4-Cyclohexenyl methyl ketone (a Diels-Alder adduct)

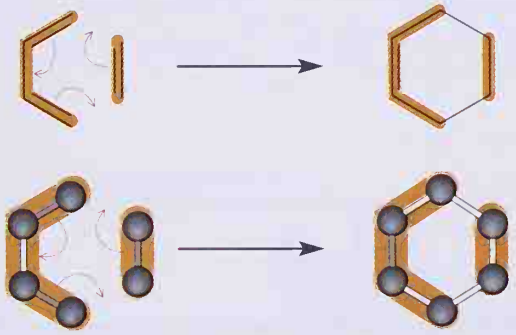


1,3-Butadiene (a diene) + Diethyl acetylenedicarboxylate (a dienophile) → Diethyl 1,4-cyclohexadiene-1,2-dicarboxylate (a Diels-Alder adduct)

Note that the four carbon atoms of the diene and two carbon atoms of the alkene or alkyne combine to form a six-member ring. Note further that there are two more sigma bonds and two fewer pi bonds in the product than in the reactants. This exchange of two pi bonds for two sigma bonds is a major driving force in Diels-Alder reactions.

The alkene or alkyne participating in a Diels-Alder reaction is given the special name of **dienophile** (diene-loving), and the product of a Diels-Alder reaction is given the special name of **Diels-Alder adduct.** The designation **cycloaddition** refers to the fact that two reactants add together to give a cyclic product.

We can write a general formula for the Diels-Alder reaction in the following way, showing only the carbon skeletons of the diene and dienophile. In this representation, curved arrows are used to show that two new sigma bonds are formed, three pi bonds are broken, and one new pi bond is formed. It must be emphasized here that the curved arrows in this diagram are not meant to show a mechanism. Rather they are intended to show which bonds are broken and which new bonds are formed in a Diels-Alder reaction.



Diene Dienophile Adduct

The special values of the reaction discovered by Diels and Alder are that (1) it is one of few reactions that can be used to form six-member rings, (2) it is one of few reactions that can be used to form two new carbon-carbon bonds at the same time, and (3) it is stereoselective. For these reasons, the Diels-Alder reaction has proved to be enormously valuable in synthetic organic chemistry.

EXAMPLE 7.5

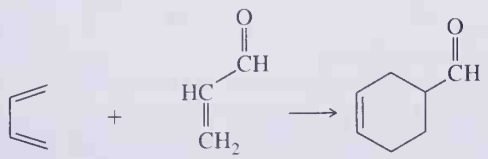
Draw a structural formula for the Diels-Alder adduct formed by reaction of each diene and dienophile pair.

(a) butadiene and 2-propenal
(b) 2,3-dimethyl-1,3-butadiene and 3-buten-2-one

Solution

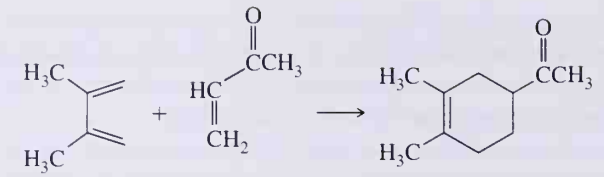
First draw the diene and dienophile so that each molecule is properly aligned to form a six-member ring. Then complete the reaction to form the six-member Diels-Alder adduct.

(a)



1,3-Butadiene 2-Propenal

(b)



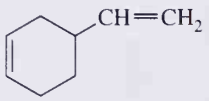
2,3-Dimethyl-1,3-butadiene

3-Buten-2-one

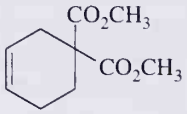
PROBLEM 7.5

What combination of diene and dienophile undergoes Diels-Alder reaction to give each adduct.

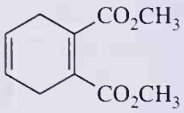
(a)



(b)



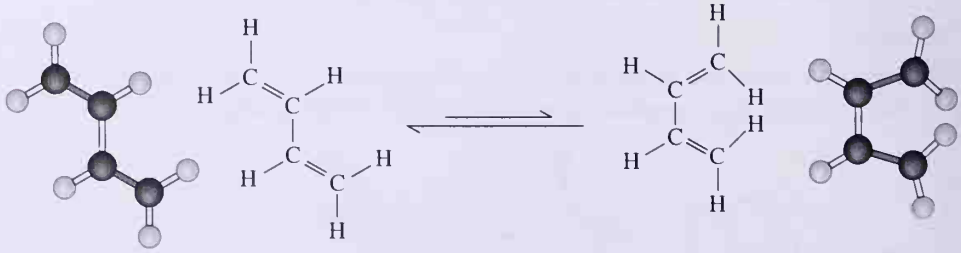
(c)



Now let us look more closely at the scope and limitations, stereochemistry, and mechanism of Diels-Alder reactions.

A. The Diene Must Be Able to Assume an s-*Cis* Conformation

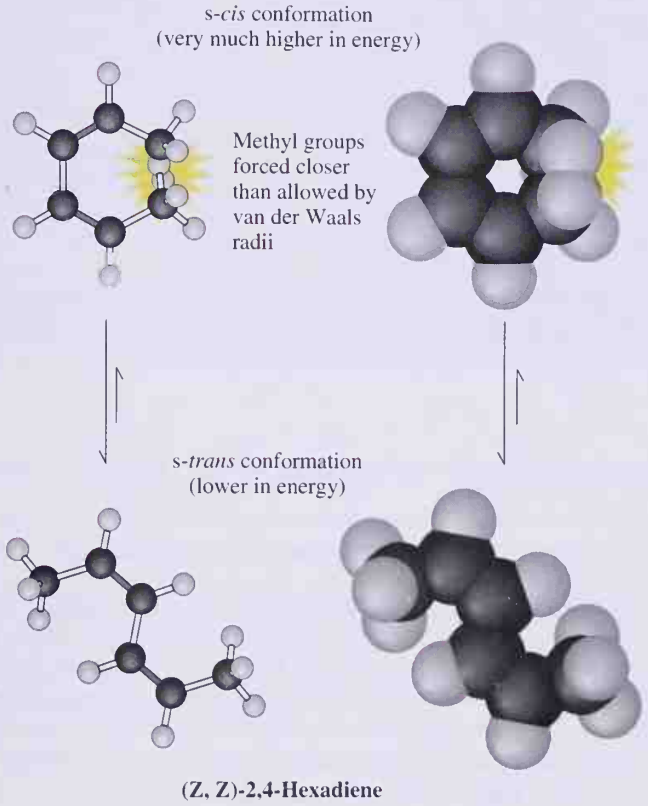
We can illustrate the significance of conformation of the diene by reference to 1,3-butadiene. For maximum stability of a conjugated diene, overlap of the four unhybridized 2*p* orbitals making up the pi system must be complete—a condition that occurs only when all four carbon atoms of the diene lie in the same plane. It follows then that if the carbon skeleton of 1,3-butadiene is planar, the six atoms bonded to the skeleton of the diene are also contained in the same plane. There are two planar conformations of 1,3-butadiene, referred to as the **s-*trans* conformation** and the **s-*cis* conformation** where the designation s refers to the carbon-carbon single bond of the diene. Of these, the s-*trans* conformation is slightly lower in energy and, therefore, slightly more stable. Thus, whereas s-*trans*-1,3-butadiene is the more stable conformation, s-*cis*-1,3-butadiene is the reactive conformation in a Diels-Alder reaction. The energy barrier for interconversion of the s-*trans* and s-*cis*



s-*trans* conformation
(slightly lower in energy)

s-*cis* conformation
(slightly higher in energy)

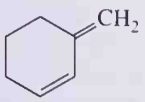
conformations for 1,3-butadiene is low (approximately 2.8 kcal/mol), and consequently, 1,3-butadiene is a reactive diene in Diels-Alder reactions. The following diene, however, is unreactive in Diels-Alder reactions because it is prevented by steric hindrance from assuming the required s-*cis* conformation.

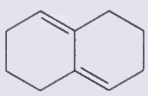


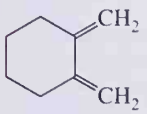
(Z, Z)-2,4-Hexadiene

EXAMPLE 7.6

Which molecules can function as dienes in Diels-Alder reactions? Explain your reasoning.

(a) 

(b) 

(c) 

Solution

The dienes in both (a) and (b) are fixed in the s-*trans* conformation and, therefore, are not capable of participation in Diels-Alder reactions. The diene in (c) is fixed in the s-*cis* conformation and, therefore, has the proper orientation to participate in Diels-Alder reactions.

PROBLEM 7.6

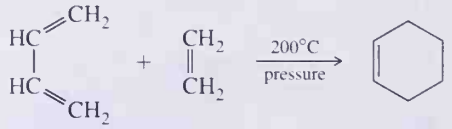
Which molecules can function as dienes in Diels-Alder reactions? Explain your reasoning.

(a)  (b) 

(c) 

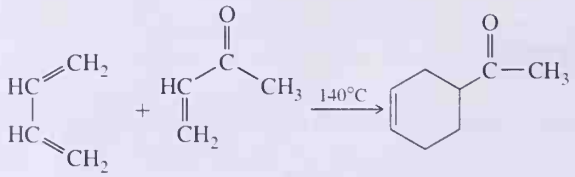
B. The Effect of Substituents on Rate

The simplest example of a Diels-Alder reaction is that between 1,3-butadiene and ethylene, both gases at room temperature. Although this reaction does occur, it is very slow and takes place only if the reactants are heated at 200°C under pressure.

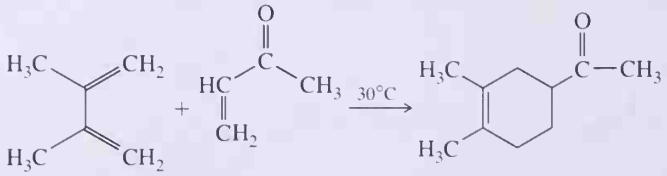


1,3-Butadiene Ethylene Cyclohexene

Diels-Alder reactions are facilitated by a combination of electron-withdrawing substituents on one of the reactants and electron-releasing substituents on the other. For example, placing a carbonyl group (electron-withdrawing because of the partial positive charge on the carbonyl carbon) on the dienophile facilitates reaction; 1,3-butadiene and 3-buten-2-one, for example, form a Diels-Alder adduct when heated at 140°C. Placing electron-releasing methyl groups on the diene further facilitates reaction; 2,3-dimethyl-1,3-butadiene and 3-buten-2-one form a Diels-Alder adduct at 30°C.



1,3-Butadiene 3-Buten-2-one



2,3-Dimethyl-1,3-butadiene 3-Buten-2-one

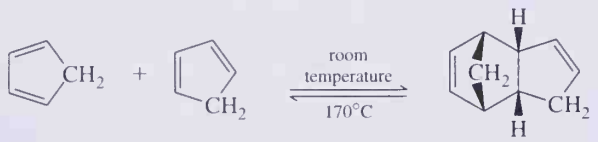
Several of the electron-releasing and electron-withdrawing groups most commonly encountered in Diels-Alder reactions are given in Table 7.2.

Table 7.2 Electron-releasing and electron-withdrawing groups

Electron-releasing Groups	Electron-withdrawing Groups
$-CH_3$	$-\overset{\overset{O}{\|}}{C}H$ (aldehyde)
$-CH_2CH_3$	$-\overset{\overset{O}{\|}}{C}R$ (ketone)
$-CH(CH_3)_2$	$-\overset{\overset{O}{\|}}{C}OH$ (carboxyl)
$-C(CH_3)$	$-\overset{\overset{O}{\|}}{C}OR$ (ester)
—R (other alkyl groups)	$-NO_2$ (nitro)
—OR (ether)	$-C\equiv N$ (cyano)
$-O\overset{\overset{O}{\|}}{C}R$ (ester)	

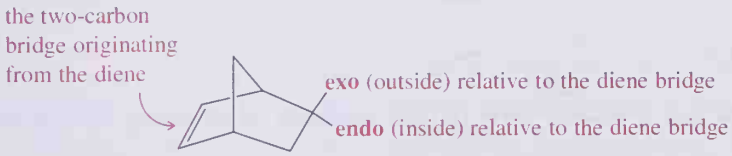
C. Diels-Alder Reactions Can Be Used to Form Bicyclic Systems

Conjugated cyclic dienes, in which the double bonds are of necessity held in an *s-cis* conformation, are highly reactive in Diels-Alder reactions. Two particularly useful dienes for this purpose are cyclopentadiene and 1,3-cyclohexadiene. In fact, cyclopentadiene is reactive both as a diene and as a dienophile, and on standing at room temperature, it forms a Diels-Alder adduct known by the common name dicyclopentadiene. When dicyclopentadiene is distilled at its normal boiling point of 170°C, a reverse Diels-Alder reaction takes place, and cyclopentadiene is reformed.

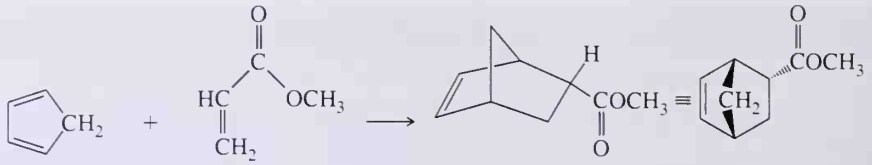


The diene The dienophile "Dicyclopentadiene" (endo form)

The terms "endo" and "exo" are used for bicyclic Diels-Alder products to describe the orientation of substituents in relation to the two-carbon diene-derived bridge. **Exo** (Greek: outside) substituents are on the opposite side from the diene-derived bridge; **endo** (Greek: within) substituents are on the same side.



For Diels-Alder reactions under kinetic control, the endo orientation of dienophile is favored. Treatment of cyclopentadiene with methyl 2-propenoate (methyl acrylate) gives the endo adduct exclusively. The exo adduct is not found.



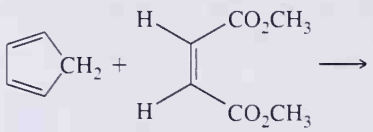
Cyclopentadiene Methyl 2-propenoate Methyl bicyclo[2.2.1]hept-5-en-endo-2-carboxylate

D. Mechanism: The Diels-Alder Reaction Is a Pericyclic Reaction

As chemists probed for details of the Diels-Alder reaction, they discovered that there is no evidence for participation of either ionic or radical intermediates. Thus, the Diels-Alder reaction is unlike any reaction we have studied so far. To account for the stereoselectivity of the Diels-Alder reaction and the fact that there is no evidence for either ionic or radical intermediates, chemists have proposed that reaction takes place in a single step during which there is a cyclic redistribution of bonding electrons. During this cyclic redistribution, bond-making and bond-breaking are concerted (simultaneous). To use the terminology of organic chemistry, the Diels-Alder reaction is a **pericyclic reaction,** that is, one that takes place in a single step, without intermediates, and involves a cyclic rearrangement of bonding electrons. We can envision a Diels-Alder reaction taking place as shown in Figure 7.5.

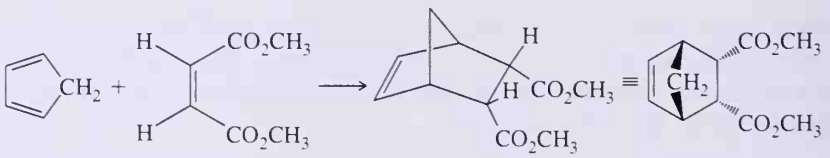
EXAMPLE 7.7

Complete the following Diels-Alder reaction, showing the stereochemistry of the product:



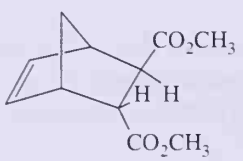
Solution

Reaction of cyclopentadiene with this dienophile forms a disubstituted bicyclo[2.2.1]hept-5-ene. The two ester groups are *cis* in the dienophile, and given the stereoselectivity of this pericyclic reaction, they are *cis* and endo in the product.



PROBLEM 7.7

What diene and dienophile might you use to prepare the following Diels-Alder adduct?



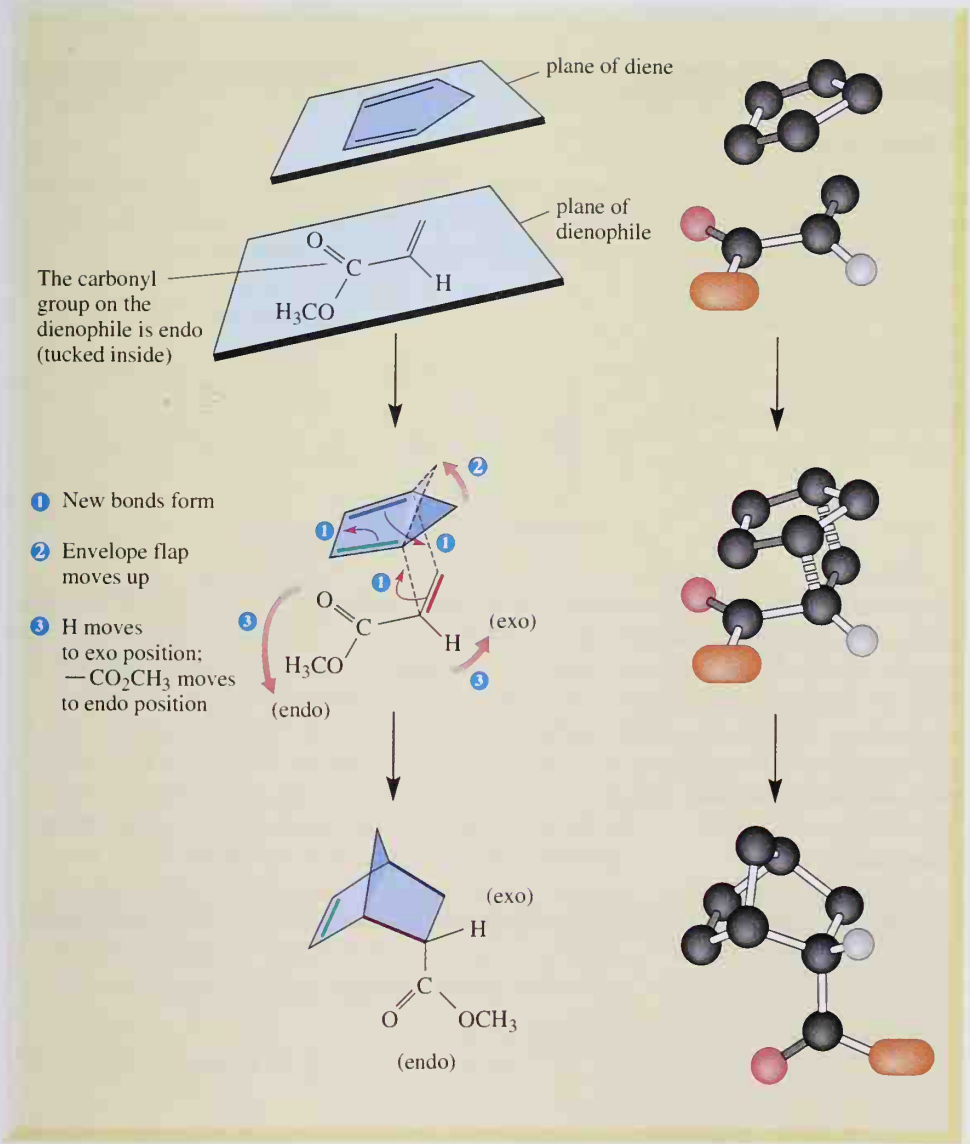
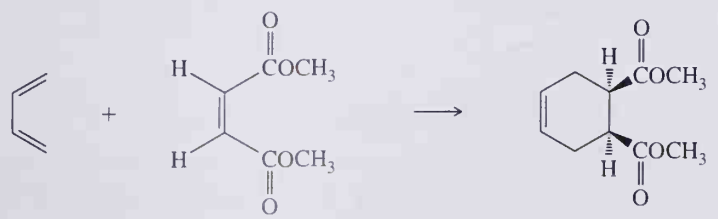


Figure 7.5
Mechanism of the Diels-Alder reaction. The diene and dienophile approach each other in parallel planes, one above the other, with the substituents on the dienophile endo to the diene. There is overlap of the pi orbitals of each molecule and syn addition of each molecule to the other. As (1) new sigma bonds form in the transition state, (2) the $-CH_2-$ rotates upward, (3) the hydrogen atom on the dienophile becomes exo, and the ester group of the dienophile becomes endo.

E. The Stereochemistry of the Dienophile Is Retained

If the dienophile is a *cis* isomer, then the substituents *cis* to each other in the dienophile are *cis* in the Diels-Alder adduct. Conversely, if the dienophile is a *trans*-isomer, substituents *trans* from each other in the dienophile are *trans* in the adduct.



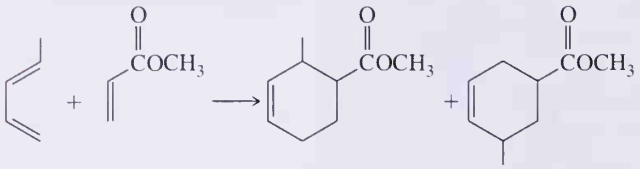
Dimethyl *cis*-2-butenedioate
(a *cis*-dienophile)

Dimethyl *cis*-4-cyclohexene-1,2-dicarboxylate

CHEMISTRY IN ACTION

Catalysts for Diels-Alder Reactions

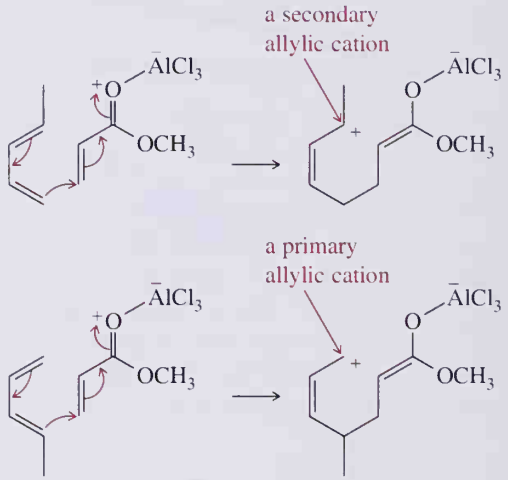
The Diels-Alder reaction is one of the most valuable reactions for creating new carbon-carbon bonds. Unlike the other reactions studied so far, the Diels-Alder reaction involves a concerted, cyclic redistribution of electrons. Finding a way to catalyze this reaction seems to be very difficult. Nevertheless, organic chemists have discovered that Lewis acids can catalyze some Diels-Alder reactions. As an example, 1,3-pentadiene and methyl acrylate react to form two Diels-Alder product isomers in the ratio 9 : 1.



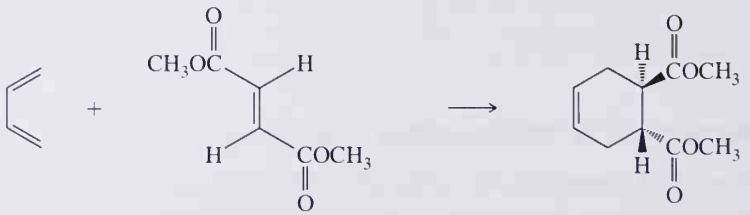
no catalyst:	90%	10%
$AlCl_3$ as catalyst:	98%	2%

With the Lewis acid catalyst $AlCl_3$, the same reaction is speeded up, and the isomer ratio improves to 49 : 1. Why should $AlCl_3$ have such a dramatic effect?

Of the two partners in this reaction, the Lewis acid interacts preferentially with the dienophile, because of the lone pairs of electrons on the carbonyl oxygen. This causes the dienophile to become polarized. It then interacts in a stepwise fashion, forming the two new carbon-carbon bonds one at a time. Depending on the orientation with which the dienophile approaches the diene, two different carbocation intermediates result.



In the first orientation, the intermediate is a more stable secondary allylic carbocation and leads to the major product. In the second orientation, the intermediate is a less stable primary allylic carbocation. Thus, using a Lewis acid in a Diels-Alder reaction makes the cycloaddition less concerted and more stepwise in character.



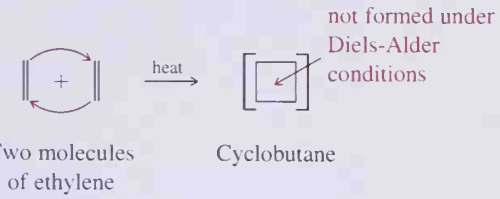
Dimethyl *trans*-2-butenedioate
(a *trans*-dienophile)

Dimethyl *trans*-4-cyclohexene-1,2-dicarboxylate

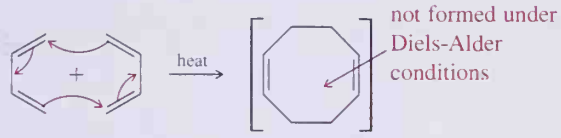
F. A Word of Caution About Electron Pushing

We developed a picture of the Diels-Alder reaction and used curved arrows to show the flow of electrons that takes place in the process of bond breaking and bond making. Diels-Alder reactions involve a four-carbon diene and a two-carbon dienophile and are termed [4+2] cycloadditions. We can write similar electron-pushing mechanisms for di-

merization of ethylene by a [2+2] cycloaddition to form cyclobutane, and for dimerization of butadiene by a [4+4] cycloaddition to form 1,5-cyclooctadiene.



Two molecules of ethylene — Cyclobutane



Two molecules of butadiene — 1,5-Cyclooctadiene

Although [2+2] and [4+4] cycloadditions bear a formal relationship to the Diels-Alder reaction, neither in fact takes place under the thermal conditions required for Diels-Alder reactions. These cycloadditions do occur, but only under experimental conditions different from those required for Diels-Alder reactions and by quite different mechanisms. The point of introducing them here is to add a note of caution. Although electron pushing is a valuable tool in electron bookkeeping, it is not in itself a full description of a reaction mechanism. Reaction mechanisms are often far more complex than use of curved arrows might suggest.

SUMMARY OF KEY REACTIONS

1. Conjugate Addition (Section 7.4)

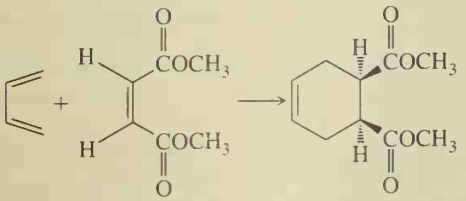
The ratio of 1,2- to 1,4-addition products depends on whether the reaction is under kinetic control or thermodynamic control.

$$CH_2{=}CHCH{=}CH_2 + HBr \longrightarrow \underset{\text{Br}}{CH_3\overset{|}{C}HCH{=}CH_2} + CH_3CH{=}CHCH_2Br$$

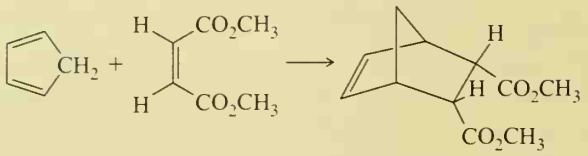
Products of reaction at −80°C:	90%	10%
Products of reaction at 40°C:	15%	85%

2. The Diels-Alder Reaction: A Pericyclic Reaction (Section 7.5)

A Diels-Alder reaction takes place in a single step, without intermediates, and involves a cyclic rearrangement of electrons in the transition state. The stereochemistry of the dienophile is preserved.



Endo approach of diene and dienophile is favored.



ADDITIONAL PROBLEMS

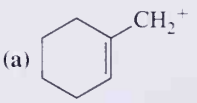
Structure and Stability

7.8 If an electron is added to 1,3-butadiene, into which molecular orbital does it go? If an electron is removed from 1,3-butadiene, from which molecular orbital is it taken?

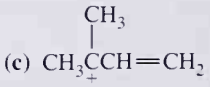
7.9 The heat of hydrogenation of allene (1,2-propadiene) to propene is −35.3 kcal/mol. Compare this with the heat of hydrogenation of 1,3-butadiene to 1-butene. Does allene have the characteristics of a conjugated or a nonconjugated diene?

7.10 Draw a potential energy diagram (potential energy versus dihedral angle 0°–360°, see Figure 2.8) for rotation about the 2,3 single bond in 1,3-butadiene.

7.11 Draw all important contributing structures for the following allylic carbocations and then rank the structures in order of relative contributions to the resonance hybrid.



(b) $CH_2{=}CHCH{=}CHCH_2^+$



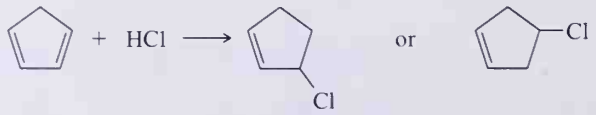
Electrophilic Addition

7.12 Predict the structure of the major product formed by 1,2-addition of HCl to 2-methyl-1,3-butadiene (isoprene). To arrive at a prediction, first consider proton transfer to carbon 1 of this diene. Second, consider proton transfer to carbon 4 of this diene. Then compare the relative stabilities of the two allylic carbocation intermediates.

7.13 Predict the major product formed by 1,4-addition (conjugate addition) of HCl to isoprene. Follow the reasoning suggested in the previous problem.

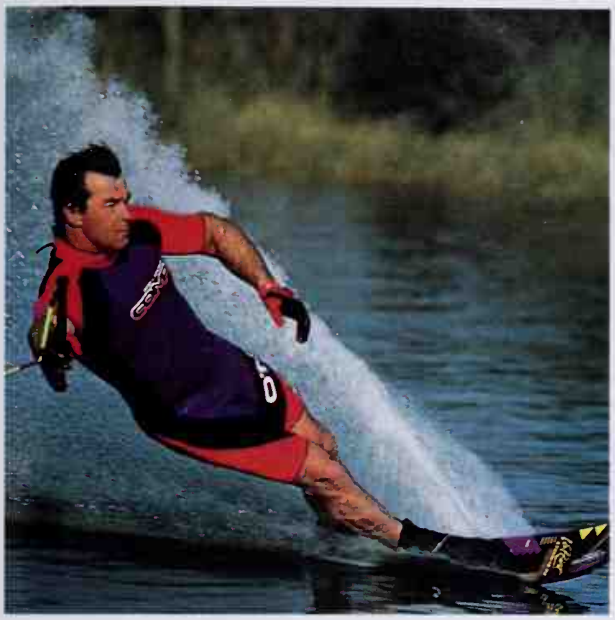
7.14 Predict the structure of the major 1,2-addition product formed by reaction of 1 mol of Br_2 with isoprene. Also predict the structure of the major 1,4-addition product formed under these conditions.

7.15 (a) Which of the two molecules shown do you expect to be the major product formed by 1,2-addition of HCl to cyclopentadiene? Explain.



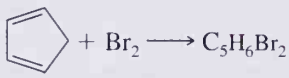
Cyclopentadiene | 3-Chloro-cyclopentene | 4-Chloro-cyclopentene

(b) Predict the major product formed by 1,4-addition of HCl to cyclopentadiene.



A wet suit fabricated from neoprene, a polymer of 2-chloro-1,3-butadiene.
(Courtesy of O'Neill, Inc.)

7.16 Draw structural formulas for the two constitutional isomers of molecular formula $C_5H_6Br_2$ formed by adding 1 mol of Br_2 to cyclopentadiene.



7.17 What are the expected kinetic and thermodynamic products from addition of 1 mol Br_2 to the following dienes:

(a) (b)

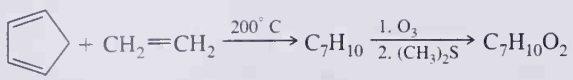
Diels-Alder Reactions

7.18 Draw structural formulas for the products of reaction of cyclopentadiene with each of the following dienophiles:

(a) $CH_2{=}CHCl$ (b) $CH_2{=}CHCOCH_3$ (c) $HC{\equiv}CH$

(d) $CH_3OCC{\equiv}CCOCH_3$

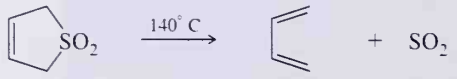
7.19 Propose structural formulas for compounds (A) and (B), and specify the configuration of compound (B).



(A) (B)

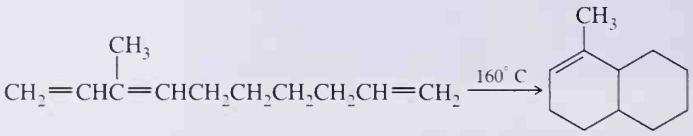
7.20 Under certain conditions, 1,3-butadiene can function both as a diene and a dienophile. Draw a structural formula for the Diels-Alder adduct formed by reaction of 1,3-butadiene with itself.

7.21 Butadiene is a gas at room temperature and requires gas-handling apparatus to use it in a Diels-Alder reaction. Butadiene sulfone is a convenient substitute for gaseous butadiene. This sulfone is a solid at room temperature (mp 66°C) and when heated above its boiling point of 110°C, decomposes by a reverse Diels-Alder reaction to give 1,3-butadiene and sulfur dioxide. Draw a Lewis structure for butadiene sulfone, and show by curved arrows the path of this reverse Diels-Alder reaction.

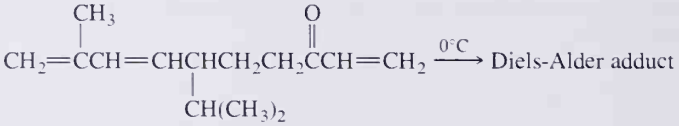


Butadiene sulfone ("3-Sulfolene") — 1,3-Butadiene — Sulfur dioxide

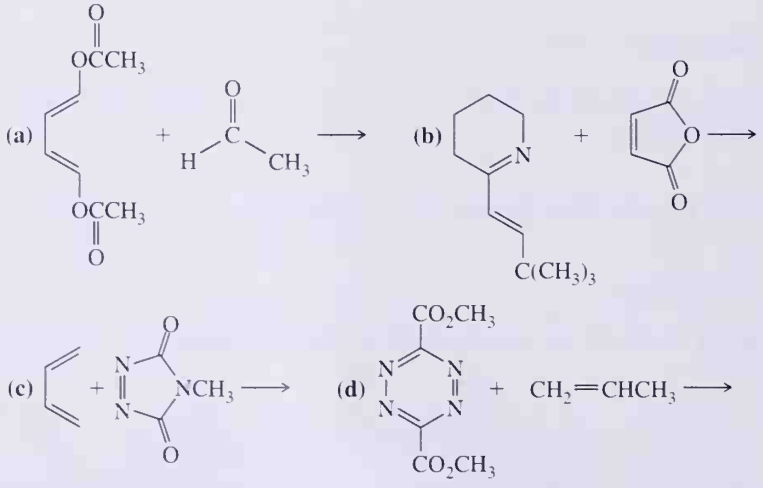
7.22 The following triene undergoes an intramolecular Diels-Alder reaction to give the product shown. Show how the carbon skeleton of the triene must be coiled to give this product, and show by curved arrows the reorganization of electron pairs that takes place to give the product.

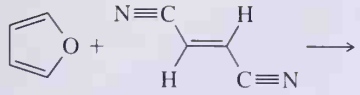


7.23 The following triene undergoes an intramolecular Diels-Alder reaction to give a bicyclic product. Propose a structural formula for the product. Account for the observation that the Diels-Alder reaction given in this problem takes place under milder conditions (at lower temperature) than the analogous Diels-Alder reaction shown in the previous problem.

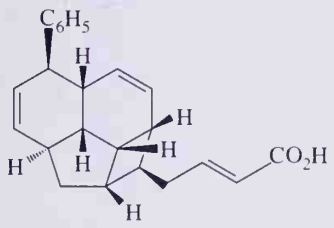


7.24 The Diels-Alder reaction is not limited to making six-member rings with only carbon atoms. Predict the products of the following reactions which produce heterocycles—rings with atoms other than carbon in them.

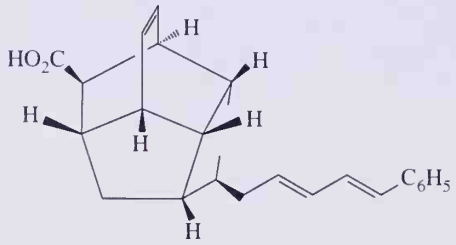


(e) 

7.25 The Diels-Alder reaction is often used by organic chemists in their syntheses of naturally occurring molecules. It is seldom used, however, by plants and animals to synthesize the molecules of nature. One exception is a class of naturally occurring molecules isolated from the Australian plant *Endiandra introrsa* (Lauraceae), which include endiandric acid B and endiandric acid C. Studies strongly suggest that the plant synthesizes precursors, which then cyclize to the observed acids. Propose the structural formula of a precursor that will undergo an intramolecular Diels-Alder reaction to produce endiandric acid C?



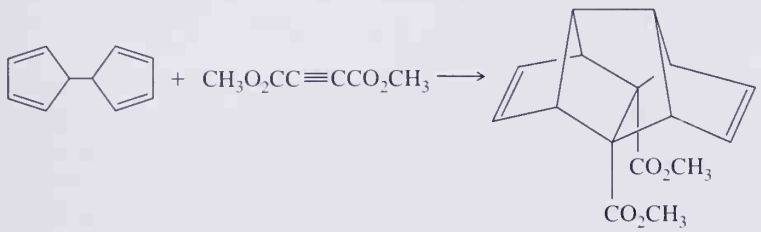
Endiandric acid B



Endiandric acid C

7.26 Because endiandric acid B has two cyclohexene rings, two possible intramolecular Diels-Alder reactions can give rise to this natural product. Keeping in mind your answer to the previous question, what is the more likely structure to undergo an intramolecular Diels-Alder reaction to produce endiandric acid B? (See Nicolaou, K. C., et al., *J. Am. Chem. Soc.*, **104,** 5555–5562 (1982).)

7.27 The first step in a synthesis of dodecahedrane involves a Diels-Alder reaction between the cyclopentadiene derivative (1) and dimethyl acetylenedicarboxylate (2). Show how these two molecules react to form the dodecahedrane synthetic intermediate (3). (Paquette, L. A., R. J. Ternansky, D. W. Balogh, et al. *J. Am. Chem. Soc.*, **105,** 5446 (1983).)

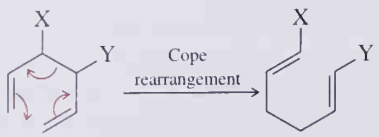


Cyclopentadienyl-cyclopentadiene (1)

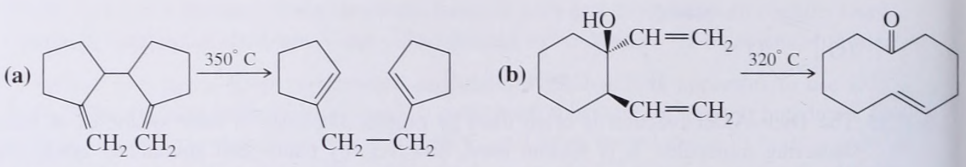
Dimethyl acetylene-dicarboxylate (2)

(3)

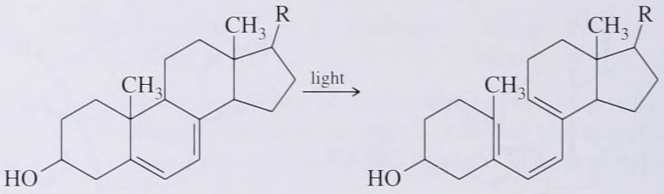
7.28 The Diels-Alder reaction proceeds through a cyclic, six-electron transition state. Another example of a reaction that takes place via such a transition state is the Cope rearrangement of 1,5-dienes.



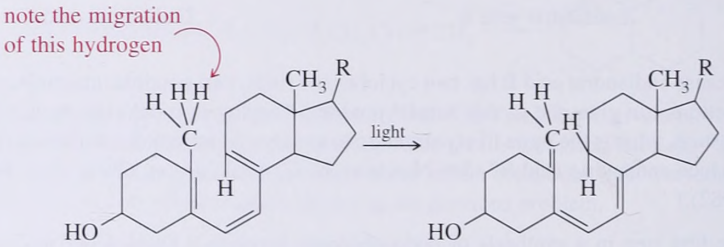
Show that the following rearrangements can be explained as Cope rearrangements.



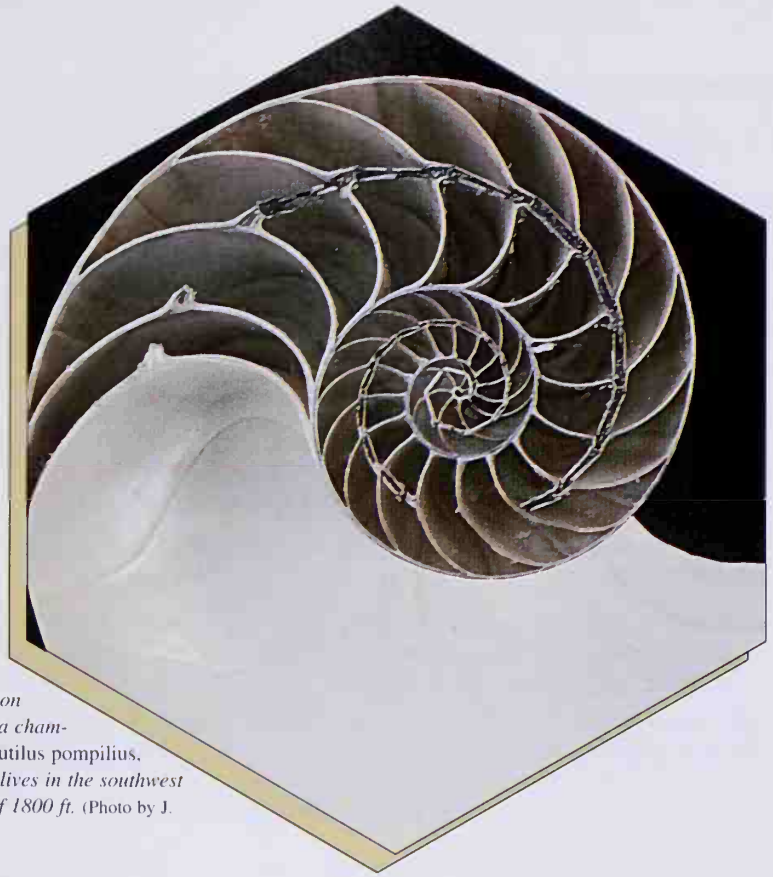
7.29 Following are two examples of photoinduced (light-induced) isomerizations. Vitamin D_3 (cholecalciferol) is produced by the action of sunlight on 7-dehydrocholesterol in the skin. First is formed precalciferol and then cholecalciferol. Use curved arrows to show the flow of electrons in these photoisomerizations. Cholecalciferol is shown here in an s-*cis* conformation. After its formation it assumes an s-*trans* conformation.



7-Dehydrocholesterol Precalciferol



Precalciferol Cholecalciferol (vitamin D_3)



Median cross section through a shell of a chambered nautilus, Nautilus pompilius, *a cephalopod that lives in the southwest Pacific to depths of 1800 ft.* (Photo by J. Kirk Cochran.)

8

CHIRALITY

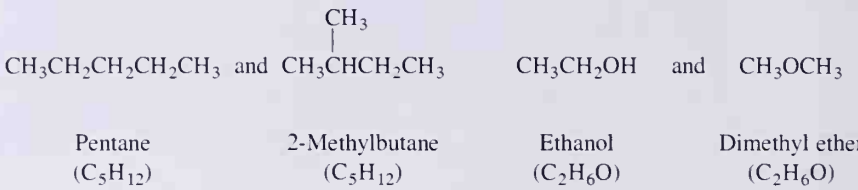
When you look in a mirror, you see a reflection of yourself. Now suppose that this reflection of yourself became a three-dimensional object. We could then ask "What is the relationship between you and your mirror image?" By relationship we mean Can your reflection be superposed on the original you in such a way that every detail of the reflection corresponds exactly to the original? The answer is that the original and mirror image are not superposable. If you have a ring on the little finger of your right hand, for example, your mirror image has the ring on the little finger of the left hand. If you part your hair on your right side, it is parted on the left side in your reflection. Simply stated, you and your mirror image are different objects. You cannot superpose one on the other.

Our goal in this chapter is to expand further our awareness of molecules as three-dimensional objects, and in particular, the relationships between three-dimensional objects and their mirror images. We develop principles and terminology for describing the spatial arrangement of atoms in molecules and their mirror images and, in so doing, gain new insights into the spatial requirements for molecular interactions. An understanding of these spatial requirements is fundamental to an understanding of organic chemistry and biochemistry.

8.1 Isomerism

Isomers are different compounds with the same molecular formula. Thus far we have encountered two types of isomers. **Constitutional isomers** (Section 1.5) have the same molecular formula but a different order of attachment of atoms in their molecules. In the past these isomers were often referred to as structural isomers. Examples of pairs of constitutional isomers are pentane and 2-methylbutane, and ethanol and dimethyl ether.

Constitutional isomers (structural isomers):



A second type of isomerism is stereoisomerism. **Stereoisomers** have the same molecular formula, the same order of attachment of atoms in their molecules, but a different three-dimensional orientation of their atoms in space. Thus far, we have seen two examples of stereoisomers: E-Z isomers (*cis-trans* isomers) in alkenes (Section 4.3), which arise because of restricted rotation about a carbon-carbon double bond, and *cis-trans* isomers in cyclic compounds (Section 2.7), which arise because of restricted rotation about bonds in a ring. The following are examples of pairs of stereoisomers.

Stereoisomers:

(Z)-2-Butene (*cis*-2-Butene)

(E)-2-Butene (*trans*-2-Butene)

cis-1,4-Dimethylcyclohexane

trans-1,4-Dimethylcyclohexane

Stereoisomers are divided into two groups: those with molecules that are mirror images of each other, and those with molecules that are not mirror images of each other. A **mirror image** is the reflection of an object in a mirror. Stereoisomers that are mirror images of each other are called **enantiomers** (Greek: *enantios* + *meros*, opposite parts). Stereoisomers that are not mirror images of each other are called **diastereomers.** We already studied diastereomers, although we did not call them that at the time. E-Z isomers and *cis-trans* isomers are diastereomers; they are stereoisomers that are not mirror images of each other. Figure 8.1 shows these relationships among isomers.

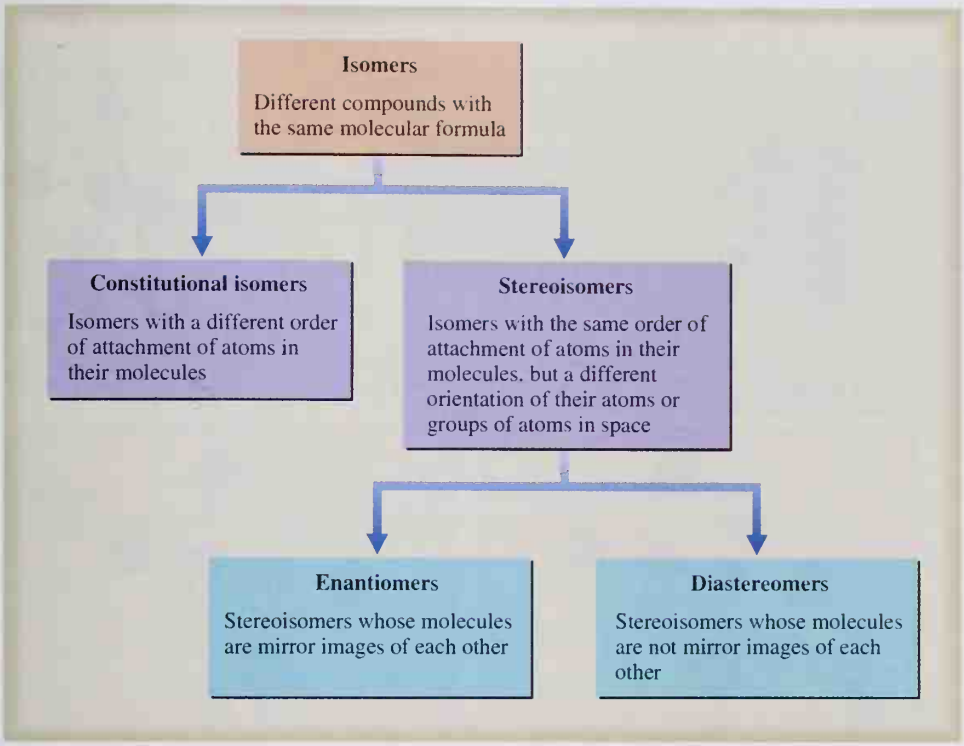
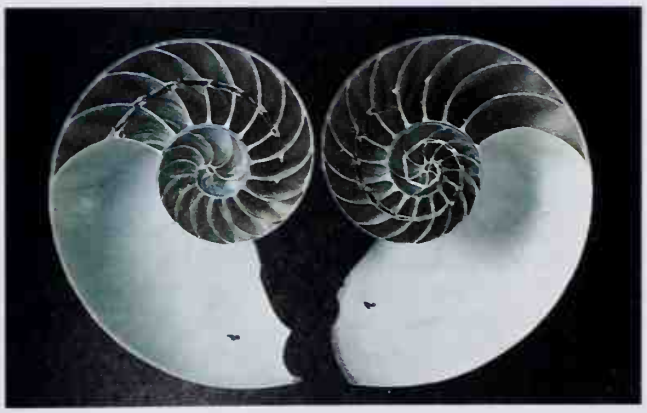


Figure 8.1
Relationships among isomers.

8.2 Chirality

Molecules that are not superposable on their mirror images are said to be **chiral** (pronounced ki-ral, to rhyme with spiral; from the Greek: *cheir*, hand). That is, they show "handedness." Chirality is encountered in three-dimensional objects of all sorts. Human hands are chiral. Chairs with left-handed or right-handed writing tables are chiral. Some crystalline solids such as quartz occur in chiral form. The helical loops in a telephone cord and a spiral binding are chiral. Machine and wood screws with right-handed or left-handed



One half of this bisected nautilus shell has a left-handed spiral; the other half has a right-handed spiral. *(J. Kirk Cochran)*

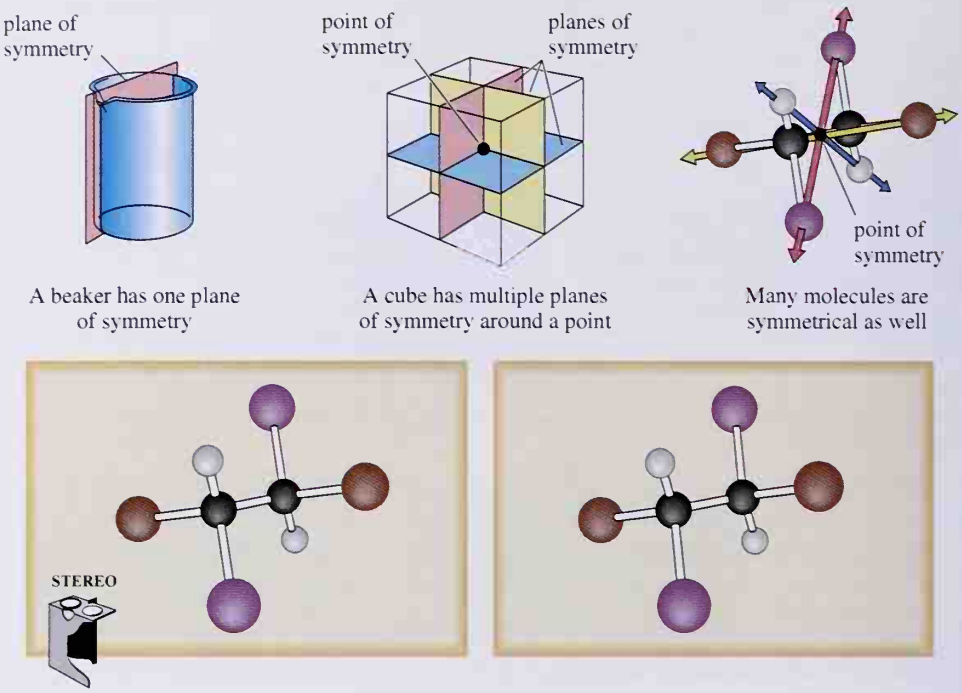


Figure 8.2
Planes of symmetry (mirror planes) in a beaker and a cube. The cube and the staggered conformation of this substituted ethane possess a point of symmetry.

twists are chiral. Airplane and ship propeller blades are chiral. As you examine the objects in the world around you, you will undoubtedly conclude that the vast majority of them are chiral as well.

The contrasting situation to chirality occurs when an object and its mirror image are superposable. An object and its mirror image are **superposable** if one of them can be oriented in space so that all of its features (corners, edges, points, designs, etc.) correspond exactly to those in the other member of the pair. If this can be done, the object and its mirror image are identical; the original object is achiral. An **achiral** object is one that lacks chirality. Examples of objects lacking chirality are chairs without writing tables, undecorated plates and cups, shells such as sand dollars, a regular tetrahedron, a cube, and a perfect sphere.

Achiral objects possess at least one plane of symmetry, or point of symmetry. A **plane of symmetry** (also called a **mirror plane**) is an imaginary plane passing through an object dividing it such that one-half is the reflection of the other half. The beaker shown in Figure 8.2 has a single plane of symmetry, while the cube has multiple planes of symmetry. A **point of symmetry** is a point so situated that identical components of the object are located equidistant from the point along any axis passing through the point. Both the cube and the staggered conformation of the substituted ethane shown in Figure 8.2 have a point of symmetry; no other conformation of this substituted ethane has such a point.

A. Chirality Arising from a Tetrahedral Stereocenter

We can illustrate the chirality of an organic molecule by considering 2-hydroxypropanoic acid, more commonly named lactic acid.

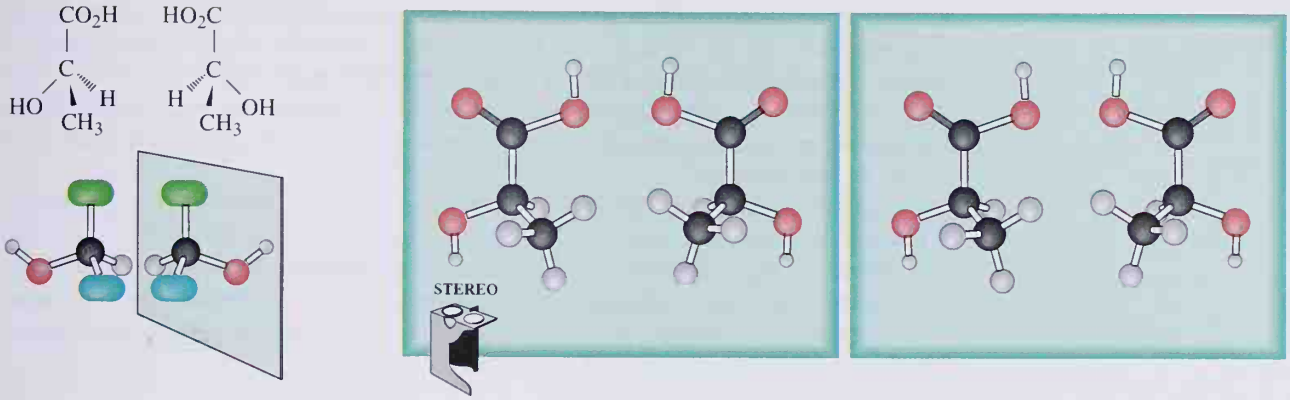
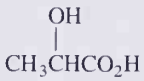


Figure 8.3
Stereorepresentations and ball-and-stick models of lactic acid and its mirror image.

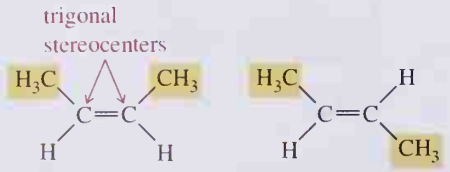


2-Hydroxypropanoic acid
(Lactic acid)

Shown in Figure 8.3 are three-dimensional representations for lactic acid and its mirror reflection. All bond angles about the central carbon atom are approximately 109.5°, and the four bonds from this carbon are directed toward the corners of a regular tetrahedron. The model of lactic acid drawn on the left in Figure 8.3 can be turned and rotated in any direction in space, but as long as bonds are not broken and rearranged, only two of the four groups attached to the central carbon can be made to coincide with those of the model on the right.

A **stereocenter** (or alternatively, a **stereogenic center**) is an atom in a molecule at which interchange of two atoms or groups of atoms bonded to it produces a different stereoisomer. A carbon atom with four different atoms or groups of atoms attached to it is a tetrahedral stereocenter. The carbon atom of lactic acid bearing the —OH, —H, —CH_3, and —CO_2H groups is an example of a stereocenter.

A properly substituted trigonal carbon can also be a stereocenter. Examples of trigonal stereocenters are carbons 2 and 3 of 2-butene. Interchanging two atoms or groups of atoms on a trigonal stereocenter produces a stereoisomer. (Z)-2-butene and (E)-2-butene are stereoisomers; because they are not mirror images, they are classified as diastereomers.



(Z)-2-Butene
(*cis*-2-Butene)

(E)-2-Butene
(*trans*-2-Butene)

Diastereomers; stereoisomers
that are not mirror images

It is important to note even though the isomeric 2-butenes each have trigonal stereocenters, these molecules are not chiral. Each is superposable on its mirror image. The presence of a trigonal stereocenter is not a sufficient condition for chirality.

Thus, we see that both trigonal stereocenters and tetrahedral stereocenters exist. In this chapter, we are concerned primarily with tetrahedral stereocenters and refer to them more simply as stereocenters.

Over the years several different terms have been used to describe chiral molecules. When chirality in organic molecules was first recognized, a tetrahedral carbon atom with four different groups attached to it was called an **asymmetric carbon.** It also has been called a **chiral carbon.** A problem with this terminology is that carbon atoms by themselves are neither asymmetric nor chiral. Rather, it is the molecule as a whole that is chiral. We, therefore, do not use either of these terms in this text.

EXAMPLE 8.1

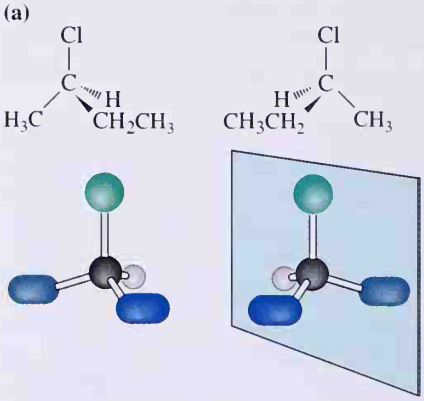
Each of these molecules has a stereocenter. Draw stereorepresentations for each pair of enantiomers.

(a) 2-chlorobutane **(b)** 1,2-propanediol **(c)** 3-chlorocyclohexene
(d) 3-penten-2-ol

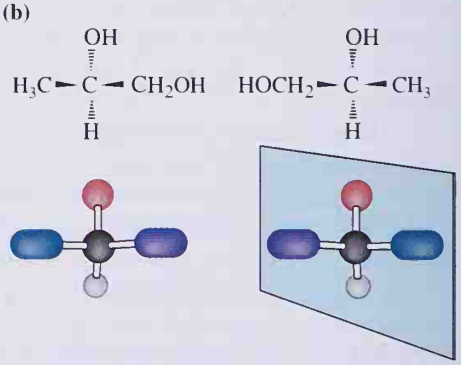
Solution

You should find it helpful to build models of each pair of enantiomers and to view each enantiomer and then its mirror image from different perspectives as is done in the following stereorepresentations.

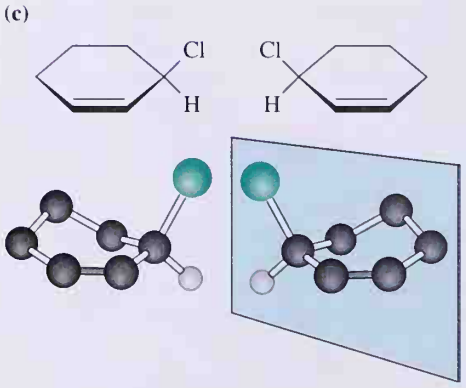
(a)



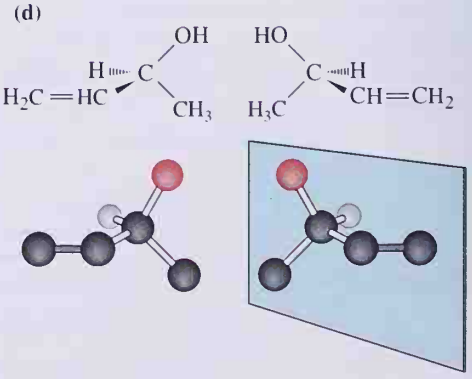
(b)



(c)

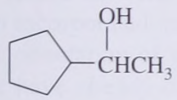


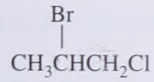
(d)

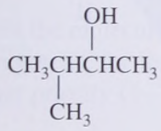


PROBLEM 8.1

Each of these molecules has a stereocenter. Draw stereorepresentations for each pair of enantiomers.

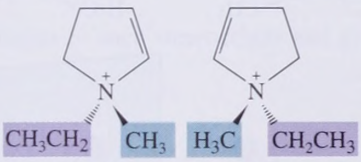
(a) 

(b) 

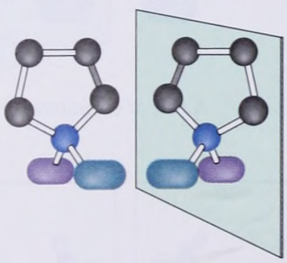
(c) 

B. Chirality Arising from Stereocenters Other than Carbon

In all of the molecules studied so far, chirality arises because of the presence of a carbon stereocenter. Stereocenters are not limited to carbon. Following are stereorepresentations of a chiral cation in which the stereocenter is nitrogen. We discuss the chirality of nitrogen stereocenters in more detail in Chapter 22. Enantiomers of tetrahedral silicon, phosphorus, and germanium compounds have also been isolated.



A pair of enantiomers



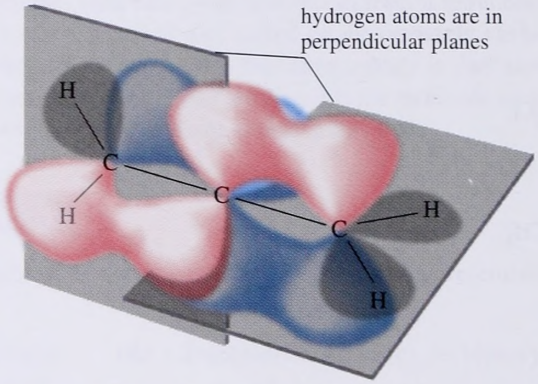
C. Chirality Without a Stereocenter

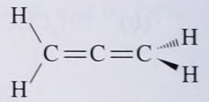
The presence of one stereocenter is a sufficient condition for chirality, but it is not a necessary condition. Certain compounds are chiral by virtue of restricted rotation about one or more carbon-carbon bonds as, for example, certain derivatives of 1,2-propadiene, more commonly named **allene.** Allene itself is achiral; it has two planes of symmetry.

Substituted allenes in which each terminal carbon contains two different atoms or groups of atoms are chiral. One such substituted allene is 2,3-pentadiene. Because rotation about the cumulated double bonds is restricted, this molecule is chiral and exists as a pair of enantiomers.

$CH_2{=}C{=}CH_2$

1,2-Propadiene
(Allene)

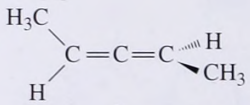


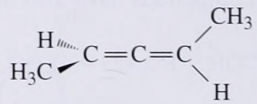


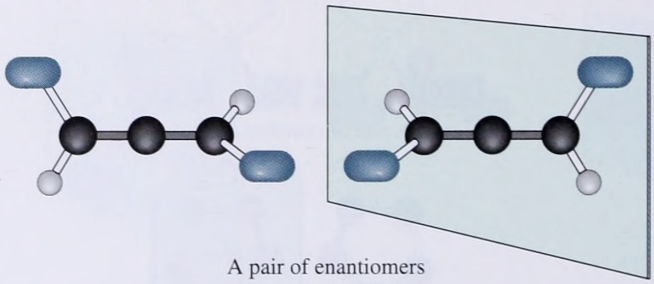
Allene is achiral; it has two planes of symmetry

$CH_3CH = C = CHCH_3$

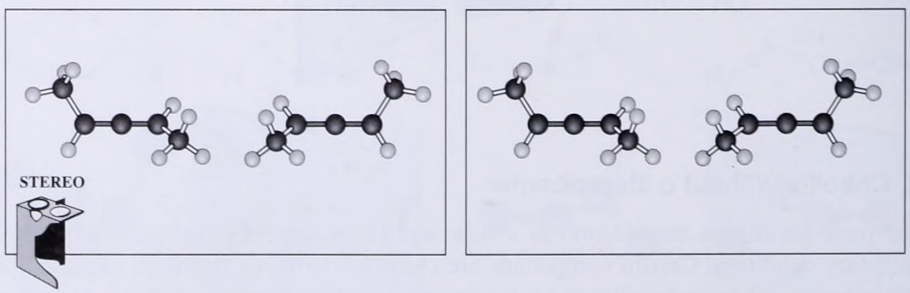
2,3-Pentadiene







A pair of enantiomers



8.3 Naming Enantiomers: The R-S System

A system for designating the configuration of a stereocenter was devised in the late 1950s by R. S. Cahn and C. K. Ingold in England along with V. Prelog of Switzerland. The system, named the Cahn-Ingold-Prelog convention, or, alternatively, the **R-S convention,** has been incorporated into the IUPAC rules of nomenclature.

The orientation of groups about a stereocenter is specified using the set of priority rules we have already outlined in Section 4.3B. To assign an R or S configuration to a stereocenter:

(1) Locate the stereocenter and identify its four substituents.

(2) Assign a priority (1, 2, 3, 4) to each substituent.

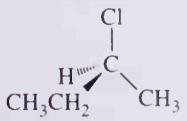
(3) Orient the molecule in space such that the group of lowest priority (4) is directed away from you as, for instance, the steering column of a car would be. The three groups of higher priority (1–3) then project toward you as the hub of the steering wheel.

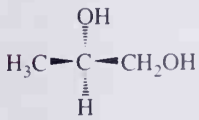
(4) Read the three groups projecting toward you in order from highest priority (1) to lowest priority (3).

(5) If reading the groups proceeds in a clockwise direction, the absolute configuration is designated as **R** (Latin: *rectus,* right, right hand); if reading proceeds in a counterclockwise direction, the absolute configuration is **S** (Latin: *sinister,* left, left hand).

EXAMPLE 8.2

Assign an R or S configuration to each stereocenter and give each molecule an IUPAC name.

(a) 

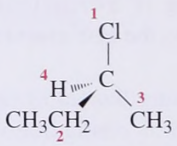
(b) 

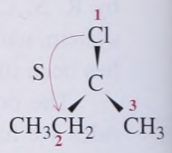
(c) 

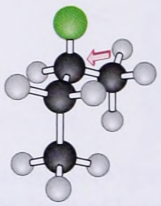
Solution

View each molecule through the stereocenter and along the bond from the stereocenter toward the group of lowest priority.

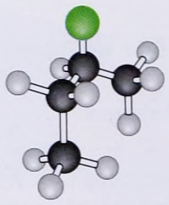
(a) The order of priority is —Cl > —CH_2CH_3 > —CH_3 > —H.



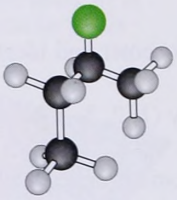


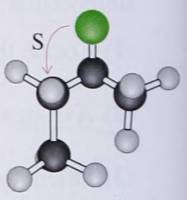


(S)-2-Chlorobutane

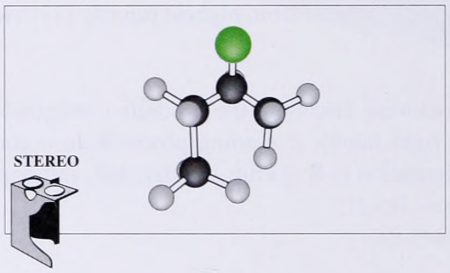


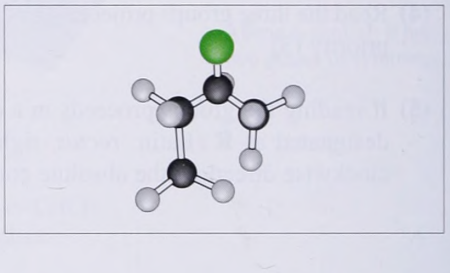
If you turn the molecule so you view it along the C—H bond to H...



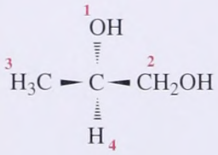


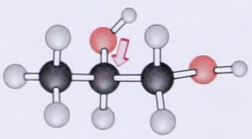
...this is what you see.



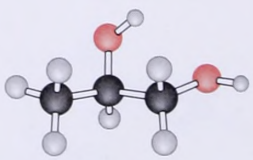


(b) The order of priority is —OH > —CH_2OH > —CH_3 > —H.

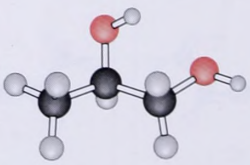


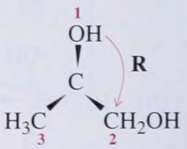


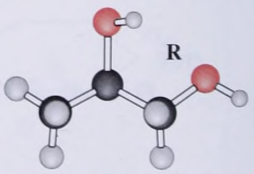
(R)-1,2-Propanediol



If you turn the molecule so you view it along the C—H bond to H...

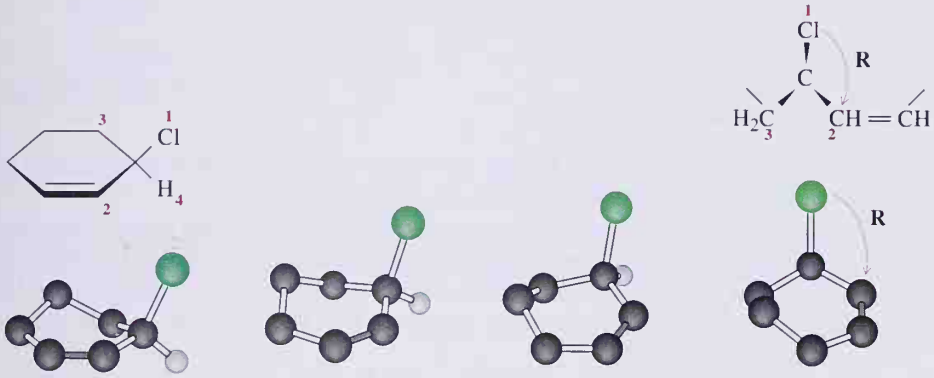






...this is what you see.

(c) The order of priority is —Cl > —CH=CH > —CH_2 > —H.



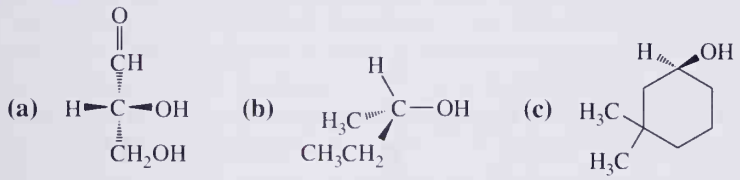
(R)-3-Chlorocyclohexene

If you turn the molecule so you view it along the C—H bond to C...

...this is what you see.

PROBLEM 8.2

Assign an R or S configuration to each stereocenter and give each molecule an IUPAC name.

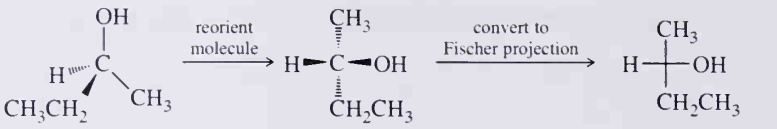


8.4 Fischer Projection Formulas

In writing structures for chiral molecules, we have thus far used lines, solid wedges, and broken wedges to indicate configuration about a stereocenter. The use of these drawing conventions accurately portrays stereochemistry and teaches you to treat molecules as three-dimensional objects. The ability to deal with molecules as three-dimensional objects is a survival skill in organic chemistry.

Nonetheless, chemists sometimes use a two-dimensional representation called a **Fischer projection** to show the configuration of chiral molecules. This convention is especially useful in portraying the stereochemistry of compounds with several stereocenters, as we shall see in Chapter 18 when we deal with the configuration of carbohydrates.

To write a Fischer projection, orient the stereocenter of a chiral molecule so that the vertical bonds to the stereocenter are directed away from you and the horizontal bonds from the stereocenter are directed toward you. You then write the molecule as a two-dimensional figure with the stereocenter indicated by the point at which bonds cross. A Fischer projection for (S)-2-butanol is derived as follows:



(S)-2-Butanol (three-dimensional formula)

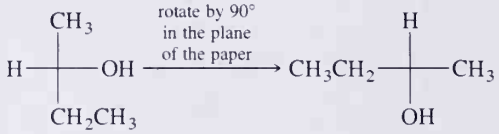
(S)-2-Butanol (Fischer projection)

The two horizontal segments of a Fischer projection represent bonds directed toward you, and the two vertical segments represent bonds directed away from you.

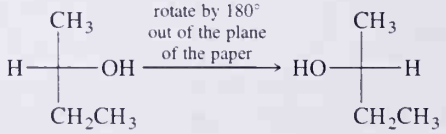
Just as Fischer projections are derived in a very precise way, they can only be manipulated in very precise ways. When using Fischer projections to test the superposability of two structures, the only allowed manipulation is rotation in the plane of the paper by 180°. Rotation by 90° in the plane of the paper, or rotation by 180° out of the plane of the paper gives a different molecule.

EXAMPLE 8.3

We said that rotation of a Fischer projection by 90° in the plane of the paper or by 180° out of the plane of the paper gives a different molecule. Following are such manipulations of the Fischer projection of (S)-2-butanol. What is the different molecule represented by each manipulation?

(a) 

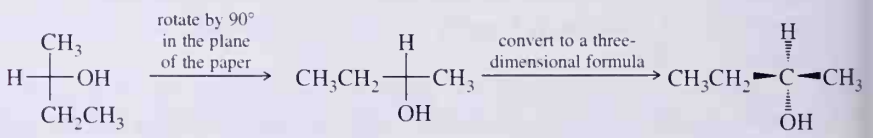
(S)-2-butanol

(b) 

(S)-2-butanol

Solution

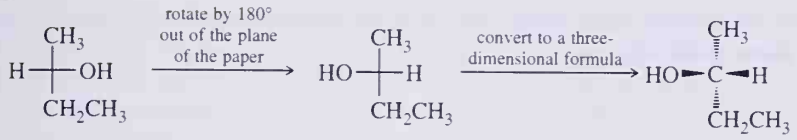
(a) Rotation by 90° in the plane of the paper converts the Fischer projection of (S)-2-butanol into a projection of (R)-2-butanol.



(S)-2-Butanol (Fischer projection)

(R)-2-Butanol

(b) Rotation by 180° out of the plane of the paper also converts the Fischer projection of (S)-2-butanol into a projection of (R)-2-butanol.

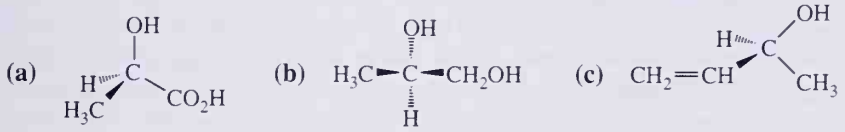


(S)-2-Butanol (Fischer projection)

(R)-2-Butanol

PROBLEM 8.3

Convert the following three-dimensional formulas to Fischer projections. Note that there is more than one correct Fischer projection corresponding to each three-dimensional formula.



8.5 Optical Activity: How Chirality Is Detected in the Laboratory

As we have already established, enantiomers are different compounds, and we must expect, therefore, that they differ in some properties. One such property is their effect on the plane of polarized light. Each member of a pair of enantiomers rotates the plane of polarized light, and for this reason enantiomers are said to be **optically active.** The phenomenon of optical activity was discovered by the French physicist Jean Baptiste Biot in 1815. To understand how optical activity is detected in the laboratory, we must first understand something about plane-polarized light and a device used to detect it—the polarimeter.

A. Plane-Polarized Light

Ordinary light consists of waves vibrating in all planes perpendicular to its path (Figure 8.4). Certain materials, such as calcite or Polaroid sheet (a plastic film containing properly oriented crystals of an organic substance embedded in it), selectively transmit light waves

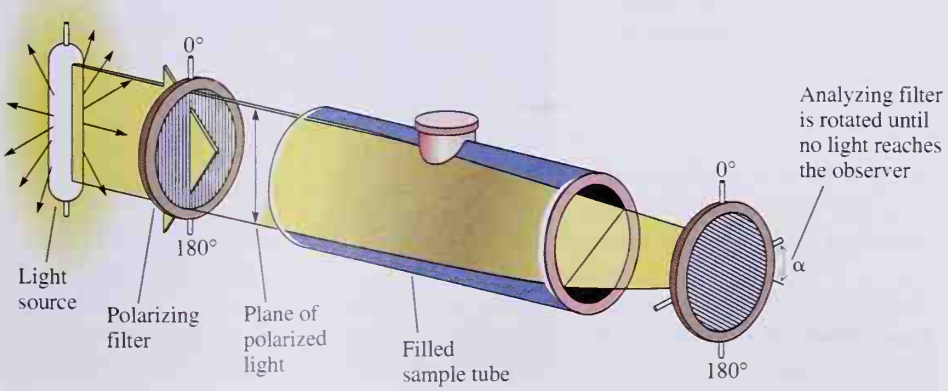


Figure 8.4
Schematic diagram of a polarimeter with its sample tube containing a solution of an optically active compound. The analyzing filter has been turned clockwise by α degrees to restore the dark field.

vibrating in one specific plane. Electromagnetic radiation vibrating in only one plane is said to be **plane-polarized.**

B. A Polarimeter

A **polarimeter** consists of a light source, a polarizing prism and an analyzing prism (each made of calcite or Polaroid), and a sample tube (Figure 8.4). If the sample tube is empty, the intensity of light reaching you is at its maximum when the polarizing axes of the two prisms are parallel. If the analyzing prism is turned either clockwise or counterclockwise, less light is transmitted. When the axis of the analyzing prism is at right angles to the axis of the polarizing prism, the field of view is dark. This position of the analyzing prism is taken as 0° on the optical scale.

One of the properties of a compound with identical chiral molecules is its ability to **rotate the plane of polarized light,** which can be observed using a polarimeter in the following way. First, a sample tube filled with solvent is placed in the polarimeter, and the analyzing prism is adjusted so that no light passes through to the observer; that is, it is set to 0°. When a solution of an optically active compound is placed in the sample tube, a certain amount of light now passes through the analyzing prism; the optically active compound has rotated the plane of light from the polarizing prism so that it is now no longer at an angle of 90° to the analyzing prism. The analyzing prism is then rotated to restore darkness in the field of view (Figure 8.4). The number of degrees, α, through which the analyzing prism must be rotated to restore darkness to the field of view is called the **observed rotation.** If the analyzing prism must be turned to the right (clockwise) to restore darkness, that is, if the plane of polarized light has been rotated to the right, we say that the compound is **dextrorotatory** (Latin: *dexter,* on the right side). If the analyzing prism must be turned to the left (counterclockwise), we say that the compound is **levorotatory** (Latin: *laevus,* on the left side).

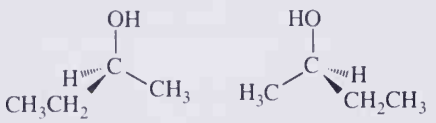
A polarimeter. *(© Richard Megna, 1992, Fundamental Photographs)*

The magnitude of the observed rotation for a particular compound depends on its concentration, the length of the sample tube, the temperature, the solvent, and the wave length of the light used. To standardize optical rotation data, chemists use a term called specific rotation. **Specific rotation, $[\alpha]$,** is defined as the observed rotation at a specific cell length and sample concentration.

$$[\alpha]_{\lambda}^{t} = \frac{\text{observed rotation (degrees)}}{\text{length (dm)} \times \text{concentration (g/mL)}}$$

The standard cell length is 1.0 decimeter (1.0 dm or 10 cm). For a pure liquid sample (or "neat" sample) the concentration is expressed in grams per milliliter (g/mL: density). The concentration of a sample dissolved in a solvent is also usually expressed as grams per milliliter of solution. The temperature (t) and wave length (λ) of light are designated, respectively, as superscript and subscript. The light source most commonly used in polarimetry is the sodium D line ($\lambda = 589.0$ nm), the same line responsible for the yellow color of sodium-vapor lamps.

In reporting either observed or specific rotation, it is common to indicate a dextrorotatory compound with a plus sign (+) and a levorotatory compound with a minus sign (−). One member of a pair of enantiomers is dextrorotatory, and the other is levorotatory. For each, the number of degrees of specific rotation is the same, but the sign is opposite. Following are the specific rotations of the stereoisomers of 2-butanol at 25°C using the D line of sodium.



(S)-(+)-2-Butanol $[\alpha]_{D}^{25} = +13.52$

(R)-(−)-2-Butanol $[\alpha]_{D}^{25} = -13.52$

C. Racemic Mixture

An equimolar mixture of two enantiomers is called a **racemic mixture,** a term derived from the name "racemic acid" (Latin: *racemus,* a cluster of grapes). Racemic acid is the name originally given to an equimolar mixture of the enantiomers of tartaric acid, a compound first isolated from grapes. Because a racemic mixture contains equal numbers of the dextrorotatory and the levorotatory molecules, the specific rotation of a racemic mixture is 0°. Alternatively, we say that a racemic mixture is optically inactive. The racemic nature of a compound is indicated by adding the prefix (±) or (R, S) to its name.

D. Optical Purity and Enantiomeric Excess

When dealing with a pair of enantiomers, it is essential to have a means of describing the composition of that mixture and the degree to which one enantiomer is in excess relative to its mirror image. The two most common ways of describing the composition of a mixture of enantiomers are optical purity and enantiomeric excess.

Optical purity of an enantiomer or of a mixture of enantiomers is defined in terms of the specific rotation of a sample compared with the specific rotation of the pure enantiomer.

$$\text{Percent optical purity} = \frac{[\alpha]_{\text{sample}}}{[\alpha]_{\text{pure enantiomer}}} \times 100$$

Enantiomeric excess, abbreviated **ee**, is defined in terms of the difference in number of moles of each enantiomer in a mixture compared with the total number of moles of both. Thus, ee is numerically equal to the percent optical purity.

$$\text{Enantiomeric excess (ee)} = \frac{\text{moles of one enantiomer} - \text{moles of other enantiomer}}{\text{moles of both enantiomers}} \times 100$$

EXAMPLE 8.4

In Figure 8.7 is a scheme for separation of the enantiomers of mandelic acid. The specific rotation of optically pure (S)-(−)-mandelic acid is −158°. Suppose that instead of isolating pure (S)-(−)-mandelic acid from this scheme, the sample is a mixture of enantiomers with a specific rotation of −134°. For this sample, calculate

(a) The percent optical purity of (S)-(−)-mandelic acid.
(b) The enantiomeric excess (ee) of (S)-(−)-mandelic acid.
(c) The percent of (S)-(−)-mandelic acid and of (R)-(+)-mandelic acid in the sample.

Solution

(a) Optical purity of (S)-(−)-mandelic acid is 84.8%, calculated as follows:

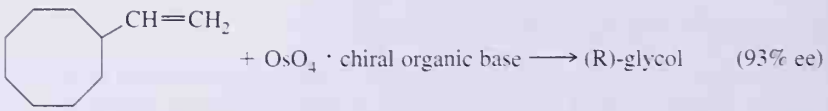
$$\text{Percent optical purity} = \frac{-134°}{-158°} \times 100 = 84.8\%$$

(b) Percent optical purity and enantiomeric excess are equivalent. There is 84.8% enantiomeric excess of (S)-(−)-mandelic acid.

(c) This sample is 84.8% (S)-(−)-mandelic acid and 15.2% racemic mixture. The racemic mixture in turn is 7.6% S enantiomer and 7.6% R enantiomer. The sample, therefore, is 92.4% S enantiomer and 7.6% R enantiomer.

PROBLEM 8.4

Professor Barry Sharpless, currently at the Research Institute of Scripps Clinic, La Jolla, California, has devised a procedure for oxidation of alkenes in which the oxidizing agent, osmium tetroxide, is bound to a chiral organic base. Thus, oxidation of the alkene to a glycol takes place in a chiral environment. Under these conditions, vinylcyclooctane is oxidized to an (R)-glycol in 93% enantiomeric excess.

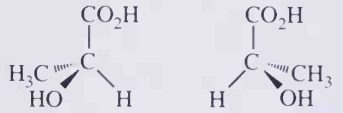


Draw the structural formula for the product of this oxidation, showing its configuration, and calculate the percentages of (R)-glycol and (S)-glycol in the product.

■

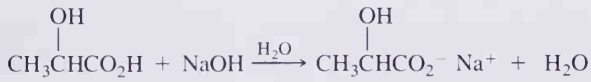
E. Relationship Between Configuration and Sign of Rotation

For more than a century after the discovery of optical activity and enantiomerism, the only method for distinguishing between enantiomers was the sign of rotation; hence the designations (+) and (−) for naming enantiomers. Furthermore, although it was possible to draw configurations for a pair of enantiomers, there was no way to determine which enantiomer had which configuration. Following are structural formulas for the enantiomers of lactic acid:



(S)-Lactic acid (R)-Lactic acid

The question we ask is then "Which is the configuration of (+)-lactic acid and which is the configuration of (−)-lactic acid? Until recently there was no way to answer this question. The problem is compounded by the fact that no simple relationship exists between the sign of rotation and the configuration of a molecule. For example, when (+)-lactic acid is treated with aqueous sodium hydroxide, (−)-sodium lactate is formed. Conversion of the carboxyl group to its sodium salt in no way affects the configuration of the stereocenter, and yet the specific rotation changes from dextrorotatory to levorotatory. Each compound has the same configuration at the stereocenter, and yet one is dextrorotatory and the other is levorotatory.

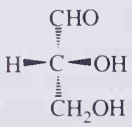


(+)-Lactic acid $[\alpha]_D^{21} = +2.6°$ (−)-Sodium lactate $[\alpha]_D^{20} = -13.5°$

The question of the configuration of the enantiomers of lactic acid and of a great many other compounds has been solved using x-ray crystallography and the analysis of crystals of pure enantiomers. We now know that (+)-lactic acid has the S configuration and, therefore, is properly named as (S)-(+)-lactic acid. The enantiomer of (S)-(+)-lactic acid is (R)-(−)-lactic acid.

EXAMPLE 8.5

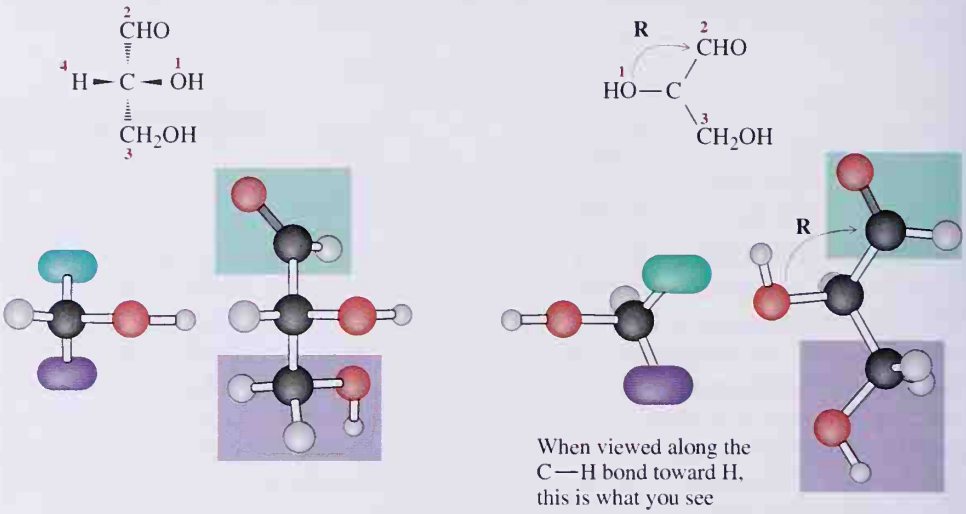
Assign an R or S configuration to (+)-2,3-dihydroxypropanal, more commonly known as (+)-glyceraldehyde.



(+)-2,3-Dihydroxypropanal
((+)-Glyceraldehyde)

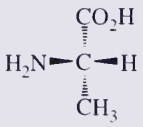
Solution

The order of priority is —OH > —CHO > —CH_2OH > —H. View the molecule from behind and to the right, through the stereocenter, and along the C—H bond toward —H. The configuration is R, and the compound is named R-(+)-glyceraldehyde.



PROBLEM 8.5

Assign an R or S configuration to (+)-2-aminopropanoic acid, more commonly known as (+)-alanine.



(+)-2-Aminopropanoic acid
((+)-Alanine)

8.6 Acyclic Molecules with Two or More Stereocenters

If a molecule has one stereocenter, the number of stereoisomers possible is $2^1 = 2$. We saw several examples of molecules with one stereocenter and verified that for each such molecule, two stereoisomers (one pair of enantiomers) are possible. If we now consider molecules with two or more stereocenters, we must be more precise in our wording, because now all we can specify by counting the number of stereocenters is the maximum number of stereoisomers possible. The maximum number of stereoisomers for a molecule with two stereocenters if $2^2 = 4$. For a molecule with three stereocenters, the maximum number of stereoisomers possible is $2^3 = 8$. To generalize, for a molecule with n stereocenters, the maximum number of steroisomers possible is $\mathbf{2^n}$.

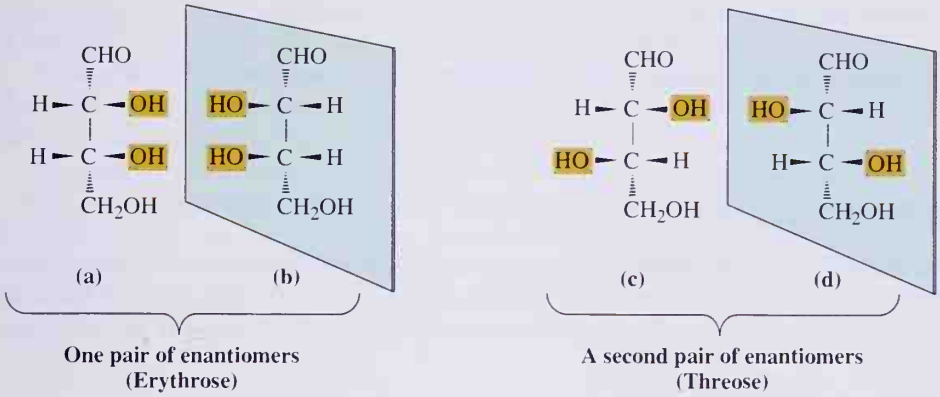
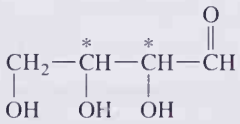


Figure 8.5
The four stereoisomers of 2,3,4-trihydroxybutanal, a compound with two stereocenters.

A. Enantiomers and Diastereomers

Let us begin our study of molecules with multiple stereocenters with 2,3,4-trihydroxybutanal, a molecule with two stereocenters, here marked by asterisks.



2,3,4-Trihydroxybutanal

The maximum number of stereoisomers possible for this molecule is $2^2 = 4$, each of which is drawn in Figure 8.5. Stereoisomers (a) and (b) are nonsuperposable mirror images of each other and are, therefore, a pair of enantiomers. Stereoisomers (c) and (d) are also nonsuperposable mirror images and are a second pair of enantiomers. One way to describe the four stereoisomers of 2,3,4-trihydroxybutanal is to say that they consist of two pairs of enantiomers. Enantiomers (a) and (b) are given the name erythrose; enantiomers (c) and (d) are given the name threose. Erythrose and threose belong to the class of compounds called carbohydrates, which we discuss in Chapter 18. Erythrose is one of the compounds synthesized in erythrocytes (red blood cells), hence the derivation of its name.

We have specified the relationship between (a) and (b) and between (c) and (d). What is the relationship between (a) and (c), between (a) and (d), between (b) and (c), and between (b) and (d)? The answer is that they are diastereomers. They are stereoisomers that are not mirror images.

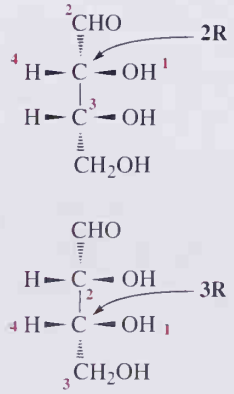
EXAMPLE 8.6

Assign (R, S) configurations to each stereocenter in the enantiomers of erythrose.

Solution

The upper drawing shows assignments of priority and configuration on carbon 2; the lower shows assigments of priority and configuration on carbon 3.

Follow the same procedure to assign configurations to the stereocenters in (b). Alternatively, because (b) is the mirror image of (a), the configuration of each stereocenter in (b) must then be the opposite of that in (a). Therefore, the configuration of (b) must be (2S, 3S)-2,3,4-trihydroxybutanal.



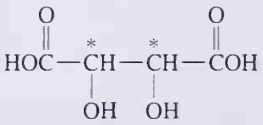
(2R,3R)-2,3,4-Trihydroxybutanal

PROBLEM 8.6

Assign R or S configurations to each stereocenter in the enantiomers of threose.

B. Meso Compounds

Certain molecules containing two or more tetrahedral stereocenters have special symmetry properties that reduce the number of stereoisomers to fewer than that predicted by the 2^n rule. One such example is 2,3-dihydroxybutanedioic acid, more commonly named tartaric acid.



2,3-Dihydroxybutanedioic acid
(Tartaric acid)

Tartaric acid is a colorless, crystalline compound occurring largely in the vegetable kingdom, especially in unripe grapes. During fermentation of grape juice, potassium bitartrate (one CO_2H group as a potassium salt, $—CO_2^-\ K^+$) deposits as a crust on the sides of wine casks. When collected and purified, it is sold commercially as cream of tartar. In tartaric acid, carbons 2 and 3 are stereocenters, and, using the 2^n rule, the maximum number of stereoisomers possible is $2^2 = 4$, stereorepresentations for which are drawn in Figure 8.6. Structures (a) and (b) are nonsuperposable mirror images and, therefore, are a pair of enantiomers. Structures (c) and (d) are also mirror images, but they are superposable. To see this, imagine that you lift (d) out of the plane of the paper, rotate it 180° while keeping it parallel to the plane of the paper, and then place it on top of (c). If you do this mental

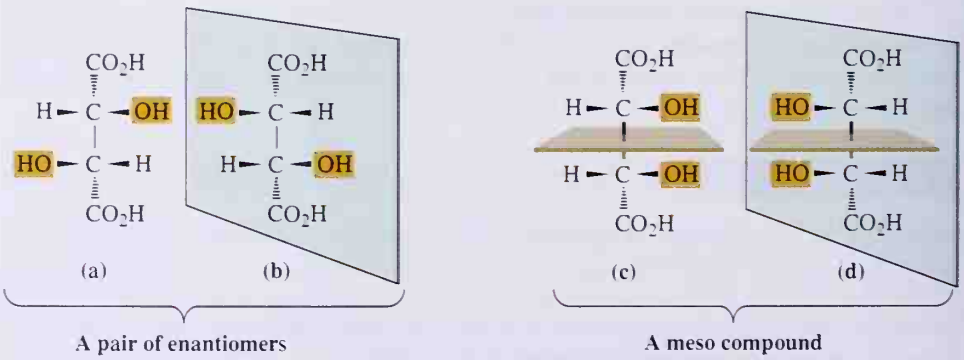


Figure 8.6
Stereoisomers of tartaric acid. One pair of enantiomers and one meso compound.

manipulation correctly, you find that (d) is superposable on (c). Therefore, (d) and (c) are not different molecules; they are the same molecule, just oriented differently.

Because (c) and its mirror image are superposable, (c) is achiral. Another way to determine that (c) is achiral is to see that it has a plane of symmetry, which bisects the molecule in such a way that the top half is the reflection of the bottom half.

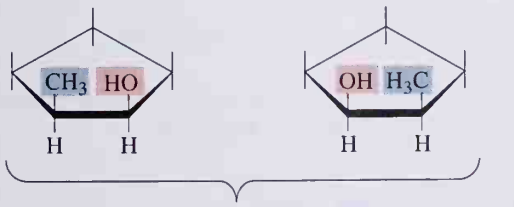
The stereoisomer of tartaric acid represented by (c) or (d) is called a meso compound. A compound is **meso** if its molecules are achiral even though they contain two or more stereocenters. We can now return to the original question: How many stereoisomers are there of tartaric acid? The answer is three: one meso compound and one pair of enantiomers.

8.7 Cyclic Molecules with Two or More Stereocenters

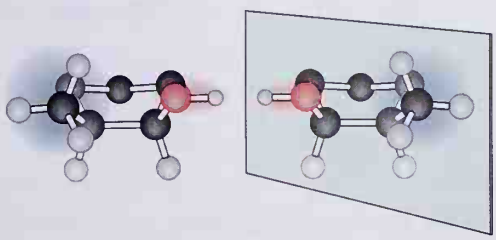
In this section, we concentrate on compounds of cyclopentane and cyclohexane containing two or more stereocenters.

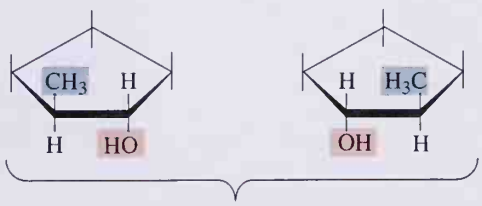
A. Disubstituted Derivatives of Cyclopentane

We can analyze multiple stereocenters in cyclic compounds in the same way we analyzed stereoisomerism in acyclic compounds. Let us start with 2-methylcyclopentanol, a compound with two stereocenters. Using the 2^n rule, we predict a maximum of $2^2 = 4$ stereoisomers. Both the *cis* and the *trans* isomer are chiral: the *cis* isomer exists as one pair of enantiomers, and the *trans* isomer exists as a second pair of enantiomers. The *cis* and *trans* isomers are stereoisomers that are not mirror images of each other; or more simply, the *cis* and *trans* isomers are diastereomers.

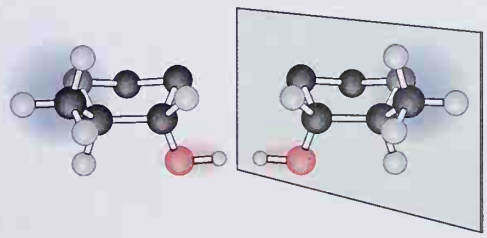


***cis*-2-Methylcyclopentanol**
(a pair of enantiomers)

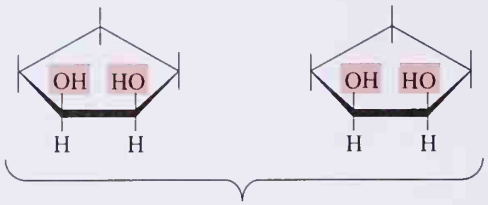




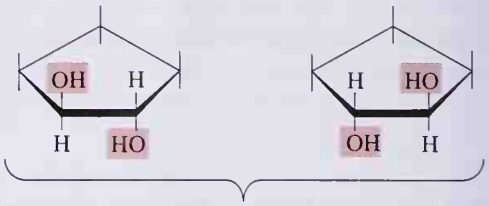
***trans*-2-Methylcyclopentanol**
(a pair of enantiomers)



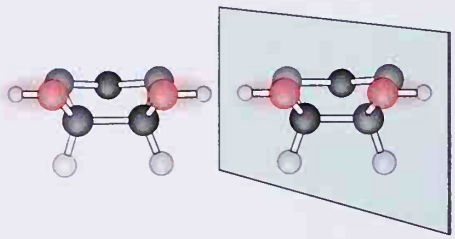
1,2-Cyclopentanediol also has two stereocenters and, therefore, the 2^n rule predicts a maximum of $2^2 = 4$ stereoisomers. As seen in the following stereodrawings, only three stereoisomers exist for this compound. The *trans* isomer is chiral and exists as a pair of enantiomers. The *cis* isomer is achiral because it and its mirror image are superposable. Alternatively, the *cis* isomer is achiral because it possesses a plane of symmetry that bisects the molecule into two mirror halves.

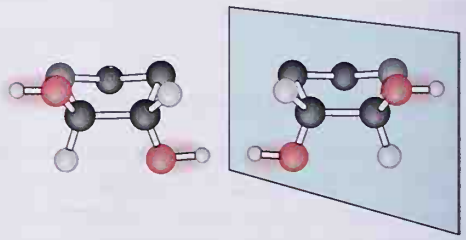


***cis*-1,2-Cyclopentanediol**
(a meso compound)



***trans*-1,2-Cyclopentanediol**
(a pair of enantiomers)



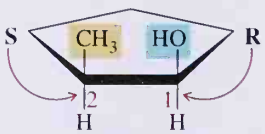


EXAMPLE 8.7

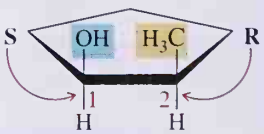
Assign R or S configurations to the enantiomers of *cis*-2-methylcyclopentanol, and show that the configuration of each stereocenter in one enantiomer is the opposite of that stereocenter in the other enantiomer.

Solution

The configuration about carbon 2 of one enantiomer is S; that of carbon 2 in its mirror image is R. The same relationship applies to the configuration at carbon 1.



(1R,2S)-*cis*-2-Methyl-cyclopentanol



(1S,2R)-*cis*-2-Methyl-cyclopentanol

PROBLEM 8.7

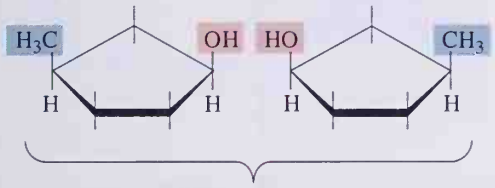
(a) Think about the configurations of the enantiomers of *trans*-1,2-cyclopentanediol, but do not go through the work of assigning priorities, and so forth. Do you

predict configurations of the enantiomers to be (1R,2S) and (1S,2R) or (1R,2R) and (1S,2S)?

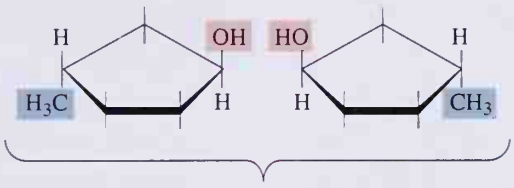
(b) Now do the work of assigning configurations. Did you predict correctly in (a)? If so, well done. If not, why not and what did you overlook?

■

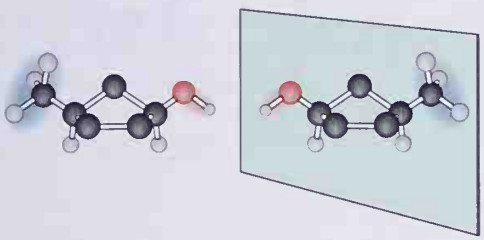
There are four stereoisomers of 3-methylcyclopentanol: the *cis* isomer exists as one pair of enantiomers; the *trans* isomer as a second pair of enantiomers. There are three stereoisomers of 1,3-cyclopentanediol: the *cis* isomer is achiral and a meso compound; the *trans* isomer exists as a pair of enantiomers.

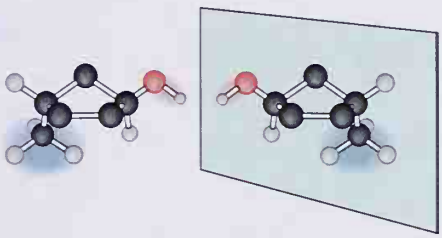


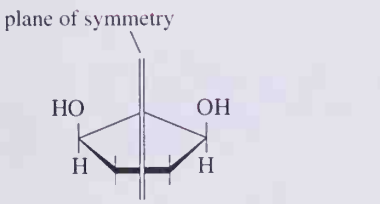
***cis*-3-Methylcyclopentanol**
(a pair of enantiomers)

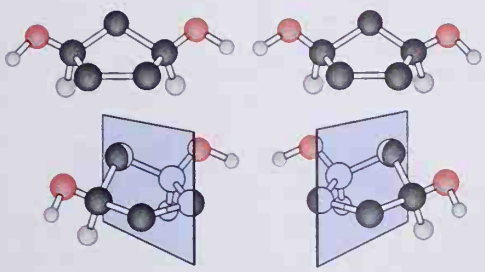


***trans*-3-Methylcyclopentanol**
(a pair of enantiomers)

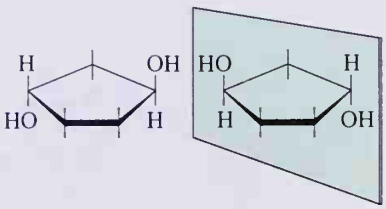


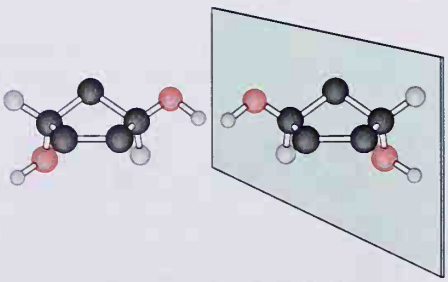






***cis*-1,3-Cyclopentanediol**
(achiral; a meso compound)

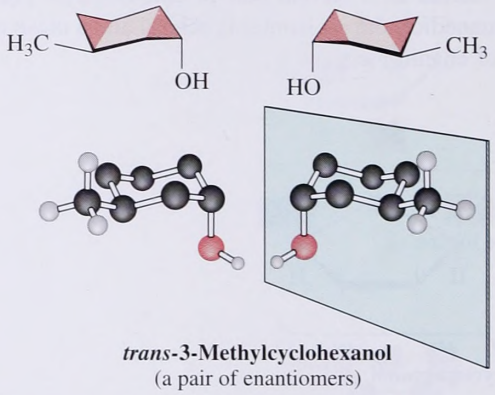




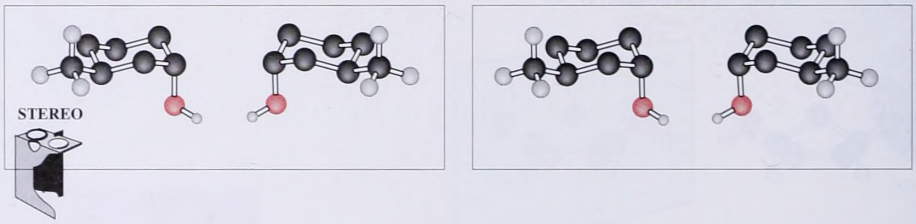
***trans*-1,3-Cyclopentanediol**
(a pair of enantiomers)

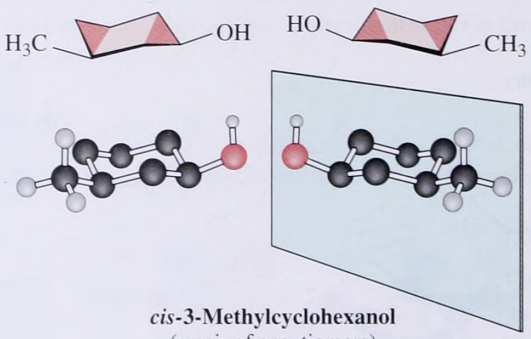
B. Disubstituted Derivatives of Cyclohexane

As an example of a disubstituted cyclohexane, let us consider the methylcyclohexanols. 4-Methylcyclohexanol can exist as two stereoisomers: a pair of *cis-trans* isomers. Neither the *cis* isomer nor the *trans* isomer has a stereocenter, and, therefore, each is achiral. 3-Methylcyclohexanol has two stereocenters and exists as $2^2 = 4$ stereoisomers. The *cis* isomer exists as one pair of enantiomers. The *trans* isomer exists as a second pair of

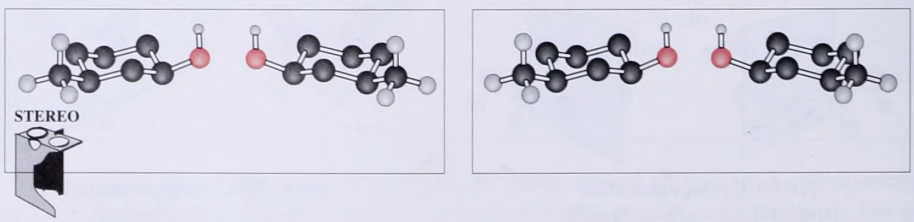


***trans*-3-Methylcyclohexanol**
(a pair of enantiomers)

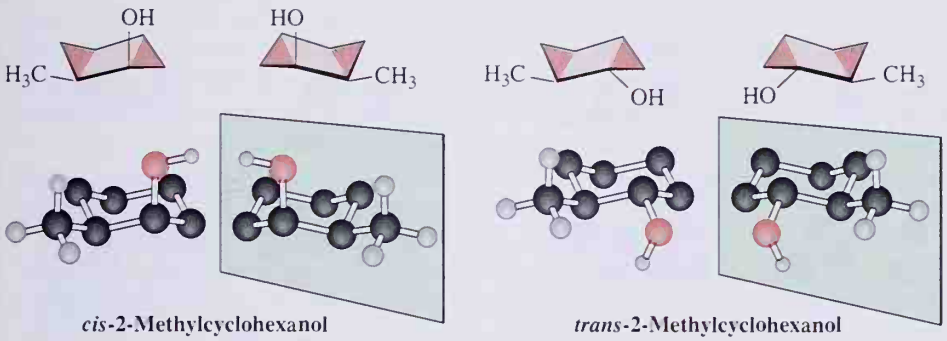




***cis*-3-Methylcyclohexanol**
(a pair of enantiomers)



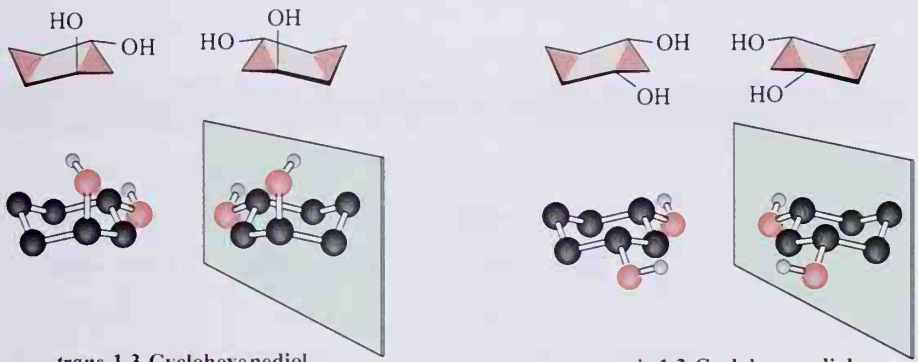
enantiomers. Similarly, 2-methylcyclohexanol has two stereocenters and exists as $2^2 = 4$ stereoisomers. The *cis* isomer exists as one pair of enantiomers, the *trans* isomer as a second pair of enantiomers.



***cis*-2-Methylcyclohexanol**
(a pair of enantiomers)

***trans*-2-Methylcyclohexanol**
(a pair of enantiomers)

We can analyze cyclohexanes with two identical substituents in a similar way. 1,4-Cyclohexanediol can exist as a pair of *cis-trans* isomers. Each is achiral. Therefore this compound can exist as two stereoisomers only. 1,3-Cyclohexanediol has two stereocenters, and according to the 2^n rule, has a maximum of $2^2 = 4$ possible stereoisomers. The *trans* isomer of this compound exists as a pair of enantiomers. The *cis* isomer has a plane of symmetry and is a meso compound. Therefore, although the 2^n rule predicts a maximum of four stereoisomers for 1,3-cyclohexanediol, only three exist: one meso compound and one pair of enantiomers.

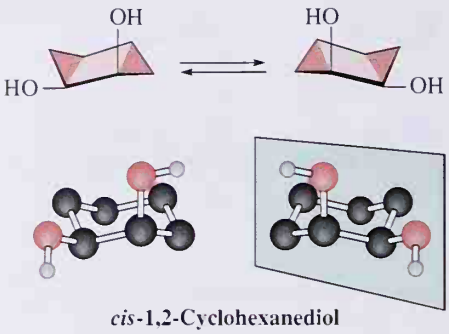


***trans*-1,3-Cyclohexanediol**
(a pair of enantiomers)

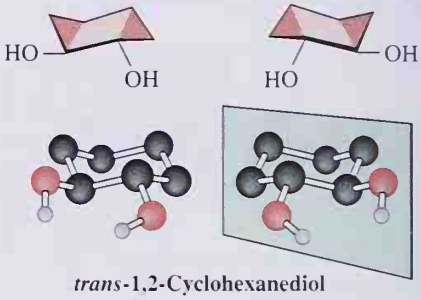
***cis*-1,3-Cyclohexanediol**
(meso)

1,2-Cyclohexanediol has two stereocenters and according to the 2^n rule, can exist as a maximum of four stereoisomers. The *cis* isomer exists as one pair of enantiomers, and the *trans* isomer exists as a second pair of enantiomers. The two enantiomers of the *cis* isomer cannot be separated at room temperature because each is converted to the other by chair-to-alternative-chair interconversion. Thus, each enantiomer interconverts to its mirror

image and forms a racemic mixture. You will find it helpful to build molecular models of the enantiomers of *cis*-1,2-cyclohexanediol and convince yourself that they cannot be resolved under any conditions for which there is sufficient energy for chair-boat-chair interconversion.



***cis*-1,2-Cyclohexanediol**
(a pair of enantiomers, but not resolvable because of chair–chair interconversion)

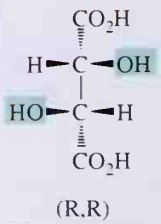
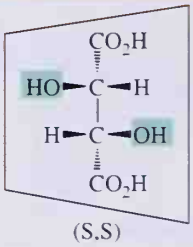
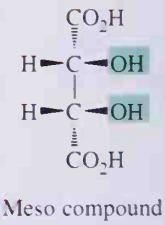


***trans*-1,2-Cyclohexanediol**
(a pair of enantiomers)

8.8 Properties of Stereoisomers

Enantiomers have identical physical and chemical properties in achiral environments. The enantiomers of tartaric acid (Table 8.1), for example, have the same melting points, the same boiling points, the same solubilities in water and other common solvents, the same values of pK_a, and undergo the same acid-base reactions. Diastereomers have different physical and chemical properties, even in achiral environments. Meso-tartaric acid has different physical properties from those of the enantiomers.

Table 8.1 Some physical properties of the stereoisomers of tartaric acid

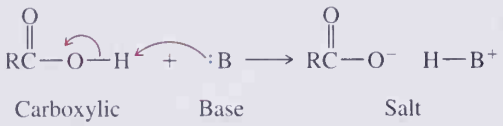
	 (R,R)	 (S,S)	 Meso compound
Specific rotation (°)	+12.7	−12.7	0
Melting point (°C)	171–174	171–174	146–148
Density at 20°C (g/cm^3)	1.7598	1.7598	1.660
Solubility in water at 20°C (g/100 mL)	139	139	125
pK_{a1} (25°C)	2.98	2.98	3.23
pK_{a2} (25°C)	4.34	4.34	4.82

8.9 Separation of Enantiomers: Resolution

The separation of a racemic mixture into its two enantiomers is called optical resolution, or more simply **resolution.** It was first accomplished by Louis Pasteur and reported in 1848. Working with salts of tartaric acid, byproducts from the wine industry, Pasteur succeeded in crystallizing the racemic salts so that they were deposited in mirror image crystalline forms. By laboriously separating left-handed and right-handed crystals with the aid of a magnifying lens and tweezers, Pasteur was able to show that solutions of each kind of crystals were optically active, even though the original solution of racemic tartrate salts was optically inactive. This mechanical resolution, which depends on the spontaneous formation of chiral crystals, is an unusual event, having been observed only rarely with other racemic mixtures since Pasteur's original experiments.

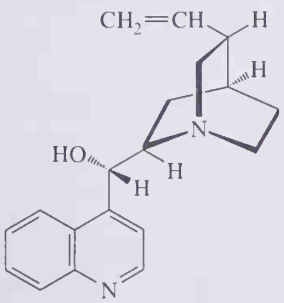
A more general scheme for separating enantiomers, also originated by Pasteur, requires chemical conversion of the pair of enantiomers into diastereomers with the aid of a chiral **resolving reagent.** This chemical resolution is successful because the diastereomers thus formed have different physical properties and can be separated by physical means (distillation, fractional crystallization, chromatography) and purified. The final step in this scheme for resolution is chemical conversion of the separated diastereomers back to individual enantiomers along with the resolving agent.

A reaction that lends itself to chemical resolution is salt formation because it is readily reversible.

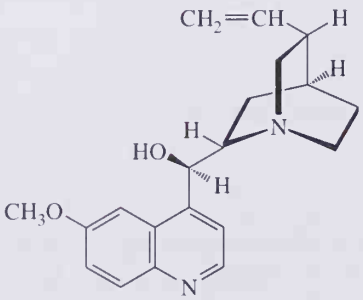


Carboxylic acid — Base — Salt

Several enantiomerically pure bases available from plants have been used as chiral resolving agents. Examples are cinchonine and quinine.



(+)-Cinchonine
$[\alpha]_D^{23} = +228°$



(−)-Quinine
$[\alpha]_D^{25} = -165°$

Quinine sulfate viewed under a polarizing microscope. *(© Mel Pollinger/Fran Heyl Associates)*

The base (+)-cinchonine is found in the bark of most species of cinchona, a genus of evergreen trees or shrubs growing in the tropical valleys of the Andes and now extensively cultivated for its bark in India, Java, and parts of South America. Extracts of its bark, commonly referred to as Jesuit's bark or Peruvian bark, have been used for centuries as a tonic and to cure the fevers associated with malaria. The genus was named by Linnaeus after the Countess of Cinchon who, when wife of the viceroy of Peru, was cured of fever by Peruvian bark and later brought a supply of it back to Spain. Also found in cinchona bark is (−)-quinine, an even more potent antimalarial drug.

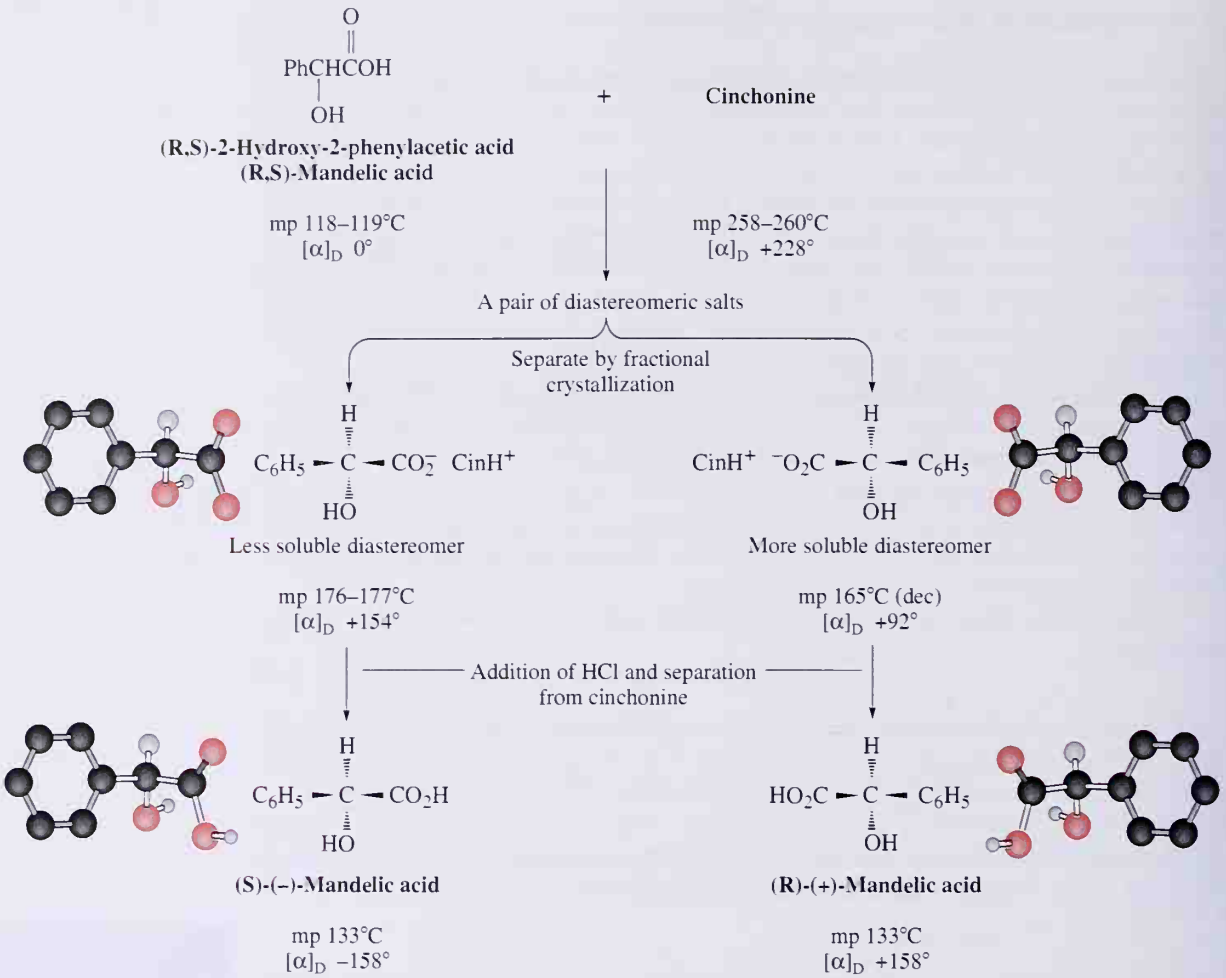
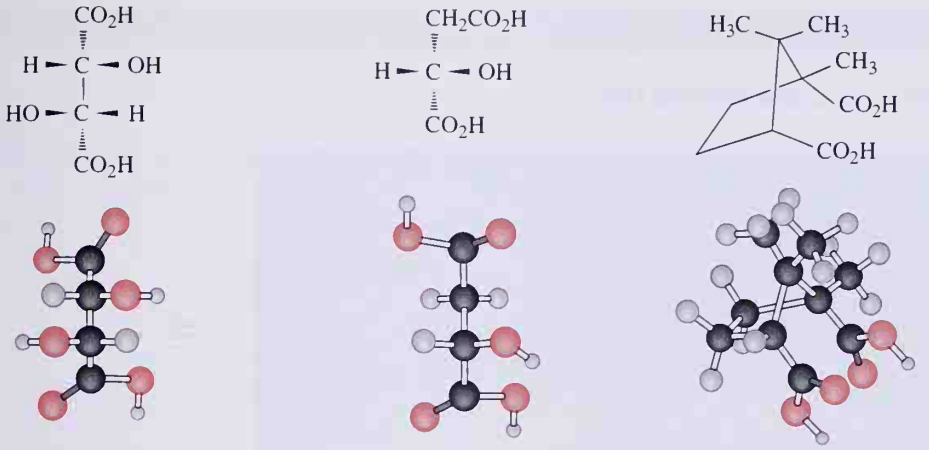


Figure 8.7
Resolution of mandelic acid.

Mandelic acid has been resolved into its enantiomers by way of its diastereomeric salts with cinchonine as illustrated in Figure 8.7. Racemic mandelic acid and optically pure (+)-cinchonine (abbreviated Cin) are dissolved in boiling water and the solution allowed to cool, whereupon the less soluble diastereomeric salt crystallizes. This salt is collected and purified by further recrystallization. The filtrates, richer in the more soluble diastereomeric salt, are concentrated to give the corresponding salt, which is then purified by further recrystallization. The purified diastereomeric salts are treated with aqueous HCl to precipitate mandelic acid. Cinchonine remains in the aqueous solution as the water-soluble salt.

Optical rotations and melting points of racemic mandelic acid, cinchonine, the purified diastereomeric salts, and the pure enantiomers of mandelic acid are given in Figure 8.7. Note the following points: (1) The melting point of (R,S)-mandelic acid is different from the melting point of the pure enantiomers. (2) The diastereomeric salts have different



(2R,3R)-(+)-Tartaric acid

$[\alpha]_D^{20}$ +12.5°

(S)-(−)-Malic acid

$[\alpha]_D^{20}$ −27°

(1R,3S)-(+)-Camphoric acid

$[\alpha]_D^{20}$ +46.5°

Figure 8.8
Some carboxylic acids used as chiral resolving agents.

specific rotations and different melting points. (3) The enantiomers of mandelic acid have identical melting points and have specific rotations, which are identical in magnitude but opposite in sign.

Resolution of a racemic base with a chiral acid is carried out in a similar way. Acids that have been used as chiral resolving agents are (+)-tartaric acid, (−)-malic acid, and (+)-camphoric acid (Figure 8.8). These and other naturally occurring chiral resolving agents are produced in plant and animal systems in the form of a single enantiomer because of the stereoselectivity of enzymes in living organisms.

8.10 The Significance of Chirality in the Biological World

Except for inorganic salts and a relatively few low-molecular-weight organic substances, the molecules in living systems, both plant and animal, are chiral. Although these molecules can exist as a number of stereoisomers, almost invariably only one stereoisomer is found in nature. Of course, instances do occur in which more than one stereoisomer is found, but these rarely exist together in the same biological system.

We can generalize further that only one of two enantiomers can be metabolized by a particular organism. Louis Pasteur discovered between 1858 and 1860, as one example of this phenomenon, that when *Penicillium glaucum,* a green mold found in aging cheese and rotting fruit, is grown in a solution containing racemic tartaric acid, the solution slowly becomes levorotatory. Pasteur concluded that the microorganism preferentially metabolizes (+)-tartaric acid. If the process is interrupted at the right time, (−)-tartaric acid can be crystallized from solution in pure form. If the process is allowed to continue, however, the microorganism eventually metabolizes (−)-tartaric acid as well. Thus, although both enantiomers are metabolized by *P. glaucum,* the (+)-enantiomer is metabolized much more rapidly.

(Text continued p. 296)

CHEMISTRY IN ACTION

Chirality and the Search for Extraterrestrial Life

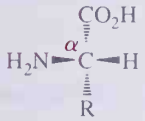
A meteor crater in the Arizona desert. *(© Francois Gohier, Photo Researchers, Inc.)*

For more than 100 years, chemists have looked for evidence of life elsewhere in the universe by analyzing the organic compounds found in meteorites. One class of meteorites, the carbonaceous chondrites, contain relatively high-molecular-weight organic molecules. How can one determine whether these molecules arose from random chemical reactions or are the residues of extraterrestrial organisms?

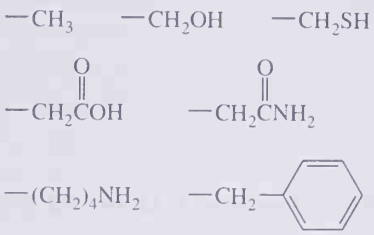
A major difference between molecules produced in living systems and those created in the laboratory is that the former are produced as single enantiomers, and the latter are usually made as racemic mixtures. Chemists have the ability to produce single enantiomers, but most of the common, inexpensive reagents and catalysts (such as HCl, $AlCl_3$, H_2-Pd/C, etc.) are not chiral. Therefore, they cannot induce chirality in their products. Likewise, the random chemical processes that took place while meteorites formed in outer space could only produce racemic mixtures.

One class of molecules isolated from carbonaceous chondrites are the α-amino acids. The vast majority of proteins in organisms of the terrestrial biological world, including humans, are synthesized from combinations of just 20 different α-amino acids. These molecules are synthesized in chiral form, and no life as we know it could exist without them. The α-amino acids differ only in the structure of the R group attached to the α-carbon. Seven R groups are shown below, each chosen to show

the diversity of functional groups present in α-amino acids. We have more to say about these molecules in Chapter 24.



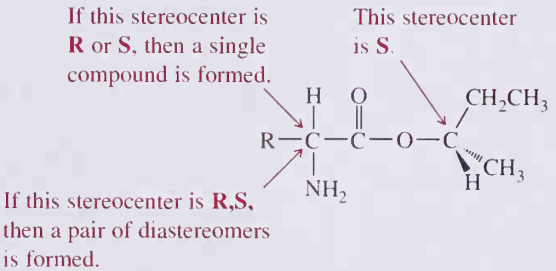
An α-amino acid



R Groups of seven α-amino acids

Living systems, however, are not the only possible sources of α-amino acids. It has been known since the 1950s that an electric discharge (or other form of energy) passed through a mixture of methane, ammonia, and water produces complex mixtures of organic compounds, including α-amino acids. Because these α-amino acids are produced from achiral precursors, they are produced as racemic mixtures. Thus, chirality provides a way to distinguish between α-amino acids produced by living and nonliving systems.

A major problem with early studies on meteorite α-amino acids was that the samples were contaminated with terrestrial material. For example, in some early studies the distributions of α-amino acids isolated from a meteorite were shown to be the same as the distribution in fingerprints. In 1970, a group of scientists analyzed α-amino acids from a meteorite which had fallen to earth near Muchinson, Australia in late 1969. Great care was taken to use material from fragments that had few cracks and exterior contamination. Only micrograms of individual α-amino acids could be isolated from each meteor fragment. Each α-amino acid isolated was treated with a chiral, enantiomerically pure alcohol to form an ester. The reasoning behind formation of diastereomeric esters was as follows. If an α-amino acid were chiral and enantiomerically pure, then a single compound would be formed. If, however, the α-amino acid were a racemic mixture, two diastereomeric esters would be formed. Because diastereomers have different physical properties from one another, they could be separated and purified.



When the α-amino acid esters were analyzed, each was found to be a mixture of two diastereomers, in approximately a 50:50 ratio. This result clearly proved that the α-amino acids found in the meteorite fragments were not the result of terrestrial contamination. Two possibilities remained. Either the α-amino acids were formed by random chemical reactions, or they were residues of extraterrestrial life, which, during the long life of the meteorite, had undergone racemization due to exposure to the conditions in outer space. Unfortunately the former, less exciting explanation turned out to have experimental support. When the hydrocarbon fractions of the meteorite's organic compounds were analyzed, their distribution was shown to be the same as the hydrocarbons formed by passing an electric discharge through methane gas. As yet, examination of meteorites has produced no evidence for extraterrestrial life.

See K. Kvenvolden et al., *Nature*, **228**:923 (1970).

A. Chirality in Biomolecules

The generalization that only one of two enantiomers is found in a given biological system and that one enantiomer is metabolized in preference to the other should be enough to convince us that we live in a chiral world. At least, our world is chiral at the molecular level. Essentially all chemical reactions in the biological world take place in a chiral environment. Perhaps the most conspicuous examples of chirality among biological molecules are the enzymes, all of which have multiple stereocenters. An illustration is chymotrypsin, an enzyme that functions very efficiently in the intestines of animals at pH between 7 and 8 in catalyzing the digestion of proteins. Chymotrypsin has 251 stereocenters. The maximum number of stereoisomers possible is 2^{251}, a staggeringly large number almost beyond comprehension. Fortunately, nature does not squander its precious energies and resources unnecessarily; only one of these stereoisomers is produced and used by any given organism.

B. How an Enzyme Distinguishes Between a Molecule and Its Enantiomer

An enzyme catalyzes a biological reaction of molecules by first positioning them at a **binding site** on its surface. These molecules may be held at the binding site by a combination of hydrogen bonds, ionic bonds, dispersion forces, or even covalent bonds.

An enzyme with specific binding sites for three of the four groups on a stereocenter can distinguish between a molecule and its enantiomer or one of its diastereomers. Assume, for example, that an enzyme involved in catalyzing a reaction of glyceraldehyde has three binding sites, one specific for —H, another specific for —OH, and the third specific for —CHO. Assume further that the three sites are arranged on the enzyme surface as shown in Figure 8.9. The enzyme can distinguish (R)-(+)-glyceraldehyde (the natural or biologically active form) from its enantiomer (S)-(−)-glyceraldehyde because the natural enantiomer can be absorbed with three groups attached to their appropriate binding sites; the other enantiomer can, at best, bind to only two of these sites.

Because interactions between molecules in living systems take place in a chiral environment, it should be no surprise that a molecule and its enantiomer or diastereomers have

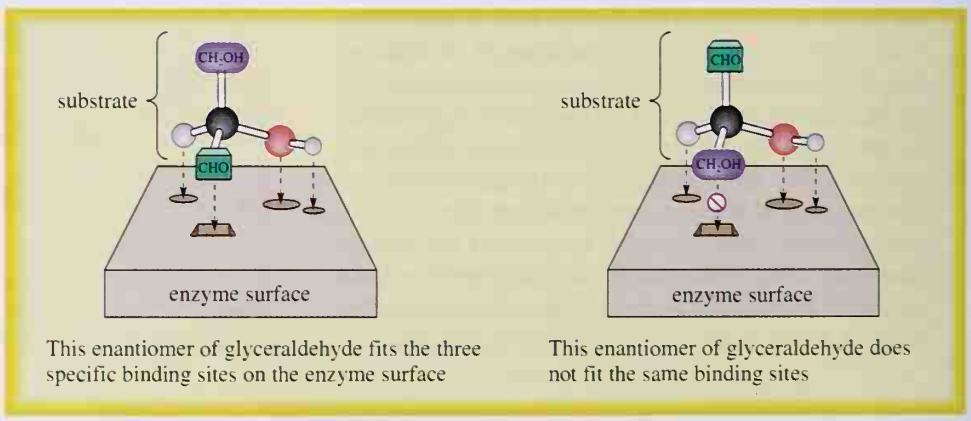
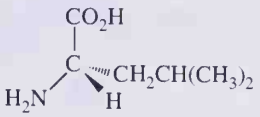
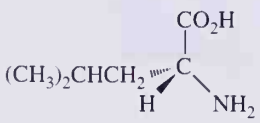


Figure 8.9
Stereospecificity of enzyme-substrate interaction. A schematic diagram of an enzyme surface capable of interacting with (R)-(+)-glyceraldehyde at three binding sites, but with (S)-(−)-glyceraldehyde at only two of these sites.

different physiological properties. It should also come as no surprise that *P. glaucum* selectively metabolizes (+)-tartaric acid, that the tricarboxylic acid cycle (Krebs, or citric acid cycle) produces and then metabolizes only S-(+)-malic acid, or that R-(−)-leucine tastes sweet, whereas its enantiomer S-(+)-leucine has a bitter taste.



(S)-(+)-Leucine
$[\alpha]_D^{23} = +15°$ (c = 2, 5 M HCl)



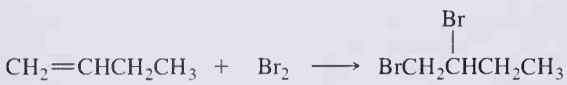
(R)-(−)-Leucine
$[\alpha]_D^{23} = -15°$ (c = 2, 5 M HCl)

That interactions between molecules in the biological world are very specific in stereochemistry is not surprising, but just how these interactions are accomplished at the molecular level with such precision and efficiency is one of the great puzzles that modern science has only recently begun to unravel.

8.11 Molecules Containing Stereocenters as Reactants or Products

As the structure of an organic compound is altered in the course of a reaction, one or more stereocenters, usually at carbon, may be created, inverted, or destroyed. Let us consider several examples of additions, eliminations, and substitutions chosen from the previous chapters to illustrate these possibilities.

Addition of bromine to 1-butene is an example of addition of an achiral reagent (bromine) to an achiral starting material (1-butene) to form a chiral product with one stereocenter.



1-Butene	Bromine	1,2-Dibromobutane
(achiral)	(achiral)	(chiral)

We now ask Is the product one of the two enantiomers or a racemic mixture? Is it optically active or optically inactive? The mechanism for electrophilic addition of bromine to 1-butene is stereoselective. It involves formation of a bridged bromonium ion intermediate (Section 5.3D) in the rate-determining step followed by anti attack of bromide ion on the bridged intermediate. In the first step of addition, reaction with bromine can occur with equal probability from above or below the plane created by the six atoms of the double bond. The bridged bromonium ions thus produced are enantiomers and form a racemic mixture. Attack of bromide ion on carbon 1 from the side opposite that of the bromonium ion bridge gives the final product as a racemic mixture (Figure 8.10).

Addition of bromine to 2-butene gives 2,3-dibromobutane, a molecule with two stereocenters. Three stereoisomers are possible for this compound: a meso compound and a pair of enantiomers. We now ask Is the product one enantiomer, a pair of enantiomers, the meso compound, or a mixture of all three stereoisomers? A partial answer is that the product formed depends on the configuration of the alkene. Let us first examine addition of bromine to *cis*-2-butene.

Attack of bromine on *cis*-2-butene from either face of the planar part of the molecule gives a bridged bromonium ion intermediate. Although this intermediate has two stereocenters, it has a plane of symmetry and is, therefore, meso (Figure 8.11). Attack of Br^- on

Figure 8.10
Anti addition of Br_2 to 1-butene. The product is a racemic mixture and optically inactive.

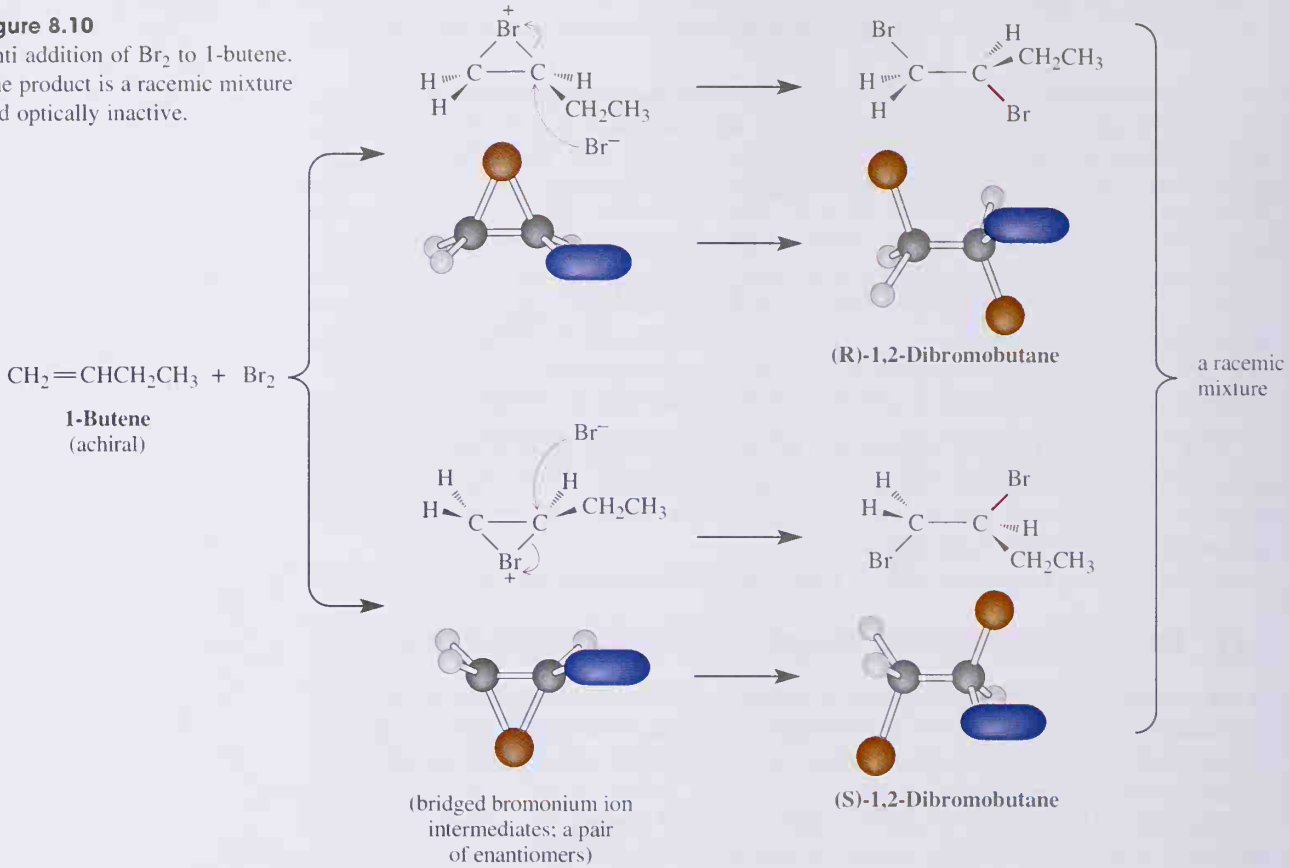
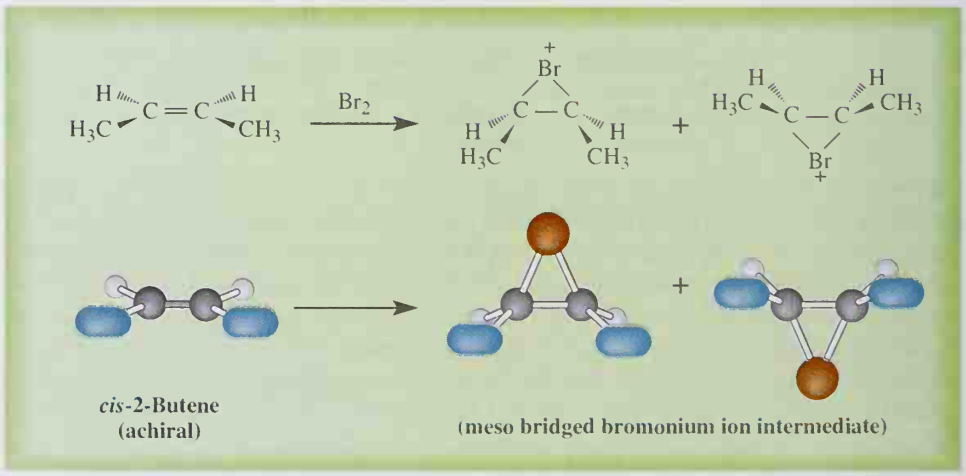


Figure 8.11
Reaction of Br_2 and *cis*-2-butene gives a meso bridged bromonium ion intermediate.



this intermediate from the side opposite that of the bromonium ion bridge gives a pair of enantiomers. The product, 2,3-dibromobutane, is formed as a racemic mixture and is optically inactive (Figure 8.12).

Addition of Br_2 to *trans*-2-butene leads to two enantiomeric bridged bromonium ion intermediates. Attack by Br^- at either carbon atom of either bromonium ion intermediate gives the meso isomer, which is optically inactive (Figure 8.13).

(Text continued p. 302)

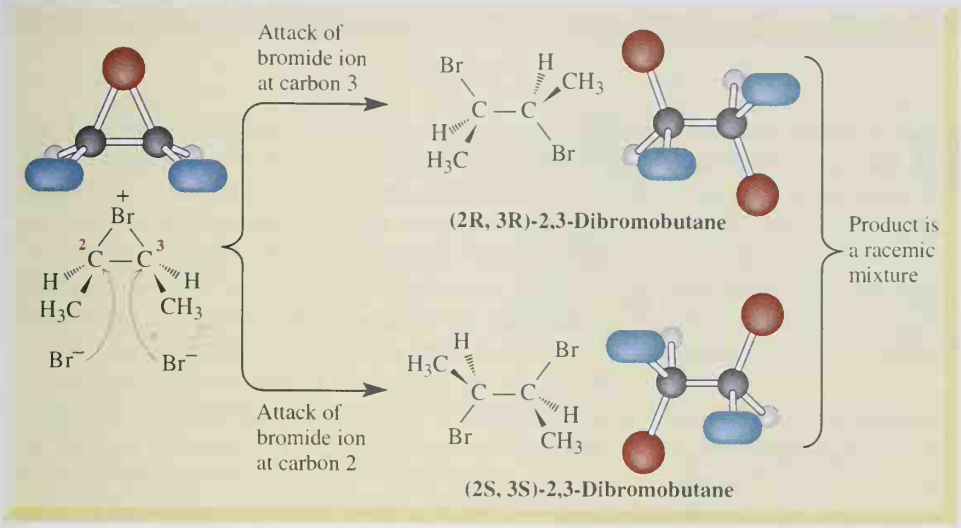


Figure 8.12
Anti addition of Br_2 to *cis*-2-butene gives 2,3-dibromobutane as a racemic mixture.

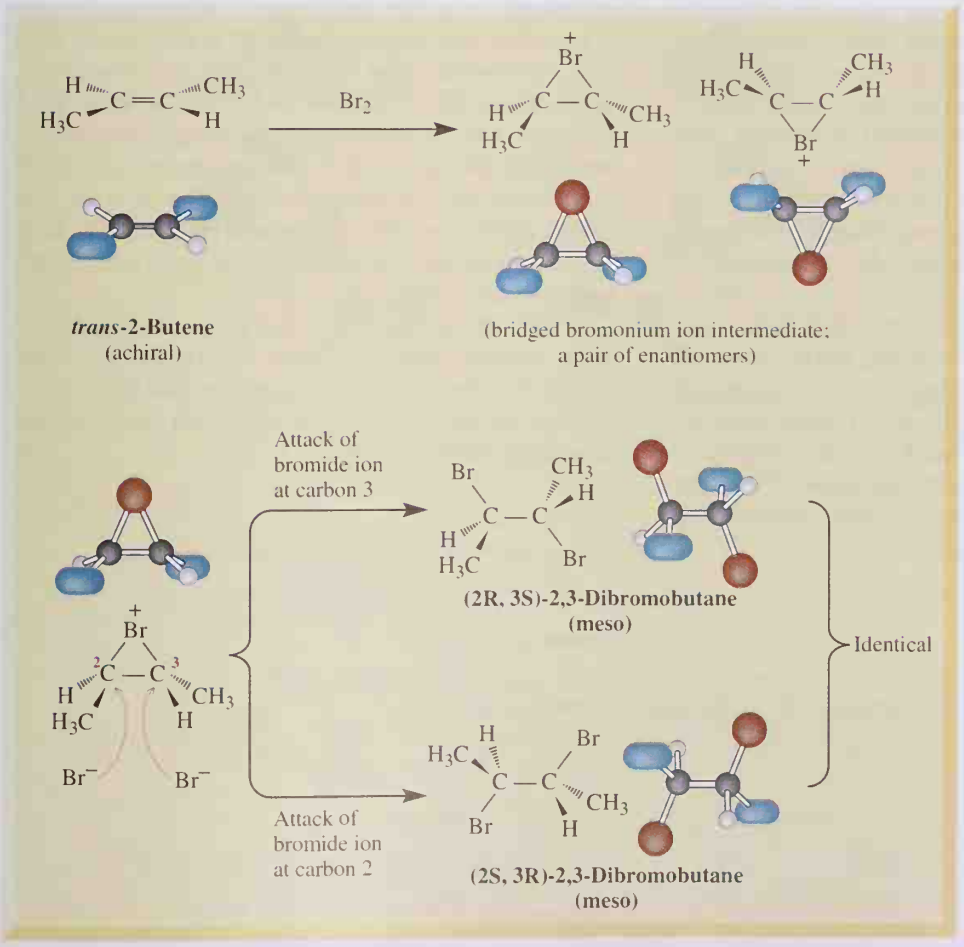


Figure 8.13
Anti addition of Br_2 to *trans*-2-butene gives meso-2,3-dibromobutane.

CHEMISTRY IN ACTION

Chiral Drugs

Some of the common drugs used in human medicine, for example, aspirin, are achiral. Others are chiral and sold as a single enantiomer. The penicillin and erythromycin classes of antibiotics and the drug captopril belong to this class. Captopril, which is very effective for the treatment of high blood pressure and congestive heart failure, was developed in a research program designed to discover effective inhibitors for angiotensin converting enzyme (ACE).

However, a large number of drugs are chiral but are sold as racemates. The popular analgesic ibuprofen is one example. For racemic drugs, most often only one enantiomer exerts the beneficial effect, whereas the other enantiomer either has no effect, or exerts a detrimental effect. Thus, enantiomerically pure drugs should, more often than not, be more effective than their racemic counterparts.

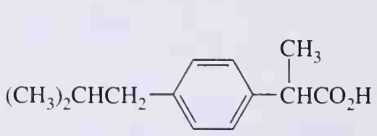
Recently, the U. S. Food and Drug Administration has established new guidelines for the testing and marketing of chiral drugs. After reviewing these guidelines, many drug companies have decided to develop only single enantiomers of new chiral drugs. In addition to regulatory pressure, there are patent considerations. If a company has patents on a racemic drug, a new patent can often be taken out on the individual enantiomers of the racemic mixture.

In the near future, for example, it may be possible to buy the pain reliever ibuprofen (the active ingredient in Motrin, Advil, and many other nonaspirin analgesics) in chiral form. Only the S enatiomer is biologically active, but in the body the R enantiomer is converted to the active S enantiomer. It is not yet known if a chiral formulation for this particular compound is faster acting or superior in some other respect.

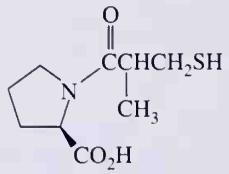
Because it is extremely wasteful to prepare both enantiomers of a drug if only one isomer is marketable, new techniques for chiral synthesis are being developed by organic chemists. One approach is to use enzymes as chiral catalysts for the large-scale synthesis of enantiomerically pure drug precursors. A class of enzymes under study are the lipases, which catalyze the formation of esters from alcohols and carboxylic acid anhydrides. In one resolution, racemic (R,S)-5-norbornen-2-ol is treated with an achiral anhydride in a reaction catalyzed by an (R)-lipase. Because the enzyme is chiral, it selects (2R)-5-norbornen-2-ol preferentially to react with the anhydride, and leaves unreacted (2S)-5-norbornen-2-ol in greater than 98% enantiomeric excess. The unreacted (2S)-alcohol is then separated from the ester. Because this lipase enzyme did not evolve specifically to catalyze reactions of 5-norbornen-2-ol, it is not 100% stereospecific for the 2R enantiomer. In this case, the product of the (R)-lipase-catalyzed reaction is a mixture of 89% (2R)-ester and 11% (2S)-ester. Because all catalysts must catalyze the reverse reaction as well as the forward reaction, the ester product is treated with water and the lipase enzyme. The ester of the (2R)-5-norbornen-2-ol is hydrolyzed preferentially, and (2R)-5-norbornen-2-ol is recovered in greater than 98% enantiomeric excess.

Thus, by this skillful blend of enzymology and creative organic chemistry, both the (R)-alcohol and (S)-alcohol can be recovered in greater than 98% enantiomeric excess and each used as a chiral precursor for enantiomerically pure drugs.

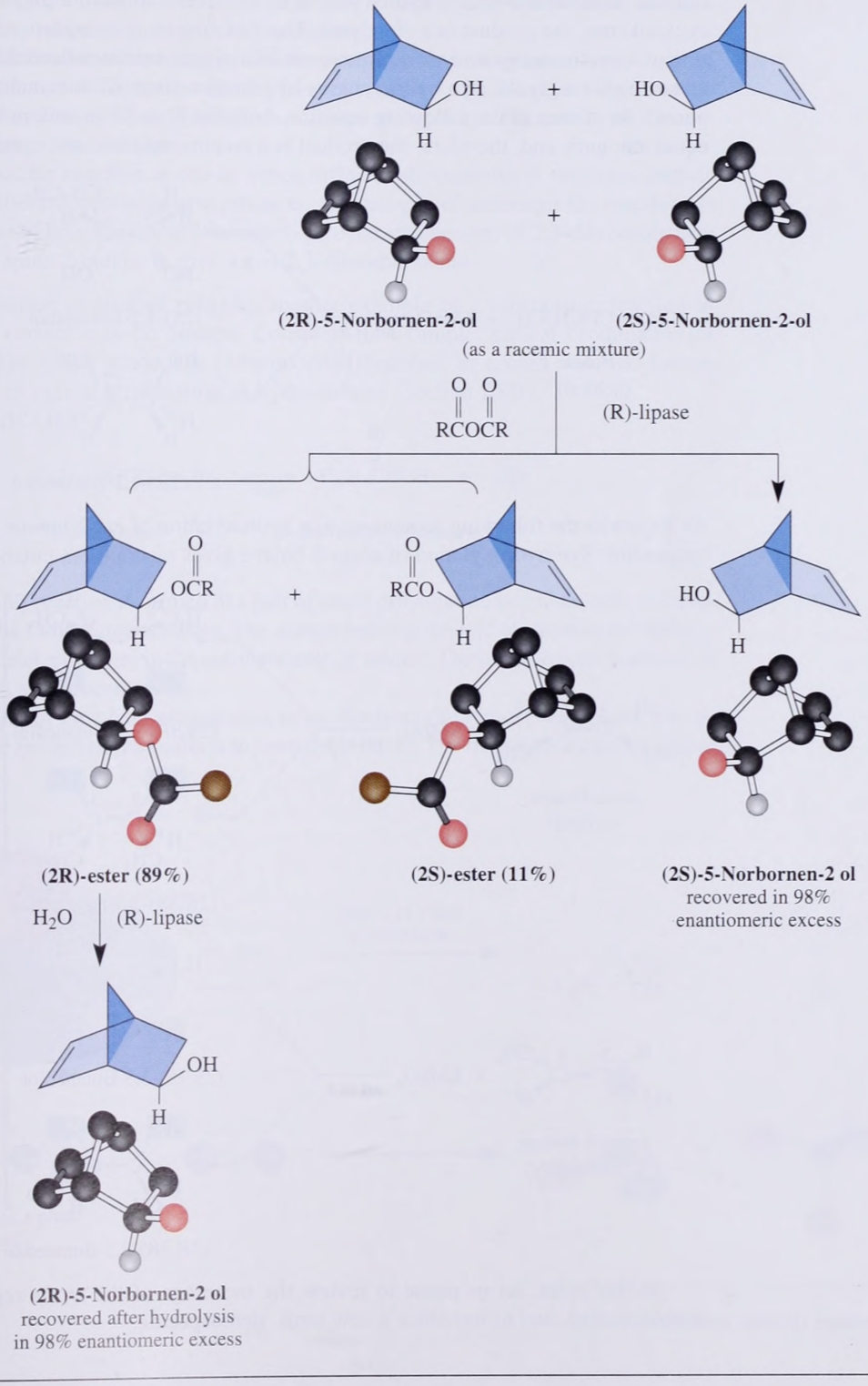
See S. C. Stinson, *Chem. Eng. News*, 46–77 Sept. 28, 1992.



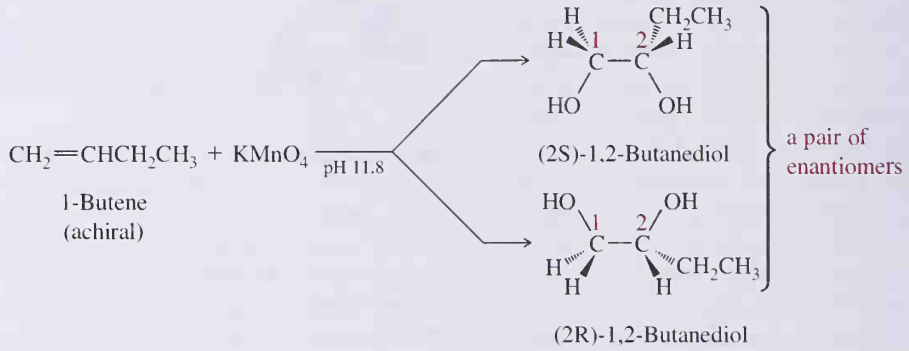
Ibuprofen



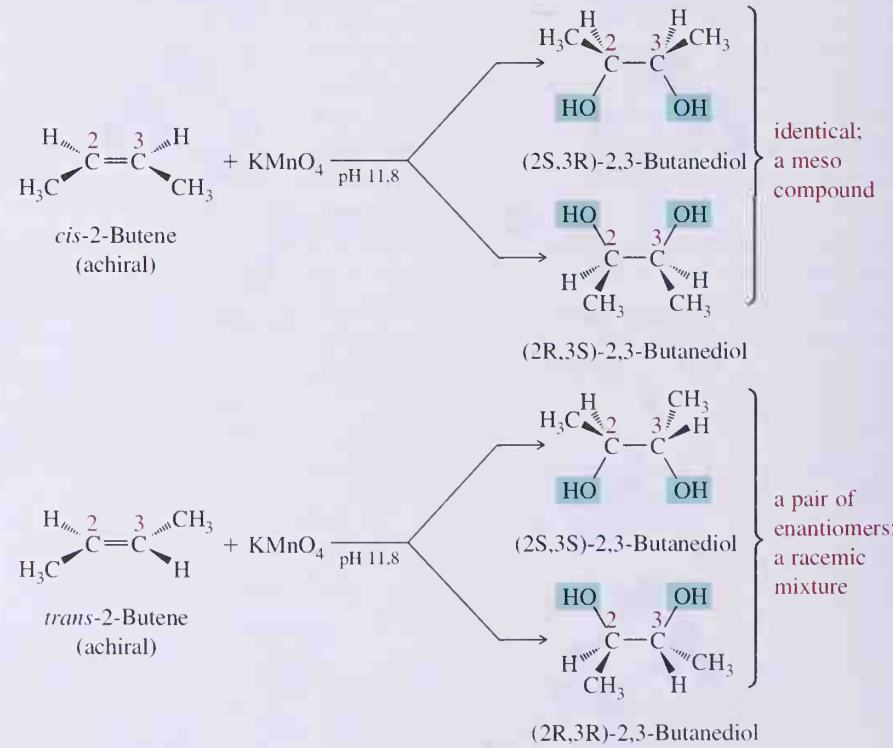
Captopril


OH
H
+
HO
H
+
(2R)-5-Norbornen-2-ol
(2S)-5-Norbornen-2-ol
(as a racemic mixture)
O O
RCOCR
(R)-lipase
O
OCR
H
+
O
RCO
H
HO
H
(2R)-ester (89%)
(2S)-ester (11%)
(2S)-5-Norbornen-2 ol
recovered in 98%
enantiomeric excess
H2O
(R)-lipase
OH
H
(2R)-5-Norbornen-2 ol
recovered after hydrolysis
in 98% enantiomeric excess

In Section 5.7B we studied oxidation of alkenes by potassium permanganate at pH 11.8 and by osmium tetroxide in the presence of hydrogen peroxide. Each of these oxidations is stereoselective: syn hydroxylation of the alkene to form a glycol. In the case of cycloalkenes, the product is a *cis*-glycol. The first step in each oxidation involves formation of a cyclic manganese or osmium-containing intermediate followed by reaction with water to give a glycol. Syn hydroxylation of 1-butene gives 1,2-butanediol, a chiral compound. As shown in the following equation, both the R and S enantiomers are formed in equal amounts, and, therefore, the product is a racemic mixture and optically inactive.



As shown in the following sequences, syn hydroxylation of *cis*-2-butene gives meso-2,3-butanediol. Syn hydroxylation of *trans*-2-butene gives racemic 2,3-butanediol.



At this point, let us pause to review the meanings of the terms regioselective and stereoselective, and to introduce a new term, stereospecific.

A **regioselective reaction** is one in which one location of bond making and bond breaking occurs preferentially over all other possible locations. Examples include hydroboration/oxidation of 1-octene to give 1-octanol and electrophilic addition of HCl to propene to give 2-chloropropane.

A **stereoselective reaction** is one in which one stereoisomer or an enantiomeric pair of stereoisomers is formed or destroyed preferentially over all others that may be formed or destroyed. An example is addition of Br_2 to cyclohexene to give *trans*-1,2-dibromocyclohexane.

A **stereospecific reaction** is one in which different stereoisomeric starting materials give different stereoisomeric products. An example of stereospecific reactions is addition of bromine to *cis*-2-butene to give the enantiomers of 2,3-dibromobutane and to *trans*-2-butene to give meso-2,3-dibromobutane.

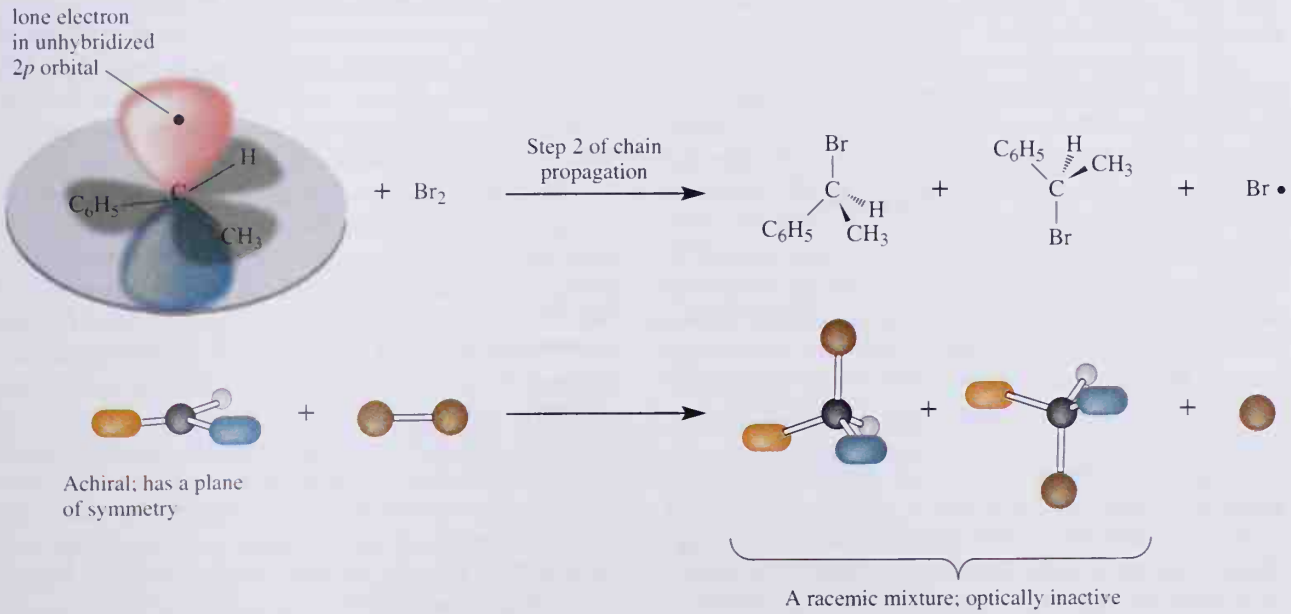
Radical halogenation of alkanes provides another example of a substitution reaction in which a chiral carbon may be created. Consider, for example, radical bromination of ethylbenzene. The major product is (1-bromoethyl)benzene, in accord with the known regioselectivity of radical bromination of hydrocarbons (Section 2.9B).

$$C_6H_5CH_2CH_3 + Br_2 \xrightarrow[\text{heat}]{} C_6H_5\underset{\displaystyle Br}{\underset{|}{C}}HCH_3 + HBr$$

Ethylbenzene (achiral) — (1-Bromoethyl)benzene (chiral)

The product in this reaction is formed in a pair of chain propagation steps, the first of which creates a benzylic radical intermediate. The carbon bearing the odd electron is sp^2-hybridized, and the lone electron lies in the unhybridized $2p$ orbital. The intermediate is achiral; it does not contain a stereocenter.

In the second of the chain propagation steps, the benzylic radical reacts with Br_2 on either face of the sp^2-hybridized carbon to form the product. The transition states leading to



formation of products are of equal energy and therefore the R and S stereoisomers are formed in equal amounts. The product is formed as a racemic mixture and is optically inactive.

A general principle emerges from these examples of addition reactions, oxidation reactions, and radical halogenations. Optical activity is never produced from optically inactive starting materials, even though the products may be chiral. Alternatively, optical activity is generated in a reaction only if at least one of the reactants itself is optically active, or if the reaction is carried out in the presence of a catalyst that is itself chiral and optically active.

SUMMARY

A **stereocenter** (Section 8.2A) is an atom in a molecule at which interchange of two atoms or groups of atoms bonded to that atom produces a different stereoisomer. A carbon atom with four different groups bonded to it is a **tetrahedral stereocenter.** Tetrahedral stereocenters are not limited to carbon. Enantiomers of tetrahedral nitrogen, silicon, phosphorus, and germanium compounds have also been prepared.

A properly substituted trigonal carbon may also be a stereocenter as, for example, carbons 2 and 3 of 2-butene. Interchange of groups on either trigonal carbon of (E)-2-butene gives its diastereomer, (Z)-2-butene.

The presence of one stereocenter is a sufficient condition for chirality, but it is not a necessary condition (Section 8.2C). Chiral molecules lacking stereocenters are properly substituted allenes.

The **configuration** at any stereocenter can be designated by the **Cahn-Ingold-Prelog convention,** known alternatively as the **R-S convention** (Section 8.3). To apply this convention, each atom or group of atoms bonded to the stereocenter is (1) assigned a priority and (2) numbered from highest priority to lowest priority. (3) The molecule is oriented in space so that the group of lowest priority is directed away from the observer, and (4) the remaining three groups are read in order from highest priority to lowest priority. If reading of groups is clockwise, the configuration is **R** (Latin: *rectus*, right hand). If reading of groups is counterclockwise, the configuration is **S** (Latin: *sinister*, left hand).

Light that vibrates in only one plane is said to be **plane-polarized** (Section 8.5A). A **polarimeter** (Section 8.5B) is an instrument used to detect and measure the magnitude of optical activity. **Observed rotation** is the number of degrees the plane of polarized light has been rotated. If the analyzing prism must be turned clockwise to restore the zero point, the compound is **dextrorotatory.** If the analyzing prism must be turned counterclockwise to restore the zero point, the compound is **levorotatory.** Each member of a pair of enantiomers rotates the plane of polarized light an equal number of degrees but opposite in direction (Section 8.5A). Any compound with identical chiral molecules rotates the plane of polarized light and is said to be **optically active. Specific rotation** is the observed rotation measured in a cell of light path 1 dm and at a concentration of 1 g/mL. A **racemic mixture** (Section 8.5C) is a mixture of equal amounts of two enantiomers and has an specific rotation of zero.

For a molecule with n stereocenters, the maximum number of stereoisomers possible is $\mathbf{2^n}$ (Sections 8.4 and 8.6). Certain molecules have special symmetry properties that reduce the number of stereoisomers to fewer than that predicted by the 2^n rule. A compound is **meso** (Section 8.6B) if it contains two or more stereocenters assembled in such a way that its molecules are achiral.

Resolution (Section 8.9) is the experimental process of separating a mixture of enantiomers into the two pure enantiomers. A common chemical means of resolving organic compounds is to treat the racemic mixture with a chiral resolving agent that converts the mixture of enantiomers into a pair of diastereomers. Diastereomers are different compounds, have different physical properties, and can be separated based on these differences in physical properties. Once the diastereomers are separated, each diastereomer is then converted back to a pure enantiomer.

Enzymes catalyze biological reactions by first positioning the molecule or molecules at binding sites and holding them there by a combination of hydrogen bonds, ionic bonds, dispersion forces, and covalent bonds. An en-

zyme with specific binding sites for three of the four groups on a stereocenter can distinguish between a molecule and its enantiomer (Section 8.10).

In the course of chemical reactions, optical activity can never be produced from optically inactive starting materials, even though the products may be chiral (Section 8.10). Conversely, optical activity is generated in a reaction only if at least one of the reactants is optically active, or if the reaction is carried out in the presence of a catalyst which is itself chiral and optically active.

ADDITIONAL PROBLEMS

Chirality

8.8 Think about the helical coil of a telephone cord or a spiral binding and suppose that you view the spiral from one end and find that it is a left-handed twist. If you view the same spiral from the other end, do you find it to be a right-handed twist, or is it a left-handed twist from that end as well?

8.9 Next time you have the opportunity to view a collection of whelks, augers, or other sea shells that have a helical twist, study the chirality of their twists. Do you find an equal number of left-handed and right-handed whelks, or are they all or mostly all of one chirality? What about the chirality of whelks compared with augers and other spiral shells?

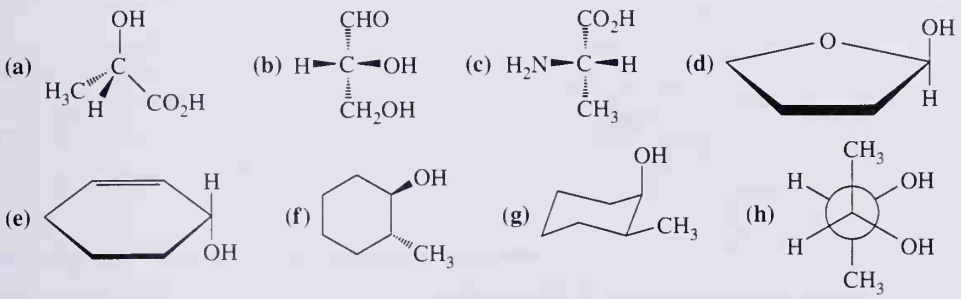
8.10 One reason we can be sure that sp^3-hybridized carbon atoms are tetrahedral is the number of stereoisomers that can exist for different organic compounds.

(a) How many stereoisomers are possible for $CHCl_3$, CH_2Cl_2, and CHClBrF if the four bonds to carbon have a tetrahedral geometry?

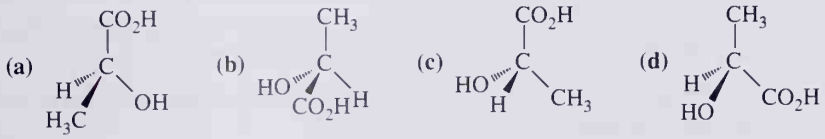
(b) How many stereoisomers are possible for each of these compounds if the four bonds to carbon have a square planar geometry?

Enantiomers

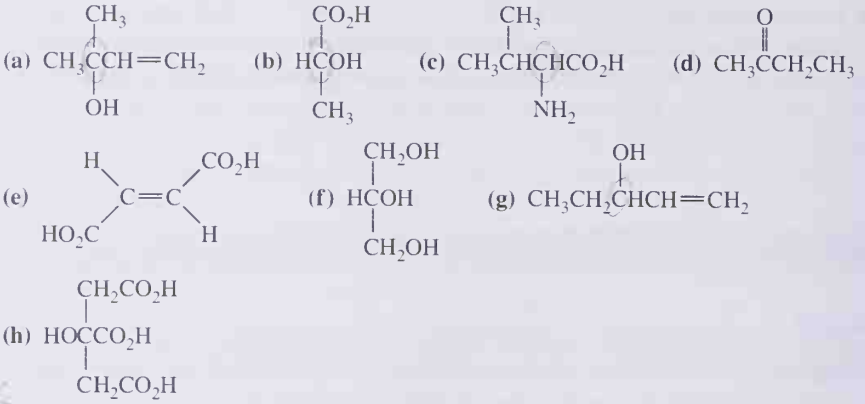
8.11 Draw mirror images for these molecules:



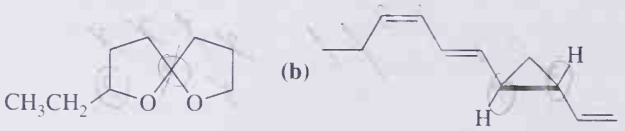
8.12 Following are several stereorepresentations for lactic acid. Take (a) as a reference structure. Which of the stereorepresentations are identical with (a) and which are mirror images of (a)?



8.13 Mark each stereocenter in the following molecules with an asterisk. How many stereoisomers are possible for each molecule?



8.14 Following are structural formulas of two natural products recently synthesized in the laboratory by Theodore Cohen of the University of Pittsburgh. How many stereoisomers are possible for each compound? Explain how you arrived at your answer.



A pheromone of the Norway spruce beetle

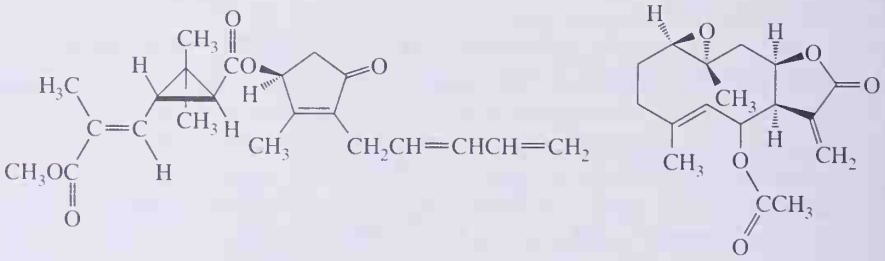
Dictyopterene B (a marine gamete attractant)

8.15 Following are structural formulas for two natural products isolated from plants of the chrysanthemum family. Pyrethrin II is a natural insecticide and is marketed as such.

(a) Label all tetrahedral stereocenters in each molecule and all carbon-carbon double bonds about which there is the possibility for *cis-trans* isomerism.

(b) State the number of stereoisomers possible for each molecule.

(c) Show that pyrethrosin is a sesquiterpene composed of three isoprene units.



Pyrethrin II

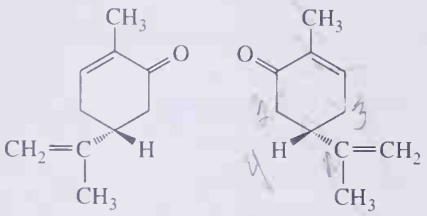
Pyrethrosin

8.16 *Trans*-cyclooctene has been resolved, and its enantiomers are stable at room temperature. *Trans*-cyclononene has also been resolved, but it racemizes with a half-life of 4 min at 0°C. How can racemization of this cycloalkene take place without breaking any bonds? Why does *trans*-cyclononene racemize under these conditions but *trans*-cyclooctene does not?

8.17 Show that butane in a gauche conformation is chiral. Do you expect that resolution of butane at room temperature is possible?

Absolute Configuration: The R-S Convention

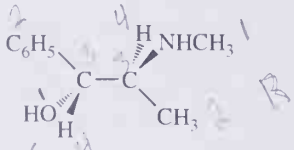
8.18 Following are structural formulas for the enantiomers of carvone. Each has a distinctive odor characteristic of the source from which it can be isolated. Assign an R-S configuration to each enantiomer.



(−)-Carvone
$[\alpha]_D^{20} = -62.5°$
(spearmint oil)

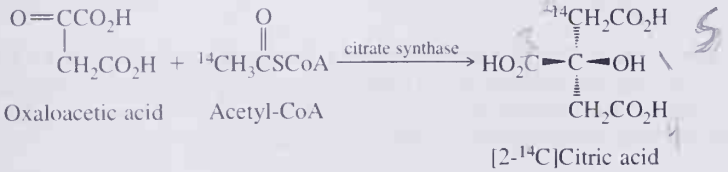
(+)-Carvone
$[\alpha]_D^{20} = +62.5°$
(caraway oil)

8.19 An organic base widely used as a chiral resolving agent is ephedrine. For centuries, Chinese herbal medicine has used extracts of *Ephedra sinica* to treat asthma. Phytochemical investigation of this plant resulted in isolation of ephedrine, a very potent dilator of the air passages of the lungs. The naturally occurring stereoisomer is levorotatory and has the following configuration. Assign an R-S configuration to each stereocenter.



Ephedrine
$[\alpha]_D^{21} = -41°$

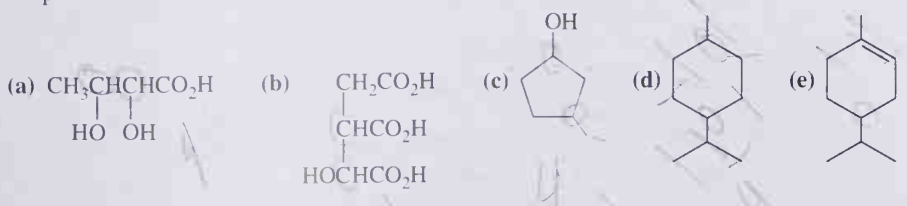
8.20 When oxaloacetic acid and acetyl coenzyme A (acetyl-CoA) labeled with radioactive carbon-14 in position 2 are incubated with citrate synthase, an enzyme of the TCA cycle, only the following enantiomer of [2-^{14}C]-citric acid is formed. Note that citric acid containing only ^{12}C is achiral. Assign an R-S configuration to this enantiomer of [2-^{14}C] citric acid.

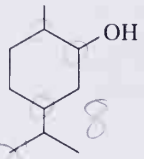


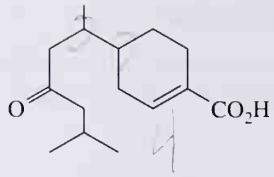
Oxaloacetic acid + Acetyl-CoA → [2-^{14}C]Citric acid

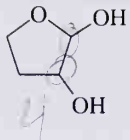
Molecules with Two or More Stereocenters

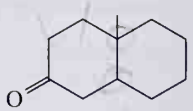
8.21 Mark each stereocenter in the following molecules with an asterisk. How many stereoisomers are possible for each molecule?



(f) 

(g) 

(h) 

(i) 

8.22 Draw the structural formula for at least one bromoalkene of molecular formula C_5H_9Br that shows:

(a) Neither E-Z isomerism nor enantiomerism

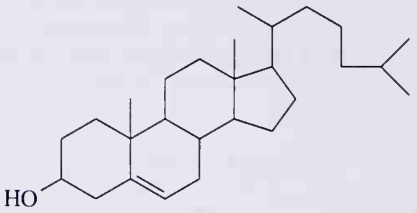
(b) E-Z isomerism but not enantiomerism

(c) Enantiomerism but not E-Z isomerism

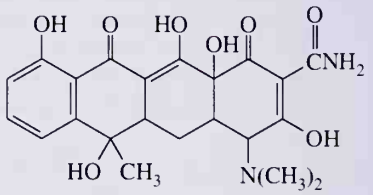
(d) Both enantiomerism and E-Z isomerism

8.23 Following are several molecules isolated from natural systems. Each is isolated as a single stereoisomer with the specific rotation given. Mark all stereocenters and state the maximum number of stereoisomers possible for each molecule.

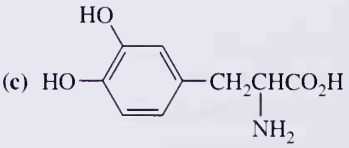
Scotch pine, *Pinus sylvestris.*
(Andrew Henderson: PHOTO/NATS)

(a) 

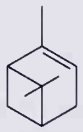
Cholesterol $[\alpha]_D^{24} = +15°$

(b) 

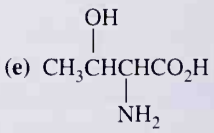
Tetracycline $[\alpha]_D^{25} = +225°$

(c) 

L-Dopa
3-(3,4-Dihydroxyphenyl)alanine
$[\alpha]_D^{27} = -11.5°$

(d) 

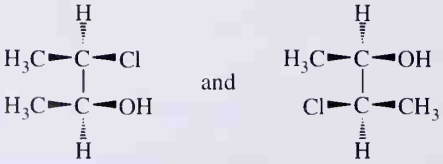
α-Pinene
$[\alpha]_D^{21} = +50.7°$

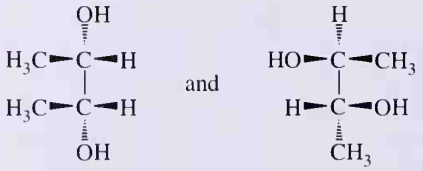
(e) 

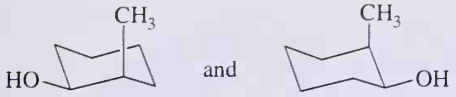
Threonine
$[\alpha]_D^{20} = -27.4°$

8.24 If the optical rotation of a new compound is measured and found to have a specific rotation of 40°, how can you tell if the actual rotation is not really 40° plus some multiple of 360° (that is, the rotation is not actually $40 + (n \times 360)°$, where n has only integer values). That is, how can you tell if the rotation is not actually a value such as 400° or 760°?

8.25 Are the formulas within each set identical, enantiomers, or diastereomers?

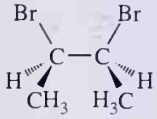
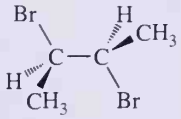
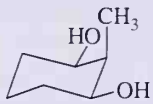
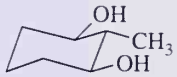
(a) 

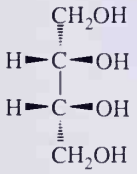
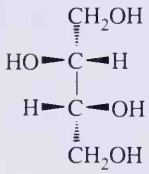
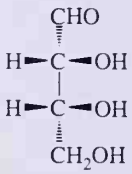
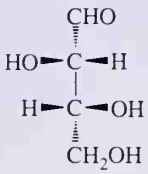
(b) 

(c)  and

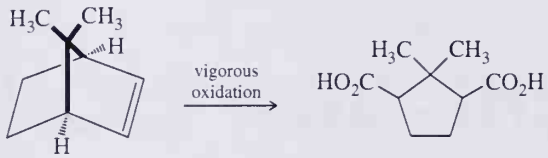
(d)  and 

8.26 Which of the following are meso compounds?

(a)  (b)  (c)  (d) 

(e)  (f)  (g)  (h) 

8.27 Vigorous oxidation of the following bicycloalkene of known configuration gives 2,2-dimethylcyclopentane-1,3-dicarboxylic acid. Assume that the conditions of oxidation have no effect on the stereocenters of either the starting bicycloalkene or the resulting dicarboxylic acid. Is the dicarboxylic acid one enantiomer, a racemic mixture, or a meso compound?



(1R,4S)-7,7-Dimethylbicyclo[2.2.1]hept-2-ene

2,2-Dimethylcyclopentane-1,3-dicarboxylic acid

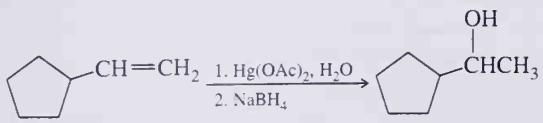
Reactions that Produce Chiral Compounds

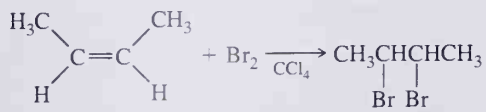
8.28 In each of the following reactions, the organic starting material is achiral. The structural formula of the product is given. For each product state:

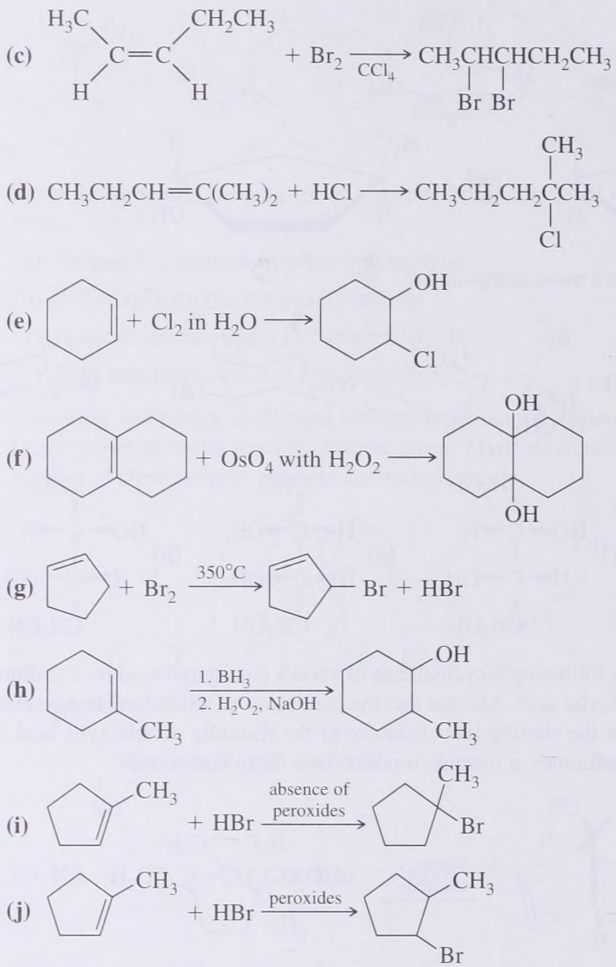
(1) How many stereoisomers are possible?

(2) Which of the possible stereoisomers is/are formed in the reaction shown?

(3) Determine whether the product is optically active or optically inactive.

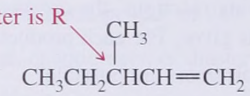
(a) 

(b) 



8.29 A long polymer chain, such as polyethylene $+CH_2CH_2+_n$, can potentially exist in solution as a chiral object. Give two examples of chiral secondary structures that a polyethylene chain could adopt.

8.30 State the number and kind of stereoisomers formed when (R)-3-methyl-1-pentene is treated with the following reagents.



(a) $Hg(OAc)_2$, H_2O followed by $NaBH_4$ **(b)** H_2/Pt
(c) BH_3 followed by H_2O_2 in NaOH **(d)** Br_2 in CCl_4

A race car fueled by methanol. (Herbert Eisenberg, Superstock)

9

ALCOHOLS AND THIOLS

In this chapter, we study the physical and chemical properties of alcohols, a class of compounds containing a hydroxyl (—OH) group bonded to a saturated carbon.

R—OH

An alcohol

Alcohols are widely distributed in nature. They are also important in laboratory transformations of organic compounds. Alcohols, for example, can be converted to several other types of compounds, including alkyl halides, aldehydes, ketones, and carboxylic acids. Not only can they be converted to these compounds, they can also be prepared from them. Thus, alcohols play a central role in the interconversion of organic compounds.

In this chapter, we also study thiols, a class of compounds containing a sulfhydryl (—SH) group bonded to a saturated carbon.

R—SH

A thiol

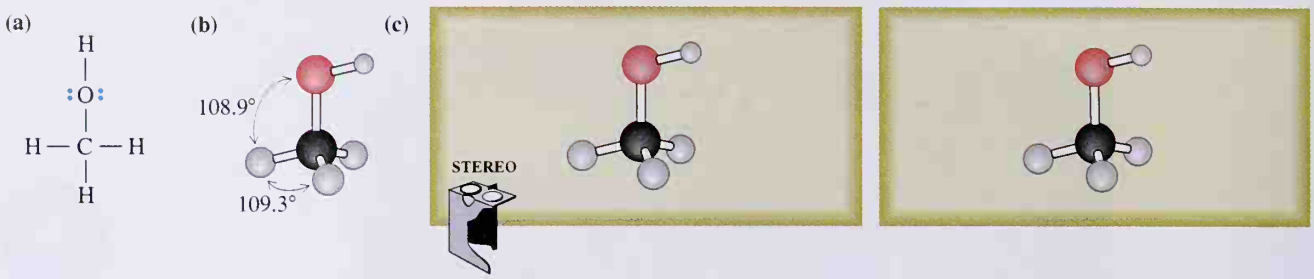


Figure 9.1
Structure of methanol, CH_3OH. (a) Lewis structure, (b) ball-and-stick model, and (c) stereopair.

Because sulfur and oxygen are both Group VI elements, thiols and alcohols undergo many of the same types of reactions. Sulfur, a third-period element, can expand its valence shell to include more than eight electrons and, therefore, thiols undergo some reactions that are not possible for alcohols.

9.1 Structure of Alcohols and Thiols

The characteristic structural feature of an alcohol is an **—OH (hydroxyl) group** bonded to an sp^3-hybridized carbon. Figure 9.1 shows a Lewis structure and a ball-and-stick model of methanol, CH_3OH, the simplest alcohol. The measured H—O—C bond angle in methanol is 108.9°, a value very close to the predicted tetrahedral angle of 109.5°.

The sulfur analog of an alcohol is called a **thiol** (thi- from the Greek: *theion*, sulfur) or, in the older literature, a **mercaptan.** The characteristic structural feature of a thiol is an **—SH (sulfhydryl) group.** Figure 9.2 shows a Lewis structure and a ball-and-stick

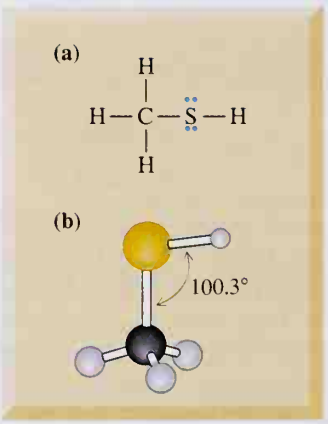


Figure 9.2
Structure of methanethiol, CH_3SH. (a) Lewis structure and (b) ball-and-stick model.

model of methanethiol, CH_3SH, the simplest thiol. The C—S—H bond angle in methanethiol is 100.3°. By way of comparison, the H—S—H bond angle in H_2S is 93.3°. If a sulfur atom is bonded to two other atoms by overlap of sp^3 hybrid orbitals, bond angles about sulfur would be approximately 109.5°; if instead a sulfur atom is bonded to two other atoms by overlap of $2p$ orbitals, bond angles would be approximately 90°. The fact that the C—S—H bond angle in methanethiol is 100.3° and the H—S—H bond angle in H_2S is 93.3° indicates that there is considerably more p character to the bonding orbitals of divalent sulfur than there is to those of divalent oxygen.

Both oxygen and sulfur are in Column VIA of the periodic table, and each has six electrons in its valence shell. For oxygen, the valence electrons are in the second principal energy level whereas for sulfur they are in the third principal energy level. Because sulfur has one more energy level of electrons than oxygen, atoms of sulfur are larger than those of oxygen. The covalent radius of divalent sulfur is approximately 0.104 nm, and that of divalent oxygen is only 0.0660 nm.

9.2 Nomenclature

Alcohols and thiols are named according to rules of the IUPAC system. Many alcohols and thiols, however, are still referred to by their common names.

A. Alcohols

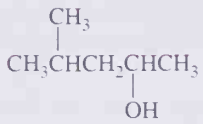
In the IUPAC system, the longest chain of carbon atoms containing the —OH group is selected as the parent compound and numbered from the end closer to —OH. To show that the compound is an alcohol, the suffix **-e** of the corresponding alkane is changed to **-ol** (Section 2.5), and a number is added to show the location of the —OH group. The location of the —OH group takes priority over alkyl groups and halogens in numbering the parent chain.

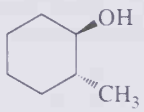
Common names for alcohols are derived by naming the alkyl group attached to —OH and then adding the word "alcohol." Figure 9.3 gives IUPAC names and, in parentheses, common names for several low-molecular-weight alcohols.

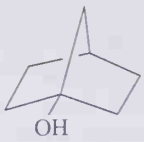
Figure 9.3
Names and structural formulas of several low-molecular-weight alcohols.

EXAMPLE 9.1

Write IUPAC names for the following alcohols:

(a) 

(b) 

(c) 

Solution

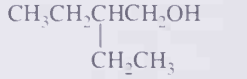
(a) The five-carbon chain is numbered so that —OH is on carbon 2. The name of this alcohol is 4-methyl-2-pentanol.

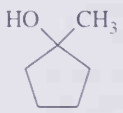
(b) In cyclic alcohols, the carbon atoms of the ring are numbered starting with the carbon bearing the —OH group. Because the —OH is automatically on carbon 1, there is no need to give a number to show its location. The name of this alcohol is *trans*-2-methylcyclohexanol.

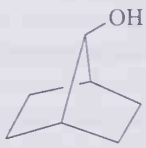
(c) Number this bicycloalkanol starting with the bridgehead carbon bearing the —OH as carbon 1. Its name is bicyclo[2.2.1]-1-heptanol.

PROBLEM 9.1

Give IUPAC names for the following alcohols:

(a) 

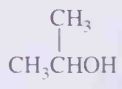
(b) 

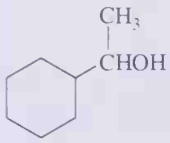
(c) 

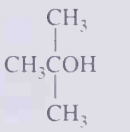
We classify alcohols as **primary (1°), secondary (2°),** or **tertiary (3°)** depending on whether the —OH group is on a primary carbon, a secondary carbon, or a tertiary carbon (Section 2.3C). General formulas of 1°, 2°, and 3° alcohols are given in Figure 9.4.

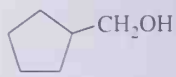
EXAMPLE 9.2

Classify each alcohol as primary, secondary, or tertiary:

(a) 

(b) 

(c) 

(d) 

Solution

(a) A secondary (2°) alcohol

(b) A secondary (2°) alcohol.

(c) A tertiary (3°) alcohol

(d) A primary (1°) alcohol

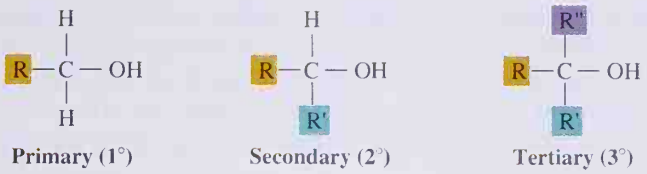
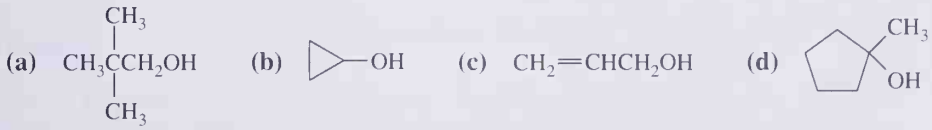


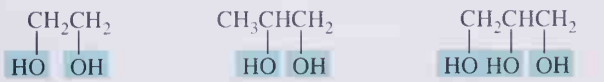
Figure 9.4
Classification of alcohols: primary, secondary, and tertiary.

PROBLEM 9.2

Classify each alcohol as primary, secondary, or tertiary.



In the IUPAC system, a compound containing two hydroxyl groups is called a **diol,** one containing three hydroxyl groups is called a **triol,** and so on. Yet as with many organic compounds, common names have persisted. Compounds containing two hydroxyl groups on adjacent carbons are often referred to as glycols (Section 5.7B). Ethylene glycol and propylene glycol are synthesized from ethylene and propylene, respectively; hence their common names. Under each of the following examples is given its IUPAC name and, in parentheses, its common name. Note that in IUPAC names for diols, triols, and so forth, the final -e (the suffix) of the parent alkane name is retained.



1,2-Ethanediol (Ethylene glycol)

1,2-Propanediol (Propylene glycol)

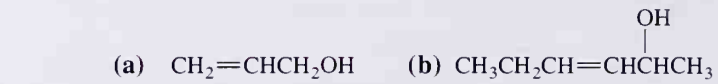
1,2,3-Propanetriol (Glycerol, glycerin)

Ethylene glycol is the major component in commercial antifreezes. *(© Dan McCoy, Rainbow)*

Compounds containing —OH and C=C groups are named as alcohols, and the parent alkane is numbered to give the —OH group the lowest possible number. The double bond is shown by changing the infix of the parent alkane from -an- to -en-, and the alcohol is shown by changing the suffix of the parent alkane from -e to -ol (Section 2.5). Numbers must be used to show the location of both the carbon-carbon double bond and the hydroxyl group.

EXAMPLE 9.3

Write IUPAC names for the following unsaturated alcohols:



(a) $CH_2{=}CHCH_2OH$ **(b)** $CH_3CH_2CH{=}CHCHCH_3$ (OH on the CHCH$_3$ carbon)

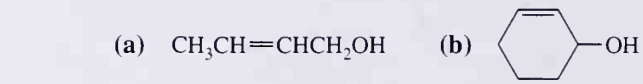
Solution

(a) The propane chain is numbered so that the —OH group is on carbon 1, and the double bond is between carbons 2 and 3. The IUPAC name of this primary unsaturated alcohol is 2-propen-1-ol. Its common name is allyl alcohol.

(b) Because the parent chain contains six carbons, this compound is named as a derivative of hexane. Its IUPAC name is 3-hexen-2-ol.

PROBLEM 9.3

Write IUPAC names for the following unsaturated alcohols:



(a) $CH_3CH{=}CHCH_2OH$ **(b)** cyclohexene with —OH

B. Thiols

According to the IUPAC system, thiols are named by selecting as the parent alkane the longest chain of carbon atoms that contains the —SH group. To show that the compound is a thiol, the final -e in the name of the parent alkane is retained and the suffix **-thiol** is added. A number must be used to locate the —SH group on the parent chain. The location of the —SH group takes priority over alkyl groups and halogens in numbering the parent chain.

In the common system of nomenclature, a thiol is known as a **mercaptan.** Common names for simple thiols are derived by naming the alkyl groups attached to —SH and then adding the word "mercaptan." Figure 9.5 lists IUPAC names and, in parentheses, common names for several low-molecular-weight thiols. In compounds containing other functional groups of higher priority, the presence of an —SH group is indicated by the prefix **mercapto-.** According to the IUPAC system, an —OH takes precedence over —SH in both numbering and naming.

Figure 9.5
Names and structural formulas for several low-molecular-weight thiols.

CH_3CH_2SH — **Ethanethiol (Ethyl mercaptan)**

$CH_3CH_2CH_2CH_2SH$ — **1-Butanethiol (Butyl mercaptan)**

CH_3CHCH_2SH (CH_3 branch) — **2-Methyl-1-propanethiol (Isobutyl mercaptan)**

$HSCH_2CH_2SH$ — **1,2-Ethanedithiol (Ethylene dimercaptan)**

$HSCH_2CH_2OH$

2-Mercaptoethanol

9.3 Physical Properties

Even though sulfur and oxygen are both Group VI elements, the physical properties of alcohols and thiols are quite different. These differences arise because of the high degree of polarity of an O—H bond compared with the very low degree of polarity of an S—H bond.

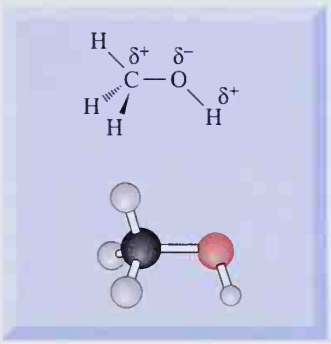


Figure 9.6
Polarity of the C—O—H bonds in alcohols.

A. Alcohols

Because of the presence of the —OH group, alcohols are polar compounds. Oxygen is more electronegative than either carbon or hydrogen, and, therefore, partial positive charges occur on carbon and hydrogen and a partial negative charge occurs on oxygen (Figure 9.6). The attraction between the positive end of one dipole and the negative end of another is called **dipole-dipole interaction.** When the positive end of one of the dipoles is a hydrogen atom bonded to a very electronegative atom (most commonly F, O, or N), the attractive interaction between dipoles is particularly strong and is given the special name of **hydrogen bonding.** The length of a hydrogen bond in water is 0.177 nm, about 80% longer than a covalent O—H bond. The energy of hydrogen bonding in water is approximately 5 kcal/mol. This value may seem small when compared with single covalent bonds (60–100 kcal/mol), but remember that hydrogen bonding is additive. The sum of multiple hydrogen bonds in nucleic acids, proteins, and carbohydrates provides one of the major forces in stabilizing particular conformations of these and other biological macromolecules and making life as we know it possible.

Extensive hydrogen bonding also exists between the partially negative oxygen atoms and partially positive hydrogen atoms of alcohols. Figure 9.7 shows the association of

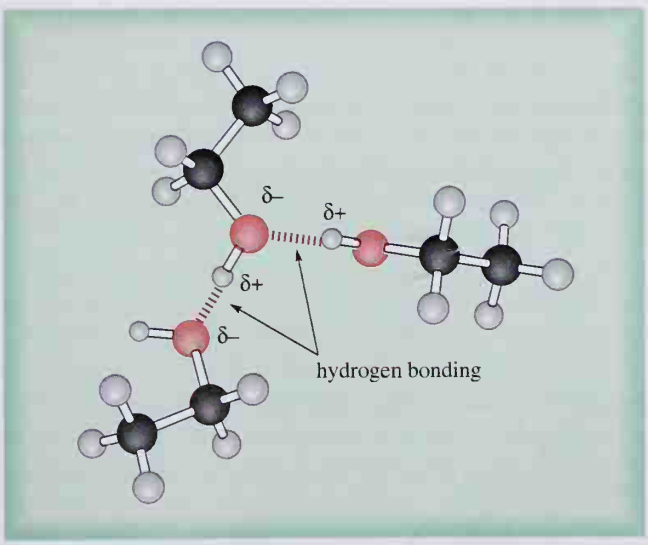


Figure 9.7
The association of ethanol in the liquid state. Each O—H can participate in up to three hydrogen bonds (one through hydrogen and two through oxygen). Only two of the three possible hydrogen bonds per molecule are shown.

Table 9.1 Boiling points and solubilities in water of several groups of alcohols and hydrocarbons of similar molecular weight

Structural Formula	Name	Molecular Weight	bp (°C)	Solubility in Water
CH_3OH	methanol	32	65	infinite
CH_3CH_3	ethane	30	−89	insoluble
CH_3CH_2OH	ethanol	46	78	infinite
$CH_3CH_2CH_3$	propane	44	−42	insoluble
$CH_3CH_2CH_2OH$	1-propanol	60	97	infinite
$CH_3CH_2CH_2CH_3$	butane	58	0	insoluble
$CH_3CH_2CH_2CH_2OH$	1-butanol	74	117	8 g/100 g
$CH_3CH_2CH_2CH_2CH_3$	pentane	72	36	insoluble
$CH_3CH_2CH_2CH_2CH_2OH$	1-pentanol	88	138	2.3 g/100 g
$HOCH_2CH_2CH_2CH_2OH$	1,4-butanediol	90	230	infinite
$CH_3CH_2CH_2CH_2CH_2CH_3$	hexane	86	69	insoluble

ethanol molecules by hydrogen bonding in the liquid state. Table 9.1 lists the boiling points and solubilities in water for several groups of alcohols and hydrocarbons of similar molecular weights. Of the groups of compounds compared in Table 9.1, alcohols have the higher boiling points because additional energy is needed to overcome the attractive forces of hydrogen bonding between their polar —OH groups. The presence of additional hydroxyl groups in a molecule further increases the significance of hydrogen bonding, as can be seen by comparing the boiling points of hexane (bp 69°C), 1-pentanol (bp 138°C), and 1,4-butanediol (bp 230°C), all of which have approximately the same molecular weight. Because of increased dispersion forces between larger molecules, boiling points of all types of molecules, including alcohols, increase with increasing molecular weight. To see this, compare the boiling points of ethanol, 1-propanol, 1-butanol, and 1-pentanol.

The effect of hydrogen bonding in alcohols is illustrated dramatically by comparing the boiling points of ethanol (bp 78°C) and its constitutional isomer dimethyl ether (bp −24°C). The difference in boiling points between these two compounds is due to the presence of a polar O—H group in the alcohol. Alcohol molecules are interconnected by hydrogen bonding; ether molecules are not.

CH_3CH_2OH	CH_3OCH_3
Ethanol (bp 78°C)	Dimethyl ether (bp −24°C)

Because alcohols can interact by hydrogen bonding with water, they are more soluble in water than are alkanes of comparable molecular weight. Methanol, ethanol, and 1-propanol are soluble in water in all proportions. As molecular weight increases, the physical properties of alcohols become more like those of hydrocarbons of comparable molecular weight. Alcohols of higher molecular weight are much less soluble in water because of the

increase in size of the hydrocarbon portion of the molecule. For example, 1-decanol is insoluble in water but is soluble in ethanol and in nonpolar hydrocarbon solvents, such as benzene and hexane.

EXAMPLE 9.4

Arrange the following compounds in order of increasing boiling points. Explain the basis for your answer.

CH_3CH_2OH	CH_3CH_2Cl	$CH_3CH_2CH_3$
Ethanol	Chloroethane	Propane

Solution

Propane is a nonpolar hydrocarbon and the only interactions between molecules in the pure liquid are dispersion forces (Section 2.8). Ethanol is a polar compound, and extensive hydrogen bonding occurs between ethanol molecules in the pure liquid; therefore, ethanol has a higher boiling point than propane. Chloroethane has a higher molecular weight than ethanol and is a polar molecule. However, because its molecules cannot associate by hydrogen bonding, chloroethane has a boiling point lower than that of ethanol. In order of increasing boiling point, the compounds are

$CH_3CH_2CH_3$	CH_3CH_2Cl	CH_3CH_2OH
bp $-42°C$ (MW 44.1)	bp $12°C$ (MW 64.5)	bp $78°C$ (MW 46.1)

PROBLEM 9.4

Arrange the following compounds in order of increasing boiling point. Explain the basis for your answer.

$CH_3OCH_2CH_2OCH_3$ $HOCH_2CH_2OH$ $CH_3OCH_2CH_2OH$

EXAMPLE 9.5

Arrange the following compounds in order of increasing solubility in water. Explain the basis of your answer.

$CH_3CH_2CH_2CH_2CH_2CH_3$ $HOCH_2CH_2CH_2CH_2OH$ $CH_3CH_2CH_2CH_2CH_2OH$

Solution

Hexane, C_6H_{14}, a nonpolar hydrocarbon, has the lowest solubility in water. Both 1-pentanol and 1,4-butanediol are polar compounds due to the presence of —OH groups, and each interacts with water molecules by hydrogen bonding. Because 1,4-butanediol has more sites within the molecule for hydrogen bonding than does 1-pentanol, it is more soluble in water than 1-pentanol. The water solubilities of these compounds are given in Table 9.1.

$CH_3CH_2CH_2CH_2CH_2CH_3$	$CH_3CH_2CH_2CH_2CH_2OH$	$HOCH_2CH_2CH_2CH_2OH$
Insoluble	2.3 g/100 g water	Infinitely soluble

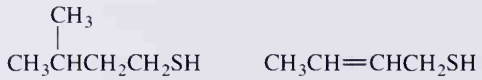
PROBLEM 9.5

Arrange the following compounds in order of increasing solubility in water:

$ClCH_2CH_2Cl$ $CH_3CH_2CH_2OH$ $CH_3CH_2CH_2CH_2OH$

B. Thiols

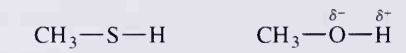
The most outstanding physical characteristic of low-molecular-weight thiols is their stench. The scent of skunks is due primarily to two thiols: 3-methyl-1-butanethiol and 2-butene-1-thiol.



3-Methyl-1-butanethiol 2-Butene-1-thiol

Traces of low-molecular-weight thiols, most commonly butyl mercaptan, are added to natural gas so that gas leaks can be detected by the smell of the thiol.

The physical properties of thiols are quite different from those of alcohols, primarily because of the large difference in polarity of the O—H bond compared with the S—H bond. The electronegativities of sulfur and hydrogen are almost identical, and the S—H bond is essentially nonpolar covalent. In comparison, the electronegativity difference between oxygen and hydrogen is 0.9 (3.0 − 2.1), and the O—H bond is polar covalent.



S—H is a nonpolar covalent bond O—H is a polar covalent bond

Because of the very low polarity of the S—H bond, thiols show little association by hydrogen bonding. Consequently, they have lower boiling points and are less soluble in

The scent of the spotted skunk is a mixture of two thiols. *(Animals, Animals, © E. R. Degginger)*

Table 9.2 Boiling points of several thiols and alcohols of the same number of carbon atoms

Thiol	bp (°C)	Alcohol	bp (°C)
methanethiol	6	methanol	65
ethanethiol	35	ethanol	78
1-butanethiol	98	1-butanol	117

water and other polar solvents than alcohols of comparable molecular weights. Table 9.2 gives structural formulas and boiling points for several low-molecular-weight thiols. Shown for comparison are boiling points of alcohols of the same number of carbon atoms. Earlier, we illustrated the importance of hydrogen bonding in alcohols by comparing the boiling points of ethanol (bp 78°C) and its constitutional isomer dimethyl ether (bp −24°C). By comparison, the boiling point of ethanethiol is 35°C, and that of its constitutional isomer dimethyl sulfide is 37°C.

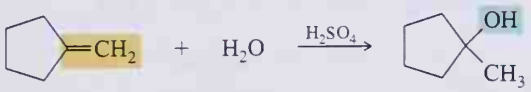
CH_3CH_2SH	CH_3SCH_3
Ethanethiol (bp 35°C)	Dimethyl sulfide (bp 37°C)

The fact that the boiling points of these constitutional isomers are almost identical indicates that little or no association by hydrogen bonding occurs between thiol molecules.

9.4 Preparation of Alcohols

We already examined three methods for the preparation of alcohols, which we recall here.

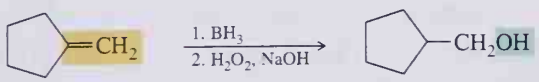
A. Acid-Catalyzed Hydration of Alkenes



Methylenecyclopentane 1-Methylcyclopentanol

Acid-catalyzed hydration of alkenes (Section 5.3C) often leads to rearrangement, especially when the carbocation intermediate formed by addition of H^+ to an alkene can rearrange to a more stable carbocation by migration of an adjacent atom or group of atoms.

B. Hydroboration of Alkenes Followed by Oxidation

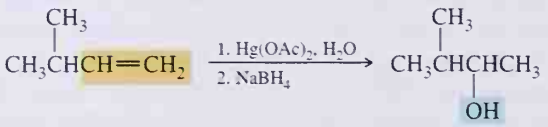


Methylenecyclopentane Cyclopentylmethanol

The particular value of this means of alcohol synthesis is that hydroboration (Section 5.4) is both regioselective (anti-Markovnikov) and stereoselective (syn addition), and given the concerted nature of borane addition, no rearrangement occurs during hydroboration. Furthermore, conversion of a trialkylborane to an alcohol is stereoselective and proceeds with retention of configuration of the alkyl group. The result is anti-Markovnikov syn addition of H—OH to an alkene.

C. Oxymercuration of Alkenes Followed by Reduction

Oxymercuration of an alkene (Section 5.3E) is regioselective and occurs without rearrangement. The result of oxymercuration followed by reduction is Markovnikov addition of H—OH to an alkene.

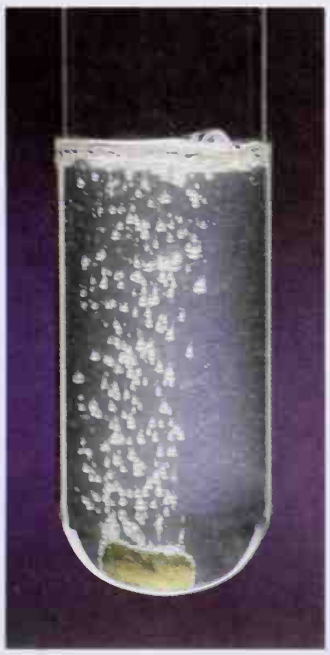


3-Methyl-1-butene 3-Methyl-2-butanol

There are other methods for preparing alcohols as we shall see in following chapters.

9.5 Reactions of Alcohols

Alcohols undergo a variety of important reactions, including formation of salts with active metals; conversion to alkyl halides; dehydration to alkenes; and oxidation to aldehydes, ketones, and carboxylic acids. Thus, alcohols are valuable starting materials for the synthesis of other classes of organic compounds.



Sodium metal dissolves in methanol with evolution of hydrogen gas. *(Charles D. Winters)*

A. Reaction with Active Metals

Alcohols react with Li, Na, K, and other active metals to liberate hydrogen and to form metal alkoxides.

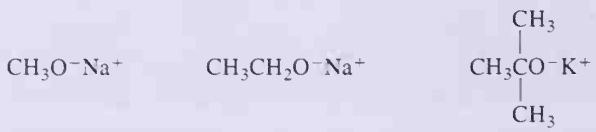
$$2CH_3OH + 2Na \longrightarrow 2CH_3ONa + H_2$$

Sodium methoxide

$$2CH_3CH_2OH + Mg \longrightarrow (CH_3CH_2O)_2Mg + H_2$$

Magnesium ethoxide

Alkoxide ions are somewhat stronger bases than hydroxide ion. The following alkoxides are commonly used in organic reactions requiring a strong base in a nonaqueous solvent, as, for example, sodium methoxide in methanol and sodium ethoxide in ethanol.



Sodium methoxide Sodium ethoxide Potassium *tert*-butoxide

Alcohols can also be converted to salts by reaction with bases stronger than alkoxides. One such base is sodium hydride, NaH.

$$CH_3CH_2OH + Na^+H^- \longrightarrow CH_3CH_2O^-Na^+ + H_2$$

Ethanol — Sodium hydride — Sodium ethoxide

Reactions of sodium hydride with compounds containing acidic hydrogens are irreversible and driven to completion by the formation of H_2, which is given off as a gas.

EXAMPLE 9.6

The bond in NaH can be described as polar covalent. Calculate the percent ionic character to the Na—H bond.

Solution

The electronegativity of hydrogen is 2.1, and that of sodium is 0.9 (Table 1.3).

$$\text{Percent ionic character} = \frac{2.1 - 0.9}{2.1} \times 100 = 57\%$$

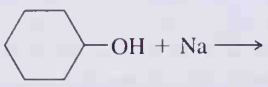
The Na—H bond is polar covalent with hydrogen (the more electronegative atom), bearing a partial negative charge, and sodium (the less electronegative atom), bearing a partial positive charge. Sodium hydride can also be written as an ionic compound to emphasize the polarity of the bond.

$$\overset{\delta^+}{Na}—\overset{\delta^-}{H} \qquad Na^+ \; :H^-$$

The high decomposition temperature of sodium hydride (800°C) is consistent with the high degree of ionic character of the sodium-hydrogen bond.

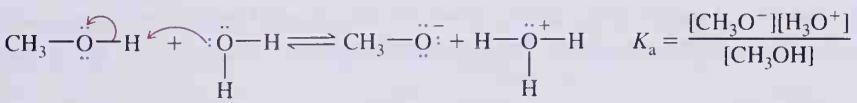
PROBLEM 9.6

Write balanced equations for the following reactions:

(a) $(CH_3)_3COH + K \longrightarrow$ (b)  $+ Na \longrightarrow$

B. Acidity of Alcohols

In dilute aqueous solution, alcohols are weakly acidic as shown for the ionization of methanol.



$$K_a = \frac{[CH_3O^-][H_3O^+]}{[CH_3OH]}$$

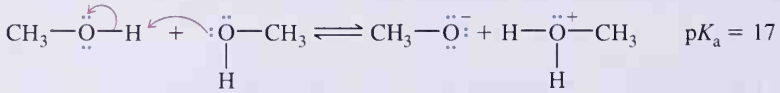
Table 9.3 pK_a Values for selected alcohols in dilute aqueous solution. Also given for comparison are pK_a values for water, acetic acid, and hydrochloric acid

Compound	pK_a
HCl	−7
CH_3CO_2H	4.8
CH_3OH	15.5
H_2O	**15.7**
CH_3CH_2OH	15.9
$(CH_3)_2CHOH$	17
$(CH_3)_3COH$	18

Increasing acid strength

Shown in Table 9.3 are acid ionization constants for several low-molecular-weight alcohols. The relative acidities of the alcohols shown in Table 9.3 can be explained by a combination of steric and inductive effects. For simple alcohols, such as methanol and ethanol, relative acidity depends primarily on the degree of solvation and stabilization of the alkoxide ion by water molecules. The negatively charged oxygen atom of the methoxide and ethoxide ions is almost as readily accessible for solvation as is the hydroxide ion, and, hence, these alcohols are about as acidic as water. As the bulk of the alkyl group attached to oxygen increases, the ability of water molecules to solvate the alkoxide ion decreases. *tert*-Butyl alcohol is a weaker acid than either methanol or ethanol, primarily because the oxygen atom of the *tert*-butoxide ion is less available for solvation by surrounding water molecules, and, therefore, the anion is less stable in solution. Note that although acetic acid is a "weak acid" compared with mineral acids, such as HCl and HBr, it still is 10^{10} times stronger as an acid than simple alcohols.

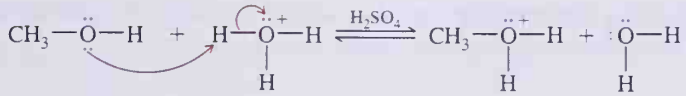
In the pure liquid, methanol, ethanol, and other simple alcohols are even weaker acids than when dissolved in aqueous solution. The pK_a for methanol as a pure liquid is approximately 17.



The reason for the reduced acidity of alcohols in pure liquid form is that the alcohol is not as effective a solvating agent (because of the bulk of the alkyl group attached to oxygen) as is water. Thus, in pure form, methanol is a weaker acid than water; conversely, methoxide ion in methanol is a stronger base than is hydroxide ion in water.

C. Basicity of Alcohols

In the presence of strong acids, the oxygen atom of an alcohol behaves as a base and reacts with an acid by proton transfer to form an oxonium ion.



A base An acid An oxonium ion

D. Conversion to Alkyl Halides

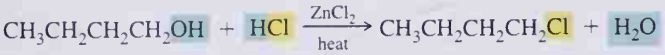
Conversion of an alcohol to an alkyl halide involves substitution of halogen for —OH at a saturated carbon. The most common reagents for this conversion are the halogen acids and the inorganic halides PCl_3, PBr_3, and $SOCl_2$. We consider the halogen acids first. These reactions are examples of a general class of reactions called **nucleophilic substitutions.** *Substitution* because one atom or group of atoms is substituted for another atom or group of atoms. *Nucleophilic* because one of the reactants is a nucleophile; it provides a pair of electrons to be shared with another atom in formation of a new covalent bond.

Reaction with HCl, HBr, and HI

Low-molecular-weight, water-soluble alcohols (generally alcohols of no more than six or seven carbon atoms) are converted to chloroalkanes by treatment with concentrated HCl, although the conditions for reaction vary considerably from primary to secondary to tertiary alcohols. Mixing a tertiary alcohol, for example, 2-methyl-2-propanol, with concentrated HCl for a few minutes at room temperature results in conversion of the alcohol to 2-chloro-2-methylpropane. Reaction is evident by formation of the water-insoluble chloroalkane that separates from the aqueous layer.

2-Methyl-2-propanol 2-Chloro-2-methylpropane

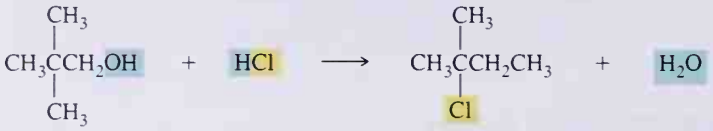
Low-molecular-weight, water-soluble primary and secondary alcohols, however, are quite unreactive under these conditions. They can be converted to chloroalkanes, however, by using the **Lucas reagent**—a solution prepared by dissolving anhydrous zinc chloride (a Lewis acid) in concentrated hydrochloric acid. Using this reagent, tertiary alcohols are converted to chloroalkanes almost instantly. Water-insoluble chloroalkanes begin to form from secondary alcohols after several minutes or after slight warming of the solution. Primary alcohols dissolve in the Lucas reagent but do not react, at least not at room temperature. When heated to reflux, however, they are converted to primary chloroalkanes as illustrated by conversion of 1-butanol to 1-chlorobutane.



1-Butanol 1-Chlorobutane

Primary alcohols with branches on the β-carbon often give large amounts of a product derived from rearrangement, which indicates formation of a carbocation intermediate during the reaction. The carbon bearing the —OH is defined as the α-carbon, and a carbon adjacent to it is a β-carbon. For example, treatment of 2,2-dimethyl-1-propanol (neopentyl

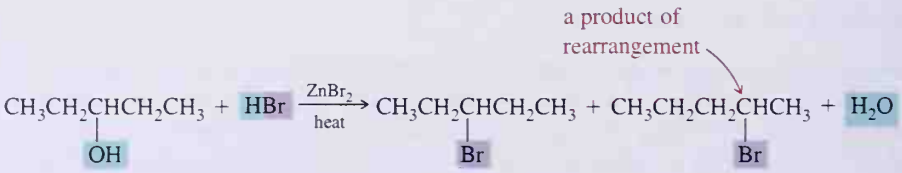
alcohol) with HCl gives rearranged product almost exclusively—clear evidence for the existence of carbocation intermediates during these reactions.



2,2-Dimethyl-1-propanol

2-Chloro-2-methylbutane
(a product of rearrangement)

Secondary alcohols generally give at least some rearranged product if rearrangement is possible. For example, reaction of 3-pentanol with HBr gives 3-bromopentane as the major product, along with some 2-bromopentane. The formation of a rearranged product in this reaction is evidence for the existence of a secondary carbocation intermediate and its conversion by rearrangement to an isomeric secondary carbocation intermediate.



3-Pentanol

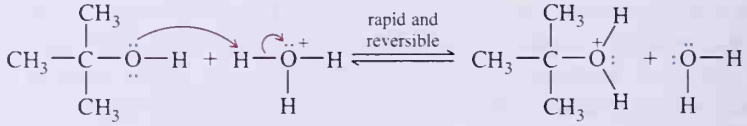
3-Bromopentane

2-Bromopentane

From these facts, particularly experimental evidence on rearrangement or lack of it, chemists have concluded that the mechanisms for conversion of a tertiary alcohol and a secondary alcohol to haloalkanes by concentrated H—X most probably involve formation of carbocation intermediates. However, for primary alcohols without extensive β-branching, carbocation intermediates are almost certainly not involved.

To account for the reaction between a tertiary alcohol and HX, chemists propose as a first step a rapid, reversible proton-transfer reaction to form an oxonium ion. Oxonium ion formation is followed by loss of a molecule of water to give a tertiary carbocation (Step 2). Once formed, the tertiary carbocation reacts with halide ion to give the observed product (Step 3).

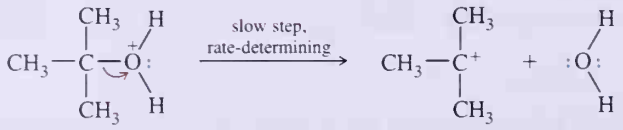
Step 1:



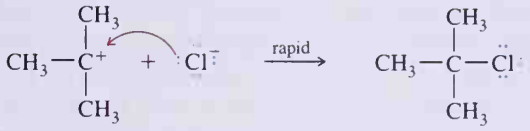
2-Methyl-2-propanol
(*tert*-butyl alcohol)

(An oxonium ion)

Step 2:



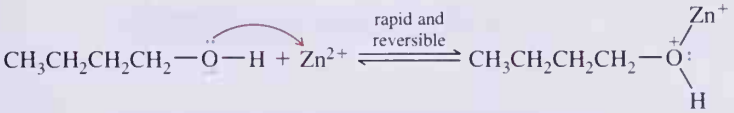
(A 3° carbocation)

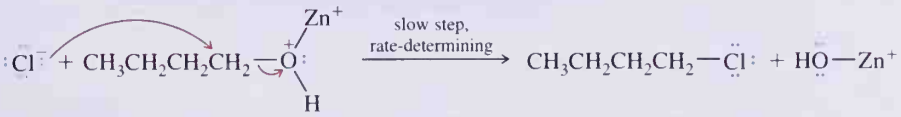
Step 3: 

2-Chloro-2-methylpropane
(*tert*-butyl chloride)

Reaction of 2-methyl-2-propanol with HCl to form 2-chloro-2-methylpropane and H_2O is classified as an **S_N1 reaction.** *S* represents the fact that one atom or group of atoms is substituted for another atom or group of atoms, in this case Cl for OH. *N* represents the nucleophile, in this case chloride ion, which provides the pair of electrons to form the new covalent bond. *1* represents the single reactant in the slow, rate-determining step, in this case the oxonium ion derived from protonation of 2-methyl-2-propanol. We study S_N1 reactions in considerable detail in Chapter 10.

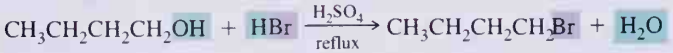
The first step of the mechanism of reaction of a primary alcohol with the Lucas reagent is the rapid and reversible reaction of the hydroxyl group with Zn^{2+} to form a zinc-coordinated oxonium ion. In Step 2, chloride ion reacts at the carbon bearing the oxonium ion to displace oxygen and form a C—Cl bond. Displacement by halide ion is from the side of the primary carbon opposite that of the leaving group.

Step 1: 

Step 2: 

Treatment of 1-butanol with HCl in the presence of zinc chloride to form 1-chlorobutane and H_2O is classified as an **S_N2 reaction.** *S* represents the fact that one atom or group of atoms is substituted for another atom or group of atoms, in this case —Cl for —OH. *N* represents the nucleophile, in this case chloride ion, which provides the pair of electrons to form the new covalent bond. *2* represents the two reactants in the slow, rate-determining step, in this case chloride ion and the oxonium ion derived from 1-butanol. We will also study S_N2 reactions in considerable detail in Chapter 10.

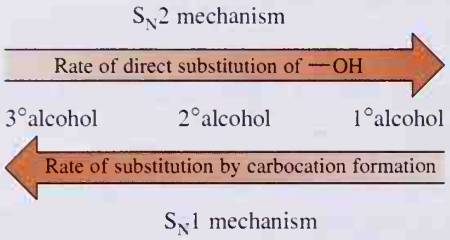
Primary, secondary, and tertiary water-soluble alcohols also react with HBr and HI to form bromoalkanes and iodoalkanes. For example, on reflux in a solution prepared by dissolving sodium bromide in concentrated sulfuric acid, 1-butanol is converted smoothly to 1-bromobutane.



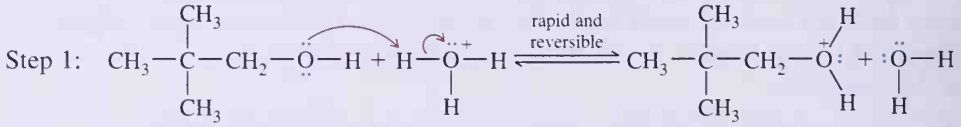
1-Butanol 1-Bromobutane

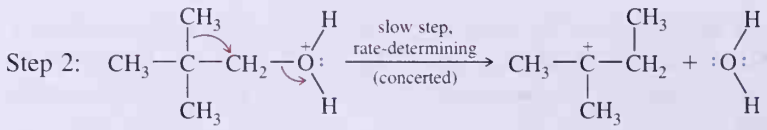
Why do primary alcohols react by direct displacement of —OH (more accurately, displacement of H_2O or $HO—Zn^+$), whereas tertiary alcohols react first by formation of a carbocation and then formation of the new carbon-halogen bond? The answer is a combination of two factors.

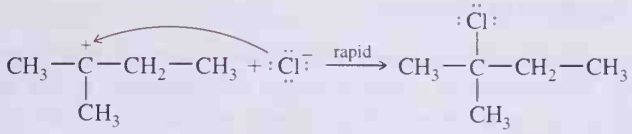
1. *Relative stabilities of carbocations:* As we learned in Section 5.3D, tertiary carbocations are the most stable (lowest energy of activation for their formation), whereas primary carbocations are the least stable (highest energy of activation for their formation). Therefore, tertiary alcohols are most likely to react by carbocation formation; secondary alcohols are intermediate, and primary alcohols rarely if ever react by carbocation formation.
2. *Steric hindrance:* To form a new carbon-halogen bond, halide ion must approach the substitution center and begin to form a new covalent bond. If we compare the ease of approach to the substitution center of a primary alcohol with that of a tertiary alcohol, we see that approach is considerably easier in the case of a primary alcohol. The substitution center of a tertiary alcohol is screened by three alkyl substituents, whereas approach to the substitution center of a primary alcohol is screened by two hydrogen atoms and only one alkyl group. We use the term **steric hindrance** to indicate the ability of groups, because of their size, to hinder access to a reaction site within a molecule. Primary alcohols are most likely to react by direct displacement of H_2O by an S_N2 mechanism. Secondary alcohols are intermediate. Tertiary alcohols rarely if ever react by an S_N2 mechanism.



For primary alcohols with extensive β-branching, reaction by direct displacement of H_2O is difficult if not impossible. Furthermore, reaction by way of a primary carbocation is also difficult if not impossible. It is believed that primary alcohols with extensive β-branching react by a mechanism involving formation of an intermediate 3° carbocation, probably by simultaneous (concerted) loss of H_2O and migration of an alkyl group. Because the slow, rate-determining step of this nucleophilic substitution involves only one reactant, namely, the protonated alcohol, it is classified as an S_N1 reaction.





Step 3: 

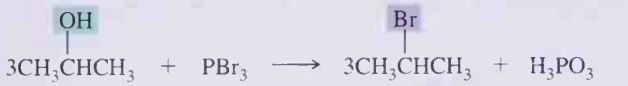
2-Chloro-2-methylbutane

2,2-Dimethyl-1-propanol (neopentyl alcohol) is a primary alcohol, and the reaction shown in Step 1 involves formation of an oxonium ion. Two concerted changes take place in Step 2. First the C—O bond cleaves and H—OH is eliminated. Second, and coupled with the loss of water, is migration of a methyl group and its pair of electrons. The result of these molecular changes is elimination of a molecule of water and formation of a tertiary carbocation. As illustrated by this example, when primary alcohols with extensive β-branching are reacted with H—X, rearrangement occurs almost invariably.

In summary, preparation of haloalkanes by reaction of ROH + HX is most useful for primary and tertiary, low-molecular-weight, water-soluble alcohols. Because of the possibility of rearrangement, the process is less useful for secondary alcohols (except for simple cycloalkanols) and for primary alcohols in which extensive branching on the β-carbon occurs.

Reaction with Phosphorus Halides

A second method for the synthesis of chloro- and bromoalkanes from alcohols is through the use of the phosphorus halides PCl_3 and PBr_3. The byproduct from each is phosphorous acid.

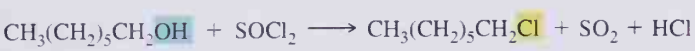


Phosphorus tribromide — Phosphorous acid

Although rearrangement sometimes occurs with PCl_3 and PBr_3, the extent is considerably less than that with hydrogen halides.

Reaction with Thionyl Chloride

Probably the most widely used reagent for the conversion of primary and secondary alcohols to chloroalkanes is thionyl chloride, $SOCl_2$. The byproducts of the reaction are HCl and SO_2, both given off as gases. We discuss the mechanism of this and the previous reaction in Section 10.8.



1-Heptanol — Thionyl chloride — 1-Chloroheptane

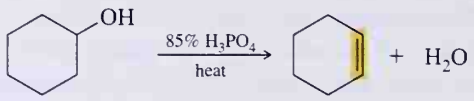
E. Dehydration of Alcohols to Alkenes

An alcohol can be converted to an alkene by elimination of a molecule of water from adjacent carbon atoms. Elimination of water is called **dehydration.** In the laboratory, dehydration of an alcohol is most often brought about by heating it with either 85% phosphoric acid or concentrated sulfuric acid at temperatures of from 100° to 200°C. For example, acid-catalyzed dehydration of ethanol yields ethylene.

$$CH_3CH_2OH \xrightarrow[180^\circ C]{H_2SO_4} CH_2{=}CH_2 + H_2O$$

Ethanol Ethylene

Dehydration of cyclohexanol in the presence of 85% phosphoric acid yields cyclohexene.



Cyclohexanol Cyclohexene

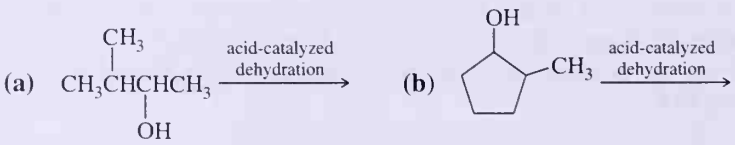
Long before the mechanism of acid-catalyzed dehydration of alcohols was understood, it was recognized that when isomeric alkenes are obtained in an elimination reaction, the alkene having the greater number of substituents on the double bond generally predominates. This generalization is known as **Zaitsev's rule,** and any elimination reaction, including dehydration of alcohols and dehydrohalogenation of haloalkanes (Section 4.5A), that gives the more substituted alkene as the major product is said to follow Zaitsev's rule. Given what we know about the relative stabilities of alkenes (Section 5.8B), Zaitsev's rule may also be stated in the following way: When isomeric alkenes are obtained in an elimination reaction, the more stable alkene generally predominates. For example, acid-catalyzed dehydration of 2-butanol gives 80% 2-butene and 20% 1-butene.

$$CH_3CH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_3 \xrightarrow[heat]{85\%\ H_3PO_4} CH_3CH{=}CHCH_3 + CH_3CH_2CH{=}CH_2$$

2-Butanol 2-Butene (80%) 1-Butene (20%)

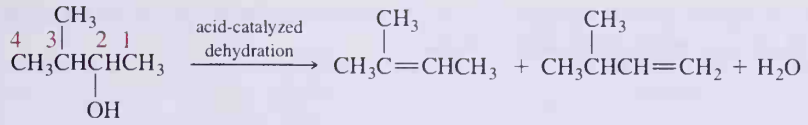
EXAMPLE 9.7

Draw structural formulas for the alkenes formed by acid-catalyzed dehydration of the following alcohols. Predict which alkene is the major product.



Solution

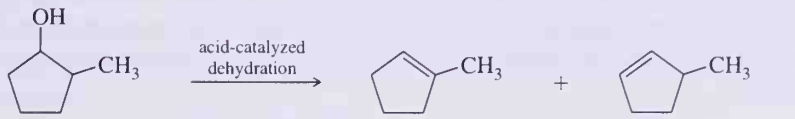
(a) Dehydration of 3-methyl-2-butanol results in the loss of —H and —OH from carbons 2 and 3 to produce 2-methyl-2-butene, and from carbons 1 and 2 to produce 3-methyl-1-butene.



3-Methyl-2-butanol | 2-Methyl-2-butene (major product) | 3-Methyl-1-butene

2-Methyl-2-butene, the major product, has three alkyl substituents (three methyl groups) on the double bond. 3-Methyl-1-butene has one alkyl substituent (an isopropyl group) on the double bond.

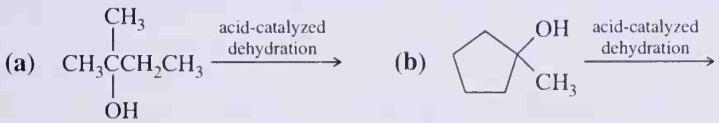
(b) The major product, 1-methylcyclopentene, has three alkyl substituents on the carbon-carbon double bond. 3-Methylcyclopentene has only two substituents on the double bond.



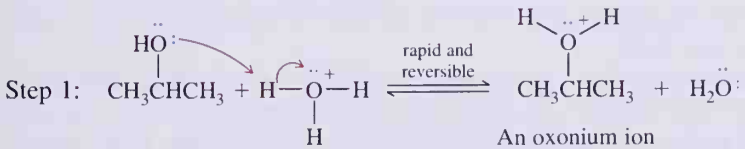
2-Methylcyclopentanol | 1-Methylcyclopentene (major product) | 3-Methylcyclopentene

PROBLEM 9.7

Draw structural formulas for the alkenes formed by acid-catalyzed dehydration of the following alcohols. For each, predict which is the major product.

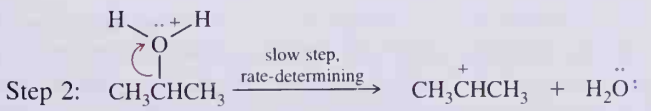


A mechanism for acid-catalyzed dehydration of an alcohol to an alkene can be written in three steps. Proton transfer from H_3O^+ to the hydroxyl group in Step 1 forms an oxonium ion.



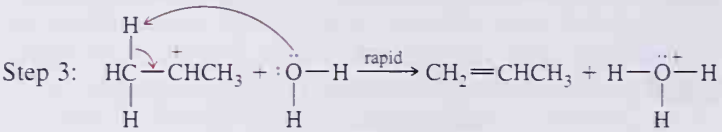
An oxonium ion

In Step 2, the C—OH_2^+ bond breaks to give a carbocation and a molecule of water. Carbocation formation is the rate-determining step in acid-catalyzed dehydration of alcohols.

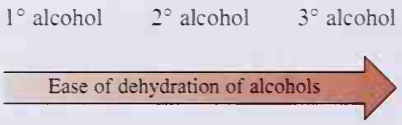


A 2° carbocation

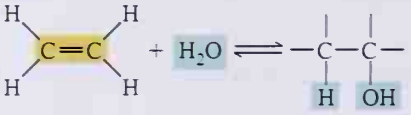
Finally, in Step 3, proton transfer from a C—H bond adjacent to the carbocation to H_2O forms H_3O^+ and the pi bond of the alkene.



Because the reactive intermediate in acid-catalyzed dehydration is the carbocation, the relative ease of dehydration of alcohols parallels the ease of formation of carbocations. Tertiary alcohols are dehydrated more readily than secondary alcohols because a tertiary carbocation is formed more readily than a secondary carbocation. For the same reason, secondary alcohols undergo acid-catalyzed dehydration more readily than primary alcohols. Primary alcohols almost certainly do not undergo acid-catalyzed dehydration by a carbocation intermediate. Their dehydration may, however, involve a carbocation if loss of H_2O from the oxonium ion intermediate is coupled with rearrangement to form a more stable secondary or tertiary carbocation. The ease of dehydration of alcohols is in this order:



In Section 5.3D we discussed a mechanism for acid-catalyzed hydration of alkenes to give alcohols. In the present section we discussed a mechanism for acid-catalyzed dehydration of alcohols to give alkenes. In fact, hydration-dehydration reactions are reversible. Alkene hydration and alcohol dehydration are competing processes, and the following equilibrium exists.



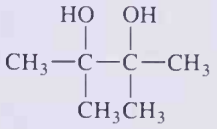
Large amounts of water favor alcohol formation, whereas experimental conditions in which water is removed favor alkene formation. Depending on experimental conditions, it is possible to use the hydration-dehydration equilibrium to prepare either alcohols or alkenes, each in high yields.

This hydration-dehydration equilibrium illustrates a very important principle in the study of reaction mechanisms—the principle of microscopic reversibility. According to the **principle of microscopic reversibility,** the sequence of transition states and reactive intermediates for any equilibrium reaction must be the same but in reverse order for the backward reaction as for the forward reaction. This does not mean, however, that the rate-determining steps are identical; only that the structure of the transition state(s) and reactive intermediate(s) are identical.

To apply the principle of microscopic reversibility to acid-catalyzed hydration-dehydration equilibria, the mechanism we presented in this section for the acid-catalyzed dehydration of 2-propanol to give propene is exactly the reverse of that presented in Section 5.3D for the acid-catalyzed dehydration of 2-propene to give 2-propanol.

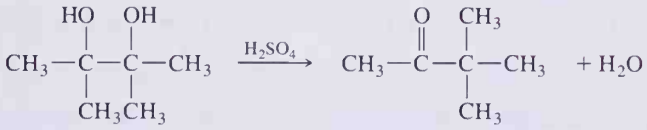
F. The Pinacol Rearrangement

Compounds containing hydroxyl groups on adjacent carbon atoms are called **1,2-diols,** or alternatively, **glycols.** Such compounds can be synthesized by a variety of methods, including oxidation of alkenes by $KMnO_4$ or OsO_4 (Section 5.7B). Following is the structure of 2,3-dimethyl-2,3-butanediol, commonly called pinacol.



2,3-Dimethyl-2,3-butanediol
(Pinacol)

The products of acid-catalyzed dehydration of glycols are quite different from those of acid-catalyzed dehydration of alcohols. For example, treatment of pinacol with concentrated sulfuric acid gives 3,3-dimethyl-2-butanone, commonly called *tert*-butyl methyl ketone, or pinacolone.

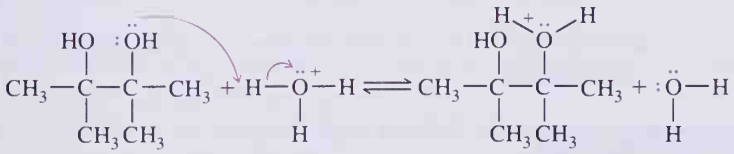


2,3-Dimethyl-2,3-butanediol (Pinacol) — 3,3-Dimethyl-2-butanone (Pinacolone)

Note two features of this reaction. It involves (1) dehydration of a glycol to a ketone, and (2) it involves migration of a methyl group from one carbon to an adjacent carbon. Acid-catalyzed conversion of pinacol to pinacolone is an example of a type of reaction called the **pinacol rearrangement.**

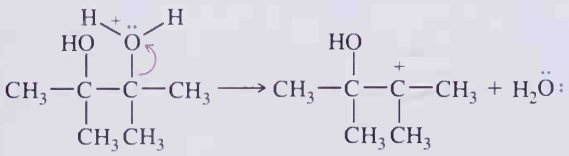
We account for the conversion of pinacol to pinacolone in the following way. Proton transfer to one of the hydroxyl groups of pinacol in Step 1 generates an oxonium ion, which then loses a molecule of water in Step 2 to form a tertiary carbocation.

Step 1:



(An oxonium ion)

Step 2:



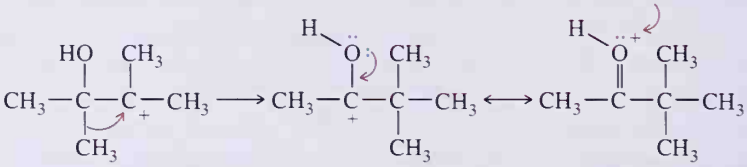
(A 3° carbocation)

So far these steps correspond to those of dehydration of a tertiary alcohol. It is at Step 3 that the pathway of the pinacol rearrangement differs from that for acid-catalyzed dehydration of an alcohol. Migration of an adjacent methyl group with its pair of electrons in

Step 3 to the positively-charged, electron-deficient carbon atom gives a resonance-stabilized cation. Of the two contributing structures drawn, the one on the right makes the greater contribution because in it, both carbon and oxygen have complete octets of valence electrons (Section 1.6D). The resonance-stabilized cation then loses a proton in Step 4 to form pinacolone.

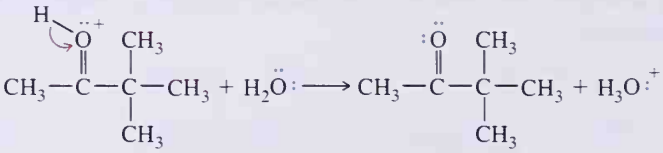
This structure makes the greater contribution because both C and O have complete valence shells.

Step 3:

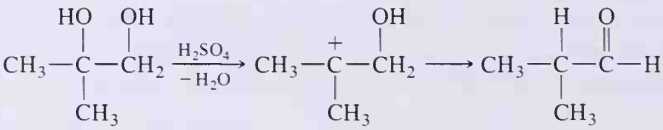


A resonance-stabilized cation

Step 4:



The pinacol rearrangement is general for all 1,2-diols. In the rearrangement of pinacol, equivalent carbocations are formed no matter which —OH is protonated and leaves. Studies of other 1,2-diols have revealed that the —OH group that is protonated and leaves is the one that gives rise to the more stable carbocation. For example, treatment of 2-methyl-1,2-propanediol with cold concentrated sulfuric acid gives a tertiary carbocation. Subsequent migration of hydride ion ($H:^-$) followed by loss of a proton from the new cation gives 2-methylpropanal.

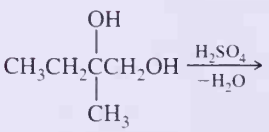


2-Methyl-1,2-propanediol — A 3° carbocation — 2-Methylpropanal

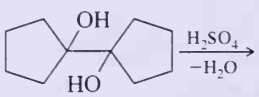
EXAMPLE 9.8

Predict the product of treatment of the following 1,2-diols with H_2SO_4.

(a)

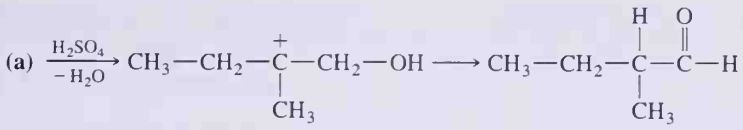


(b)



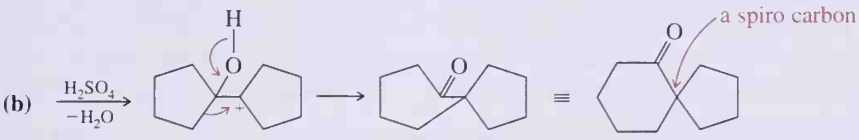
Solution

(a) Protonation of the tertiary alcohol followed by loss of a molecule of water gives a tertiary carbocation. Migration of hydride ion from the adjacent carbon and loss of a proton gives 2-methylbutanal.



A 3° carbocation 2-Methylbutanal

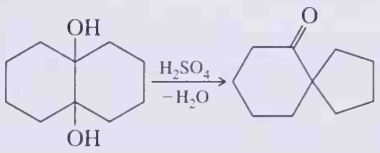
(b) Protonation of either hydroxyl followed by loss of a molecule of water gives a tertiary carbocation. The group that then migrates is one of the carbon-carbon bonds of the five-member ring, and the product is a bicyclic ketone. This compound belongs to the class of compounds called spiroketones (Section 2.4B), bicyclic ketones in which two rings share only one atom.



(A 3° carbocation) Spiro[4.5]decan-6-one

PROBLEM 9.8

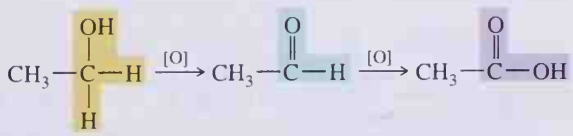
Propose a mechanism to account for the following transformation:



G. Oxidation of Primary and Secondary Alcohols

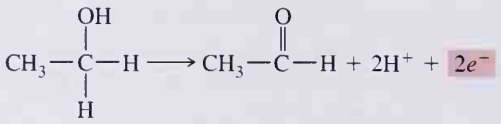
In this and the following section, we are concerned with oxidation of alcohols to compounds with other functional groups. As we shall see, a primary alcohol is oxidized initially to an aldehyde followed by oxidation to a carboxylic acid. Secondary alcohols are oxidized to ketones. Tertiary alcohols are not oxidized.

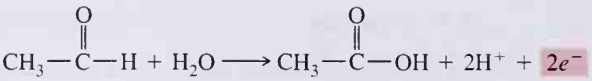
Following are a series of transformations in which a primary alcohol is oxidized first to an aldehyde and then to a carboxylic acid.



A primary alcohol An aldehyde A carboxylic acid

The fact that each transformation involves oxidation is indicated by the symbol O in brackets over the reaction arrow. Inspection of balanced half-reactions (Section 5.7A) shows that each transformation in this series is a two-electron oxidation.

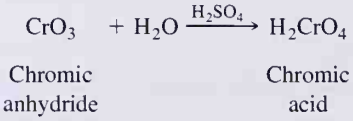




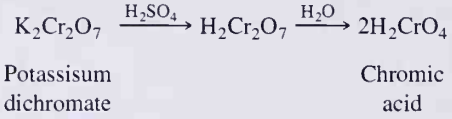
The oxidizing agents most commonly used in the laboratory for the conversion of primary alcohols to aldehydes or carboxylic acids, and secondary alcohols to ketones are compounds of chromium(VI). Following are formulas of three such compounds:

CrO_3	$K_2Cr_2O_7$	H_2CrO_4
Chromium(VI) oxide (Chromic anhydride)	Potassium dichromate	Chromic acid

Chromium(VI) oxide, known alternatively as chromic anhydride, is a red solid that dissolves in aqueous sulfuric acid to form chromic acid.

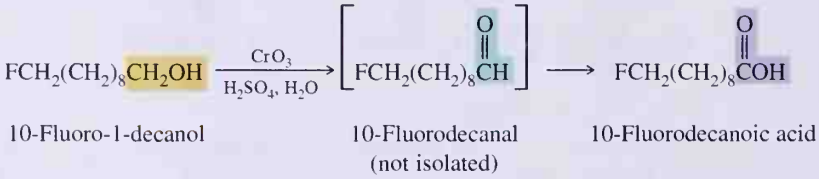


Potassium dichromate, also a red solid, dissolves in aqueous sulfuric acid to form $H_2Cr_2O_7$, a compound that reacts further with water to form chromic acid, H_2CrO_4.



When used as an oxidizing agent, chromic acid is usually prepared from either chromic anhydride or potassium dichromate.

The products of treatment of primary alcohols with Cr(VI) oxidizing agents depend on the form of chromium(VI) employed and the solvent. Carboxylic acids are generally the major product when oxidation is carried out in aqueous media. Oxidation of 10-fluoro-1-decanol, for example, using chromic acid in aqueous sulfuric acid gives 10-fluorodecanoic acid in high yield. These experimental conditions are more than sufficient to oxidize the intermediate aldehyde to a carboxylic acid.



10-Fluoro-1-decanol — 10-Fluorodecanal (not isolated) — 10-Fluorodecanoic acid

Aldehydes are the major product when oxidation is carried out in anhydrous media. The form of Cr(VI) very commonly used for anhydrous oxidation of primary alcohols to aldehydes is prepared by dissolving CrO_3 in aqueous HCl and adding pyridine to precipitate **pyridinium chlorochromate (PCC)** as a solid.

CHEMISTRY IN ACTION

Blood Alcohol Screening

Potassium dichromate is a strong oxidizing agent, and under appropriate experimental conditions, it oxidizes primary alcohols to carboxylic acids. Potassium dichromate oxidation of ethanol to acetic acid is the basis for the original blood alcohol screening test used by law enforcement agencies to determine a person's blood alcohol content (BAC). The test is based on the difference in color between the potassium dichromate reagent (reddish orange) and the chromic ion product (green). Thus, color change can be used as a measure of the quantity of ethanol present in a sample.

$$CH_3CH_2OH + Cr_2O_7^{2-} \xrightarrow[H_2O]{H_2SO_4} CH_3\overset{\overset{O}{\|}}{C}OH + Cr^{3+}$$

Ethanol — Dichromate ion (reddish orange) — Acetic acid — Chromic ion (green)

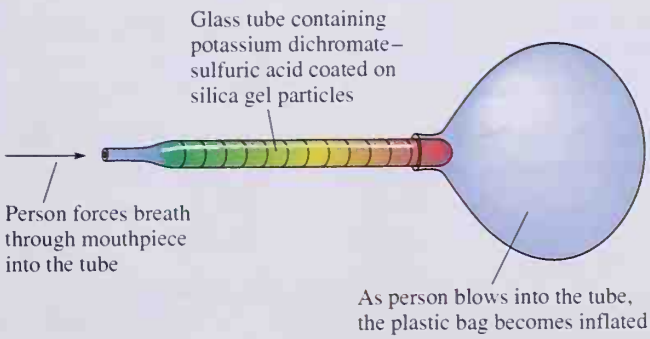
In its simplest form, a blood alcohol screening test consists of a sealed glass tube containing a potassium dichromate reagent impregnated on silica gel. To administer the test, the ends of the tube are broken off, a mouthpiece is fitted to one end, and the other end is inserted into the neck of a plastic bag. The person being tested then blows into the mouthpiece until the plastic bag is inflated.

As breath containing ethanol vapor passes through the tube, reddish orange dichromate ion is reduced to green chromic ion. The concentration of ethanol in the breath is then estimated by measuring how far the green chromic ion color extends along the length of the tube. When the green color extends beyond the halfway point, the person is judged as having a sufficiently high breath alcohol content to warrant further, more precise testing.

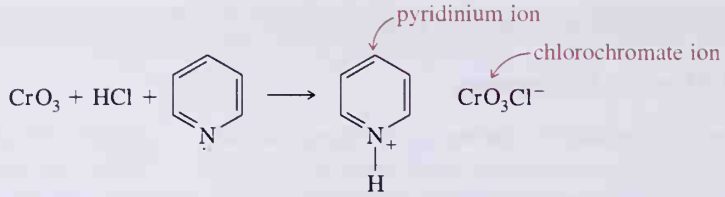
The Breathalyzer, a more precise testing device, operates on the same principles as the simplified breath screening test. In a Breathalyzer test, a measured volume of breath is bubbled through a solution of potassium dichromate dissolved in aqueous sulfuric acid, and the color change is measured spectrophotometrically.

These tests measure alcohol in the breath. The legal definition of being under the influence of alcohol, however, is based on blood alcohol content, not breath alcohol content. The chemical correlation between these two measurements is that air deep within the lungs is in equilibrium with blood passing through the pulmonary arteries, and an equilibrium is established between blood alcohol and breath alcohol. It has been determined by simultaneous tests that 2100 mL of breath contains the same weight of ethanol as 1.00 mL of blood.

See W. C. Timmer, *J. Chem. Ed.*, **63**:897 (1986).

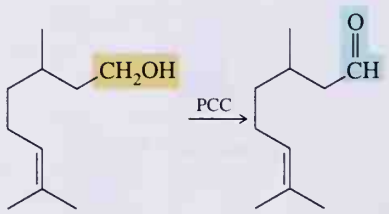


Taking a breathalyser test. *(E. R. Degginger, © Color-Pic, Inc.)*

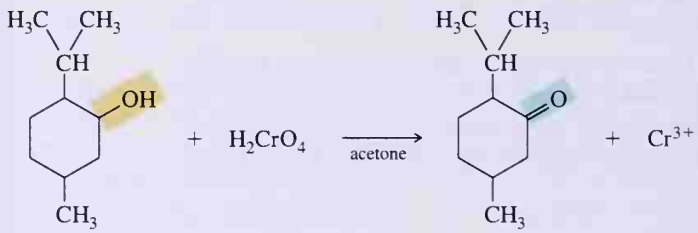


Pyridine — Pyridinium chlorochromate (PCC)

This reagent is not only very selective for the oxidation of primary alcohols to aldehydes, but in contrast to other strong oxidizing agents, it also has little effect on carbon-carbon double bonds or other easily oxidized functional groups. In the following example, a primary terpene alcohol is oxidized to an aldehyde without affecting the carbon-carbon double bond.

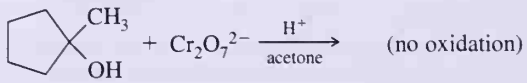


Secondary alcohols are oxidized to ketones by PCC and other strong oxidizing agents. Another form of Cr(VI) commonly employed for oxidation of secondary alcohols is **Jones' reagent,** a solution of chromic acid and sulfuric acid in water. The alcohol is dissolved in acetone, and the two solutions are mixed. Oxidation is rapid, and yields of ketone are generally high. Green chromium(III) salts precipitate and can be separated by filtration of the acetone solution.



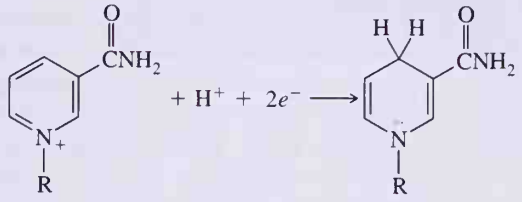
2-Isopropyl-5-methylcyclohexanol (Menthol) — 2-Isopropyl-5-methylcyclohexanone (Menthone)

Tertiary alcohols are resistant to oxidation because the carbon bearing the —OH is already bonded to three other carbon atoms and, therefore, cannot form a carbon-oxygen double bond.



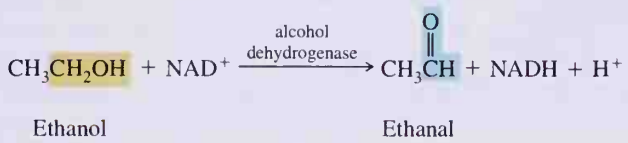
1-Methylcyclopentanol

In the human body and other biological systems, the compound involved in the oxidation of most primary and secondary alcohols is **nicotinamide adenine dinucleotide,** abbreviated as **NAD^+**. The reactive portion of NAD^+ is a substituted pyridine ring (Section 15.2D). In the following structural formula, the remainder of this large organic molecule is represented by the symbol "R." When acting as an oxidizing agent, the pyridine ring of NAD^+ is reduced to NADH. Following is a balanced half-reaction showing NAD^+ as a two-electron oxidizing agent:

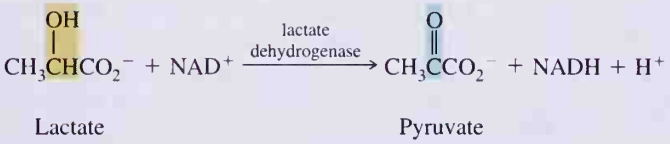


NAD^+ NADH

The following examples illustrate the oxidation of a primary alcohol and a secondary alcohol by NAD^+. Each oxidation is catalyzed by a specific enzyme.



Ethanol Ethanal

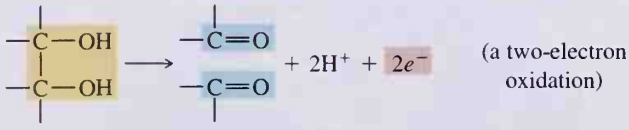


Lactate Pyruvate

Oxidation of ethanol by NAD^+ in the liver is the first step in the detoxification of ingested ethanol. Oxidation of lactate to pyruvate also occurs to a large extent in the liver. During periods of strenuous activity, muscle cells metabolize glucose to produce energy, and in the process lactate accumulates. As it accumulates, muscle tissue becomes fatigued. To relieve this muscle fatigue, lactate is carried by the bloodstream to the liver where it is oxidized to pyruvate, which is in turn used to produce more energy.

H. Oxidations of Glycols: Cleavage of a Carbon-Carbon Bond

Periodic acid, H_5IO_6, (or alternatively $HIO_4 \cdot 2H_2O$), is a white crystalline solid, mp 122°C. Its major use in organic chemistry is cleavage of glycols to carbonyl-containing compounds (a two-electron oxidation). In the process, periodic acid is reduced to iodic acid (a two-electron reduction).



(a two-electron oxidation)

$HIO_4 + 2H^+ + 2e^- \longrightarrow HIO_3 + H_2O$ (a two-electron reduction)

Periodic acid Iodic acid

(Text continued on p. 342)

CHEMISTRY IN ACTION

Cytochrome P-450: A Versatile Biological Oxidant

Most of the reactions that take place in biological systems have close parallels to reactions covered in beginning organic chemistry. One type of biochemical reaction, however, cannot yet be duplicated by organic chemists, namely, selective oxidation to C—OH groups of unactivated C—H bonds in complex organic molecules. This selective oxidation is catalyzed by biomolecules of the cytochrome P-450 family. The designation P-450 refers to the wavelength at which these biomolecules absorb light.

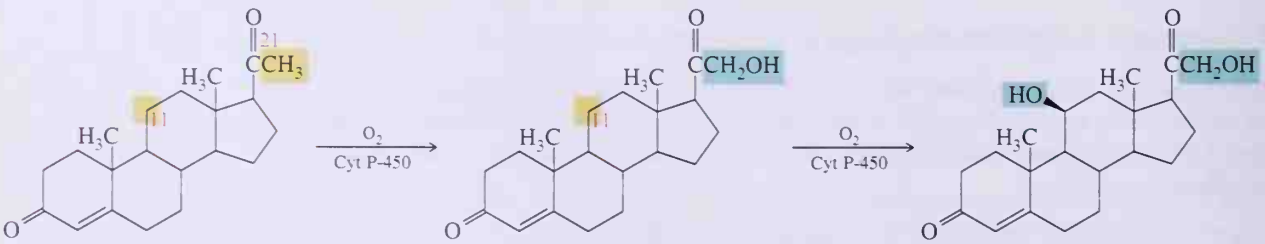
Several important biological processes rely on cytochrome P-450. For example, compounds foreign to the body, including many drug molecules, are often nonpolar and tend to accumulate in fat. Without some mechanism by which to remove these molecules, they could build to toxic levels. Cytochrome P-450 in the liver oxidizes these nonpolar molecules at selected C—H bonds to generate polar metabolites that are then excreted by the kidneys.

Cytochrome P-450 is also involved in the synthesis of certain hormones, including the glucocorticoid and mineralocorticoid hormones. Corticosterone, for example, is synthesized in biological systems from progesterone by enzyme-catalyzed selective oxidations at carbon 21 and at carbon 11. Although many C—H bonds in progesterone might be oxidized to C—OH, only two of them undergo reaction, and only a single final product is formed.

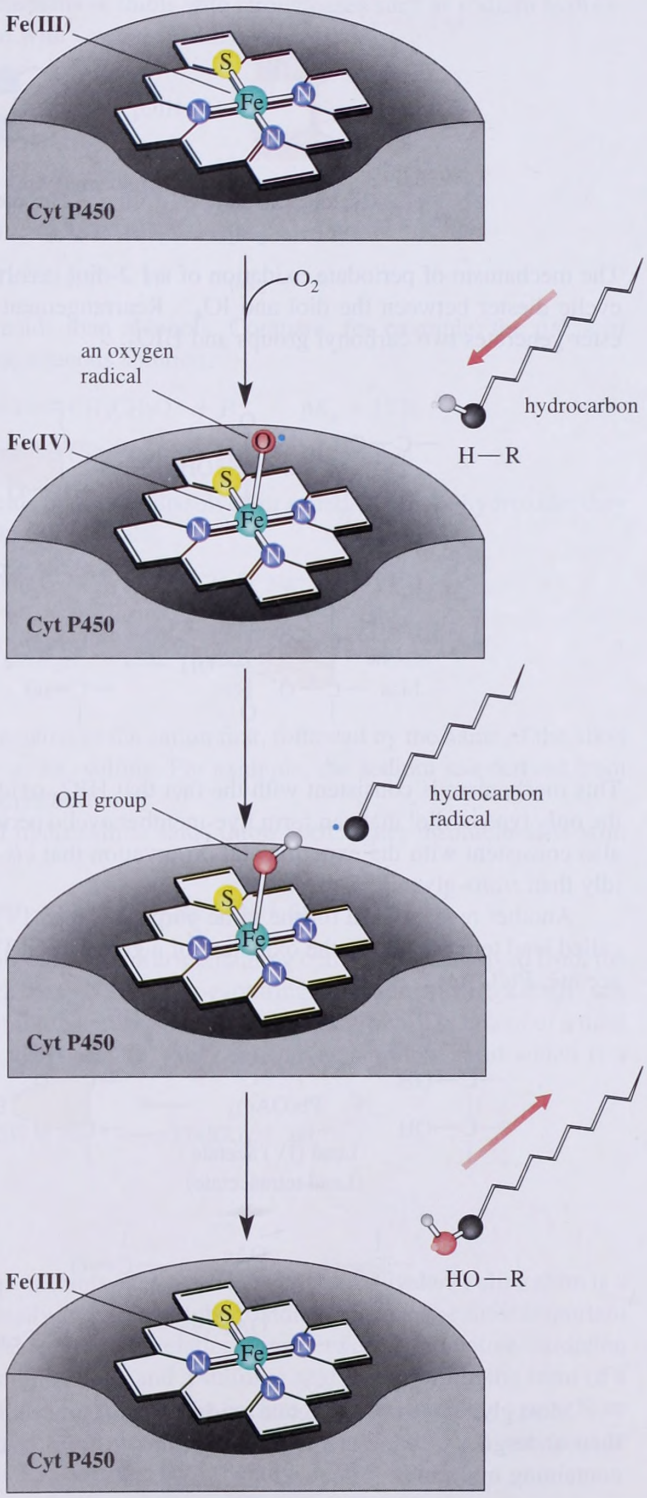
To understand better these regioselective and stereoselective enzyme-catalyzed cytochrome P-450 oxidations, chemists and biochemists have sought to establish (1) what kind of molecule is reactive enough to oxidize a simple carbon-hydrogen bond and (2) how oxidation can be directed to a specific C—H bond. The oxidant in cytochrome P-450 reactions is an atom of iron(III) held in a complex environment and bound to four nitrogen atoms (only three are shown in the figure) and one sulfur atom. Molecular oxygen, a diradical (Section 1.9B), reacts with iron(III) of cytochrome P-450 to produce an iron(IV)-oxygen radical, which then abstracts a hydrogen from an organic molecule to produce a carbon radical. Hydroxyl transfer from Fe(IV)—OH to the carbon radical produces the alcohol and regenerates cytochrome P-450.

The regioselectivity and stereoselectivity of cytochrome P-450 oxidations is not due to iron itself, but rather to the shape of the cavity in which the iron(IV)-oxygen radical is situated. The iron oxidant is sequestered in a cavity that binds the organic substrate in such a way that only one C—H bond is close enough to the iron(IV)-oxygen radical to react. It is the inability of organic chemists to design and build the proper cavity, and not an inability to generate an active oxidizing species that prevents the imitation of these reactions.

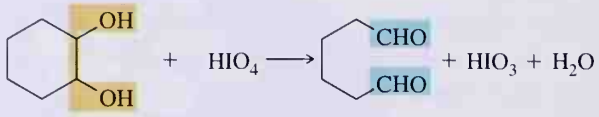
Note that not all enzyme-catalyzed cytochrome P-450 oxidations are beneficial. Hexane, an inert, water-insoluble compound, is oxidized by a relatively nonspecific cytochrome P-450 system. One of the products of this oxidation is 2-hexanone, which acts as a neurotoxin.



Progesterone 11-Deoxycorticosterone Corticosterone

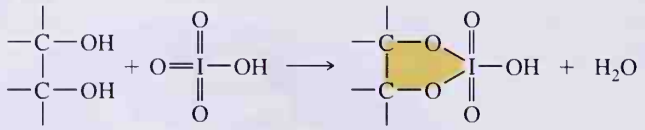

Fe(III)
S
Fe
N
N
N
Cyt P450
O_2
an oxygen radical
hydrocarbon
H—R
Fe(IV)
O
Cyt P450
OH group
hydrocarbon radical
Cyt P450
HO—R
Fe(III)
Cyt P450

For example, when treated with periodic acid, 1,2-cyclohexanediol is oxidized to hexanedial.

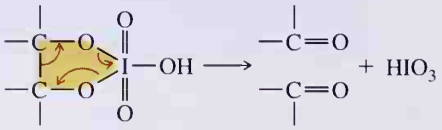


1,2-Cyclohexanediol Hexanedial

The mechanism of periodate oxidation of a 1,2-diol involves formation of a five-member cyclic diester between the diol and IO_4^-. Rearrangement of electrons within this cyclic ester generates two carbonyl groups and HIO_3.

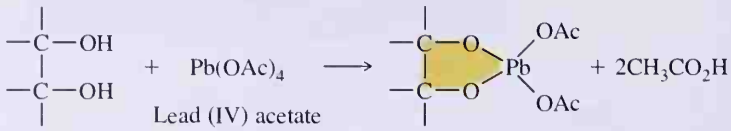


A cyclic periodate ester

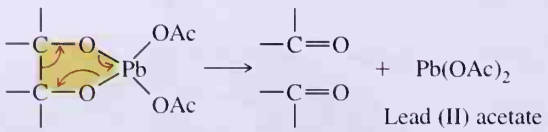


This mechanism is consistent with the fact that HIO_4 oxidations are restricted to glycols, the only type of diol that can form five-member cyclic periodate esters. This mechanism is also consistent with the experimental observation that *cis*-glycols are oxidized more rapidly than *trans*-glycols.

Another reagent used for the same purpose is lead(IV) acetate, $Pb(OAc)_4$, commonly called lead tetraacetate. In the oxidation of a glycol, lead(IV) acetate is reduced to lead(II) acetate, $Pb(OAc)_2$.



Lead (IV) acetate
(Lead tetraacetate)



Lead (II) acetate

Most glycol–lead(IV) acetate oxidations also proceed via a cyclic intermediate, which then undergoes a rearrangement of electrons to form lead(II) acetate and two carbonyl-containing molecules.

9.6 Reactions of Thiols

In this section, we talk about reactions of thiols with strong bases such as sodium hydroxide, with heavy metal salts, and with several oxidizing agents.

A. Acidity

Hydrogen sulfide is a stronger acid than water.

$$H_2O \rightleftharpoons HO^- + H^+ \qquad pK_a = 15.7$$

$$H_2S \rightleftharpoons HS^- + H^+ \qquad pK_a = 7.0$$

Similarly, thiols are stronger acids than alcohols. Compare, for example, the pK_a's of ethanol and ethanethiol in dilute aqueous solution.

$$CH_3CH_2OH \rightleftharpoons CH_3CH_2O^- + H^+ \qquad pK_a = 15.9$$

$$CH_3CH_2SH \rightleftharpoons CH_3CH_2S^- + H^+ \qquad pK_a = 8.5$$

Thiols are sufficiently strong acids that when dissolved in aqueous sodium hydroxide, they are converted completely to alkylsulfide salts.

$$CH_3CH_2SH + Na^+OH^- \longrightarrow CH_3CH_2S^-Na^+ + H_2O$$

$pK_a = 8.5$			$pK_a = 15.7$
stronger acid	stronger base	weaker base	weaker acid

To name salts of thiols, give the name of the cation first, followed by the name of the alkyl group to which is attached the suffix -sulfide. For example, the sodium salt derived from ethanethiol is named sodium ethylsulfide.

Like hydrogen sulfide and hydrosulfide salts, thiols form water-insoluble salts with most heavy metals.

$$2RSH + Hg^{2+} \longrightarrow Hg(SR)_2 + 2H^+$$

In fact, the common name of this class of sulfur-containing compounds is derived from the Latin *mercurium captans,* which means "mercury-capturing." Treatment with a Pb(II) salt is often used as a qualitative test for the presence of a sulfhydryl group. Treatment of a thiol with a saturated solution of lead(II) acetate, $Pb(OAc)_2$, gives a yellow solid which is a positive test for a thiol.

$$2RSH + Pb^{2+} \longrightarrow Pb(SR)_2 + 2H^+$$

B. Oxidation of Thiols

Many of the chemical properties of thiols stem from the fact that a divalent sulfur atom is a reducing agent; it is oxidized easily to several higher oxidation states, the most important of which are summarized in Table 9.4. The relationships between the relative oxidation states of a thiol, a disulfide, a sulfinic acid, and a sulfonic acid are shown in the form of a sequence of balanced half-reactions. To bring about each requires an oxidizing agent. Note that the valence shell of sulfur contains 8 electrons in a thiol and a disulfide, 10 electrons in a sulfinic acid, and 12 electrons in a sulfonic acid (Section 1.2E).

Table 9.4 Functional groups formed by oxidation of thiols

A thiol can be converted to the following higher oxidation states

$$2R{-}S{-}H \longrightarrow R{-}S{-}S{-}R + 2H^+ + 2e^-$$

A thiol — A disulfide

$$R{-}S{-}H + 2H_2O \longrightarrow R{-}\overset{\overset{O}{\|}}{S}{-}O{-}H + 4H^+ + 4e^-$$

A thiol — A sulfinic acid

$$R{-}\overset{\overset{O}{\|}}{S}{-}O{-}H + H_2O \longrightarrow R{-}\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{S}}{-}O{-}H + 2H^+ + 2e^-$$

A sulfinic acid — A sulfonic acid

We discuss the conversion of thiols to disulfides in some detail because of the importance of these functional groups in biological chemistry. Thiols are oxidized by mild oxidizing agents such as iodine, I_2, to disulfides.

$$2RSH + I_2 \longrightarrow RSSR + 2H^+ + 2I^-$$

A thiol — A disulfide

They are also oxidized to disulfides by molecular oxygen. In fact, thiols are so susceptible to oxidation that they must be protected from contact with air during storage.

$$2RSH + \frac{1}{2}O_2 \longrightarrow RSSR + H_2O$$

A thiol — A disulfide

The disulfide bond is an important structural feature of many biomolecules, including proteins (Chapter 24).

9.7 Methanol: A Key Industrial Alcohol

By far the most important alcohol, at least in terms of bulk, is methanol. In 1993, production of synthetic methanol in the United States was 10.5 billion pounds. Virtually all synthetic methanol is manufactured by reaction of carbon monoxide and hydrogen (synthesis gas, Section 2.10C).

$$C{=}O + 2H_2 \xrightarrow{\text{catalyst}} CH_3OH$$

Methanol

The major derivative of methanol is formaldehyde, prepared on an industrial scale by air oxidation. In a typical oxidation process, air and methanol vapor are passed over a zinc oxide–chromium oxide catalyst at elevated temperature and pressure.

$$2CH_3OH + O_2 \xrightarrow{\text{catalyst}} 2HCH{=}O + 2H_2O$$

Methanol — Methanal (Formaldehyde)

The most important end use of formaldehyde is in the manufacture of adhesives for plywood and particle board, and of a variety of polymers.

A derivative of methanol, *tert*-butyl methyl ether (MTBE), illustrates another important use for this primary organic chemical. The search for antiknock and octane-improving gasoline additives dates back to the early 1920s (Section 2.10B). The most effective and widely used additive was tetraethyllead, introduced in 1921. In the 1960s and early 1970s, concern about the long-term environmental effects of automotive lead emissions resulted in legislation requiring gradual removal of organolead octane improvers. Methanol and ethanol have received particular attention, because in addition to being octane improvers, they represent ways of converting coal (via synthesis gas) and biomass (via fermentation) into liquid fuels.

As an octane-improving additive, MTBE is superior to both methanol and ethanol. A blend of 15% MTBE with gasoline improves octane rating by approximately 5 units. On an industrial scale, MTBE is manufactured by passing a mixture of methanol vapor and 2-methylpropene (isobutylene) over a solid-supported acid catalyst at moderate temperatures and pressures.

$$CH_3OH + CH_2{=}C(CH_3)CH_3 \xrightarrow{\text{catalyst}} CH_3OC(CH_3)_2CH_3$$

2-Methylpropene (Isobutylene) — 2-Methoxy-2-methylpropane (*tert*-Butyl methyl ether; MTBE)

It is expected that demand for MTBE will grow steadily in the coming years, and the factor limiting its expansion will be the availability of methanol.

Cars of the type that race at Indianapolis are fueled by methanol. *(Photo by Herbert Eisenberg, Superstock.)*

SUMMARY OF KEY REACTIONS

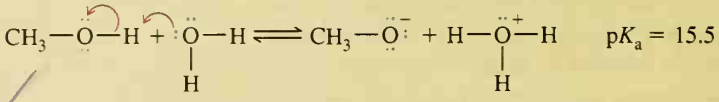
1. Reaction with Active Metals (Section 9.5A)

Alcohols react with Li, Na, K, and other active metals to form metal alkoxides, which are somewhat stronger bases than NaOH and KOH.

$$CH_3CH_2OH + Na \longrightarrow CH_3CH_2O^-Na^+ + H_2$$

2. Acidity of Alcohols (Section 9.5B)

In dilute aqueous solution, methanol and ethanol are comparable in acidity to water. Secondary and tertiary alcohols are weaker acids.

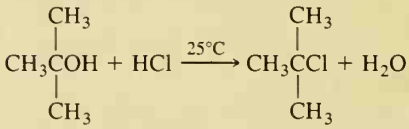


3. Reaction with HCl, HBr, or HI to Form Haloalkanes (Section 9.5D)

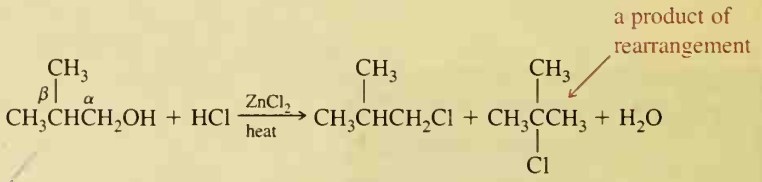
Primary alcohols react by an S_N2 mechanism.

$$CH_3CH_2CH_2CH_2OH + HCl \xrightarrow[\text{heat}]{ZnCl_2} CH_3CH_2CH_2CH_2Cl + H_2O$$

Tertiary alcohols react by a carbocation intermediate in an S_N1 mechanism. The carbocation intermediate may undergo rearrangement.

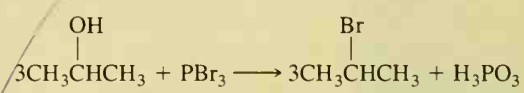


Secondary alcohols may react by either S_N1 or S_N2 depending on the alcohol and the experimental conditions. Primary alcohols with extensive β-branching react by an S_N1 mechanism involving carbocation formation and rearrangement.



4. Reaction with PCl_3 and PBr_3 (Section 9.5D)

Although some carbocation rearrangement may occur with these reagents, it is less likely than in reaction with HCl, HBr, or HI.



5. Reaction with $SOCl_2$ (Section 9.5D)

This is often the method of choice for converting an alcohol to an alkyl halide.

$$CH_3(CH_2)_5CH_2OH + SOCl_2 \longrightarrow CH_3(CH_2)_5CH_2Cl + SO_2 + HCl$$

6. Acid-Catalyzed Dehydration (Section 9.5E)

When isomeric alkenes are possible, the major product is generally the more substituted alkene (Zaitsev's rule).

$$CH_3CH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_3 \xrightarrow[\text{heat}]{85\%\ H_3PO_4} CH_3CH{=}CHCH_3 + CH_3CH_2CH{=}CH_2$$

Major product

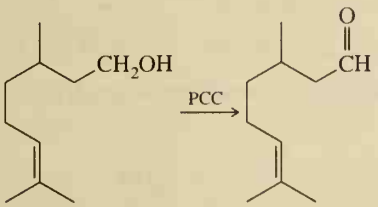
7. Pinacol Rearrangement (Section 9.5F)

Dehydration of a glycol involves formation of a carbocation, rearrangement by a 1,2-shift, and loss of H^+ to give an aldehyde or ketone.

$$CH_3-\underset{\displaystyle CH_3}{\underset{|}{\overset{\displaystyle HO}{\overset{|}{C}}}}-\underset{\displaystyle CH_3}{\underset{|}{\overset{\displaystyle OH}{\overset{|}{C}}}}-CH_3 \xrightarrow{H_2SO_4} CH_3-\overset{\displaystyle O}{\overset{\|}{C}}-\underset{\displaystyle CH_3}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}-CH_3 + H_2O$$

8. Oxidation of a Primary Alcohol to an Aldehyde (Section 9.5G)

This oxidation is most conveniently carried out using pyridinium chlorochromate (PCC).



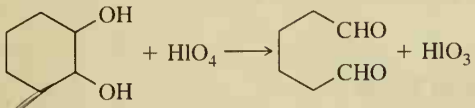
9. Oxidation of a Secondary Alcohol to a Ketone (Section 9.5G)

Secondary alcohols are oxidized to ketones by PCC and other strong oxidizing agents, including Jones' reagent.

$$CH_3(CH_2)_4\underset{\displaystyle OH}{\underset{|}{C}}HCH_3 + H_2CrO_4 \xrightarrow[\text{acetone}]{} CH_3(CH_2)_4\overset{\displaystyle O}{\overset{\|}{C}}CH_3 + Cr^{3+}$$

10. Oxidative Cleavage of a Glycol (Section 9.5H)

HIO_4 and $Pb(OAc)_4$ react with a glycol to form a five-member cyclic intermediate that then undergoes carbon-carbon bond cleavage to form two carbonyl groups.



11. Acidity of Thiols (Section 9.6A)

Thiols are weak acids, pK_a 8–9, but stronger acids than alcohols, pK_a 16–18.

$$CH_3CH_2SH \rightleftharpoons CH_3CH_2S^- + H^+ \qquad pK_a = 8.5$$

12. Oxidation of Thiols (Section 9.6B)

Oxidation by weak oxidizing agents such as O_2 and I_2 gives disulfides.

$$2RSH + \frac{1}{2}O_2 \longrightarrow RSSR + H_2O$$

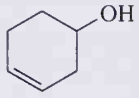
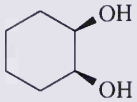
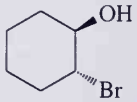
ADDITIONAL PROBLEMS

Structure and Nomenclature

9.9 Name each of the following:

(a) $CH_3CH_2CH_2CH_2CH_2OH$ (b) $HOCH_2CH_2CH_2CH_2OH$ (c) $CH_2{=}C(CH_3)CH_2CH_2OH$

(d) $CH_3CH(OH)CH_2Cl$ (e) $HOCH_2CH{=}CHCH_2OH$ (f) $HOCH_2CH_2CH(CH_3)CH_3$

(g)  (h)  (i) $CH_3CH(OH)CH(OH)CH_3$ (j) 

(k) $CH_3CH_2CH_2CH_2SH$ (l) $CH_3CH{=}CHCH_2SH$ (m) $HSCH_2CH_2SH$

(n) $CH_3(CH_2)_4CH(OH)C{\equiv}CH$ (o) $CH_3C(CH_3){=}CHCH_2CH_2C(CH_3){=}CHCH_2OH$

9.10 Write structural formulas for the following:

(a) isopropyl alcohol
(b) propylene glycol
(c) 5-methyl-2-hexanol
(d) 2-methyl-2-propyl-1,3-propanediol
(e) 1-chloro-2-hexanol
(f) *cis*-3-isobutylcyclohexanol
(g) 2,2-dimethyl-1-propanol
(h) 2-mercaptoethanol
(i) allyl alcohol
(j) *trans*-2-vinylcyclohexanol
(k) (Z)-5-methyl-2-hexen-1-ol
(l) 2-propyn-1-ol
(m) 3-chloro-1,2-propanediol
(n) *cis*-3-pentene-1-ol
(o) bicyclo [2.2.1]-heptan-7-ol

9.11 Name and draw structural formulas for the eight isomeric alcohols of molecular formula $C_5H_{12}O$. In addition, classify each as primary, secondary, or tertiary.

Physical Properties of Alcohols and Thiols

9.12 Arrange the compounds in each set in order of decreasing boiling point (highest to lowest). Explain the basis for your answers.

(a) $CH_3CH_2CH_3$ $CH_3CH_2CH_2CH_2CH_2CH_2CH_3$ $CH_3CH_2CH_2CH_2CH_3$

(b) N_2H_4 H_2O_2 CH_3CH_3

(c) $CH_3\underset{\underset{OH}{|}}{C}HCH_3$ $CH_3\underset{\underset{HO}{|}}{C}H\underset{\underset{OH}{|}}{C}H_2$ $CH_2\underset{\underset{HO}{|}}{C}H\underset{\underset{OH}{|}}{C}H_2$

9.13 Arrange the compounds in each set in order of decreasing boiling point (highest to lowest). Explain the basis for your answers.

(a) $CH_3CH_2CH_2CH_2CH_3$ $CH_3CH_2CH_2CH_3$ $CH_3CH_2CH_2CH_2OH$

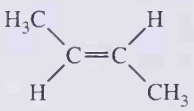
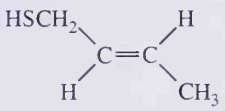
(b) CH_3CH_2SH $CH_3CH_2CH_2OH$ $CH_3CH_2CH_2CH_3$

(c) CH_3CH_2F CH_3OCH_3 CH_3CH_2OH

9.14 Compounds that contain an N—H group show evidence of association by hydrogen bonding. Do you expect this association to be stronger or weaker than that of compounds containing O—H groups? Explain.

9.15 Which of the following compounds can participate in hydrogen bonding with water. For each that can, indicate which site(s) can function as a hydrogen bond acceptor; which can function as a hydrogen bond donor.

(a) $CH_3CH_2CH_2CH_2CH_2OH$ **(b)** $CH_3CH_2CH_2OCH_2CH_2OH$ **(c)** $(CH_3CH_2)_2NH$

(d) $CH_3\overset{\overset{O}{\|}}{C}CH_3$ **(e)** $CH_3C{\equiv}CH$ **(f)**  **(g)** 

(h) $CH_3CH_2\overset{\overset{O}{\|}}{C}OH$ **(i)** $CH_3\overset{\overset{O}{\|}}{S}CH_3$

9.16 From each pair of compounds, select the more soluble in water; explain the basis for your reasoning.

(a) CH_2Cl_2 or CH_3OH **(b)** $CH_3\overset{\overset{O}{\|}}{C}CH_3$ or $CH_3\overset{\overset{CH_2}{\|}}{C}CH_3$

(c) $CH_3CH_2CH_2SH$ or $CH_3CH_2CH_2OH$ **(d)** CH_3CH_2Cl or NaCl

(e) AgCl or $NaNO_3$ **(f)** $CH_3CH_2\underset{\underset{OH}{|}}{C}HCH_2CH_3$ or $CH_3CH_2\overset{\overset{O}{\|}}{C}CH_2CH_3$

9.17 Arrange the compounds in each set in order of decreasing solubility in water; explain the basis for your answers.

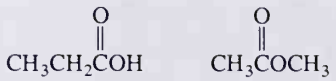
(a) ethanol; butane; diethyl ether **(b)** 1-hexanol; 1,2-hexanediol; hexane

9.18 Diethyl ether and 1-butanol have about the same solubility in water (8 g/100 mL of water); they differ in boiling points by approximately 82°C.

$CH_3CH_2CH_2CH_2OH$	$CH_3CH_2OCH_2CH_3$
1-Butanol	Diethyl ether
8 g/100 mL water	8 g/100 mL water
bp 117°C	bp 35.6°C

How do you account for the similar solubilities of these two compounds but their widely differing boiling points?

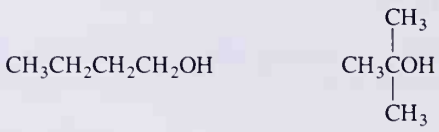
9.19 Propanoic acid and methyl acetate are constitutional isomers and both liquids at room temperature. One of these compounds has a boiling point of 141°C, the other of 57°C.



Propanoic acid Methyl acetate

Which compound has the higher boiling point? Explain your reasoning.

9.20 Following are structural formulas along with boiling points and solubilities in water of 1-butanol and 2-methyl-2-propanol, a pair of constitutional isomers.



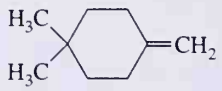
1-Butanol	2-Methyl-2-propanol
bp 117°C	bp 82°C
8 g/100 mL H_2O	soluble in all proportions

(a) How might you account for the observation that the boiling point of 2-methyl-2-propanol is lower than that of 1-butanol?

(b) How might you account for the observation that the solubility of 2-methyl-2-butanol in water is greater than that of 1-butanol?

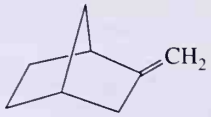
Synthesis of Alcohols

9.21 Draw the alcohol formed when 1,1-dimethyl-4-methylenecyclohexane is treated with each set of reagents.

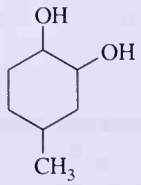


(a) $\xrightarrow[2.\ H_2O_2,\ NaOH]{1.\ BH_3}$ **(b)** $\xrightarrow[2.\ NaBH_4]{1.\ Hg(OAc)_2,\ H_2O}$ **(c)** $\xrightarrow{H_2O,\ H_2SO_4}$

9.22 Oxymercuration of an alkene followed by reduction with sodium borohydride is both regioselective and stereoselective. Oxymercuration of the following bicycloalkene followed by reduction gives a single alcohol in better than 95% yield. Propose a structural formula for the alcohol formed and account for the stereoselectivity of this reaction sequence.



9.23 Following is the structural formula of 4-methyl-1,2-cyclohexanediol.



4-Methyl-1,2-cyclohexanediol

(a) How many stereoisomers are possible for this compound?

(b) Which of the possible stereoisomers are formed by oxidation of 4-methylcyclohexene with either osmium tetroxide or potassium permanganate?

(c) Are the products formed in part (b) optically active or optically inactive?

Acidity of Alcohols

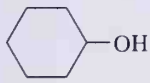
9.24 Complete the following acid-base reactions. In addition, show all valence electrons on the interacting atoms and show by the use of curved arrows the flow of electrons in each reaction.

(a) $CH_3CH_2OH + H_3O^+ \longrightarrow$

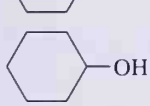
(b) $CH_3CH_2OCH_2CH_3 + HOS(=O)(=O)OH \longrightarrow$

(c) $CH_3CH_2CH_2CH_2CH_2OH + HI \longrightarrow$

(d) $CH_3CH_2CH_2C(=O)OH + HOS(=O)(=O)OH \longrightarrow$

(e)  $+ BF_3 \longrightarrow$

(f) $CH_3CH{=}CH\overset{+}{C}HCH_3 + HOH \longrightarrow$

(g)  $+ HOP(=O)(OH)OH \longrightarrow$

9.25 Select the stronger acid from each pair and explain your reasoning. For each stronger acid, write a structural formula for its conjugate base.

(a) H_2O or H_2CO_3 (b) CH_3OH or CH_3CO_2H

(c) CH_3CH_2OH or $CH_3C{\equiv}CH$ (d) CH_3CH_2OH or CH_3CH_2SH

9.26 From each pair, select the stronger base. For each stronger base, write the structural formula of its conjugate acid.

(a) OH^- or CH_3O^- (each in H_2O) (b) $CH_3CH_2O^-$ or $CH_3C{\equiv}C^-$

(c) $CH_3CH_2S^-$ or $CH_3CH_2O^-$ (d) $CH_3CH_2O^-$ or NH_2^-

9.27 For the following equilibria, label the stronger acid, stronger base, weaker acid, and weaker base. Also predict the position of each equilibrium.

(a) $CH_3CH_2O^- + CH_3C{\equiv}CH \rightleftharpoons CH_3CH_2OH + CH_3C{\equiv}C^-$

(b) $CH_3CH_2O^- + HCl \rightleftharpoons CH_3CH_2OH + Cl^-$

(c) $CH_3C(=O)OH + CH_3CH_2O^- \rightleftharpoons CH_3C(=O)O^- + CH_3CH_2OH$

Reactions of Alcohols

9.28 Write equations for the reaction of 1-butanol, a primary alcohol, with the following reagents. Although you should show formulas for all products, you need not balance equations. Where you predict no reaction, write NR.

(a) Na metal **(b)** PCl_3 **(c)** HCl, cold

(d) HCl, $ZnCl_2$, heat **(e)** PBr_3 **(f)** $K_2Cr_2O_7$, H_2SO_4, heat

(g) HIO_4 **(h)** $SOCl_2$ **(i)** pyridinium chlorochromate (PCC)

9.29 Write equations for the reaction of 2-butanol, a secondary alcohol, with the following reagents. Although you should show formulas for all products, you need not balance equations. Where you predict no reaction, write NR.

(a) Na metal **(b)** H_2SO_4, heat **(c)** HBr, cold

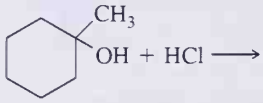
(d) HBr, $ZnBr_2$, heat **(e)** PBr_3 **(f)** $K_2Cr_2O_7$, H_2SO_4, heat

(g) HIO_4 **(h)** $SOCl_2$ **(i)** pyridinium chlorochromate (PCC)

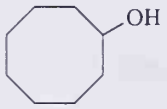
9.30 Complete the following equations. Show structural formulas for the major products, but do not balance.

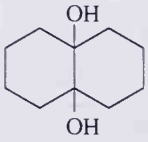
(a) $CH_3CH_2CH_2OH + H_2CrO_4 \longrightarrow$

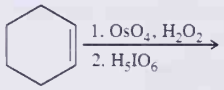
(b) $CH_3\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2CH_2OH + SOCl_2 \longrightarrow$

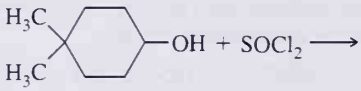
(c) 

(d) $HOCH_2CH_2CH_2CH_2OH + HCl \xrightarrow{ZnCl_2}$

(e) 

(f) 

(g) 

(h) 

9.31 Show how you might bring about the conversion of 4-methylcyclohexanol to the following:

(a) 

(b) 

(c) 

(d) 

(e) 

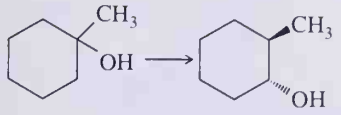
(f) $HCCH_2CH_2CHCH_2CH$ (O, O; CH_3 on the CHCH$_2$CH unit)

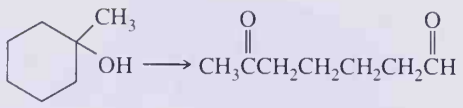
(g) $HOCCH_2CH_2CHCH_2COH$ (O, O; CH_3 on the CHCH$_2$CO unit)

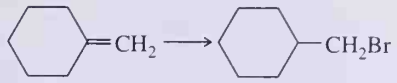
9.32 Show how you might bring about the following conversions. For any conversion involving more than one step, show each intermediate compound formed.

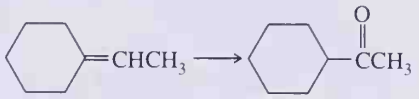
(a) $CH_3\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2OH \longrightarrow CH_3\underset{\displaystyle CH_3}{\underset{|}{C}}{=}CH_2$

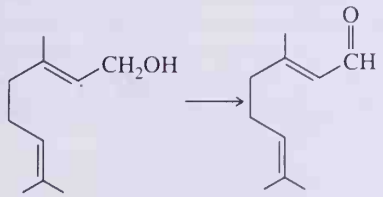
(b) $CH_3\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2OH \longrightarrow CH_3\underset{\displaystyle OH}{\underset{|}{C}}HCH_3$

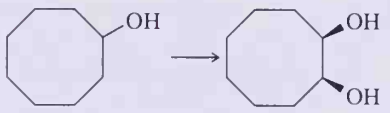
(c) 

(d) 

(e) 

(f) 

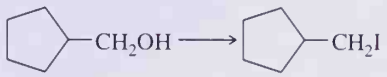
(g) 

(h) 

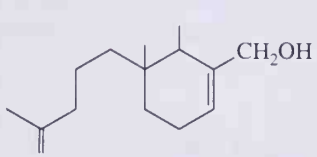
(i) $CH_3(CH_2)_4C{\equiv}CH \longrightarrow CH_3(CH_2)_6OH$

(j) $CH_3(CH_2)_4C{\equiv}CH \longrightarrow CH_3(CH_2)_4\overset{\overset{O}{\|}}{C}CH_3$

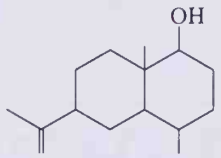
(k) $CH_3(CH_2)_4C{\equiv}CH \longrightarrow CH_3(CH_2)_4CH_2\overset{\overset{O}{\|}}{C}H$

(l) 

9.33 Following are structural formulas for two constitutional isomers of molecular formula $C_{15}H_{26}O$:



A



B

(a) How might you oxidize the primary alcohol of (A) to an aldehyde without affecting either of the carbon-carbon double bonds?

(b) How might you oxidize the secondary alcohol of (B) to a ketone without affecting the carbon-carbon double bond?

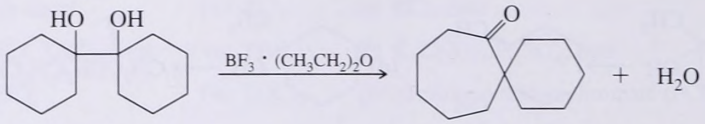
(c) How many *cis-trans* isomers are possible for each compound?

(d) Draw the most stable *cis-trans* isomer of alcohol (B), showing each cyclohexane ring in a chair conformation. *Hint:* Review the relative stabilities of axial and equatorial substituents (Section 2.6B), and of *cis*-decalin and *trans*-decalin (Section 2.7B).

(e) Show that the carbon skeleton of each can be divided into three isoprene units joined head to tail and then cross-linked at one or more places.

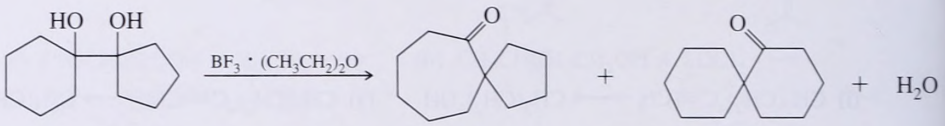
Pinacol Rearrangement

9.34 Heating six-member and larger cyclic diols with concentrated sulfuric acid gives mainly dienes and only small amounts of spiroketones by way of a pinacol rearrangement. Pinacol rearrangement of six-member and larger cyclic diols can be effected, however, by use of boron trifluoride etherate at 0°C. Propose a mechanism for the following boron trifluoride etherate catalyzed pinacol rearrangement:



Spiro[5.6]dodecan-7-one

9.35 It is one of the postulates of the internal strain theory of rings that (1) a six-member ring with all sp^3-hybridized carbons is less strained than a five-member ring with all sp^3-hybridized carbons and (2) a five-member ring with an sp^2 carbon is less strained than a six-member ring with an sp^2 carbon. The following cyclic diol can, in principle, undergo pinacol rearrangement catalyzed by boron trifluoride etherate to give isomeric spiroketones. In practice, only one of the possible spiroketones is formed. Using the above-mentioned postulates, predict which of the two is formed.



Spiro[4.6]undecan-6-one Spiro[5.5]undecan-1-one

Qualitative Organic Analysis

9.36 Show how you might distinguish between the members of each pair of compounds by a simple chemical test. In each case, tell what test you perform, what you expect to observe, and write an equation for each positive test.

(a) cyclohexanol and cyclohexene

(b) cyclohexanol and cyclohexane

(c) ethanol and 1,2-dimethoxyethane

(d) 1-butanol and 2-methyl-2-propanol

(e) 1-pentanol and 1-pentanethiol

Compact disks are made of polyvinyl chloride. (Charles D. Winters)

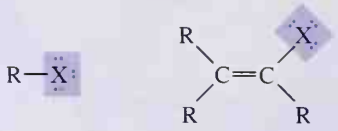
10

ALKYL HALIDES

Compounds containing a halogen covalently bonded to an sp^3 carbon are named haloalkanes, or in the common system of nomenclature, alkyl halides. Compounds of this class can be synthesized easily from alkanes, alkenes, and alcohols and so are readily available. In this chapter we review reactions by which alkyl halides can be synthesized and then study two of their characteristic reactions: nucleophilic substitution and β-elimination. By these reactions alkyl halides can be converted to compounds with other functional groups, including alcohols, ethers, thiols, thioethers, amines, nitriles, alkenes, and alkynes. Thus, an understanding of nucleophilic substitution and β-elimination opens entirely new areas of organic chemistry for you.

10.1 Structure

The general symbol for an **alkyl halide** is R—X, where —X may be —F, —Cl, —Br, or —I. If halogen is bonded to a double bond of an alkene, it belongs to a class called **vinylic halides.**



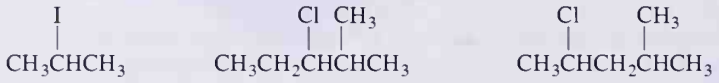
A haloalkane (An alkyl halide) A haloalkene (A vinylic halide)

In this chapter, we are concerned only with the synthesis, physical properties, and reactions of alkyl halides. Vinylic halides are unreactive toward the reaction conditions we describe.

10.2 Nomenclature

A. IUPAC System

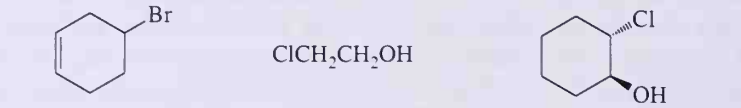
IUPAC names for haloalkanes are derived by naming the parent hydrocarbon according to the rules given in Section 2.3. The halogen atom or atoms are named as substituents (fluoro-, chloro-, bromo-, iodo-) and are listed in alphabetical order with other substituents. The location of each halogen atom on the parent chain is given by a number preceding the name of the halogen.



2-Iodopropane 3-Chloro-2-methylpentane 2-Chloro-4-methylpentane

In the second example, we apply the "lower number to the substituent first encountered" rule (rule 7, Section 2.3A). In the third example, numbering the chain from either direction gives a substituent on carbon 2. In this case, numbering the parent chain is determined by the location of the substituent named first in alphabetical order (rule 7, Section 2.3A).

In haloalkenes and haloalkynes, numbering the parent hydrocarbon is determined by the location of the carbon-carbon double or triple bond. In molecules containing functional groups designated by a suffix (for example, -ol, -al, -one, -oic acid), numbering is determined by the location of the functional group indicated by the suffix.



4-Bromocyclohexene 2-Chloroethanol *trans*-2-Chlorocyclohexanol

B. Common Names

Common names of haloalkanes consist of the common name of the alkyl group followed by the name of the halide as a separate word. Hence, the name **alkyl halide** is a common name for this class of compounds. In the following examples, the IUPAC name of the compound is given first and then, in parentheses, its common name.

CH_3CH_2Cl	$CH_2{=}CHCl$	$CH_2{=}CHCH_2Cl$
Chloroethane (Ethyl chloride)	Chloroethene (Vinyl chloride)	3-Chloropropene (Allyl chloride)
$CH_3CH_2CH_2Cl$	$CH_3\underset{\displaystyle Br}{\underset{\vert}{C}}HCH_3$	$CH_3\underset{\displaystyle I}{\underset{\vert}{C}}HCH_2CH_3$
1-Chloropropane (Propyl chloride)	2-Bromopropane (Isopropyl bromide)	2-Iodobutane (*sec*-Butyl iodide)

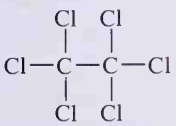
Several of the polyhalomethanes are common solvents and are generally referred to by their common, or trivial, names. Compounds of the type CHX_3 are called **haloforms.** The common name for $CHCl_3$, for example, is chloroform. It is from the name "chloroform" that the common name "methyl chloroform" is derived for the compound CH_3CCl_3. Methyl chloroform, known also as "trichlor," is a common solvent for commercial dry cleaning.

CH_2Cl_2	$CHCl_3$	CCl_4
Dichloromethane (Methylene chloride)	Trichloromethane (Chloroform)	Tetrachloromethane (Carbon tetrachloride)

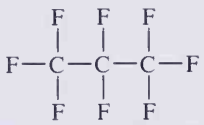
CH_3CCl_3

1,1,1-Trichloroethane
(Methyl chloroform, Trichlor)

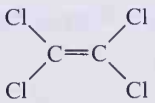
Hydrocarbons in which all hydrogens are replaced by halogens are named perhaloalkanes or perhaloalkenes.



Perchloroethane



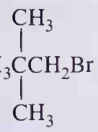
Perfluoropropane



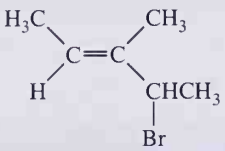
Perchloroethylene

EXAMPLE 10.1

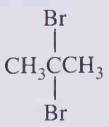
Give the IUPAC name and, where possible, a common name for each compound.

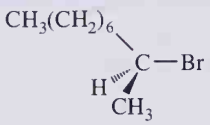
(a) 

(b) $(CH_3CH_2)_2CHCl$

(c) 

(d) CCl_2F_2

(e) 

(f) 

Solution

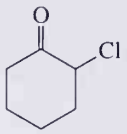
(a) 1-bromo-2,2-dimethylpropane. Its common name is neopentyl bromide.

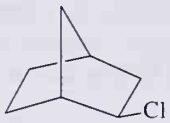
(b) 3-chloropentane. There is no common name for this alkyl group so there is no common name for this alkyl halide.
(c) (E)-4-bromo-3-methyl-2-pentene
(d) dichlorodifluoromethane, sold under the trade name Freon-12.
(e) 2,2-dibromopropane.
(f) (S)-2-bromononane.

PROBLEM 10.1

Give the IUPAC name, and where possible, a common name for each compound.

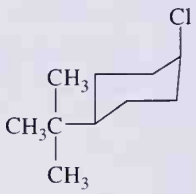
(a) CH_3CHCH_2Br (with CH_3 branch)

(b) 

(c) 

(d) $ClCH_2CH_2CH_2COH$ (with O double bond)

(e) $CH_3CHCHCH_3$ (with HO and Cl)

(f) 

10.3 Physical Properties

A. Polarity

Each of the halogens is more electronegative than carbon (Table 1.3) and hence a C—X bond is polarized with a partial negative charge on halogen and a partial positive charge on carbon. Table 10.1 shows that each of the halomethanes has a substantial dipole moment. The magnitude of a dipole moment depends on the size of the partial charges and the distance between them. For the halomethanes, it decreases as the electronegativity of halogen decreases, and increases as the bond length increases. These two trends run counter to each other, with the result that chloromethane has the largest dipole moment of the series.

Table 10.1 Dipole moments (gas phase) of halomethanes

Halomethane	Electronegativity of Halogen	Bond Length (nm)	Dipole Moment (debyes: D)
CH_3F	4.0	0.138	1.82
CH_3Cl	3.0	0.177	1.94
CH_3Br	2.8	0.194	1.79
CH_3I	2.5	0.214	1.64

B. Boiling Point

Boiling points of several low-molecular-weight alkyl halides and the alkanes from which they are derived are given in Table 10.2. There are several trends to be noticed from this data.

First, constitutional isomers with branched chains have lower boiling points than straight-chain isomers (Section 2.8). Compare, for example, the boiling points of straight-chain butyl bromide (bp 100°C) with the more spherical and compact *tert*-butyl bromide (bp 72°C). Branched-chain isomers have lower boiling points because they have a more spherical shape and, therefore, decreased area of contact and magnitude of van der Waals forces between them.

Second, for an alkane and alkyl halide of comparable size and shape, the alkyl halide has a higher boiling point. Compare, for example, the boiling points of ethane (bp −89°C) and methyl bromide (bp 4°C). Although both molecules are roughly the same size (the sizes of $-CH_3$ and —Br are almost identical) and have roughly the same effective contact area, the boiling point of methyl bromide is considerably higher than that of ethane. This difference is due almost entirely to the greater **polarizability** of the three unshared pairs of electrons on halogen compared with the polarizability of the shared electron pairs in the hydrocarbon of comparable size and shape. Recall from Section 2.8 that the strength of dispersion forces, the weakest of all intermolecular forces, depends on the polarizability of electrons, which in turn depends on how tightly they are held to the nucleus. The higher the principal quantum number of electrons, the greater their polarizability. In addition, unshared electron pairs have a higher polarizability than electrons shared in a covalent bond.

Third, the boiling points of alkyl fluorides are even lower than those of hydrocarbons of comparable molecular weight. Compare, for example, the boiling points of hexane (MW 86.2, bp 69°C) and 1-fluoropentane (MW 90.1, bp 63°C), and of the boiling points of 2-methylpropane (MW 58.1, bp −1°C) and 2-fluoropropane (MW 62.1, bp −11°C). These differences are due to the small size of fluorine, the tightness with which its electrons are held, and their particularly low polarizability. The distinctive properties of fluorocarbons, for example, the nonstick properties of polytetrafluoroethylene (Teflon), are also a consequence of the uniquely low polarizability of electron pairs of fluorine.

Table 10.2 Boiling points of some low-molecular-weight alkanes and alkyl halides

		Boiling Point (°C)				
Alkyl Group	Name	H	F	Cl	Br	I
CH_3—	methyl	−161	−78	−24	4	43
CH_3CH_2—	ethyl	−89	−37	13	38	72
$CH_3(CH_2)_2$—	propyl	−45	3	46	71	102
$(CH_3)_2CH$—	isopropyl	−45	−11	35	60	89
$CH_3(CH_2)_3$—	butyl	0	32	77	100	130
$CH_3CH_2(CH_3)CH$—	*sec*-butyl	0	25	67	90	119
$(CH_3)_2CHCH_2$—	isobutyl	−1	16	68	91	120
$(CH_3)_3C$—	*tert*-butyl	−1	12	51	72	98
$CH_3(CH_2)_4$—	pentyl	36	63	108	129	157
$CH_3(CH_2)_5$—	hexyl	69	92	134	155	181

Table 10.3 Densities of some low-molecular-weight alkyl halides

		Density of Liquid (g/mL) at 25°C		
Alkyl Group	Name	Cl	Br	I
CH_3—	methyl	—	—	2.279
CH_3CH_2—	ethyl	—	1.460	1.936
$CH_3(CH_2)_2$—	propyl	0.891	1.354	1.749
$(CH_3)_2CH$—	isopropyl	0.862	1.314	1.703
$CH_3(CH_2)_3$—	butyl	0.886	1.276	1.615
$(CH_3)_3C$—	*tert*-butyl	0.842	1.221	1.545
$CH_3(CH_2)_5$—	hexyl	0.879	1.174	1.440

C. Density

The densities of liquid alkyl halides are greater than those of hydrocarbons of comparable molecular weight because of the halogens' larger mass to volume ratio. A bromine atom and a methyl group have almost identical sizes, and yet bromine has a mass of 79.9 atomic mass units (amu) compared with 15 amu for methyl. Table 10.3 gives densities for some low-molecular-weight alkyl halides that are liquid at 25°C. The densities of all liquid alkyl bromides and alkyl iodides are greater than that of water. Although the density of liquid alkyl chlorides is less than that of water, further substitution of chlorine increases the density to the point where polychloroalkanes have a greater density than water (Table 10.4).

D. Bond Lengths and Bond Strengths

With the exception of C—F bonds, C—X bonds are weaker than C—H bonds (Table 10.5). The length of a C—X bond increases as the strength of the bond decreases and as the atomic size of the halogen increases. These relationships between bond strength and bond length help us to understand the difference in the ease with which alkyl halides undergo reactions that involve breaking C—X bonds. Alkyl fluorides, for example, with the strongest and shortest C—X bonds, are highly resistant to bond breaking under most conditions. It is this characteristic inertness that makes polyfluoroalkanes, such as Teflon, such useful materials.

Table 10.4 Density of polyhalomethanes

	Density of Liquid (g/mL) at 25°C		
Alkyl Group	X = Cl	Br	I
CH_2X_2	1.327	2.497	3.325
CHX_3	1.483	2.890	4.008
CX_4	1.594	3.273	4.23

Table 10.5 Average bond dissociation energies for C—H and C—X bonds

Bond	Bond Length (nm)	Bond Dissociation Energy (kcal/mol)
C—H	0.109	90–100
C—F	0.142	105
C—Cl	0.178	80
C—Br	0.193	65
C—I	0.214	50

10.4 Preparation

Alkyl halides are most commonly prepared from alcohols. They can also be prepared by halogenation of alkanes, and by addition of HX and X_2 to alkenes. Let us briefly review these methods of preparation.

A. Conversion of an Alcohol to an Alkyl Halide

Reaction with HX

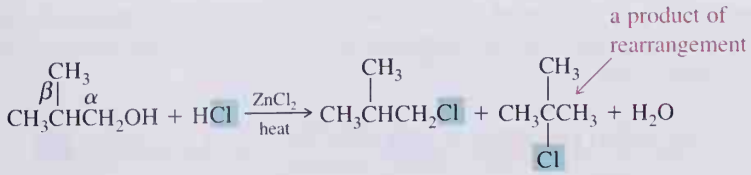
Treatment of an alcohol with concentrated HCl, HBr, or HI converts the alcohol to an alkyl halide (Section 9.5D). Reaction of all classes of alcohols with these reagents begins by proton transfer to oxygen to form an oxonium ion. Primary alcohols then react with halide ion by direct displacement of H_2O in an S_N2 mechanism.

$$CH_3CH_2CH_2CH_2OH + HCl \xrightarrow[\text{heat}]{ZnCl_2} CH_3CH_2CH_2CH_2Cl + H_2O$$

Tertiary alcohols react by an S_N1 mechanism. Loss of water from the oxonium ion forms a carbocation intermediate, which then reacts with halide ion to give the alkyl halide.

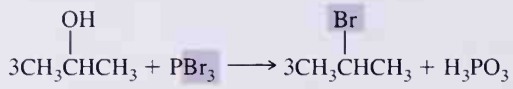
$$\begin{array}{l} CH_3 \\ | \\ CH_3COH \\ | \\ CH_3 \end{array} + HCl \xrightarrow{25^\circ} \begin{array}{l} CH_3 \\ | \\ CH_3CCl \\ | \\ CH_3 \end{array} + H_2O$$

Secondary alcohols react by loss of H_2O to form a carbocation intermediate, which may react with halide ion, or which may undergo rearrangement to a more stable carbocation and then react with halide ion. Primary alcohols with extensive β-branching react by simultaneous loss of water and rearrangement.



Reaction with Phosphorus Halides

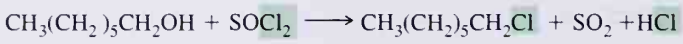
Treatment of an alcohol with PCl_3 or PBr_3 converts the alcohol to an alkyl chloride or bromide (Section 9.5D). Although some carbocation rearrangement may occur with these reagents, there is less than in reaction with HCl, HBr, or HI.



$$3CH_3CHCH_3 + PBr_3 \longrightarrow 3CH_3CHCH_3 + H_3PO_3$$

Reaction with Thionyl Chloride

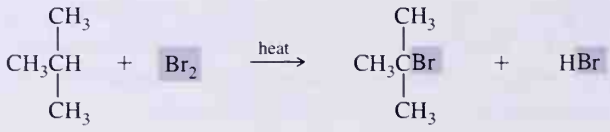
Thionyl chloride, $SOCl_2$, is often the reagent of choice to convert an alcohol to an alkyl chloride.



$$CH_3(CH_2)_5CH_2OH + SOCl_2 \longrightarrow CH_3(CH_2)_5CH_2Cl + SO_2 + HCl$$

B. Halogenation of Alkanes

Radical halogenation of alkanes (Section 2.9B) is seldom used in the laboratory for the preparation of alkyl halides, except in cases in which regioselectivity is very high, as for example, radical bromination of 2-methylpropane. The regioselectivity of radical bromination is very high for 3° versus 1° hydrogens, and only one product is formed.

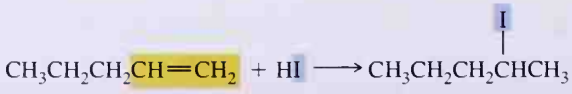


$$(CH_3)_2CHCH_3 + Br_2 \xrightarrow{\text{heat}} (CH_3)_3CBr + HBr$$

2-Methylpropane (Isobutane) — 2-Bromo-2-methylpropane (*tert*-butyl bromide)

C. Addition of HX to Alkenes

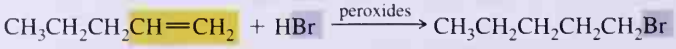
Electrophilic addition of HX to alkenes (Section 5.3B) is highly regioselective, especially so when the reactive intermediate is a 3° carbocation. Thus, this method generally leads to a single constitutional isomer.



$$CH_3CH_2CH_2CH{=}CH_2 + HI \longrightarrow CH_3CH_2CH_2CHCH_3$$

1-Pentene — 2-Iodopentane

The regioselectivity of addition of HBr (but not of HCl or HI) to an alkene is reversed in the presence of peroxides (Section 5.5). Under these conditions, reaction proceeds by a radical chain mechanism.

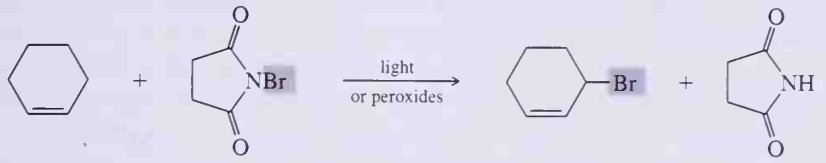


$$CH_3CH_2CH_2CH{=}CH_2 + HBr \xrightarrow{\text{peroxides}} CH_3CH_2CH_2CH_2CH_2Br$$

1-Pentene — 1-Bromopentane

D. Allylic Halogenation

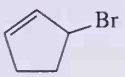
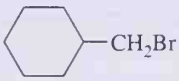
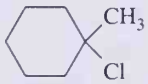
Because of the unique stability of allylic radicals (Section 5.6), radical substitution by halogen takes place regioselectively at allylic carbons and leads to the corresponding halides in good yield. By using *N*-bromosuccinimide as a source of bromine, allylic brominations can be carried out at or slightly above room temperature.



Cyclohexene *N*-Bromosuccinimide (NBS) 3-Bromocyclohexene Succinimide

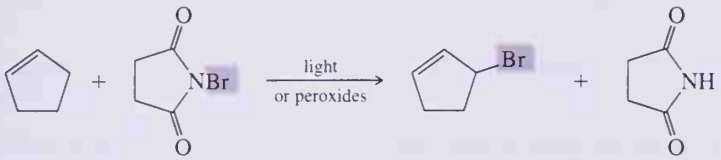
EXAMPLE 10.2

What alkene or alkenes and reaction conditions give each compound in good yield?

(a)  **(b)**  **(c)** 

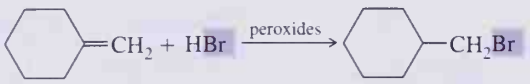
Solution

(a) This allylic bromide can be formed by radical bromination of cyclopentene. Use bromine at elevated temperature or *N*-bromosuccinimide at room temperature.

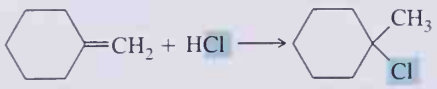


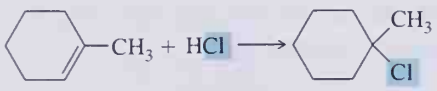
Cyclopentene NBS 3-Bromocyclopentene Succinimide

(b) This primary alkyl bromide can be formed by radical addition of HBr to methylenecyclohexane in the presence of peroxides (Section 5.5).



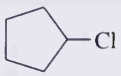
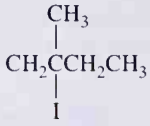
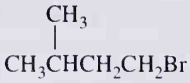
(c) This tertiary alkyl chloride can be formed by electrophilic addition of HCl to either methylenecyclohexane or to 1-methylcyclohexene.





PROBLEM 10.2

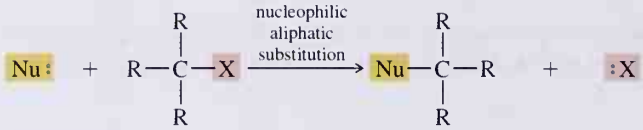
What alcohol and reaction conditions give each compound in good yield?

(a)  (b)  (c) 

10.5 Reactions with Bases and Nucleophiles

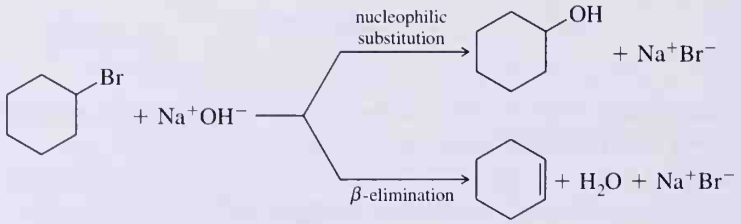
By far the most carefully studied behavior of alkyl halides is their reaction with electron-rich reagents, such as HO^- and RO^-. These electron-rich reagents are both Lewis bases and nucleophiles.

A **nucleophile** (nucleus-seeking) is any reagent that can donate an unshared pair of electrons to form a new covalent bond. In this section we study nucleophilic aliphatic substitution. In the following equation Nu: is the nucleophile, X is the leaving group, and substitution takes place on an sp^3-hybridized carbon atom. This equation ignores charges for the moment. As we shall see, the nucleophile may be either neutral or negative, and the leaving group may also be either neutral or negative.



Nucleophile (Lewis base) — Leaving group (also a Lewis base)

Because all electron-rich reagents are both bases and nucleophiles, it follows that nucleophilic substitution and base-promoted **β-elimination** (Section 4.5) are competing reactions. Hydroxide ion, for example, is both a nucleophile and a base. In the following example, it undergoes reaction with bromocyclohexane as a nucleophile to give cyclohexanol, and reaction as a base to give cyclohexene.



In this chapter, we consider first nucleophilic substitution, and then base-induced β-elimination. After we consider each reaction type separately, we consider them together and the nature of the competition between them.

10.6 Nucleophilic Aliphatic Substitution

Nucleophilic substitution, any reaction in which one nucleophile is substituted for another, is one of the most important reactions of alkyl halides and can lead to the formation of a wide variety of new functional groups, many of which are illustrated in Table 10.6.

As illustrated in Table 10.6, if the nucleophile is negatively charged, then the atom donating the pair of electrons in a substitution reaction becomes neutral in the product. If the nucleophile is neutral, then the atom donating the pair of electrons in the substitution reaction becomes positively charged in the product.

The solvent plays an essential role in nucleophilic substitutions. First and foremost, it provides a medium in which the reactants are dissolved and in which reaction takes place. Common solvents in which nucleophilic substitution reactions are carried out can be divided into two groups: protic solvents and aprotic solvents. **Protic solvents** are hydrogen bond donors; the most common of these contain —OH groups and for this reason are often called hydroxylic solvents. **Aprotic solvents** cannot serve as hydrogen bond donors; nowhere in the molecule is a hydrogen bonded to an atom of high electronegativity.

Furthermore, solvents are classified as polar and nonpolar. **Dielectric constant,** the most commonly used measure of solvent polarity, is defined by reference to the electrostatic force of attraction between two charges, Q and Q', of opposite sign separated by a distance r in a vacuum. This force of attraction is reduced if a substance that provides a degree of insulation is placed between the two charges.

Table 10.6 Some nucleophilic substitution reactions

Reaction: $Nu:^- + CH_3Br \longrightarrow CH_3Nu + Br^-$

Nucleophile		Product	Class of Compound
$HO:^-$	$\longrightarrow$	$CH_3—\ddot{O}H$	an alcohol
$RO:^-$	$\longrightarrow$	$CH_3—\ddot{O}R$	an ether
$HS:^-$	$\longrightarrow$	$CH_3—\ddot{S}H$	a thiol (mercaptan)
$RS:^-$	$\longrightarrow$	$CH_3—\ddot{S}R$	a sulfide (thioether)
$HC{\equiv}C:^-$	$\longrightarrow$	$CH_3—C{\equiv}CH$	an alkyne
$:C{\equiv}N:^-$	$\longrightarrow$	$CH_3—C{\equiv}N:$	a nitrile
$:\ddot{I}:^-$	$\longrightarrow$	$CH_3—\ddot{I}:$	an alkyl iodide
$:NH_3$	$\longrightarrow$	$CH_3—NH_3^+$	an alkylammonium ion
$H\ddot{O}H$	$\longrightarrow$	$CH_3—\overset{+}{\ddot{O}}(H)—H$	an alcohol (after proton transfer)
$CH_3\ddot{O}H$	$\longrightarrow$	$CH_3—\overset{+}{\ddot{O}}(H)CH_3$	an ether (after proton transfer)

Table 10.7 Common protic solvents

Solvent	Structure	Dielectric Constant
Polar		
Water	H_2O	79
Formic acid	HCO_2H	59
Methanol	CH_3OH	33
Ethanol	CH_3CH_2OH	24
Nonpolar		
Acetic acid	CH_3CO_2H	6.2

$$\text{Force of attraction} = \frac{Q \times Q'}{\text{dielectric constant} \times r^2}$$

The greater the value of the dielectric constant for a solvent, the smaller the interaction between ions of opposite charge dissolved in that solvent. As an arbitrary guideline, we say that a solvent is polar if it has a dielectric constant of 20 or greater. A solvent is nonpolar if it has a dielectric constant of less than 20.

The common protic solvents for nucleophilic substitution reactions are water, low-molecular-weight alcohols, and low-molecular-weight carboxylic acids (Table 10.7). Each is able to solvate ionic substances by electrostatic interaction between its partially negatively charged oxygen(s) and cations, and between its partially positively charged hydrogen and anions. By our arbitrary guideline, water, formic acid, methanol, and ethanol are classified as **polar protic solvents.** Acetic acid is classified as a **nonpolar protic solvent.**

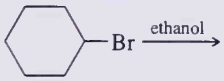
Table 10.8 Common aprotic solvents

Solvent	Structure	Dielectric Constant
Polar		
Dimethyl sulfoxide	$CH_3\overset{\overset{O}{\|}}{S}CH_3$	48.9
Acetonitrile	$CH_3C{\equiv}N$	37.5
N,*N*-Dimethylformamide	$HC\overset{\overset{O}{\|}}{N}(CH_3)_2$	36.7
Acetone	$CH_3\overset{\overset{O}{\|}}{C}CH_3$	20.7
Nonpolar		
Dichloromethane	CH_2Cl_2	9.1
Diethyl ether	$CH_3CH_2OCH_2CH_3$	4.3
Benzene		2.3

The aprotic solvents most commonly used for nucleophilic substitution reactions are given in Table 10.8. Of these, dimethyl sulfoxide (DMSO), acetonitrile, dimethylformamide (DMF), and acetone are classified as **polar aprotic solvents.** Dichloromethane, diethyl ether, and benzene are classified as **nonpolar aprotic solvents.**

EXAMPLE 10.3

Complete the following nucleophilic substitutions:

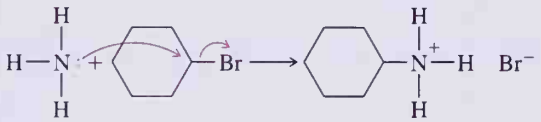
(a) $NaI + CH_3CH_2CH_2Cl \xrightarrow{\text{acetone}}$ **(b)** $NH_3 +$  $\xrightarrow{\text{ethanol}}$

(c) $CH_3CH_2ONa + CH_2{=}CHCH_2Cl \xrightarrow{\text{ethanol}}$

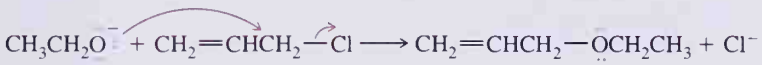
Solution

(a) The nucleophile is iodide ion, and it displaces chloride ion.

(b) The nucleophile is ammonia, and it displaces bromide ion.

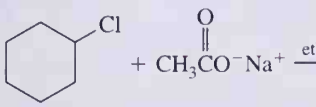
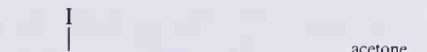


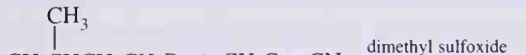
(c) The nucleophile is ethoxide ion, and it displaces chloride ion.



PROBLEM 10.3

Complete the following nucleophilic substitution reactions:

(a)  **(b)** 

(c) 

10.7 Mechanisms of Nucleophilic Aliphatic Substitution

On the basis of a wealth of experimental observations developed over a 50-year period, two limiting mechanisms for nucleophilic substitutions were proposed. A fundamental difference between them is the timing of bond breaking between carbon and the leaving group and bond making between carbon and the nucleophile. At one extreme, the two processes are concerted, meaning that bond breaking and bond making occur simultaneously. Thus, departure of the leaving group is assisted by the incoming nucleophile. This mechanism is

designated S_N2, where S stands for *S*ubstitution, N for *N*ucleophilic, and *2* for the molecularity determined by kinetics. A **bimolecular reaction** is one in which two reactants (for an S_N2 reaction of an alkyl halide, both the alkyl halide and the nucleophile) undergo a chemical change in the transition state of the rate-determining step.

Illustrated in Figure 10.1 is an S_N2 mechanism for reaction of hydroxide ion and methyl bromide to form methanol and bromide ion. Note that the nucleophile is shown

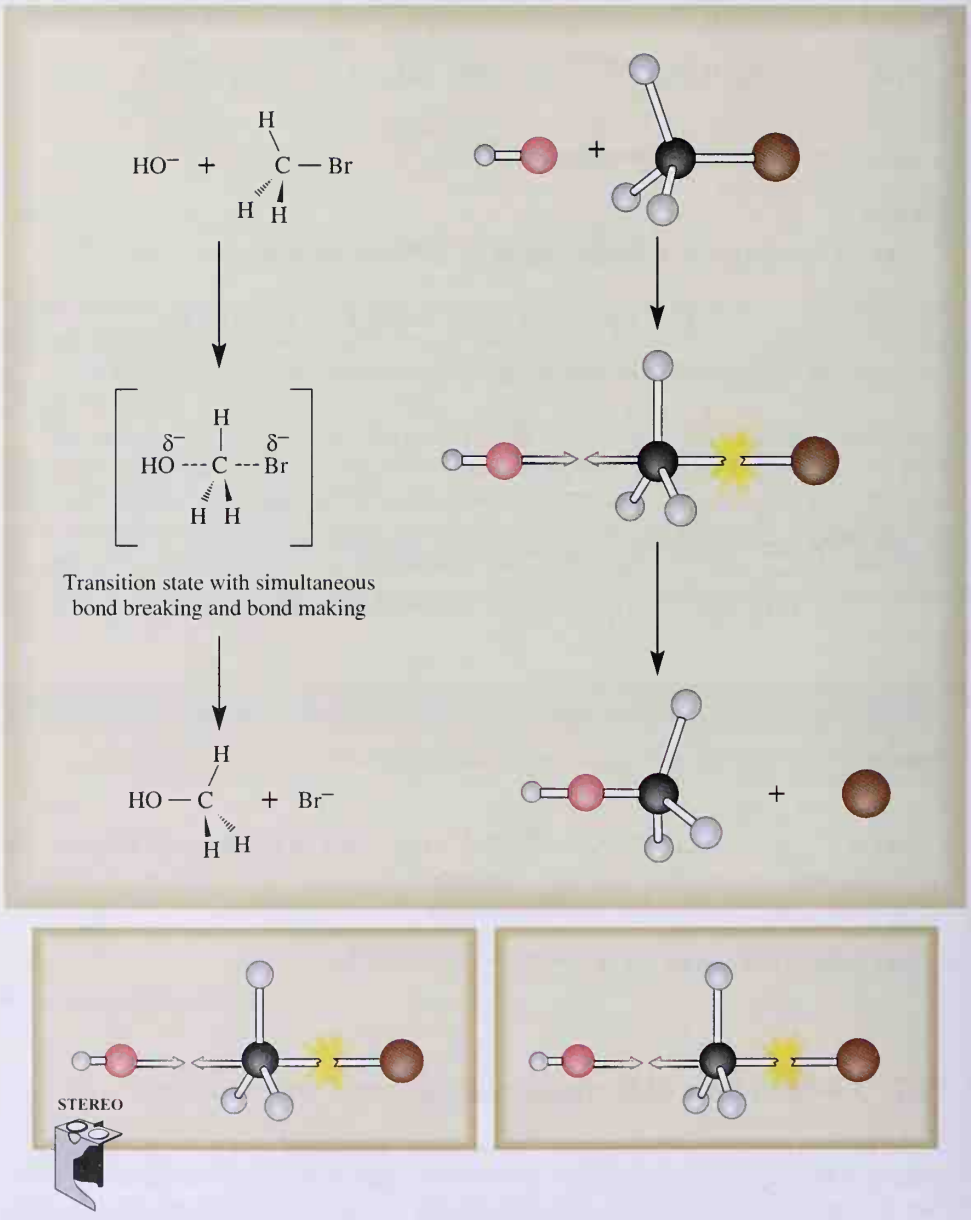


Figure 10.1
An S_N2 mechanism for reaction of methyl bromide with hydroxide ion. Bond making and bond breaking are concerted.

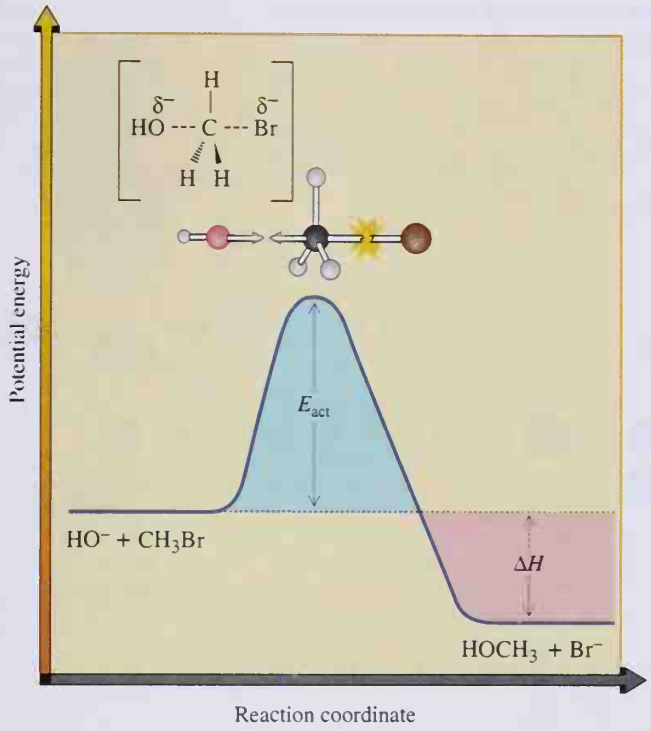


Figure 10.2
An energy diagram for an S_N2 reaction. There is one transition state and no reactive intermediate.

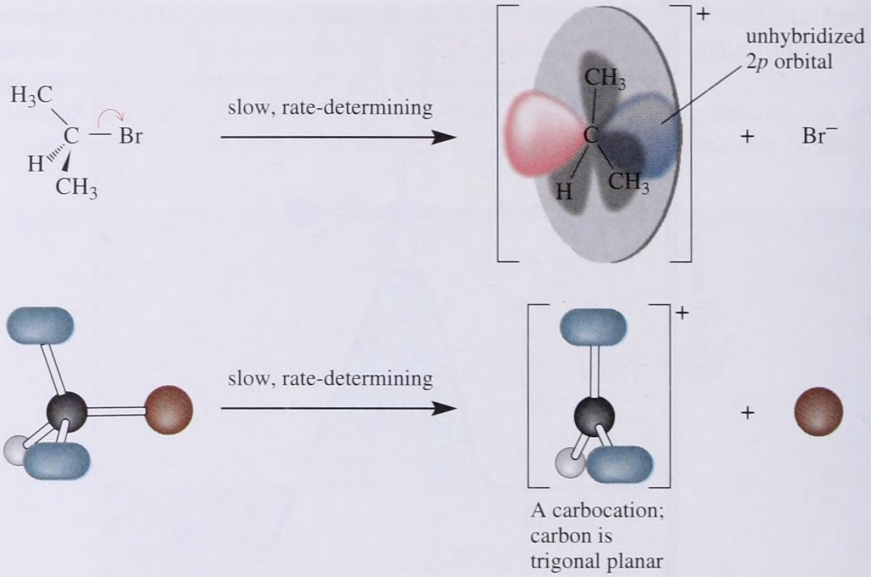
attacking the reactive center from the side of the molecule opposite from the leaving group; that is, reaction involves backside attack of the nucleophile. We present evidence in the following section to show that backside attack is a necessary characteristic of all S_N2 reactions. Shown in Figure 10.2 is a energy diagram for an S_N2 reaction. There is a single transition state and no reactive intermediate.

At the other extreme, bond breaking is entirely completed before bond making with the nucleophile begins. This mechanism is known as $\mathbf{S_N1}$, where S stands for *S*ubstitution, N for *N*ucleophilic, and *1* for the molecularity of the reaction. A **unimolecular reaction** is one in which only one reactant (for an S_N1 reaction of an alkyl halide, only the alkyl halide) is involved in the transition state for the rate-determining step. The two steps of an S_N1 reaction are illustrated by the reaction between 2-bromopropane with methanol to form isopropyl methyl ether and HBr (Figure 10.3). In this example, the nucleophile is also the solvent, and the reaction is called solvolysis. **Solvolysis** is a nucleophilic substitution in which the nucleophile is a molecule of the solvent.

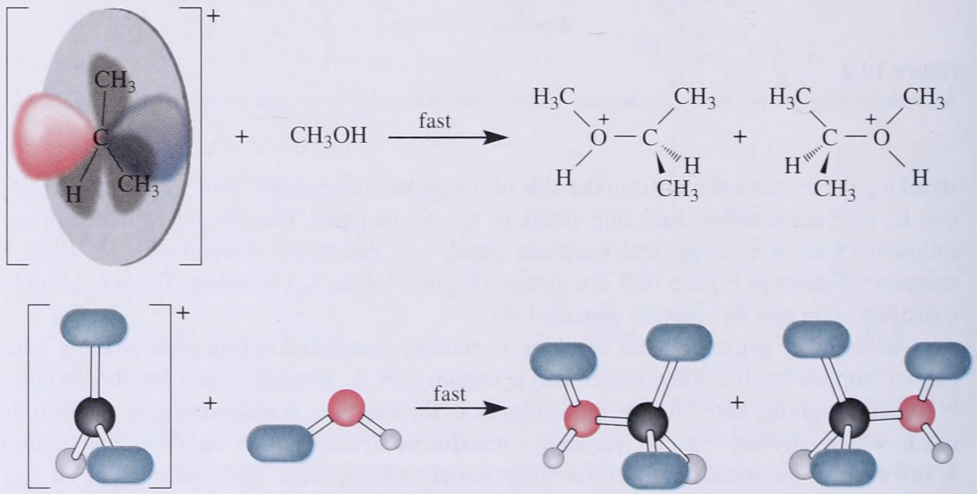
$$\underset{\text{2-Bromopropane}}{CH_3CHCH_3 \\ | \\ Br} + \underset{\text{Methanol}}{CH_3OH} \xrightarrow{\text{methanol}} \underset{\text{Isopropyl methyl ether}}{CH_3CHCH_3 \\ | \\ OCH_3} + HBr$$

Ionization of the C—X bond occurs in Step 1 to form a carbocation, which then undergoes reaction with methanol, the nucleophile, in Step 2 to give an oxonium ion. Attack of the

Step 1: Ionization of C—X bond to form a carbocation.



Step 2: Reaction of the carbocation with a nucleophile.



Step 3: Proton transfer to methanol to give isopropyl methyl ether.

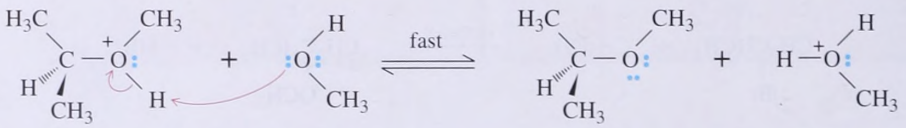


Figure 10.3
An S_N1 mechanism for solvolysis of 2-bromopropane in methanol. Bond breaking is completed in Step 1 before bond making begins in Step 2. Proton transfer in Step 3 gives isopropyl methyl ether and solvated HBr.

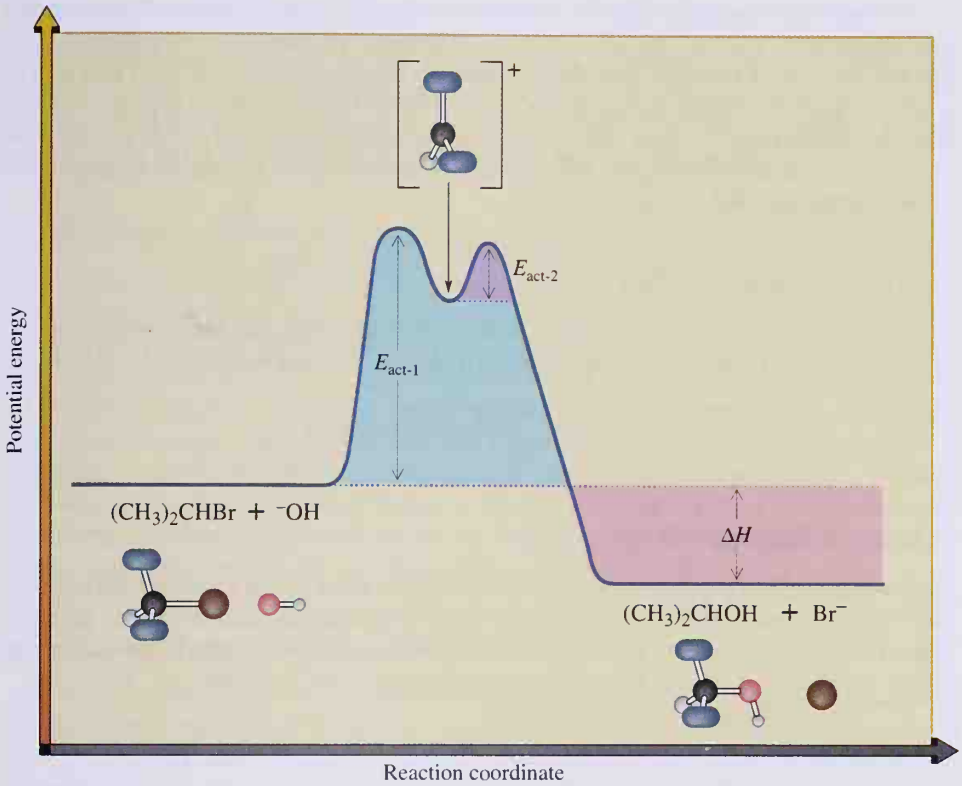


Figure 10.4
An energy diagram for an S_N1 reaction of 2-bromopropane and hydroxide ion. There are two transition states and one reactive intermediate. Step 1 has the higher energy of activation and is the rate-determining step.

nucleophile occurs with equal probability from either face of the planar carbocation intermediate. Loss of H^+ from the oxonium ion then gives isopropyl methyl ether. The energy of activation for formation of the carbocation in Step 1 is greater than that for reaction of the carbocation with the nucleophile in Step 2, and, hence, the first step in this mechanism is rate-determining. For the reaction shown in Figure 10.4, one transition state leads to formation of the carbocation intermediate and another to reaction of the carbocation intermediate with hydroxide ion to give the product.

Let us examine now the experimental evidence on which these two contrasting mechanisms are based. As we do, we consider the following questions:

1. What are the kinetics of nucleophilic substitutions?
2. What effect does the structure of the nucleophile have on the rate of reaction?
3. What is the stereochemistry of nucleophilic substitution when the leaving group is displaced from a tetrahedral stereocenter?
4. What effect does the structure of the alkyl halide have on the rate of reaction?
5. What effect does the structure of the leaving group have on the rate of reaction?
6. What is the role of the solvent?

A. Kinetics

The kinetic order of nucleophilic substitutions can be studied by measuring the effect on rate of varying concentrations of alkyl halide and nucleophile. Those reactions dependent only on concentration of alkyl halide are classified as S_N1; those dependent on concentration of both alkyl halide and nucleophile are classified as S_N2.

Because the transition state for formation of the carbocation intermediate in an S_N1 mechanism involves only the alkyl halide and not the nucleophile, it is a unimolecular process; the rate of the slow step depends only on the concentration of alkyl halide. The result is a first-order reaction; that is, the overall rate for the S_N1 reaction is proportional to [RX] and independent of [Nu]. In the following rate equation, the term k is called a specific rate constant. In this instance, the rate of reaction is expressed as the rate of disappearance of the starting material, 2-bromopropane.

$$\text{Rate} = -\frac{d[(CH_3)_2CHBr]}{dt} = k[(CH_3)_2CHBr]$$

By contrast, there is only one step in the S_N2 mechanism, and the transition state is bimolecular. The reaction is second-order: first-order in RX and first-order in nucleophile.

$$\text{Rate} = -\frac{d[CH_3Br]}{dt} = k[CH_3Br][OH^-]$$

B. Relative Nucleophilicity

Nucleophilicity is a kinetic property measured by the rate at which a nucleophile attacks a reference compound under a standardized set of experimental conditions. For example, relative nucleophilicities for a series of nucleophiles can be established by measuring the rate at which each displaces bromide ion from ethyl bromide in ethanol at 25°C.

$$CH_3CH_2Br + NH_3 \longrightarrow CH_3CH_2\overset{+}{N}H_3 + Br^-$$

From these studies, we can then make correlations between the structure of a nucleophile and its relative nucleophilicity.

Basicity is an equilibrium property measured by the position of equilibrium in an acid-base reaction, as, for example, the acid-base reaction between ammonia and water.

$$NH_3 + H_2O \rightleftharpoons NH_4^+ + OH^- \qquad K_b = \frac{[NH_4^+][OH^-]}{[NH_3]} = 1.8 \times 10^{-5}$$

Because all nucleophiles are bases as well, we also study correlations between nucleophilicity and basicity.

The solvent in which nucleophilic substitution is carried out has a marked effect not only on the rate of substitution but also on relative nucleophilicities. For a fuller understanding of the role of the solvent, let us consider nucleophilic substitution reactions carried out in the gas phase (where there is no solvent), in polar aprotic solvents, and in polar protic solvents. An organizing principle for substitution reactions in the gas phase and in solution is the following: The freer the nucleophile, the greater its nucleophilicity.

Table 10.9 Relative nucleophilicities (gas phase) of ions within a family

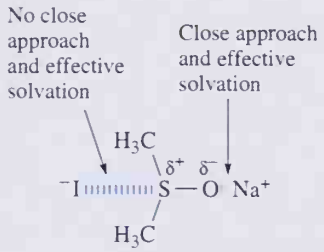
Family	Increasing nucleophilicity →						
Halogen family	I^-	<	Br^-	<	Cl^-	<	F^-
Oxygen family	CH_3S^-	<	CH_3O^-				

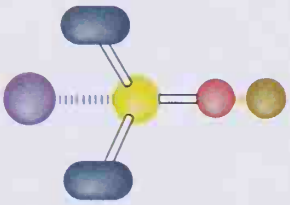
Nucleophilicity in the Gas Phase

For S_N2 reactions studied in the gas phase, a direct correlation exists between nucleophilicity and basicity; the stronger the base, the greater its nucleophilicity (Table 10.9). Among the halide ions, fluoride ion is the strongest base; it is also the strongest nucleophile. Iodide ion is the weakest base; it is also the weakest nucleophile.

Nucleophilicity in Polar Aprotic Solvents

The most commonly used polar aprotic solvents (DMSO, acetone, acetronitrile, and DMF) are very effective in solvating cations but are not nearly so effective in solvating anions. Consider, for example, DMSO. Because the negative end of its dipole can come close to the center of positive charge in a cation, it is effective in solvating cations. The positive end of its dipole, however, is shielded by surrounding groups (two methyls and one oxygen) and is less effective in solvating anions. The sodium ion of sodium iodide, for example, is effectively solvated by DMSO and acetone, but the iodide ion is only poorly solvated. Because anions are only poorly solvated in polar aprotic solvents, they participate readily in nucleophilic substitution reactions, and the relative nucleophilicities of halide ions are of the same order as those in the gas phase, that is, $F^- > Cl^- > Br^- > I^-$.





Nucleophilicity in Polar Protic Solvents

The relative nucleophilicities of halide ions in polar protic solvents are quite different from those in aprotic solvents (Table 10.10). In polar protic solvents, iodide ion, the least basic of the halide ions, has the greatest nucleophilicity. Conversely, fluoride ion, the most basic of the halide ions, has the smallest nucleophilicity. The reason for this reversal of correlation between nucleophilicity and basicity lies in the degree of solvation of anions in protic solvents compared with aprotic solvents. In polar aprotic solvents, anions are only weakly solvated and, therefore, relatively free to participate in nucleophilic substitution reactions. In polar protic solvents, however, anions are highly solvated by hydrogen bonding between the anion and solvent molecules. The negative charge on fluoride ion, the smallest of the halide ions, is concentrated in a small volume, and the very tightly held solvent shell constitutes a barrier between fluoride ion and substrate. Fluoride ion must be at least partially removed from its tightly held solvation shell before it can participate in nucleophilic substitution. The negative charge on iodide ion, the largest of the halide ions, is far less concentrated, the solvent shell is less tightly held, and iodide is considerably freer to participate in nucleophilic substitution reactions.

Table 10.10 Relative nucleophilicities of halide ions in aprotic and protic solvents

Solvent	Increasing nucleophilicity →						
Polar aprotic	I^-	<	Br^-	<	Cl^-	<	F^-
Polar protic	F^-	<	Cl^-	<	Br^-	<	I^-

Table 10.11 Relative nucleophilicities of atoms within a period

Period	Increasing nucleophilicity →						
Period 2	F^-	<	OH^-	<	NH_2^-	<	CH_3^-
Period 3	Cl^-	<	SH^-	<	PH_2^-		

Table 10.12 The effect of charge on nucleophilicity

Increasing nucleophilicity →

H_2O	<	OH^-
ROH	<	RO^-
NH_3	<	NH_2^-
RSH	<	RS^-

Table 10.13 Correlation of nucleophilicity and basicity for reagents with the same nucleophilic atom

Nucleophile	RCO^-	HO^-	RO^-
	Carboxylate ion	Hydroxide ion	Alkoxide ion
	Increasing nucleophilicity →		
Conjugate acid	RCOH	HOH	ROH
pK_a	4–5	15.7	16–18
	Decreasing acidity of conjugate acid →		

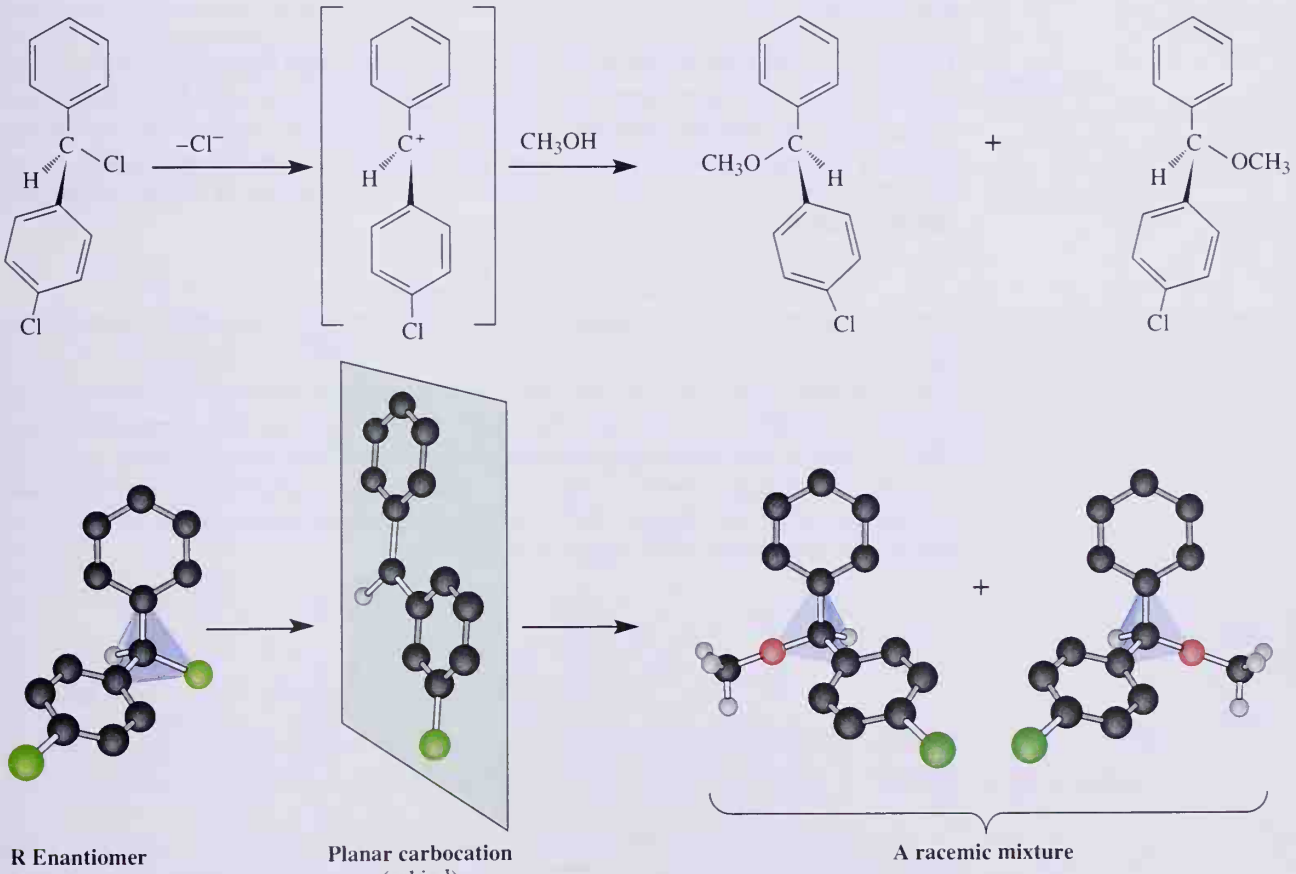
We can make the following additional generalizations about nucleophilicity:

1. Within a period of the periodic table, nucleophilicity increases from right to left (Table 10.11).
2. In a series of reagents with the same nucleophilic atom, anionic reagents are stronger nucleophiles than neutral reagents (Table 10.12).
3. When comparing reagents within a group where the nucleophilic atom is the same, the stronger the base, the greater the nucleophilicity. The oxygen nucleophiles in Table 10.13 are listed in order of increasing nucleophilicity. Below each, for comparison, is given the formula and pK_a of its conjugate acid. In this series, the carboxylic acid is the strongest acid, and, consequently, its anion is the weakest base. The carboxylate anion, the weakest base, is also the poorest nucleophile.

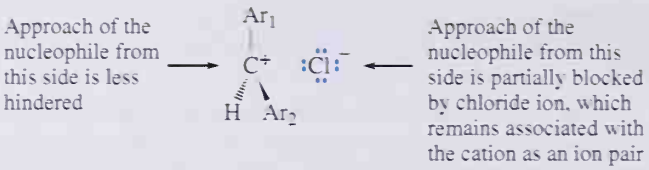
C. Stereochemistry

S_N1 Reactions

Experiments in which nucleophilic substitution takes place at a stereocenter provide us with information about the stereochemistry of the reaction. One of the first molecules to be studied was the chloride shown in the figure. When either enantiomer of this molecule undergoes nucleophilic substitution by an S_N1 pathway, the product is almost completely racemized. On ionization, this secondary halide forms an achiral carbocation. Attack of the nucleophile from the right gives the R enantiomer; attack from the left gives the S enantiomer. The R and S enantiomers are formed in equal amounts, and the product is a racemic mixture.



The S_N1 mechanism as initially proposed requires complete racemization of any product in which the carbon being substituted is a tetrahedral stereocenter. Although examples of complete racemization have been observed, it is much more common to find only partial racemization, with the more prevalent product being the one with inversion of configuration at the stereocenter undergoing reaction. This observation is accounted for by proposing that although bond breaking between carbon and the leaving group is complete, the leaving group remains associated for some time with the carbocation as an ion pair.



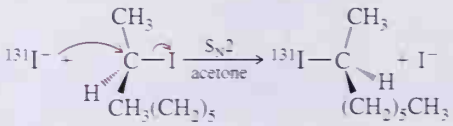
To the extent that the leaving group remains associated as an ion pair, it hinders approach of the nucleophile from that side of the carbocation with the result that more than 50% of the product is formed by attack of the nucleophile from the side of the carbocation opposite that of the leaving group.

S_N2 Reactions

That every second-order nucleophilic substitution proceeds with inversion of configuration was shown in an ingenious experiment designed by the English chemists E. D. Hughes and C. K. Ingold to study the exchange reaction between optically active 2-iodooctane and iodine-131, a radioactive isotope of iodine that decays by β-emission with a half-life of 8.07 days. Iodine-127, the naturally occurring isotope of iodine, is stable; it does not undergo radioactive decay.

$$CH_3(CH_2)_5\underset{\displaystyle I}{\underset{|}{C}}HCH_3 + {}^{131}I^- \xrightarrow[\text{acetone}]{S_N2} CH_3(CH_2)_5\underset{\displaystyle {}^{131}I}{\underset{|}{C}}HCH_3 + I^-$$

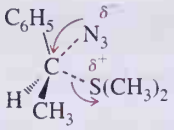
They first demonstrated that the reaction is second-order: first-order in 2-iodooctane and first-order in iodide ion. Therefore, the reaction proceeds by an S_N2 mechanism. They observed further that the rate of racemization of optically pure 2-iodooctane is exactly 2 times the rate of incorporation of iodine-131. This observation must mean, they reasoned, that each displacement of iodine-127 by iodine-131 proceeds with inversion of configuration as illustrated in the following equation:



Inversion of configuration in one molecule cancels the rotation of one molecule that has not reacted, so that two molecules become racemic. Inversion of configuration in 50% of the molecules results in 100% racemization.

For the majority of second-order substitution reactions studied early in these investigations, the incoming group was a negative ion and the leaving group departed as a negative ion. The transition state of minimum energy, it was argued, would have these two negatively charged species separated as far as possible, that is, at an angle of 180°. Thus, backside attack provides the transition state of minimum energy. But what would happen, it was asked, if the incoming nucleophile and leaving group were of opposite charge types? Would nucleophilic substitution then proceed with retention of configuration at the site of reaction? As a test case, Hughes and Ingold designed an experiment in which the incoming nucleophile was negatively charged and the leaving group was positively charged and departs as a neutral molecule.

Question: Might there be frontside attack if incoming and leaving groups are of opposite charge types?



They began with optically pure 1-chloro-1-phenylethane (Figure 10.5). In one set of reactions, the (S)-alkyl chloride was treated in Step 1 with azide ion, an S_N2 reaction known to involve inversion of configuration. The resulting (R)-azide was then treated in Step 2 with hydrogen in the presence of a transition metal catalyst to give an (R)-amine.

In another set of reactions, the (S)-alkyl chloride was treated in Step 3 with hydrosulfide ion in an S_N2 reaction also known to involve inversion of configuration. The (R)-thiol from Step 3 was then treated in Step 4 with methyl iodide to give an (R)-sulfonium ion. Reaction of this sulfonium ion with azide ion in Step 5 was the key reaction. If this nucleophilic substitution involved inversion of configuration, then the azide formed would have the S configuration, and reduction in Step 6 would give the (S)-amine. If, however, Step 5 involved frontside displacement, then the product would be the (R)-azide, which in turn would give the (R)-amine. The observed products of Steps 5 and 6 were the (S)-azide and the (S)-amine. The conclusion, then, was that even this nucleophilic substitution, involving incoming and leaving groups of opposite charge types, proceeds with inversion of configuration.

(Text continued on p. 380)

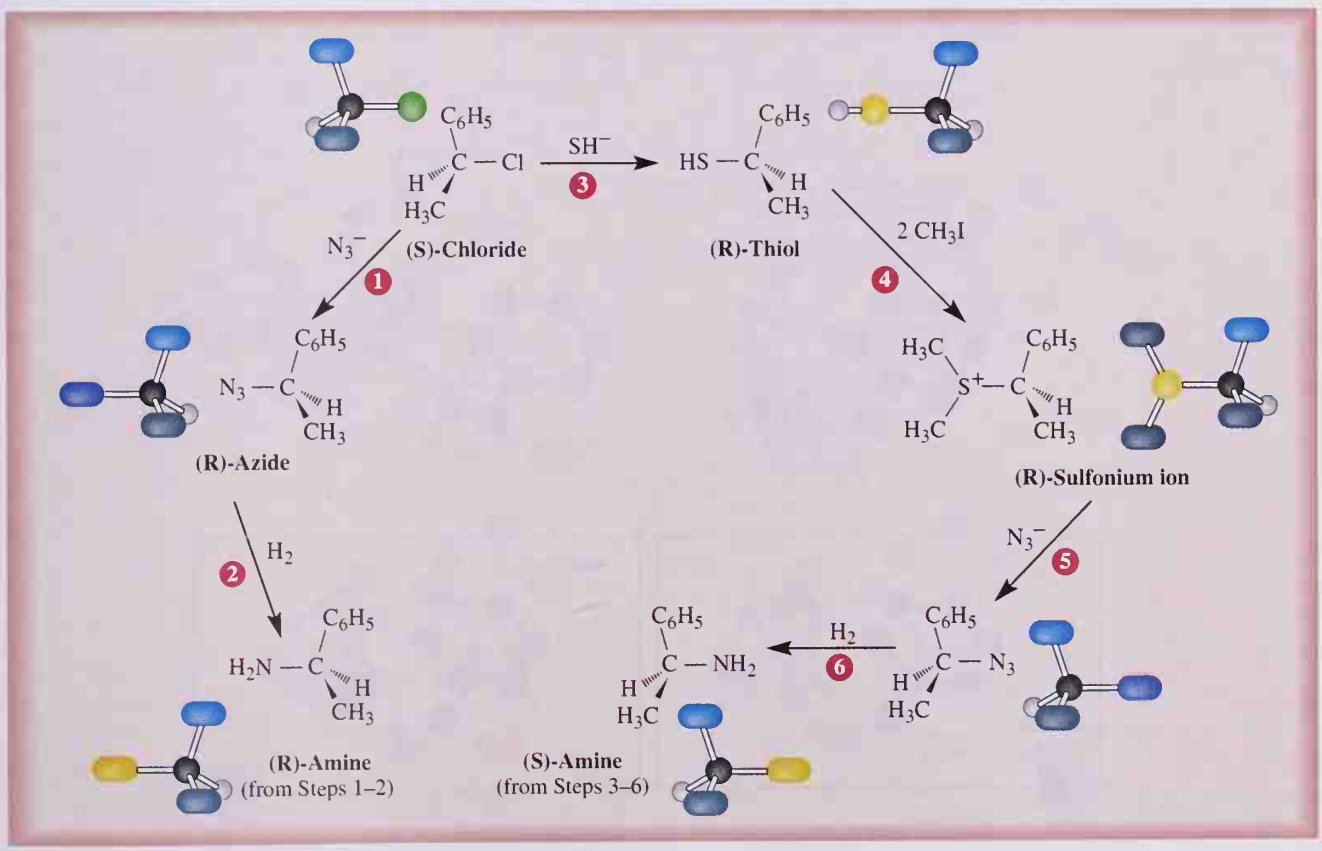
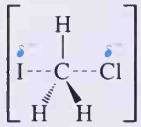


Figure 10.5
Inversion of configuration in S_N2 reactions, even when the nucleophile and leaving group are of opposite charge types.

CHEMISTRY IN ACTION

Testing the Shape of the S_N2 Transition State

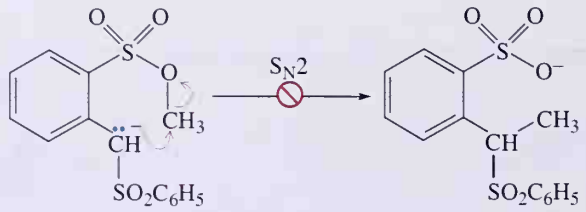
The S_N2 reaction is one of the most carefully investigated reactions in organic chemistry. Many studies have focused on S_N2 reactions at tetrahedral stereocenters, all of which have been shown to involve inversion of configuration. But not all carbons are stereocenters. For example, in the reaction of I^- with CH_3Cl, we predict that the reaction proceeds via a transition state characteristic of S_N2 reactions, with the entering group I^- and the leaving group Cl^- opposite each other.



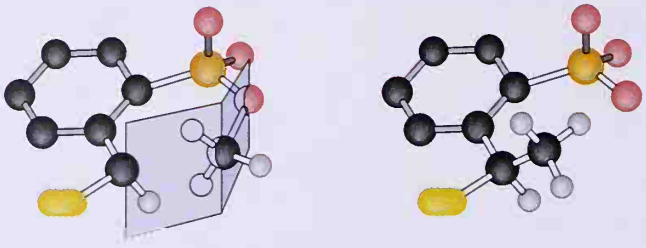
S_N2 transition state

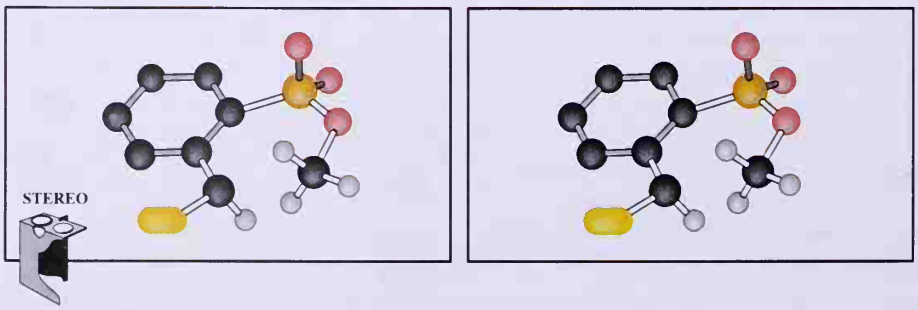
But, in this case, we have no easy way to correlate the geometry of the product CH_3I with the geometry of the starting material. In such cases, how can we be sure of the geometry of the transition state?

One solution to this problem has been provided by Professor Albert Eschenmoser and his coworkers at the Swiss Federal Institute of Technology who investigated the nucleophilic substitution reaction shown in the figure below. In this reaction, the nucleophile is R_2CH^-, and the leaving group is $C_6H_5SO_3^-$, both in the same molecule. Nucleophilic substitution does occur, but kinetic studies prove that the reaction is intermolecular; the nucleophile of one molecule displaces the leaving group of a second molecule. Eschenmoser and his colleagues explained this unusual and quite unexpected result in the



(The nucleophile and leaving group cannot achieve a coplanar geometry)

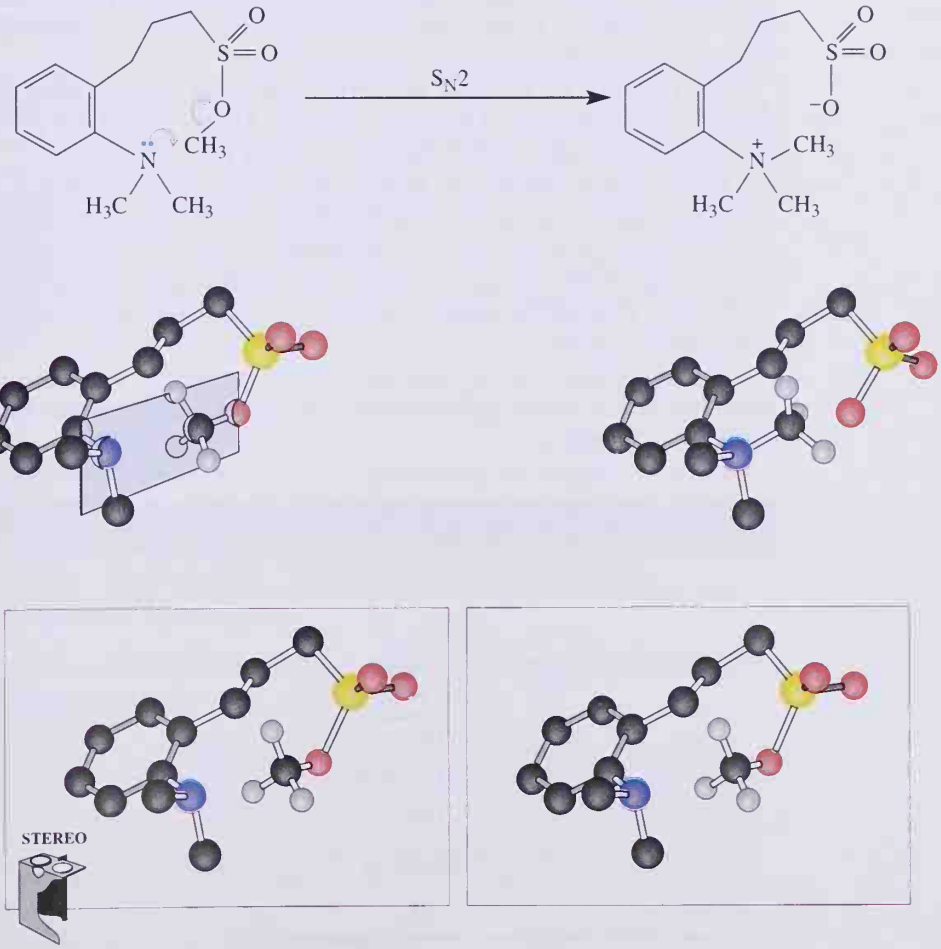




following way. Because of the geometry of the reacting molecule, the nucleophile and leaving group cannot achieve the 180° bond angle characteristic of the S_N2 transition state. The bond lengths in the six-member transition state are too short to allow such a geometry. Thus, the reaction is forced to be intermolecular (in much of organic chemistry, geometry is destiny).

Synthesizing a molecule when the transition state is enclosed in a larger ring permits intramolecular nucleophilic substitution reactions to take place. In the following reaction, for example, the transition state for intramolecular substitution is part of a nine-member ring in which it is possible to have a linear orientation between nucleophile and leaving group. Experiments of this type provide convincing experimental evidence that a linear arrangement of entering and leaving groups is a necessary requirement for all S_N2 reactions, including the reaction of I^- and CH_3Cl given at the beginning of this box.

P. Beak, *Accts. Chem. Res.*, **25**, 216 (1992).



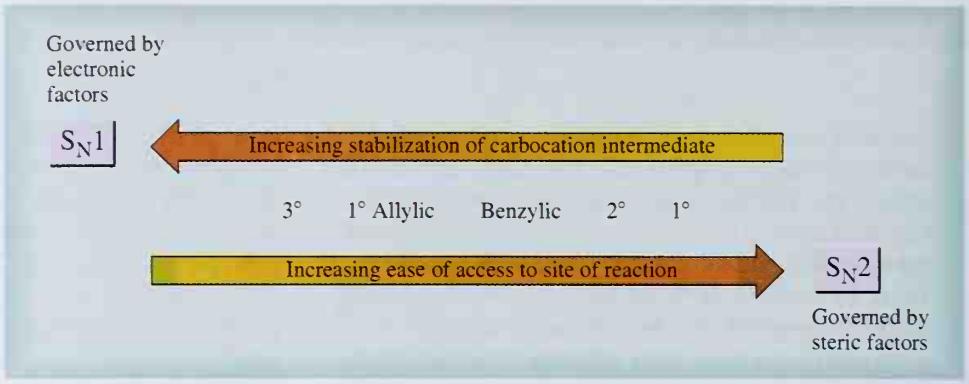


Figure 10.6
Effect of steric factors and electronic factors in competition between S_N1 and S_N2 reactions of alkyl halides.

D. Structure of the Alkyl Halides

S_N1 reactions are governed by **electronic factors,** namely the relative stabilities of carbocation intermediates. Tertiary and allylic carbocations are particularly stable. Tertiary halides react by S_N1; they rarely if ever react by S_N2.

S_N2 reactions are governed by **steric factors** and are particularly sensitive to steric hindrance (crowding) about the site of reaction. Methyl halides and primary halides with little β-branching react by S_N2; they rarely if ever react by S_N1.

Primary allylic halides can be made to react by either S_N1 or S_N2 mechanisms, depending on the solvent and the nucleophile; they are primary (the steric factor favoring S_N2), and at the same time they can lose halide ion to form a stable allylic carbocation (the electronic factor favoring S_N1). In polar protic solvents, they undergo solvolysis by an S_N1 mechanism. They can be made to undergo S_N2 reactions in aprotic solvents by treatment with good nucleophiles.

Secondary allylic halides may also be made to react by either S_N1 or S_N2 pathways, depending on the choice of nucleophile and solvent. Tertiary allylic halides react exclusively by S_N1 pathways.

Table 10.14 Effect of β-branching on the rate of S_N2 reactions

Alkyl Bromide	Relative Rate
CH_3Br	1
CH_3CH_2Br	3.2×10^{-2}
$CH_3CH_2CH_2Br$	1.3×10^{-2}
CH_3CHCH_2Br (CH$_3$ on CH)	3.9×10^{-5}
CH_3CCH_2Br (CH$_3$ on C)	3.7×10^{-7}

Table 10.15 Correlation of basicity and leaving ability for the halogens

Property	Increasing property						
Leaving ability	F^-	<	Cl^-	<	Br^-	<	I^-
Basicity	I^-	<	Br^-	<	Cl^-	<	F^-

The competition between steric factors and electronic factors, and their effect on relative rates of nucleophilic substitution reactions for alkyl halides are summarized in Figure 10.6. We see a similar effect of steric hindrance on S_N2 reactions in molecules with branching at the β-carbon. Shown in Table 10.14 are relative rates of S_N2 reactions on a series of primary alkyl bromides. In these data, the rate of nucleophilic substitution of methyl bromide is taken as a reference. To see the effects of β-branching, compare the relative rates of ethyl bromide (no β-branching) with that of 1-bromo-2,2-dimethylpropane (neopentyl bromide), a compound with three β-branchings. The rate of S_N2 substitution in neopentyl bromide is only 10^{-5} that of ethyl bromide.

E. The Leaving Group

In the transition state for nucleophilic substitution of alkyl halides or compounds containing other neutral leaving groups by both S_N1 and S_N2 mechanisms, the leaving group develops a partial negative charge. Its ability, therefore, to function as a leaving group is related to how stable it is when negatively charged, which is in turn related to its basicity. The lower the basicity of the leaving group, the better it is able to function as a leaving group. The relative rates of displacement of halogens is shown in Table 10.15. Iodide ion, the weakest base, is the best leaving group. Fluoride ion, the strongest base, is the poorest leaving group. The correlation between basicity and leaving group ability holds for other classes of compounds as well as alkyl halides.

F. The Solvent

To appreciate the important role of the solvent in nucleophilic substitution reactions we need to be specific about whether the substitution is S_N2 (nucleophile-assisted) or S_N1 (nucleophile-unassisted). Let us first take up the effect of solvent on S_N2 reactions.

The Effect of Solvent on S_N2 Reactions

The most common type of S_N2 reaction involves a negatively charged nucleophile and a negatively charged leaving group.

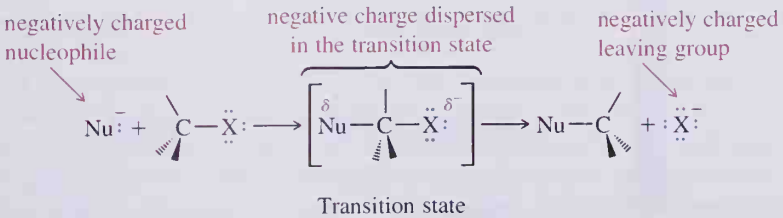


Table 10.16 Rates of S_N2 reactions as a function of solvent

$$CH_3CH_2CH_2CH_2Br + N_3^- \xrightarrow[\text{solvent}]{S_N2} CH_3CH_2CH_2CH_2N_3 + Br^-$$

Solvent Type	Solvent	$\frac{k_{solvent}}{k_{(methanol)}}$
Polar protic	CH_3OH	1
	H_2O	7
Polar aprotic	$(CH_3)_2S{=}O$	1300
	$(CH_3)_2NCHO$	2800
	$CH_3C{\equiv}N$	5000

The stronger the solvation of the nucleophile, the greater the energy required to remove the nucleophile from its solvation shell to reach the transition state, and hence the slower the rate of the S_N2 reaction.

Because of their good ability to solvate cations but only poor ability to solvate anions (nucleophiles), polar aprotic solvents have a particularly dramatic effect on the rate of S_N2 reactions. Reactions of the same substrate and nucleophile are accelerated, often by several orders of magnitude, when carried out in aprotic solvents compared with the rate obtained in protic solvents. Shown in Table 10.16 are ratios of specific rate constants for the S_N2 reaction of 1-bromobutane with sodium azide as a function of solvent. The rate of reaction in methanol is taken as a reference.

The Effect of Solvent on S_N1 Reactions

Because nucleophilic substitution by an S_N1 pathway involves creation and separation of opposite charges in the transition state of the rate-determining step, the rate of S_N1 reactions depends on the ability of the solvent to keep opposite charges separate as well as its

Table 10.17 Rates of an S_N1 reaction as a function of solvent

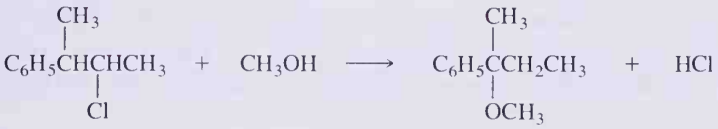
$$\begin{array}{l} CH_3 \\ | \\ CH_3CCl \\ | \\ CH_3 \end{array} + ROH \xrightarrow{\text{solvolysis}} \begin{array}{l} CH_3 \\ | \\ CH_3COR \\ | \\ CH_3 \end{array} + HCl$$

	Solvent	$\frac{k_{(solvent)}}{k_{(ethanol)}}$
Increasing solvent polarity ↓	ethanol	1
	40% water: 60% ethanol	100
	80% water: 20% ethanol	14,000
	water	100,000

ability to stabilize both positive and negative sites by solvation. The solvents that meet these requirements best are the polar protic solvents such as H_2O, ROH, and to a lesser degree RCO_2H. As seen in Table 10.17, the rate of solvolysis of 2-chloro-2-methylpropane (*tert*-butyl chloride) increases by a factor of over 10^5 when the solvent is changed from ethanol to water.

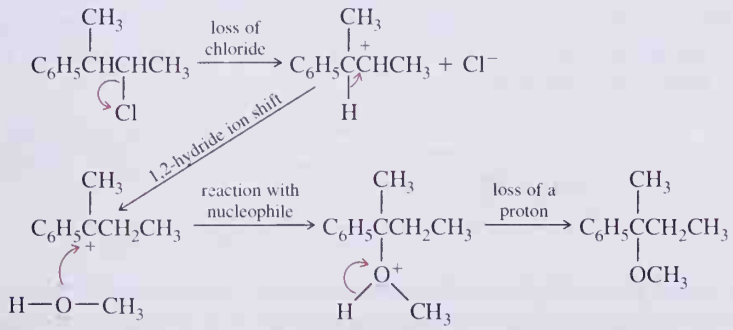
G. Skeletal Rearrangement

Skeletal rearrangement is typical of reactions in which the original carbocation can be converted to a more stable one. Because there is little or no carbocation character at the substitution center, S_N2 reactions are generally free of rearrangement. In contrast, S_N1 reactions often proceed with rearrangement. An example of an S_N1 reaction involving rearrangement is solvolysis of 2-chloro-3-phenylbutane in methanol, a polar protic solvent and a weak nucleophile.



2-Chloro-3-phenylbutane 2-Methoxy-2-phenylbutane

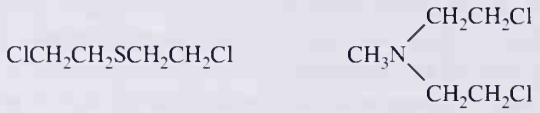
The secondary carbocation initially formed rearranges to a considerably more stable tertiary carbocation by shift of a hydride ion from the adjacent carbon. The major substitution product is the ether with rearranged structure.



H. An Alternative Terminology: Nucleophile-Assisted/Nucleophile-Unassisted Substitutions

So far we have considered two limiting mechanisms for nucleophilic substitutions which focus on the degree of covalent bonding between the nucleophile and the substitution center during departure of the leaving group. In an S_N2 mechanism, the leaving group is assisted in its departure from carbon by the nucleophile; that is, substitution is nucleophile-assisted. In an S_N1 mechanism, the leaving group is not so assisted in departing; that is, substitution is nucleophile-unassisted. An essential criterion for distinguishing between these two pathways is the order of reaction; nucleophile-assisted substitutions are second-order (first-order in RX, and first-order in nucleophile), whereas nucleophile-unassisted substitutions are first-order (first-order in RX, and zero-order in nucleophile).

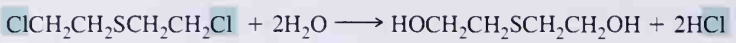
Chemists recognize that certain types of molecules undergo nucleophile-assisted substitutions, even though they have all of the kinetic characteristics of first-order (S_N1) substitutions. All such reactions have in common participation of an internal nucleophile in the departure of the leaving group. The **mustard gases** are one group of compounds that react in this manner. The characteristic structural feature of a mustard gas is a two-carbon chain, with a halogen on one carbon and a divalent sulfur or trivalent nitrogen on the other carbon (X—C—C—S or X—C—C—N). An example of a mustard gas is bis-(2-chloroethyl) sulfide, a poison gas used extensively in World War I. This compound is a deadly vesicant (blistering agent) and quickly causes conjunctivitis and blindness.



Bis(2-chloroethyl)sulfide (a sulfur mustard gas)

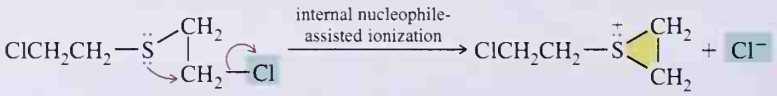
Bis(2-chloroethyl)methylamine (a nitrogen mustard gas)

Bis(2-chloroethyl)sulfide and bis(2-chloroethyl)methylamine are not gases at all. They are oily liquids. The designation "gas" comes from the fact that they react very rapidly with moisture in the air and in the mucous membranes of the eyes, nose, and throat to produce HCl, which then burns and blisters these sensitive tissues.



For insight into how mustard gases were recognized as potential starting points for the synthesis of effective drugs for the treatment of certain kinds of cancer, see the Chemistry in Action box "Mustard Gases and the Treatment of Neoplastic Diseases" in Chapter 25.

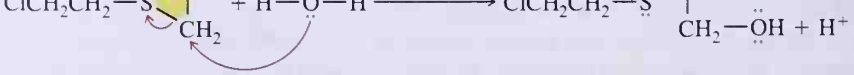
The reason for the extremely rapid hydrolysis of mustard gases is an intramolecular nucleophile-assisted displacement of chloride ion to form a cyclic sulfonium ion (or ammonium ion from a nitrogen mustard).



A cyclic sulfonium ion

At this point, you should review halogenation and oxymercuration of alkenes (Sections 5.3D and 5.3E) and compare the cyclic halonium and mercurinium ions formed there with the cyclic sulfonium ion formed here.

The cyclic sulfonium ion contains a highly strained three-member ring and reacts rapidly with an external nucleophile such as water to open the ring. The net effect of these reactions is nucleophilic substitution of —OH for —Cl.



Thus, although the external nucleophile has no role in ionization of chlorine and formation of the cyclic sulfonium ion intermediate, the reaction nonetheless involves nucleophile-assisted ionization. Note that although this reaction has the kinetic characteristics of an S_N1 reaction, it actually involves two successive S_N2 reactions.

We continue to retain the use of S_N2 and S_N1 as a useful way to describe nucleophilic substitution reactions. Realize, however, that these mechanisms do not adequately describe all nucleophilic substitution reactions. More general terms for these reactions are nucleophile-assisted and unassisted reactions.

I. An Analysis of Several Nucleophilic Substitution Reactions

Predictions about the mechanism for a particular nucleophilic substitution reaction must be based on considerations of the structure of the alkyl halide, the nucleophile, the leaving group, and the nature of the solvent. Following are five nucleophilic substitution reactions, the mechanism by which each substitution takes place, and analyses of the factors that contribute to favoring the mechanism given for each.

Nucleophilic Substitution 1

$$\underset{\text{Cl}}{\text{CH}_3\text{CHCH}_2\text{CH}_3} + \text{CH}_3\text{OH in H}_2\text{O} \xrightarrow{S_N1} \underset{\text{OH}}{\text{CH}_3\text{CHCH}_2\text{CH}_3} + \underset{\text{OCH}_3}{\text{CH}_3\text{CHCH}_2\text{CH}_3} + \text{HCl}$$

2-Chlorobutane is a secondary alkyl halide that can ionize to form a fairly stable secondary carbocation. The mixture of methanol and water is a polar protic solvent and a good ionizing solvent. Both water and methanol are poor nucleophiles. Therefore, the mechanism is nucleophile-unassisted ionization of the secondary chloride to give a carbocation intermediate that then reacts with either water or methanol as the nucleophile to give the observed products.

Nucleophilic Substitution 2

$$\underset{\text{CH}_3}{\text{CH}_3\text{CHCH}_2\text{Br}} + \text{NaCN} \xrightarrow[\text{DMSO}]{S_N2} \underset{\text{CH}_3}{\text{CH}_3\text{CHCH}_2\text{CN}} + \text{NaBr}$$

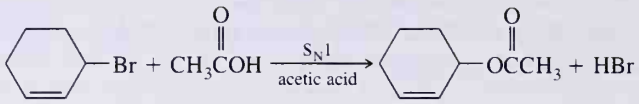
This is a primary alkyl bromide in the presence of cyanide ion, a good nucleophile. Dimethyl sulfoxide (DMSO), a polar aprotic solvent, is a particularly good solvent in which to carry out nucleophile-assisted substitution reactions because its ability to solvate cations (in this case, Na^+) is good, but its ability to solvate anions (in this case, CN^-) is poor.

Nucleophilic Substitution 3

$$\underset{\text{Br}}{\text{CH}_3\text{CHCH}_2\text{CH}_3} + \text{CH}_3\text{SNa} \xrightarrow[\text{acetone}]{S_N2} \underset{\text{SCH}_3}{\text{CH}_3\text{CHCH}_2\text{CH}_3} + \text{NaBr}$$

Bromide ion is a good leaving group and it is on a secondary carbon. The sulfide ion is a very strong nucleophile. Acetone, a polar aprotic solvent, is a good medium in which to carry out S_N2 reactions but a poor medium in which to carry out S_N1 reactions.

Nucleophilic Substitution 4



Ionization of bromide ion, a good leaving group, forms a resonance-stabilized secondary, allylic carbocation. Acetic acid is a poor nucleophile, which reduces the likelihood of an S_N2 reaction. Although it is a nonpolar solvent, it is nonetheless a protic (hydroxylic) solvent that favors S_N1 reaction.

Nucleophilic Substitution 5

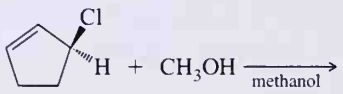
$$CH_3(CH_2)_5CH_2Br + (CH_3)_3P \xrightarrow[DMSO]{S_N2} CH_3(CH_2)_5CH_2P^+(CH_3)_3\ Br^-$$

The alkyl bromide is primary, and bromide ion is a good leaving group. Trivalent compounds of phosphorus, a third-row element, are excellent nucleophiles. DMSO is a polar aprotic solvent. Given the combination of a primary halide, a good leaving group, an excellent nucleophile, and a polar aprotic solvent, predict reaction by an S_N2 pathway.

EXAMPLE 10.4

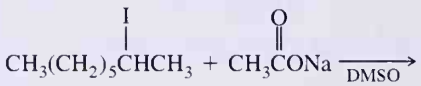
Write the expected substitution product(s) for each reaction and predict the mechanism by which each product is formed. Note that each alkyl halide is chiral and present as one pure enantiomer.

(a)



S Enantiomer

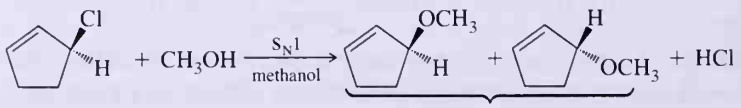
(b)



R Enantiomer

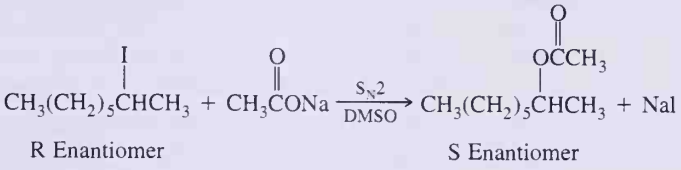
Solution

(a) This 2° allylic chloride is treated with methanol, a weak nucleophile and a polar protic solvent. Ionization of chlorine forms a resonance-stabilized secondary allylic cation. Therefore, predict reaction by an S_N1 mechanism. The intermediate cation is achiral and would be expected to give a racemic mixture of ethers. However, to the extent that the departing chloride ion remains associated with the carbocation as an ion pair and blocks approach to one face of the carbocation, the product has a slight excess of ether with inversion of configuration.



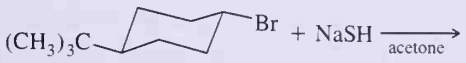
S Enantiomer — A racemic mixture

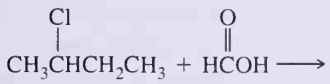
(b) Iodide is a good leaving group on a moderately accessible secondary carbon. Acetate ion dissolved in a polar aprotic solvent is a good nucleophile. Predict substitution by an S_N2 pathway with inversion of configuration at the stereocenter.



PROBLEM 10.4

Write the expected substitution product(s) for each reaction and predict the mechanism by which each product is formed.

(a) 

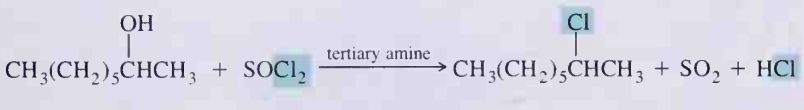
(b) 

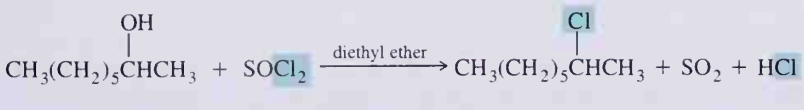
R Enantiomer

10.8 Conversion of Alcohols to Alkyl Chlorides: A Closer Look

Probably the most widely used reagent for the conversion of alcohols to alkyl chlorides is thionyl chloride, $SOCl_2$. The byproducts of the reaction are HCl and SO_2, both given off as gases, which results in a relatively pure product. A particular value of the reaction of alcohols with thionyl chloride is that it is stereoselective; it can be made to proceed with either retention or inversion of configuration, depending on the choice of experimental conditions.

Reaction of thionyl chloride with (R)-2-octanol in the presence of a tertiary amine or a heterocyclic aromatic amine such as pyridine (Section 14.2D) proceeds with inversion of configuration and gives (S)-2-chlorooctane. The same reaction in diethyl ether as the solvent proceeds with retention of configuration and gives (R)-2-chlorooctane.





CHEMISTRY IN ACTION

Why Life Exists

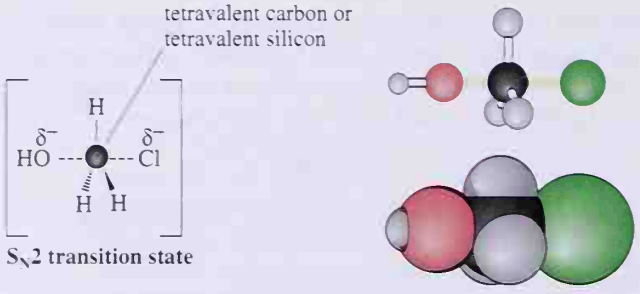
A question we might ask is: Why is carbon the fundamental building block of living systems? It is not the most abundant element in the earth's crust. Silicon, which is just below carbon in the periodic table, is far more common. Could an alternative "organic chemistry" exist based on silicon, with computer chips and photocells as natural products?

This question was posed by Michael J. S. Dewar and Eamonn Healy, in an article entitled "Why Life Exists." These authors point out that a characteristic of life is the need for stable, slow-reacting compounds. This requirement is met by many organic molecules. Even when there is a large thermodynamic driving force for a reaction, many carbon compounds do not react at measurable rates. For example, the reaction of carbon tetrachloride with water to generate carbon dioxide and HCl is exothermic but proceeds very slowly at room temperature. In contrast, if silicon tetrafluoride and water are combined, the reaction is violent. In general, substitution reactions at tetravalent carbon are much slower than substitution reactions at tetravalent silicon. A silicon-based life form would have to solve the problem of potential reactivity at many more sites in its molecules than a carbon-based life form does.

Having recognized this important feature of carbon compounds, Dewar and Healey then asked why carbon is so much less reactive than silicon toward substitution. Both elements undergo substitution by an S_N2 mechanism (see the figure). When Dewar and Healy carried out theoretical calculations for S_N2 reactions at carbon and silicon, omitting any consideration of silicon's 3*d* orbitals from their calculations, they found that the calculations predict a much faster reaction at silicon than at carbon.

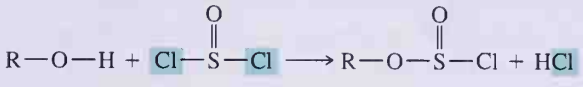
The reason for this difference in chemical reactivity appears to be the relative sizes of carbon and silicon atoms. Carbon has a covalent atomic radius of 0.0774 nm, whereas that for silicon is 0.111 nm. This difference becomes more important in the transition state for S_N2 reactions. It is difficult to pack five atoms around a small carbon atom as happens in the S_N2 transition state. In contrast, the larger silicon atom has little trouble accommodating five atoms in an S_N2 transition state. Thus, the energy difference between the ground and transition states is large for S_N2 reactions at carbon but much smaller for S_N2 reactions at silicon, leading to a great difference in relative rates. If bond lengths to carbon were only a little longer than they actually are, life as we know it might be impossible.

See Dewar, M.J.S., and Healy, E., *Organometallics*, **1**: 1705 (1982).



S_N2 transition state

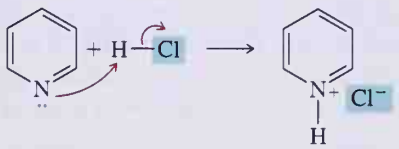
To account for these experimental observations, it has been proposed that alcohols first react with thionyl chloride to form an **alkyl chlorosulfite.**



Thionyl chloride — An alkyl chlorosulfite

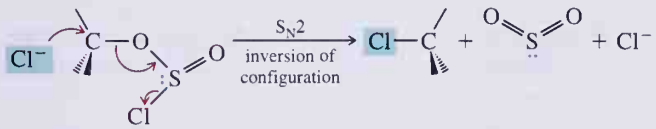
If the reaction between an alcohol and thionyl chloride is carried out at 0°C or below, alkyl chlorosulfites can be isolated. However, when warmed, they decompose to give alkyl chlorides and SO_2.

The function of the tertiary amine or pyridine is to react with the HCl generated in formation of the alkyl chlorosulfite to form an amine salt and thus increase the concentration of chloride ion in solution. In this acid-base reaction, pyridine (a weak base) is converted to its conjugate acid.

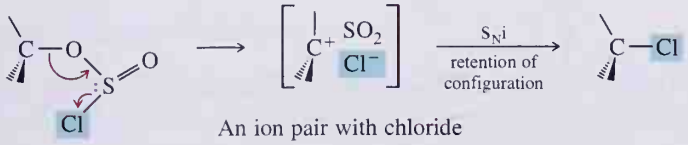


Pyridine — Pyridinium chloride

Chloride ion (a moderately good nucleophile) displaces the chlorosulfite as SO_2 and Cl^- (both good leaving groups) in an S_N2 reaction with inversion of configuration.



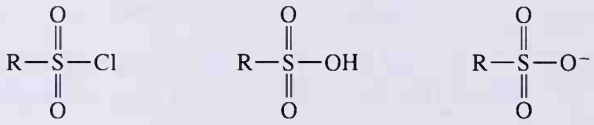
In diethyl ether, most of the HCl generated during formation of the alkyl chlorosulfite is given off as gas, and consequently the concentration of chloride ion in solution is very low. The chlorine atom in the final alkyl chloride comes instead from decomposition of the alkyl chlorosulfite. This ester first undergoes decomposition to give SO_2 and an ion pair in which chloride ion is not far separated from the carbocation. Reaction of the carbocation and chloride ion then takes place with retention of configuration to give the final product.



An ion pair with chloride ion tightly associated with the carbocation

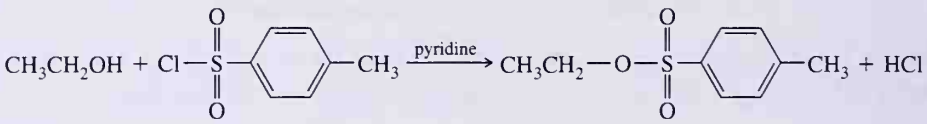
The frontside displacement of a leaving group by a nucleophile is called an **S_Ni reaction** (*S*ubstitution, *N*ucleophilic, *i*nternal) and is very rare. The reaction of alcohols with $SOCl_2$ in the presence of diethyl ether is one of the few known examples.

As we just saw, alcohols react with thionyl chloride by displacement of chloride ion to form alkyl chlorosulfites. They also react with compounds called sulfonyl chlorides to form alkyl sulfonates. Sulfonyl chlorides are derived from sulfonic acids, compounds that are very strong acids, comparable in strength to sulfuric acid. What is important for us at this point is that a sulfonate anion is a very weak base and, hence, a good leaving group in nucleophilic substitution reactions.

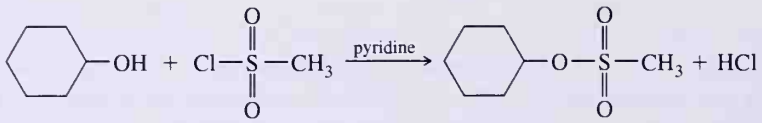


A sulfonyl chloride | A sulfonic acid (a very strong acid) | A sulfonate anion (a very weak base)

Two of the most commonly used sulfonyl chlorides are methanesulfonyl chloride (abbreviated mesyl chloride, Ms-Cl) and *p*-toluenesulfonyl chloride (abbreviated tosyl chloride, Ts-Cl). Treatment of ethanol with *p*-toluenesulfonyl chloride in the presence of pyridine gives ethyl *p*-toluenesulfonate. Pyridine is added to neutralize HCl formed as a byproduct. Cyclohexanol is converted to cyclohexyl methanesulfonate by a similar reaction. In each case, reaction involves breaking the O—H bond of the alcohol; it does not affect the C—O bond in any way.

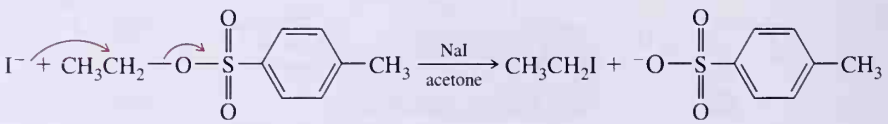


Ethanol | *p*-Toluenesulfonyl chloride | Ethyl *p*-toluenesulfonate (Ethyl tosylate)



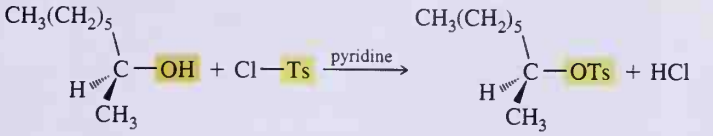
Cyclohexanol | Methanesulfonyl chloride | Cyclohexyl methanesulfonate (Cyclohexyl mesylate)

A particular advantage of sulfonate esters is that through them, a hydroxyl group, a very poor leaving group, can be converted to a tosylate or mesylate, each a very good leaving group that is readily displaced by nucleophilic substitution.

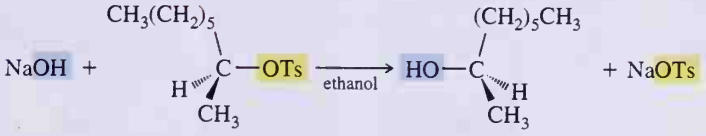


Ethyl *p*-Toluenesulfonate | *p*-Toluenesulfonate anion (a good leaving group)

Following is a two-step sequence for conversion of (R)-2-octanol to (S)-2-octanol via a tosylate. The first step involves cleavage of the O—H bond and proceeds with retention of configuration at the stereocenter. The second step involves nucleophilic displacement of tosylate and proceeds with inversion of configuration at the stereocenter.



(S)-2-Octanol (S)-2-Octyl tosylate



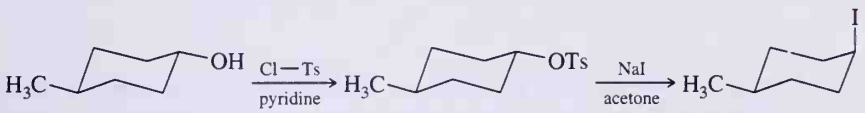
(S)-2-Octyl tosylate (R)-2-Octanol

EXAMPLE 10.5

Show how you might convert *trans*-4-methylcyclohexanol to *cis*-1-iodo-4-methylcyclohexane via a tosylate.

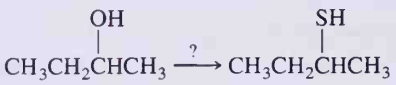
Solution

Treat the alcohol with *p*-toluenesulfonyl chloride in pyridine to form a tosylate with retention of configuration. Then treat the tosylate with sodium iodide in acetone. The S_N2 reaction with inversion of configuration gives the product.



PROBLEM 10.5

Show how you might convert (R)-2-butanol to (S)-2-butanethiol via a tosylate.



(R)-2-Butanol (S)-2-Butanethiol

10.9 Phase-Transfer Catalysis

Very often, nucleophilic displacement involves reaction between a covalent organic compound and an ionic compound, as for example between 1-chlorooctane and sodium cyanide.

$$CH_3(CH_2)_6CH_2Cl + Na^+CN^- \longrightarrow CH_3(CH_2)_6CH_2CN + Na^+ Cl^-$$

1-Chlorooctane Nonanenitrile

The reaction is simple to write, but for it to occur, both compounds must be brought together so they can react. The solubility characteristics of these reactants are quite different. Sodium cyanide is an ionic solid, soluble in water and a few other polar solvents but

When aqueous potassium permanganate and hexane are mixed in the test tube on the left, the purple color of permanganate ion is present only in the lower aqueous layer. When a phase-transfer catalyst has been added (test tube on the right), permanganate ion is transported into the upper hexane layer. *(Charles D. Winters)*

insoluble in organic solvents such as methylene chloride. 1-Chlorooctane, on the other hand, is insoluble in water but quite soluble in nonpolar organic solvents such as methylene chloride. One way to bring these reactants together is to dissolve them in DMSO, DMF, or other polar aprotic solvents. The advantages of DMSO and DMF are that each dissolves both organic and ionic compounds. When 1-chlorooctane and sodium cyanide are dissolved in DMSO, reaction between them occurs very readily.

Although DMSO and DMF are excellent solvents in which to carry out organic reactions, they have certain disadvantages. Both are several times more expensive than solvents such as methylene chloride and ethanol, and on an industrial scale, solvent cost can be an important consideration. Furthermore, because DMSO and DMF are so soluble in water, it is often difficult to recover them from mixtures with water. Finally, because they have higher boiling points than other common solvents (189°C for DMSO and 153°C for DMF compared with 78°C for ethanol and 40°C for methylene chloride), it is often difficult to remove them entirely from organic reaction products.

Another way to bring about reaction between 1-chlorooctane and cyanide ion is by a technique called phase-transfer catalysis, which works in the following way. Suppose sodium cyanide is dissolved in water, 1-chlorooctane is dissolved in methylene chloride, and the solutions mixed. Because water and methylene chloride are immiscible, a two-phase system results (Figure 10.7[a]). No reaction takes place between 1-chlorooctane and cyanide ion because they are in different phases. A **phase-transfer catalyst** is a substance that "pulls," or transports, anions, inorganic as well as organic, from an aqueous phase into

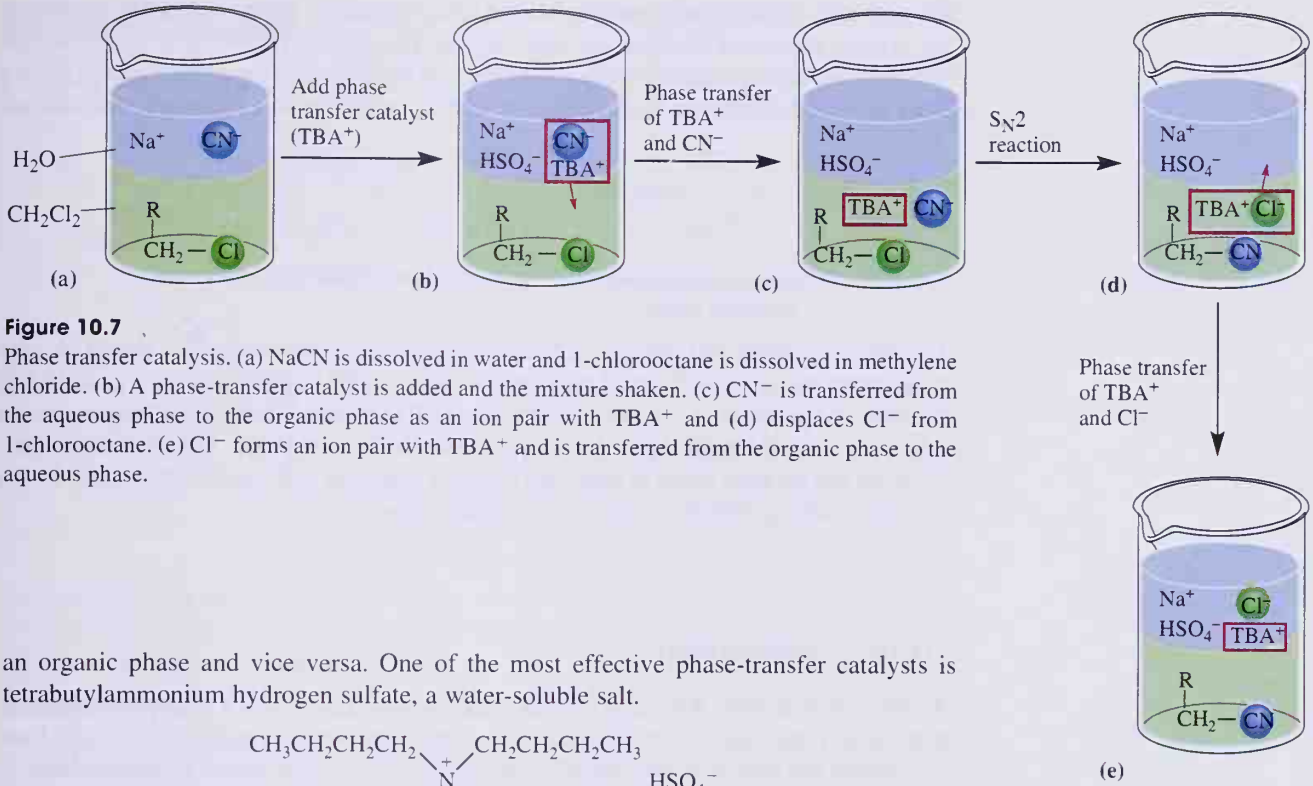
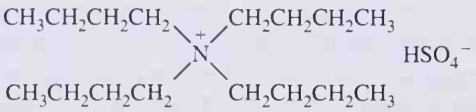


Figure 10.7
Phase transfer catalysis. (a) NaCN is dissolved in water and 1-chlorooctane is dissolved in methylene chloride. (b) A phase-transfer catalyst is added and the mixture shaken. (c) CN^- is transferred from the aqueous phase to the organic phase as an ion pair with TBA^+ and (d) displaces Cl^- from 1-chlorooctane. (e) Cl^- forms an ion pair with TBA^+ and is transferred from the organic phase to the aqueous phase.

an organic phase and vice versa. One of the most effective phase-transfer catalysts is tetrabutylammonium hydrogen sulfate, a water-soluble salt.



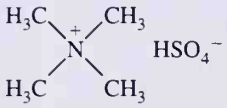
Tetrabutylammonium hydrogen sulfate
($TBAHSO_4$)

The tetrabutylammonium ion (TBA^+) has both hydrophilic and hydrophobic regions. **Hydrophilic** means "having an affinity for water; capable of dissolving in water." **Hydrophobic** means "having fear of water; incapable of dissolving in water." The positively charged nitrogen atom of the tetrabutylammonium ion is hydrophilic and interacts with water, with other polar molecules, and with anions. The four butyl groups attached to nitrogen in TBA^+ are hydrophobic and do not interact with or dissolve in water; instead they tend to dissolve in methylene chloride and other organic solvents. The hydrogen sulfate ion has a high degree of polarity, is highly solvated in water, and shows little or no interaction with most organic solvents.

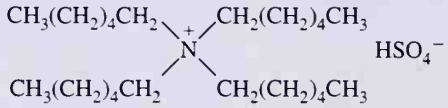
When added to a two-phase system consisting of 1-chlorooctane in methylene chloride and sodium cyanide in water, tetrabutylammonium hydrogen sulfate dissolves in the aqueous phase (Figure 10.7[b]). TBA^+ and CN^- then form an ion pair, which is transferred into the organic phase. CN^- displaces the chlorine atom, and Cl^- is transferred as an ion pair with TBA^+ to the aqueous phase. The process is repeated until all cyanide ions have been transferred to the organic phase and have reacted with 1-chlorooctane.

The characteristics necessary for an effective phase-transfer agent for anions are a balanced combination of (1) hydrophilic character so as to dissolve in water and to form an

ion pair with the anion to be transported and (2) hydrophobic character so as to dissolve in the organic phase and transport the anion into it. The reasons for the particular effectiveness of tetrabutylammonium hydrogen sulfate can be illustrated by comparing it with two other tetraalkylammonium ions, neither of which is effective as a phase-transfer catalyst.



Tetramethylammonium hydrogen sulfate

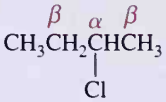


Tetrahexylammonium hydrogen sulfate

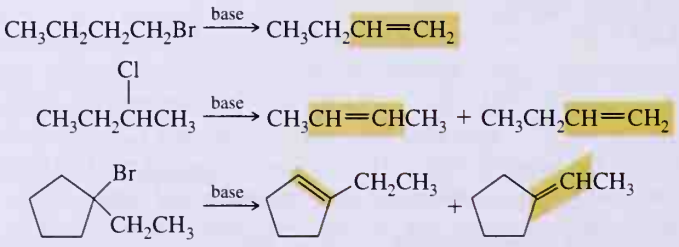
Tetramethylammonium hydrogen sulfate is not an effective phase-transfer catalyst because its nonpolar regions are too small relative to its polar region to pull it into an organic phase. Tetrahexylammonium hydrogen sulfate is ineffective because its nonpolar regions are so large relative to the polar region that it remains in the organic phase. The tetrabutylammonium ion has the right blend of polar and nonpolar character to be an effective agent for the transfer of anions between water and an organic phase.

10.10 β-Elimination

As we saw in Section 4.5, alkyl halides undergo elimination of HX (**dehydrohalogenation**) in the presence of bases. Because these eliminations involve removal of halogen from one carbon and hydrogen from an adjacent carbon, they are also called ***β*-eliminations.** In this terminology, the designation α refers to the carbon bearing the halogen, and β refers to a carbon adjacent to the α-carbon. There may be one, two, or three β-carbons, depending on the degree of substitution of the α-carbon. Following is the example of 2-chlorobutane, which has two different β-carbons.



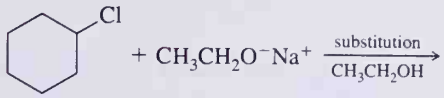
Strong bases which serve effectively in β-eliminations are OH^-, OR^-, and NH_2^-. Weaker bases such as CN^-, $CH_3CO_2^-$, and even water and alcohols can also be used to bring about β-eliminations. Following are three examples of base-promoted β-eliminations.

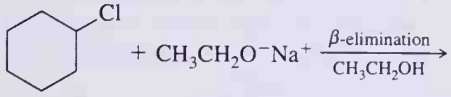


Note that where there is more than one β-carbon bearing a hydrogen or where the product can show *cis-trans* isomerism, isomeric alkenes are possible.

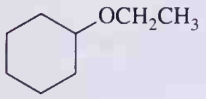
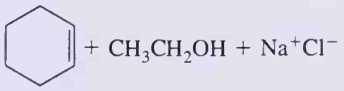
EXAMPLE 10.6

Complete the indicated reactions.

(a) 

(b) 

Solution

(a)  **(b)** 

PROBLEM 10.6

Complete the indicated reactions.

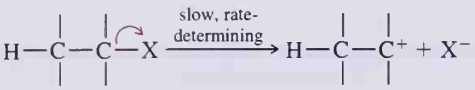
(a) $CH_3CHCH_2CH_2CH_2Br + CH_3C{\equiv}C^-Na^+ \xrightarrow[DMSO]{\text{substitution}}$

(b) $CH_3CHCH_2CH_2CH_2Br + CH_3C{\equiv}C^-Na^+ \xrightarrow[DMSO]{\beta\text{-elimination}}$

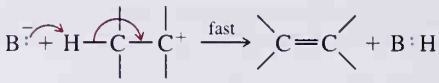
Because elimination and nucleophilic substitution are competing processes, the wealth of information gathered in the study of substitution reactions of alkyl halides provides insight into the mechanisms of elimination reactions as well. Chemists have proposed two limiting mechanisms for β-eliminations. A fundamental difference between them is the timing of the bond-breaking and bond-making steps.

At one extreme, breaking of the C—X bond is complete before any reaction occurs with base to lose a hydrogen and form the carbon-carbon double bond. This mechanism is designated **E1,** where E stands for *E*limination and *1* stands for unimolecular, the molecularity of the reaction. It is proposed that an E1 mechanism involves two steps. Step 1 is a slow, rate-determining ionization of the C—X bond to form a carbocation. In Step 2, the carbocation reacts with a base to lose a hydrogen and form the alkene.

Step 1: Ionization of the C—X bond to form a carbocation

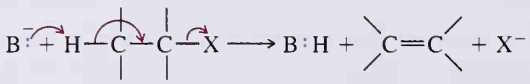


Step 2: Reaction with base to lose a β-hydrogen



In an E1 mechanism, one transition state exists for formation of the carbocation in Step 1 and a second transition state for loss of a hydrogen in Step 2 (Figure 10.8).

At the other extreme is a concerted process. This mechanism is designated **E2**, where E stands for *E*limination and *2* stands for bimolecular, the molecularity of the reaction.



In the transition state, base removes a β-hydrogen at the same time the C—X bond is broken to form halide ion (Figure 10.9), and, hence, the transition state has considerable double-bond character.

Let us examine some of the experimental evidence on which these two contrasting mechanisms are based. As we do, we consider the following questions:

1. What are the kinetics of base-promoted β-eliminations?
2. Where two or more alkenes are possible, what factors determine the ratio of the possible products?
3. What is the stereochemistry of β-elimination?

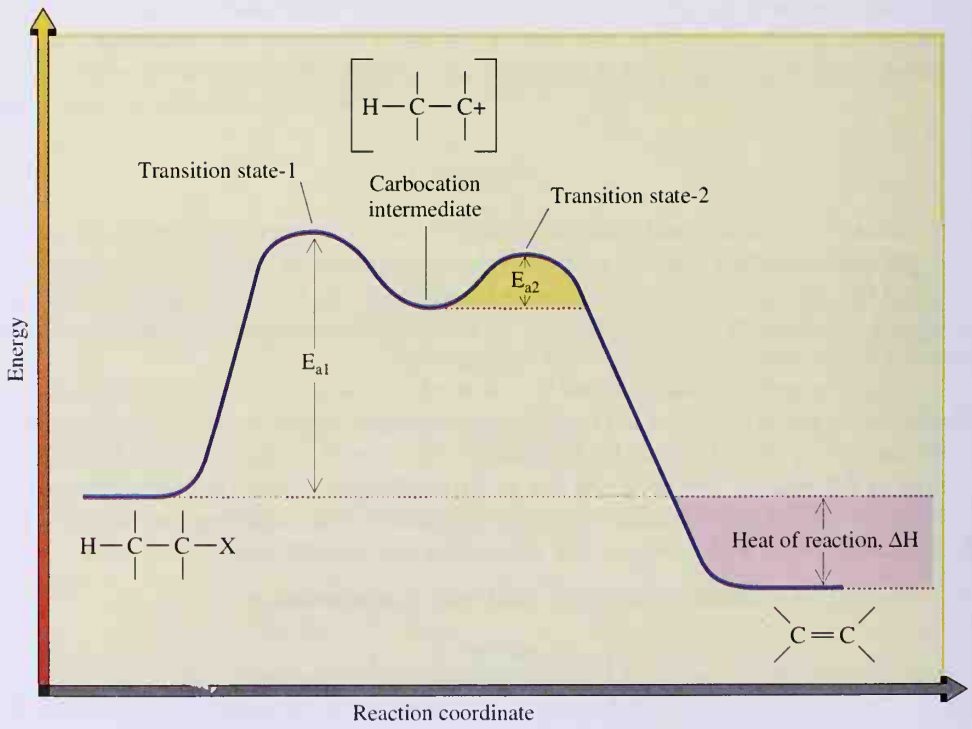


Figure 10.8
A potential energy diagram for an E1 reaction showing two transition states and one carbocation intermediate.

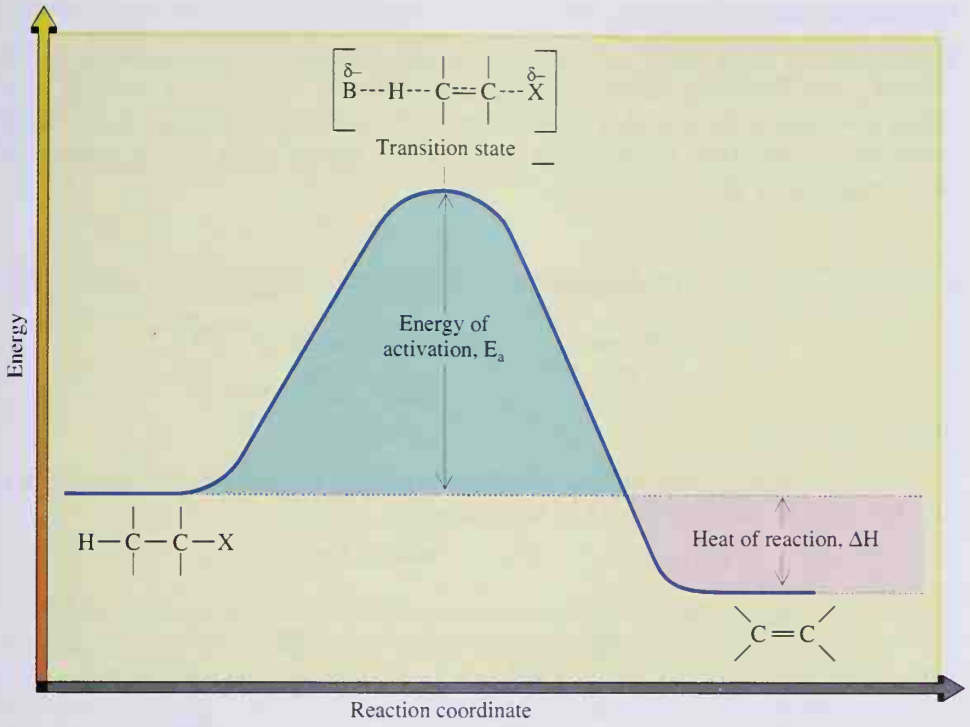


Figure 10.9
A potential energy diagram for an E2 reaction. There is considerable double bond character in the transition state.

A. E1 Reactions

Kinetics

The rate-determining step in an E1 reaction is ionization of the halide to form a carbocation. Because this step involves only the solvated alkyl halide and not the base, it is unimolecular.

$$\text{Rate} = -\frac{d[\text{RX}]}{dt} = k[\text{RX}]$$

Recall that the first step in an S_N1 reaction is also formation of a carbocation. Thus, for both S_N1 and E1 reactions, formation of the carbocation is the rate-determining step. Once the carbocation is formed, it may then (1) lose a hydrogen to complete β-elimination (E1), (2) react with a nucleophile to complete nucleophilic substitution (S_N1), or (3) rearrange and then do (1) or (2).

B. E2 Reactions

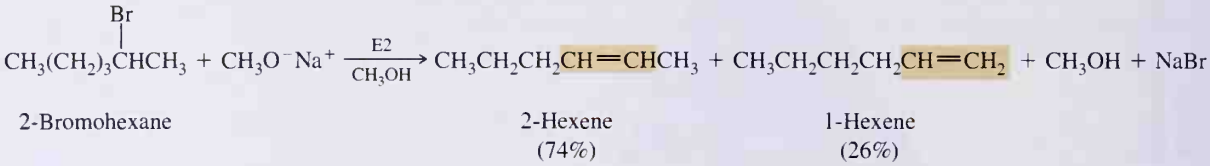
Kinetics

Only one step occurs in an E2 mechanism, and the transition state is bimolecular. The reaction is second order: first-order in RX, and first-order in base.

$$\text{Rate} = -\frac{d[\text{RX}]}{dt} = k[\text{RX}][\text{base}]$$

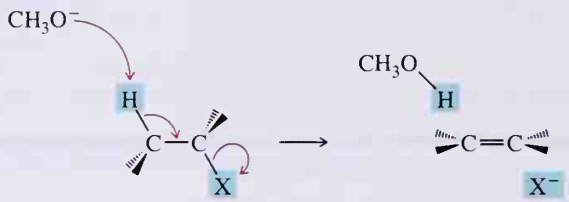
Regioselectivity

For E2 reactions using strong base, and in which the leaving group is halide ion, the major product is that formed by Zaitsev elimination (Section 4.5). Double-bond character is so highly developed in the transition state that the relative stability of possible alkenes is the determining factor. Thus, the transition state of lowest energy is that leading to the most stable, most highly substituted alkene.



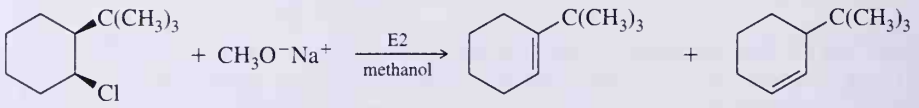
Stereoselectivity

A requirement of the E2 mechanism is that X and H must be oriented anti and coplanar (at a dihedral angle of 180°, Section 2.6A) to one another.



—H and —X are anti and coplanar
(dihedral angle 180°)

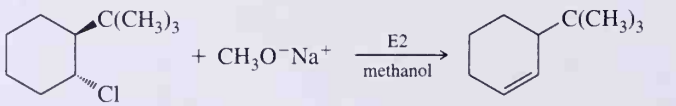
This requirement can be demonstrated clearly in chlorocyclohexanes. In these molecules, anti and coplanar corresponds to *trans*, diaxial. Consider base-promoted E2 reaction of the *cis* and *trans* isomers of 1-*tert*-butyl-2-chlorocyclohexane. From the *cis* isomer, the major product is 1-*tert*-butylcyclohexene, the more substituted cycloalkene. From the *trans* isomer, only 3-*tert*-butylcyclohexene is formed.



cis-1-*tert*-Butyl-2-chlorocyclohexane

1-*tert*-Butylcyclohexene (major product)

3-*tert*-Butylcyclohexene



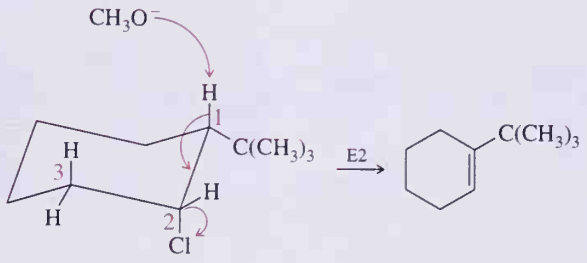
trans-1-*tert*-Butyl-2-chlorocyclohexane

3-*tert*-Butylcyclohexene

In the more stable chair conformation of the *cis* isomer, the considerably larger *tert*-butyl group is equatorial, and the smaller chlorine is axial. In this chair conformation, —H on carbon 1 and —Cl on carbon 2 are anti and coplanar. Concerted E2 elimination gives

1-*tert*-butylcyclohexene, a trisubstituted alkene, as the major product. Note that —H on carbon 3 and —Cl are also anti and coplanar. Dehydrohalogenation of this combination of —H and —Cl gives 3-*tert*-butylcyclohexene, a disubstituted and, therefore, less stable alkene.

E2 reaction of *cis*-1-*tert*-butyl-2-chlorocyclohexane:

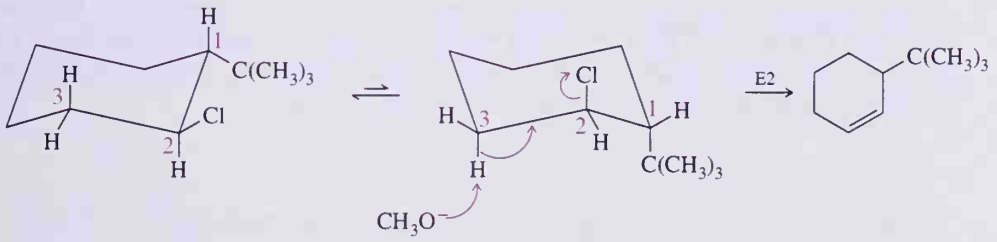


More stable chair (—H and —Cl are *trans* and coplanar)

1-*tert*-Butylcyclohexene

In the more stable chair conformation of the *trans* isomer, both *tert*-butyl and chlorine are equatorial. In this conformation, hydrogens on carbon 1 and carbon 3 are *trans* to —Cl, but neither of them is anti and coplanar with —Cl. In the alternative, less stable chair conformation of the *trans* isomer, both *tert*-butyl and chlorine are axial. In this conformation, the axial hydrogen in carbon 3 is anti and coplanar to chlorine and E2 β-elimination gives 3-*tert*-butylcyclohexene.

E2 reaction of *trans*-1-*tert*-butyl-2-chlorocyclohexane



More stable chair (no —H is *trans* and coplanar to —Cl)

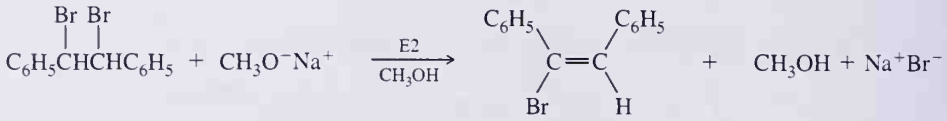
Less stable chair (—H on carbon 3 is *trans* and coplanar to —Cl)

3-*tert*-Butylcyclohexene

The rate at which the *cis* isomer undergoes E2 reaction is considerably greater than the rate for the *trans* isomer. We can account for this observation in the following manner. The more stable chair conformation of the *cis* isomer has —H and —Cl anti and coplanar, and the energy of activation for the reaction is that required to reach the transition state. The more stable chair conformation of the *trans* isomer, however, cannot undergo anti elimination. To react, it must first interconvert to the less stable chair. Thus, the energy of activation for the *trans* isomer includes (1) the energy necessary to convert the more stable chair to the less stable chair, and (2) the energy to reach the transition state from this conformation.

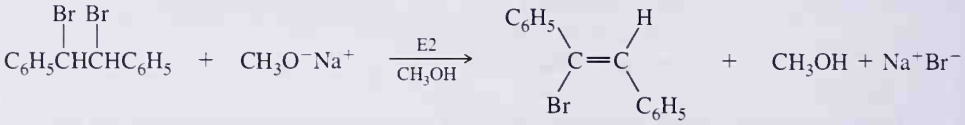
EXAMPLE 10.7

Treatment of 1,2-dibromo-1,2-diphenylethane with sodium ethoxide in ethanol gives 1-bromo-1,2-diphenylethene. The meso isomer gives (E)-1-bromo-1,2-diphenylethene, whereas the racemic mixture produces (Z)-1-bromo-1,2-diphenylethene. How do you account for the stereospecificity of these β-eliminations?



Meso-1,2-dibromo-1,2-diphenylethane

(E)-1-Bromo-1,2-diphenylethene

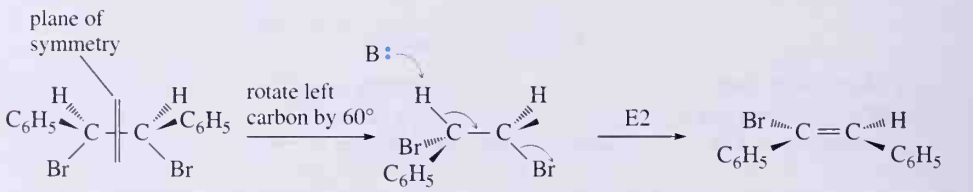


Racemic-1,2-dibromo-1,2-diphenylethane

(Z)-1-Bromo-1,2-diphenylethene

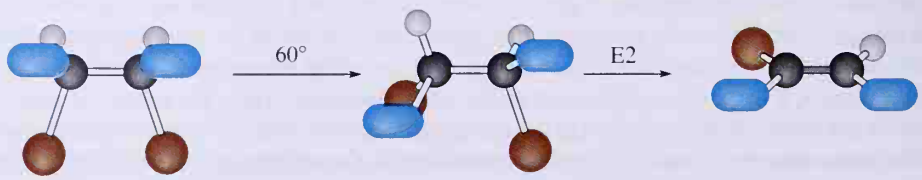
Solution

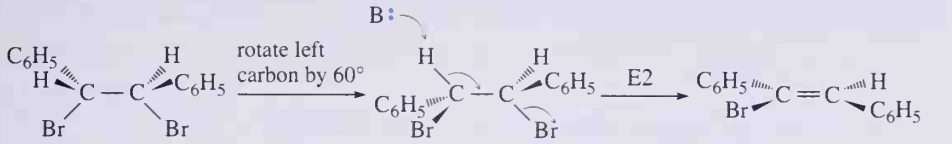
It is a requirement for an E2 reaction that —H and —X be anti and coplanar. Following is a stereorepresentation of the meso isomer, drawn to show the plane of symmetry. Rotation of the left carbon by 60° brings —H and —Br into an anti and coplanar relationship. E2 reaction of this conformation gives the (E)-alkene. E2 reaction of the proper conformation of either enantiomer of the racemic mixture gives the (Z)-alkene.



Meso isomer

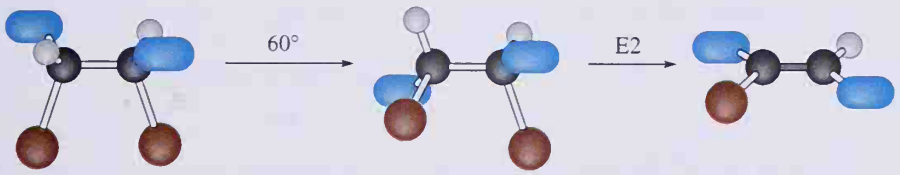
(E)-1-Bromo-1,2-diphenylethene





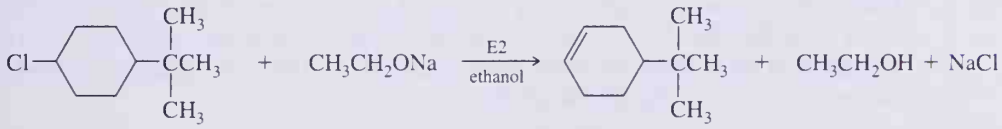
One enantiomer of the racemic mixture

(Z)-1-Bromo-1,2-diphenylethene



PROBLEM 10.7

1-*tert*-Butyl-4-chlorocyclohexane exists as two stereoisomers: one *cis* and one *trans*. Treatment of either isomer with sodium ethoxide in ethanol gives 4-*tert*-butylcyclohexene by an E2 reaction.



1-*tert*-Butyl-4-chlorocyclohexane

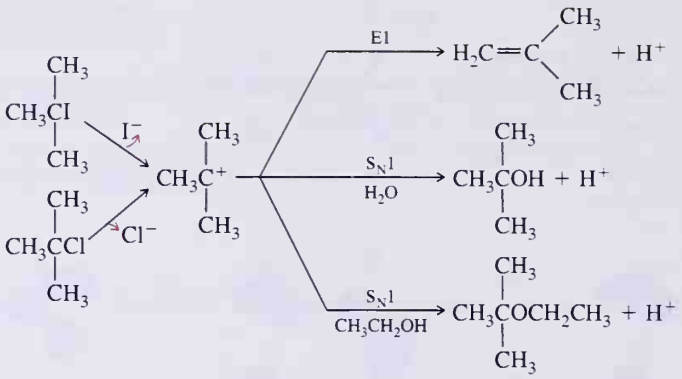
4-*tert*-Butylcyclohexene

The *cis* isomer undergoes E2 reaction several orders of magnitude faster than the *trans* isomer. How do you account for this experimental observation?

10.11 Substitution versus Elimination

A. S_N1 versus E1

First-order reactions of alkyl halides in polar protic solvents give mixtures of substitution and elimination products that arise by formation of a common carbocation intermediate, followed by reaction of the carbocation by one or more of its characteristic reactions: (1) loss of a hydrogen (E1) to give an alkene, (2) reaction with solvent (S_N1) to give a substitution product, or (3) rearrangement followed by reaction (1) or (2). In polar protic solvents, the products formed depend only on the structure of the particular carbocation. For example, *tert*-butyl chloride and *tert*-butyl iodide in 80% aqueous ethanol both react with solvent giving the same mixture of substitution versus elimination products. Because iodide ion is a better leaving group than chloride ion, *tert*-butyl iodide reacts over 100 times faster than *tert*-butyl chloride. Yet the ratio of products is the same.

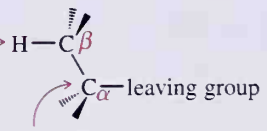


It is difficult to predict the ratio of substitution to elimination products for first-order reactions of alkyl halides. A generalization we can make, however, is that a high concentration of nucleophile or a strong nucleophile favors substitution (S_N1) over elimination (E1).

B. S_N2 versus E2

It is considerably easier to predict the ratio of substitution to elimination products for second-order reactions of alkyl halides with reagents that act both as nucleophiles and bases. The guiding principle is that branching at the α-carbon or β-carbon(s) increases steric hindrance about the α-carbon and significantly retards S_N2 reactions. Conversely, branching at the α-carbon or β-carbon(s) increases the rate of E2 reaction because of the increased stability of the alkene product.

Attack of base on a β-hydrogen by E2 is only slightly affected by branching at the α-carbon; alkene formation is accelerated.



S_N2 attack of a nucleophile at the α-carbon is impeded by branching at the α-carbon.

Tertiary halides react with all electron-rich reagents, regardless of the strength of the attacking reagent as a nucleophile, to give elimination products. Because of the degree of branching on the α-carbon in tertiary halides, S_N2 reactions on them cannot compete effectively with E2 reactions.

Primary halides react with electron-rich reagents to give substitution products predominantly. With strong bases, such as hydroxide ion and ethoxide ion, a percentage of the product is formed by an E2 reaction, but it is generally small compared with that formed by S_N2 reaction.

Secondary halides are borderline, and substitution or elimination may be favored depending on the particular nucleophile/base, solvent, and temperature at which the reaction is carried out. With strong nucleophiles but weak bases such as I^- and CH_3S^-, S_N2 generally predominates. With strong bases, such as HO^- and RO^-, E2 generally predominates. These generalizations about substitution versus elimination reactions of methyl, primary, secondary, and tertiary alkyl halides are summarized in Table 10.18.

Table 10.18 Summary of substitution versus elimination reactions of alkyl halides

Halide	Reaction	Comments
Methyl Halides		
$CH_3—X$	S_N2	Methyl cation is never formed in solution, and, therefore, S_N1 reactions of methyl halides are never observed.
Primary Halides		
$RCH_2—X$	S_N2	Common, especially in reactions with strong nucleophiles and weak bases such as I^- and $CH_3CO_2^-$.
	E2	The main reaction with strong, sterically hindered bases such as potassium *tert*-butoxide.
		Primary cations are rarely formed in solution, and, therefore, S_N1 and E1 reactions of primary halides are rarely observed.
Secondary Halides		
$R_2CH—X$	S_N2	Main reaction with weak bases such as I^- and RCO_2^-
	E2	Main reaction with strong bases such as RO^- and HO^-
		S_N1 and E1 are common in solvolysis reactions, as for example, heating a secondary alkyl halide in methanol or ethanol.
Tertiary Halides		
$R_3C—X$	E2	Main reaction with strong bases such as RO^- and HO^-
	S_N1/E1	Main reaction in solvolysis. S_N1 is favored by a high concentration of a good nucleophile such as Br^-.
		S_N2 reactions of tertiary halides are never observed.

EXAMPLE 10.8

Predict whether each reaction proceeds predominantly by substitution, elimination, or whether the two compete. Write structural formulas for the major organic product(s).

(a) $$CH_3CCH_2CH_3 + NaOH \xrightarrow[H_2O]{80^\circ}$$ (Cl on the central carbon)

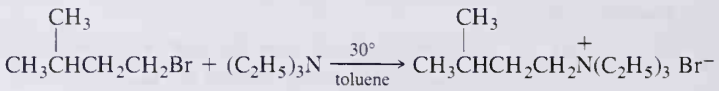
(b) $$CH_3CHCH_2Br + (C_2H_5)_3N \xrightarrow[\text{toluene}]{30^\circ}$$

Solution

(a) A 3° halide is heated with a strong base–strong nucleophile. Elimination by an E2 reaction predominates to give 2-methyl-2-butene as the major product.

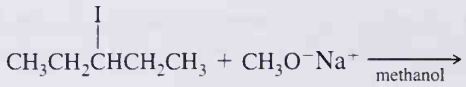
$$CH_3CCH_2CH_3 + NaOH \xrightarrow[H_2O]{80^\circ} CH_3C{=}CHCH_3 + NaCl + H_2O$$

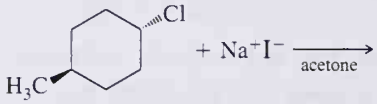
(b) Reaction of a 1° halide and a good nucleophile–weak base gives substitution by an S_N2 reaction.

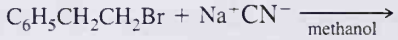


PROBLEM 10.8

Predict whether each reaction proceeds predominantly by substitution, elimination, or whether the two compete. Write structural formulas for the major organic product(s).

(a) 

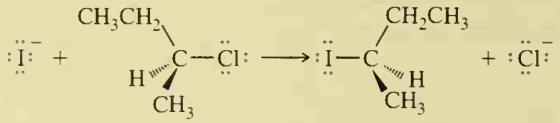
(b) 

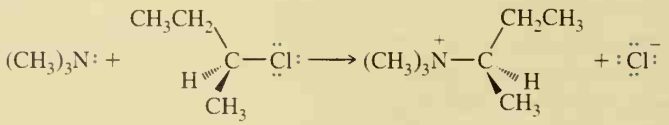
(c) 

SUMMARY OF KEY REACTIONS

1. Nucleophilic Aliphatic Substitution: S_N2 (Section 10.7)

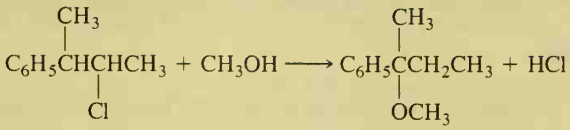
A second-order reaction involving inversion of configuration at the reactive center. The nucleophile may be negatively charged as in the first example, or neutral as in the second example. S_N2 reactions are accelerated in polar aprotic solvents compared with polar protic solvents.





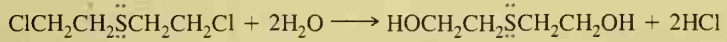
2. Nucleophilic Aliphatic Substitution: S_N1 (Section 10.7)

A first-order reaction involving a carbocation intermediate. Reaction at a tetrahedral stereocenter gives largely racemization often accompanied with some slight excess of inversion of configuration. Reactions often involve carbocation rearrangements and are accelerated by polar protic solvents.



3. Nucleophile-Assisted First-Order Substitution Reactions (Section 10.7H)

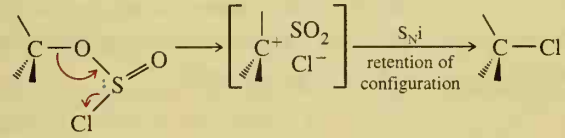
First-order kinetics but with participation of an internal nucleophile in departure of the leaving group, as in hydrolysis of a mustard gas. The mechanism for these reactions involves two successive S_N2 reactions.



4. Frontside Displacement of a Nucleophile: S_Ni Reaction (Section 10.8)

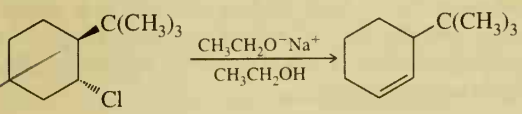
Only a few examples of this type of nucleophilic displacement have been observed. The best known example is reaction of an alcohol with thionyl chloride by way of an alkyl chlorosulfite intermediate to give retention of configuration at the site of reaction.

(R)-2-Octanol (S)-2-Chlorooctane



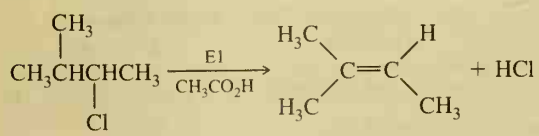
5. β-Elimination: E2 (Section 10.10)

Elimination of atoms or groups of atoms from adjacent carbon atoms by a reaction that is first order in the base and first order in the compound undergoing elimination. Elimination is concerted and stereoselective requiring an anti and coplanar arrangement of groups eliminated.



6. β-Elimination: E1 (Section 10.10)

Elimination of atoms or groups of atoms from adjacent carbons by a reaction that is zero order in the base and first order in the compound undergoing elimination. Reaction involves a carbocation intermediate, and carbocation rearrangements are common.

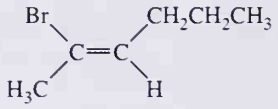


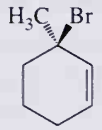
(major product)

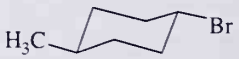
ADDITIONAL PROBLEMS

Nomenclature

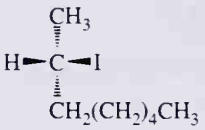
10.9 Give IUPAC names for the following compounds. Where stereochemistry is shown, include a designation of configuration in your answer.

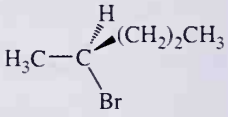
(a) 

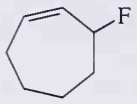
(b) 

(c) 

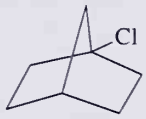
(d) $ClCH_2CH_2CH_2CH_2Cl$

(e) 

(f) 

(g) 

(h) CH_3CHCH_2Br

(i) 

10.10 Draw structural formulas for the following compounds:

(a) Allyl iodide
(b) (R)-2-Chlorobutane
(c) Meso-2,3-dibromobutane
(d) *trans*-1-Bromo-3-isopropylcyclohexane
(e) Neopentyl iodide
(f) Cyclobutyl bromide

Physical Properties

10.11 Water and methylene chloride are insoluble in each other. When each is added to a test tube, two layers form. Which layer is water and which layer is methylene chloride? Explain.

10.12 The boiling point of methylcyclohexane (C_7H_{14}, MW 98.2) is 101°C. The boiling point of perfluoromethylcyclohexane (C_7F_{14}, MW 350) is 76°C. Account for the fact that although the molecular weight of perfluoromethylcyclohexane is over 3 times that of methylcyclohexane, its boiling point is lower than that of methylcyclohexane.

10.13 Account for the fact that among the chlorinated derivatives of methane, chloromethane has the largest dipole moment and tetrachloromethane has the smallest dipole moment.

Name	Molecular Formula	Dipole Moment (D)
chloromethane	CH_3Cl	1.87
dichloromethane	CH_2Cl_2	1.60
trichloromethane	$CHCl_3$	1.01
tetrachloromethane	CCl_4	0

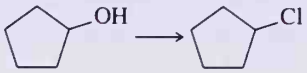
Synthesis of Alkyl Halides

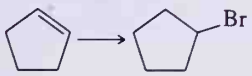
10.14 Show reagents and conditions to bring about the following conversions:

(a) 

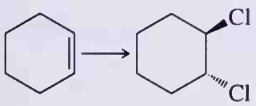
(b) $CH_3CH{=}CHCH_3 \longrightarrow CH_3CH{=}CHCH_2Br$

(c) $CH_3CH{=}CHCH_3 \longrightarrow CH_3\underset{Br}{C}H\underset{Br}{C}HCH_3$

(d) 

(e) 

(f) $CH_3CH_2C{\equiv}CH \longrightarrow CH_3CH_2\overset{Br}{\overset{|}{C}}CH_3$ (Br)

(g) 

(h) $CH_3\overset{CH_3}{\overset{|}{C}}CH_2CH_2OH \longrightarrow CH_3\overset{CH_3}{\overset{|}{C}}CH_2CH_2Cl$ (CH_3)

Nucleophilic Aliphatic Substitution

10.15 Draw a structural formula for the most stable carbocation of each molecular formula and indicate how each might be formed.

(a) $C_4H_9^+$ (b) $C_3H_7^+$ (c) $C_8H_{15}^+$ (d) $C_3H_7O^+$

10.16 Reaction of 1-bromopropane and sodium hydroxide in ethanol follows an S_N2 mechanism. What happens to the rate of this reaction if

(a) The concentration of NaOH is doubled?

(b) The concentrations of both NaOH and 1-bromobutane are doubled?

(c) The volume of the solution in which the reaction is carried out is doubled?

10.17 From each pair, select the stronger nucleophile.

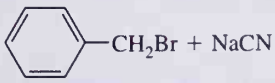
(a) H_2O or OH^- (b) $CH_3\overset{O}{\overset{\|}{C}}O^-$ or OH^-

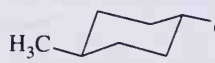
(c) CH_3SH or CH_3S^- (d) Cl^- or I^- in DMSO

(e) Cl^- or I^- in methanol (f) CH_3OCH_3 or CH_3SCH_3

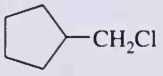
10.18 Draw the structural formula for the product of each S_N2 reaction. Where configuration of the starting material is given, show the configuration of the product.

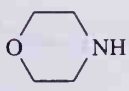
(a) $CH_3CH_2CH_2Cl + CH_3CH_2ONa \xrightarrow[\text{ethanol}]{}$ (b) $(CH_3)_3N + CH_3I \xrightarrow[\text{acetone}]{}$

(c)  $+ NaCN \xrightarrow[\text{acetone}]{}$

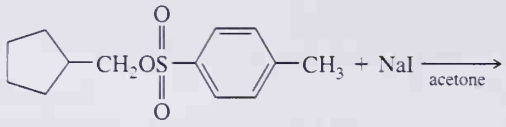
(d)  $+ CH_3SNa \xrightarrow[\text{ethanol}]{}$

(e) $CH_3CH_2CH_2Cl + CH_3C{\equiv}C^-Na^+ \longrightarrow$

(f)  $+ NH_3 \xrightarrow[\text{ethanol}]{}$

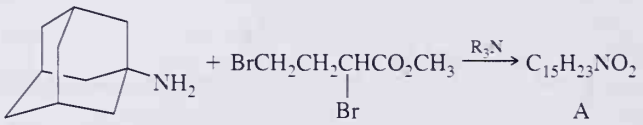
(g)  $+ CH_3(CH_2)_6CH_2Cl \xrightarrow[\text{ethanol}]{}$

(h) $CH_3CH_2CH_2O\overset{O}{\overset{\|}{S}}CH_3\overset{O}{\overset{\|}{}} + NaCN \xrightarrow[\text{acetone}]{}$

(i) 

10.19 You were told that each reaction in the previous problem proceeds by an S_N2 mechanism. Suppose you were not told the mechanism. Describe how you could conclude from the structure of the alkyl halide, the nucleophile, and the solvent that each reaction is in fact an S_N2 reaction.

10.20 Treatment of 1-aminoadamantane with methyl 2,4-dibromobutanoate involves two successive S_N2 reactions and gives compound A, an intermediate in the synthesis of carmantidine. Propose a structural formula for this intermediate. Carmantidine has been used in treating the spasms associated with Parkinson's disease.



10.21 Select the member of each pair that shows the faster rate of S_N2 reaction with KI in acetone.

(a) $CH_3CH_2CH_2CH_2Cl$ or CH_3CHCH_2Cl (CH_3 on the CH)

(b) $CH_3CH_2CH_2CH_2Cl$ or $CH_3CH_2CH_2CH_2Br$

(c) $CH_3CHCH_2CH_2Cl$ (CH_3 on the CH) or CH_3CCH_2Cl (two CH_3 on the C)

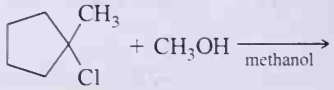
(d) $CH_3CH_2CH_2CHCH_3$ (Br on the CH) or $CH_3CHCHCH_3$ (Br on the first CH, CH_3 on the second CH)

10.22 What hybridization best describes the reacting carbon in the S_N2 transition state? Would electron-withdrawing groups or electron-donating groups stabilize the transition state better?

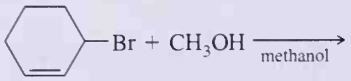
10.23 Attempts to prepare optically active iodides by nucleophilic displacement on optically active compounds with I^- normally produce racemic alkyl iodides. Why are the product alkyl iodides racemic?

10.24 Draw the structural formula for the product of each S_N1 reaction. Where configuration of the starting material is given, show the configuration of the product.

(a) (S)-$PhCHCH_2CH_3$ (Cl on the CH) + CH_3CH_2OH $\xrightarrow[\text{ethanol}]{}$

(b) 

(c) $CH_3CCl(CH_3)_2$ + CH_3COH (O double-bonded) $\xrightarrow[\text{acetic acid}]{}$

(d) 

10.25 You were told that each reaction in the previous problem proceeds by an S_N1 mechanism. Suppose you were not told the mechanism. Describe how you could conclude from the structure of the alkyl halide, the nucleophile, and the solvent that each reaction is in fact an S_N1 reaction.

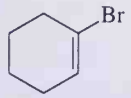
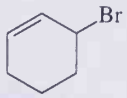
10.26 Vinylic halides such as vinyl bromide, $CH_2{=}CHBr$, do not undergo S_N1 reactions. Nor do they undergo S_N2 reactions. What factors account for this lack of reactivity of vinylic halides?

10.27 Select the member of each pair that undergoes S_N1 solvolysis in aqueous ethanol more rapidly.

(a) $CH_3CH_2CH_2CH_2Cl$ or $(CH_3)_3CCl$ **(b)** $(CH_3)_3CCl$ or $(CH_3)_3CBr$

(c) $CH_2{=}CHCH_2Cl$ or $CH_3CH_2CH_2Cl$ **(d)** $(H_3C)_2C{=}CHCH_2Cl$ or $H_2C{=}CHCH_2Cl$

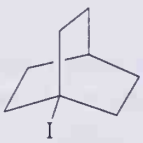
(e) $CH_3(CH_2)_3CH_2Cl$ or $CH_3(CH_2)_2CHClCH_3$

(f)  or 

10.28 Account for the following relative rates of solvolysis under experimental conditions favoring S_N1 reaction.

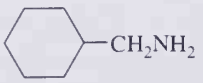
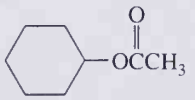
	$CH_3\ddot{O}CH_2CH_2Cl$	$CH_3CH_2CH_2CH_2Cl$	$CH_3CH_2\ddot{O}CH_2Cl$
relative rate of solvolysis (S_N1)	0.2	1	10^9

10.29 Not all tertiary halides are prone to undergo S_N1 reactions. For example, 1-iodobicyclo[2.2.2]octane is very unreactive toward S_N1 chemistry. What feature of this molecule is responsible for such lack of reactivity?

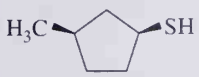


1-Iodobicyclo[2.2.2]octane

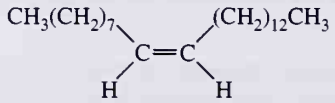
10.30 Show how you might synthesize the following compounds from an alkyl halide and a nucleophile:

(a)  **(b)**  **(c)** 

(d) $CH_3(CH_2)_3CH_2SH$ **(e)** $CH_3(CH_2)_5C{\equiv}CH$ **(f)** $CH_3CH_2OCH_2CH_3$

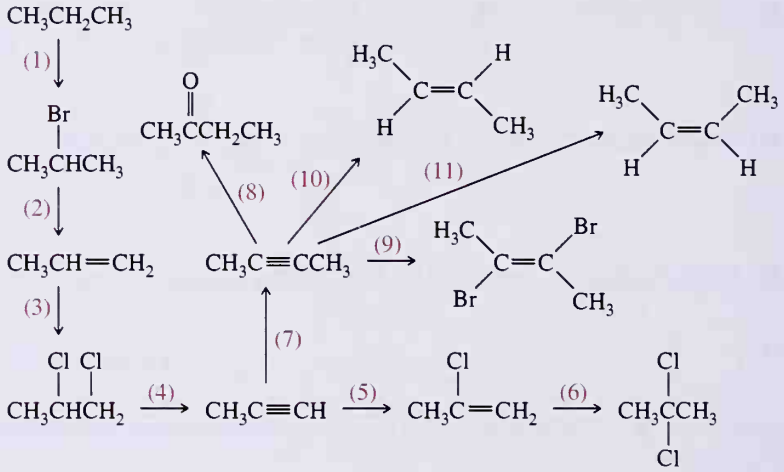
(g) 

10.31 Propose a synthesis for (Z)-9-tricosene (muscalure), the sex pheromone for the common house fly *(Musca domestica)* starting with acetylene and alkyl halides as sources of carbon atoms.



Muscalure

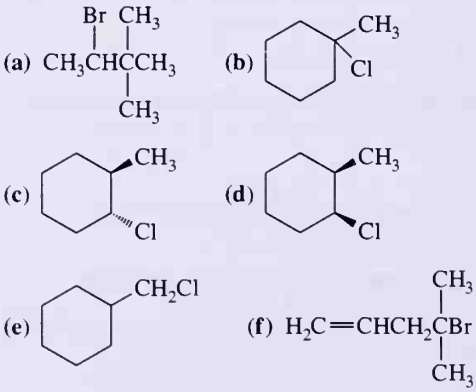
10.32 Show reagents and experimental conditions required to bring about the following transformations:



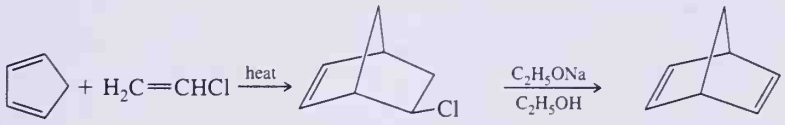
10.33 When the phase-transfer catalyst tetrabutylammonium hydrogen sulfate is used at elevated temperatures, some decomposition of the catalyst occurs. For example, when the nucleophile is NaCN, the catalyst decomposition products are tributylamine (Bu_3N) and $CH_3CH_2CH_2CH_2CN$. How are these products formed?

β-Eliminations

10.34 Draw structural formulas for the alkene(s) formed by treatment of each haloalkane with sodium ethoxide in ethanol. Assume that elimination is by an E2 mechanism.

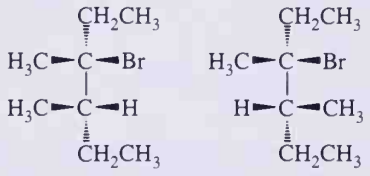


10.35 Bicyclo[2.2.1]-2,5-heptadiene can be prepared in two steps from cyclopentadiene and vinyl chloride. Provide a mechanism for each step. *Hint:* Review the Diels-Alder reaction (Section 7.5).



bicyclo[2.2.1]-2,5-heptadiene

10.36 Following are diastereomers (A) and (B) of 3-bromo-3,4-dimethylhexane. On treatment with sodium ethoxide in ethanol, each gives 3,4-dimethyl-3-hexene as the major product. One of these diastereomers gives the (E)-alkene, and the other gives the (Z)-alkene. Which diastereomer gives which alkene? Account for the stereospecificity of each β-elimination.



(A) (B)

Substitution versus Elimination

10.37 Consider the following statements in reference to S_N1, S_N2, S_Ni, E1, and E2 reactions of alkyl halides. To which mechanism(s), if any, does each statement apply?

(a) Involves a carbocation intermediate

(b) Is first-order in alkyl halide and first-order in nucleophile

(c) Involves inversion of configuration at the site of substitution

(d) Involves retention of configuration at the site of substitution

(e) Substitution at a stereocenter gives predominantly a racemic product.

(f) Is first-order in alkyl halide and zero-order in base

(g) Is first-order in alkyl halide and first-order in base

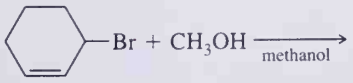
(h) Is greatly accelerated in protic solvents of increasing polarity

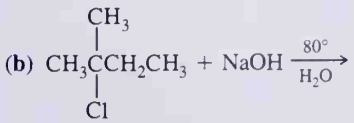
(i) Rearrangements are common.

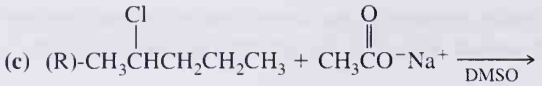
(j) Order of reactivity is 3° > 2° > 1° > methyl.

(k) Order of reactivity is methyl > 1° > 2° > 3°.

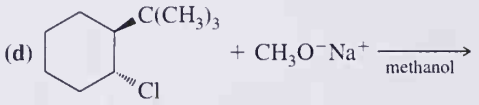
10.38 Draw a structural formula for the major organic product of each reaction and specify the most likely mechanism for formation of the product you have drawn.

(a) 

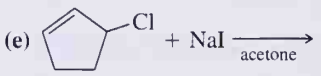
(b) 



(c) (R)-$CH_3CHCH_2CH_2CH_3$ + $CH_3CO^-Na^+$ $\xrightarrow[\text{DMSO}]{}$

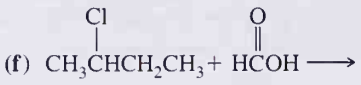


(d) + $CH_3O^-Na^+$ $\xrightarrow[\text{methanol}]{}$



(e) + NaI $\xrightarrow[\text{acetone}]{}$

R Isomer

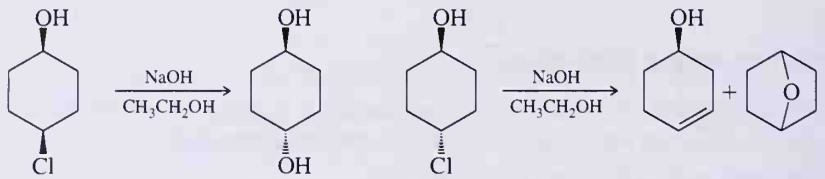


(f) $CH_3CHCH_2CH_3$ + HCOH $\longrightarrow$

R Isomer

(g) CH_3CH_2ONa + $CH_2{=}CHCH_2Cl$ $\xrightarrow{\text{ethanol}}$

10.39 When *cis*-4-chlorocyclohexanol is treated with sodium hydroxide in ethanol, it gives only the substitution product *trans*-1,4-cyclohexanediol (1). Under the same reaction conditions, *trans*-4-chlorocyclohexanol gives 3-cyclohexenol (2) and the bicyclic ether (3).



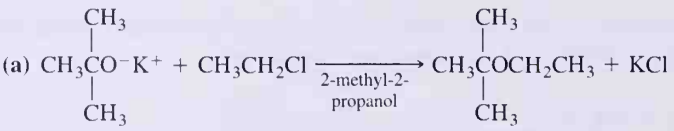
cis-4-Chloro-cyclohexanol (1) *trans*-4-Chloro-cyclohexanol (2) (3)

(a) Propose mechanisms for formation of product (1), and account for its configuration.

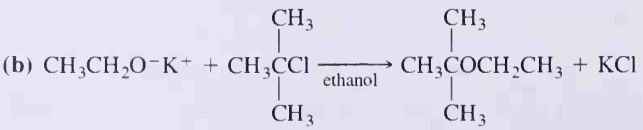
(b) Propose a mechanism for formation of product (2).

(c) Account for the fact that the bicyclic ether (3) is formed from the *trans* isomer but not from the *cis*-isomer.

10.40 The Williamson ether synthesis involves reaction of an alkyl halide with a metal alkoxide. Following are two reactions intended to give *tert*-butyl ethyl ether. One reaction gives the ether in good yield, the other reaction does not. Which reaction gives the ether? What is the major product of the other reaction, and how do you account for its formation?



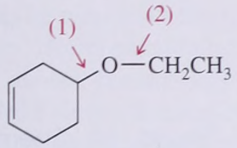
(a) $(CH_3)_3CO^-K^+$ + CH_3CH_2Cl $\xrightarrow[\text{2-methyl-2-propanol}]{}$ $CH_3COCH_2CH_3$ + KCl



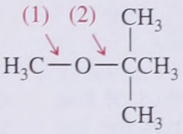
(b) $CH_3CH_2O^-K^+$ + $(CH_3)_3CCl$ $\xrightarrow[\text{ethanol}]{}$ $CH_3COCH_2CH_3$ + KCl

10.41 The following ethers can, in principle, be synthesized by two different combinations of alkyl halide and metal alkoxide. Show one combination of alkyl halide and alkoxide that forms ether bond (1) and another that forms ether bond (2). Which combination gives the higher yield of ether?

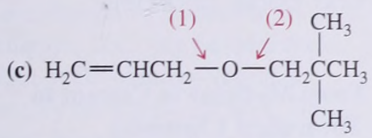
(a)



(b)



(c)



ROALD HOFFMANN

Roald Hoffmann is a remarkable individual. When he was only 44 years old, he shared the 1981 Nobel Prize in Chemistry with Kenichi Fukui of Japan for work in applied theoretical chemistry. In addition, he has received awards from the American Chemical Society in both organic chemistry and inorganic chemistry, the only person to have achieved this honor. And, in 1990, he was awarded the Priestley Medal, the highest award given by the American Chemical Society.

The numerous honors celebrating his achievements in chemistry tell only part of the story of his life. He was born to a Polish Jewish family in Zloczow, Poland, in 1937, and was named Roald after the famous Norwegian explorer Roald Amundsen. Shortly after World War II began in 1939 the Nazis first forced him and his parents into a ghetto and then into a labor camp. However, his father smuggled Hoffmann and his mother out of the camp, and they were hidden for more than a year in the attic of a school house in the Ukraine. His father was later killed by the Nazis after trying to organize an attempt to break out of the labor camp. After the war, Hoffmann, his mother, and his stepfather made their way west to Czechoslovakia, Austria, and then Germany. They finally emigrated to the United States, arriving in New York in 1949. That Hoffmann and his mother survived these years is our good fortune. Of the 12,000 Jews living in Zloczow in 1941 when the Nazis took over, only 80 people, three of them children, survived the Holocaust. One of those three children was Roald Hoffmann.

On arriving in New York, Hoffmann learned his sixth language, English. He went to public schools in New York City and then to Stuyvesant High School, one of the city's select science schools. From there he went to Columbia University and then on to Harvard University, where he earned his Ph.D. in 1962. Shortly thereafter, he began the work with Professor R.B. Woodward that eventually led to the Nobel Prize. Since 1965 he has been a professor at Cornell University.

In addition to his work in chemistry, Professor Hoffmann also writes popular articles on science for the *American Scientist* and other magazines, and he has published two volumes of his poetry. Finally, he appeared in a series of 26 half-hour television programs for a chemistry course called "World of Chemistry," which airs on public television and cable channels.

From Medicine to Cement to Theoretical Chemistry

Professor Hoffmann's office at Cornell University is full of mineral samples, molecular models, and Japanese art. When asked what brought him into chemistry he said, "I came rather late to chemistry, I was not interested in it from childhood." However, he clearly feels that one can come late to chemistry, and that it can be a very positive thing. "I am always worried about fields in which people exhibit precocity, like music and mathematics. Precocity is some sort of evidence that you have to have talent. I don't like that. I like the idea that human beings can do anything they want to. They need to be trained sometimes. They need a teacher to awaken the intelligence within them. But to be a chemist requires no special talent, I'm glad to say. Anyone can do it, with hard work."

He took a standard chemistry course in high school. He recalls that it was a fine course, but apparently he found biology more enjoyable because, in his high school yearbook, "under the picture of me with a crew cut, it says 'medical research' under my name." Indeed, he says that "medical research was a compromise between my interest in science and the typical Jewish middle class family pressures to become

a medical doctor. The same kind of pressures seem to apply to Asian-Americans today."

When he went to Columbia University, Hoffmann enrolled as a pre-med student, but says that there were several factors that shifted him away from a career in medicine. One of these was his work at the National Bureau of Standards in Washington, D.C., for two summers and then at Brookhaven National Laboratory for a third summer. He says that these experiences gave him a feeling for the excitement of chemical research. Nonetheless, during his first summer at the Bureau of Standards, he "did some not very exciting work on the thermochemistry of cement." During his second summer there, he went over to the National Institutes of Health to find out what medical research was about. "To my amazement," he says, "most of the people had Ph.D.'s and not M.D.'s. I just didn't know. Young people do not often know what is required for a given profession. Once I found that out, and found that I did well in chemistry, it made me feel that I didn't really have to do medicine, that I could do some research in chemistry or biology. Later, what influenced me to decide on theoretical chemistry was an excellent instructor.

"At the very same time I was being exposed to the humanities, in part because of Columbia's core curriculum—which I think is a great idea—that had so-called contemporary civilization and humanities courses. I took advantage of the liberal arts education to the hilt, and that has remained with me all my life. The humanities teachers have remained permanently fixed in my mind and have changed my ways of thinking. These were the people who really had the intellectual impact on me and helped to shape my life.

"To trace the path, I was a latecomer to chemistry and was inspired by research. I think *research* is the way in. It just gives you a different perception."

A Love for Complexity

Having discussed what brought him into chemistry, we were interested in his view of the qualities that a student should possess to pursue a career in the field. He said, "One thing one needs to be a chemist is a love for complexity and richness. To some extent that is true of biology and natural history, too. I think one of the things that is beautiful about chemistry is that there are 10,000,000 compounds, each with different properties. What's beautiful when you make a molecule is that you can make derivatives in which you can vary substituents, the pieces of a molecule, and we know that those substituents give a molecule function, give it complexity and richness. That's why a protein or nucleic acid with all its variety is essential for life. That's why to me, intellectually, isomerism and stereochemistry in organic chemistry are at the heart of chemistry. I think we should teach that much earlier. It requires no mathematics, only a little model building; you can do this without theory. I think it is no accident that organic chemistry drew to it the intellects of its time."

"That's why to me, intellectually, isomerism and stereochemistry in organic chemistry are at the heart of chemistry."

Experiment and Theory

Professor Hoffmann has spent his career immersed in the theories of chemistry. However, he believes that fundamentally "chemistry is an experimental science, in spite of some of my colleagues saying otherwise. However, the educational process certainly favors theory. It's in the nature of things for teacher and student both to want to understand and then give primacy to the soluble and the understood at the expense of other things. We also have this reductionist philosophy of science, the idea that the social sciences derive from biology, that biology follows from chemistry, chemistry from physics, and so on. This notion gives an inordinate amount of importance to theoretical thinking, the more mathematical the better. Of course this is not true in reality, but it's an ideology; it is a religion of science."

There is of course a role for theory. "You can't report just the facts and nothing but the facts; by themselves they are dull. They have to be woven into a framework so that there is understanding. That's accomplished usually by a theory. It may not be mathematical, but a qualitative network of relationships." Indeed, Hoffmann believes that the incorporation of theory into chemistry "is what made American science better than that in many other countries. The emphasis in chemistry on theory and theoretical understanding is very important, but not nearly as important as the syntheses and reactions of molecules.

"Although I think chemists need to like to do experiments, that

doesn't mean there is no role for people like me. It turns out that I am really an experimental chemist hiding as a theoretician. I think that is the key to my success. That is, I think I can empathize with what bothers the experimentalists. In another day I could have become an experimentalist."

Major Issues in Chemistry and Science Today

Professor Hoffmann has worked, and is presently working, at the forefront of several major areas of chemistry. He is presently quite intrigued by surface science. "For instance, there is the Fischer-Tropsch process, a pretty incredible thing in detail. Carbon monoxide and hydrogen gas come onto a metal catalyst, a surface of some sort, and off come long chain hydrocarbons and alcohols. The richness of all these things happening is intriguing, and we are on the verge of understanding. We now have structural information on surfaces that's reliable, and we are just beginning to get kinetic information. Surface science is at a crossing of chemistry, physics, and engineering. The field is in some danger of being spun off on its own, but I would like to keep it in chemistry.

"Bioinorganic chemistry is another such field. In my research group we are doing some work trying to understand the mechanism of oxygen production in photosynthesis, the last steps. What is known is very little. There is an enzyme in photosystem II that involves 3 to 4 manganese atoms, and they are at oxidation state 3 to 4. And they somehow take oxide or hydroxide to peroxide and eventually to molecular oxygen. That's all we know. Experimentally, not theoretically, I think bioinorganic chemistry is a very interesting field."

Finally, Hoffmann remarked, "There are going to be finer and finer ways of controlling the synthesis of molecules, the most essential activity of chemists. If I were to point to a single thing that chemists do, it would be that they make molecules. Chemistry is the science of molecules and their transformations. The transformations are the essential part. I think there are exciting possibilities for chemical intervention into biological systems with an ever finer degree of control. We need not be afraid of nature. We can mimic it, and even surpass its synthetic capabilities. And find a way to cooperate with it."

Scientific Literacy and Democracy

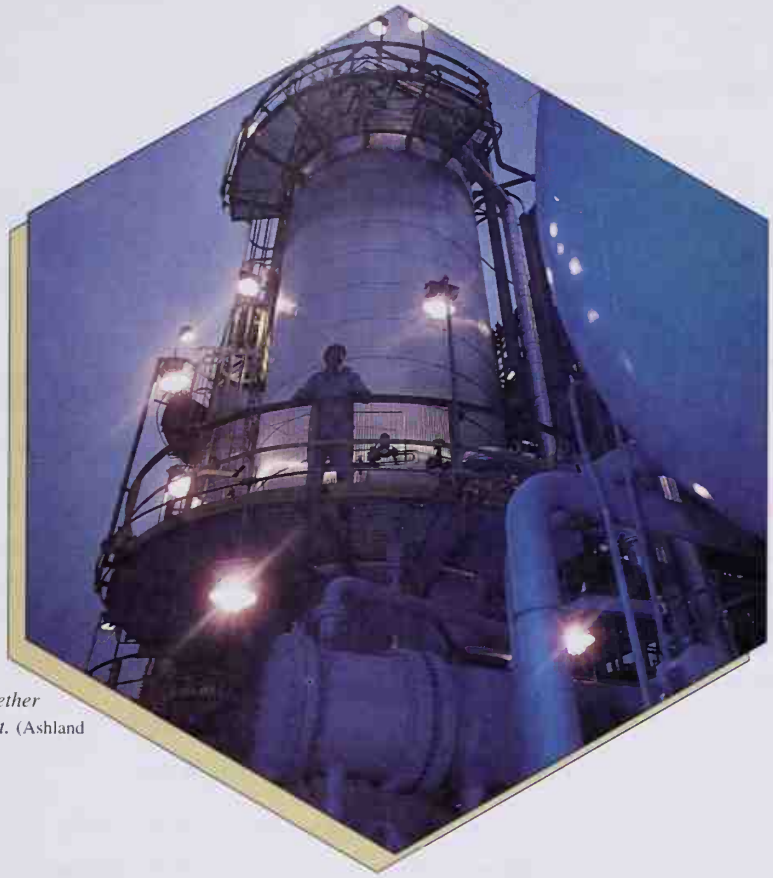
Roald Hoffmann is very concerned not only about science in general and chemistry in particular, but also about our society. One of his concerns is scientific literacy because "some degree of scientific literacy is absolutely necessary today for the population at large as part of a democratic system of government. People have to make intelligent decisions about all kinds of technological issues." He recently offered his comments on this important issue in the *New York Times*. He wrote, "What concerns me about scientific, or humanistic, illiteracy is the barrier it poses to rational democratic governance. Democracy occasionally gives in to *technocracy*—a reliance on experts on matters such as genetic engineering, nuclear waste disposal, or the cost of medical care. That is fine, but the people must be able to vote intelligently on these issues. The less we know as a nation, the more we must rely on experts, and the more likely we are to be misled by demagogues. We must know more."

The Responsibility of Scientists

"Scientists have a great obligation to speak to the public," Hoffmann says. "We have an obligation as educators to train the next generation of people. We should pay as much attention to those peole who are *not* going to be chemists, and sometimes need to make compromises about what is to be taught and what is the nature of our courses. I think scientists have an obligation to speak to the public broadly, and here I think they have been negligent. I think society is paying scientists money to do research, and can demand an accounting in plain language. That's why I put in a lot of time on that television show [*The World of Chemistry*]."

A Teacher of Chemistry—and Proud of It

In the Nobel Yearbook, Professor Hoffmann wrote that the technical description of his work "does not communicate what I think is my major contribution. I am a teacher, and I am proud of it. At Cornell University I have taught primarily undergraduates. . . . I have also taught chemistry courses to nonscientists and graduate courses in bonding theory and quantum mechanics. To the chemistry community at large, and to my fellow scientists, I have tried to teach 'applied theoretical chemistry': a special blend of computations stimulated by experiment and coupled to the construction of general models—frameworks for understanding." His success in this area is unquestioned.



A tert-*butyl methyl ether manufacturing plant.* (Ashland Petroleum)

11

ETHERS AND EPOXIDES

In this chapter, we first discuss the structure, nomenclature, and physical properties of ethers, and compare their physical properties with those of structurally isomeric alcohols. Next, we study the preparation and reactions of ethers, and, as we shall see, their most important reactions involve nucleophilic substitution. In a sense then, this chapter is an extension of the discussion of S_N1 and S_N2 reaction mechanisms begun in the previous chapter.

11.1 Structure of Ethers

The characteristic structural feature of an **ether** is an atom of oxygen bonded to two carbon atoms. In an ether, sp^3 hybrid orbitals of oxygen form sigma bonds to the two carbon atoms. Each of the remaining sp^3 hybrid orbitals contains an unshared pair of electrons. Figure 11.1 shows a Lewis structure and a ball-and-stick model of dimethyl ether, CH_3OCH_3, the simplest ether. The C—O—C bond angle in dimethyl ether is 110.3°, a value close to the predicted tetrahedral angle of 109.5°.

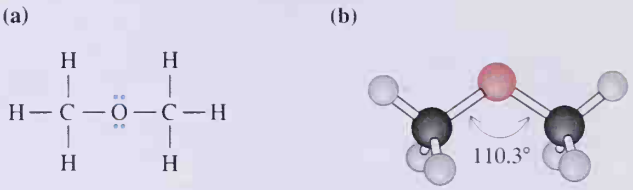
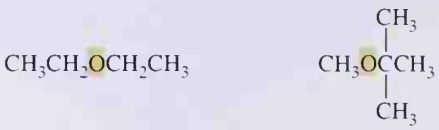


Figure 11.1
The structure of dimethyl ether, CH_3OCH_3: (a) Lewis structure and (b) ball-and-stick model.

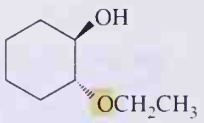
11.2 Nomenclature of Ethers

In the IUPAC system, ethers are named by selecting the longest carbon chain as the parent compound and naming the —OR group as an **alkoxy** substituent. Common names are derived by listing the alkyl groups attached to oxygen in alphabetical order and adding the word "ether." Following are the IUPAC names and, in parentheses, the common names for several low-molecular-weight ethers.

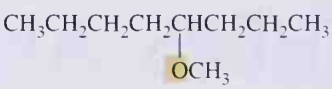


Ethoxyethane
(Diethyl ether)

2-Methoxy-2-methylpropane
(*tert*-Butyl methyl ether)



trans-2-Ethoxycyclohexanol

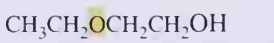


4-Methoxyoctane

Chemists almost invariably use common names for low-molecular-weight ethers. For example, although ethoxyethane is the IUPAC name for $CH_3CH_2OCH_2CH_3$, it is rarely called that but rather, diethyl ether, ethyl ether, or even more commonly, simply "ether." The abbreviation for *tert*-butyl methyl ether, an ether that is becoming increasingly important as an octane-improving additive to gasolines, is MTBE after the incorrect common name of methyl *tert*-butyl ether.

Three other ethers deserve special mention. 2-Methoxyethanol and 2-ethoxyethanol, more commonly known as Methyl Cellosolve and Ethyl Cellosolve, are good polar protic solvents in which to carry out organic reactions and are also used commercially in some paint strippers. *Di*ethylene *gly*col di*m*ethyl *e*ther, more commonly known by its acronym, diglyme, is a common solvent for hydroboration reactions.

2-Methoxyethanol
(Methyl Cellosolve)



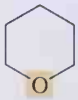
2-Ethoxyethanol
(Ethyl Cellosolve)

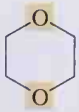
Diethylene glycol dimethyl ether
(Diglyme)

Heterocyclic ethers, that is, cyclic compounds in which the ether oxygen is one of the atoms in a ring, are given special names.


Ethylene oxide

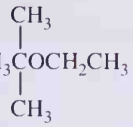

Tetrahydrofuran

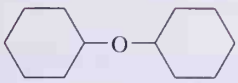

Tetrahydropyran


1,4-Dioxane

EXAMPLE 11.1

Give common names and IUPAC names for the following ethers:

(a) 

(b) 

(c) $CH_2{=}CHOCH_3$

Solution

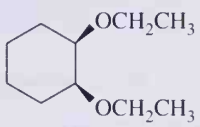
(a) *tert*-Butyl ethyl ether. The IUPAC name of this ether is 2-ethoxy-2-methylpropane.
(b) Dicyclohexyl ether. Its IUPAC name is cyclohexoxycyclohexane.
(c) Methyl vinyl ether. Its IUPAC name is methoxyethene.

PROBLEM 11.1

Give common names for the following ethers:

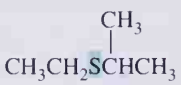
(a) 

(b) $CH_3OCH_2CH_2OCH_3$

(c) 

Sulfur analogs of ethers are named by using the word **sulfide** to show the presence of the —S— group. Following are common names of two sulfides:


Dimethyl sulfide


Ethyl isopropyl sulfide

The characteristic structural feature of a **disulfide** is the presence of an —S—S— group. Common names of disulfides are derived by listing the names of the groups attached to sulfur and adding the word "disulfide."


Dimethyl disulfide

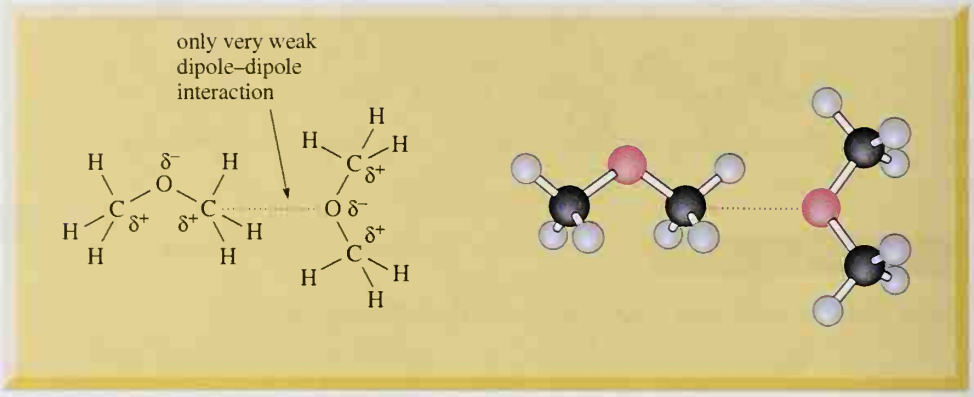


Figure 11.2
Ethers are polar molecules, but because of steric hindrance, there is only weak dipole-dipole interaction between molecules in the pure liquid.

11.3 Physical Properties of Ethers

Ethers have weakly polar molecules in which oxygen bears a partial negative charge and each attached carbon bears a partial positive charge (Figure 11.2).

Because ethers are weakly polar, there is the possibility for dipole-dipole interaction between molecules in the pure liquid. Recall from Section 2.8 that dipole-dipole interactions are important only when the interacting centers are close together. The fact that each partially positive carbon atom of an ether is surrounded by other atoms minimizes effective dipole-dipole interaction between ether molecules. Thus, although ethers are polar molecules, only weak dipole-dipole interaction exists between molecules in the pure state, and, consequently, boiling points of ethers are close to those of hydrocarbons of comparable

Table 11.1 Boiling points and solubilities in water of some ethers and alcohols of comparable molecular weight

Structural Formula	Name	Molecular Weight	bp (°C)	Solubility in Water
CH_3CH_2OH	ethanol	46	78	infinite
CH_3OCH_3	dimethyl ether	46	−24	7 g/100 g
$CH_3CH_2CH_2OH$	1-propanol	60	97	infinite
$CH_3OCH_2CH_3$	ethyl methyl ether	60	11	soluble
$CH_3CH_2CH_2CH_2OH$	1-butanol	74	117	8 g/100 g
$CH_3CH_2OCH_2CH_3$	diethyl ether	74	35	8 g/100 g
$CH_3CH_2CH_2CH_2CH_2OH$	1-pentanol	88	138	2.3 g/100 g
$HOCH_2CH_2CH_2CH_2OH$	1,4-butanediol	90	230	infinite
$CH_3CH_2CH_2CH_2OCH_3$	butyl methyl ether	88	71	slight
$CH_3OCH_2CH_2OCH_3$	ethylene glycol dimethyl ether	90	84	infinite

molecular weight. Boiling points of ethers are much lower than those of alcohols of comparable molecular weight (Table 11.1) because of the ability of alcohols to form intermolecular hydrogen bonds.

Because the oxygen atom of an ether carries a partial negative charge, ethers are hydrogen bond acceptors (Figure 11.3) and, therefore, are more soluble in water than hydrocarbons of comparable molecular weight and shape (compare data in Tables 2.5 and 11.1).

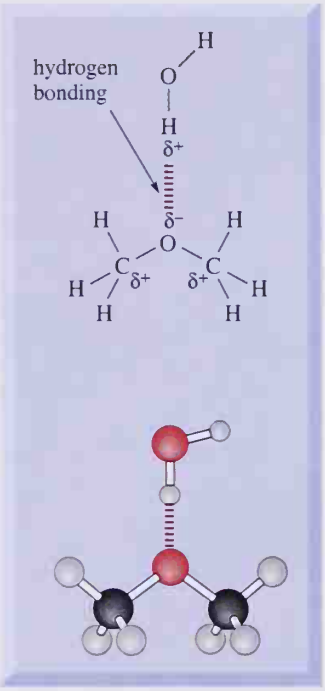


Figure 11.3
Ethers are hydrogen bond acceptors only. They are not hydrogen bond donors.

EXAMPLE 11.2

Arrange the following compounds in order of increasing solubility in water:

$CH_3OCH_2CH_2OCH_3$	$CH_3CH_2OCH_2CH_3$	$CH_3CH_2CH_2CH_2CH_2CH_3$
Ethylene glycol dimethyl ether	Diethyl ether	Hexane

Solution

Water is a polar solvent. Hexane, a nonpolar hydrocarbon, has the lowest solubility in water. Both diethyl ether and ethylene glycol dimethyl ether are polar compounds due to the presence of polar C—O—C bonds, and each interacts with water as a hydrogen bond acceptor. Because ethylene glycol dimethyl ether has more sites within the molecule for hydrogen bonding than diethyl ether, it is the more soluble of the two in water.

$CH_3CH_2CH_2CH_2CH_2CH_3$	$CH_3CH_2OCH_2CH_3$	$CH_3OCH_2CH_2OCH_3$
Insoluble	8 g/100 g water	Soluble in all proportions

PROBLEM 11.2

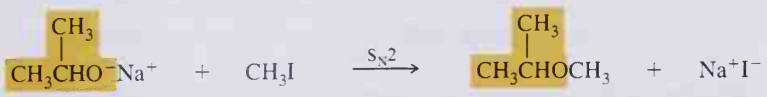
Arrange the following compounds in order of increasing boiling point:

$CH_3OCH_2CH_2OCH_3$ $HOCH_2CH_2OH$ $CH_3OCH_2CH_2OH$

11.4 Preparation of Ethers

A. Williamson Ether Synthesis

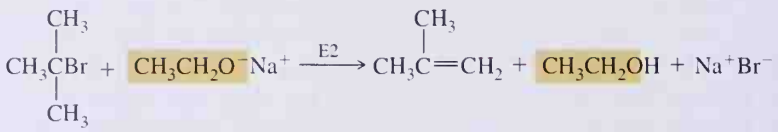
The most common general method for the synthesis of ethers, the **Williamson ether synthesis,** is a direct application of second-order nucleophilic substitution (S_N2) at a saturated carbon. We already illustrated this reaction several times in Chapter 10, although at that point it was not given a specific name. The Williamson ether synthesis involves nucleophilic displacement of a halide ion or other good leaving group by an alkoxide ion.



Sodium isopropoxide	Iodomethane (Methyl iodide)	2-Methoxypropane (Isopropyl methyl ether)

In planning a Williamson ether synthesis, it is best to use a combination of reactants that maximizes nucleophilic substitution and minimizes the competing β-elimination reaction (Section 10.11B). As expected for an S_N2 reaction, yields of ether are highest when the halide is displaced from methyl or a primary carbon. Yields are lower in the displacement of secondary halides (because of competing β-elimination), and the reaction fails altogether with tertiary halides, in which case β-elimination by an E2 mechanism is the predominant reaction. For example, *tert*-butyl ethyl ether can be prepared by reaction of potassium *tert*-butoxide and bromoethane. With the alternative combination of sodium ethoxide and *tert*-butyl bromide, no ether is formed. Rather, 2-methylpropene is formed by dehydrohalogenation.

Potassium *tert*-butoxide — Bromoethane — *tert*-Butyl ethyl ether



tert-Butyl bromide — Sodium ethoxide — 2-Methyl-propene

EXAMPLE 11.3

Show a combination of alcohol and alkyl halide that can be used to prepare the following ethers by the Williamson ether synthesis:

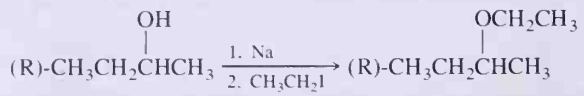
(a) $CH_3(CH_2)_3OCH(CH_3)_2$ **(b)** (R)-$CH_3CH_2CH(OCH_2CH_3)CH_3$

Solution

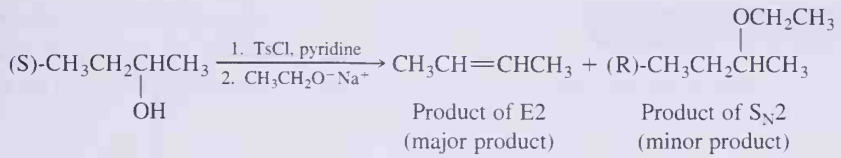
(a) Treat 2-propanol with sodium metal to form sodium isopropoxide. Then treat this metal alkoxide with 1-bromobutane.

$$CH_3(CH_2)_3Br + (CH_3)_2CHO^-Na^+ \xrightarrow{S_N2} CH_3(CH_2)_3OCH(CH_3)_2$$

(b) Treat (R)-2-butanol with sodium metal to form the metal alkoxide. Reaction involves only the O—H bond and does not affect the stereocenter. Then treat this metal alkoxide with an ethyl halide to give the desired product.

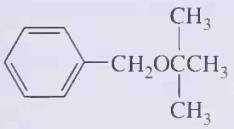


An alternative synthesis is to convert the (S)-2-butanol to its tosylate followed by treatment with sodium ethoxide. This synthesis gives only a low yield of the desired product. Recall from Section 10.11B that when a 2° halide or tosylate is treated with a strong base/strong nucleophile, E2 is the major reaction.



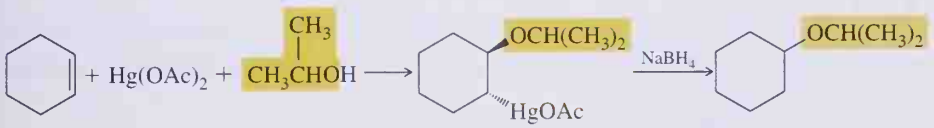
PROBLEM 11.3

Show how you might use the Williamson ether synthesis to prepare the following ethers:

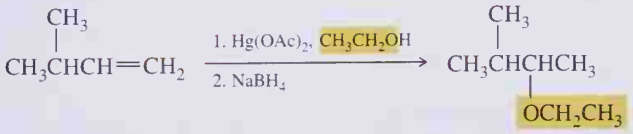
(a)  (b) $(CH_3CH_2CH_2CH_2)_2O$

B. Alkoxymercuration/Reduction

A second and very versatile method for the synthesis of ethers is an extension of a reaction we already studied in Section 5.3E: (1) regioselective and stereoselective oxymercuration of an alkene followed by (2) reduction of the resulting carbon-mercury bond with $NaBH_4$. If oxymercuration is carried out in water, the final product is an alcohol. If it is carried out in an alcohol as the nucleophile, the final product is an ether and the process is called **alkoxymercuration/reduction.** Following are two examples of alkoxymercuration/reduction.



Isopropoxycyclohexane
(Cyclohexyl isopropyl ether)

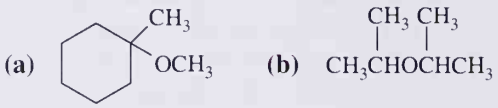


3-Methyl-1-butene 2-Ethoxy-3-methylbutane

Alkoxymercuration/reduction gives good yields of ethers from the reaction of alkenes with primary, secondary, and tertiary alcohols. Alkoxymercuration has an advantage over the Williamson ether synthesis in that it gives good yields of ethers of the type $R_2CH—O—CHR_2$ and $R_3C—O—CHR_2$. To synthesize ethers of this type by the Williamson ether synthesis, it is necessary to use a secondary halide as one of the starting materials, in which case β-elimination (E2) rather than substitution (S_N2) is the major reaction. Ethers of the type $R_3C—O—CR_3$ cannot be synthesized by either of these methods.

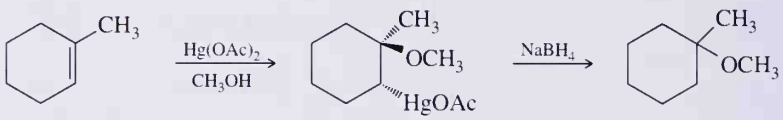
EXAMPLE 11.4

Propose a synthesis for the following ethers using alkoxymercuration followed by sodium borohydride reduction.



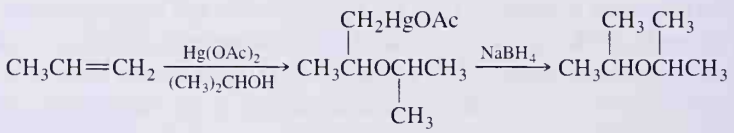
Solution

(a) Treatment of 1-methylcyclohexene with mercuric acetate in methanol followed by sodium borohydride reduction of the organomercury intermediate.



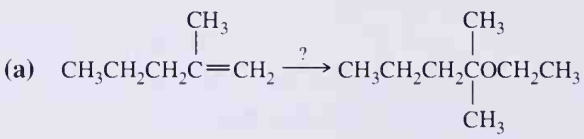
(HgOAc and methanol add *trans* and coplanar to each other)

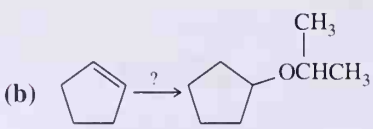
(b) Treatment of propene with mercuric acetate in 2-propanol (isopropyl alcohol) followed by reduction with sodium borohydride.



PROBLEM 11.4

Propose a synthesis for the following ethers using alkoxymercuration followed by sodium borohydride reduction.

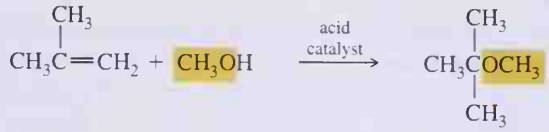




C. Acid-Catalyzed Addition of Alcohols to Alkenes

The net effect of alkoxymercuration followed by reduction is addition of an alcohol to an alkene in a two-step process. In some instances, the same transformation can be accomplished in one step. An example is the commercial synthesis of *tert*-butyl methyl ether, an

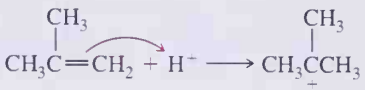
antiknock, octane-improving gasoline additive. 2-Methylpropene and methanol are passed over an acid catalyst to give the ether.



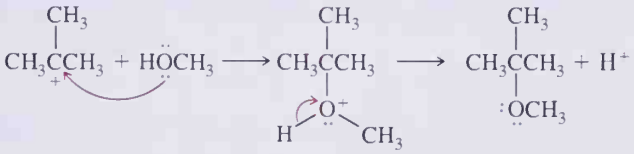
2-Methoxy-2-methylpropane
(*tert*-Butyl methyl ether)

The mechanism for this ether synthesis involves electrophilic attack of H^+ on the carbon-carbon double bond to generate a carbocation followed by addition of the nucleophile and loss of H^+ to give the final product.

Electrophilic attack of H^+ on the alkene to form a carbocation:



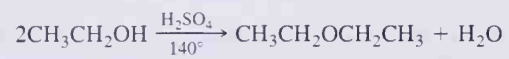
Reaction of the carbocation with methanol to form an oxonium ion followed by loss of H^+:



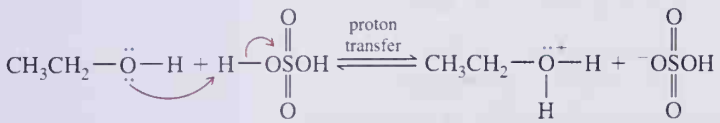
The usefulness of this ether synthesis is limited to the interaction of primary alcohols and alkenes that can form 3° carbocations.

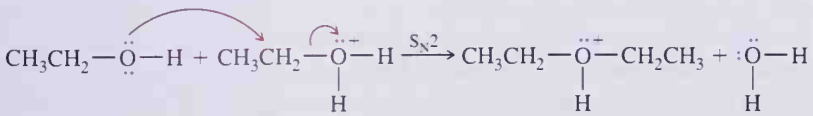
D. Acid-Catalyzed Dehydration of Alcohols

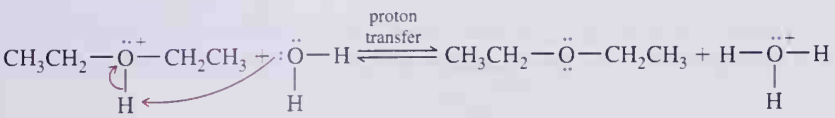
Diethyl ether and several other commercially available ethers are synthesized by acid-catalyzed dehydration of primary alcohols.



Acid-catalyzed intermolecular dehydration of alcohols is a specific example of an S_N2 reaction in which a poor leaving group, OH, is transformed into a better leaving group, OH_2^+, in the presence of acid.







This plant produces the gasoline additive *tert*-butyl methyl ether (MTBE). *(Ashland Petroleum)*

Intramolecular dehydration of ethanol to ethylene is a competing reaction, and it too is reversible. In practice, experimental conditions can be adjusted to favor either formation of ethylene or diethyl ether.

Yields of ethers from acid-catalyzed intermolecular dehydration of alcohols are highest for symmetrical ethers formed from primary unbranched alcohols. Examples of symmetrical ethers formed in good yield by this method are dimethyl ether, diethyl ether, and dibutyl ether. From secondary alcohols, yields of ether are lower because of competition from acid-catalyzed dehydration (Section 9.5E). In the case of tertiary alcohols, dehydration is the major reaction.

EXAMPLE 11.5

Explain why the following reaction does not give a good yield of ethyl hexyl ether.

$$CH_3(CH_2)_4CH_2OH + CH_3CH_2OH \xrightarrow[\text{heat}]{H_2SO_4} CH_3(CH_2)_4CH_2OCH_2CH_3 + H_2O$$

Solution

From this reaction expect a mixture of three ethers: diethyl ether, ethyl hexyl ether, and dihexyl ether.

PROBLEM 11.5

Show how ethyl hexyl ether might be synthesized by a Williamson ether synthesis, and by alkoxymercuration/reduction.

11.5 Preparation of Thiols and Sulfides

The most common preparation of thiols, RSH, depends on the very high nucleophilicity of hydrosulfide ion, HS^- (Section 10.7B). Sodium hydrosulfide is prepared by bubbling H_2S through a solution of NaOH in water or aqueous ethanol. Reaction of HS^- with an alkyl halide gives a thiol.

$$CH_3(CH_2)_8CH_2I + Na^+SH^- \xrightarrow{S_N2} CH_3(CH_2)_8CH_2SH + Na^+I^-$$

1-Iododecane — Sodium hydrosulfide — 1-Decanethiol

In practice, the scope and limitations of this reaction are governed by competition between substitution and β-elimination (Section 10.11), as well as formation of sulfides. The reaction is most useful for preparation of thiols from primary halides. Yields are low from secondary halides because of the competing β-elimination reaction. With tertiary halides, β-elimination predominates, and the alkene formed by dehydrohalogenation is the major product.

In a commercial application of thiol formation by nucleophilic substitution, thioglycolic acid is prepared by the reaction of sodium hydrosulfide and sodium iodoacetate.

$$Na^+SH^- + ICH_2CO^-Na^+ \xrightarrow{S_N2} HSCH_2CO^-Na^+ + Na^+I^-$$

Sodium hydrosulfide — Sodium iodoacetate — Sodium mercaptoacetate (Sodium thioglycolate)

The sodium and ammonium salts of thioglycolic acid are used in cold waving of hair; the calcium salt is used as a depilatory, that is, to remove body hair.

$$(HSCH_2CO_2^-)_2Ca^{2+}$$

Calcium mercaptoacetate
(Calcium thioglycolate)

Symmetrical sulfides, RSR, are prepared by the reaction of 1 mol of Na_2S (where S^{2-} is the nucleophile) with 2 mol of alkyl halide. This method of sulfide formation is the sulfur analog of the Williamson ether synthesis (Section 11.5A).

$$2RX + Na_2S \longrightarrow RSR + 2NaX$$

(A sulfide)

This same reaction can also be used to prepare cyclic sulfides. Treatment of a 1,4-dihalide with Na_2S gives a five-member cyclic sulfide; treatment of a 1,5-dihalide with Na_2S gives a six-member cyclic sulfide.

$$ClCH_2CH_2CH_2CH_2Cl + Na_2S \longrightarrow \text{(S-heterocycle)} + 2Na^+Cl^-$$

1,4-Dichlorobutane — Tetrahydrothiophene

$$ClCH_2CH_2CH_2CH_2CH_2Cl + Na_2S \longrightarrow \text{(S-heterocycle)} + 2Na^+Cl^-$$

1,5-Dichloropentane — Tetrahydrothiopyran

Package label of a hair waving kit. *(Charles D. Winters)*

Unsymmetrical sulfides, RSR′, are prepared by converting a thiol to a sodium salt with either sodium hydroxide or sodium ethoxide and then allowing the salt to react with an alkyl halide.

$$CH_3(CH_2)_8CH_2S^-Na^+ + CH_3I \longrightarrow CH_3(CH_2)_8CH_2SCH_3 + Na^+I^-$$

Sodium 1-decanethiolate — 1-(Methylthio)decane (Decyl methyl sulfide)

Note that all of these reactions leading to thiols and sulfides are direct applications of nucleophilic substitution reactions (Chapter 10).

11.6 Reactions of Ethers and Sulfides

Ethers resemble hydrocarbons in their resistance to chemical reaction. They do not react with oxidizing agents, such as potassium dichromate or potassium permanganate. They are not affected by most acids or bases at moderate temperatures. Because of their general inertness to chemical reaction and good solvent characteristics, ethers are excellent solvents in which to carry out many organic reactions.

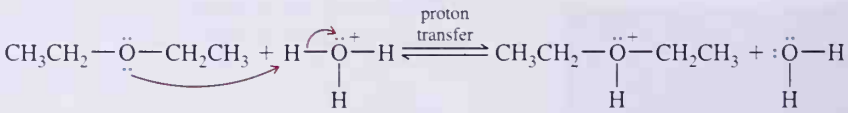
A. Acid-Catalyzed Cleavage by Concentrated HX

Ethers are cleaved when treated with concentrated aqueous HI (57%) or HBr (48%). For example, diethyl ether reacts with hot concentrated HBr to give two molecules of bromoethane.

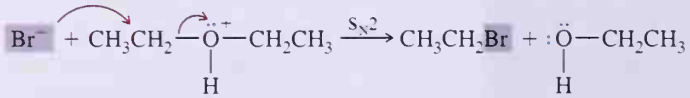
$$CH_3CH_2OCH_2CH_3 + 2HBr \xrightarrow[\text{heat}]{} 2CH_3CH_2Br + H_2O$$

Concentrated HCl (38%) is far less effective in cleaving ethers, primarily because Cl^- is a weaker nucleophile in water than either I^- or Br^-.

The mechanism of cleavage of dialkyl ethers begins with protonation of the ether oxygen to form an oxonium ion.

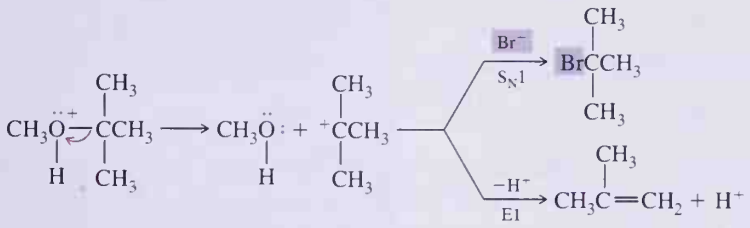


The next step in ether cleavage depends on the nature of the group attached to oxygen. Where both carbons are primary, cleavage is by an S_N2 reaction in which halide ion is the nucleophile. In this example, the leaving group is CH_3CH_2OH, a weak base and a weak nucleophile.



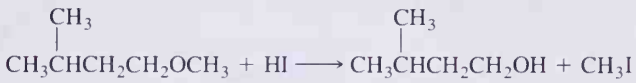
Cleavage produces one molecule of alkyl bromide and one molecule of alcohol. In the presence of excess concentrated HBr, the alcohol is converted to a second molecule of alkyl bromide by another S_N2 process.

If one of the alkyl groups attached to oxygen is tertiary, cleavage of the C—O bond gives a tertiary carbocation. The resulting carbocation may (1) react with bromide ion to give an alkyl bromide, (2) lose a hydrogen to give an alkene, or (3) rearrange, followed by options (1) or (2).



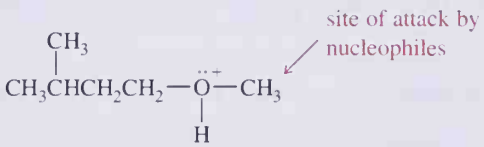
EXAMPLE 11.6

Account for the fact that reaction of most methyl ethers with concentrated HI gives CH_3I and ROH as the initial major products rather than CH_3OH and RI. For example:



Solution

The first step is protonation of the ether oxygen to give an oxonium ion. Cleavage is by an S_N2 pathway on the less hindered methyl carbon.

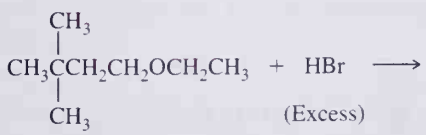


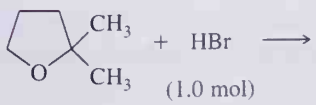
PROBLEM 11.6

Account for the fact that treatment of *tert*-butyl methyl ether with a limited amount of concentrated HI gives methanol and *tert*-butyl iodide rather than methyl iodide and *tert*-butyl alcohol.

EXAMPLE 11.7

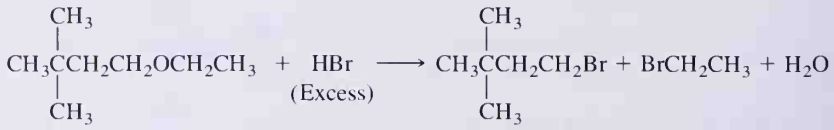
Draw structural formulas for the major products of the following reactions:

(a) 

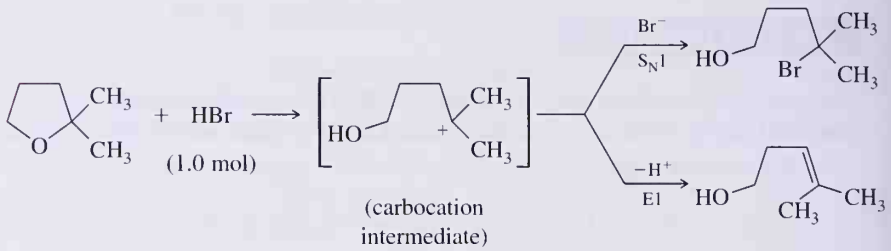
(b) 

Solution

(a) Cleavage on either side of the ether oxygen by an S_N2 mechanism gives an alcohol and an alkyl bromide. Reaction of the alcohol then gives a second molecule of alkyl bromide.

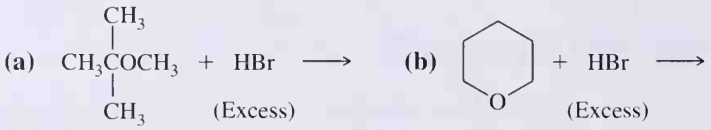


(b) Protonation of the ether oxygen followed by cleavage gives a tertiary carbocation, which may then (1) react with bromide ion to give a bromoalcohol or (2) lose a hydrogen to give an unsaturated alcohol.



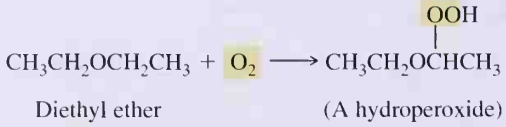
PROBLEM 11.7

Draw structural formulas for the major products of the following reactions:



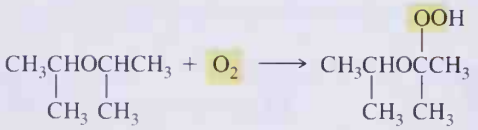
B. Formation of Hydroperoxides

Two hazards must be avoided when working with diethyl ether and other low-molecular-weight ethers. First, they are highly flammable. Consequently, open flames and electric appliances with sparking contacts must be avoided where ethers are being used. Second, anhydrous ethers react with molecular oxygen at a C—H bond adjacent to the ether oxygen to form hydroperoxides by a radical process. The characteristic structural feature of a **hydroperoxide** is ROOH.



Rates of hydroperoxide formation increase dramatically if the C—H bond adjacent to oxygen is on a secondary carbon, as for example in diisopropyl ether, because of favored generation of a stable 3° radical intermediate.

Anhydrous diethyl ether is stabilized by addition of butylated hydroxytoluene (BHT) as radical trap. (See Problem 16.22 for the synthesis of BHT.) *(Charles D. Winters)*

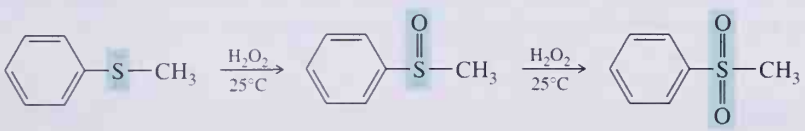


Diisopropyl ether (A hydroperoxide)

Hydroperoxides are dangerous because they are explosive. Furthermore, they react with some metals to form hydroperoxide salts, which are also explosive and especially sensitive to shock. Peroxides can be detected by shaking an ether with a 10% aqueous solution of potassium iodide, KI. Peroxides oxidize iodide ion to iodine, I_2, which gives a yellow color to the solution. This is converted to a blue-purple color by the addition of starch, due to formation of a starch-iodine complex. Hydroperoxides can be removed by treatment with a reducing agent. One effective procedure is to shake the hydroperoxide-contaminated ether with a solution of iron(II) sulfate dissolved in dilute aqueous sulfuric acid.

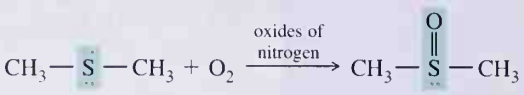
C. Oxidation of Sulfides

Many of the properties of sulfides stem from the fact that divalent sulfur is a reducing agent; it is easily oxidized to two higher oxidation states. Treatment of a sulfide with 1 mol of 30% aqueous hydrogen peroxide at room temperature gives a sulfoxide as illustrated by oxidation of methyl phenyl sulfide to methyl phenyl sulfoxide. Several other oxidizing agents, including sodium metaperiodate, $NaIO_4$, also bring about the same conversion. Treatment of a sulfoxide with a second mole of hydrogen peroxide brings about its oxidation to a sulfone.



Methyl phenyl sulfide (a sulfide) Methyl phenyl sulfoxide (a sulfoxide) Methyl phenyl sulfone (a sulfone)

Dimethyl sulfoxide (DMSO) is manufactured on an industrial scale by air oxidation of dimethyl sulfide in the presence of oxides of nitrogen.

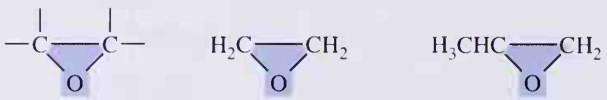


Dimethyl sulfide — Dimethyl sulfoxide

11.7 Epoxides

A. Structure and Nomenclature

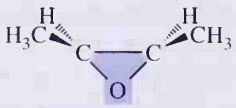
An **epoxide** is a cyclic ether in which oxygen is one atom of a three-member ring. Following is the characteristic structural feature of an epoxide along with structural formulas for several specific epoxides:



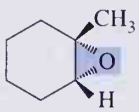
Characteristic structural feature

Oxirane (1,2-Epoxyethane) (Ethylene oxide)

Methyloxirane (1,2-Epoxypropane) (Propylene oxide)



cis-2,3-Dimethyloxirane (*cis*-2,3-Epoxybutane) (*cis*-2-Butene oxide)



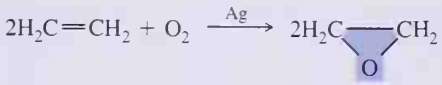
1-Methyl-1,2-epoxycyclohexane (1-Methylcyclohexene oxide)

The name "epoxide" is a common name. In the IUPAC system, these compounds are members of a class called **oxiranes.** The prefix **ox-** indicates the presence of an atom of oxygen in the ring. The infix **-ir-** is a reversal of the last two letters of tri- and indicates a ring of three atoms. The suffix **-ane** indicates that the carbon-carbon bond of the ring is a single bond. Substituents are listed as prefixes to the parent name "oxirane" as illustrated by the name methyloxirane.

Common names of epoxides are derived by listing the location of the two carbons of the parent chain to which the atom of oxygen is attached followed by the prefix epoxy- and then the name of the parent chain. Examples of this type of common name are 1,2-epoxyethane and *cis*-2,3-epoxybutane. Alternatively, other types of common names are derived by giving the name of the alkene from which the epoxide might have been derived followed by the word "oxide"; an example is *cis*-2-butene oxide.

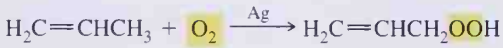
B. Synthesis

Ethylene oxide, one of the few epoxides manufactured on an industrial scale, is prepared by passing a mixture of ethylene and air (or oxygen) over a silver catalyst.



Oxirane
(Ethylene oxide)

Propylene oxide, the next member of the epoxide family, cannot be prepared by air oxidation of propylene. Rather than epoxidation, propene and other alkenes with allylic hydrogens react with oxygen by a radical chain mechanism (Section 5.5) to form hydroperoxides.

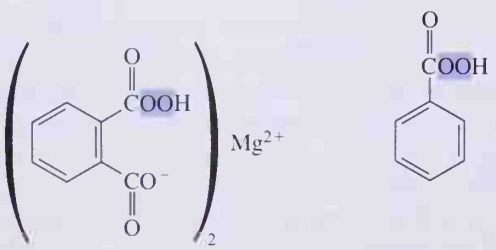


(A hydroperoxide)

The most common methods for preparation of epoxides in the laboratory are (1) oxidation with peroxycarboxylic acids and (2) treatment of a halohydrin with aqueous base.

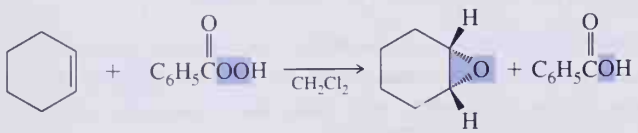
Oxidation of Alkenes with Peroxyacids

The most common laboratory method for the synthesis of epoxides from alkenes is oxidation with a peroxycarboxylic acid (a peracid). Two peroxyacids commonly used for epoxidation of alkenes are the magnesium salt of monoperoxyphthalic acid and peroxybenzoic acid.



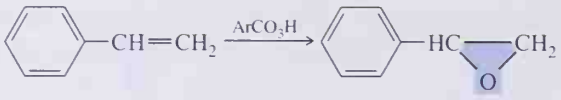
Magnesium monoperoxyphthalate Peroxybenzoic acid

Following is a balanced equation for the epoxidation of cyclohexene by peroxybenzoic acid. In the process, peroxybenzoic acid is reduced to benzoic acid.

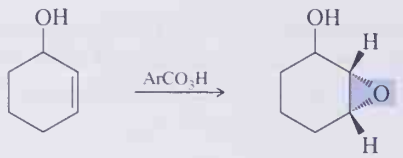


Cyclohexene Peroxybenzoic acid Cyclohexene oxide Benzoic acid

Following are two more examples of conversion of alkenes to epoxides. Conversion of styrene to styrene oxide illustrates the fact that a benzene ring is unaffected by this reagent. Similarly, conversion of 2-cyclohexenol to its epoxide illustrates that alcohols are also unaffected.

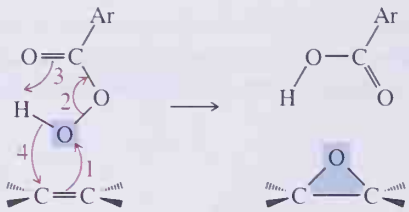


Phenylethene (Styrene) — Phenyloxirane (Styrene oxide)



2-Cyclohexenol — 2,3-Epoxycyclohexanol

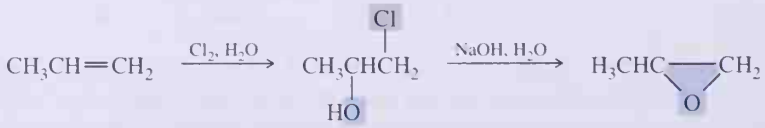
A mechanism for epoxidation by a peroxyacid must take into account the following facts: (1) The reaction takes place in nonpolar solvents, which means that the reaction cannot involve the formation of ions or any species with large separation of unlike charges; (2) The reaction is stereospecific with retention of configuration; *trans* alkenes give *trans* epoxides and *cis* alkenes give *cis* epoxides, which means that even though the pi bond is broken, at no time does free rotation occur about the remaining sigma bond. Following is a mechanism consistent with these observations.



To help you see a pattern to the flow of electron pairs, curved arrows are numbered 1 through 4. Arrow 1 shows interaction of the pi electrons of the carbon-carbon double bond with an oxygen atom of the peroxyacid and formation of a new C—O bond. Arrows 2 and 3 show shifts of electrons within the peroxyacid, and arrow 4 shows formation of the second carbon-oxygen bond. The numbering of these arrows does not imply a precise order in which covalent bonds are broken and made. Rather they are meant as a guide to help you understand the mechanism. It is thought that the entire combination of bond-making and bond-breaking steps is concerted, or nearly so.

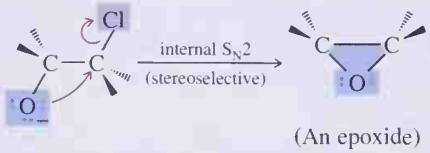
Internal Nucleophilic Substitution in Halohydrins

A second method for preparation of epoxides from alkenes involves (1) treatment of the alkene with chlorine or bromine in water to form a chlorohydrin or bromohydrin followed by (2) treatment of the halohydrin with base and elimination of HX. By these steps, propene is first converted to 1-chloro-2-propanol and then to methyloxirane (propylene oxide).



Propene — 1-Chloro-2-propanol (a chlorohydrin) — Methyloxirane (Propylene oxide)

We already studied the reaction of alkenes with chlorine or bromine in water to form halohydrins (Section 5.3F) and saw that it is both regioselective and stereoselective. Treatment of a halohydrin with base in the second step of this sequence is stereoselective as well and can be viewed as an internal S_N2 reaction. Hydroxide ion or other base abstracts a hydrogen from the halohydrin to form an alkoxide ion, a nucleophile, which then displaces halogen on the adjacent carbon. As with all S_N2 reactions, attack of the nucleophile is from the backside of the C—X bond.



(An epoxide)

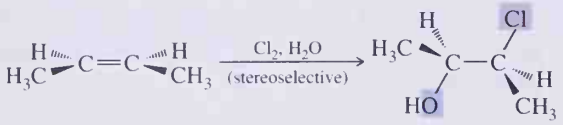
Note that displacement of halide by the oxygen anion can also be viewed as an intramolecular variation of the Williamson ether synthesis we studied in Section 11.4A. In this case, the displacing alkoxide and leaving halide ion are on adjacent carbon atoms.

EXAMPLE 11.8

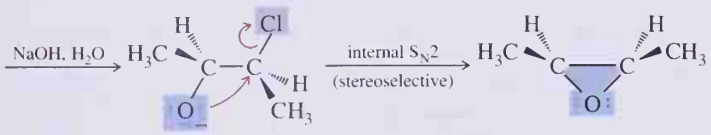
Conversion of an alkene to a halohydrin and internal displacement of halide ion by alkoxide ion are both stereoselective. Use this information to demonstrate that the configuration of the alkene is preserved in the epoxide. As an illustration, show that reaction of *cis*-2-butene by this two-step sequence gives *cis*-2,3-dimethyloxirane (*cis*-2-butene oxide).

Solution

Addition of HOCl to an alkene occurs by anti and coplanar addition of —OH and —Cl to the double bond. The conformation of the product formed by anti and coplanar addition is also the conformation that undergoes backside displacement of halide ion by alkoxide ion. Thus, a *cis* alkene gives a *cis* epoxide, and a *trans* alkene gives a *trans* epoxide.



cis-2-butene (A chlorohydrin)



(A *cis* epoxide)

PROBLEM 11.8

Consider possibilities for stereoisomerism in the halohydrin and epoxide formed in Example 11.8.

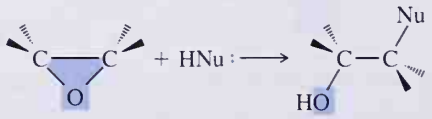
(a) How many stereoisomers are possible for the chlorohydrin? Which of the possible chlorohydrins are formed by reaction of *cis*-2-butene with HOCl?

(b) How many stereoisomers are possible for the epoxide? Which of the possible stereoisomers is (are) formed in this reaction sequence?

11.8 Reactions of Epoxides

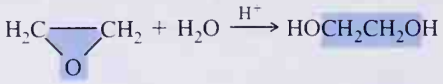
Although epoxides are technically classed as ethers, we discuss them separately because of their exceptional chemical reactivity compared with other ethers. Because of the strain associated with the three-member ring, epoxides undergo a variety of ring-opening reactions, the characteristic feature of which is nucleophilic substitution at one of the carbons of the epoxide ring with oxygen as the leaving group.

Characteristic reaction of epoxides:



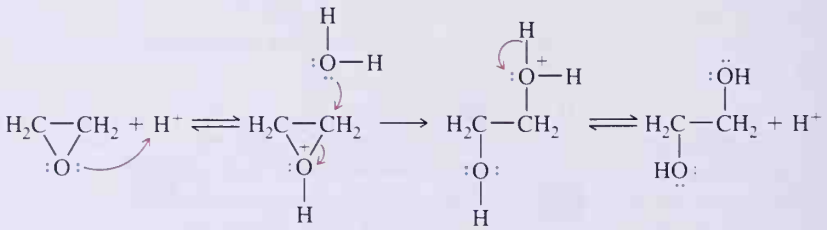
A. Acid-Catalyzed Ring Opening

In the presence of an acid catalyst, most commonly perchloric acid, epoxides are hydrolyzed to 1,2-diols. As an example, acid-catalyzed hydrolysis of ethylene oxide gives 1,2-ethanediol (ethylene glycol).

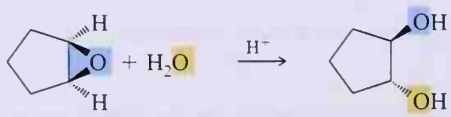


Oxirane (Ethylene oxide) — 1,2-Ethanediol (Ethylene glycol)

Under acidic conditions, the oxygen atom of the epoxide is protonated to form a bridged oxonium ion intermediate. S_N2 attack of the nucleophile on this intermediate results in ring opening; water is the nucleophile, and —OH is the leaving group. Perchloric is the acid of choice because the perchlorate anion, ClO_4^-, is a very poor nucleophile and does not compete effectively with water.

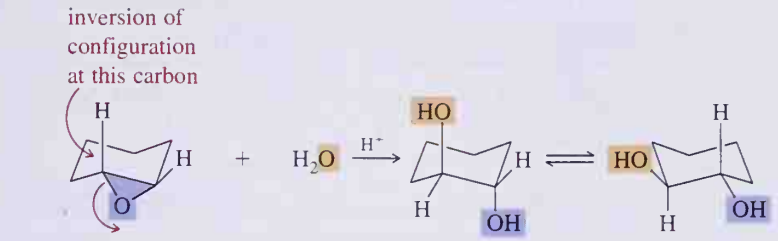


Attack of a nucleophile on a protonated epoxide shows a stereoselectivity typical of S_N2 reactions; the nucleophile attacks anti and coplanar to the leaving hydroxyl group, and the —OH groups in the glycol thus formed are anti and coplanar.



trans-1,2-Cyclopentanediol

In opening of an epoxide derived from a cyclohexene ring, the —OH groups become *trans* and diaxial. This *trans* diaxial conformation is in equilibrium with the more stable *trans* diequatorial conformation.

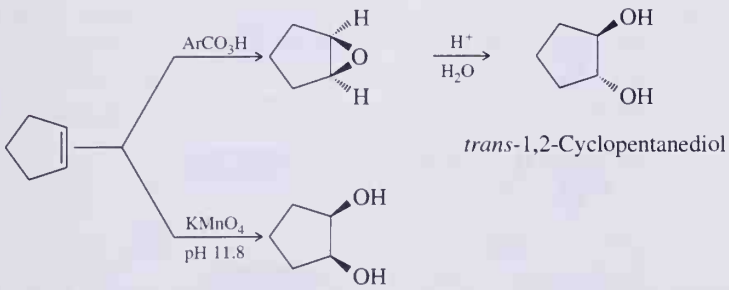


cis-1,2-Epoxycyclohexane (*trans* Diaxial conformation) (*trans* Diequatorial conformation)

trans-1,2-Cyclohexanediol

Note the similarity in ring opening of this bridged oxonium ion intermediate, the bridged halonium ion intermediate in electrophilic addition of halogens to an alkene (Section 5.3D), and the bridged mercurinium ion intermediates in oxymercuration (Section 5.3E) and alkoxymercuration of an alkene (Section 11.4B). In each case, the intermediate is a three-member ring with a heteroatom bearing a positive charge, and attack of the nucleophile is anti to the leaving group.

At this point, let us compare the stereochemistry of the glycol formed by acid-catalyzed hydrolysis of an epoxide with that formed by oxidation of an alkene with alkaline potassium permanganate or osmium tetroxide (Section 5.7B). Each reaction sequence is stereoselective but for a different stereoisomer. Acid-catalyzed hydrolysis of cyclopentene oxide gives *trans*-1,2-cyclopentanediol; potassium permanganate or osmium tetroxide oxidation of cyclopentene gives *cis*-1,2-cyclopentanediol. Thus, a cycloalkene can be converted to either a *cis*-glycol or a *trans*-glycol by the proper choice of reagents.

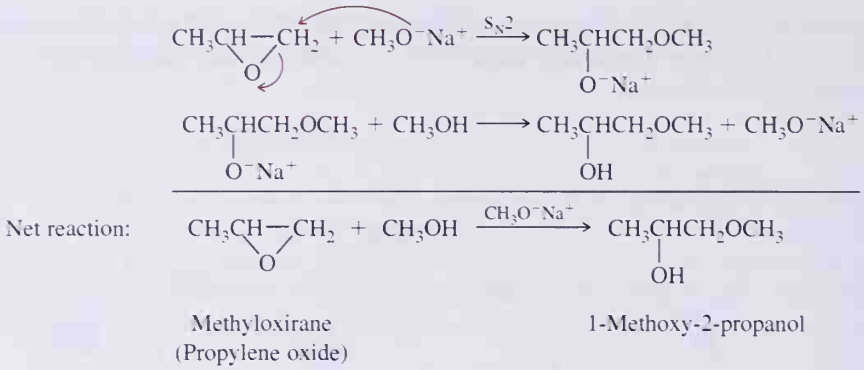


trans-1,2-Cyclopentanediol

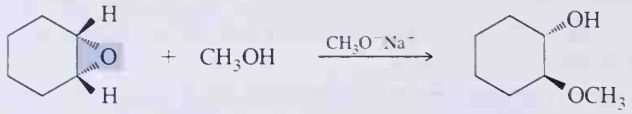
cis-1,2-Cyclopentanediol

B. Nucleophilic Ring Opening

Ethers are not normally susceptible to reaction with nucleophiles. Because of the strain associated with a three-member ring, however, epoxides undergo ring-opening reactions with a variety of nucleophiles. Strong nucleophiles attack an epoxide ring by an S_N2 mechanism and show a regioselectivity typical of such reactions, namely, attack of the nucleophile at the less hindered carbon. Following is the reaction of methyloxirane (propylene oxide) with sodium methoxide in methanol:

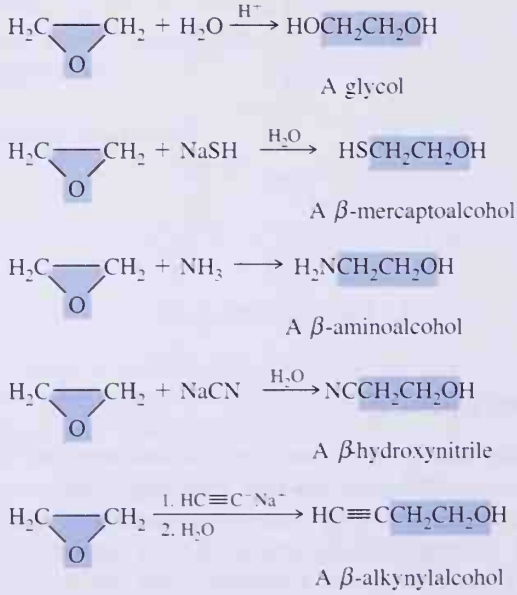


In the reaction of propylene oxide with methanol in the presence of sodium methoxide, the nucleophile methoxide ion attacks the primary carbon in preference to the secondary carbon and displaces $-O^-$. Nucleophilic ring opening of epoxides is also stereoselective: as expected of an S_N2 reaction, attack of the nucleophile is anti to the leaving group as illustrated by the reaction of cyclohexene oxide with methanol in the presence of sodium methoxide to give *trans*-2-methoxycyclohexanol.

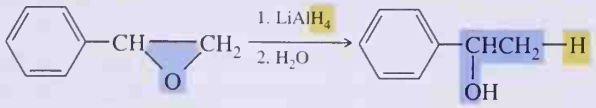


Cyclohexene oxide *trans*-2-Methoxycyclohexanol

The value of epoxides lies in the number of nucleophiles that bring about ring opening and the combinations of functional groups that can be prepared from them. Following are reactions of ethylene oxide with several nucleophiles:



Finally, treatment with $LiAlH_4$ reduces an epoxide to an alcohol. In reduction of a substituted epoxide by $LiAlH_4$, preferential attack of the hydride reducing agent occurs at the less hindered carbon of the epoxide, an observation consistent with S_N2 reactivity.



Phenyloxirane (Styrene oxide)

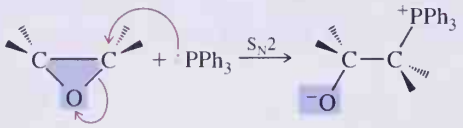
1-Phenylethanol

Another reagent that brings about ring opening of epoxides by nucleophilic attack is triphenylphosphine. The opened ring product undergoes further reaction to form an alkene and triphenylphosphine oxide.

Triphenylphosphine

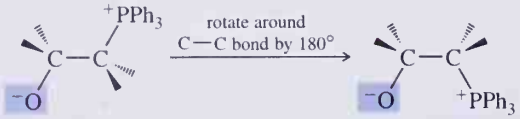
Triphenylphosphine oxide

Following is a mechanism for this type of reaction. Triphenylphosphine is a weak base and a strong nucleophile. Nucleophilic substitution gives a compound containing a negative charge on oxygen and a positive charge on phosphorus. A neutral substance with nonadjacent negative and positive charges is called a **betaine.**

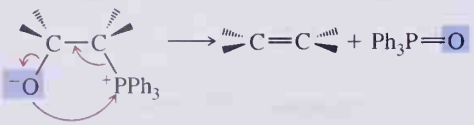


A betaine

Because of the stereoselectivity of the S_N2 reaction, the charged atoms in the betaine are anti and coplanar to each other as the ring is opened. Rotation by 180° about the carbon-carbon single bond places the charged atoms syn and coplanar to each other. The driving force for rotation is the electrostatic attraction between the two oppositely charged atoms.

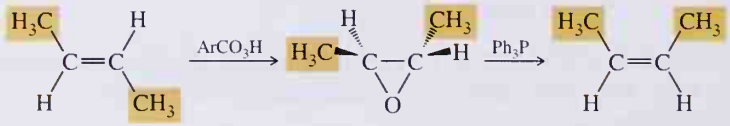


The final step is a four-center reaction involving oxygen-carbon-carbon-phosphorus bonds to give the alkene and triphenylphosphine oxide. This step is a stereoselective β-elimination in which the leaving groups are syn and coplanar to each other. Although the stereoselectivity of the majority of β-elimination reactions is anti (Section 10.10), a number of important β-elimination reactions occur, including this one, in which stereoselectivity is syn.



Key elements in the stereochemistry of this sequence of reactions are (1) retention of configuration in the epoxidation of the alkene, (2) inversion of configuration in the S_N2 reaction of the epoxide with triphenylphosphine, (3) rotation by 180° of the betaine from an anti coplanar conformation to a syn coplanar conformation, and (4) the four-center syn coplanar β-elimination reaction.

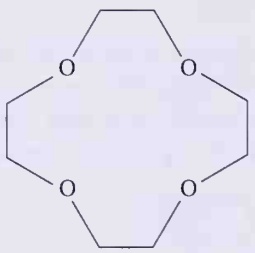
The value of the triphenylphosphine/epoxide reaction is that it can be used in conjunction with epoxidation to convert a *cis* alkene to a *trans* alkene and vice-versa, as illustrated by the conversion of *trans*-2-butene to *cis*-2-butene.



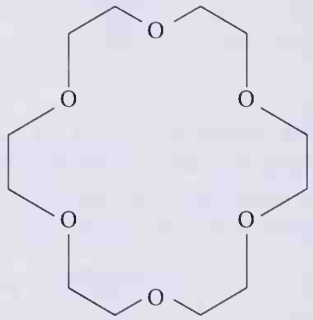
trans-2-Butene *cis*-2-Butene

11.9 Crown Ethers

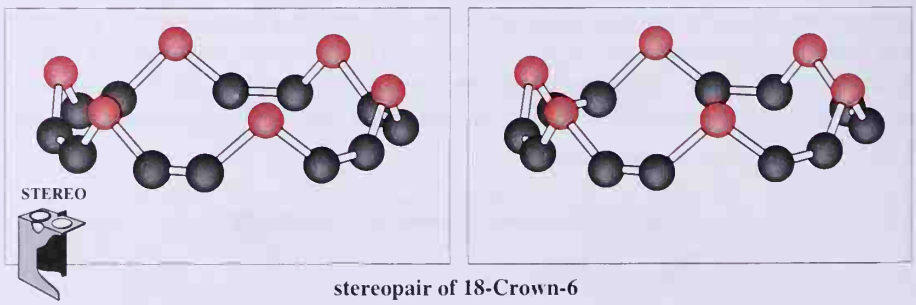
In the early 1960s, Charles Pedersen of Du Pont discovered a family of cyclic polyethers derived from ethylene glycol and substituted ethylene glycols. Compounds of this structure were given the name **crown ethers** because one of their most stable conformations resembles the shape of a crown. Although crown ethers do have IUPAC names, they are more commonly referred to by the shorthand notation devised by Pedersen. The parent name is "crown." It is preceded by a number describing the size of the ring and followed by a number describing the number of oxygens in the ring. The figure shows names and structural formulas for two commercially available crown ethers.



12-Crown-4
(a cyclic tetramer)



18-Crown-6
(a cyclic hexamer)



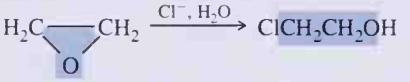
stereopair of 18-Crown-6

CHEMISTRY IN ACTION

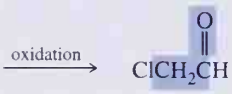
Ethylene Oxide and the Body's Defenses

There is a useful distinction in the toxicological classification of agents that are toxic themselves and those that must be metabolically activated before they show significant toxicity. Benzene, for example, is not particularly reactive, but when partially oxidized by enzymes in the body, it becomes a dangerous carcinogen. Because ethylene oxide is such a strained, reactive molecule, it is an example of a toxic compound that reacts directly with biological materials. In mice, one-half of the ethylene oxide breathed in reacts within 9 min. At sufficiently high concentrations, ethylene oxide reacts with enough molecules in cells to cause the death of microorganisms. This toxic property is the basis for using ethylene oxide as a chemical sterilant. In hospitals, surgical instruments and other items that cannot be made disposable are sterilized by exposure to ethylene oxide.

In addition to reacting with biomolecules containing amine and thiol groups, ethylene oxide can also react with chloride ion to give 2-chloroethanol, which in turn can be oxidized to chloroacetaldehyde. Treatment of deoxyribonucleic acids (DNAs) with either ethylene oxide or chloroacetaldehyde can produce mutations and chromosomal abnormalities.

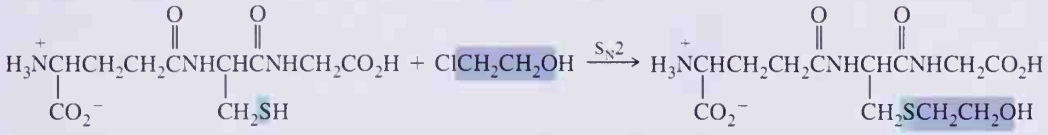


Ethylene oxide — 2-Chloroethanol



Chloroacetaldehyde

Glutathione, the most prevalent sulfur-containing molecule in most cells, is one of the body's chemical defense agents. With its nucleophilic —SH group, it is able to trap reactive electrophiles before they damage DNAs. The glutathione adducts are then broken down into smaller, harmless fragments, which are excreted in the urine.



Glutathione — 2-Chloroethanol — (*S*)-2-Hydroxyethylglutathione

A remarkable structural feature of crown ethers is that the diameter of the cavity created by the repeating oxygen atoms of the ring is comparable to the diameter of alkali metal ions. The diameter of the cavity in 18-crown-6, for example, is between 0.26 and 0.32 nm, approximately the diameter of a potassium ion. When a potassium ion is inserted into the cavity of 18-crown-6, the unshared electron pairs on the six oxygens of the crown ether are close enough to the potassium ion so that a strong electrostatic interaction occurs, thus providing very effective "solvation" for K^+. 18-Crown-6 forms somewhat weaker complexes with rubidium (a somewhat larger ion) and with sodium ion (a somewhat smaller ion). It does not coordinate to any appreciable degree with lithium ion (a considerably smaller ion). 12-Crown-4, however, with its smaller cavity, does form a strong complex with lithium ion.

CHEMISTRY IN ACTION

Crown Ethers and Chirality Sensors

Crown ethers form complexes with many types of cations. An 18-crown-6 ether, for example forms complexes with primary alkylammonium ions, RNH_3^+, stabilized by hydrogen bonding between oxygens of the ether and hydrogens of the ammonium ion.

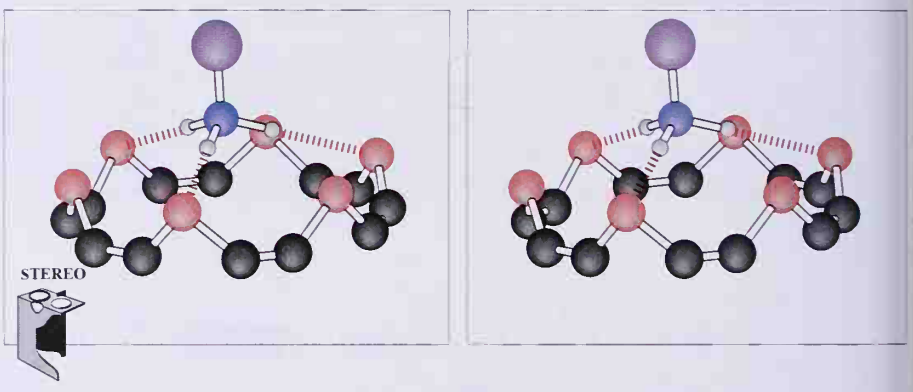
Crown ethers such as this have been incorporated into molecular devices the properties of which change depending on the amine bound inside the crown ether's cavity. One such device incorporates crown ethers into liquid crystals, producing a molecule that detects chirality by a color change.

Liquid crystals are materials that retain some of the order properties of a crystalline solid, even though they are liquids. In solid crystals, molecules are ordered in all three dimensions. In liquid crystals, molecules are ordered in one or two dimensions only.

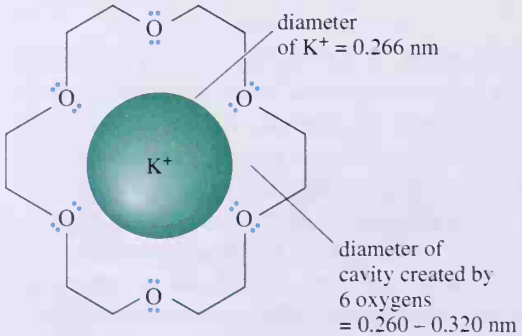
Solid crystal
(3-dimensional order)

Liquid crystal
(1- or 2-dimensional order)

Because of its ordered arrangement of molecules, a liquid crystal may act like a miniature diffraction grat-



Ion	Diameter (nm)
Li^+	0.136
Na^+	0.194
K^+	0.266
Rb^+	0.294
Mg^{2+}	0.164
Ca^{2+}	0.286



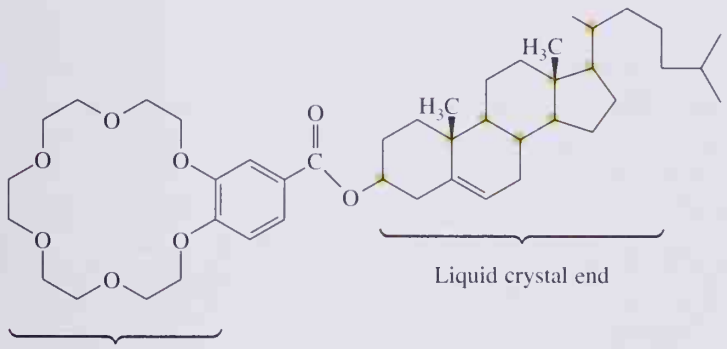
A complex of K^+ and 18-crown-6

ing and produce colors depending on the exact ordering of the molecules within it. This property of liquid crystals is used to make a molecular device that can detect chirality and distinguish an R enantiomer from an S enantiomer. Chemists first synthesized a molecule with a crown ether part and a liquid crystal part. The liquid crystal part is based on cholesterol, a naturally occurring steroid, which, because of its rodlike shape, forms stable liquid crystal phases. Cholesterol contains eight chiral centers, each marked in color, and is readily available from natural sources as a single stereoisomer.

When the liquid crystal (1) is treated with an optically active amine as, for example, (R)- or (S)-phenylalanine methyl ester hydrochloride (2), the $-NH_3^+$ group complexes to the crown ether part of the liquid crystal. The 1 + 2(R) and 1 + 2(S) complexes are diastereomers and thus have different physical properties. One difference is that they stack together with different spacings in their liquid crystal phase. The liquid crystal complex with the S enantiomer reflects light at 500 nm and appears green. The complex with the R enantiomer reflects light at 440 nm and appears blue. Thus, the crown ether/liquid crystal (1) acts as a molecular chirality sensor, changing colors depending on the chirality of its amine guest.

See T. Nishi, A. Ikeda, T. Matsuda, et al. *J. Chem. Soc., Chem. Commun.* 339, (1991).

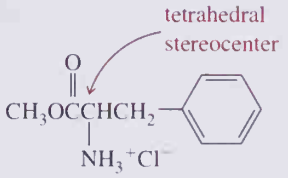
(1)



18-Crown-6 end

Liquid crystal end

(2)



Phenylalanine methyl ester hydrochloride

The cavity of a crown ether is a polar region, and the unshared pairs of electrons on the oxygen atoms lining the cavity provide effective solvation for alkali metal ions. The outer surface of the crown is nonpolar and hydrocarbon-like, and thus crown ethers and their alkali metal ion complexes dissolve readily in nonpolar organic solvents.

Crown ethers have proven to be particularly valuable for the same reasons that phase-transfer catalysts have proven so valuable, namely, for their ability to dissolve inorganic salts in nonpolar aprotic organic solvents, such as methylene chloride, hexane, and benzene. Potassium permanganate, for example, does not dissolve in benzene. If, however, an 18-crown-6 is added to benzene, the solution takes on the purple color characteristic of permanganate ion. The resulting "purple benzene" is a valuable reagent for the oxidation of higher-molecular-weight, water-insoluble alkenes.

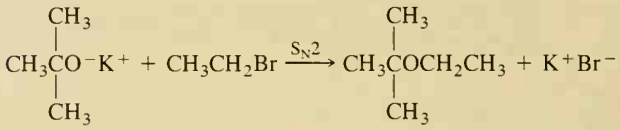
Crown ethers have also proven valuable in nucleophilic displacement reactions. The cations of potassium salts, such as KF, KCN, or KN_3, are very tightly bound within the

solvation cavity of 18-crown-6 molecules. The anion, however, is only weakly solvated, and because of the geometry of cation binding within the cavity of the crown, only loose ion-pairing occurs between the anion and cation. In nonpolar aprotic solvents, these anions are without any appreciable solvent shell and are, therefore, highly reactive as nucleophiles. The nucleophilicity of F^-, CN^-, N_3^-, and other anions in nonpolar aprotic solvents containing an 18-crown-6 equals and often exceeds their nucleophilicity in polar aprotic solvents, such as DMSO and acetonitrile.

SUMMARY OF KEY REACTIONS

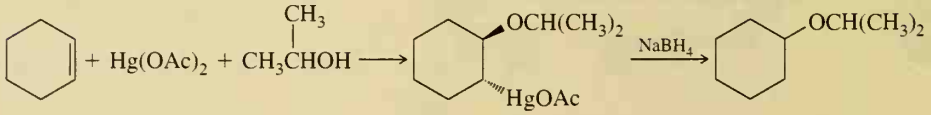
1. Williamson Ether Synthesis (Section 11.4A)

S_N2 reaction of a metal alkoxide with an alkyl halide. Yields are highest with primary halides and lower with secondary halides because of competition from E2 elimination. Reaction fails altogether with tertiary halides.



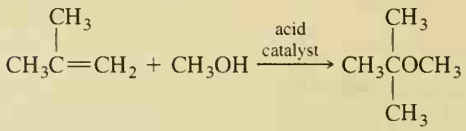
2. Alkoxymercuration / Reduction of Alkenes (Section 11.4B)

Alkoxymercuration is regioselective and stereoselective (anti coplanar addition). Good yields are obtained using primary, secondary, and tertiary alcohols. Di-*tert*-alkyl ethers cannot be prepared by this method.



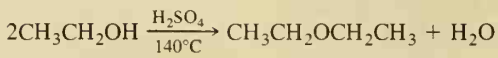
3. Acid-Catalyzed Addition of Alcohols to Alkenes (Section 11.4C)

Reaction of an alkene with H^+ generates a carbocation. Nucleophilic addition of an alcohol to the carbocation gives the ether.



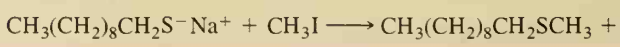
4. Acid-Catalyzed Dehydration of Alcohols (Section 11.4D)

Yields are highest for symmetrical ethers formed from primary alcohols.



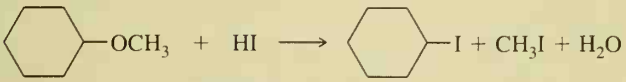
5. Preparation of Sulfides by an S_N2 Reaction (Section 11.5)

A Williamson ether synthesis with a sulfide ion as the nucleophile.



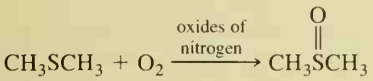
6. Acid-Catalyzed Cleavage of Dialkyl Ethers (Section 11.6A)

Cleavage of ethers requires both a strong acid and a good nucleophile, hence the use of concentrated HBr and HI. Cleavage of primary and secondary alkyl ethers is by an S_N2 pathway. Cleavage of a tertiary alkyl ether is by an S_N1 pathway.



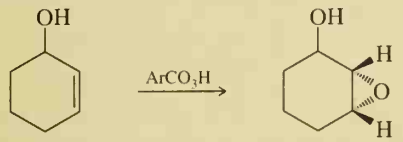
7. Oxidation of Sulfides (Section 11.6C)

Oxidation of a sulfide gives either a sulfoxide or a sulfone, depending on the oxidizing agent and experimental conditions. Air oxidation of dimethyl sulfide gives dimethyl sulfoxide, a common polar aprotic solvent.



8. Oxidation of Alkenes by Peroxyacids to Epoxides (Section 11.7B)

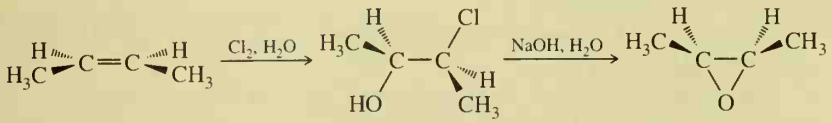
The two most commonly used peroxyacid oxidizing agents are peroxybenzoic acid and the magnesium salt of monoperoxyphthalic acid.



2-Cyclohexenol 2,3-Epoxycyclohexanol

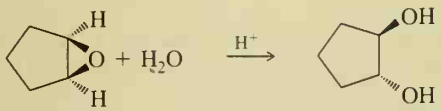
9. Synthesis of Epoxides from Halohydrins (Section 11.7B)

Both formation of the halohydrin and the following intramolecular S_N2 reaction are stereoselective.



10. Acid-Catalyzed Hydrolysis of Epoxides (Section 11.8A)

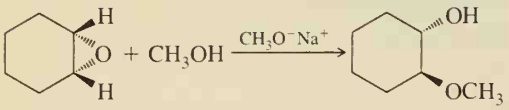
Hydrolysis of an epoxide from a cycloalkene gives a *trans*-glycol.



trans-1,2-Cyclopentanediol

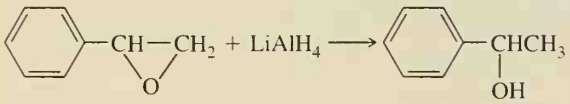
11. Nucleophilic Ring Opening of Epoxides (Section 11.8B)

Regioselective attack on the epoxide by an S_N2 mechanism with the nucleophile attacking the less substituted carbon of the epoxide.



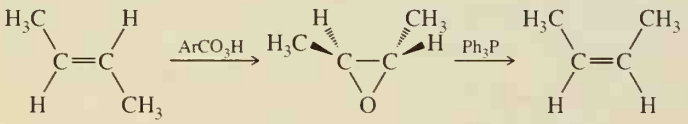
12. Reduction of an Epoxide to an Alcohol (Section 11.8B)

Regioselective hydride ion transfer from lithium aluminum hydride to the less hindered carbon of the epoxide.



13. Conversion of an Epoxide to an Alkene (Section 11.8B)

Nucleophilic attack on an epoxide by triphenylphosphine opens the ring to give a betaine, which then undergoes syn β-elimination of triphenylphosphine oxide to give an alkene.

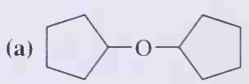


trans-2-Butene — *trans*-2-Butene oxide — *cis*-2-Butene

ADDITIONAL PROBLEMS

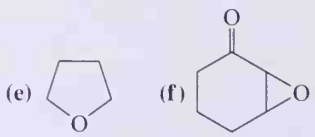
Structure and Nomenclature

11.9 Write names for the following compounds. Where possible, write both IUPAC names and common names.



(c) $CH_3CH_2OCH_2CH_2OH$

(d) $CH_3CH_2OCH_2CH_2OCH_2CH_3$



(g) $CH_3CH(CH_2)_5CH_3$ with SCH_2CH_3 on the second carbon

(h) $[CH_3(CH_2)_4]_2O$

11.10 Draw structural formulas for the following compounds:

(a) diisopropyl ether (b) *trans*-2,3-diethyloxirane

(c) *trans*-2-ethoxycyclopentanol (d) divinyl ether

(e) cyclohexene oxide (f) allyl cyclopropyl ether

(g) (R)-methyloxirane (h) 1,1-dimethoxycyclohexane

Physical Properties

11.11 Each compound given in this problem is a common organic solvent. From each pair of compounds, select the solvent with the greater solubility in water.

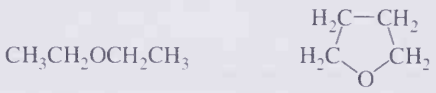
(a) CH_2Cl_2 and CH_3CH_2OH

(b) $CH_3CH_2OCH_2CH_3$ and CH_3CH_2OH

(c) $CH_3\overset{\overset{O}{\|}}{C}CH_3$ and $CH_3CH_2OCH_2CH_3$

(d) $CH_3CH_2OCH_2CH_3$ and $CH_3(CH_2)_3CH_3$

11.12 Following are structural formulas, boiling points, and solubilities in water for diethyl ether and tetrahydrofuran. Account for the fact that tetrahydrofuran is so much more soluble in water than diethyl ether.

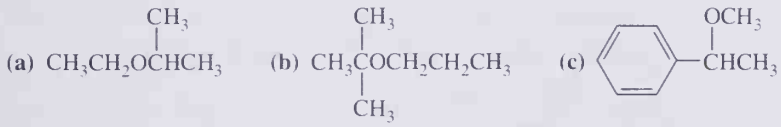


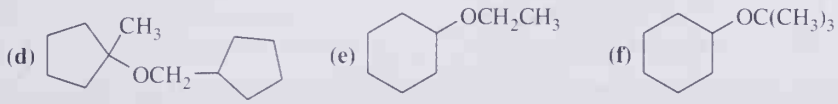
Diethyl ether	Tetrahydrofuran
bp 35°C	bp 67°C
8 g/100 mL water	very soluble in water

11.13 Because of the Lewis base properties of ether oxygens, crown ethers are excellent complexing agents for Na^+, K^+, and NH_4^+. What kind of molecule might serve as a complexing agent for Cl^- or Br^-?

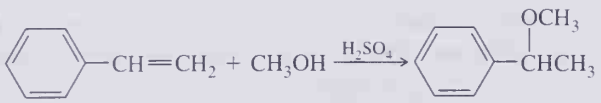
Preparation of Ethers

11.14 Write equations to show a combination of reactants to prepare each ether in good yield by (1) a Williamson ether synthesis and (2) by alkoxymercuration/reduction. Which, if either method, gives the better yield? Explain your reasoning.



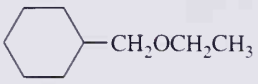


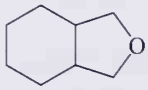
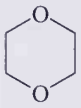
11.15 Propose a mechanism for the following reaction:



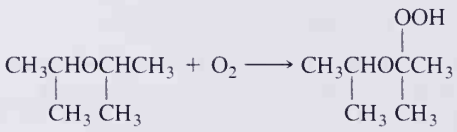
Reactions of Ethers

11.16 Draw structural formulas for the products formed when each of the following compounds is refluxed in concentrated HI:

(a) $CH_3CH_2OCH_2CH_2CH_3$ (b) 

(c)  (d) 

11.17 Following is an equation for the reaction of diisopropyl ether and oxygen to form a hydroperoxide:



Diisopropyl ether (A hydroperoxide)

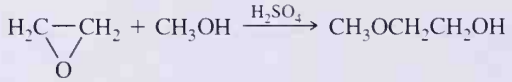
Formation of an ether hydroperoxide can be written as a radical chain reaction.

(a) Write a pair of chain propagation steps that accounts for the formation of ether hydroperoxides. Assume that initiation is by an oxygen molecule that itself is a diradical (Section 1.9B).

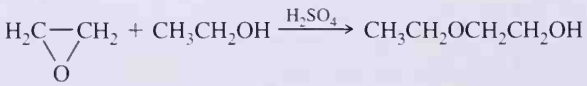
(b) Account for the fact that hydroperoxidation of ethers is regioselective, that it occurs preferentially at a carbon adjacent to the ether oxygen.

Synthesis and Reactions of Epoxides

11.18 Ethylene oxide is the starting material for the synthesis of both Methyl Cellosolve and Ethyl Cellosolve, two important industrial solvents. Propose a mechanism for each of these reactions.

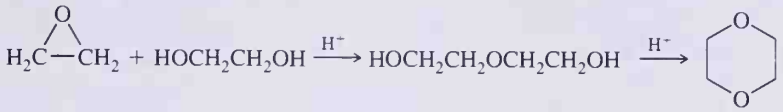


Oxirane (Ethylene oxide) 2-Methoxyethanol (Methyl Cellosolve)



Oxirane (Ethylene oxide) 2-Ethoxyethanol (Ethyl Cellosolve)

11.19 Ethylene oxide is the starting material for the synthesis of 1,4-dioxane. Propose a mechanism for each step in this synthesis.



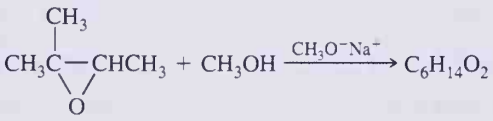
1,4-Dioxane

11.20 Propose a synthesis for each of the following ethers, starting with ethylene oxide and any readily available alcohols.

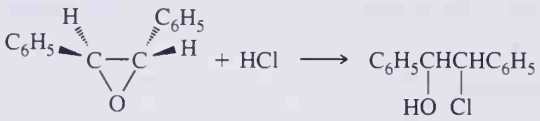
(a) $CH_3OCH_2CH_2OCH_3$ **(b)** $CH_3OCH_2CH_2OCH_2CH_2OCH_3$

11.21 Propose a synthesis for 18-crown-6. If a base is used in your synthesis, does it make a difference if it is a lithium salt or a potassium salt?

11.22 Predict the structural formula of the major product of the reaction of 2,2,3-trimethyloxirane with methanol in the presence of sodium methoxide.



11.23 The following equation shows the reaction of *trans*-2,3-diphenyloxirane with hydrogen chloride in benzene to form 2-chloro-1,2-diphenylethanol.



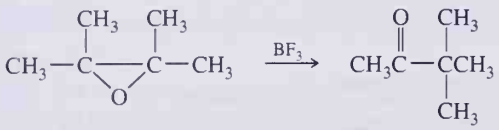
trans-2,3-Diphenyloxirane

2-Chloro-1,2-diphenylethanol

(a) How many stereoisomers are possible for 2-chloro-1,2-diphenylethanol? Draw a suitable stereorepresentation for each.

(b) Given that opening of the epoxide ring in this reaction is stereoselective, predict which of the possible stereoisomers of 2-chloro-1,2-diphenylethanol is (are) formed in the reaction. Explain.

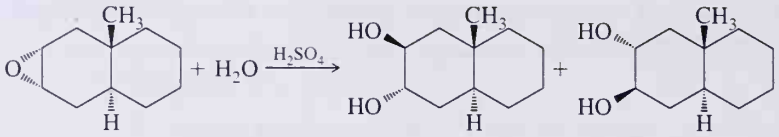
11.24 Propose a mechanism to account for the observation that when tetramethyloxirane is treated with boron trifluoride, it is isomerized to 3,3-dimethyl-2-butanone.



Tetramethyloxirane

3,3-Dimethyl-2-butanone

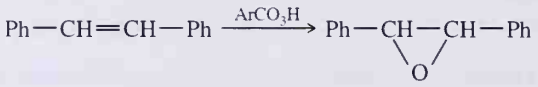
11.25 Following is the structural formula for an epoxide derived from 9-methyldecalin. Acid-catalyzed hydrolysis of this epoxide gives a *trans*-diol. Of the two possible *trans*-diols, only one is formed. How do you account for this stereoselectivity? *Hint:* Begin by drawing *trans*-decalin with each six-member ring in the more stable chair conformation (Section 2.7B), and then determine whether each substituent in the isomeric glycols is axial or equatorial.



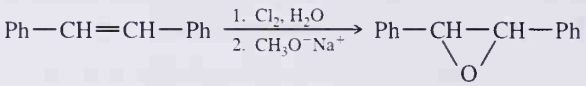
Only this glycol is formed

This glycol is not formed

11.26 Following are two reaction sequences for converting 1,2-diphenylethylene into 2,3-diphenyloxirane.



1,2-Diphenylethylene 2,3-Diphenyloxirane



1,2-Diphenylethylene 2,3-Diphenyloxirane

Suppose that the starting alkene is *trans*-1,2-diphenylethylene.

(a) What is the configuration of the oxirane formed in each sequence?

(b) Does the oxirane formed in either sequence rotate the plane of polarized light? Explain.

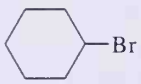
11.27 In each pair, select the molecule with the greater indicated property:

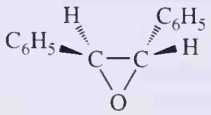
(a) Stronger base: $(CH_3)_3N$: or $(CH_3)_3P$:

(b) Better nucleophile: $(CH_3)_3N$: or $(CH_3)_3P$:

11.28 Write equations for the reaction of triphenylphosphine with the following:

(a) CH_3CH_2I

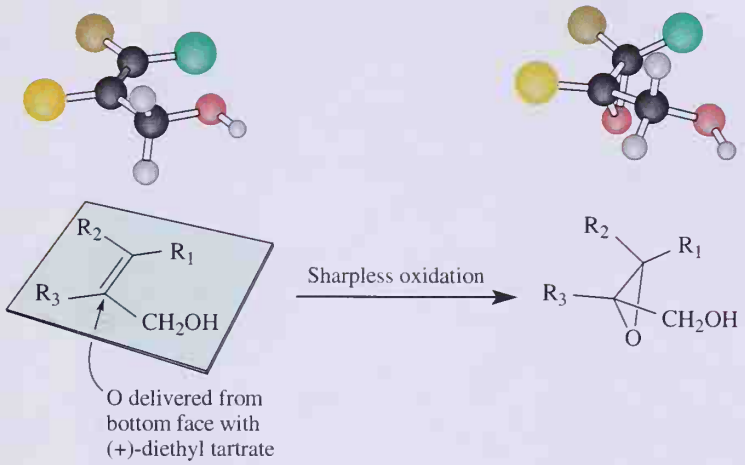
(b) 

(c) 

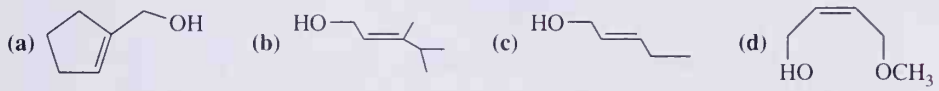
11.29 Write a series of reactions by which you might convert *cis*-cyclooctene into *trans*-cyclooctene.

11.30 One of the most useful organic reactions discovered in the last 15 years is the titanium-catalyzed asymmetric epoxidation of allylic alcohols developed by Professor Barry Sharpless and coworkers.* The reagent combination consists of $Ti(O\text{-}iPr)_4$, a hydroperoxide, and a chiral

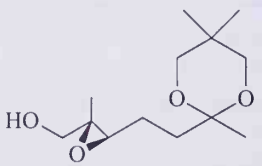
* See K. B. Sharpless et al., *Pure and Appl. Chem.*, **55**, 589 (1983).



molecule such as (+)-diethyl tartrate. Two new stereocenters are created in the product. If (+)-diethyl tartrate is used in the reaction, the product arises by delivery of O from the hydroperoxide to the bottom face of the molecule, and the product epoxide is the stereoisomer shown. If (−)-diethyl tartrate is used, the product is the enantiomer of the stereoisomer shown. Draw the expected products of Sharpless epoxidation of the following allylic alcohols using (+)-diethyl tartrate:



11.31 The following chiral epoxide is an intermediate in the synthesis of the insect pheromone, frontalin. How can this epoxide be prepared from an allylic alcohol precursor, using the Sharpless epoxidation reaction described in problem 11.30?

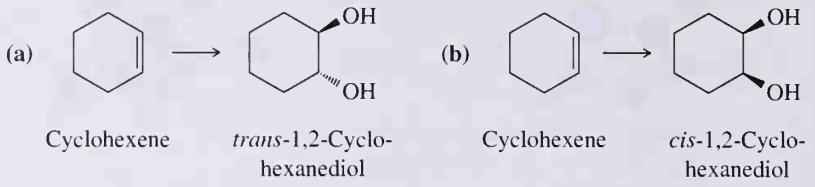


Synthesis

11.32 Show reagents and experimental conditions to synthesize the following compounds from 1-butanol. Any derivative of 1-butanol already prepared in an earlier part of this problem may then be used for a later synthesis.

(a) butanal
(b) butanoic acid
(c) 1-butene
(d) 2-butanol (two ways)
(e) 2-bromobutane
(f) 1-chlorobutane
(g) 1,2-dibromobutane
(h) 1-butyne
(i) 2-butanone (two ways)
(j) 1-chloro-2-butanol
(k) ethyloxirane
(l) dibutyl ether (two ways)
(m) butyl *sec*-butyl ether
(n) 2-butoxy-1-butanol
(o) 1-butoxy-2-butanol
(p) 1,2-butanediol (two ways)

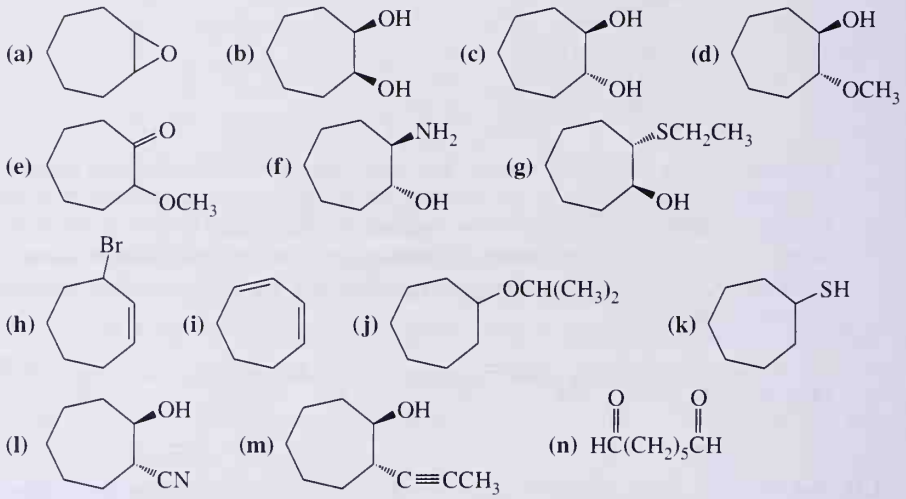
11.33 Show how you might bring about the following conversions:



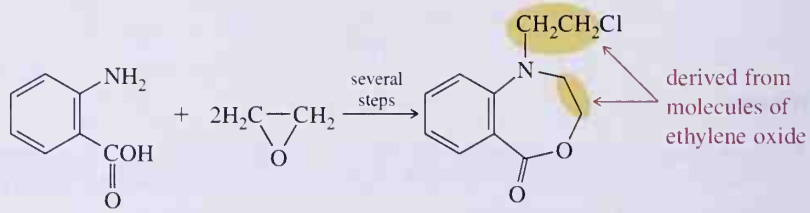
Cyclohexene — *trans*-1,2-Cyclohexanediol

Cyclohexene — *cis*-1,2-Cyclohexanediol

11.34 Show reagents and experimental conditions by which you might convert cycloheptene to the following. Any compound made in an earlier part of this problem may be used as an intermediate in any following conversion.

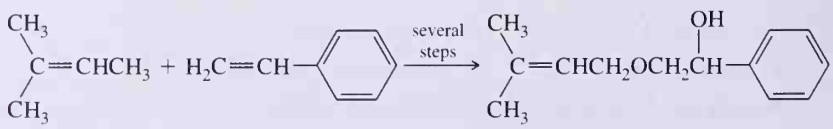


11.35 The following compound is one of a group of β-chloroamines, many of which have antitumor activity. Describe a synthesis of this compound from anthranilic acid and ethylene oxide. *Hint:* To see how the seven-member ring might be formed, review the chemistry of the nitrogen mustards (Section 10.7H).



2-Aminobenzoic acid (Anthranilic acid)

11.36 The following compound was wanted for a study of the Claisen rearrangement (Section 15.5D). Describe the synthesis of this compound from styrene and 2-methyl-2-butene.



Crystals of dopamine viewed under a polarizing light. (© Herb Charles Ohlmeyer/Fran Heyl Associates)

12

MASS SPECTROMETRY

Determination of molecular structure is a central theme in organic chemistry. Before the 1950s, chemists relied largely on chemical methods. They used qualitative organic tests to detect the presence or absence of particular functional groups. Alkenes, for example, can be detected by their ability to decolorize solutions of bromine in carbon tetrachloride. Chemists also used specific chemical reactions, as for example ozonolysis of alkenes, to break molecules apart into smaller, more easily identified fragments. Then through a combination of chemical sleuthing, they proposed a structure or structures for the unknown compound. Structure was often confirmed by converting the unknown compound by well-understood chemical reactions into a compound the structure of which was already known. Alternatively, the structure was confirmed by synthesis of the unknown compound from starting materials of known structure using well-understood chemical reactions. Determination of the structure of an unknown compound in this way was often a long and laborious task.

Fortunately for us today, determination of structure is far simpler. We now rely almost exclusively on instrumental methods of analyses, four of which we discuss in this text. We begin in this chapter with the study of mass spectrometry (MS). Then, in the following three chapters, we study nuclear magnetic resonance (NMR) spectroscopy, infrared (IR) spectroscopy, and ultraviolet-visible (UV-Vis) spectroscopy.

12.1 Mass Spectrometry

In a mass spectrometer, electrons are removed from atoms or molecules to produce a stream of positive ions, which is accelerated in an electric field and then passed through a magnetic field, causing its path to curve. The extent of curvature of the path of individual ions depends on the ratio of mass to charge (m/e) of the ion. Differences in curvature allow separation of ions on the basis of their masses. Thus, the measurements of mass spectrometry are those of the mass to the charge of positive ions.

In 1913, J. J. Thomson recorded the first mass spectrum, that of neon, and discovered that this element can be separated into a more abundant isotope with a mass of 20 amu, and a less abundant isotope of mass 22 amu. Using improved instrumentation, F. W. Aston showed that most of the naturally occurring elements are mixtures of isotopes. It was found, for example, that approximately 75% of chlorine atoms in nature are ^{35}Cl, and 25% are ^{37}Cl.

Beginning in the 1950s, organic chemists recognized the potential of mass spectrometry as an analytical tool, and today it is their most valuable method for the determination of precise molecular weights and molecular formulas. Furthermore, extensive information about molecular structure can be obtained from analysis of mass spectra.

12.2 A Mass Spectrometer

A **mass spectrometer** is designed to

1. Convert neutral atoms or molecules into a beam of positively charged ions.
2. Separate positively charged ions on the basis of their mass-to-charge (m/e) ratio.
3. Measure the relative abundance of each type of positively charged ion.

Figure 12.1 shows a schematic diagram of a mass spectrometer.

Whatever the nature of the sample to be analyzed, gas, liquid, or solid, it must be converted to the vapor state and introduced as a stream of molecules into the **ionization chamber** (Figure 12.1). Samples of gases and volatile liquids can be introduced directly. For less volatile liquids and solids, the sampling system is heated in an oven to produce a sufficiently high concentration of molecules in the vapor state.

An extremely useful method for introducing a sample into the ionization chamber is to link a gas chromatograph (GC) directly to the mass spectrometer. Each fraction eluted from the GC is monitored and passed directly into the ionization chamber of the mass spectrometer.

Once in the ionization chamber, molecules of the sample are bombarded with a stream of electrons emitted from a heated filament and then accelerated through a voltage gradient. Electrons produced in this manner have energies of approximately 70 eV (1.000 eV = 23.05 kcal/mol) and are termed high-energy electrons. To put this energy in perspective, bond dissociation energies (Appendix I) for carbon-hydrogen bonds are 85 to 130 kcal/mol. Bond dissociation energies are 70 to 95 kcal/mol for carbon-carbon single bonds, 160 to 175 kcal/mol for carbon-carbon double bonds, and 220 to 230 kcal/mol for carbon-carbon triple bonds.

Collision between molecules of the sample and high-energy electrons results in loss of electrons from sample molecules to form positively charged ions. The species formed by removal of a single electron from a molecule is called a **molecular ion, $M^{+\cdot}$**. A molecular ion belongs to a class of ions called radical cations. A **radical cation** is a species that contains both an odd number of electrons and a positive charge.

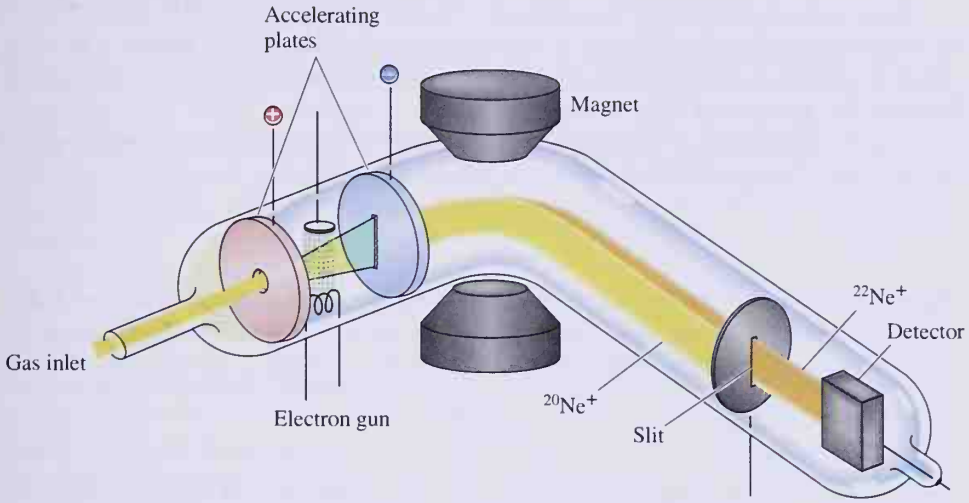
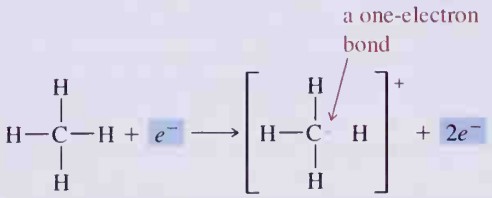


Figure 12.1
A simplified schematic diagram of a mass spectrometer. A sample is vaporized and introduced into an evacuated ionization chamber. There it is bombarded with high-energy electrons which cause electrons to be stripped from molecules of the sample. The resulting positive ions are accelerated by a series of negatively charged accelerator plates into an analyzing chamber about which is placed a magnetic field perpendicular to the direction of flow of the ion beam. The magnetic field causes the path of the ion beam to curve. The radius of curvature of each ion in the ion beam depends on the charge on the ion, the mass of the ion, the accelerating voltage, and the strength of the magnetic field. A mass spectrum is a plot of relative ion abundance versus *m/e* ratio.

$$M + e^- \longrightarrow M^{+\cdot} + 2e^-$$

A neutral molecule — A molecular ion (a radical cation)

When methane, for example, is bombarded with high-energy electrons, an electron is dislodged from a C—H single bond to give a molecular ion of *m/e* ratio 16.



Molecular ion

Except for the simplest molecular ions, it is generally not possible to specify which electron has been removed, and, therefore, we write the molecular formula of the parent molecule in brackets and use a plus sign to show that it is a cation and a dot to show that it is a radical. *Caution:* The dot does not mean that the molecule has gained an electron, but rather that it has lost an electron.

$$CH_4 + e^- \longrightarrow [CH_4]^{+\cdot} + 2e^-$$

Molecular ion

Once molecular ions have been formed, a positively charged **repeller plate** (Figure 12.1) directs them toward a series of negatively charged **accelerator plates,** a process which produces a rapidly travelling ion beam. The ion beam is then focused by one or more focusing slits and passed into a **mass analyzer.**

The kinetic energies of the positive ions entering the mass analyzer are determined by the potential of the accelerating plates according to the equation

$$\frac{1}{2}mv^2 = eV$$

where m is the mass of the ion; v is the velocity of the ion; e is the charge on the ion; and V is the potential of the accelerating plates. In the presence of a magnetic field, B, ions in the mass analyzer are deflected along a circular flight path according to the equation

$$r = \frac{mv}{eB}$$

where B is the strength of applied magnetic field, and r is the radius of curvature of the ion path. Combining these two equations and eliminating velocity, v, gives the following equation, which governs the behavior of ions in the mass analyzer of a mass spectrometer.

$$\frac{m}{e} = \frac{B^2r^2}{2V}$$

As can be determined from this equation, ions with larger mass are deflected less (a larger value of r) than those with smaller mass. The mass analyzer of a mass spectrometer is constructed with a fixed radius of curvature. Thus, by varying either the accelerating voltage or the strength of the magnetic field, ions of the same m/e ratio can be focused on a detector, where the ion current is recorded. Modern ion current detectors are capable of detecting single ions and of scanning a mass-to-charge region in a few tenths of a second or less. Data can then be displayed in various forms, the most common of which is a bar graph displaying relative intensities of all peaks in the scan.

A **mass spectrum** is a plot of relative ion abundance versus mass-to-charge ratio. The most abundant ion recorded by the detector gives rise to the tallest peak in the mass spectrum and is called the **base peak.** The relative abundances of all other peaks in a mass spectrum are reported as percentages of abundance of the base peak. Shown in Figure 12.2 is a mass spectrum of dopamine, a neurotransmitter in the brain's caudate nucleus, a center involved with coordination and integration of fine muscle movement. A deficiency of dopamine is an underlying biochemical defect in Parkinson's disease.

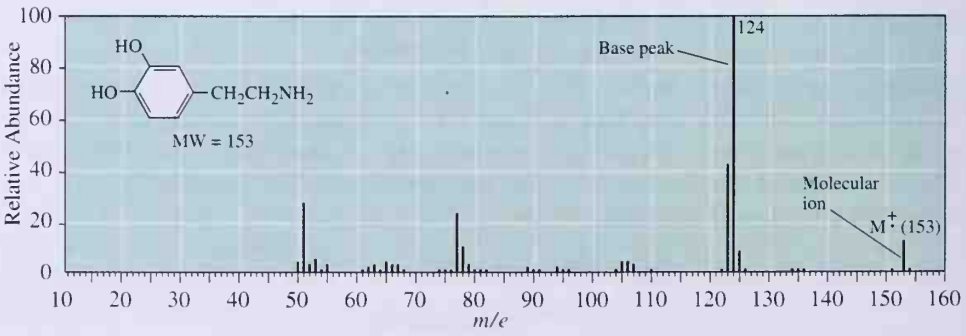


Figure 12.2
A mass spectrum of dopamine. A mass spectrum is a plot of relative ion abundance against mass-to-charge (m/e) ratio. The base peak in a mass spectrum is the tallest peak.

12.3 Features of a Mass Spectrum

From the foregoing discussion, it might appear that the mass spectrum of a compound consists of a single peak representing the molecular ion formed by loss of a single electron from molecules entering the ionization chamber. In fact, mass spectra are considerably more complicated. To understand their complexity, we need to understand some of the relationships between mass spectra and resolution, the presence of isotopes, and fragmentation of molecules and molecular ions in both the ionization chamber and the analyzing chamber.

A. Resolution

An important operating characteristic of a mass spectrometer is its **resolution,** that is, how well it separates ions of different mass. Low-resolution mass spectrometry refers to instruments capable of distinguishing between ions of different **nominal mass,** that is, ions that differ by one or more mass units.

High-resolution mass spectrometry refers to instruments capable of distinguishing between ions that differ in mass by as little as one or more parts in the third decimal place, that is, between ions that differ in **exact mass** by as little as 0.001 amu.

To illustrate, compounds of molecular formulas $C_{16}H_{16}O_2$ and $C_{14}H_{26}O_3$ have nominal masses of 240 and 242 and can be resolved by low-resolution mass spectrometry. The compounds $C_{16}H_{16}O_2$ and $C_{18}H_8O$, however, have the same nominal mass and cannot be distinguished by low-resolution mass spectrometry. If we calculate the exact mass of each using the data in Table 12.1 (Section 12.3B), we see that they differ by 0.045 amu and can, therefore, be distinguished by high-resolution mass spectrometry.

Molecular Formula	Nominal Mass	Exact Mass
$C_{16}H_{16}O_2$	240	240.057
$C_{18}H_8O$	240	240.102

It is precisely because of this resolving power that mass spectrometry has become an invaluable tool to chemists in the determination of precise molecular weights and molecular formulas. Our interest in mass spectrometry throughout the remainder of this chapter, however, is not as a tool for determination of molecular formulas. Rather we want to know the types of information it can give us about molecular structure, and for this purpose, we need be concerned only with low-resolution mass spectrometry.

B. The Presence of Isotopes

Virtually all of the elements common to organic compounds, including H, C, N, O, S, Cl, and Br, are mixtures of isotopes. Exceptions are fluorine, phosphorus, and iodine, which occur in nature exclusively as ^{19}F, ^{31}P, and ^{127}I. Table 12.1 shows atomic weights for the elements most common to organic compounds along with the mass and relative abundance in nature of the stable isotopes of each. Chlorine in nature, for example, is 75.77% ^{35}Cl and 24.23% ^{37}Cl. The atomic weight of chlorine reported in the periodic table is the weighted average of these numbers, that is, $0.7577 \times 34.969 + 0.2423 \times 36.966$, or 35.453.

Table 12.1 Precise masses and relative abundances of elements common to organic compounds

Element	Atomic Weight	Isotope	Mass (amu)	Abundance in Nature (%)	Ratios*
hydrogen	1.0079	^{1}H	1.0078	99.98	$^{1}H/^{2}H = 5000/1$
		^{2}H	2.0140	0.02	
carbon	12.011	^{12}C	12.000	98.90	$^{12}C/^{13}C = 90/1$
		^{13}C	13.003	1.10	
nitrogen	14.007	^{14}N	14.003	99.63	$^{14}N/^{15}N = 270/1$
		^{15}N	15.000	0.37	
oxygen	15.999	^{16}O	15.995	99.76	$^{16}O/^{18}O = 500/1$
		^{17}O	16.999	0.04	
		^{18}O	17.999	0.20	
sulfur	32.066	^{32}S	31.972	95.02	$^{32}S/^{34}S = 22/1$
		^{33}S	32.972	0.75	
		^{34}S	33.968	4.21	
chlorine	35.453	^{35}Cl	34.969	75.77	$^{35}Cl/^{37}Cl = 3/1$
		^{37}Cl	36.966	24.23	
bromine	79.904	^{79}Br	78.918	50.69	$^{79}Br/^{81}Br = 1/1$
		^{81}Br	80.917	49.31	

* Approximate ratios of the most abundant isotope to the next most abundant isotope.

The ratios of $M^{+\cdot}$ to $(M^{+\cdot} + 1)$ or $(M^{+\cdot} + 2)$ peaks can give valuable information about the elemental composition of a compound. A ratio of $M^{+\cdot}$ to $(M^{+\cdot} + 2)$ of approximately 3 : 1, for example, indicates the presence of a single chlorine atom in a compound. Similarly, a ratio of $M^{+\cdot}$ to $(M^{+\cdot} + 2)$ of approximately 1 : 1 indicates the presence of a single bromine atom in a compound.

EXAMPLE 12.1

Calculate the mass of the following ions to five significant figures. Unless otherwise indicated, use the mass of the most abundant isotope of each element.

(a) $[CH_2Cl_2]^{+\cdot}$ **(b)** $[^{13}CH_2Cl_2]^{+\cdot}$ **(c)** $[CH_2Cl^{37}Cl]^{+\cdot}$

Solution

(a) 83.954 **(b)** 84.957 **(c)** 85.951

PROBLEM 12.1

Calculate the nominal mass of the following ions:

(a) $[CH_3{}^{79}Br]^{+\cdot}$ **(b)** $[CH_3{}^{81}Br]^{+\cdot}$ **(c)** $[^{13}CH_3{}^{79}Br]^{+\cdot}$ **(d)** $[^{13}CH_3{}^{81}Br]^{+\cdot}$

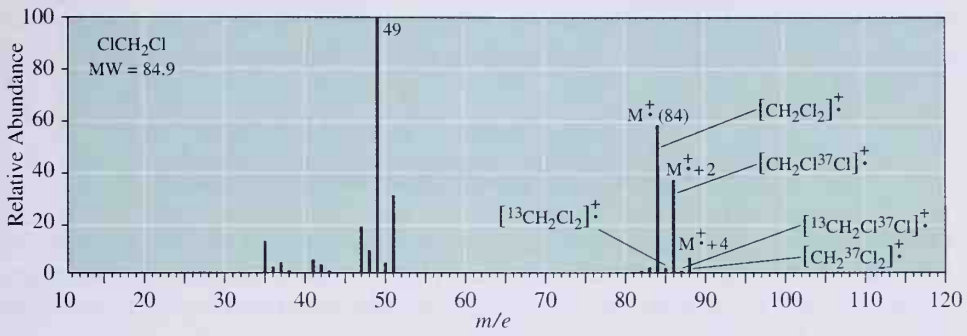
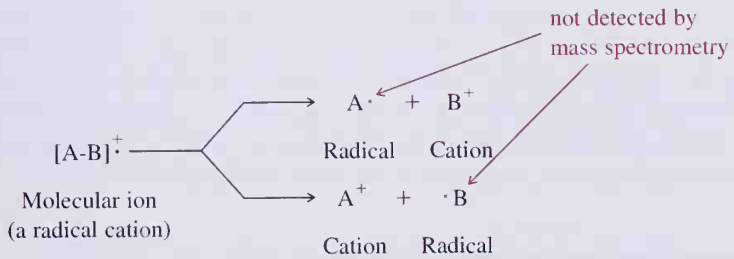


Figure 12.3
Mass spectrum of dichloromethane.

The portion of the mass spectrum of dichloromethane shown in Figure 12.3 illustrates several important features associated with the presence of isotopes. The molecular ion appears at *m/e* 84. The peak of mass 86 ($M^{+\cdot} + 2$) corresponds to the ion $[CH_2Cl^{37}Cl]^{+\cdot}$. Because two chlorine atoms are in CH_2Cl_2, either of which might be ^{37}Cl, the peaks at mass 84 and mass 86 are in the ratio (0.758×0.758) to $(2 \times 0.758 \times 0.242)$, or approximately 3 : 2. The peak at mass 88 ($M^{+\cdot} + 4$) corresponds to $[CH_2{}^{37}Cl_2]^{+\cdot}$. The probability of two chlorine-37 atoms appearing in CH_2Cl_2 is 0.242×0.242. Therefore, the peaks at mass 84 and mass 88 are in the ratio (0.758×0.758) to (0.242×0.242), or approximately 10 : 1.

C. Fragmentation of Molecular Ions

The ionization potential (the energy required to remove a single electron from an atom or molecule) of most organic molecules is in the range of 8 to 15 eV (180–345 kcal/mol). To attain high efficiency of radical cation formation and to give reproducible mass spectra, it is common to use electrons with energies of 70 eV (approximately 1600 kcal/mol). This energy is sufficient not only to dislodge one or more electrons from a molecule but also to cause extensive fragmentation. These fragments may be unstable as well and, in turn, break apart into even smaller fragments.



The molecular ions for some molecules have a sufficiently long lifetime that they are observed in the mass spectrum, often as the base (most intense) peak. Molecular ions of other molecules have a shorter lifetime and are observed either in only low abundance or not at all. Furthermore, many fragment ions undergo further fragmentation. As a result, the mass spectrum of a compound typically (but not always) consists of a peak for the molecular ion and series of peaks for fragment ions. The fragmentation pattern and relative abundances of peaks is unique for each compound and characteristic of that compound.

A great deal of the chemistry of ion fragmentation can be understood in terms of the formation and relative stabilities of carbocations in solution. Where fragmentation occurs,

forming a new carbocation, the mode of fragmentation that gives the most stable carbocation is favored. Thus, the probability of fragmentation to form a new carbocation increases in the order.

$$CH_3^+ < 1° < 2° = 1° \text{ allylic} < 3° = 2° \text{ allylic} < 3° \text{ allylic}$$

Increasing carbocation stability

Molecular rearrangements are also characteristic of certain types of functional groups. We concentrate in this chapter on the fragmentation patterns common to the functional groups we have already encountered, and we describe fragmentation patterns of new functional groups as we encounter them in later chapters.

12.4 Interpreting Mass Spectra

Chemists rely on mass spectra primarily for identification of the mass of the molecular ion, and on the appearance of $(M^{+\cdot} + 1)$ and $(M^{+\cdot} + 2)$ peaks as evidence for the presence of heteroatoms, such as Br and Cl. Given this information, the molecular formula of an unknown compound can be calculated. Very rarely, however, do chemists attempt a full interpretation of a mass spectrum, and very rarely do they rely only on mass spectrometry for a complete determination of molecular structure. The mass spectra of even relatively low-molecular-weight compounds can be very complex and difficult to interpret. The mass spectrum of dopamine (Figure 12.1), for example, contains at least 45 peaks. The base peak appears at *m/e* 124 and the molecular ion at *m/e* 153. In addition to these two peaks, only 26 other peaks appear with an intensity greater than 1% of the base peak, and of these, only four appear with an intensity greater than 10% of the base peak. At least 17 peaks in the mass spectrum of dopamine appear with intensity 1.0% or less of the base peak.

In our analyses of mass spectra, we concentrate on (1) determination of the molecular formula and (2) fragmentation mechanisms giving rise to major peaks.

A. Alkanes

Two rules will help you interpret the mass spectra of alkanes. (1) Fragmentation tends to occur in the middle of unbranched chains rather than at the ends. (2) The differences in energy among tertiary, secondary, primary, and methyl carbocations in the gas phase are much greater than differences among tertiary, secondary, primary, and methyl radicals. Therefore, where alternative modes of fragmentation are possible, the more stable carbocation tends to be formed in preference to the more stable radical.

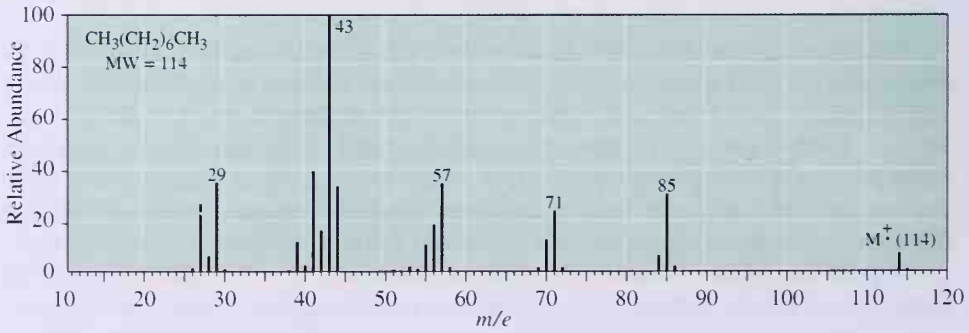


Figure 12.4
Mass spectrum of octane.

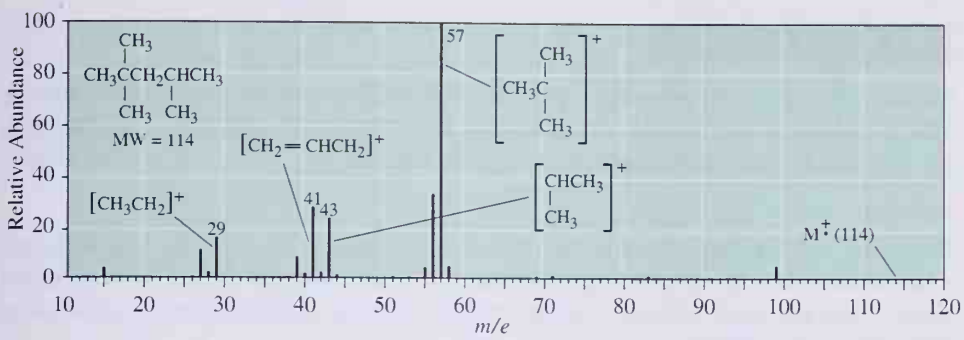


Figure 12.5
Mass spectrum of 2,2,4-trimethylpentane. The peak due to the molecular ion is of such low abundance that it does not appear in this spectrum.

Unbranched alkanes fragment to form a homologous series of cations differing by 14 amu (a CH_2 group). The mass spectrum of octane (Figure 12.4) shows a peak for the molecular ion, as well as peaks for the hexyl cation (*m/e* 85), the pentyl cation (*m/e* 71), the butyl cation (*m/e* 57), the propyl cation (*m/e* 43), and the ethyl cation (*m/e* 29). Fragmentation of the CH_2—CH_3 bond is not observed; there is no peak corresponding to a methyl cation (CH_3^+, *m/e* 15), nor is there one corresponding to a heptyl cation (*m/e* 99).

Fragmentation of branched-chain alkanes can lead to formation of secondary and tertiary carbocations, and because these cations are more easily formed than methyl and primary carbocations, extensive fragmentation is more likely. The molecular ion of branched-chain hydrocarbons is often very weak or absent entirely. The molecular ion corresponding to *m/e* 114 is not observed, for example, in the highly branched 2,2,4-trimethylpentane (Figure 12.5). The base peak for this hydrocarbon is at *m/e* 57 due to the *t*-butyl cation ($C_4H_9^+$). Other prominent peaks are *m/e* 43, due to the isopropyl cation, and *m/e* 41, due to the allyl cation ($CH_2{=}CHCH_2^+$).

Sometimes peaks occur in a mass spectrum the origin of which seems to defy any of the rules of molecular logic we have encountered so far. For example, the prominent peak at *m/e* 29 in the mass spectrum of 2,2,4-trimethylpentane (Figure 12.5) is due to the ethyl cation, $CH_3CH_2^+$. There is, however, no ethyl group in the parent molecule! We can only conclude that this cation must be formed by some combination of fragmentation and rearrangement quite beyond anything that we have seen up to this point.

The most common fragmentation patterns of cycloalkanes are loss of side chains and loss of ethylene, $CH_2{=}CH_2$. The peak at *m/e* 69 in the mass spectrum of methylcyclopentane (Figure 12.6) is due to loss of the one-carbon side chain to give the cyclopentyl cation, $C_5H_9^+$. The base peak at *m/e* 56 is due to loss of ethylene and corresponds to a cation of molecular formula $C_4H_8^+$.

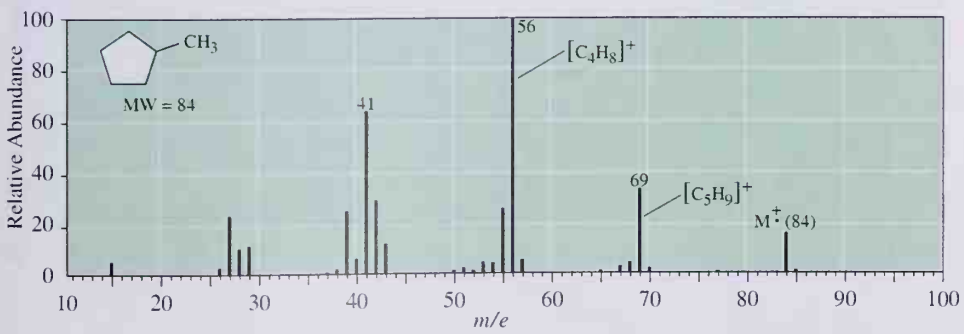


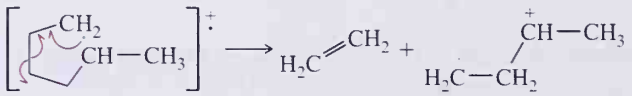
Figure 12.6
Mass spectrum of methylcyclopentane.

EXAMPLE 12.2

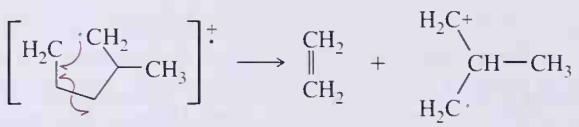
The base peak at *m/e* 56 in the mass spectrum of methylcyclopentane corresponds to loss of ethylene to give a radical cation of molecular formula $C_4H_8^{+\cdot}$. Propose a structural formula for this radical cation and show how it might be formed.

Solution

Following are structural formulas for two radical cations that might be formed in the ionizing chamber. In each, a single electron has been dislodged from a carbon-carbon single bond. Rearrangement of bonding electrons in these radical cations gives ethylene and a new radical cation.



Molecular ion (a radical cation) — Ethylene — A new radical cation



Molecular ion (a radical cation) — Ethylene — A new radical cation

PROBLEM 12.2

Propose a structural formula for the cation of *m/e* 41 observed in the mass spectrum of methylcyclopentane.

B. Alkenes

Alkenes characteristically show a strong molecular ion peak, formed most probably by removal of one electron from the pi bond. Furthermore, they cleave readily to form relatively stable allylic cations, such as that seen at *m/e* 41 in the mass spectrum of 1-butene

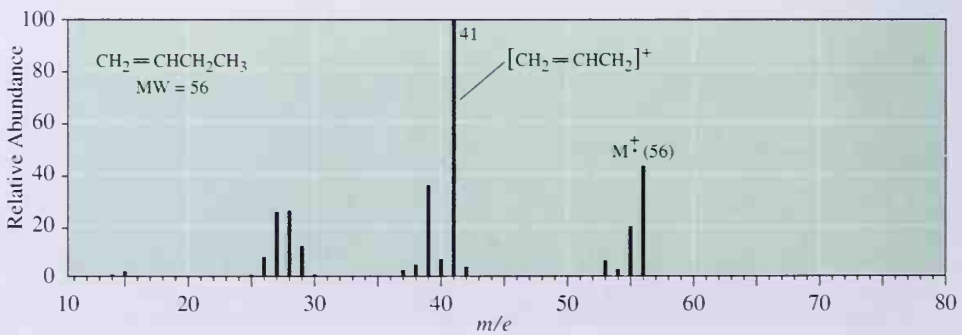
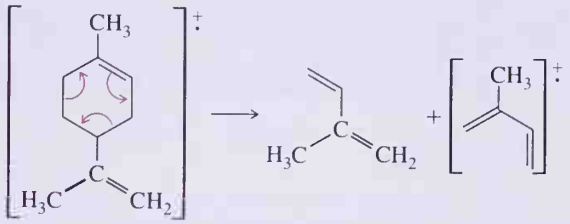


Figure 12.7
Mass spectrum of 1-butene.

(Figure 12.7). Cyclohexenes show a characteristic fragmentation pattern that is a reverse Diels-Alder reaction (Section 7.5). The terpene, limonene, a disubstituted cyclohexene, for example, fragments by a reverse Diels-Alder reaction to give two molecules of 2-methyl-1,3-butadiene (isoprene): one formed as a neutral diene and the other formed as a diene radical cation.



Limonene A neutral diene A radical cation

C. Alkynes

As with alkenes, alkynes show a strong peak due to the molecular ion. Their fragmentation patterns are also similar to those of alkenes. One of the most prominent peaks in the mass spectrum of most alkynes is due to the propargyl cation (*m/e* 39) or a substituted propargyl cation.

Propargyl cation

Both the molecular ion, *m/e* 68, and the propargyl cation, *m/e* 39, are seen in the mass spectrum of 1-pentyne (Figure 12.8). Also seen is the ethyl cation, *m/e* 29.

D. Alcohols

The intensity of the molecular ion from primary and secondary alcohols is normally quite low, and there is usually no molecular ion detectable for tertiary alcohols. One of the most common fragmentation patterns for alcohols is loss of a molecule of water to give a peak

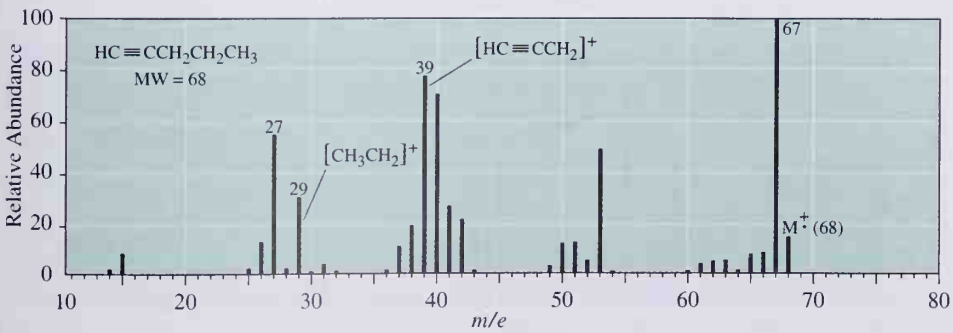
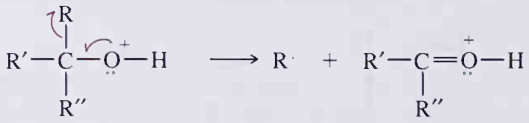
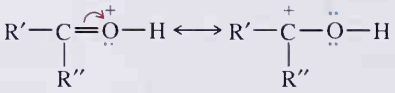


Figure 12.8
Mass spectrum of 1-pentyne.

corresponding to the molecular ion minus 18 ($M^{+\cdot} - 18$). Another common pattern is loss of an alkyl group from the carbon bearing the —OH group to form an oxonium ion and an alkyl radical. The oxonium ion is particularly stable because of resonance delocalization of charge.

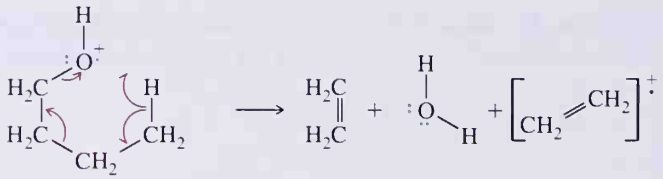


Molecular ion (a radical cation) | A radical | An oxonium ion



(resonance stabilization of the oxonium ion)

Each of these patterns is found in the mass spectrum of 1-butanol (Figure 12.9). The molecular ion appears at *m/e* 74. The prominent peak at *m/e* 56 corresponds to loss of a molecule of water from the molecular ion ($M^{+\cdot} - 18$). The base peak (*m/e* 31) corresponds to cleavage of a propyl group ($M^{+\cdot} - 43$) from the carbon bearing the —OH group. The propyl group is visible at *m/e* 43. The mass spectrum of 1-butanol also shows a fragmentation called a McLafferty rearrangement. In a **McLafferty rearrangement,** a heteroatom with an odd electron, most commonly oxygen, abstracts a hydrogen five atoms away; reaction occurs through a six-member ring transition state. McLafferty rearrangement of 1-butanol gives ethylene, water, and an ethylene radical cation of *m/e* 28.



Molecular ion (a radical cation) | An alkene | Water | A new radical cation

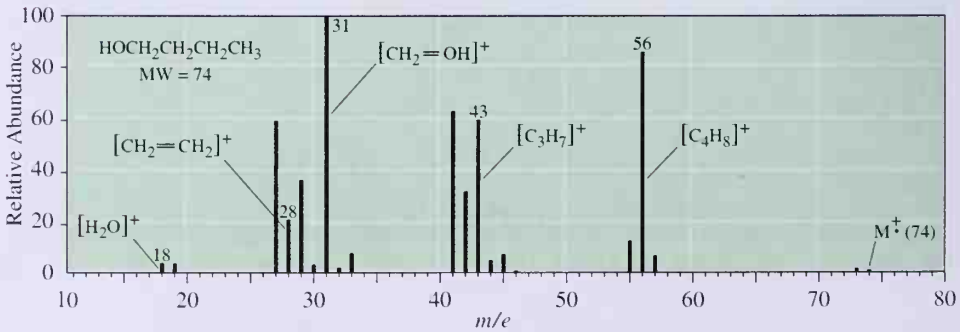


Figure 12.9
Mass spectrum of 1-butanol.

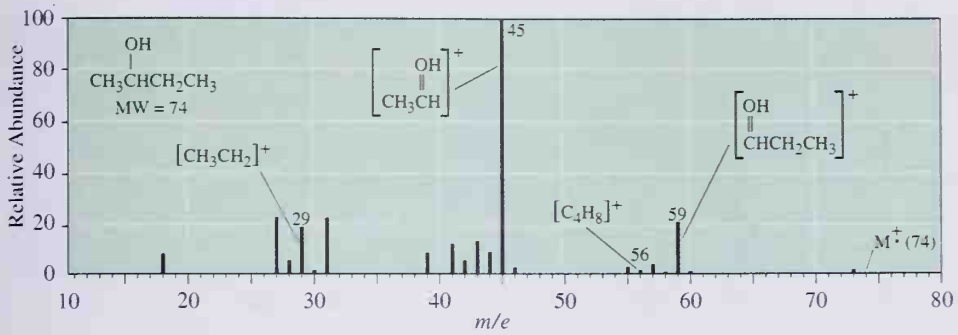


Figure 12.10
Mass spectrum of 2-butanol.

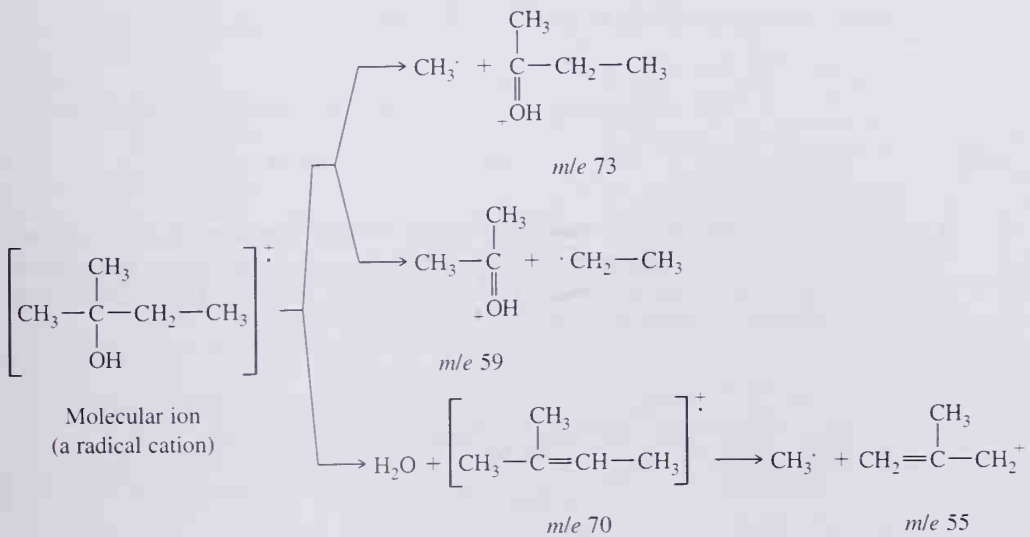
The molecular ion, *m/e* 74, in the mass spectrum of 2-butanol (Figure 12.10) is of such low intensity that it is not visible. Peaks resulting from cleavage at the carbon bearing the —OH group are visible at *m/e* 59 ($M^{+\cdot} - 15$) and at *m/e* 45 ($M^{+\cdot} - 29$). Here, as in other cases in which alternative modes of fragmentation occur, loss of the larger alkyl fragment is favored. Because there is no suitably placed hydrogen, 2-butanol does not undergo a McLafferty rearrangement.

EXAMPLE 12.3

A low-resolution mass spectrum of 2-methyl-2-butanol (MW 88) shows 16 peaks. The molecular ion is absent. Account for peaks at *m/e* 73, 70, 59, and 55, and propose a structural formula for each cation.

Solution

The peak at *m/e* 73 ($M^{+\cdot} - 15$) corresponds to loss of a methyl radical from the molecular ion. The peak at *m/e* 59 ($M^{+\cdot} - 29$) corresponds to loss of an ethyl radical. Loss of water as a neutral molecule from the molecular ion gives an alkene of *m/e* 70 ($M^{+\cdot} - 18$) as a radical cation. Loss of methyl from this radical cation gives an allylic carbocation of *m/e* 55. McLafferty rearrangement is not possible for this alcohol because the carbon chain is not long enough to transfer a hydrogen to oxygen through formation of a six-member ring transition state.



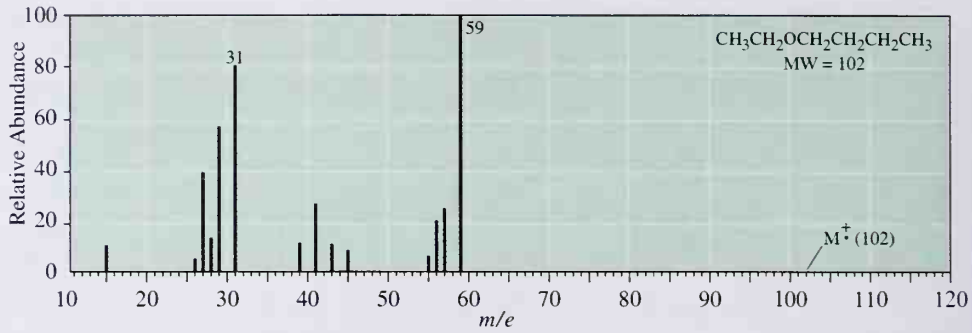


Figure 12.11
Mass spectrum of butyl ethyl ether.

PROBLEM 12.3

The low-resolution mass spectrum of 2-pentanol shows 15 peaks. Account for the formation of the peaks at *m/e* 73, 70, 55, 45, 43, 42, 41, and 28. (*Hint:* Consider (1) the loss of water to form an alkene and the fragmentations the resulting alkene might then undergo, (2) the fragmentation of bonds to the carbon bearing the —OH group, and (3) McLafferty rearrangement along with subsequent fragmentation its products might undergo.)

E. Ethers

A characteristic fragmentation pattern of aliphatic ethers is cleavage of a carbon-carbon bond adjacent to the ether oxygen to give an oxonium ion. This fragmentation pattern gives rise to the base peak at *m/e* 59 in the mass spectrum of butyl ethyl ether (Figure 12.11).

$$\left[CH_3CH_2-\ddot{O}-CH_2CH_2CH_2CH_3\right]^{+\cdot} \xrightarrow{\text{cleavage of C—C bond adjacent to the ether oxygen}} CH_3CH_2-\overset{+}{\ddot{O}}=CH_2 + \cdot CH_2CH_2CH_3$$

m/e 59

A second fragmentation pattern often observed in the mass spectrum of ethers is rearrangement of a fragment ion by migration of a hydride ion beta to the oxygen and elimination of an alkene. This pattern gives rise to the peak at *m/e* 31, the second most intense peak in the mass spectrum of butyl ethyl ether.

$$\begin{matrix} H \\ | \\ CH_2-CH_2-\overset{+}{\ddot{O}}=CH_2 \end{matrix} \longrightarrow CH_2=CH_2 + H-\overset{+}{\ddot{O}}=CH_2$$

m/e 31

SUMMARY OF KEY REACTIONS

1. Formation of a Molecular Ion (Section 12.2)

Formation of a molecular ion (a radical cation) occurs when a molecule is bombarded with high-energy electrons in the ionization chamber of a mass spectrometer.

$$CH_4 + e^- \longrightarrow [CH_4]^{+\cdot} + 2e^-$$

Molecular ion

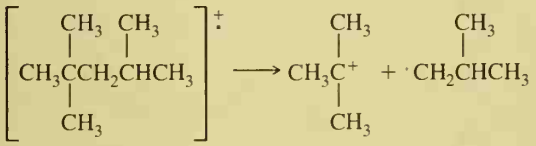
2. Mass Spectrometry of Straight-Chain Alkanes (Section 12.4A)

Unbranched alkanes commonly undergo fragmentation by breaking carbon-carbon bonds to form a homologous series of cations differing in mass by 14 units (a methylene group, CH_2).

$$[CH_3(CH_2)_6CH_3]^{+\cdot} \longrightarrow CH_3CH_2CH_2^+ + \cdot CH_2(CH_2)_3CH_3$$

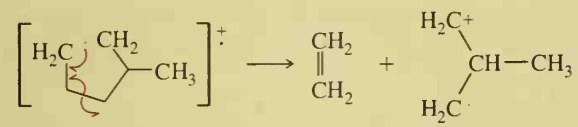
3. Mass Spectrometry of Branched-Chain Alkanes (Section 12.4A)

Branched-chain alkanes commonly undergo fragmentation at a branch point to give secondary and tertiary carbocations. Because of the ease of fragmentation of the molecular ion from branched-chain alkanes, the molecular ion itself is often absent.



4. Mass Spectrometry of Cycloalkanes (Section 12.4A)

Common fragmentation patterns are loss of side chains and cleavage of the ring with loss of ethylene or a substituted ethylene.



5. Mass Spectrometry of Alkenes (Section 12.4B)

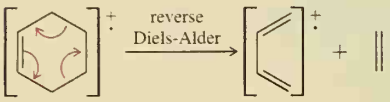
A common fragmentation pattern is cleavage of the molecular ion to give a resonance-stabilized allylic cation.

$$[H_2C{=}CHCH_2CH_2CH_3]^{+\cdot} \longrightarrow H_2C{=}CHCH_2^+ + \cdot CH_2CH_3$$

Allyl cation

6. Mass Spectrometry of Cyclohexenes (Section 12.4B)

A common fragmentation pattern of cyclohexene and substituted cyclohexenes is a reverse Diels-Alder reaction.



7. Mass Spectrometry of Alkynes (Section 12.4C)

Fragmentation patterns of alkynes are similar to those of alkenes. A prominent peak in the mass spectrum of most alkynes is the propargyl cation or a substituted propargyl cation.

$$\left[HC{\equiv}CCH_2CH_2CH_3\right]^{+\cdot} \longrightarrow HC{\equiv}CCH_2^{+} + \cdot CH_2CH_3$$

Propargyl cation

8. Mass Spectrometry of Alcohols (Section 12.4D)

A common fragmentation of alcohols is loss of water to give a peak at $(M^{+\cdot} - 18)$.

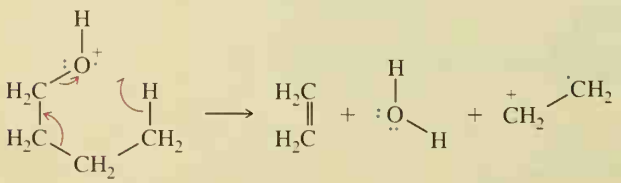
$$\left[\begin{array}{l} H \quad OH \\ | \quad\ | \\ RCH{-}CHR' \end{array}\right]^{+\cdot} \longrightarrow [RCH{=}CHR']^{+\cdot}$$

A second common fragmentation pattern of alcohols is loss of an alkyl radical from the carbon bearing the —OH group to give an oxonium ion. When alternative fragmentations are possible, loss of the larger alkyl radical is favored.

$$\left[\begin{array}{c} CH_3 \\ | \\ CH_3CCH_2CH_3 \\ | \\ OH \end{array}\right]^{+\cdot} \longrightarrow \begin{array}{c} CH_3 \\ | \\ CH_3C \\ \| \\ {}_{+}OH \end{array} + \cdot CH_2CH_3$$

9. McLafferty Rearrangement of Alcohols (Section 12.4D)

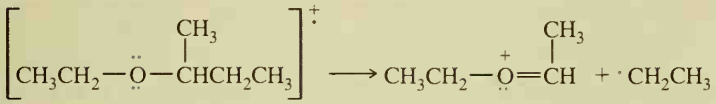
Transfer of a hydrogen five atoms away to oxygen by way of a six-member ring transition state gives water, an alkene, and an alkene radical cation.



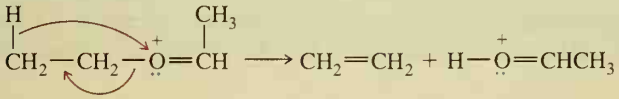
Molecular ion (a radical cation) | An alkene | Water | A new radical cation

10. Mass Spectrometry of Ethers (Section 12.4E)

A characteristic fragmentation pattern of aliphatic ethers is cleavage of a carbon-carbon bond adjacent to the ether oxygen to give an oxonium ion.

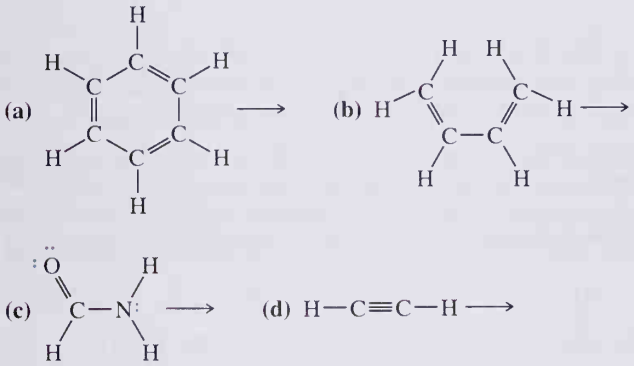


A second characteristic fragmentation pattern is rearrangement of a hydrogen beta to the positively charged oxygen atom and loss of an alkene.

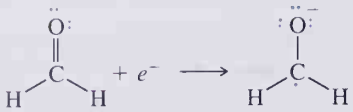


ADDITIONAL PROBLEMS

12.4 Draw acceptable Lewis structures for the molecular ion (radical cation) formed from the following molecules when each is bombarded by high-energy electrons in a mass spectrometer.

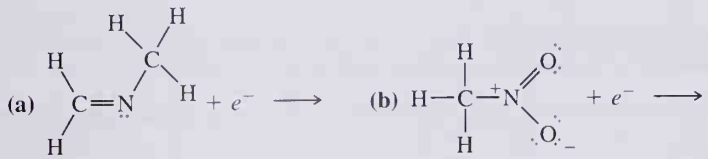


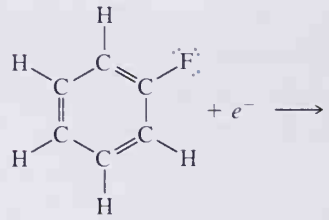
12.5 Some organic molecules can add a single electron to form a normally unstable class of species called radical anions. A radical anion possesses both a negative charge and an unpaired electron. For example,



A radical anion

Draw an acceptable Lewis structure for a radical anion formed from the following molecules:



(c)  $+ e^- \longrightarrow$

12.6 The molecular ion for compounds containing only C, H, and O is always at an even mass-to-charge value. What can you say about mass-to-charge values of ions that arise from fragmentation of one bond in the molecular ion? From fragmentation of two bonds in the molecular ion?

12.7 For which compounds containing a heteroatom (an atom other than carbon or hydrogen) does a molecular ion have an even-numbered mass and for which does it have an odd-numbered mass?

(a) A chloroalkane of molecular formula $C_nH_{2n+1}Cl$

(b) A bromoalkane of molecular formula $C_nH_{2n+1}Br$

(c) An alcohol of molecular formula $C_nH_{2n+1}OH$

(d) A primary amine of molecular formula $C_nH_{2n+1}NH_2$

(e) A thiol of molecular formula $C_nH_{2n+1}SH$

12.8 The so-called nitrogen rule states that if a molecular ion has an even mass value, then it contains either no nitrogen atom or an even number of nitrogen atoms. Explain the basis of this rule.

12.9 The molecular ions of both $C_5H_{10}S$ and $C_6H_{14}O$ appear at *m/e* 102 in low-resolution mass spectrometry. Show how determination of the correct molecular formula can be made from the appearance and relative intensity of the $(M^{+\cdot} + 2)$ peak of each compound.

12.10 Water-^{18}O in which enrichment is 10 atom % ^{18}O is available commercially. Also available, at a considerably higher price, is water-^{18}O in which enrichment is 97 atom % ^{18}O. The oxygen-18 label can be transferred from water to acetone by establishing the following acid-catalyzed equilibrium. (We discuss the chemistry of this equilibration in Chapter 17).

$$CH_3-\overset{\overset{O}{\|}}{C}-CH_3 + H_2{}^{18}O \overset{H^+}{\rightleftharpoons} CH_3-\overset{\overset{{}^{18}O}{\|}}{C}-CH_3 + H_2O$$

Suppose 5.00 g of water-^{18}O, 97 atom % ^{18}O, is mixed with 11.6 g of acetone-^{16}O in the presence of an acid catalyst until equilibrium is established. Assume for the purposes of this problem that the value of K_{eq}, the equilibrium constant for this reaction, is 1.00.

(a) Calculate the atom percent enrichment in acetone recovered after equilibration.

(b) Show how the ratio of $(M^{+\cdot} + 2)/M^{+\cdot}$ can be used to verify the atom percent enrichment.

Interpretation of Mass Spectra

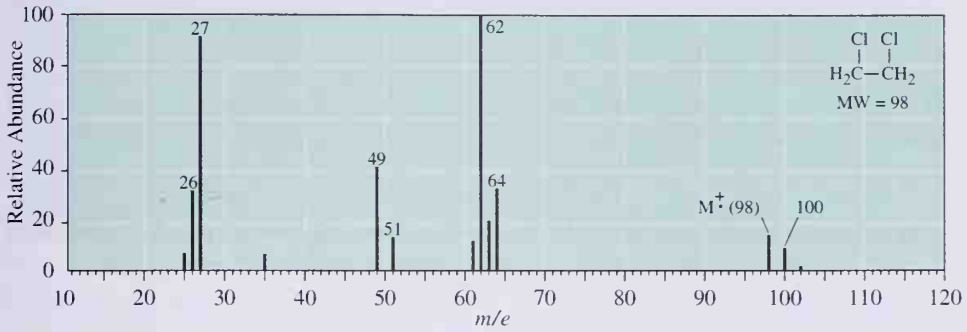
12.11 Carboxylic acids often give strong fragment ions at *m/e* $(M^{+\cdot} - 17)$. What is the likely structure of these ions, and how might they be formed?

12.12 The molecular ion in the mass spectrum of 2-methyl-1-pentene appears at *m/e* 84. Propose structural formulas for the prominent peaks at *m/e* 69, 55, 41, and 29.

12.13 Following is the mass spectrum of 1,2-dichloroethane. The molecular ion appears at *m/e* 98.

(a) Account for the appearance of an $(M^{+\cdot} + 2)$ peak with approximately two-thirds the intensity of the molecular ion peak.

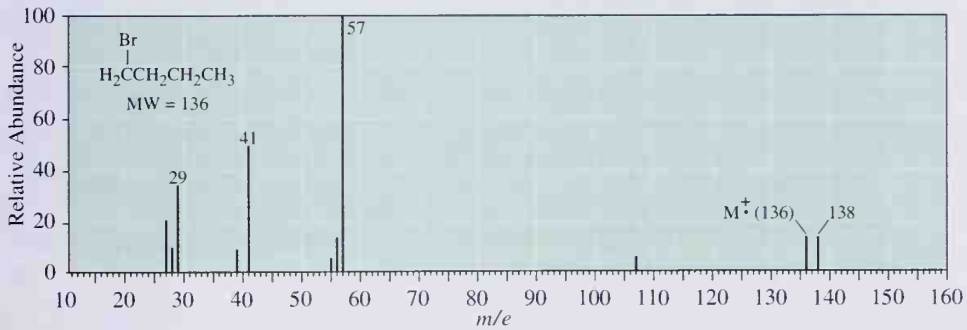
(b) Propose structural formulas for the cations of all labeled peaks.



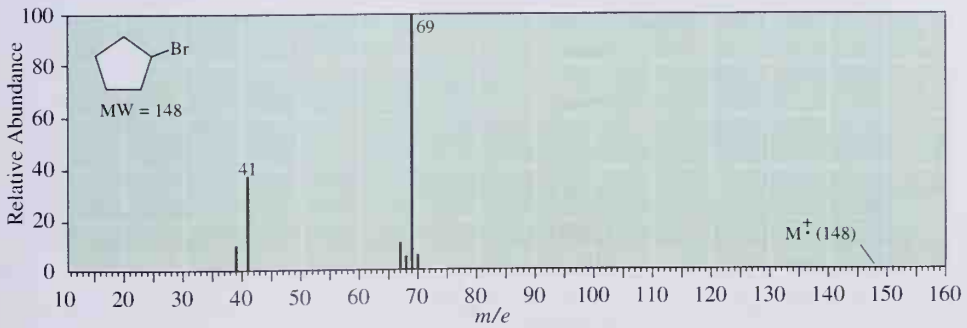
12.14 Following is the mass spectrum of 1-bromobutane. The molecular ion appears at *m/e* 136.

(a) Account for the appearance of the $(M^{+\cdot} + 2)$ peak of approximately 90% the intensity of molecular ion peak.

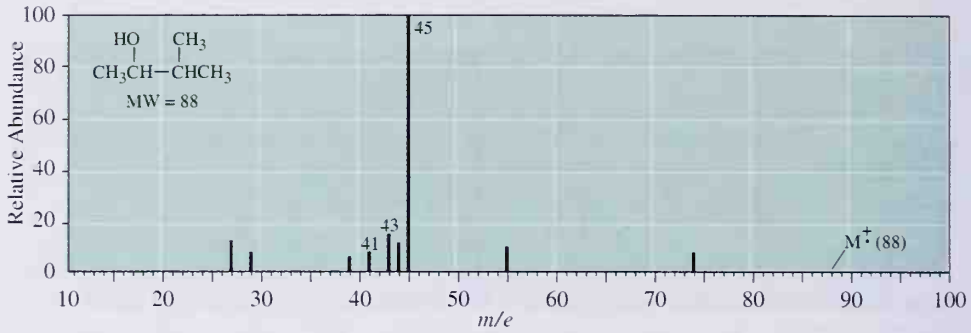
(b) Propose structural formulas for the cations of *m/e* 57, 41, and 29.



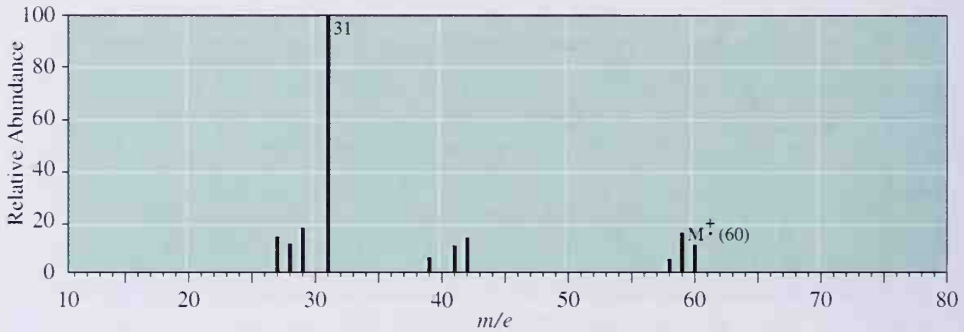
12.15 Following is the mass spectrum of bromocyclopentane. The molecular ion *m/e* 148 is of such low intensity that it does not appear in this spectrum. Assign structural formulas for the cations of *m/e* 69 and 41.



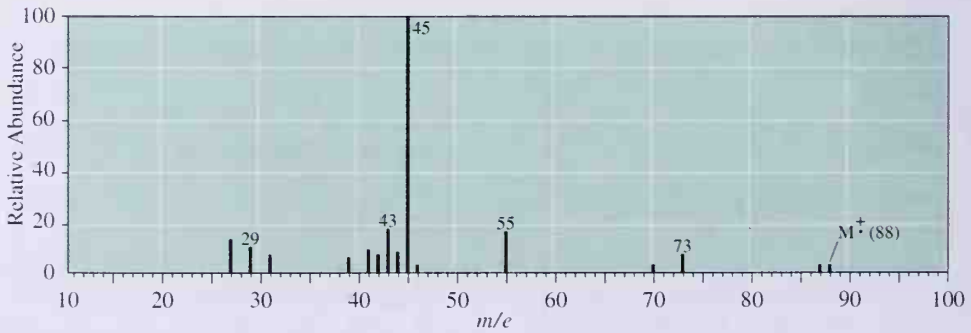
12.16 Following is the mass spectrum of 3-methyl-2-butanol. The molecular ion *m/e* 88 does not appear in this spectrum. Propose structural formulas for the cations of *m/e* 45, 43, and 41.

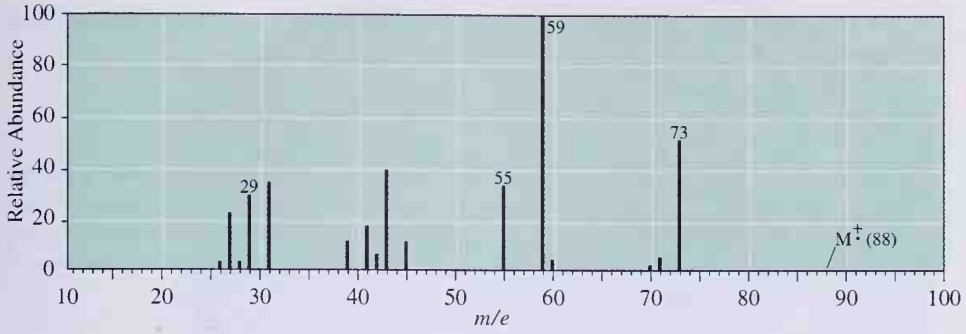


12.17 The following is the mass spectrum of a compound A, C_3H_8O. Compound A is infinitely soluble in water, undergoes reaction with sodium metal with the evolution of a gas, and undergoes reaction with thionyl chloride to give a water-insoluble chloroalkane. Propose a structural formula for compound A, and write equations for each of its reactions.

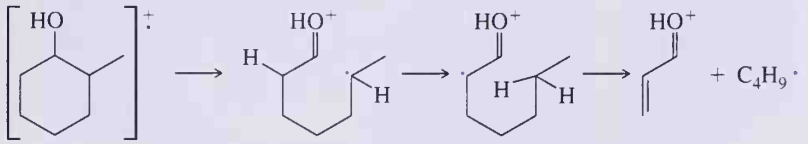


12.18 Following are mass spectra for the constitutional isomers 2-pentanol and 2-methyl-2-butanol. Assign each isomer its correct spectrum.





12.19 2-Methylcyclohexanol has its base peak at *m/e* 57. Fragmentation to produce this ion is thought to proceed in the following way:

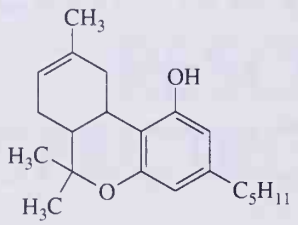


2-Methylcyclohexanol *m/e* 57

A second major fragment is at *m/e* 71. What is its likely structure, and how might it be formed?

12.20 Examination of many mass spectra usually shows peaks at *m/e* 28, 32, and 40. What is the likely source of these peaks?

12.21 Because of the sensitivity of mass spectrometry, it is often used to detect the presence of drugs in blood, urine, or other biological fluids. Tetrahydrocannabinol, a component of marijuana, exhibits two strong fragment ions at *m/e* 246 and 231 (the base peak). What is the likely structure of each ion?



Tetrahydrocannabinol
($C_{21}H_{30}O_2$)

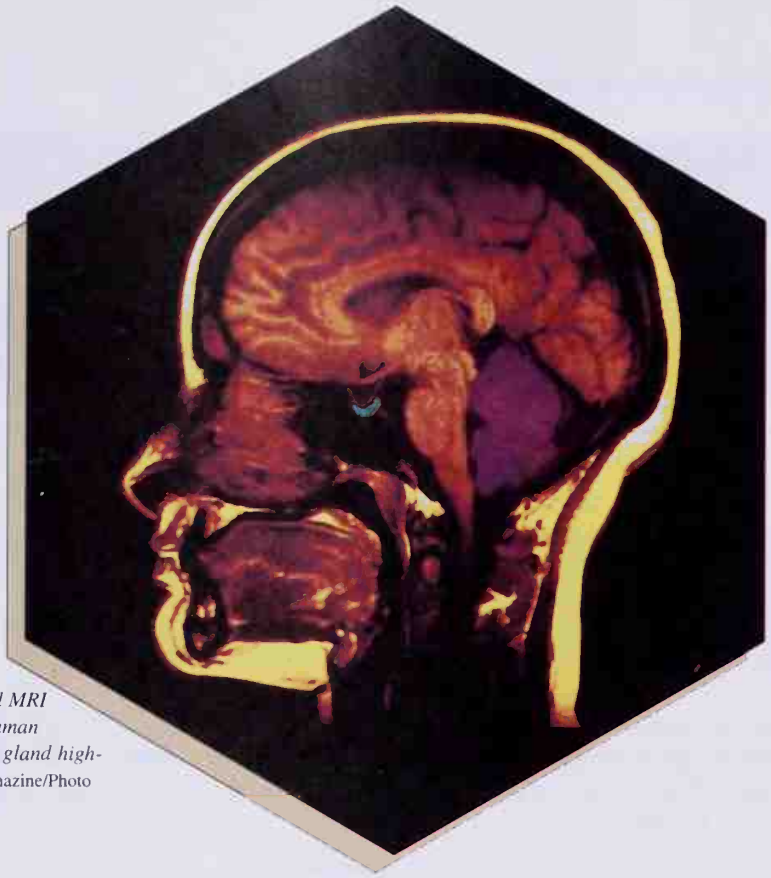
12.22 Ion-spray mass spectrometry is a recently developed technique for looking at large molecules with a mass spectrometer. In this technique, molecular ions, each normally associated with one or more H^+ ions, are prepared under mild conditions in the mass spectrometer. As an example, a protein (P) with a molecular weight of 11,812 amu gives clusters of the type $(P + 8H)^{8+}$, $(P + 7H)^{7+}$, and $(P + 6H)^{6+}$. At what mass-to-charge values do these three clusters appear in the mass spectrum?

12.23 Occasionally, weak, broad peaks are observed in a mass spectrum. These often have fractional mass-to-charge values, for example, 46.3 or 30.2. These are called metastable ion peaks and arise when an ion fragments *after* exiting the ionization chamber while it is passing into the analyzer region of the mass spectrometer. The observed mass m^* of a metastable ion depends

on the mass of the precursor ion (m_1) and the product ion (m_2) according to the following equation.

$$m^* = \frac{(m_2)^2}{m_1}$$

An ion of mass 59, for example, that fragments into an ion of mass 41 while passing into the analyzing chamber gives a metastable peak at $(41)^2/(59)$, or m/e 28.49. Metastable ions link two peaks together, as for example the peaks at m/e 59 and 41 and thus are useful in analyzing proposed fragmentation patterns. What metastable ion results from the fragmentation of $(CO_2CH_3)^+$ to $(OCH_3)^+$?



Computer-enhanced MRI scan of a normal human brain with pituitary gland highlighted. (© Scott Camazine/Photo Researchers)

13

NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

Nuclear magnetic resonance spectroscopy was developed in the early 1960s and within a decade became the single most important technique available to chemists for the determination of molecular structure. In this chapter we first develop a basic understanding of the theory behind this type of spectroscopy and then concentrate on the interpretation of spectra and the types of information they can provide us about details of molecular structure.

13.1 Electromagnetic Radiation

Electromagnetic radiation can be described in terms of its wavelength and its frequency. **Wavelength** is the distance between any two consecutive identical points on a wave. Wavelength is given the symbol λ (lambda) and is usually expressed in the SI base unit of meters. Other derived units commonly used to express wavelength are given in Table 13.1.

Table 13.1 Common units used to express wavelength (λ)

Unit	Relation to Meter	Equivalent Term Found in the Older Literature
meter (m)	—	—
millimeter (mm)	1 mm = 10^{-3} m	—
micrometer (μm)	1 μm = 10^{-6} m	micron (μ)
nanometer (nm)	1 nm = 10^{-9} m	millimicron (mμ)
Angstrom (Å)	1 Å = 10^{-10} m	—

Frequency, the number of full cycles of a wave that pass a given point in a fixed period of time, is given the symbol ν (nu) and is reported in **Hz** (hertz). One MHz = 10^6 Hz. Wavelength and frequency are inversely proportional, and one can be calculated from the other using the following relationship:

$$\nu = \frac{c}{\lambda}$$

where ν is the frequency in hertz; c is the velocity of light, 3.00×10^8 m/s; and λ is the wavelength in meters. For example, consider infrared radiation, or heat radiation as it is also called, of wavelength 15×10^{-6} m (15 μm). The frequency of this radiation is 2.0×10^{13} Hz.

$$\nu = \frac{3.0 \times 10^8 \text{ m/s}}{15 \times 10^{-6} \text{ m}} = 2.0 \times 10^{13} \text{ Hz}$$

An alternative way to describe electromagnetic radiation is as a stream of particles. We call these particles **photons.** The energy in a mole of photons is related to the frequency of radiation by the equation

$$E = h\nu$$

where E is the energy in kilocalories per mole; h is Planck's constant, 9.537×10^{-14} kcal-sec-mol^{-1}; and ν = frequency in hertz. A direct relationship exists between the frequency of electromagnetic radiation and its energy: The greater the frequency, the greater its energy. Thus, ultraviolet radiation of frequency 10^{15} Hz has a greater energy than infrared radiation of frequency 10^{13} Hz. Wavelengths, frequencies, and energies of various regions of the electromagnetic spectrum are summarized in Table 13.2. In this text, we are concerned primarily with three broad regions of this spectrum: radiofrequency radiation, infrared radiation, and ultraviolet-visible radiation.

EXAMPLE 13.1

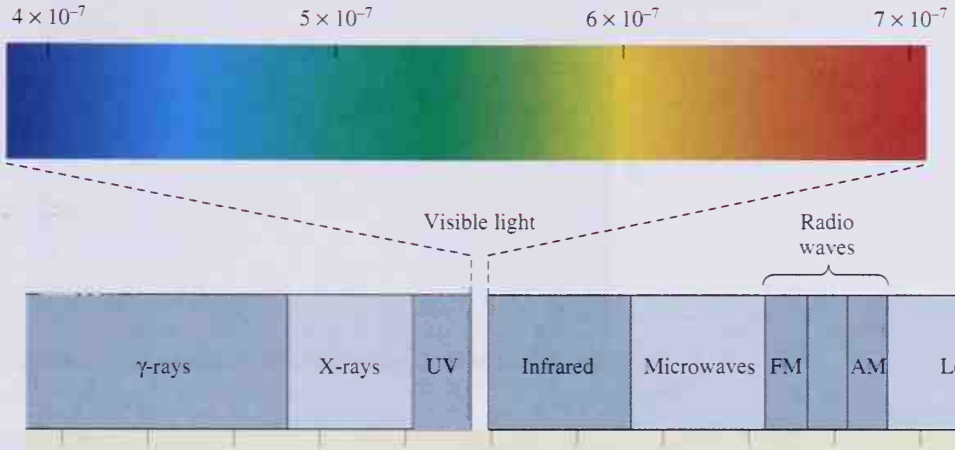
Calculate the energy in kilocalories per mole of radiation of wavelength 2.50 μm.

Solution

Use the relationship $E = hc/\lambda$. Make certain that dimensions for distance are consistent; if the dimension of wavelength is meters, then express the velocity of light in meters per second. Also be certain to use a value of h in the appropriate dimensions.

$$E = \frac{hc}{\lambda} = 9.54 \times 10^{-14} \frac{\text{kcal-s}}{\text{mol}} \times 3.00 \times 10^8 \frac{\text{m}}{\text{s}} \times \frac{1}{2.50 \times 10^{-6} \text{ m}} = 11.4 \text{ kcal/mol}$$

Table 13.2 Wavelength, frequency, and energy relationships of some regions of the electromagnetic spectrum



Wavelength (m)	3×10^{-16}	3×10^{-14}	3×10^{-12}	3×10^{-10}	3×10^{-8}	3×10^{-6}	3×10^{-4}	3×10^{-2}	3	3×10^{2}	3×10^{4}	3×10^{6}	3×10^{8}
Frequency (Hz)	10^{24}	10^{22}	10^{20}	10^{18}	10^{16}	10^{14}	10^{12}	10^{10}	10^{8}	10^{6}	10^{4}	10^{2}	10
Energy (kcal)	10^{13}	10^{11}	10^{9}	10^{7}	10^{5}	10^{3}	10^{1}	10^{-1}	10^{-3}	10^{-5}	10^{-7}	10^{-9}	10^{-11}

PROBLEM 13.1

Calculate the energy of red light (680 nm) in kilocalories per mole. Which form of radiation carries more energy, infrared radiation of wavelength 2.50 μm or red light of wavelength 680 nm?

13.2 Molecular Spectroscopy

Organic molecules are surprisingly flexible structures. As we discussed in Chapter 2, atoms and groups of atoms can rotate about covalent bonds. In addition, covalent bonds can stretch and bend just as if the atoms themselves were joined by flexible springs. Furthermore, electrons within molecules can move from one electronic energy level to another, as for example promotion of an electron from a pi bonding molecular orbital to a pi antibonding molecular orbital. Finally, certain nuclei behave as if they are spinning tops and can change from one spin energy level to another. We know from experimental observations and from theories of molecular structure that all energy changes within a molecule are quantized; that is, bonds within molecules can undergo transitions only between allowed vibrational energy levels, electrons can undergo transitions only between allowed electronic energy levels, and so on.

An atom or molecule can be made to undergo a transition from energy state E_1 to a higher energy state, E_2, by irradiating it with electromagnetic radiation corresponding to

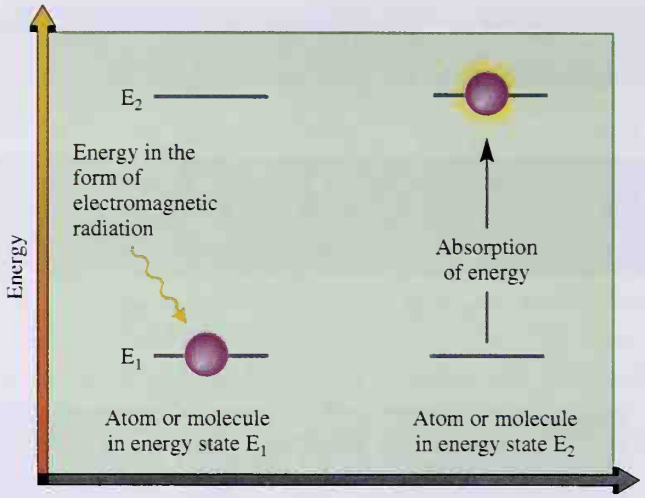


Figure 13.1
Absorption of energy in the form of electromagnetic radiation causes an atom or molecule in energy state E_1 to change to a higher energy state E_2.

the energy difference between states E_1 and E_2 as illustrated schematically in Figure 13.1. When the atom or molecule returns to the ground state E_1, an equivalent amount of energy is emitted.

Molecular spectroscopy is the experimental process of measuring which frequencies of radiation are absorbed or emitted by a particular substance and then attempting to correlate patterns of energy absorptions or emissions with details of molecular structure. The regions of the electromagnetic spectrum of most interest to us and the relationships of each to changes in atomic and molecular energy levels are summarized in Table 13.3.

In this chapter, we concentrate on absorption of radio-frequency radiation which causes transitions between nuclear spin energy levels; that is, we concentrate on nuclear magnetic resonance spectroscopy. The phenomenon of nuclear magnetic resonance was first detected in 1946 by Felix Bloch and Edward Purcell, both of the United States, and for their discoveries they shared in the Nobel Prize in physics in 1952. The particular value of **nuclear magnetic resonance (NMR) spectroscopy** is that it gives us information about the number and types of atoms in a molecule: for example, about the number and types of hydrogens in **^{1}H-NMR spectroscopy**, and about the number and types of carbons in **^{13}C-NMR spectroscopy**.

Table 13.3 Types of energy transitions resulting from absorption of energy from three regions of the electromagnetic spectrum

Region of the Electromagnetic Spectrum	Absorption of Electromagnetic Radiation Results in Transition Between
radio frequency	nuclear spin energy levels
infrared	vibrational energy levels of chemical bonds
ultraviolet-visible	electronic energy levels of pi and nonbonding electrons

Table 13.4 Spin quantum numbers and allowed nuclear spin states for selected isotopes of elements common to organic compounds

Element	Percent Natural Abundance	Spin Quantum Number	Number of Nuclear Spin States
^{12}C	98.89	0	1
^{16}O	99.76	0	1
^{32}S	95.02	0	1
^{1}H	99.99	$\frac{1}{2}$	2
^{13}C	1.11	$\frac{1}{2}$	2
^{31}P	100.00	$\frac{1}{2}$	2
^{14}N	99.63	1	3

13.3 Nuclear Spin States

You are already familiar from general chemistry with the concept that an electron has a spin, that electron spin is quantized (limited to certain values) with allowed values of $+\frac{1}{2}$ and $-\frac{1}{2}$, and that a spinning charge creates an associated magnetic field. In effect, an electron behaves as if it is a tiny bar magnet and has what is called a **magnetic moment.** According to the Pauli exclusion principle (Section 1.1), two electrons can occupy the same atomic or molecular orbital only if their spins are paired (opposite in sign).

Nuclei of ^{1}H and ^{13}C, isotopes of the two elements most common to organic compounds, also behave as if they are spinning on an axis and have associated magnetic moments. Both ^{1}H and ^{13}C nuclei have spin quantum numbers of $\frac{1}{2}$ and, like electrons, have two allowed spin states with values of $+\frac{1}{2}$ and $-\frac{1}{2}$. Spin quantum numbers and allowed nuclear spin states for these nuclei along with the nuclei of other elements common to organic compounds are shown in Table 13.4. Note that ^{12}C and ^{16}O each have a spin quantum number of 0 and only one allowed nuclear spin state. We are concerned primarily with nuclear spin states of ^{1}H and ^{13}C and, therefore, confine our discussion in this text to nuclear spin states of $+\frac{1}{2}$ and $-\frac{1}{2}$.

13.4 Orientation of Nuclear Spins in an Applied Magnetic Field

Within a collection of atoms the nuclear spins are completely random in orientation. In the presence of an **applied magnetic field, B_0,** however, interactions between the nuclear spin and the applied magnetic field are quantized, with the result that only certain orientations of nuclear magnetic moments are allowed. For hydrogen nuclei, ^{1}H, and for ^{13}C nuclei as well, two orientations are allowed, as illustrated in Figure 13.2. By convention, nuclei with spin $+\frac{1}{2}$ are aligned with the applied field and in the lower energy state; nuclei with spin $-\frac{1}{2}$ are aligned against the applied field and in the higher energy state.

The difference in energy between nuclear spin states increases with the strength of the applied field (Figure 13.3). At 1.41 T, the magnetic field strength used by many earlier NMR spectrometers, the energy difference between the two nuclear spin states of ^{1}H nuclei is 0.00572 cal/mol. At an applied field strength of 7.05 T, a field strength readily available

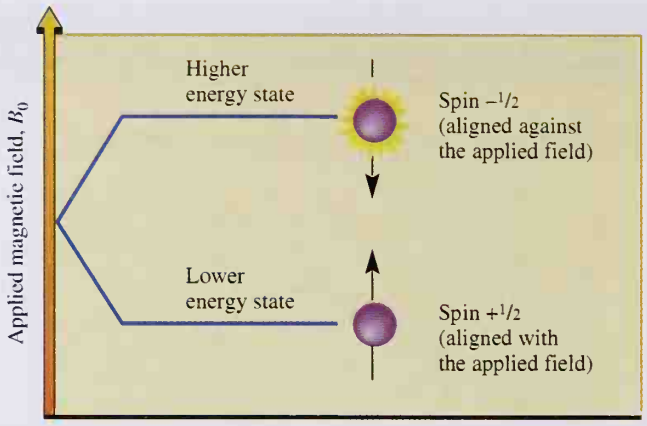


Figure 13.2
^1H and ^{13}C nuclei with spin $+\frac{1}{2}$ are aligned with the applied magnetic field, B_0, and in the lower energy state; those with spin $-\frac{1}{2}$ are aligned against the applied magnetic field and in the higher energy state.

with present-day superconducting electromagnets, the energy difference is 0.0286 cal/mol. A note on the unit in which magnetic field strength is expressed: The SI unit is the tesla (symbol T). The unit still in common use is the gauss (symbol G). Values of T and G are related by the equation $1T = 10^4$ G.

To put these values for nuclear spin energy levels in perspective, bear in mind that energies for transitions between vibrational energy levels observed in infrared spectroscopy are 2 to 10 kcal/mol and energies for transitions between electronic energy levels observed in ultraviolet-visible spectroscopy are 30 to 140 kcal/mol.

The difference in energy between nuclear spin states corresponds to electromagnetic radiation in the radio-frequency range. An energy of 0.0286 cal/mol, for example, corre-

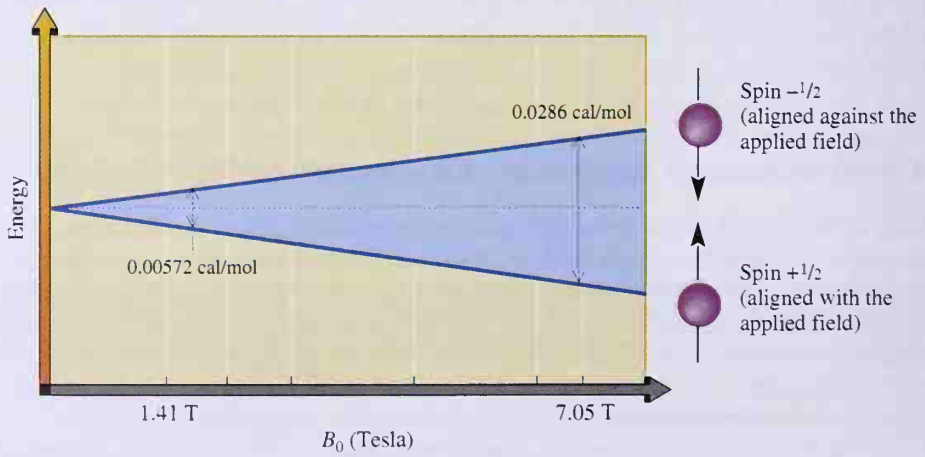


Figure 13.3
The energy difference between allowed spin states for nuclei increases linearly with applied field strength. Values shown are for ^1H nuclei.

sponds to radiation of approximately 300 MHz (300,000,000 Hz). Herein lies the key to our ability to observe transitions between nuclear spin energy levels; we can use electromagnetic radiation to detect changes in nuclear spin state. In the next several sections we describe how these measurements are made for ^1H and for ^{13}C nuclear spin energy levels and then how this information can be correlated with molecular structure.

13.5 Nuclear Magnetic "Resonance"

When hydrogen nuclei are placed in an applied field, a small majority of nuclear spins are aligned with the applied field in the lower energy state. When nuclei in the lower energy spin state are irradiated with a radio frequency of the appropriate energy, energy is absorbed and nuclear spins flip from the lower energy state to the higher energy state.

To understand the mechanism by which a spinning nucleus absorbs energy and the meaning of resonance in this context, imagine a nucleus spinning about an axis perpendicular to its direction of spin. When the applied field of strength B_0 is turned on, the nucleus becomes aligned with the applied field in an allowed spin energy state. The nucleus then begins to **precess** as shown in Figure 13.4(a) and trace out a cone-shaped surface in much the same manner as a spinning top or gyroscope traces out a cone-shaped surface as it precesses in the earth's gravitational field. We can express the **rate of precession** as a frequency expressed in hertz.

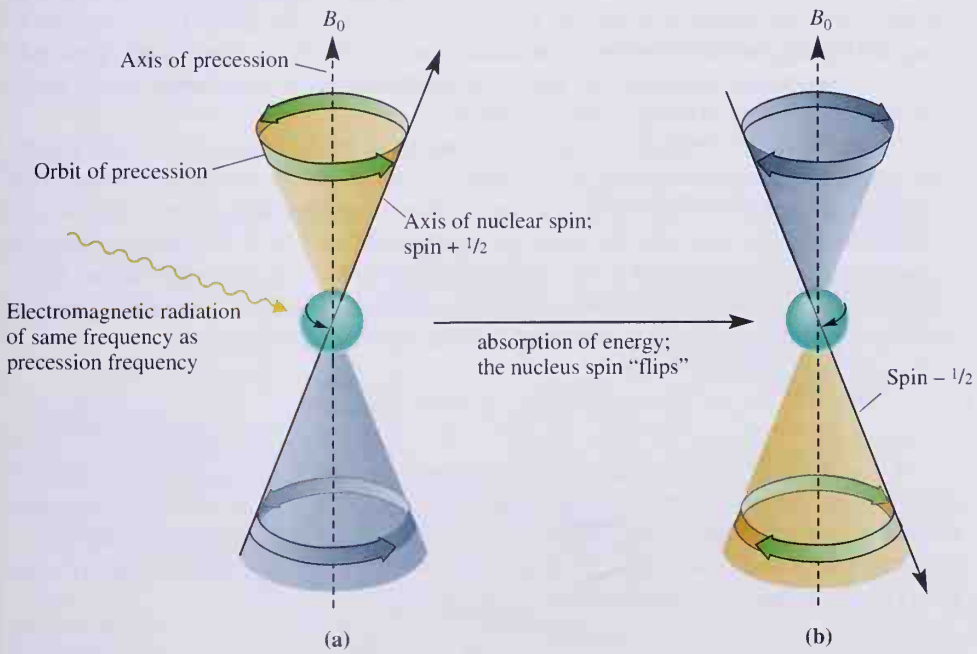


Figure 13.4
Precession of a spinning nucleus in a magnetic field. (a) In the presence of an applied magnetic field. For ^1H in a field of 7.05 T, the frequency of precession is approximately 300 MHz. For ^{13}C in the same field, it is approximately 75 MHz. (b) Absorption of electromagnetic radiation occurs when the frequency of radiation is equal to the frequency of precession.

If the precessing nucleus is irradiated with electromagnetic radiation of the same frequency as the precession frequency, then the two frequencies couple, energy is absorbed, and the nuclear spin is "flipped" from spin state $+\frac{1}{2}$ (with the applied field) to spin state $-\frac{1}{2}$ (against the applied field) as illustrated in Figure 13.4(b). Herein lies the reason for the use of the term "resonance." **Resonance** in this context is the absorption of electromagnetic radiation by a precessing nucleus and the resulting flip of nuclear spin state. The instrument used to detect this coupling of precession frequency and electromagnetic radiation records it as a resonance **signal.**

If we were dealing with "free" hydrogens (the same argument applies equally well to "free" carbons), that is, hydrogen nuclei isolated from all other atoms and electrons, any combination of applied field and electromagnetic radiation that would produce a resonance signal for one hydrogen would produce a resonance signal for all hydrogens. In other words, free hydrogens would be indistinguishable one from another. However, hydrogens in a molecule are not free. They are surrounded by electrons, which themselves have spin and thereby create **local magnetic fields** that oppose the applied field. Although these local fields are orders of magnitude weaker than the applied fields used in NMR spectroscopy, they are nonetheless significant at the molecular level. Thus, hydrogens are shielded from the applied field by local magnetic fields. The effective magnetic field experienced by a hydrogen is the applied field less any local magnetic fields.

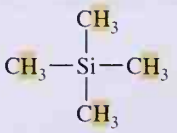
$$B_{\text{effective}} = B_{\text{applied}} - B_{\text{local}}$$

The degree of **shielding** depends on several factors which we will take up very soon. For the moment, however, it is sufficient to realize that the greater the shielding of a particular hydrogen by local magnetic fields, the greater the strength of the applied field required to bring that hydrogen into resonance. Conversely, the less the shielding of a hydrogen, or as it is more commonly expressed, the greater its **deshielding,** the lower the strength of the applied field required to bring it into resonance.

The differences in resonance frequencies among the various hydrogens within a molecule due to shielding-deshielding are generally very small. The difference between the resonance frequencies of hydrogens in chloromethane compared with those in fluoromethane, for example, is only 360 Hz under an applied field of 7.05 T. Considering that the radio-frequency radiation used at this applied field is approximately 300 MHz, the difference in resonance frequencies between these two sets of hydrogens is only slightly greater than 1 part per million (1 ppm) compared with the irradiating frequency.

$$\frac{360 \text{ Hz}}{300 \times 10^6 \text{ Hz}} \times 10^6 = 1.2 \text{ ppm}$$

It is difficult to measure individual resonance frequencies (for example, 300,000,000 and 300,000,360) with any precision. What is done instead is to measure the resonance frequencies of individual hydrogens relative to the resonance frequency of hydrogens in a reference compound. The reference compound now universally accepted is **tetramethylsilane (TMS),** a liquid at room temperature, bp 26.5°C.



Tetramethylsilane (TMS)

TMS was chosen as a reference compound because it is soluble in most solvents used in NMR spectroscopy, it is unreactive toward most organic compounds, and, because of the low electronegativity of silicon, the hydrogens of its methyl groups are more shielded (resonate at a higher applied field) than those in most other organic compounds. Thus, when the spectrum of a compound is determined, the resonance signals of its hydrogens are reported by how far they are shifted from the resonance signal of the 12 hydrogens in TMS.

The same argument we have just given applies as well to carbon-13 nuclei in a molecule. When a ^{13}C-NMR spectrum is determined, the resonance frequencies of its carbons are reported by how far they are shifted from the resonance signal of the four carbons in TMS.

Another part of the reporting problem is that the shift in resonance frequency from TMS is directly proportional to the operating frequency of the spectrometer. Two spectrometers operating at different frequencies report different values for the shift in resonance frequency from TMS. To standardize reporting of NMR data, workers have adopted the unit called chemical shift. **Chemical shift (δ)** is defined as the frequency shift from TMS times 10^6 divided by the operating radio frequency of the spectrometer.

$$\delta = \frac{\text{shift in frequency from TMS (Hz)}}{\text{frequency of spectrometer (Hz)}} \times 10^6$$

Thus, by definition, chemical shift is independent of the operating frequency.

13.6 An NMR Spectrometer

The essential elements of an NMR spectrometer are a powerful magnet, a radio-frequency generator, a radio-frequency detector, and a sample tube (Figure 13.5).

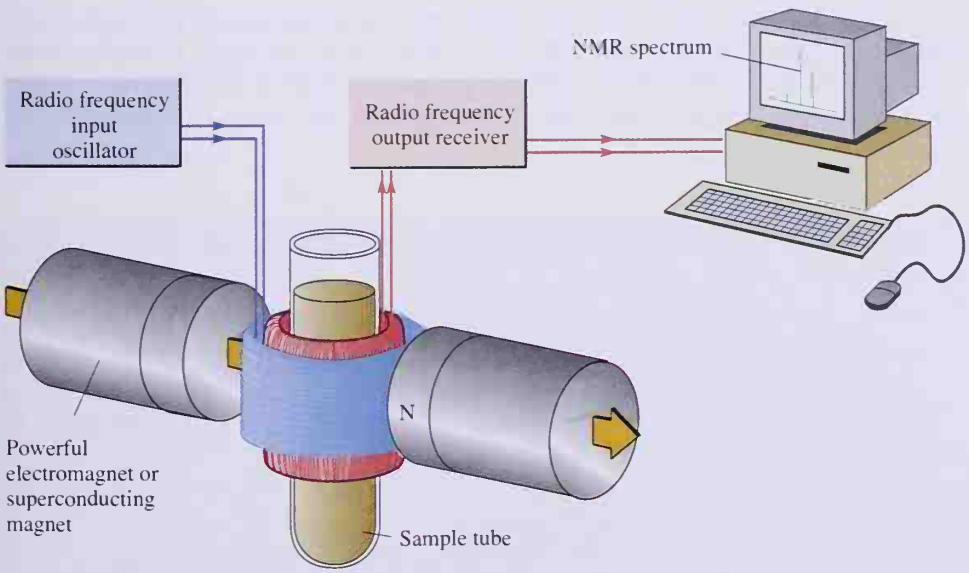


Figure 13.5
Schematic diagram of a nuclear magnetic resonance spectrometer.

The sample is dissolved in a solvent having no hydrogens, as for example carbon tetrachloride (CCl_4), deuterochloroform ($CDCl_3$), or deuterium oxide (D_2O). The sample cell is a small glass tube suspended in the gap between the pole pieces of the magnet and set spinning on its long axis to ensure that all parts of the sample experience a homogeneous applied field.

The resonance frequencies of hydrogens within a molecule can be determined in two ways. Earlier NMR spectrometers operated by holding the radio frequency constant and varying the magnetic field to cause each hydrogen or set of hydrogens in turn to resonate. With this "field sweep" method, a spectrum can be recorded in 2 to 5 min. Newer, more modern Fourier transform NMR (FT-NMR) spectrometers operate in a different manner. The magnetic field is held constant, and the sample is irradiated with a short pulse (approximately 10^{-35} s) of radio-frequency energy that spin flips all hydrogen nuclei at once. The electronically recorded spectrum, which can be produced in as little as 2 s, contains information about all hydrogens as their magnetic moments return to their equilibrium states. The process by which each nucleus returns to its equilibrium state produces a sine wave at the frequency of its resonance signal. The intensity of the sine wave decays with time and falls to zero as nuclei resonating at that frequency reach their equilibrium state. A computer records this information digitally and then uses a mathematical process called Fourier transformation to convert the intensity-versus-time information to intensity-versus-frequency information. An FT-NMR spectrum can be recorded in about 2 s. A particular advantage of FT-NMR spectroscopy is that a large number of spectra (as many as several thousand for a sample) can be recorded and digitally summed to give a time averaged-spectrum. Instrumental electronic noise is random and time averages to zero, but sample signals accumulate and, when time-averaged, become much stronger than would be observed from a single spectrum.

All NMR spectra shown in this text were recorded and displayed using FT techniques. All ^{1}H-NMR spectra were recorded at 7.05 T and 300 MHz. All ^{13}C-FT-NMR spectra were recorded at 7.05 T and 75 MHz.

Figure 13.6 shows a 300-MHz ^{1}H-NMR spectrum of methyl acetate. The lower axis is calibrated in units of the delta scale. The small signal at δ 0 is due to the hydrogens of the reference compound, TMS. The remainder of the spectrum consists of two signals: one for the three hydrogens on the methyl adjacent to oxygen and one for the three hydrogens on

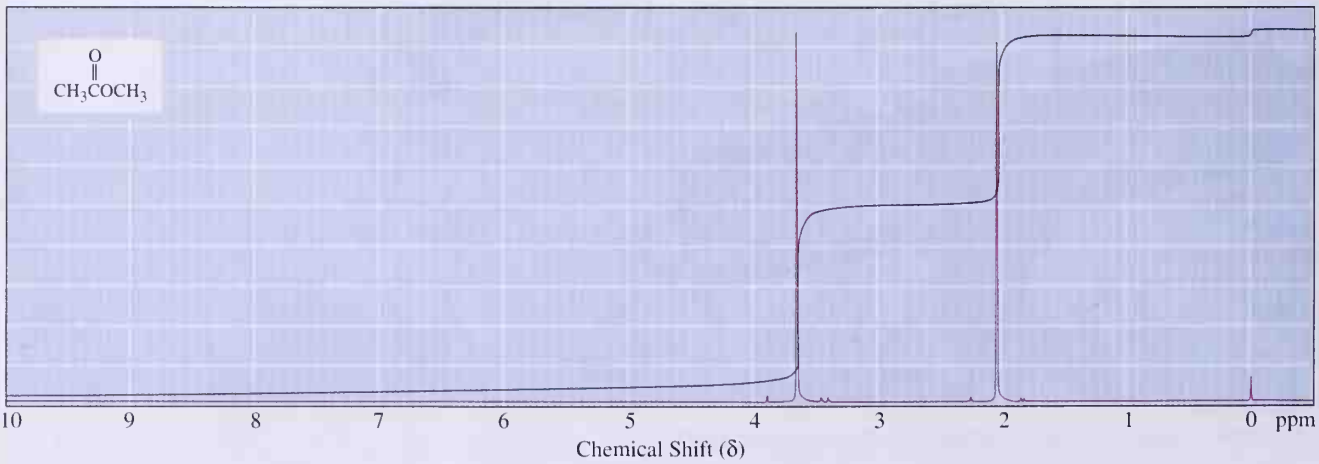


Figure 13.6
^{1}H-NMR spectrum of methyl acetate.

the methyl adjacent to the carbonyl group. It is not our purpose at the moment to determine which hydrogens give rise to which signal but only to recognize the form in which an NMR spectrum is recorded and the origin of the calibration marks.

13.7 Equivalent Hydrogens

All **equivalent hydrogens** have the same chemical environment (Section 2.3C) within a molecule and have identical chemical shifts. All 12 hydrogens in tetramethylsilane, for example, have identical environments, identical chemical shifts, and give rise to one signal. Shown in Figure 13.7 are several organic compounds, each of which has one set of equivalent hydrogens and gives one signal in its ^{1}H-NMR spectrum.

Molecules with two or more sets of equivalent hydrogens (Figure 13.8) give rise to a different resonance signal for each set. Chloroethane, for example, has one set of three equivalent hydrogens and another set of two equivalent hydrogens; two resonance signals exist in its ^{1}H-NMR spectrum.

You should be able to see immediately that valuable information about molecular structure can be obtained simply by counting the number of signals in the ^{1}H-NMR spec-

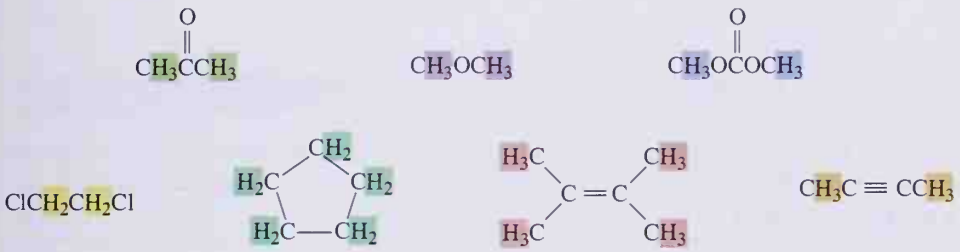


Figure 13.7
Examples of molecules with one set of equivalent hydrogens. Each has one signal in its ^{1}H-NMR spectrum.

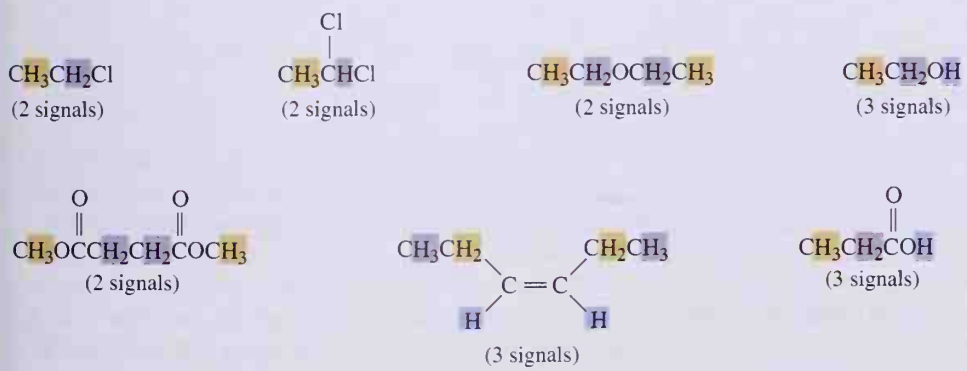


Figure 13.8
Molecules with two or more sets of equivalent hydrogens give rise to one ^{1}H-NMR signal for each set.

trum of a compound. Consider, for example, the two constitutional isomers of molecular formula $C_2H_4Cl_2$. The compound 1,2-dichloroethane (Figure 13.7) has one set of equivalent hydrogens and one resonance signal in its ^{1}H-NMR spectrum. Its constitutional isomer 1,1-dichloroethane (Figure 13.8) has two sets of equivalent hydrogens and two signals in its ^{1}H-NMR spectrum. Thus, simply counting signals allows you to distinguish between these two compounds.

EXAMPLE 13.2

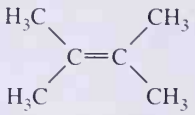
Each of the following compounds gives only one signal in its ^{1}H-NMR spectrum. On the basis of this information, propose a structural formula for each compound:

(a) C_2H_6O **(b)** $C_3H_6Cl_2$ **(c)** C_6H_{12} **(d)** C_4H_6

Solution

Following are structural formulas for each part:

(a) CH_3OCH_3 **(b)** $CH_3\overset{\displaystyle Cl}{\overset{|}{C}}CH_3$ (Cl)

(c)  or  **(d)** $CH_3C{\equiv}CCH_3$

PROBLEM 13.2

Each of the following compounds gives rise to a single absorption signal in its ^{1}H-NMR spectrum. On the basis of this information, propose a structural formula for each compound.

(a) C_3H_6O **(b)** $C_2H_4Cl_2$ **(c)** C_5H_{12} **(d)** $C_4H_6Cl_4$

13.8 Signal Areas

We have just seen that the number of signals in an ^{1}H-NMR spectrum gives us information about the number of sets of equivalent hydrogens. The relative areas of the signals provide additional information in the following way. All modern NMR spectrometers can electronically integrate the area under each signal. After the spectrum is run, the instrument is switched to an integration mode, and the spectrum is recorded again, this time in the form of a **line of integration** superposed on the original spectrum. The vertical rise of the line of integration over each signal is proportional to the area under that signal, which, in turn, is proportional to the number of hydrogens giving rise to that signal. Figure 13.9 shows an integrated ^{1}H-NMR spectrum of *tert*-butyl acetate. The spectrum shows signals at δ 1.44 and δ 1.95. The integrated signal heights are in the ratio 3 : 1, consistent with the presence of one set of nine equivalent hydrogens and one set of three equivalent hydrogens.

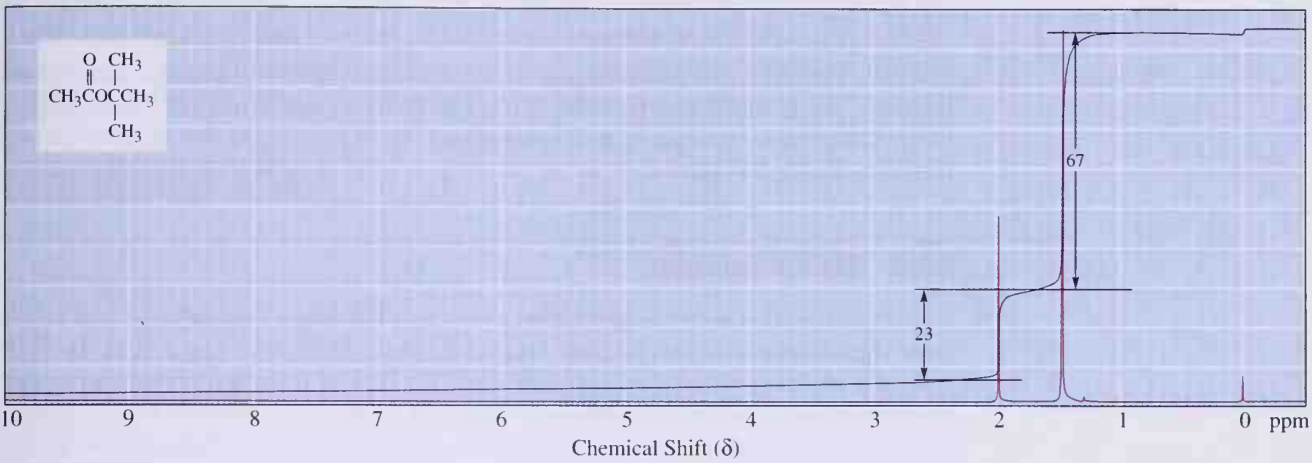
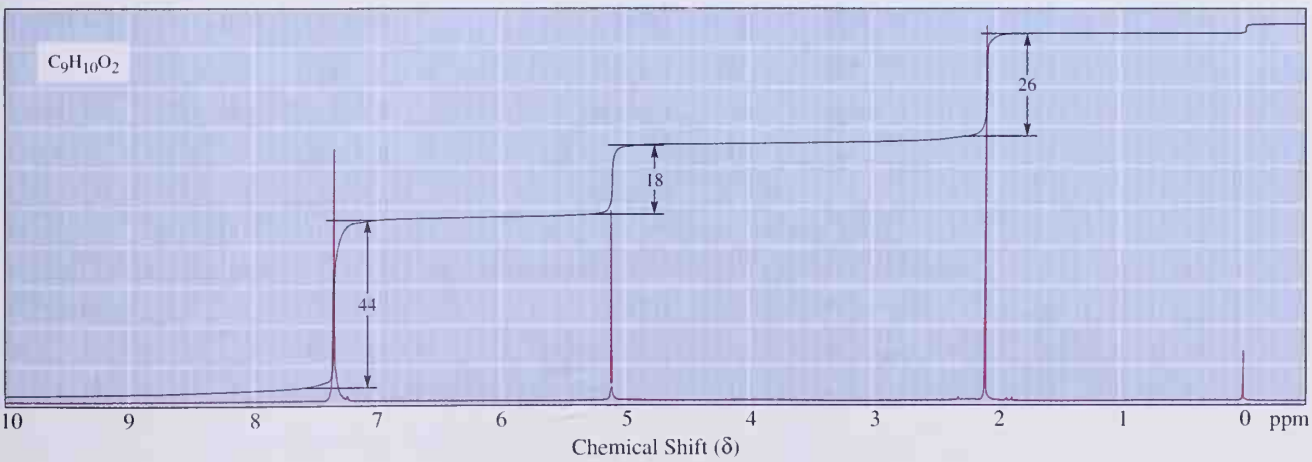


Figure 13.9
300 MHz ^{1}H-NMR spectrum of *tert*-butyl acetate showing integration of the peaks. The rise in the line of integration is 67 chart divisions for the signal at δ 1.44 and 23 chart divisions for the signal at δ 1.95. Thus ratio of hydrogens in each set is 3 : 1.

EXAMPLE 13.3

Following is an ^{1}H-NMR spectrum for a compound of molecular formula $C_9H_{10}O_2$. From an analysis of the integration line, calculate the number of hydrogens giving rise to each signal.



Solution

The total vertical rise in the line of integration is 88 chart divisions. From these numbers, we can calculate that 44/88 × 10, or 5, of the hydrogens give rise to the signal at δ 7.31. Similar calculations for the signals at δ 5.08 and δ 2.06 show that they arise from two hydrogens and three hydrogens, respectively.

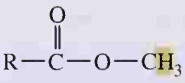
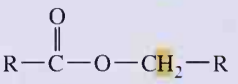
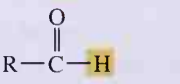
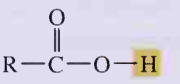
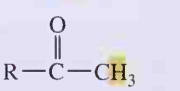
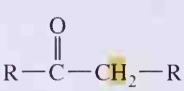
PROBLEM 13.3

The line of integration of the two signals in the ^{1}H-NMR spectrum of a ketone of molecular formula $C_7H_{14}O$ shows a vertical rise of 62 chart divisions and 10 chart divisions, respectively. Calculate the number of hydrogens giving rise to each signal, and propose a structural formula for this ketone.

13.9 Chemical Shifts

Each type of equivalent hydrogen within a molecule has only a limited range of δ values over which it resonates, and, thus, the value of the chemical shift for a peak in an ^{1}H-NMR spectrum can give valuable information about the type of hydrogen giving rise to that absorption. As examples of patterns in chemical shifts, hydrogens on methyl groups bonded to sp^3-hybridized carbons resonate near δ 1.0 (Figure 13.9). Hydrogens on methyl groups bonded to a carbonyl carbon resonate near δ 2.0 (compare Figures 13.6 and 13.9). Hydrogens on a methyl group bonded to an sp^3-hybridized oxygen resonate near δ 3.6 (Figure 13.6). Tabulated in Table 13.5 are average chemical shifts for most of the types of hydrogens we deal with in this course. Notice that most of these values fall within a rather narrow range of 8 to 9 chemical shift units.

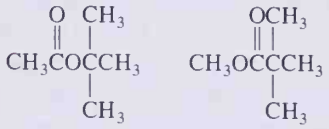
Table 13.5 Average values of chemical shifts of representative types of hydrogens

Type of Hydrogen (R = Alkyl, Ar = Aryl)	Chemical Shift (δ)	Type of Hydrogen (R = Alkyl, Ar = Aryl)	Chemical Shift (δ)
$(CH_3)_4Si$	0 (by definition)		3.4–3.8
R—OH	0.5–6.0		3.9–4.3
R—NH_2	0.6–3.0	R—CH_2I	3.1–3.3
R—CH_3	0.8–1.0	R—CH_2Br	3.4–3.6
R—CH_2—R	1.2–1.4	R—CH_2Cl	3.6–3.8
R_3CH	1.4–1.7	R—CH_2F	4.4–4.5
R_2C=CR—CHR_2	1.6–1.9	Ar—OH	4.5–7.7
R—C≡C—H	2.5–3.1	R_2C=CH_2	4.6–5.0
Ar—CH_3	2.2–2.5	R_2C=CH—R	5.2–5.7
Ar—CH_2—R	2.3–2.8	Ar—H	6.5–8.5
R—CH_2OH	3.3–4.0		9.5–9.6
R—CH_2OR	3.3–3.9		10–13
	2.1–2.6		
	2.0–2.4		

A note on terminology. If a signal is shifted toward the left on the chart paper, we say that it is shifted **downfield,** meaning it comes into resonance at a weaker applied field. Conversely, if a signal is shifted toward the right on the chart paper, we say that it is shifted **upfield,** meaning that it comes into resonance at a stronger applied field.

EXAMPLE 13.4

Following are structural formulas for two constitutional isomers of molecular formula $C_6H_{12}O_2$:

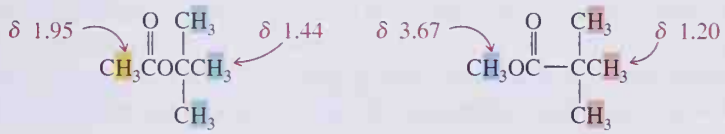


(1) (2)

(a) Predict the number of signals in the ^{1}H-NMR spectrum of each isomer.
(b) Predict the ratio of areas of the signals in each spectrum.
(c) Show how you can distinguish between these isomers on the basis of chemical shift.

Solution

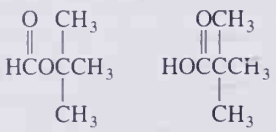
The ^{1}H-NMR spectrum of each consists of two singlets in the ratio 9 : 3, or 3 : 1. Distinguish between these constitutional isomers by the chemical shift of the single $-CH_3$ group. The hydrogens of CH_3O are deshielded (appear farther downfield) than the hydrogens of $CH_3C{=}O$. See Table 13.5 for approximate values for each chemical shift. Experimentally determined values are:



(1) (2)

PROBLEM 13.4

Following are structural formulas for two constitutional isomers of molecular formula $C_5H_{10}O_2$:



(1) (2)

(a) Predict the number of signals in the ^{1}H-NMR spectrum of each isomer.
(b) Predict the ratio of areas of the signals in each spectrum.
(c) Show how you can distinguish between these isomers on the basis of chemical shift.

The chemical shift of a particular type of hydrogen depends primarily on three factors: (1) the electronegativity of the adjacent atom or atoms, (2) the hybridization of the adjacent atom, and (3) magnetic induction within an adjacent pi system. Let us consider these one at a time.

A. Electronegativity of Adjacent Atoms

As illustrated in Table 13.6 for the chemical shift of methyl hydrogens in the series of $CH_3—X$, the greater the electronegativity of X, the greater the chemical shift. The effect of an electronegative substituent falls off quickly with distance. The effect of an electronegative substituent two atoms away is only about 10% of that when it is on the adjacent atom. The effect of an electronegative substituent three atoms away is almost negligible.

How are electronegativity and chemical shift related? The answer starts with the fact that an applied magnetic field also affects electrons and through them creates **induced local magnetic fields.** These induced fields oppose the applied field and thereby shield nearby hydrogens. Now consider what happens if an electronegative atom is nearby. The electronegative atom reduces electron density and its shielding effect on nearby hydrogens, thus causing them to resonate farther downfield (at a weaker applied field and with a larger chemical shift).

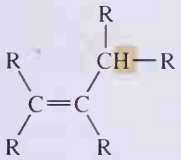
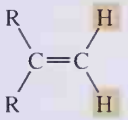
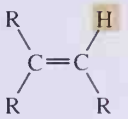
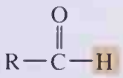
B. Hybridization of Adjacent Atoms

Hydrogens attached to an sp^3-hybridized carbon typically absorb at δ 0.8 to 1.7. Vinylic hydrogens (those on a carbon-carbon double bond) are considerably deshielded and resonate at δ 4.6 to 5.7 (Table 13.7). Part of the explanation for the greater deshielding of vinylic hydrogens compared with alkyl hydrogens lies in the state of hybridization of carbon. Because a sigma bonding orbital of an sp^2-hybridized carbon has more *s* character than a sigma bonding orbital of an sp^3-hybridized carbon (33% compared with 25%), an sp^2-hybridized carbon atom is more electronegative. Vinylic hydrogens are deshielded by this electronegativity effect and resonate farther downfield (at a weaker applied field and

Table 13.6 Dependence of chemical shift of CH_3X on the electronegativity of X

$CH_3—X$	Electronegativity of X	Chemical Shift (δ) of Methyl Hydrogens
$CH_3—F$	4.0	4.26
$CH_3—OH$	3.5	3.47
$CH_3—Cl$	3.1	3.05
$CH_3—Br$	2.8	2.68
$CH_3—I$	2.5	2.16
$CH_3—C(CH_3)_3$	2.1	0.86
$CH_3—Si(CH_3)_3$	1.8	0.00 (by definition)

Table 13.7 The effect of hybridization on chemical shift

Structure (R = Alkyl)	Type of Hydrogen	Chemical Shift (δ)
$R-CH_2-CH_3$	alkyl	0.9
$R-CH_2-R$	alkyl	1.2–1.4
R_3CH	alkyl	1.4–1.7
	allylic	1.6–1.9
	vinylic (terminal)	4.6–5.0
	vinylic (internal)	5.0–5.7
	aldehyde	9–10
$R-C\equiv C-H$	acetylenic	2.0–3.0

with a larger chemical shift) relative to alkyl hydrogens. Similarly, acetylenic and aldehyde hydrogens also appear farther downfield compared with alkyl hydrogens.

Differences in chemical shifts of vinylic and acetylenic hydrogens cannot be accounted for on the basis of the hybridization of carbon alone. If the chemical shift of vinylic hydrogens to δ 4.6 to 5.7 were due entirely to changes in hybridization of carbon, then the chemical shift of acetylenic hydrogens should be even greater than that of vinylic hydrogens. Yet the chemical shift of acetylenic hydrogens is only δ 2.0 to 3.0. It seems that either the chemical shift of acetylenic hydrogens is anomalously small or the chemical shift of vinylic hydrogens is anomalously large. In either case, another factor must be contributing to the magnitude of the chemical shift. Theoretical and experimental evidence (neither of which we take the time to develop here) suggest that the chemical shifts of hydrogens attached to pi-bonded carbons are influenced not only by the relative electronegativities of sp^2- and sp-hybridized carbon atoms but also by magnetic induction through the pi system.

C. Magnetic Induction in a Pi System

To understand the influence of a pi system on the chemical shift of an acetylenic hydrogen, imagine that the alkyne is oriented as shown in Figure 13.10 with respect to the applied field. In accord with the laws of magnetic induction, the applied field induces a circulation

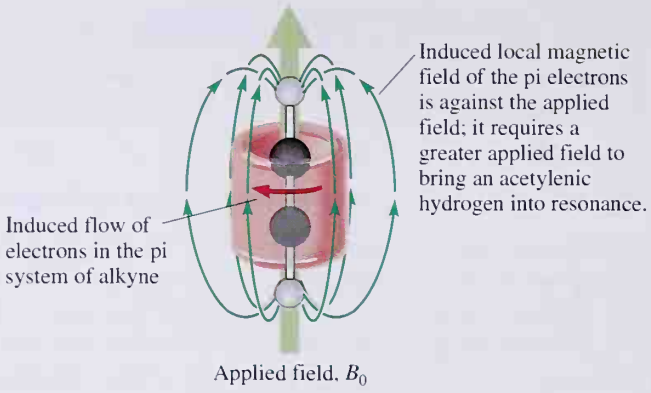


Figure 13.10
A magnetic field induced in the pi system of the alkyne decreases the chemical shift of acetylenic hydrogens.

of electrons in the pi system, which in turn produces an induced magnetic field. Given the geometry of an alkyne and the cylindrical nature of its pi system, the induced magnetic field is in opposition to the applied field in the vicinity of the ≡CH hydrogen, and, therefore, a greater applied field is required to make an acetylenic hydrogen resonate; the local magnetic field induced in the pi system decreases the chemical shift of an acetylenic hydrogen.

The effect of the induced circulation of pi electrons on a vinylic hydrogen (Figure 13.11) is opposite to that of an acetylenic hydrogen. The spatial orientation of the induced magnetic field in an alkene is parallel to the applied field in the region of the vinylic hydrogens. The induced magnetic field provides a part of the field strength needed for resonance of vinylic hydrogens and, thus, increases their chemical shift. The presence of the pi electrons of the carbonyl group (Section 17.4B) has a similar effect on the chemical shift of aldehyde hydrogens.

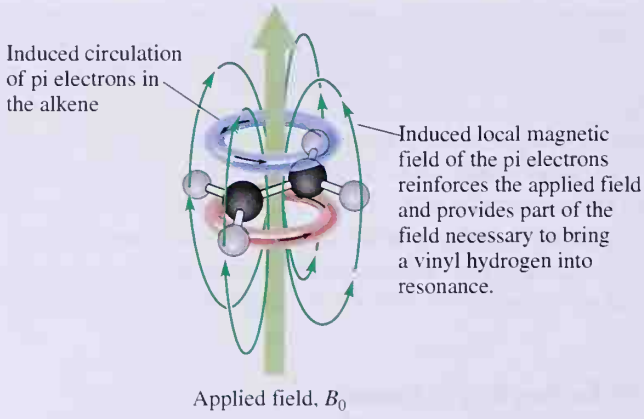


Figure 13.11
A magnetic field induced in the pi bond of an alkene increases the chemical shift of vinylic hydrogens.

13.10 The (*n* + 1) Rule

We have now seen three kinds of information that can be derived from examination of an ^{1}H-NMR spectrum:

1. From the number of signals we can determine the number of sets of equivalent hydrogens.
2. From integration of signal areas we can determine the ratios of hydrogens giving rise to each signal.
3. From the chemical shift of each signal we can derive information about the types of hydrogens in each set.

A fourth kind of information can be derived from the splitting pattern of each signal. Consider, for example, the ^{1}H-NMR spectrum of 1,1-dichloroethane shown in Figure 13.12. This molecule contains two sets of hydrogens and, according to what we have learned so far, we would predict two signals with relative areas 3 : 1 corresponding to the three hydrogens of the $—CH_3$ group and the one hydrogen of the $—CHCl_2$ group. You see from the spectrum, however, that there are in fact six peaks. The grouping of two peaks (called a doublet) at δ 2.1 is the signal for the three hydrogens of the $—CH_3$ group, and the grouping of four peaks (called a quartet) at δ 5.9 is the signal for the single hydrogen of the $—CHCl_2$ group. We say that the CH_3 resonance at δ 2.1 is split into a doublet and that the CH resonance at δ 5.9 is split into a quartet. This phenomenon is called spin-spin splitting. In **spin-spin splitting,** the ^{1}H-NMR signal from one set of hydrogens is split by the influence of neighboring hydrogens nonequivalent to it.

Empirically, the degree of spin-spin splitting can be predicted on the basis of the (*n* + 1) rule. According to the **(*n* + 1) rule,** if a hydrogen has a set of *n* nonequivalent hydrogens on the same or adjacent atom(s), its NMR signal is split into (*n* + 1) peaks. It should be noted here that the nuclei of all adjacent hydrogens couple. It is only when coupling is between nonequivalent hydrogens that the coupling results in spin-spin splitting; coupling between equivalent hydrogens, whether they are on the same or adjacent atoms, does not result in spin-spin splitting.

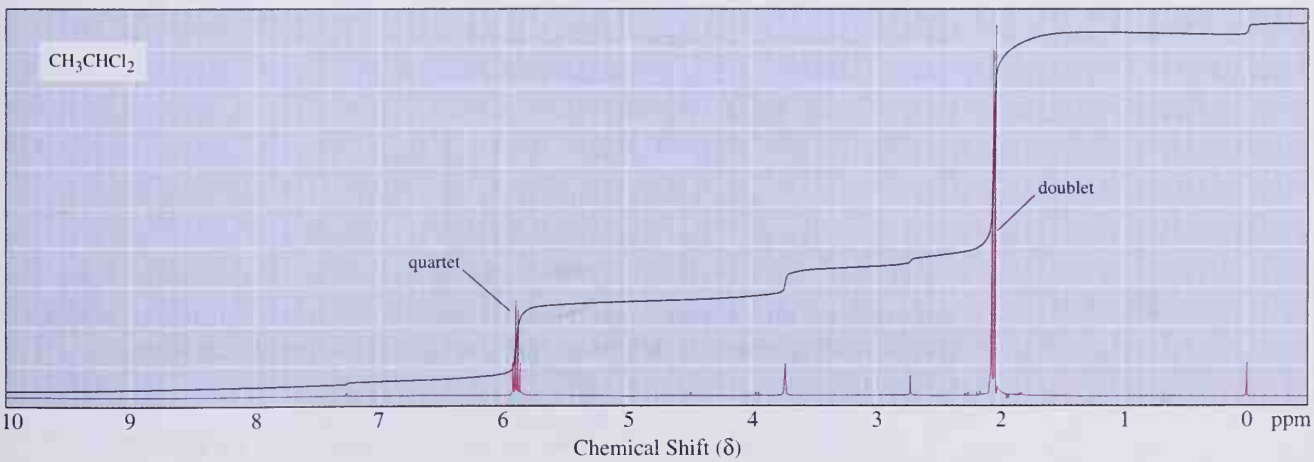
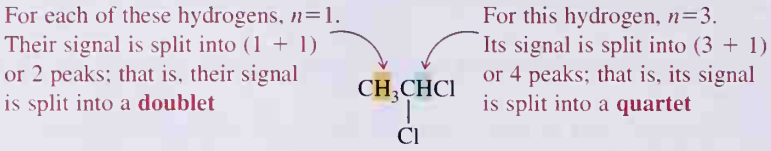


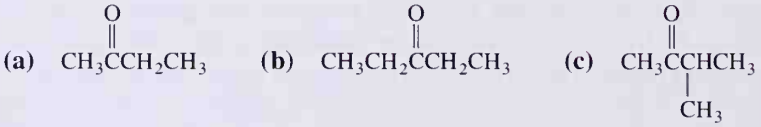
Figure 13.12
^{1}H-NMR spectrum of 1,1-dichloroethane.

Let us apply the $(n + 1)$ rule to the analysis of the spectrum of 1,1-dichloroethane. The three hydrogens of the $—CH_3$ group have one nonequivalent neighbor hydrogen ($n = 1$), and, therefore, this signal is split into a doublet. The single hydrogen of the $—CHCl_2$ group has three nonequivalent neighbor hydrogens ($n = 3$), and its signal is split into a quartet.



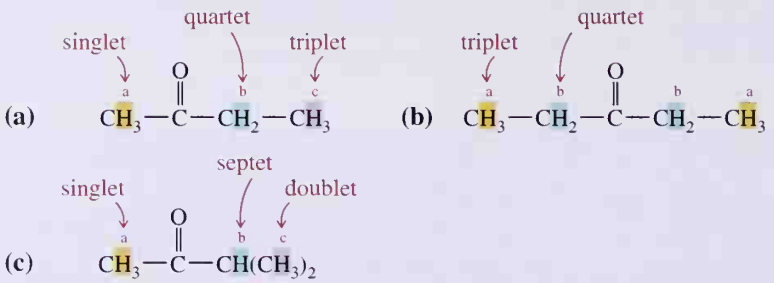
EXAMPLE 13.5

Predict the number of signals and the splitting pattern of each signal in the ^{1}H-NMR spectrum of following molecules:



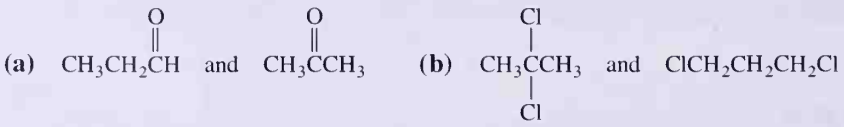
Solution

The sets of equivalent hydrogens in each molecule are labeled a, b, and c. Molecule (a) has three sets of equivalent hydrogens; its NMR spectrum shows a singlet, a quartet, and a triplet in the ratio 3 : 2 : 3. Molecule (b) has two sets of equivalent hydrogens; its NMR spectrum shows a triplet and a quartet in the ratio 3 : 2. Molecule (c) has three sets of equivalent hydrogens; its NMR spectrum shows a singlet, a septet, and a doublet with relative areas in the ratio 3 : 1 : 6.



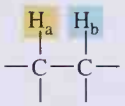
PROBLEM 13.5

Following are pairs of constitutional isomers. State the number of signals to be expected in the ^{1}H-NMR spectrum of each isomer and the splitting pattern of each signal.



13.11 The Origins of Spin-Spin Splitting

When the chemical shift of one nucleus is influenced by the spin of another, the two are said to be **coupled.** Consider, for example, the situation in which nonequivalent hydrogens, H_a and H_b, exist on adjacent carbons.



The chemical shift of H_a is influenced by whether the spin of H_b is aligned with the applied field or aligned against it. If the spin of H_b is aligned with the applied field and adds to it, then H_a absorbs at a lower applied field. If, on the other hand, the spin of H_b is aligned against the applied field and subtracts from it, then H_a absorbs at a higher applied field.

As a result of coupling between nonequivalent hydrogens, H_a and H_b, the signal of hydrogen H_a is split into two peaks. Because there is an equal probability of H_a experiencing the $+\frac{1}{2}$ spin state and the $-\frac{1}{2}$ spin state of H_b, each peak of the doublet is of equal area and each is half the area the H_a signal would be if hydrogen H_b were not present (Figure 13.13). Note that spin splitting is reciprocal; if H_a is split by H_b, then H_b is equally split by H_a. If neither of these hydrogens has any other neighbors, then their ^{1}H-NMR signals are doublets of equal area.

Spin-spin splitting patterns for a hydrogen with zero, one, two, and three equivalent neighbors are summarized in Table 13.8. The ratios of the areas of the peaks in these and any other splitting patterns can be derived from an analysis of spin combinations for adjacent hydrogens. With three adjacent hydrogens, for example, areas within the resulting

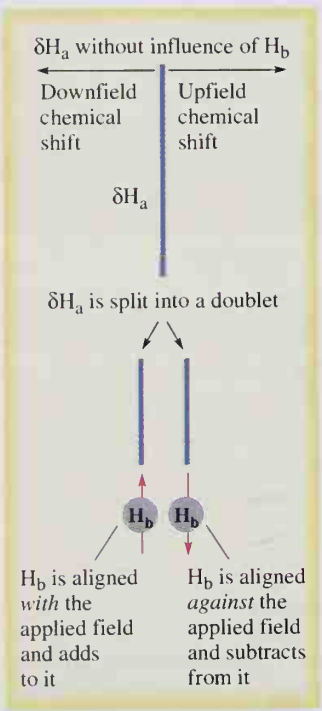


Figure 13.13
The signal of H_a is split into two peaks of equal area (a doublet) by its nonequivalent neighbor H_b.

Table 13.8 Observed spin-spin splitting patterns for a hydrogen with zero, one, two, and three equivalent neighboring hydrogens

Structure	Spin states of H_b	Signal of H_a*
H_a — C — C —		δH_a
H_a H_b — C — C —	↑ ↓	1 : 1 δH_a
H_a H_b — C — C — H_b	↑↑ ↑↓ ↓↓	1 : 2 : 1 δH_a
H_a H_b — C — C — H_b H_b	↑↑↑ ↑↑↓ ↑↓↓ ↓↓↓	1 : 3 : 3 : 1 δH_a

* The area of integration is the same in all signals.

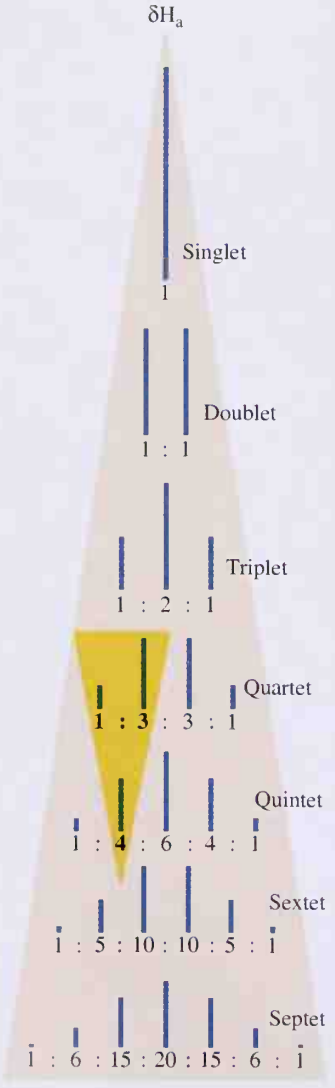


Figure 13.14
Pascal's triangle. As illustrated by the entries in bold face, each entry is the sum of the values immediately above it to the left and the right.

quartet are 1 : 3 : 3 : 1. Alternatively, the ratio of peak areas in any multiplet can be derived from a mathematical mnemonic device called Pascal's triangle (Figure 13.14). A note of caution in counting the number of peaks in a multiplet. If the signal of a particular hydrogen is of low intensity compared with others in the spectrum, it may not be possible to distinguish some of the smaller side peaks because of electronic noise in the baseline of the spectrum.

13.12 Coupling Constants

A **coupling constant** (J) is the distance between adjacent peaks in a multiplet and is a quantitative measure of the shielding-deshielding influence of the magnetic moments of adjacent hydrogens. The magnitude of a coupling constant is expressed in hertz and is measured on the same scale as the chemical shift. Because the value of J depends only on internal forces within a molecule and is independent of the value of the applied field, it has

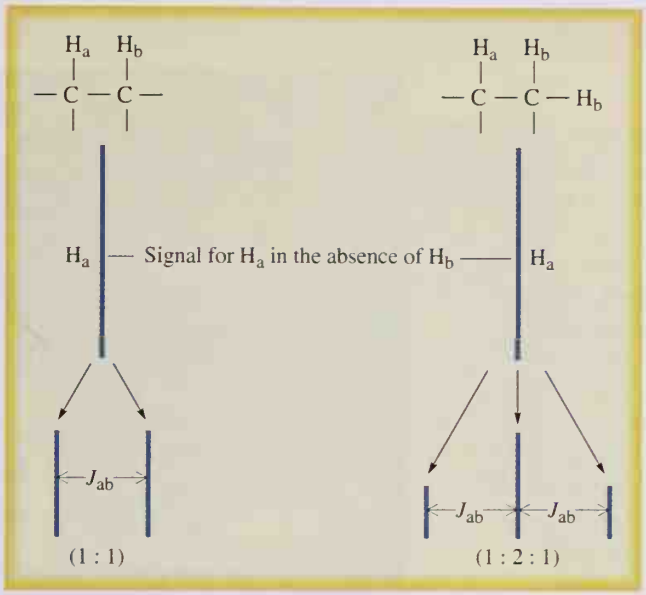


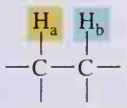
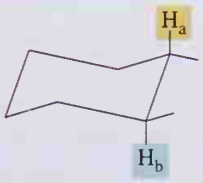
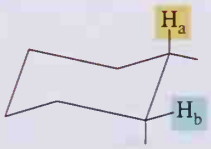
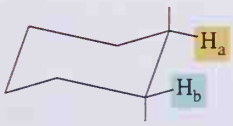
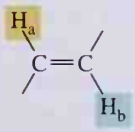
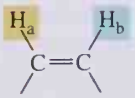
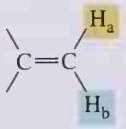
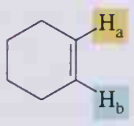
Figure 13.15
Measurement of the coupling constant, J_{ab}, for a doublet (ratio 1 : 1) and a triplet (ratio 1 : 2 : 1) derived from spin-spin splitting of the H_a signal by nonequivalent hydrogen(s) H_b.

the same value whether the spectrometer operates at 7.05 T (and 300 MHz) or at any other applied magnetic field.

Measurements of coupling constants for hydrogens with one and then two equivalent neighboring hydrogens are illustrated in Figure 13.15.

Given in Table 13.9 are approximate values for coupling constants of hydrogens in alkanes and alkenes. We will have more to say in later sections about the use and interpretation of coupling constants for these and other functional groups. Suffice it to say now that these values are relatively small compared with the chemical shifts observed in ^{1}H-NMR spectroscopy. A coupling constant of 10 Hz at a radio frequency of 300 MHz, for example, corresponds to a chemical shift of only δ 0.03.

Table 13.9 Approximate values of *J* (in Hz) for some alkanes and alkenes

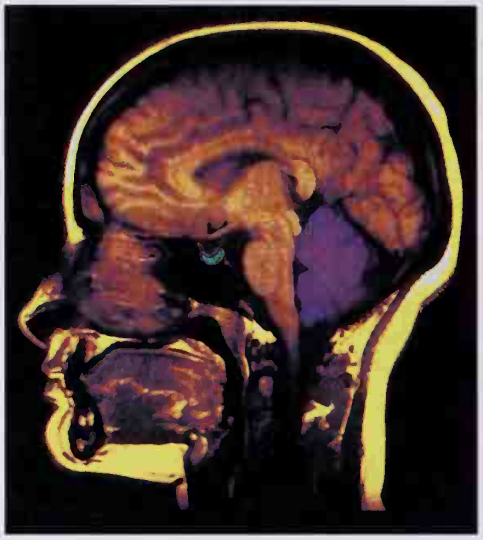
			
6–8 Hz	8–14 Hz	0–7 Hz	0–5 Hz
			
11–18 Hz	5–14 Hz	0–5 Hz	8–11 Hz

CHEMISTRY IN ACTION

Magnetic Resonance Imaging

The NMR effect was discovered and explained by physicists in the 1940s, and by the 1960s, it had become an invaluable analytical tool for chemists. It was realized by the early 1970s that imaging of parts of the body using NMR could be a valuable addition to diagnostic medicine. Because the term "nuclear magnetic resonance" sounds to many people as if the technique might involve radioactive material, most hospitals and clinicians prefer to call the technique "magnetic resonance imaging (MRI)." Although the body contains several nuclei that in theory could be used for MRI, only hydrogens are sufficiently concentrated to give useful signals. Most of the signal comes from the hydrogens of water, with the remainder coming largely from the hydrogens of fats.

For chemists, ^{1}H-NMR spectroscopy is used to obtain information about chemical shifts, integration, and coupling constants. In MRI, three kinds of information can also be recorded: hydrogen density, spin lattice relaxation times (T_1), and spin-spin relaxation times (T_2). Recall that in NMR spectroscopy, energy in the form of radio-frequency radiation is absorbed by nuclei in the sample. Relaxation time is the rate at which nuclei give up this energy and relax to their ground state. Energy can be given off by nuclei in two ways. In T_2 relaxation, one nucleus gives up its energy to another nucleus, a process which causes no net loss of energy among the nuclei. In T_1 relaxation, a nucleus gives up its energy to its surroundings. For large amounts of energy, T_1 relaxation causes the surroundings to heat up.



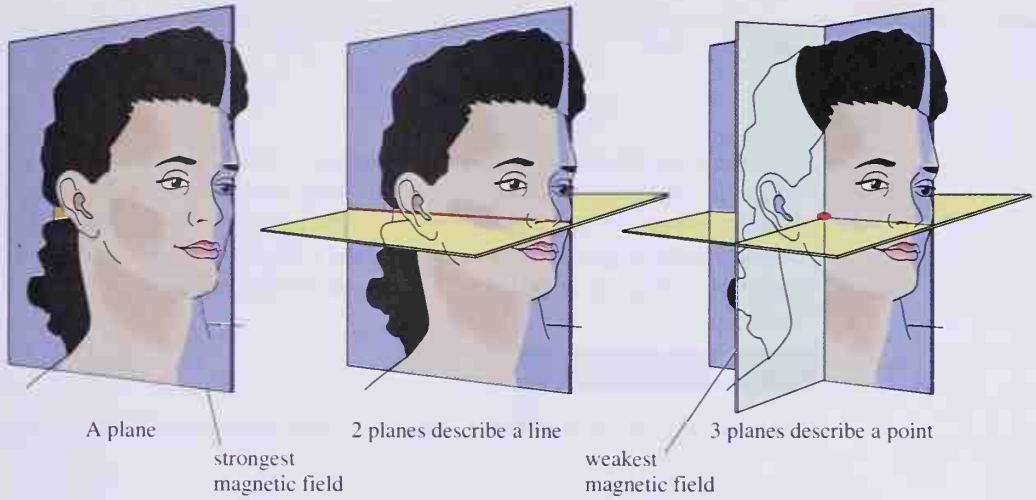
© *Scott Camazine/Photo Researchers*

In 1971, it was discovered that the T_1 relaxation of water in certain cancerous tumors is much longer than the T_1 relaxation of water in normal cells. Thus, if a T_1 relaxation image of the body could be obtained it might be possible to identify tumors at an early stage. Subsequent work demonstrated that many tumors can be identified in this way. Another important application of MRI is in the examination of the brain and spinal cord. White and gray matter are easily distinguished by MRI, which is useful in the study of such diseases as multiple sclerosis. Magnetic resonance and x-ray imaging are in

13.13 ^{13}C-NMR Spectroscopy

Carbon-12, the most abundant (98.89%) natural isotope of carbon, has only one allowed nuclear spin state (Table 13.4) and is not detected by NMR spectroscopy. Carbon-13 (natural abundance 1.11%), however, can be detected by NMR spectroscopy in the same manner as hydrogens can be detected.

The development of **^{13}C-NMR spectroscopy** lagged behind ^{1}H-NMR spectroscopy primarily because of two technical problems having to do with instrument design and operation. One problem is the particularly low natural abundance of ^{13}C and the resulting weak signal. The second problem is that the magnetic moment of ^{13}C is considerably smaller than that of ^{1}H. Taken in combination, these two factors mean that ^{13}C resonance signals are only about 10^{-4} times the strength of ^{1}H resonance signals. Whereas ^{1}H-NMR



many cases complementary. The hard, outer layer of bone is essentially invisible to MRI, but shows up extremely well in x-ray images.

The key to any medical imaging technique is to know which part of the body is producing which signal. In MRI, spatial information can be encoded using magnetic field gradients. Recall that a linear relationship exists between the frequency at which a nucleus resonates and the magnetic field. In MRI, all hydrogen signals have more or less the same chemical shifts, and in a homogeneous magnetic field they all absorb at the same frequency. But, in MRI, the patient is placed in a gradient magentic field that can be varied from place to place. Nuclei in a weaker magnetic field absorb at a lower frequency. Nuclei elsewhere in a stronger magnetic field absorb at a higher frequency. In a variable magnetic field, a correlation exists between the absorption frequency of a nucleus and its position in space. A gradient along a single axis images a plane. Two mutually perpendicular gradients image a line segment, and three mutually perpendicular gradients image a point. In practice, more complicated procedures are used to obtain magnetic resonance images, but they are all based on the idea of magnetic field gradients.

spectroscopy became a routine analytical tool in the mid-1960s, it was not until 20 years later with the development of FT-NMR techniques that ^{13}C-NMR spectroscopy became widely available as a routine analytical tool.

Several modes of operation are possible for a ^{13}C-NMR spectrometer. In the most common, a **hydrogen-decoupled mode,** the sample is irradiated with two different radio frequencies. The first is used to scan for ^{13}C absorptions. The second is a broad spectrum of frequencies that causes all hydrogens in the molecule to undergo rapid transitions among their nuclear spin states. On the time scale of the NMR spectrometer, each hydrogen is in an average or effectively constant nuclear spin state with the result that all ^{1}H-^{13}C spin-spin interactions are decoupled. In a hydrogen-decoupled spectrum, all ^{13}C signals appear as singlets. The hydrogen-decoupled ^{13}C-NMR spectrum of 1-bromobutane (Figure 13.16) consists of four singlets.

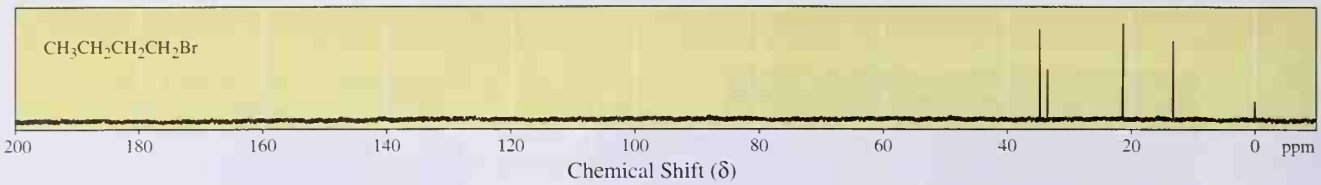


Figure 13.16
Hydrogen-decoupled ^{13}C-NMR spectrum of 1-bromobutane.

A great advantage of ^{13}C-NMR spectroscopy is that it is generally possible to count the number of types of carbon in a molecule. One caution here, however. Because of the particular manner in which spin-flipped ^{13}C nuclei return to their equilibrium states, integration of peak heights is often unreliable, and it is generally not possible to determine the number of carbons of each type based on peak heights.

EXAMPLE 13.6

How many signals do you expect in the ^{13}C-NMR spectrum of the following compounds?

(a) CH_3COCH_3 **(b)** $CH_3CH_2CH_2CCH_3$ **(c)** $CH_3CH_2CCH_2CH_3$

(d) $CH_3CHOCHCH_3$ (CH$_3$ CH$_3$) **(e)** CH_3COCCH_3 (CH$_3$) **(f)** 

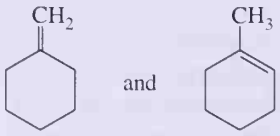
Solution

Following are the number of signals in each spectrum, along with the chemical shifts of each signal. The chemical shifts of the carbonyl carbons are quite distinctive (Table 13.10) and in these examples occur at δ 171.37, 208.85, 211.97, and 170.30.

(a) methyl acetate: three signals (δ 171.37, 51.53, and 20.63)
(b) 2-pentanone: five signals (δ 208.85, 45.68, 29.79, 17.35, and 13.68)
(c) 3-pentanone: three signals (δ 211.97, 35.45, and 7.92)
(d) diisopropyl ether: two signals (δ 68.35 and 22.88)
(e) *tert*-butyl acetate: four signals (δ 170.30, 80.00, 28.10, and 22.40)
(f) cyclohexane: one signal (δ 27.02)

PROBLEM 13.6

Explain how to distinguish between the members of each pair of constitutional isomers based on the number of signals in the ^{13}C-NMR spectrum of each member.

(a)  and

(b) $CH_3CH{=}CHCH_2CH_2CH_3$ and $CH_3CH_2CH{=}CHCH_2CH_3$

Table 13.10 ^{13}C-NMR chemical shifts

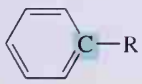
Type of Carbon	Chemical Shift (δ)	Type of Carbon	Chemical Shift (δ)
$R-CH_3$	0–40	$R-C(=O)-OR$	160–170
$R-CH_2-R$	15–55	$R-C(=O)-NR_2$	165–180
R_3CH	20–60	$R-C(=O)-OH$	175–185
$R-CH_2-I$	0–40	$R-C(=O)-H$	200–210
$R-CH_2-Br$	25–65	$R-C(=O)-R$	200–215
$R-CH_2-Cl$	35–80		
R_3COH	40–80		
R_3COR	40–80		
$R-C\equiv C-R$	65–85		
$R_2C=CR_2$	100–150		
	110–160		

Table 13.10 shows approximate chemical shifts for carbon-13 spectroscopy. Notice how much broader the range of chemical shifts is for ^{13}C-NMR spectroscopy than for ^{1}H-NMR spectroscopy. Whereas most chemical shifts for ^{1}H-NMR spectroscopy fall within a rather narrow range of 8 to 9 δ units, those for ^{13}C-NMR spectroscopy cover a much wider range of up to 200 δ units. Because of this expanded scale, it is very unusual to find any two nonequivalent carbons in the same molecule with identical chemical shifts. Most commonly, each different type of carbon within a molecule has a distinct peak clearly resolved from all other peaks.

Notice further that the chemical shift of carbonyl carbons is quite distinct from those of sp^3-hybridized carbons and of other types of sp^2-hybridized carbons. The presence or absence of a carbonyl carbon is quite easy to recognize in a ^{13}C-NMR spectrum.

13.14 Interpreting NMR Spectra

A. Alkanes

Because all hydrogens in alkanes are in very similar chemical environments, chemical shifts of alkane hydrogens fall within a narrow range of δ 0.9 to δ 1.5. ^{13}C chemical shifts in alkanes fall within the range δ 0 to δ 60.

B. Alkenes

The chemical shifts of vinylic hydrogens are larger than those of alkane hydrogens because of deshielding by the sp^2-hybridized carbons of the double bond (Section 13.9B) and the local magnetic field induced in the pi system of alkenes (Section 13.9C). Furthermore, the

^{31}P-NMR Spectroscopy as a pH Meter

We have seen that NMR spectra can be obtained from ^{1}H and ^{13}C nuclei. ^{31}P (Table 13.4) is another nucleus that provides useful spectroscopic information. The chemical shift for ^{31}P in phosphate ion depends on the pH of its environment. At or near neutral pH, phosphate ion is an equilibrium mixture of $H_2PO_4^-$ and HPO_4^{2-}. $H_2PO_4^-$ is a weak acid and ionizes according to the following equilibrium equation. The acid ionization constant K_a for this equilibrium is 6.2×10^{-8}. The chemical shift of ^{31}P in HPO_4^{2-} is 21.05, whereas its chemical shift in $H_2PO_4^-$ is 24.90.

$$\underset{\delta\ 24.90}{H_2PO_4^-} \rightleftharpoons \underset{\delta\ 21.05}{HPO_4^{2-}} + H^+$$

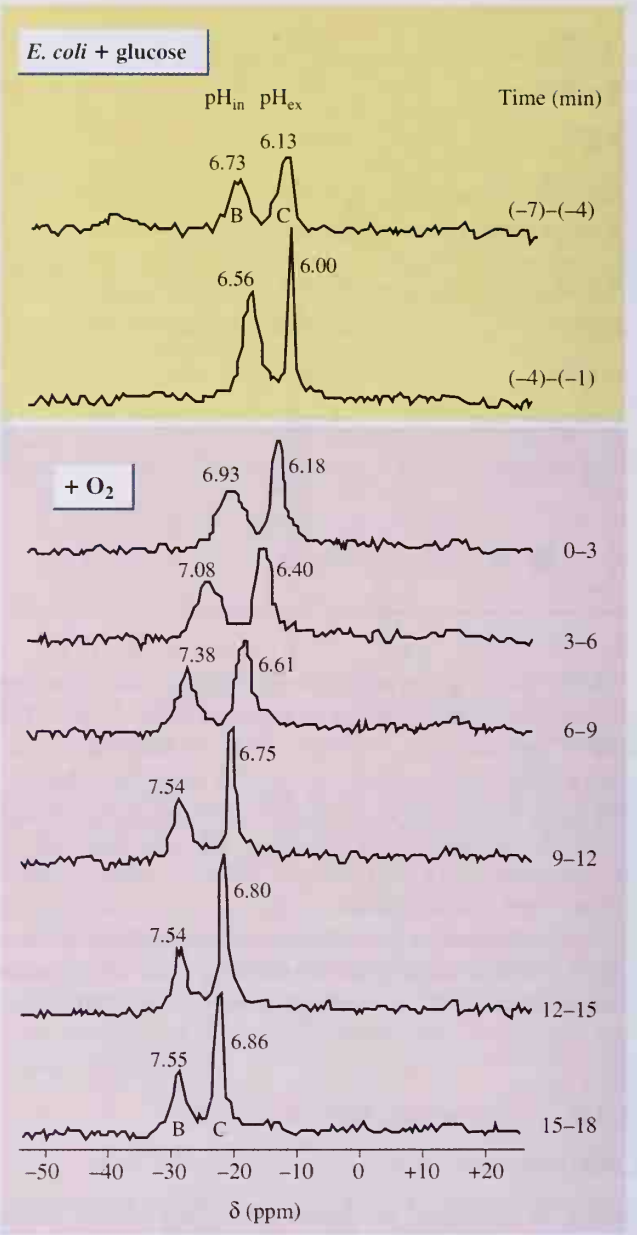
$$K_a = \frac{[HPO_4^{2-}][H^+]}{[H_2PO_4^-]} = 6.2 \times 10^{-8}$$

Solving the K_a expression for hydrogen ion concentration and then taking the negative logarithm of both sides of this equation gives an equation that relates pH directly to the ratio of the molar concentrations of HPO_4^{2-} and $H_2PO_4^-$.

$$pH = 7.21 - \log \frac{[H_2PO_4^-]}{[HPO_4^{2-}]}$$

The equilibrium between $H_2PO_4^-$ and HPO_4^{2-} is very fast. Because a ^{31}P-NMR spectrum is like a camera with a slow shutter speed, only a single peak, which is a mole-weighted average of the chemical shifts of HPO_4^{2-} and $H_2PO_4^-$, is observed for phosphate. Because the ratio of HPO_4^{2-} to $H_2PO_4^-$ is a function of pH, measuring the chemical shift of ^{31}P is equivalent to measuring the pH of the phosphate's environment.

Thus, ^{31}P-NMR provides a noninvasive way to measure the pH of regions that are difficult to measure, such as the inside of cells. In an early application of ^{31}P-NMR to the measurement of cellular pH, a group from Bell Laboratories* recorded ^{31}P-NMR spectra of *Escherichia coli* cells, which were supplied with glucose and either deprived of oxygen or supplied with oxygen. The spectra they recorded are shown in the figure. Peak B is intracellular phosphate ion, and peak C is from phosphate ion in the medium. Initially the cells were under nitrogen and their interior was slightly acidic (pH 6.93). However, as oxygen is supplied, the cells are able to begin active respiration, which causes the interior to become more basic (pH 7.55 for this bacterium). An advantage of the NMR method is that, under conditions of higher sensitivity, the concentrations of other phosphorus-containing biological molecules, such as ATP, can be followed along with changes in pH.



* G. Navon, S. Ogawa, R. G. Shulman, and T. Yamane, *Proc. Natl. Acad. Sci., USA* **74**, 888 (1977).

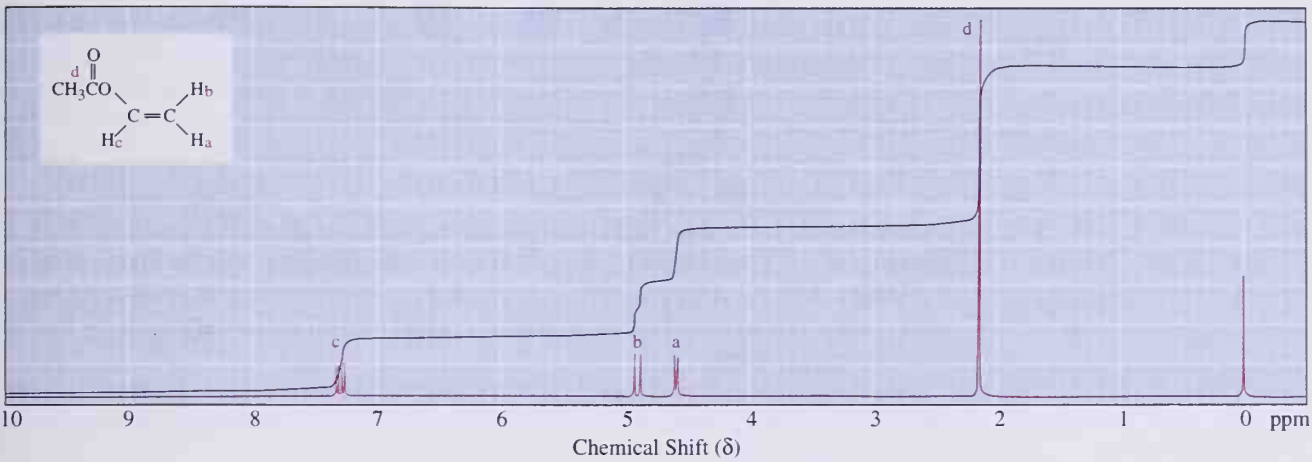
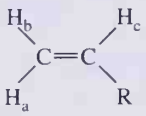
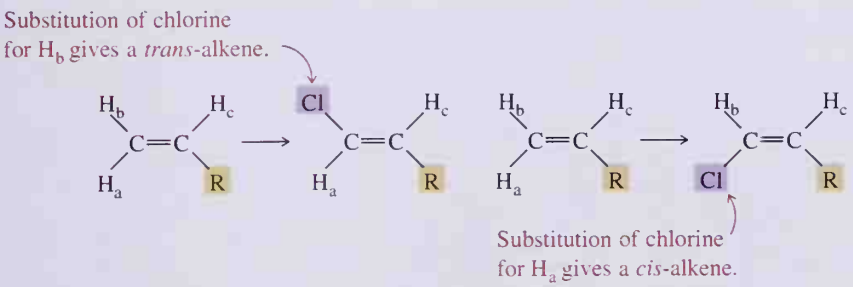


Figure 13.17
^{1}H-NMR spectrum of vinyl acetate.

hydrogens on a monosubstituted alkene are nonequivalent, and, therefore each (1) gives a separate signal and (2) is split by the other two. Consider, for example the following monosubstituted alkene:

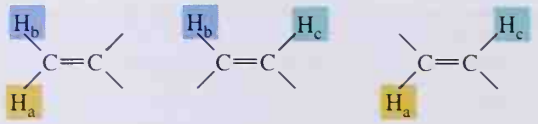


H_b and H_c are nonequivalent and give separate signals. To understand why H_a and H_b are also nonequivalent, apply the mental test of substitution of chlorine (Section 2.3C) for each in turn. Substitution of chlorine for H_b gives a *trans*-alkene, whereas substitution of chlorine for H_a gives a *cis*-alkene. The *trans*-alkene and *cis*-alkene are different compounds, and, therefore, H_a and H_b are nonequivalent hydrogens; each gives a separate signal and each splits the other.



The splitting pattern observed in the ^{1}H-NMR spectrum of vinyl acetate (Figure 13.17) is typical of monosubstituted alkenes. The singlet at δ 2.12 represents the three hydrogens of the methyl group. The terminal vinylic hydrogens appear at δ 4.58 and δ 4.90. The internal vinylic hydrogen, which normally appears in the range of δ 5.2 to 5.7, is shifted farther downfield to δ 7.30 by the adjacent electronegative oxygen atom of the ester.

Coupling constants are generally largest for *trans*-vinylic hydrogens, and it is often possible to distinguish between *cis* and *trans* alkenes by an analysis of their coupling constants.



If the value of J is less than 10 Hz, then you can say with confidence that the alkene is *cis*. If the value of J is greater than 15 Hz, you can say with confidence that the alkene is *trans*. For intermediate coupling constants, it is necessary to determine the ^{1}H-NMR spectrum of each isomer; the one with the larger value of J is the *trans*-alkene; the one with the smaller value is the *cis*-alkene.

As shown in the graphical analysis of the spectrum of vinyl acetate (Figure 13.18), the coupling constant J_{ac}*(trans)* has the largest value, J_{bc}*(cis)* is intermediate, and J_{ab} has the smallest value.

The sp^2-hybridized carbons of alkenes come into resonance in ^{13}C-NMR spectroscopy in the range δ 100 to 150 (Table 13.10), which is considerably downfield from the reso-

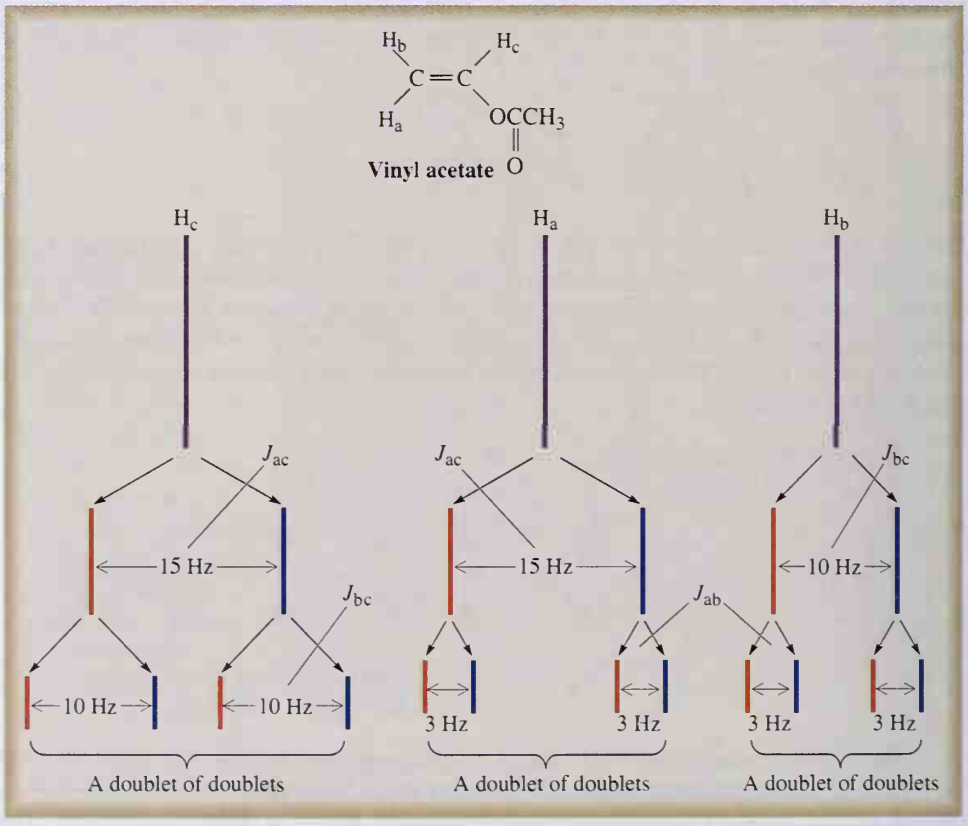
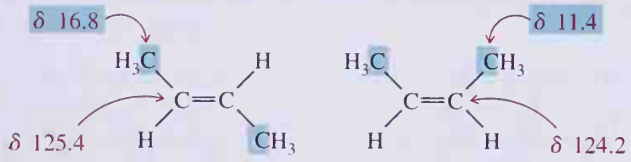


Figure 13.18
Graphical analysis of the spin-spin splitting patterns of the three vinylic hydrogens in vinyl acetate. The largest coupling constant, J_{ac} (15 Hz), is that for the trans vinylic hydrogens. The smallest coupling constant, J_{ab} (3 Hz), is that for the terminal vinylic hydrogens.

nances of sp^3-hybridized carbons. It is often possible to distinguish between *cis* and *trans* alkenes based on the chemical shifts of sp^3-hybridized carbons on the double bond. As seen in the *cis* and *trans* isomers of 2-butene, the chemical shift of sp^3-hybridized carbons *trans* on C=C is greater by approximately δ 5 than the chemical shift of sp^3-hybridized carbons *cis* on C=C.



trans-2-Butene *cis*-2-Butene

C. Alcohols

The chemical shift of a hydroxyl hydrogen in an ^{1}H-NMR spectrum is variable and depends on the purity of the sample, the solvent, and the temperature. It normally appears in the range δ 2.0 to 6.0, but depending on experimental conditions, it may appear as high as δ 0.5. Hydrogens on the carbon bearing the —OH group are deshielded by the electron-withdrawing inductive effect of the hydroxyl group and their absorptions typically appear in the range δ 3.5 to 4.5. Shown in Figure 13.19 is the ^{1}H-NMR spectrum of 1-propanol. This spectrum consists of four signals. The hydroxyl hydrogen appears at δ 3.20 as a narrowly spaced triplet. Hydrogens on the oxygen-bearing carbon in 1-propanol appear as a narrowly spaced multiplet at δ 3.60. Spin-spin splitting between the hydrogen on O—H and its neighbors on the adjacent —CH_2— group is seen in the ^{1}H-NMR spectrum of 1-propanol. More commonly, however, this splitting is rarely seen. The reason is that most samples of alcohol contain traces of acid, base, or other impurities that catalyze hydrogen exchange between —OH groups. Under ordinary conditions at room temperature, the rate of exchange of hydroxyl hydrogens is approximately 10^5 hydrogens/s which means that the

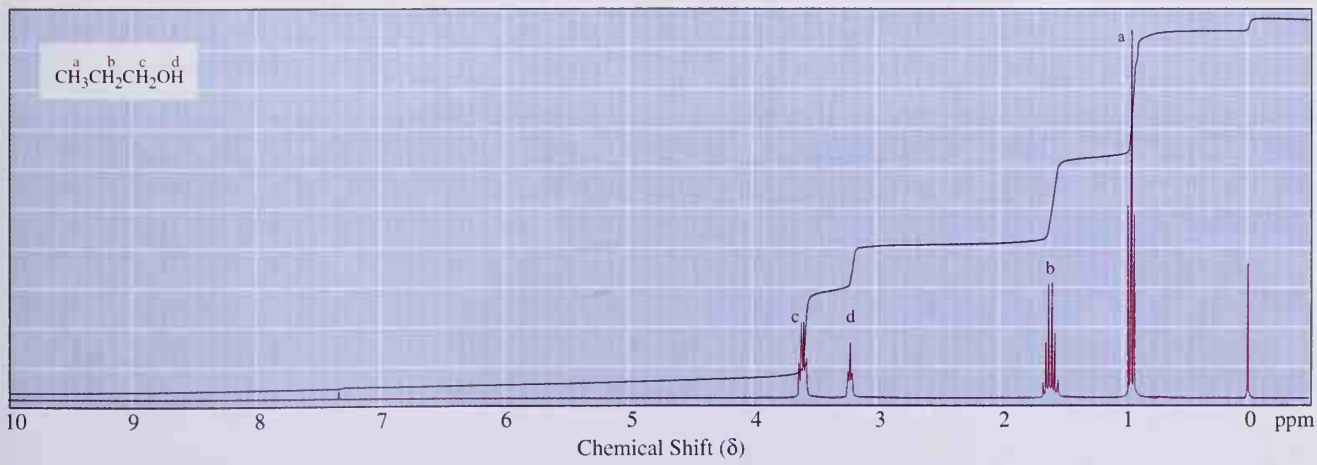
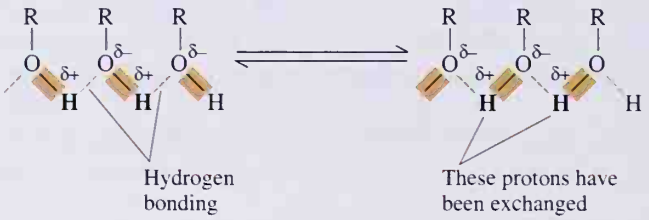


Figure 13.19
^{1}H-NMR spectrum of 1-propanol.

average time a hydrogen is bonded to a particular oxygen is 10^{-5} s. The time required for a nuclear transition to occur and to be recorded is approximately 10^{-2} to 10^{-3} s. Thus, over the time scale of an NMR measurement, a hydroxyl hydrogen "sees" the spins of adjacent hydrogens only as a single time-averaged configuration. The time average of spin configurations $+\frac{1}{2}$ and $-\frac{1}{2}$ is zero, which means that, because of the hydroxyl hydrogen's rapid exchange rate, it senses homogeneity in the local field, and its signal is unsplit.



D. Ethers

The most distinctive feature of the ^{1}H-NMR spectrum of ethers is the chemical shift of hydrogens on carbon attached to the ether oxygen. Resonance signals for this type of hydrogen fall in the range δ 3.3 to 4.0, which corresponds to a downfield shift of approximately 2.4 units compared with their normal position in alkanes. In this regard, chemical shifts of **H**—C—O— hydrogens in ethers are similar to those seen for comparable hydrogens in alcohols, **H**—C—OH. Shown in Figure 13.20 is the ^{1}H-NMR spectrum of 3-methoxypropanenitrile along with an assignment of chemical shifts. The singlet —CH_3 signal is shifted downfield to δ 3.40 from its normal position of δ 1.00 in an alkane.

13.15 Solving NMR Problems

One of the first steps in determining molecular structure is establishing the molecular formula. In the past, this was most commonly done by elemental analysis, combustion to determine percent composition, and so forth. More commonly today, molecular weight and

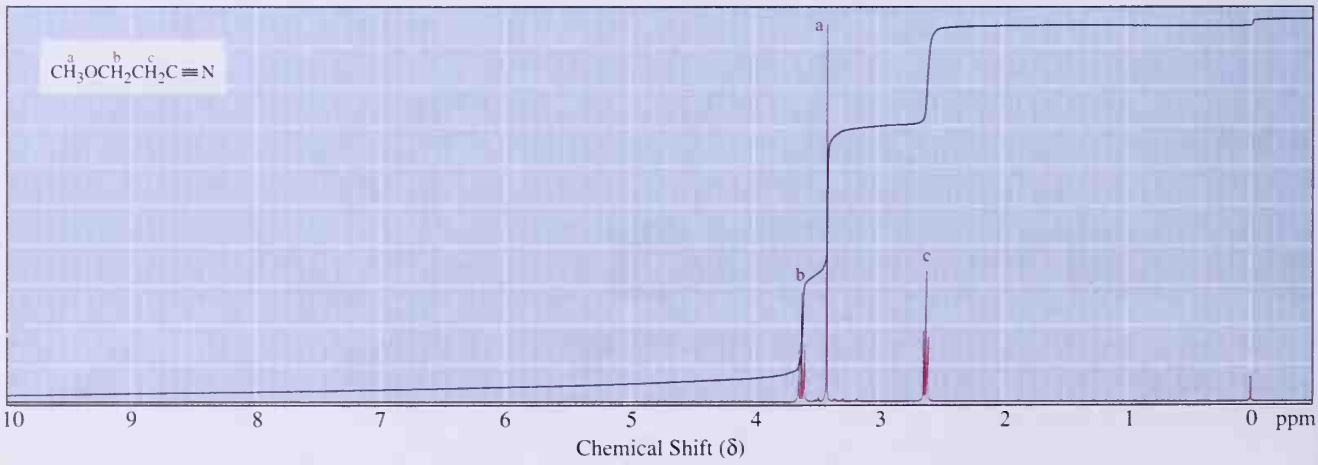


Figure 13.20
^{1}H-NMR spectrum of 3-methoxypropionitrile.

molecular formula are determined by mass spectrometry (Chapter 12). In the examples that follow, we assume that the molecular formula of any unknown compound has already been determined, and we proceed from there using spectral analysis to determine a structural formula.

A. Index of Hydrogen Deficiency

Valuable information about the structural formula of an unknown compound can be obtained from inspection of its molecular formula. In addition to learning the number of atoms of carbon, hydrogen, oxygen, nitrogen, and so on in the molecule of the compound, we can also determine what is called its index of hydrogen deficiency. The **index of hydrogen deficiency** is the number of rings and pi bonds in a molecule and is determined by comparing the number of hydrogens in the molecular formula of a compound of unknown structure with the number of hydrogens in a **reference compound** of the same number of carbon atoms and with no rings or pi bonds. The molecular formula of a reference hydrocarbon is C_nH_{2n+2} (Section 2.1).

$$\text{Index of hydrogen of deficiency} = \frac{H_{\text{reference}} - H_{\text{molecule}}}{2}$$

EXAMPLE 13.7

1-Hexene has the molecular formula C_6H_{12}. Calculate the index of hydrogen deficiency for 1-hexene, and account for this deficiency by reference to its structural formula.

Solution

The molecular formula of the reference hydrocarbon of six carbon atoms is C_6H_{14}. The index of hydrogen deficiency of 1-hexene $(14 - 12)/2 = 1$ and is accounted for by the one pi bond in 1-hexene.

PROBLEM 13.7

Calculate the index of hydrogen deficiency of cyclohexene, and account for this deficiency by reference to its structural formula.

To determine the molecular formula for a reference compound containing elements besides carbon and hydrogen, write the formula of the reference hydrocarbon, add other elements to the reference hydrocarbon, and make the following adjustments to the number of hydrogen atoms:

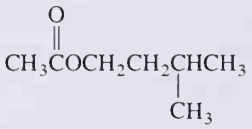
1. For each element of Group VII (F, Cl, Br, I) added to the reference hydrocarbon, subtract one hydrogen; halogen substitutes for hydrogen and reduces the number of hydrogens by one per halogen.
2. No correction is necessary for addition of divalent elements of Group VI (O, S, Se) to the reference hydrocarbon. Insertion of a divalent Group VI element into a reference hydrocarbon does not change the number of hydrogens.
3. For each trivalent element of Group V (N, P, As) added to the formula of the reference hydrocarbon, add one hydrogen. Insertion of a trivalent Group V element adds one hydrogen to the molecular formula of the reference compound.

EXAMPLE 13.8

Isopentyl acetate, a compound with a banana-like odor, is a component of the alarm pheromone of honey bees. The molecular formula of isopentyl acetate is $C_7H_{14}O_2$. Calculate the index of hydrogen deficiency of this compound.

Solution

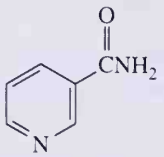
The molecular formula of the reference hydrocarbon is C_7H_{16}. Adding oxygens to this formula does not require any correction in the number of hydrogens. The molecular formula of the reference compound is $C_7H_{16}O_2$, and the index of hydrogen deficiency is $(16 - 14)/2 = 1$, indicating either one ring or one pi bond. Following is the structural formula of isopentyl acetate. It contains one pi bond, in this case, a carbon-oxygen double bond.



Isopentyl acetate

PROBLEM 13.8

The index of hydrogen deficiency of niacin is 5. Account for this index of hydrogen deficiency by reference to the structural formula of niacin.



Nicotinamide
(Niacin)

B. From a Spectrum to a Structural Formula

In practice, rarely does a determination of molecular structure rest on NMR data alone. Invariably there is also information about a compound from its physical properties, types of chemical reactions it undergoes or does not undergo, the reaction sequence by which it might have been synthesized, as well as other spectral data. To begin with, we concentrate on ^{1}H-NMR information. The following steps may prove helpful as a system for approaching spectral problems.

Step 1: **Molecular formula and index of hydrogen deficiency.** Examine the molecular formula, calculate the index of hydrogen deficiency, and deduce what information you can about the presence or absence of rings or pi bonds.

Step 2: **The number of signals.** Count the number of signals to arrive at a minimum number of different types of hydrogens in the compound.

Step 3: **Line of integration.** If a line of integration is given, use it and the molecular formula to determine the number of hydrogens giving rise to each signal.

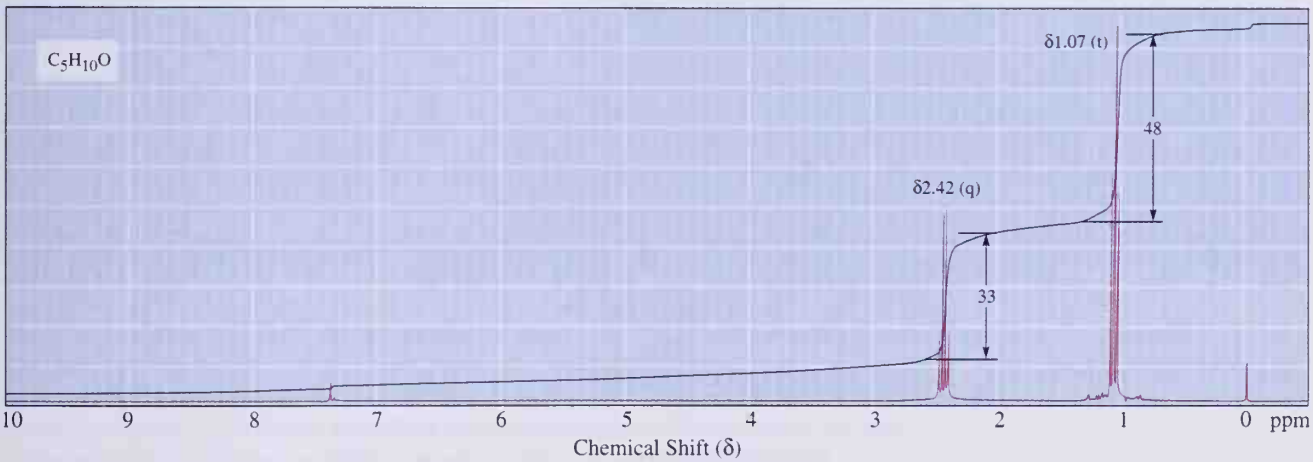
Step 4: **Pattern of chemical shifts.** Examine the NMR spectrum for signals characteristic of the following types of equivalent hydrogens. Keep in mind that these are broad ranges and that hydrogens of each type may be shifted either farther upfield or farther downfield depending on details of molecular structure.

δ 0.9 to 1.9	Alkyl hydrogens
δ 2.1 to 2.6	Hydrogens on a carbon adjacent to a carbonyl group
δ 3.4 to 4.3	Hydrogens on a carbon adjacent to oxygen
δ 4.6 to 5.9	Vinylic hydrogens
δ 9.0 to 10.5	Aldehyde hydrogens
δ 10 to 13	Carboxyl hydrogens

Step 5: **Spin-spin splitting patterns.** Examine splitting patterns for information about the number of nearest nonequivalent hydrogen neighbors.

Step 6: **Structural formula.** Write a structural formula consistent with the previous information.

Spectral Problem 1: Molecular formula $C_5H_{10}O$



Analysis of Spectral Problem 1

Step 1: **Molecular formula and index of hydrogen deficiency.** The reference compound is $C_5H_{12}O$, and, therefore, the index of hydrogen deficiency is 1; the molecule contains either one ring or one pi bond.

Step 2: **Number of signals.** There are two signals (a triplet and a quartet), and, therefore, two sets of equivalent hydrogens.

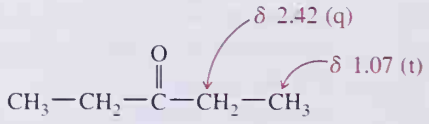
Step 3: **Line of integration.** From the line of integration, calculate that the numbers of hydrogens giving rise to the two signals are in the ratio 3 : 2. Because there are ten hydrogens, they must be in the ratio of 6 : 4.

Step 4: **Pattern of chemical shifts.** The signal at δ 1.07 is in the alkyl region and, based on its chemical shift, is most probably a methyl group. No signal occurs in the region δ 4.6 to 5.9; there are no vinylic hydrogens. If a carbon-carbon double bond is in the molecule, no hydrogens are on it (that is, it is tetrasubstituted).

Step 5: **Splitting pattern.** The methyl signal at δ 1.07 is split into a triplet (t); it must have two neighbors, indicating $—CH_2CH_3$. The signal at δ 2.42 is split into a quartet (q); it must have three neighbors. An ethyl group accounts for the two

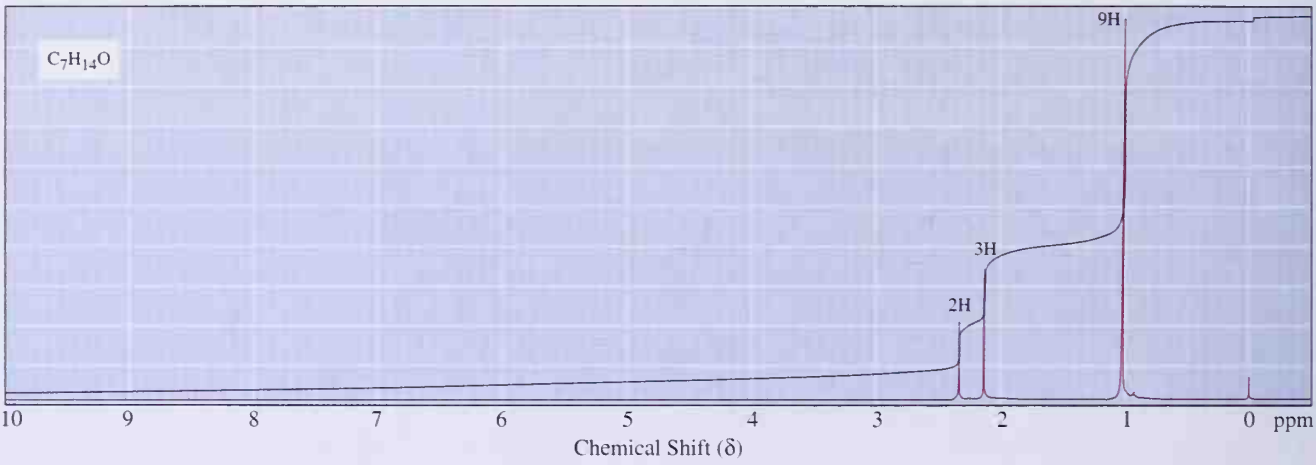
signals. No other signals occur in the spectrum, and, therefore, there are no other types of hydrogens in the molecule.

Step 6: **Structural formula.** Put this information together to arrive at the following structural formula. The chemical shift of the methylene group (—CH_2—) at δ 2.42 is consistent with an alkyl group adjacent to a carbonyl group.



3-Pentanone

Spectral Problem 2: Molecular formula $C_7H_{14}O$.



Analysis of Spectral Problem 2

Step 1: **Molecular formula and index of hydrogen deficiency.** Calculate an index of hydrogen deficiency of 1; the compound contains one ring or one pi bond.

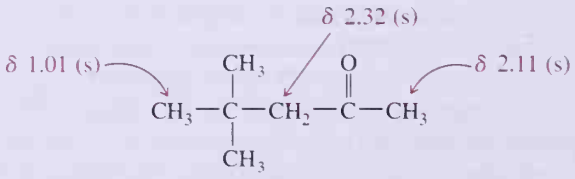
Step 2: **Number of signals.** There are three signals and, therefore, three sets of equivalent hydrogens.

Step 3: **Line of integration.** Reading from left to right, peaks are in the ratio 2H : 3H : 9H.

Step 4: **Pattern of chemical shifts.** The singlet at δ 1.01 is characteristic of a methyl group adjacent to an sp^3 hybridized carbon. The singlets at δ 2.11 and δ 2.32 are characteristic of an alkyl group adjacent to a carbonyl group.

Step 5: **Splitting pattern.** All signals are singlets (s).

Step 6: **Structural formula.** The compound is 4,4-dimethyl-2-pentanone.



4,4-Dimethyl-2-pentanone

SUMMARY

Electromagnetic radiation (Section 13.1) can be described in terms of its **wavelength** (λ) and its **frequency** (ν). Frequency is reported in **Hz** (hertz). An alternative way to describe electromangetic radiation is in terms of its energy where $E = h\nu$.

Molecular spectroscopy (Section 13.2) is the experimental process of measuring which frequencies of radiation are absorbed or emitted by a substance and then attempting to correlate patterns of energy absorption or emission with details of molecular structure. Interaction of molecules with **radio-frequency radiation** gives us information about nuclear spin energy levels; interaction with **infrared radiation** gives us information about vibrational energy levels, and interaction with **ultraviolet-visible radiation** gives us information about electronic energy levels of pi and nonbonding electrons.

^{1}H and ^{13}C have a **nuclear spin quantum number** of $\frac{1}{2}$ and allowed **nuclear spin states** of $+\frac{1}{2}$ and $-\frac{1}{2}$ (Section 13.3). In the presence of an **applied magnetic field, B_0,** nuclei with spin $+\frac{1}{2}$ are aligned with the applied field and in the lower energy state; nuclei with spin $-\frac{1}{2}$ are aligned against the applied field and in the higher energy state (Section 13.4).

When a spinning nucleus is placed in an applied magnetic field (Section 13.5), it becomes aligned in an allowed spin state and begins to **precess** about an axis parallel to the direction of the applied field. **Resonance** is the absorption of electromagnetic radiation by a precessing nucleus and the resulting "flip" of its nuclear spin from a lower energy spin state to a higher energy spin state. An NMR spectrometer records resonance as a **signal.**

The experimental conditions required to cause nuclei to resonate are affected by the local chemical and magnetic environment. Electrons also have spin (Section 13.5) and create local magnetic fields that **shield** nuclei from the applied field. Any factors that increase the exposure of nuclei to an applied field are said to **deshield** them.

The resonance signals in ^{1}H-NMR spectra are reported by how far they are shifted from the resonance signal of the 12 equivalent hydrogens in **tetramethylsilane (TMS).** The resonance signals in ^{13}C-NMR spectra are reported by how far they are shifted from the resonance signal of the four equivalent carbons in tetramethylsilane (TMS). **Chemical shift, δ** (Section 13.5), is defined as the frequency shift from TMS times 10^6 divided by the operating frequency of the spectrometer. Because of the manner in which chemical shift is defined, it is independent of the instrument operating frequency.

All **equivalent hydrogens** within a molecule have identical chemical shifts (Section 13.7). The chemical shift of a particular set of equivalent hydrogens depends primarily on three factors: (a) Adjacent electronegative atoms have a deshielding effect. (b) The greater the percent of s character in a hybrid orbital, the greater the deshielding effect of the atom to which the orbital belongs. And (c) induced local magnetic fields in pi bonds either add to or subtract from the applied field. The area of an ^{1}H-NMR signal is proportional to the number of equivalent hydrogens giving rise to that signal (Section 13.8).

In **spin-spin splitting,** the ^{1}H-NMR signal from one hydrogen or set of equivalent hydrogens is split by the influence of nonequivalent hydrogens on the same or adjacent atoms (Section 13.10). According to the **$(n + 1)$ rule,** if a hydrogen has n hydrogens nonequivalent to it but equivalent among themselves on the same or adjacent atom(s), its ^{1}H-NMR signal is split into $(n + 1)$ lines, or peaks. Splitting patterns are commonly referred to as singlets (s), doublets (d), triplets (t), quartets (q), quintets, and multiplets (m). Spin-spin splitting has its origin in the patterns of nuclear alignments of adjacent hydrogens. The ratios of peaks in a multiplet can be predicted from an analysis of spin combinations for adjacent hydrogens (Table 13.9) or from the mnemonic device called **Pascal's triangle** (Section 13.11).

A **coupling constant** (J) is the distance between adjacent peaks in a spin-spin split signal and is reported in hertz (Section 13.12). The value of J depends only on internal forces within a molecule and is independent of machine operating parameters.

^{13}C-NMR spectra (Section 13.13) are commonly recorded in a hydrogen-decoupled instrumental mode. In this mode, all ^{13}C signals appear as singlets.

The chemical shifts of **vinylic hydrogens** in ^{1}H-NMR spectra appear in the range δ 4.6 to 5.7 (Section 13.14A). Coupling constants for *trans*-vinylic hydrogens are typically larger (J = 11–18 Hz) than those for *cis*-vinylic hydrogens (J = 5–14 Hz). The ^{13}C-NMR chemical shifts of sp^2-hybridized carbons in alkenes appear in the range δ 100 to 150 and are considerably downfield from signals from sp^3-hybridized carbons. Chemical shifts of hydroxyl hydrogens in ^{1}H-NMR spectra (Section 13.14B) are highly variable but generally fall in the range δ 2.0 to 6.0. Because rapid exchange occurs between hydrogens from one hydroxyl group to another, most hydroxyl hydrogens show no evidence of spin-spin coupling with hydrogens on adjacent primary or secondary carbons.

ADDITIONAL PROBLEMS

Index of Hydrogen Deficiency

13.9 Complete the following table:

Class of Compound	Molecular Formula	Index of Hydrogen Deficiency	Reason for Hydrogen Deficiency
alkane	C_nH_{2n+2}	0	(reference hydrocarbon)
alkene	C_nH_{2n}	1	one pi bond
alkyne	_____	_____	_____
alkadiene	_____	_____	_____
cycloalkane	_____	_____	_____
cycloalkene	_____	_____	_____
bicycloalkane	_____	_____	_____

13.10 Calculate the index of hydrogen deficiency of the following compounds:

(a) Aspirin: $C_9H_8O_4$ **(b)** Ascorbic acid (vitamin C): $C_6H_8O_6$

(c) Pyridine: C_5H_5N **(d)** Urea: CH_4N_2O

(e) Cholesterol: $C_{27}H_{46}O$ **(f)** Trichloroacetic acid: $C_2HCl_3O_2$

Interpretation of ^{1}H-NMR and ^{13}C-NMR Spectra

13.11 A radio frequency of 282 MHz is required to spin-flip a fluorine-19 nucleus in an applied field of 7.05 T. Calculate the energy (calories per mole) associated with this transition.

13.12 Complete the following table. Which nucleus requires the least energy to flip its spin at this applied field? Which nucleus requires the most energy?

Nucleus	Applied Field (T)	Radio Frequency (MHz)	Energy (cal/mol)
^{1}H	7.05	300	_____
^{13}C	7.05	75.5	_____
^{19}F	7.05	282	_____

13.13 The natural abundance of ^{13}C is only 1.1%. Furthermore, its sensitivity in NMR spectroscopy (a measure of the energy difference between a spin aligned with or against an external magnetic field) is only 1.6% that of ^{1}H. What are the relative signal intensities expected for the ^{1}H-NMR and ^{13}C-NMR spectra of the same sample of $Si(CH_3)_4$?

13.14 The percent *s* character of carbon participating in a C—H bond can be established by measuring the ^{13}C-^{1}H coupling constant and using the relationship

$$\text{Percent } s \text{ charater} = 0.2J(^{13}\text{C}—^1\text{H})$$

The ^{13}C—^{1}H coupling constant observed for methane, for example, is 125 Hz, which gives 25% *s* character, the value expected for an sp^3-hybridized carbon atom.

(a) Calculate the expected ^{13}C—^{1}H coupling constant in ethylene and acetylene.

(b) In cyclopropane, the $^{13}C—^{1}H$ coupling constant is 160 Hz. What is the hybridization of carbon in cyclopropane?

13.15 ^{13}C-NMR spectroscopy of "labeled bonds" can be used to follow connectivity changes in chemical reactions. Suppose you carried out a Diels-Alder reaction with $H_2C{=}{}^{13}CH—{}^{13}CH{=}CH_2$ and ethylene. Show how ^{13}C-NMR spectroscopy can be used to establish that the 2,3-bond of 1,3-butadiene remains intact in the cyclohexene product.

13.16 Following are structural formulas for three constitutional isomers of molecular formula $C_7H_{16}O$ and three sets of ^{13}C-NMR spectral data. Assign each constitutional isomer its correct spectrum.

(a) $CH_3CH_2CH_2CH_2CH_2CH_2CH_2OH$

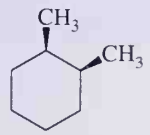
(b) $CH_3C(OH)(CH_3)CH_2CH_2CH_2CH_3$

(c) $CH_3CH_2C(OH)(CH_2CH_3)CH_2CH_3$

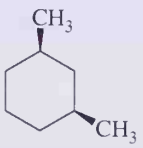
Spectrum 1:	Spectrum 2:	Spectrum 3:
74.66	70.97	62.93
30.54	43.74	32.79
7.73	29.21	31.86
	26.60	29.14
	23.27	25.75
	14.09	22.63
		14.08

13.17 Following are structural formulas for the *cis* isomers of 1,2-, 1,3-, and 1,4-dimethylcyclohexanes and three sets of ^{13}C-NMR spectral data. Assign each constitutional isomer its correct spectrum.

(a)



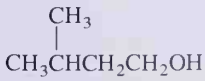
(b)



(c)

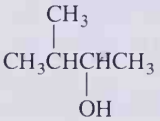
Spectrum 1:	Spectrum 2:	Spectrum 3:
31.35	34.20	44.60
30.67	31.30	35.14
20.85	23.56	32.88
	15.97	26.54
		23.01

13.18 The ^{13}C-NMR spectrum of 3-methyl-1-butanol shows four signals, indicating that there are four sets of nonequivalent carbon atoms. The ^{13}C-NMR spectrum of 3-methyl-2-butanol shows five signals, indicating five nonequivalent carbon atoms. How do you account for the presence of four signals in the spectrum 3-methyl-1-butanol but five signals in the spectrum of 3-methyl-2-butanol?



^{13}C-NMR (δ)
61.14 24.73
41.71 22.62

3-methyl-1-butanol



^{13}C-NMR (δ)
72.73 18.16
35.07 17.90
19.99

3-methyl-2-butanol

13.19 Following are structural formulas, dipole moments, and ^{1}H-NMR chemical shifts for acetonitrile, fluoromethane, and chloromethane.

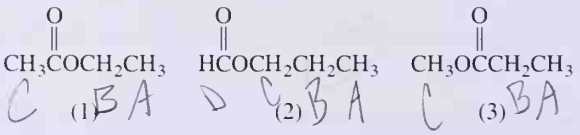
$CH_3—C\equiv N$	$CH_3—F$	$CH_3—Cl$
Acetonitrile	Fluoromethane	Chloromethane
3.92 D	1.85 D	1.87 D
δ 1.97	δ 4.26	δ 3.05

(a) How do you account for the fact that the dipole moments of fluoromethane and chloromethane are almost identical even though fluorine is considerably more electronegative than chlorine?

(b) How do you account for the fact that the dipole moment of acetonitrile is considerably greater than that of either fluoromethane or chloromethane?

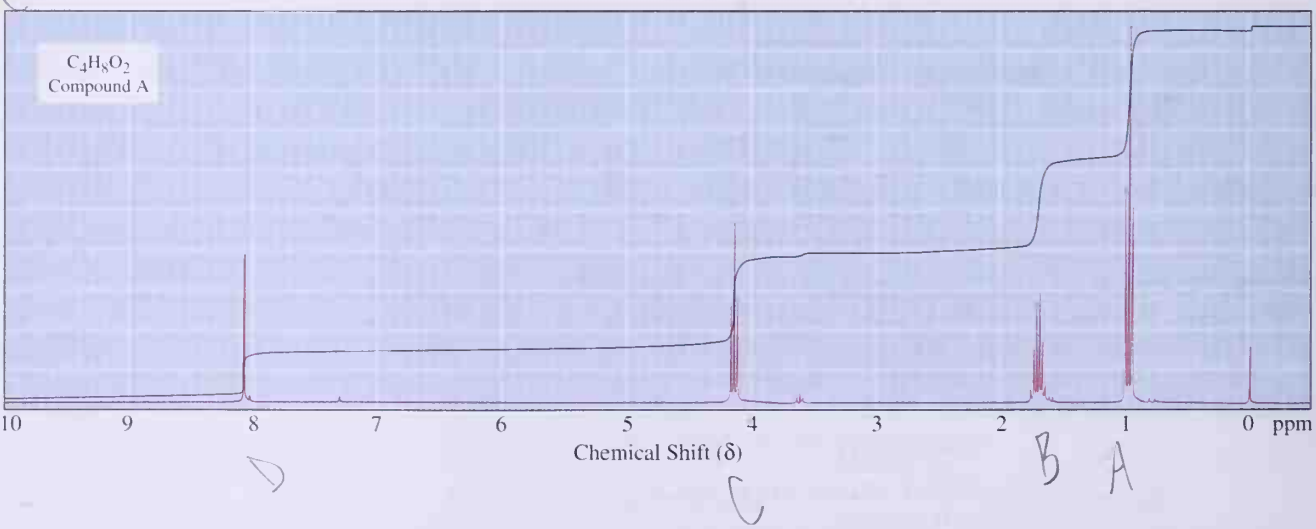
(c) How do you account for the fact that the chemical shift of the methyl hydrogens in acetonitrile is considerably less than that for either fluoromethane or chloromethane? *Hint:* Consider the magnetic induction in the pi system of acetonitrile and the orientation of this molecule in an applied magnetic field.

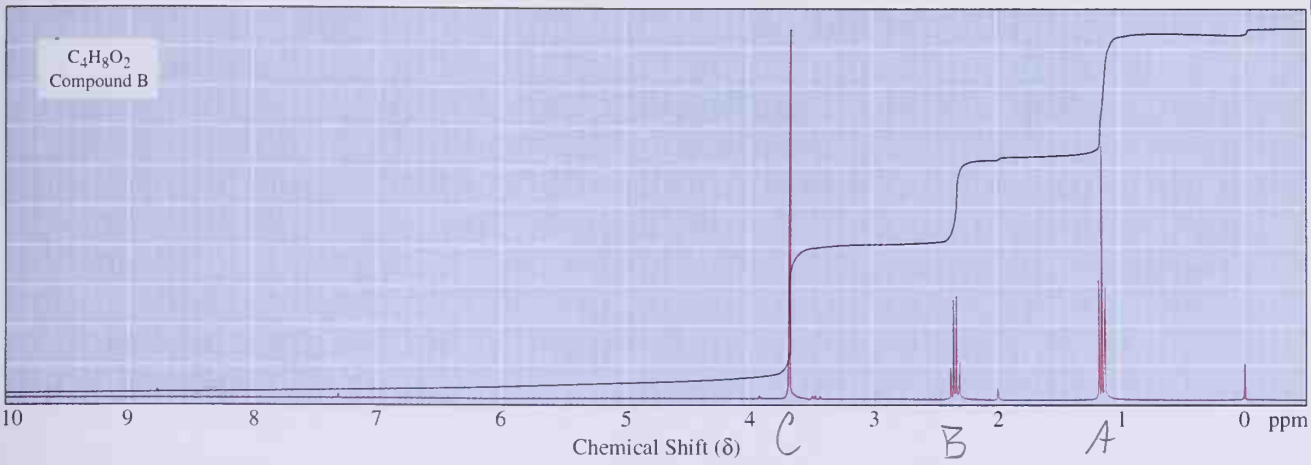
13.20 Following are three compounds of molecular formula $C_4H_8O_2$, and three ^{1}H-NMR spectra:

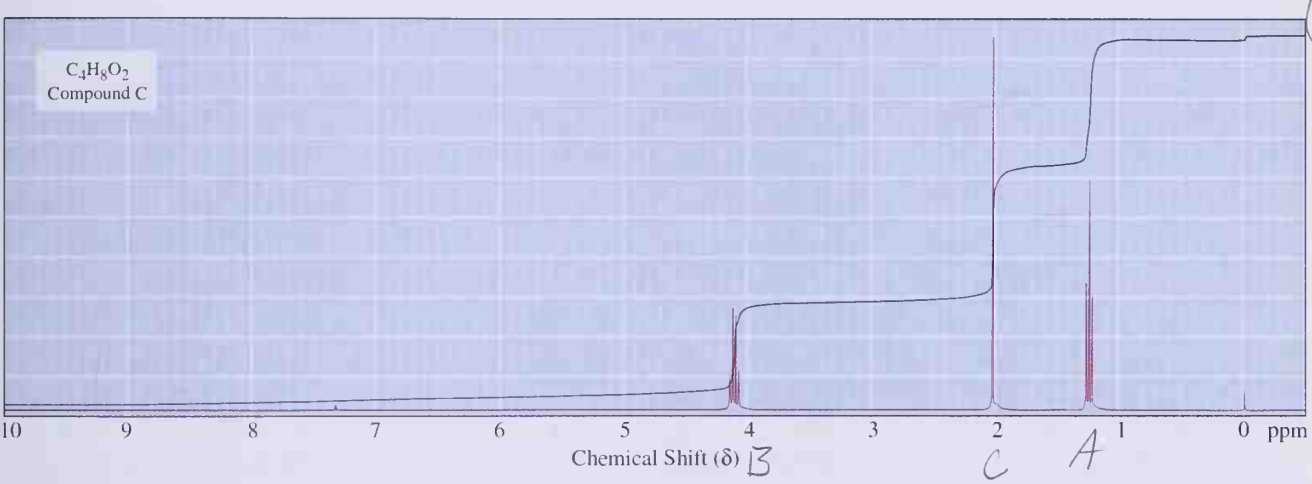


(a) Assign each compound its correct spectrum and assign all signals to their corresponding hydrogens.

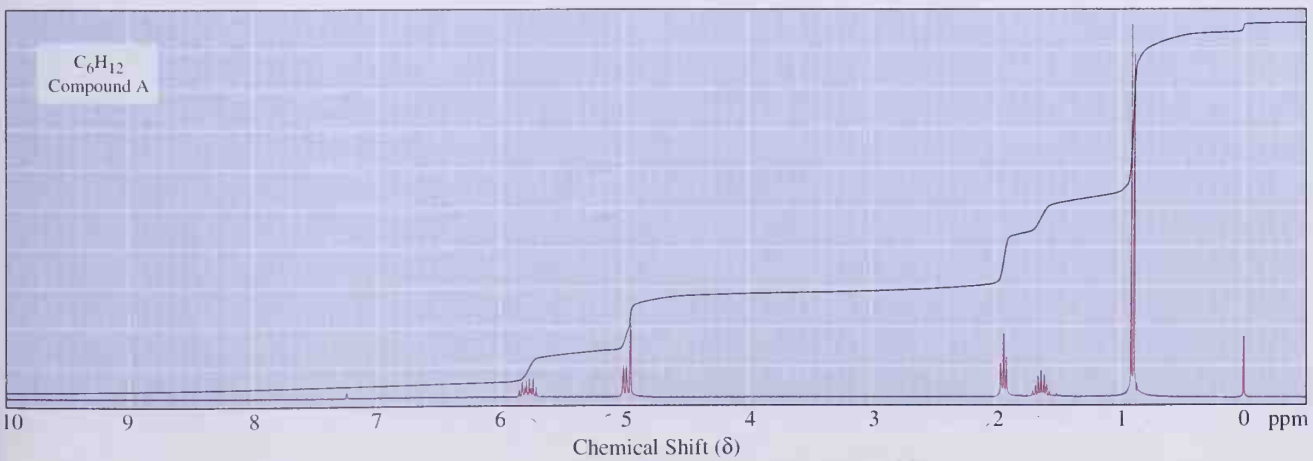
(b) From your study of these three compounds and spectra, begin to develop your own table of chemical shifts. For example, assign δ values to $H_3C—O$, to $—CH_2—O—$, and so forth.

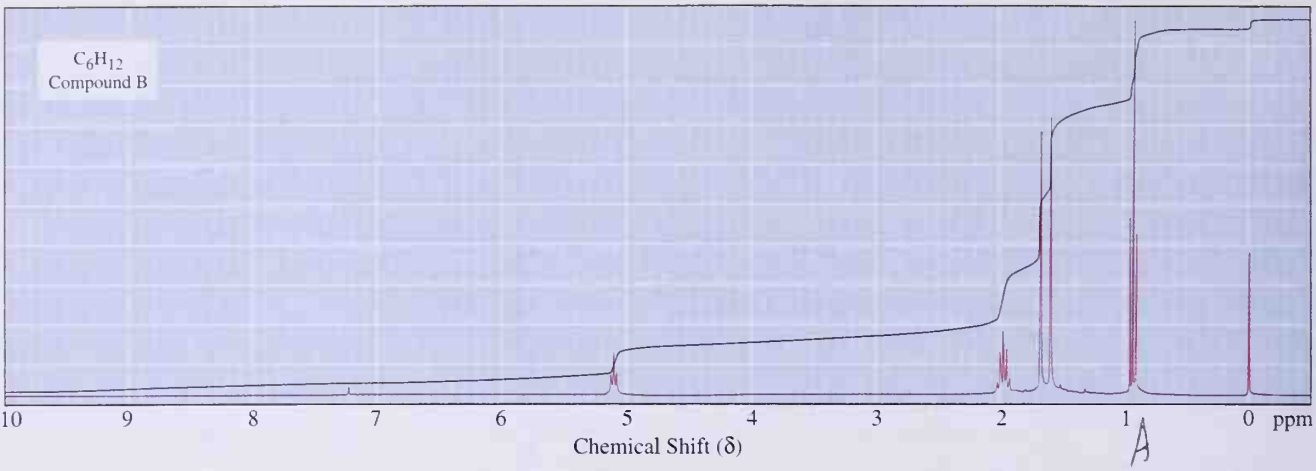


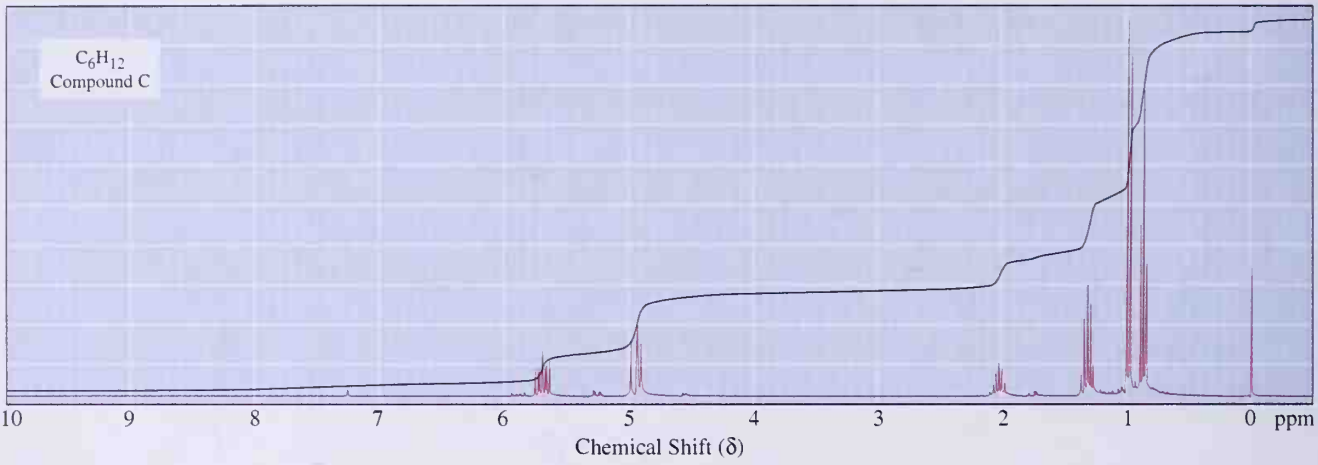




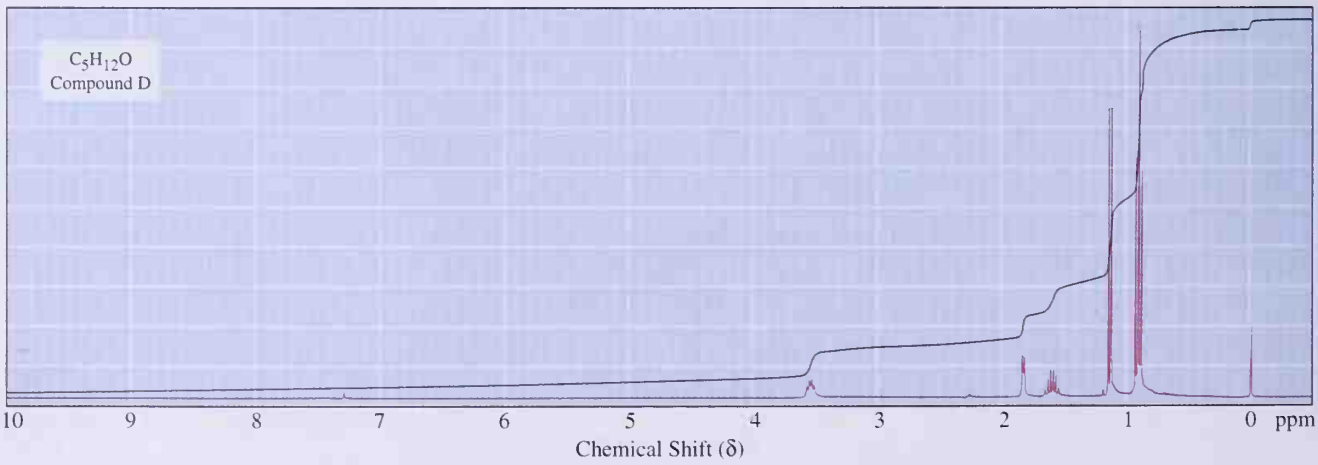
13.21 Following are ^{1}H-NMR spectra for compounds A, B, and C, each of molecular formula C_6H_{12}. Each readily decolorizes a solution of Br_2 in CCl_4 and also decolorizes aqueous $KMnO_4$ with formation of a brown precipitate of MnO_2. Deduce the structural formulas of compounds A, B, and C, and account for the observed patterns of spin-spin splitting.

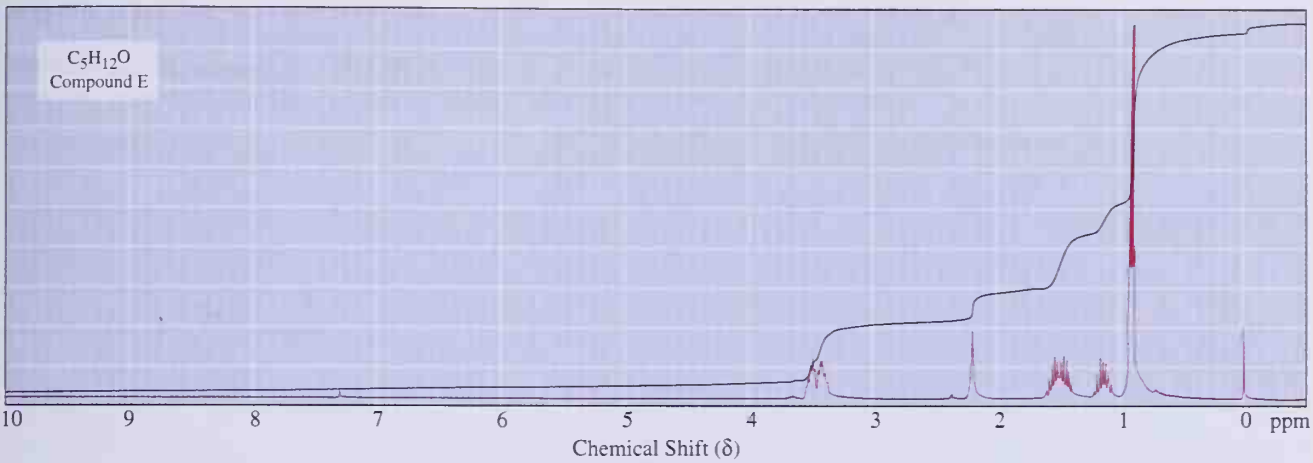


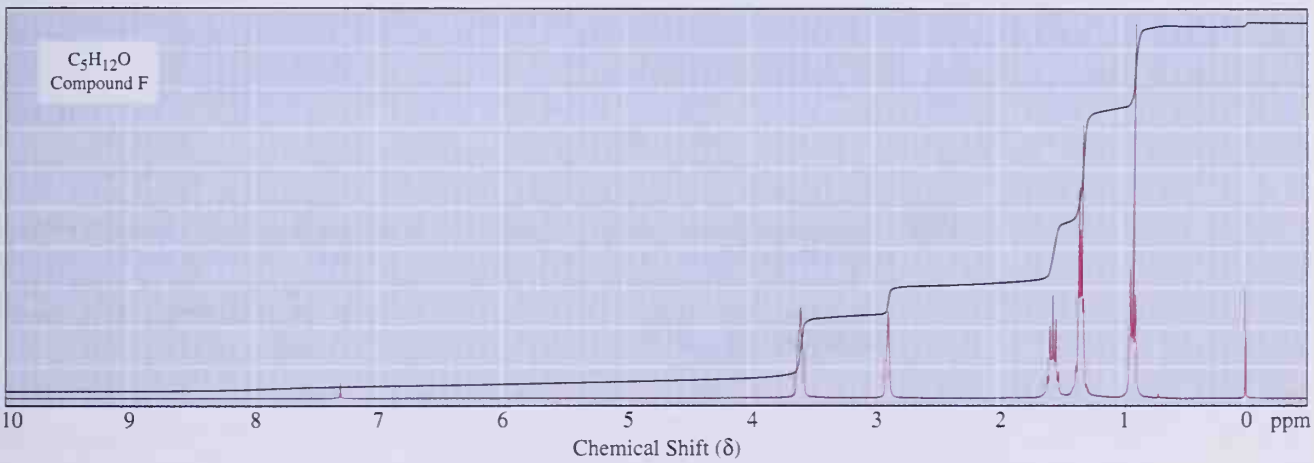




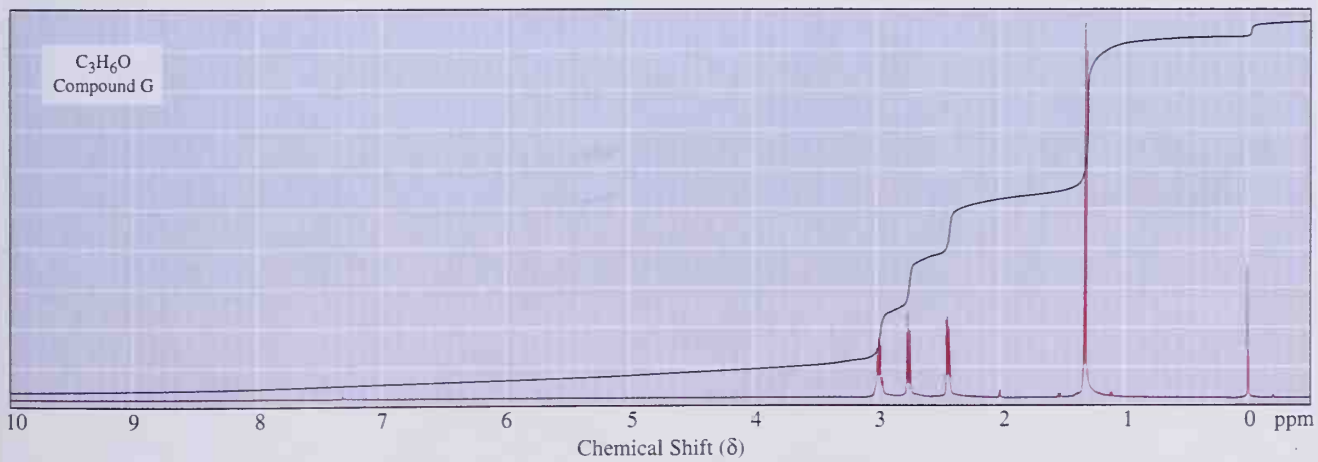
13.22 Following are ^{1}H-NMR spectra for compounds D, E, and F, each of molecular formula $C_5H_{12}O$. Each is a liquid at room temperature, slightly soluble in water, and reacts with sodium metal with the evolution of a gas. Deduce the structural formulas of compounds D, E, and F.



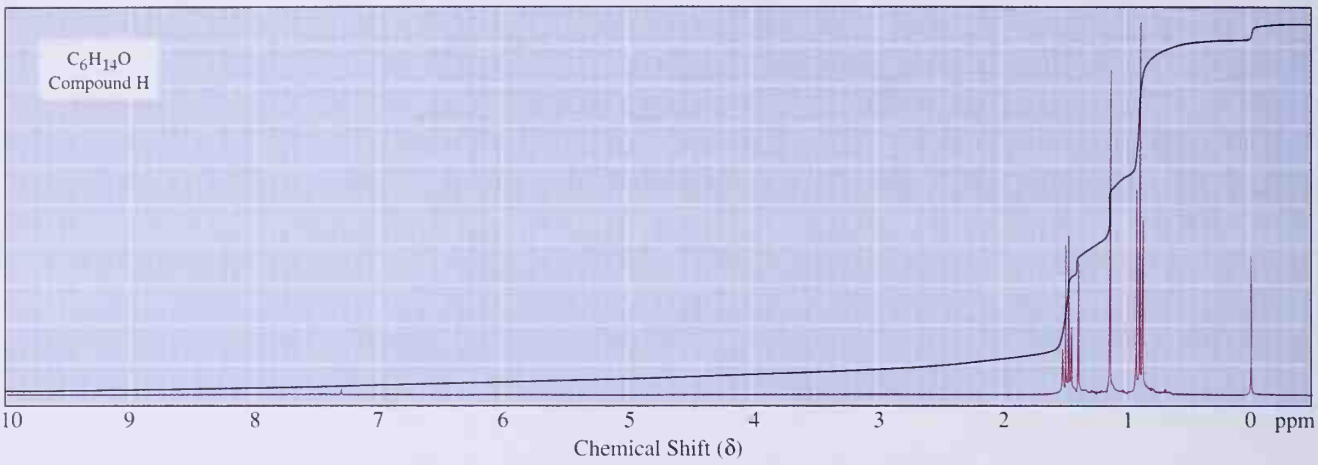




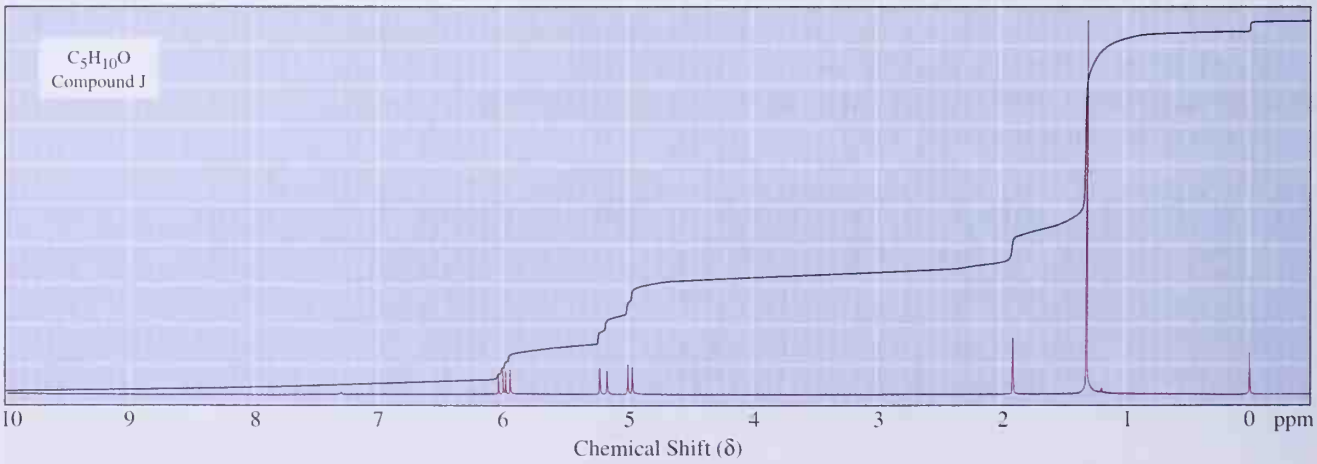
13.23 Propose a structural formula for compound G, molecular formula C_3H_6O, consistent with the following ^{1}H-NMR spectrum:



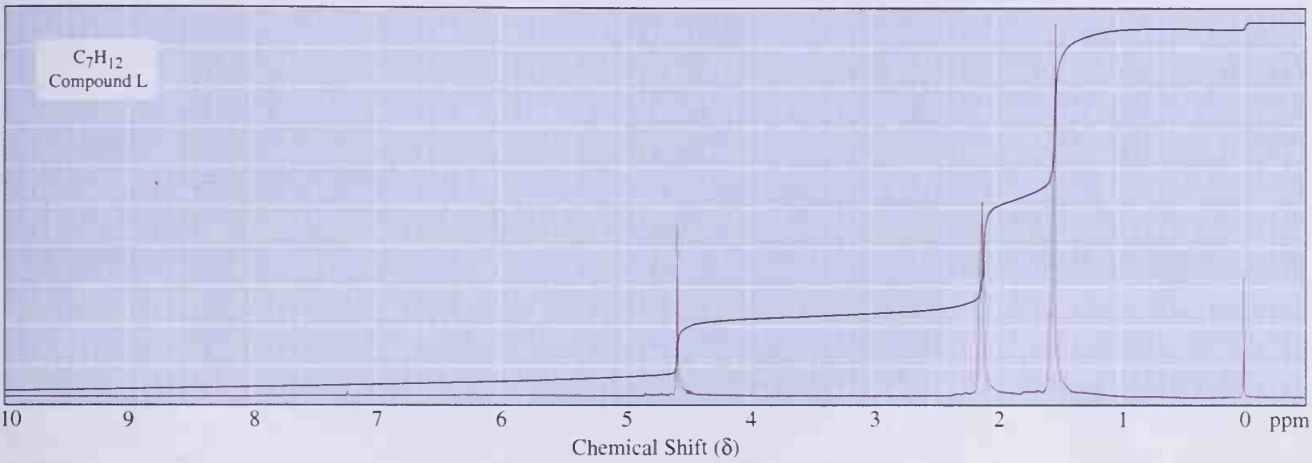
13.24 Compound H, molecular formula $C_6H_{14}O$, readily undergoes acid-catalyzed dehydration when warmed with phosphoric acid to give compound I, molecular formula C_6H_{12}, as the major organic product. Following is the ^{1}H-NMR spectrum of compound H. The ^{13}C-NMR spectrum of compound H shows peaks at 72.98, 33.72, 25.85, and 8.16. Deduce the structural formulas of compounds H and I.



13.25 Compound J, molecular formula $C_5H_{10}O$, readily decolorizes Br_2 in CCl_4, reacts with sodium metal with the evolution of a gas, and is converted by H_2 and Ni into compound K, molecular formula $C_5H_{12}O$. Following is the ^{1}H-NMR spectrum of compound J. The ^{13}C-NMR spectrum of compound J shows peaks at 146.12, 110.75, 71.05, and 29.38. Deduce the structural formulas of compounds J and K.



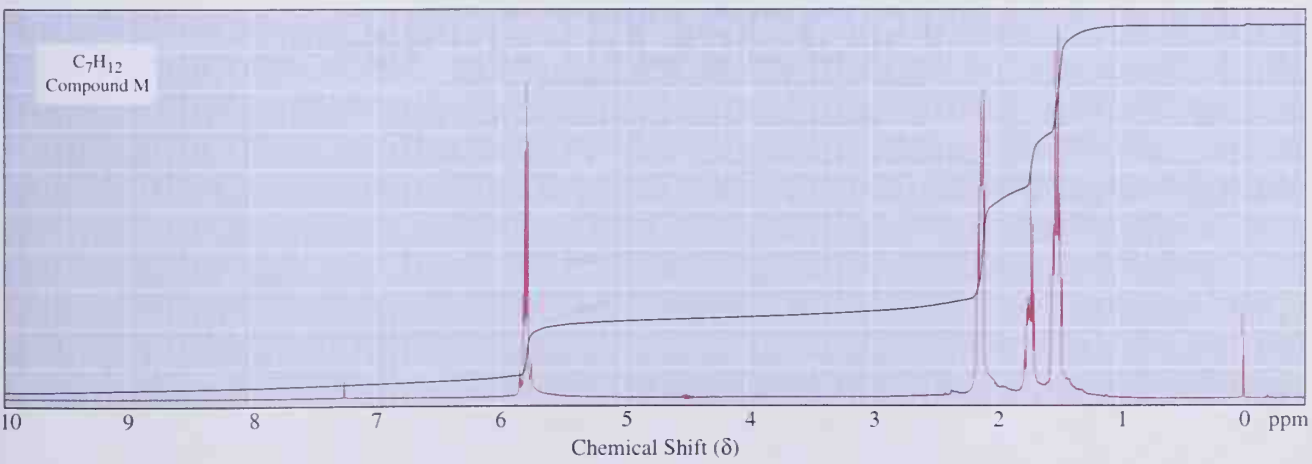
13.26 Following is the ^{1}H-NMR spectrum compound L, molecular formula C_7H_{12}. The ^{13}C-NMR spectrum of this compound shows peaks at 150.12, 106.43, 35.44, 28.36, and 26.36. Deduce the structural formula of compound L.

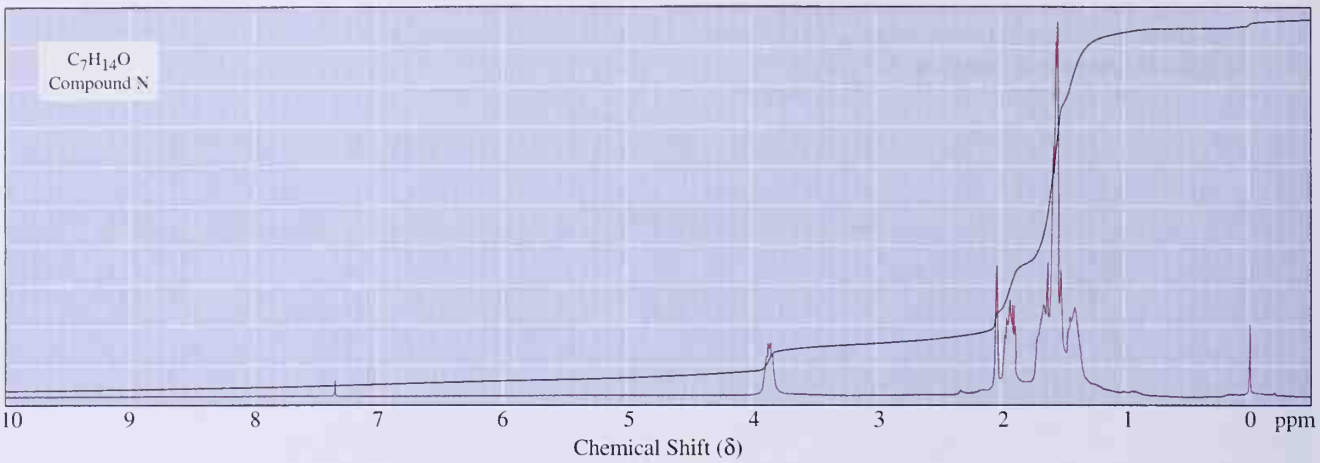


13.27 Treatment of compound M with BH_3 followed by H_2O_2 and NaOH gives compound N. Following are ^{1}H-NMR spectra for compounds M and N along with ^{13}C-NMR spectral data. From this information, deduce structural formulas for compounds M and N.

$$\underset{\text{(M)}}{C_7H_{12}} \xrightarrow[2.\ H_2O_2,\ NaOH]{1.\ BH_3} \underset{\text{(N)}}{C_7H_{14}O}$$

^{13}C-NMR	
(M)	(N)
132.38	72.71
32.12	37.59
29.14	28.13
27.45	22.68





13.28 Compound O is known to contain only C, H, and O. Its mass spectrum shows a weak molecular ion peak at M(102) and prominent peaks at *m/e* 87, 45, and 43. Its ^{1}H-NMR spectrum consists of two signals: δ 1.1 (doublet, 12H) and δ 3.6 (septet, 2H). Propose a structural formula for compound O consistent with this information.

13.29 Write structural formulas for the following compounds:

(a) $C_2H_4Br_2$: δ 2.5 (d, 3H) and 5.9 (q, 1H)

(b) $C_4H_8Cl_2$: δ 1.60 (d, 3H), 2.15 (m, 2H), 3.72 (t, 2H), and 4.27 (m, 1H)

(c) $C_5H_8Br_4$: δ 3.6 (s, 8H)

(d) C_4H_8O: δ 1.0 (t, 3H), 2.1 (s, 3H), and 2.4 (q, 2H)

(e) $C_4H_8O_2$: δ 1.2 (t, 3H), 2.1 (s, 3H), and 4.1 (q, 2H); contains an ester group

(f) $C_4H_8O_2$: δ 1.2 (t, 3H), 2.3 (q, 2H), and 3.6 (s, 3H); contains an ester group

(g) C_4H_9Br: δ 1.1 (d, 6H), 1.9 (m, 1H), and 3.4 (d, 2H)

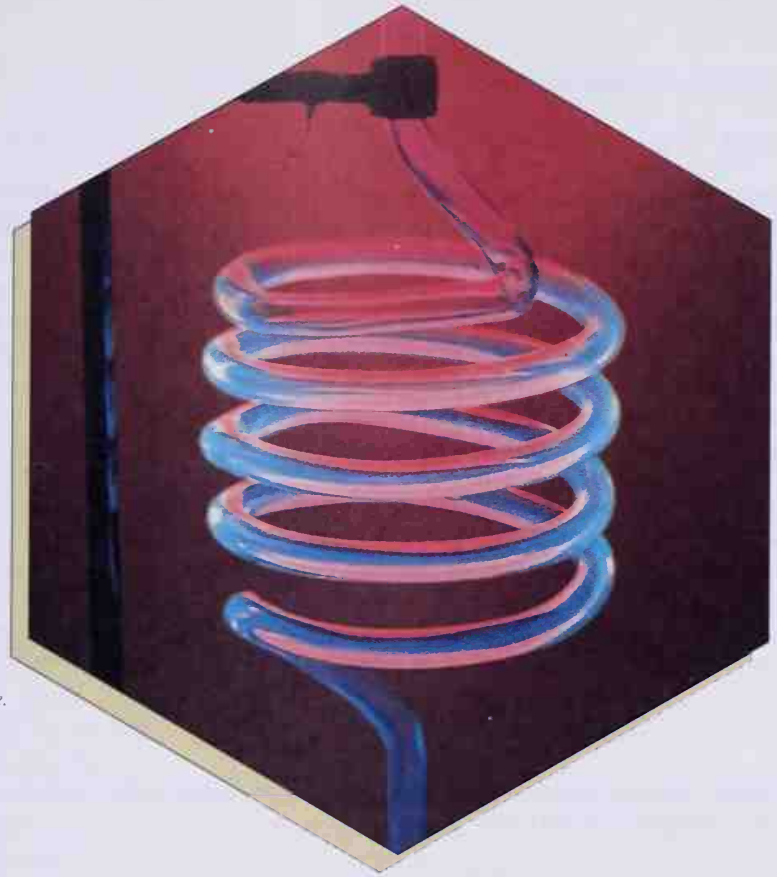
(h) $C_6H_{12}O_2$: δ 1.5 (s, 9H) and 2.0 (s, 3H)

(i) $C_7H_{14}O$: δ 0.9 (t, 6H), 1.6 (m, 4H), and 2.4 (t, 4H)

(j) $C_5H_{10}O_2$: δ 1.2 (d, 6H), 2.0 (s, 3H), and 5.0 (septet, 1H)

(k) $C_5H_{11}Br$: δ 1.1 (s, 9H) and 3.2 (s, 2H)

(l) $C_7H_{15}Cl$ δ 1.1 (s, 9H) and 1.6 (s, 6H)



Chemiluminescence.
(Charles D. Winters)

14

INFRARED AND ULTRAVIOLET-VISIBLE SPECTROSCOPY

Nuclear magnetic resonance spectroscopy gives us information about the number, kinds, and chemical environments of ^{1}H, ^{13}C, ^{19}F, ^{31}P, and other nuclei with a spin quantum number greater than zero. Infrared and ultraviolet-visible spectroscopy give us information about functional groups. By means of infrared spectroscopy, we can detect functional groups by the vibrations of the atoms constituting the functional group. Using ultraviolet-visible spectroscopy, we detect functional groups by the electronic transitions of their pi and nonbonding electrons.

14.1 Infrared Spectroscopy

Covalent bonds vibrate, that is, they bend and stretch just as if the atoms bonded together are joined by flexible springs. The energies required to excite transitions between vibrational states correspond to radiation in the infrared (IR) region of the electromagnetic spectrum (review Sections 13.1 and 13.2). In this section we study correlations between absorption of infrared radiation and molecular structure in order to understand how infrared spectroscopy is used as a tool for determination of molecular structure.

A. The Vibrational Infrared Spectrum

The infrared region of the electromagnetic spectrum (Table 13.2) extends from the upper end of the visible spectrum (approximately 0.80 μm) to the lower end of the microwave spectrum (wavelength 400 μm). We are concerned only with the portion of the infrared spectrum called the **vibrational infrared,** which extends from 2.5 μm to 25 μm.

Radiation in this region of the electromagnetic spectrum can be referred to by its wavelength (in micrometers) or its **wavenumber ($\bar{\nu}$)** in reciprocal centimeters (cm^{-1}).

$$\bar{\nu} = \frac{1}{\lambda\ (\text{cm})} = \frac{10{,}000}{\lambda\ (\mu\text{m})}$$

When expressed in wavenumbers, the vibrational region of the infrared spectrum extends from 4000 cm^{-1} to 667 cm^{-1}.

$$\bar{\nu} = \frac{10{,}000}{2.5\ \mu\text{m}} = 4000\ \text{cm}^{-1} \qquad \bar{\nu} = \frac{10{,}000}{25\ \mu\text{m}} = 400\ \text{cm}^{-1}$$

An advantage of using wavenumbers is that they are directly proportional to energy; the higher the wave number, the higher the energy of the radiation.

EXAMPLE 14.1

Some infrared spectrophotometers are calibrated to record spectra on an ordinate that is linear in wavelength (μm), whereas others record data on an ordinate that is linear in wavenumbers (cm^{-1}). Carry out the following conversions.

(a) 7.05 μm to centimeters^{-1} **(b)** 3.35 μm to centimeters^{-1}
(c) 3280 cm^{-1} to micrometers

Solution

(a) 1418 cm^{-1} **(b)** 2985 cm^{-1} **(c)** 3.05 μm

PROBLEM 14.1

Which is higher in energy?

(a) Infrared radiation of wavenumber 1710 cm^{-1} or 2800 cm^{-1}?
(b) Microwave radiation of frequency 300 MHz or of 60 MHz?

B. Molecular Vibrations

Atoms joined by covalent bonds are not permanently fixed in one position but rather undergo continual vibrations relative to each other. The energies associated with these vibrations are quantized, which means that within a molecule only specific vibrational energy levels are allowed. The energies associated with transitions between vibrational energy levels in most covalent molecules range from 2 to 10 kcal/mol and can be induced by absorption of radiation in the infrared region of the electromagnetic spectrum.

For a molecule to absorb infrared radiation, two criteria must be met. First, the frequency of radiation must match the frequency of an allowed vibration. Second, the bond undergoing vibration must have a dipole moment, that is, it must be a polar bond; the greater the polarity of the bond the more intense the absorption. Any vibration that meets these two criteria is said to be **infrared-active.** Covalent bonds in homonuclear diatomics, such as H_2, Br_2, and C=C and C≡C bonds in symmetrical alkenes and alkynes do not absorb infrared radiation because they do not have dipole moments.

For a nonlinear molecule containing n atoms, $3n$-6 allowed fundamental vibrations exist. For a molecule as simple as CH_4 with only five atoms, nine fundamental vibrations exist. For ethanol, C_2H_6O, there are 21 fundamental vibrations, and for hexanoic acid, $C_6H_{12}O_2$, there are 54. Thus, for even relatively simple molecules a large number of vibrational energy levels exist, and the patterns of energy absorption for these and larger molecules are very complex.

The simplest vibration motions in molecules giving rise to absorption of infrared radiation are **stretching** and **bending.** Illustrated in Figure 14.1 are the fundamental stretching and bending vibrations for a methylene group.

C. Characteristic Absorption Patterns

Analysis of the modes of vibration for a molecule is very complex because all of the atoms contribute to the vibrational modes. It is possible, however, to make a series of useful generalizations about where particular vibration modes will appear in the infrared spectrum by considering each bond one at a time and ignoring other bonds in the molecule. As a

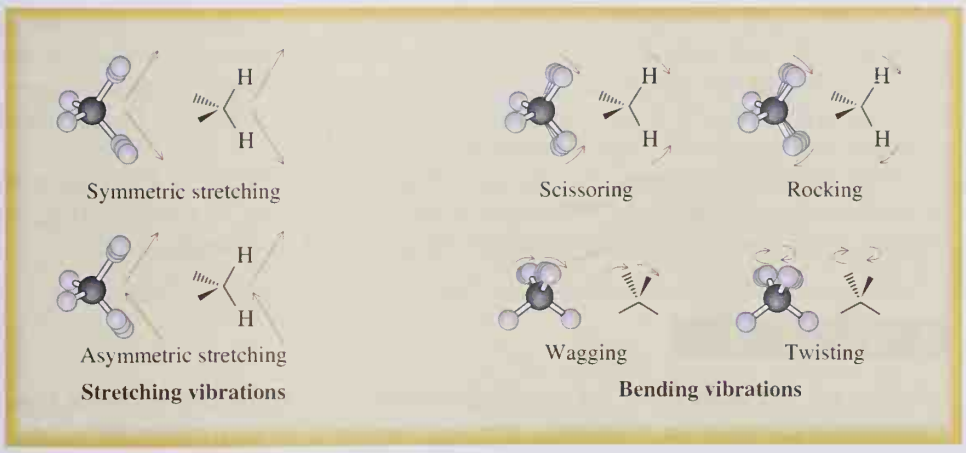


Figure 14.1
Fundamental modes of vibration for a methylene group.

simplifying assumption, let us consider two bonded atoms as two vibrating masses connected by a spring. As the bond vibrates, its energy continually changes from kinetic to potential and vice versa. The total energy (the sum of potential and kinetic energies) is proportional to the frequency of vibration. For a simple harmonic oscillator, the frequency of vibration is given by the following equation, which is derived from **Hooke's law** for a vibrating spring.

$$\bar{\nu} = \frac{1}{2\pi c}\sqrt{\frac{NK}{\mu}}$$

where $\bar{\nu}$ is the wavenumber of vibration in reciprocal centimeters (cm^{-1}); c is the velocity of light, 2.998×10^{10} cm/s; N is Avogadro's number, 6.022×10^{23} atoms/mol; K, the force constant, is a measure of bond strength in dynes per centimeter (g/s^2); and μ is the reduced mass in grams per atom $= (m_1 m_2)/(m_1 + m_2)$ (where m is the mass of an atom in grams). In calculating reduced mass, the mass of each atom must be expressed in units of grams per atom. The mass of one atom of carbon-12, for example, is calculated as follows:

$$\text{for carbon-12:} \qquad \text{Mass per atom} = \frac{12 \text{ g}}{6.022 \times 10^{23} \text{ atoms}} = 1.99 \times 10^{-23} \text{ g/atom}$$

Collecting and substituting values for all constants (Avogadro's number, pi, and the velocity of light) gives

$$\bar{\nu} = \frac{\sqrt{6.022 \times 10^{23}}}{2 \times 3.142 \times 2.998 \times 10^{10}}\sqrt{\frac{K}{\mu}} = 4.120\sqrt{\frac{K}{\mu}}$$

Force constants for single, double, and triple bonds are approximately 5×10^5, 10×10^5, and 15×10^5 dynes/cm, respectively. Using the value for the force constant for a single bond, we can calculate the wavenumber for the stretching vibration of a single bond between carbon-12 and hydrogen-1 as follows:

$$\text{for } {}^{12}\text{C—}{}^{1}\text{H stretching: Reduced mass } (\mu) = \frac{(12 \times 1) \text{ g}^2/\text{atom}^2}{(12 + 1) \text{ g/atom}} = 0.9231 \text{ g/atom}$$

$$\bar{\nu} = 4.120\sqrt{\frac{5 \times 10^5}{0.9231}} = 3032 \text{ cm}^{-1}$$

$$\text{Experimental value} = 2900 \text{ cm}^{-1}$$

The experimentally determined value for the wavenumber of an alkyl C—H stretching vibration is approximately 2900 cm^{-1}. Given the simplifying assumptions made in this calculation and the fact that the value of the force constant for a single bond is an average value and expressed only to one significant figure, the agreement between the calculated value and the experimental value is remarkably good.

From a practical standpoint, Hooke's law indicates that the *position* of absorption in an IR spectrum depends mainly on the strength of the vibrating bond. As we saw earlier, the *intensity* of the absorption depends mainly on the polarity of the vibrating bond.

EXAMPLE 14.2

Calculate the wavenumber for the stretching vibration of a carbon-carbon double bond. Assume each carbon is the isotopically most abundant form, namely, carbon-12.

Solution

Assume a force constant for 10×10^5 dynes/cm for C=C. The calculated wavenumber is 1682 cm^{-1}, a value close to the experimental value of 1630 cm^{-1}.

for C=C stretching: $\bar{\nu} = 4.120\sqrt{\dfrac{10 \times 10^5}{(12 \times 12)/(12 + 12)}} = 1682 \text{ cm}^{-1}$

Experimental value = 1630 cm^{-1}

PROBLEM 14.2

Without doing the calculation, which member of each pair do you expect to occur at the higher wavenumber?

(a) C=O or C=C stretching? **(b)** C=O or C—O stretching?
(c) C≡C or C=C stretching? **(d)** C—H or C—Cl stretching?

D. Recording an Infrared Spectrum

The instrument used to determine an infrared spectrum is called an **infrared spectrophotometer.** This instrument plots positions and relative intensities of all infrared absorptions on a piece of calibrated chart paper. The wavenumber scale is often divided into two or more regions. For all spectra reproduced in this text, it is divided into three linear regions: 4000 to 2200 cm^{-1}, 2220 to 1000 cm^{-1}, and 1000 to 400 cm^{-1}.

Shown in Figure 14.2 is an infrared spectrum of 3-methyl-2-butanone. The horizontal axis at the bottom of the chart paper is calibrated in wavenumbers; that at the top is calibrated in micrometers. The vertical axis is percentage transmittance with 100% trans-

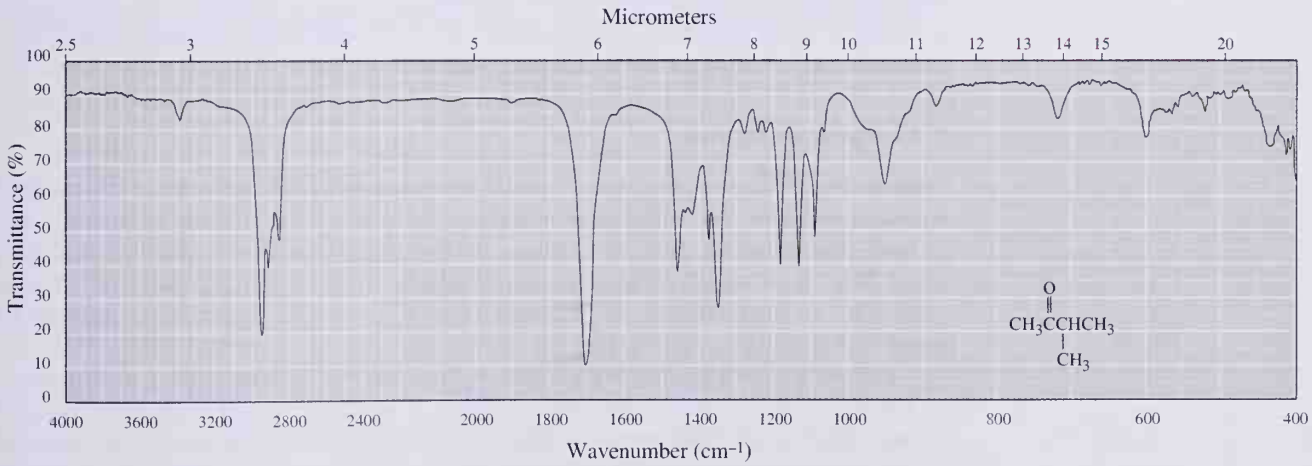


Figure 14.2
Infrared spectrum of 3-methyl-2-butanone.

A Perkin-Elmer Paragon 1000 Fourier Transform infrared spectrometer. Infrared spectra are shown on the monitor. *(Courtesy of the Perkin-Elmer Corporation)*

mittance at the top and 0% transmittance at the bottom. Thus, the baseline for an infrared spectrum (100% transmittance of radiation through the sample, 0% absorption) is at the top of the chart paper, and absorption of radiation corresponds to a trough or valley. Strange as it may seem, we commonly refer to infrared absorptions as peaks, even through they are upside down for peaks.

The spectrum in Figure 14.2 was recorded on a **neat** sample, which means using the pure liquid. A few drops of the liquid are placed between two sodium chloride discs and spread to give a thin film through which infrared radiation is then passed. Liquid and solid samples may also be dissolved in carbon tetrachloride or another solvent with minimal infrared absorption and infrared radiation passed through the solution. Another way to obtain the infrared spectrum of a solid is to mix it with potassium bromide and then compact the mixture under high pressure to a thin wafer which is then placed in the beam of the spectrophotometer. Both NaCl and KBr are transparent to infrared radiation. Infrared spectra of gas samples are determined using specially constructed gas-handling cells.

Interpretation of most infrared spectra is difficult because of the complexity of vibrational modes. In addition to the fundamental vibrational modes we already described, other types of absorptions occur resulting in so-called overtone and coupling peaks. **Overtone peaks** are higher frequency harmonics of fundamental vibrations and occur at or near integral multiples of the fundamental vibration. For example, an infrared absorption at 600 cm^{-1} may well have weaker overtone peaks near 1200 cm^{-1}, 1800 cm^{-1}, 2400 cm^{-1}, and so on. **Coupling peaks** result from the coupling of two vibrations by addition ($\bar{\nu}_1 + \bar{\nu}_2$) and by subtraction ($\bar{\nu}_1 - \bar{\nu}_2$). Only certain combinations of these coupling vibrations are allowed, meaning that only certain combinations are possible within the constraints of quantum mechanics.

To one skilled in the interpretation of infrared spectra, the absorption patterns can yield an enormous amount of information about chemical structure. We, however, have neither the time nor the need to develop this level of understanding. The value of infrared spectra for us is that they can be used to determine the presence or absence of characteristic functional groups. A carbonyl group, for example, typically shows strong absorption within the range 1715 $\pm$ 50 cm^{-1}. The position of absorption for a particular carbonyl group depends on whether it is that of an aldehyde, a ketone, a carboxylic acid, an ester, or, if in a ring, on the size of the ring. In Chapters 17, 19, and 20 we discuss how structural variations, such as ring size or conjugation, affect this value.

E. Correlation Tables

Data on absorption patterns of characteristic functional groups are collected in tables called **correlation tables.** The correlation table given in Table 14.1 is a listing of characteristic infrared absorptions for the types of bonds and functional groups with which we deal most often. With each new functional group introduced in the following chapters, we also present a correlation table for that functional group. A cumulative correlation chart can be found in Appendix 4 at the back of the text.

The intensity of a particular absorption is often referred to as **strong** (s), **medium** (m), or **weak** (w). Recall that to be infrared-active, a vibrating system must have a dipole moment and that the dipole moment must change with vibration. The greater the change in dipole moment for a particular vibration, the more intense (the stronger) its absorption peak.

In general, we pay most attention to the region from 4000 cm^{-1} to 1600 cm^{-1} because the characteristic bending and stretching vibrations for most functional groups are found in this region. Vibrations in the region 1600 cm^{-1} to 400 cm^{-1} are much more complex and

Table 14.1 Characteristic infrared absorptions of selected functional groups

Bond	Absorption Band (cm^{-1})	Intensity
O—H	3600	strong and broad
N—H	3500	medium
C—H	3000	medium to strong
C≡C	2150	weak
C=O	1715	strong
C=C	1650	weak
C—O	1100	strong

far more difficult to analyze. Because even slight variations in molecular structure and absorption patterns are most obvious in this region, it is often called the **fingerprint region.** If two compounds have even slightly different structures, the differences in their infrared spectra are most clearly discernible in this region of the infrared spectrum.

14.2 Interpreting Infrared Spectra

A. Alkanes

Infrared spectra of alkanes are usually simple with few peaks, the most common of which are given in Table 14.2. Because a number of bands appear in the C—H stretch region, it is generally not useful to try to interpret them other than to determine if the C—H band is due to an alkane (near 2900 cm^{-1}), an alkene (near 3000 cm^{-1}), or an alkyne (near 3300 cm^{-1}).

Table 14.2 Characteristic vibration frequencies of alkanes, alkenes, and alkynes

Hydrocarbon	Vibration	Frequency (cm^{-1})	Intensity
Alkane			
C—H	stretching	2900	medium to strong
CH_2	bending	1450	medium
CH_3	bending	1375	weak to medium
C—C	(not useful for interpretation—too many bands)		
Alkene			
C—H	stretching	3000	medium to strong
C=C	stretching	1650	weak
		conjugation moves this peak to the right (to lower frequency) and increases its intensity	
Alkyne			
C—H	stretching	3300	medium to strong
C≡C	stretching	2150	weak

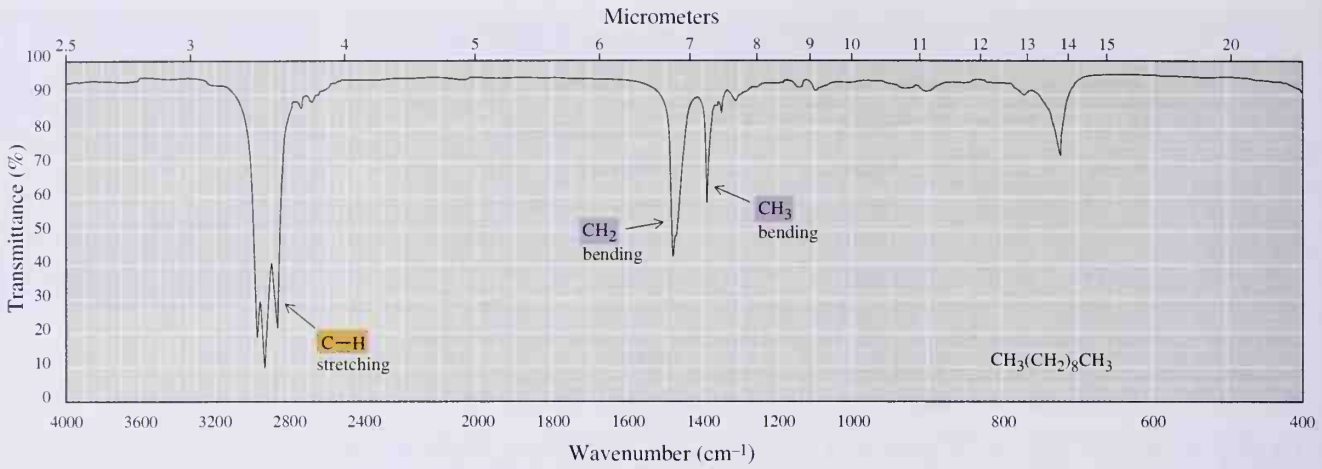


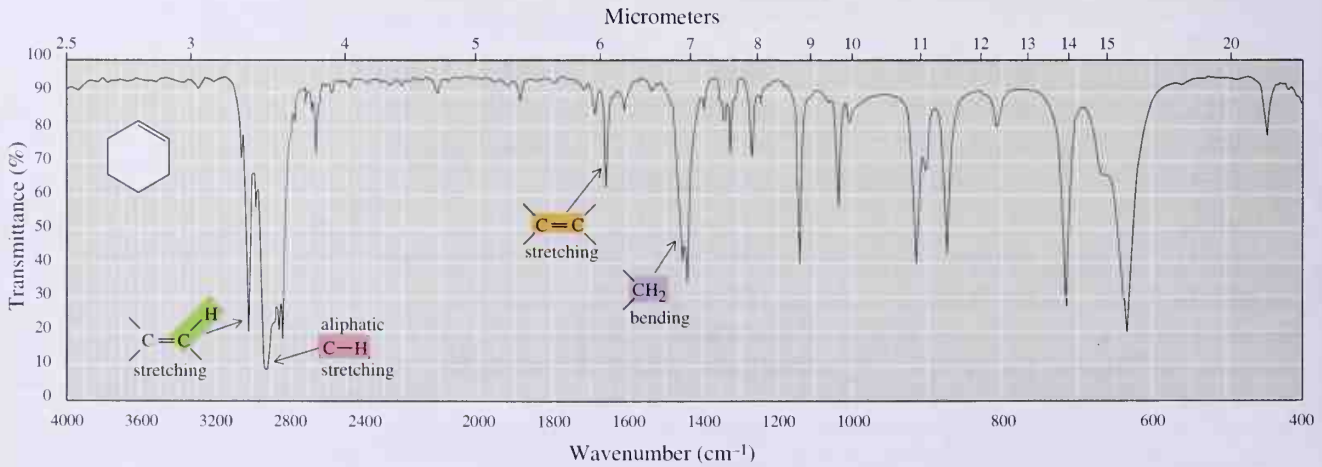
Figure 14.3
Infrared spectrum of decane (neat liquid, salt plates).

Shown in Figure 14.3 is an infrared spectrum of decane. The strong peak with multiple splittings between 2850 and 2950 cm^{-1} is characteristic of C—H stretching. The other prominent peaks in this spectrum are methylene bending absorption at 1465 cm^{-1} and methyl bending absorption at 1380 cm^{-1}.

B. Alkenes

The most easily recognized alkene absorption is the vinylic C—H stretching slightly to the left (at slightly greater frequency) of 3000 cm^{-1}. Also characteristic of alkenes is C=C stretching at 1600 to 1660 cm^{-1}. This vibration, however, is often weak and difficult to observe. Conjugation moves the C=C stretch to the right and increases its intensity. Both vinylic C—H stretching and C=C stretching can be seen in the infrared spectrum of cyclohexene (Figure 14.4). Also visible are the aliphatic C—H stretching near 2900 cm^{-1} and methylene bending near 1440 cm^{-1}.

Figure 14.4
Infrared spectrum of cyclohexene (neat liquid, salt plates).



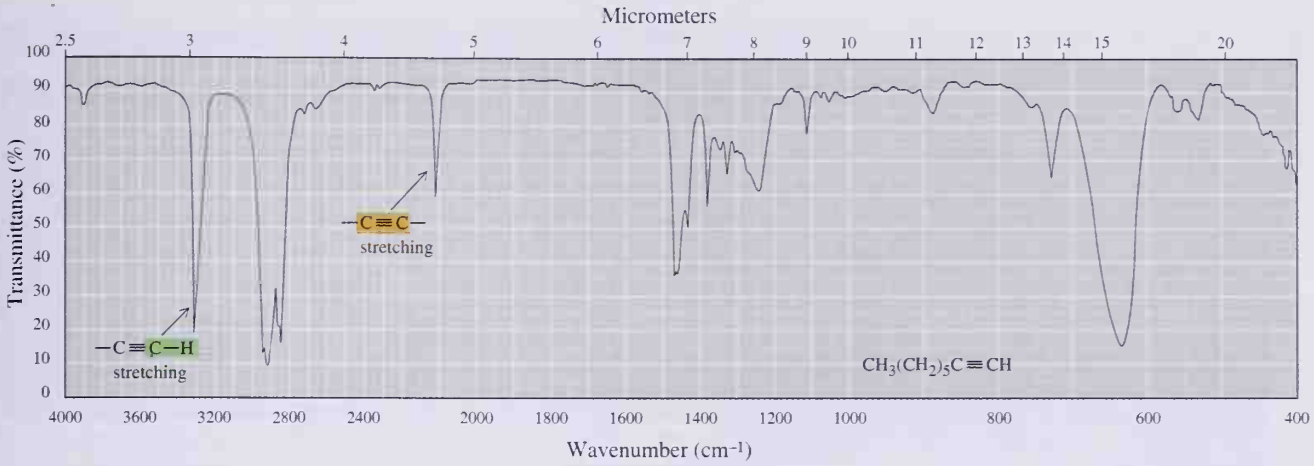


Figure 14.5
Infrared spectrum of 1-octyne (neat liquid, salt plates).

C. Alkynes

Alkyne C—H stretching occurs near 3300 cm^{-1}, a frequency higher than that for either alkyl C—H or vinylic C—H stretching. This peak is usually sharp and strong. Also observed in alkynes is absorption near 2150 cm^{-1} due to C≡C stretching. Both of these peaks can be seen in the infrared spectrum of 1-octyne (Figure 14.5).

D. Alcohols

Both the position of the O—H stretching frequency and its intensity depend on the extent of hydrogen bonding. If there is no hydrogen bonding, a situation that occurs only in a dilute solution of an alcohol in a nonhydroxylic solvent, the free O—H occurs as a sharp peak of weak intensity near 3625 cm^{-1}. Hydrogen-bonded O—H stretching occurs as a broad peak at 3500 to 3200 cm^{-1}, which sometimes overlaps C—H stretching absorptions. The C—O stretching is in the range 1200 to 1000 cm^{-1} and can often be used to determine if an alcohol is primary, secondary, or tertiary (Table 14.3). Shown in Figure 14.6 is an infrared spectrum of 1-hexanol. The hydrogen-bonded O—H stretching appears as a strong, very broad band centered at 3340 cm^{-1}. The C—O stretching appears near 1050 cm^{-1}, a value characteristic of primary alcohols.

Table 14.3 Characteristic stretching frequencies of alcohols

Bond	Vibration	Frequency (cm^{-1})	Intensity
O—H (free)	stretching	3625	weak
O—H (hydrogen bonded)	stretching	3350	strong, broad
C—O (primary)	stretching	1050	medium
(secondary)	stretching	1100	medium
(tertiary)	stretching	1150	medium

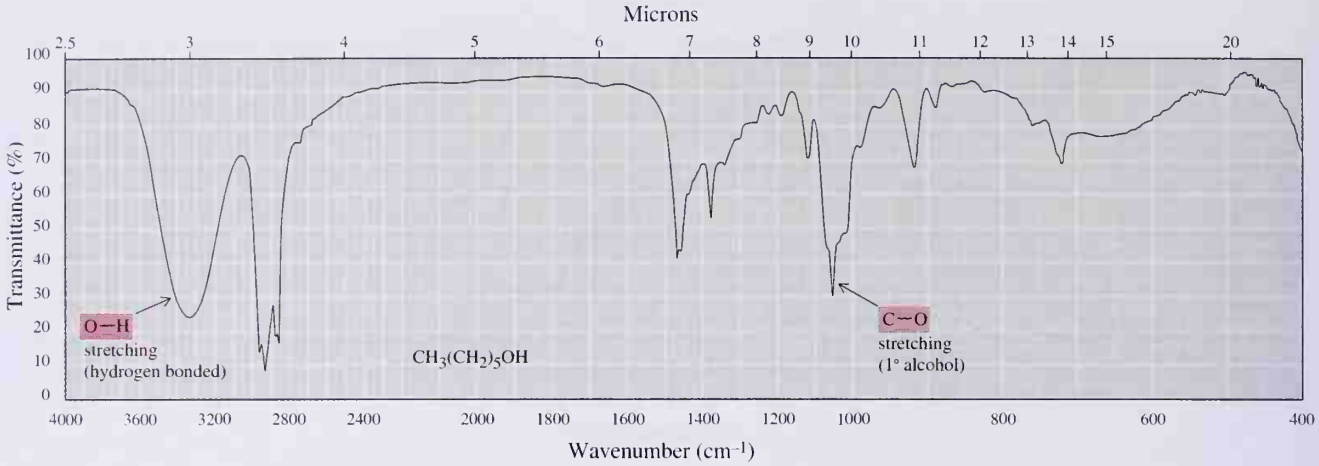


Figure 14.6
Infrared spectrum of 1-hexanol (neat liquid, salt plates).

E. Ethers

The most important feature in the infrared spectrum of ethers is strong absorption in the region 1000 to 1300 cm^{-1} associated with the C—O stretching vibration. Dialkyl ethers typically show a single absorption in this region between 1070 and 1150 cm^{-1}, as can be seen in the infrared spectrum of dibutyl ether (Figure 14.7).

The C—O stretching frequencies of ethers are similar to those observed in alcohols and esters. The presence or absence of O—H stretching at 3200 to 3500 cm^{-1} can be used to distinguish between an ether and an alcohol. As we shall see in Chapter 20, C—O stretching vibration is also present in an ester. In this case, the presence or absence of C=O stretching can be used to distinguish between an ether and an ester.

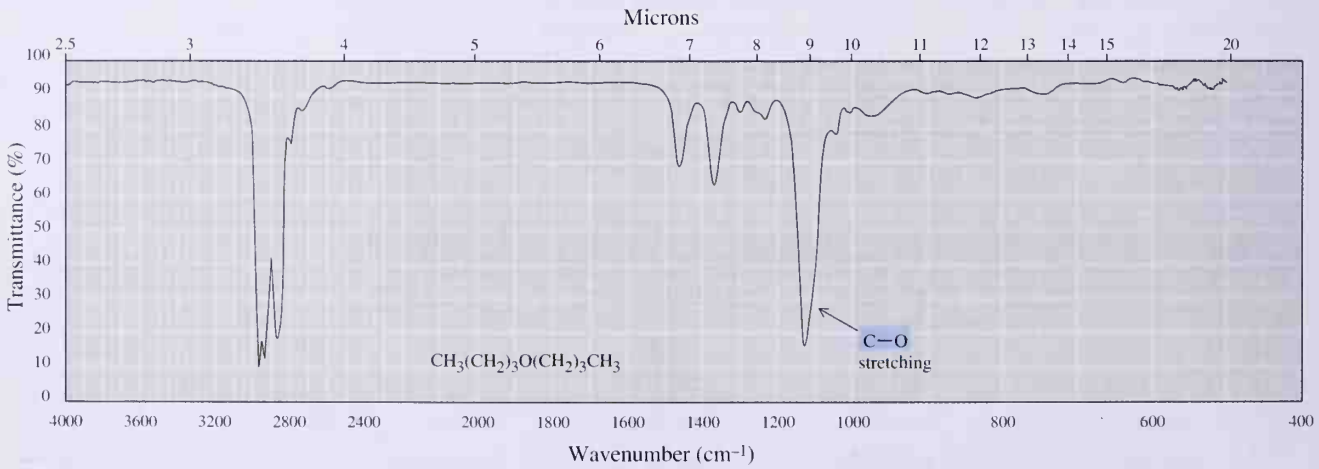
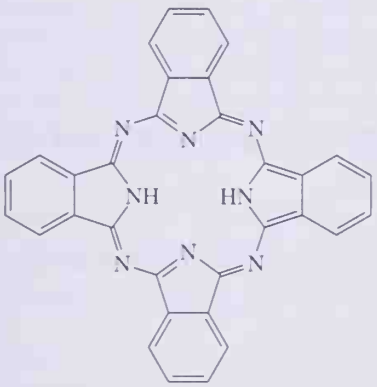


Figure 14.7
Infrared spectrum of dibutyl ether.

CHEMISTRY IN ACTION

Dyes That Absorb in the Infrared

With the discovery of solid state lasers based on gallium aluminium arsenide and indium phosphide that emit light in the near infrared region ($< 14{,}000\ cm^{-1}$), computer companies have started research to find dyes that absorb in this region. One application for such dyes is the WORM (write once, read many) optical storage disc. In this technology, a layer of near-infrared dye is dispersed under a transparent plastic sheet. A laser beam forms a series of small pits where the dye absorbs the energy. Then a second, lower power laser detects the pits due to differences in reflectivity. An important class of near-infrared dyes are the phthalocyanins (1). These compounds can have many different groups attached to the aromatic rings. Some also have a metal atom (such as lead) at the center of the molecule.

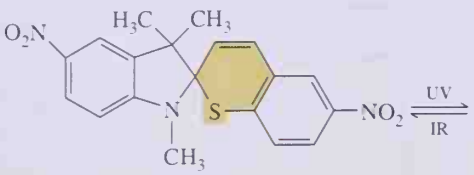


(1)

A great deal of current research is underway to perfect optical discs that can be erased and then rewritten, similar to the magnetic discs found in most computers. What is needed for this technology to work is a compound that can be switched from colorless to colored with a beam of light. The class of molecules called spiropyrans are under investigation for this application. The spiro compound (2), for example, is colorless. However, when it is irradiated with a beam of ultraviolet light, the molecule rearranges to give the colored compound (3). With an infrared laser, (3) can be switched back into the colorless spiro compound (2), erasing the information stored as a colored bit. Unfortunately, these particular compounds are not suitable as components for erasable storage discs because they degrade after only a few cycles of color changes. Related molecules are under study, and it is hoped that through them will come a major advance in the technology of information storage on optical discs.

Optical storage disks use light sensitive dyes. *(© Dan McCoy, Rainbow)*

See J. Fabian, H. Nakazumi, and M. Masuoka, *Chem Rev.*, **92**:1197: (1992).



(2) Colorless

(3) Colored

14.3 Ultraviolet-Visible Spectroscopy

At the molecular level, absorption of ultraviolet-visible radiation (Table 13.2) causes transitions between electronic energy levels of pi and nonbonding electrons. In this section we study correlations between absorption of ultraviolet-visible radiation and the information these absorptions give us about the presence and substitution patterns of carbon-carbon double bonds and of conjugation of carbon-carbon and carbon-oxygen double bonds.

A. Introduction

The region of the electromagnetic spectrum covered by most ultraviolet spectrophotometers runs from 200 to 400 nm, a region commonly referred to as the **near-ultraviolet.** Because oxygen of the atmosphere absorbs ultraviolet (UV) radiation at wavelengths below 200 nm, spectra obtained in this region must be run in an atmosphere of pure nitrogen or in a vacuum, hence, the name **vacuum ultraviolet.** Because of the special instrumentation required for vacuum ultraviolet, this region is little used for routine analysis. The region covered by most visible spectrophotometers runs from 400 nm (violet light) to 800 nm (red light). Typically UV-visible spectra consist of a small number of peaks, sometimes just one peak.

An ultraviolet-visible spectrophotometer. *(Courtesy of the Perkin-Elmer Corporation.)*

EXAMPLE 14.3

Calculate the energy of radiation at either end of the near-ultraviolet spectrum, that is, 200 nm and 400 nm (review Section 13.1).

Solution

Use the relationship $E = hc/\lambda$. Be certain to express the dimension of length in consistent units.

$$E = \frac{hc}{\lambda}$$

$$= 9.54 \times 10^{-14} \text{ kcal} \cdot \text{s/mol} \times 3.00 \times 10^{8} \text{ m/s} \times \frac{1}{200 \times 10^{-9} \text{ m}} = 143 \text{ kcal/mol}$$

By similar calculation, the energy of radiation of wavelength 400 nm is 71.5 kcal/mol.

PROBLEM 14.3

Wavelengths in ultraviolet-visible spectroscopy are commonly expressed in nanometers; wavelengths in infrared spectroscopy are commonly expressed in micrometers. Carry out the following conversions:

(a) 2.5 μm to nanometers **(b)** 200 nm to micrometers

Wavelengths and corresponding energies for near-ultraviolet and visible radiation are summarized in Table 14.4.

Ultraviolet and visible spectral data are recorded on chart paper as plots of wavelength on the horizontal axis and **absorbance** (A) on the vertical axis.

Table 14.4 Wavelengths and energies for near-ultraviolet and visible radiation

Region of Spectrum	Wavelength (nm)	Energy of Radiation (kcal/mol)
ultraviolet	200–400	143.0–71.5
visible	400–800	71.5–35.8

$$\text{Absorbance } (A) = \log \frac{I_0}{I}$$

where I_0 is the intensity of radiation incident on the sample; and I is the intensity of radiation transmitted through the sample.

Figure 14.8 is an ultraviolet absorption spectrum of 2,5-dimethyl-2,4-hexadiene. Absorption of ultraviolet radiation by this conjugated diene begins at wavelengths below 200 nm and continues to almost 270 nm. An irregularly shaped peak occurs with maximum absorption at 242 nm. This spectrum is reported as a single absorption peak using the notation λ_{max} 242 nm.

The extent of absorption of ultraviolet-visible radiation is proportional to the number of molecules capable of undergoing the observed electronic transition, and, therefore, ultraviolet-visible spectroscopy can be used for quantitative analysis of samples. The relationship between absorbance, concentration, and length of the sample cell is known as the **Beer-Lambert law.** The proportionality constant in this equation is given the name molar extinction coefficient, or, more simply, the **extinction coefficient** (ϵ), also known as molar absorbtivity.

$$\text{Beer-Lambert law:} \qquad A = \epsilon c l$$

where A is the absorbance; ϵ is the extinction coefficient (in liters per centimeter per mole); c is the concentration of solute (in moles per liter); and, l is the length of sample cell (in centimeters).

The extinction coefficient is a characteristic property of a compound and is not affected by its concentration or the length of the light path. Values range from zero to 10^6.

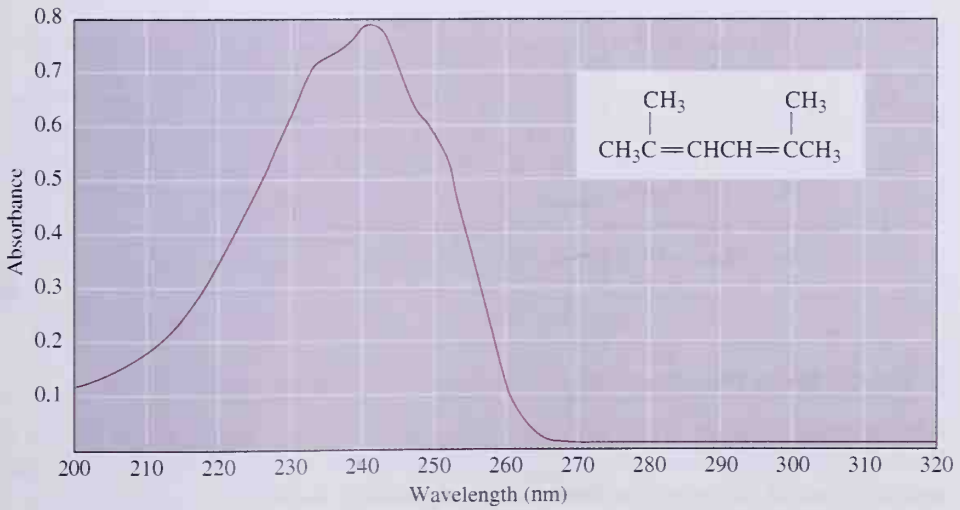


Figure 14.8
Ultraviolet spectrum of 2,5-dimethyl-2,4-hexadiene (in methanol).

Values above 10^4 correspond to high-intensity absorptions; values below 10^4 correspond to low-intensity absorptions. The extinction coefficient for 2,5-dimethyl-2,4-hexadiene, for example, is 13,100, which corresponds to a high-intensity absorption.

EXAMPLE 14.4

The extinction coefficient for 2,5-dimethyl-2,4-hexadiene is 13,100. What concentration of this diene in methanol is required to give an absorbance of 1.6? Assume a light path of 1.00 cm. Calculate concentration in units of:

(a) moles per liter **(b)** milligrams per milliliter

Solution

Solve the Beer-Lambert equation for concentration, and substitute appropriate values for length, absorbance, and extinction coefficient.

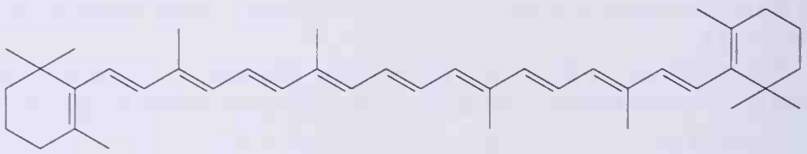
(a) $$c = \frac{A}{l \times \epsilon} = \frac{1.6}{1.00 \text{ cm} \times 13{,}100 \text{ L} \cdot \text{mol}^{-1} \cdot \text{cm}^{-1}} = 1.22 \times 10^{-4} \text{ mol/L}$$

(b) The molecular weight of 2,5-dimethyl-2,4-hexadiene is 110 g/mol. The concentration of the sample in milligrams per milliliter is

$$1.22 \times 10^{-4} \text{ mol/L} \times 110 \text{ g/mol} \times 1 \text{ L}/1000 \text{ mL} \times 1000 \text{ mg/g} = 1.23 \times 10^{-2} \text{ mg/mL}$$

PROBLEM 14.4

The visible spectrum of the tetraterpene β-carotene dissolved in hexane shows intense absorption maxima at 463 nm and 494 nm, both in the blue-green region. Because light of these wavelengths is absorbed by β-carotene, we perceive the color of this compound as that of the complement to blue-green, namely, red-orange.



β-Carotene

λ_{max} 463 (log ε 5.10); 494 (log ε 4.77)

(a) β-Carotene contains 40 carbons. The molecular formula of the reference hydrocarbon of 40 carbons is $C_{40}H_{82}$. Given the fact that β-carotene contains 11 pi bonds and two rings, calculate the index of hydrogen deficiency (Section 13.15A) of this molecule, and write its molecular formula.

(b) Calculate the concentration in milligrams per milliliter of β-carotene that gives an absorbance of 1.8 at λ_{max} 463.

B. The Origin of Transitions Between Electronic Energy Levels

Absorption of radiation in the near-ultraviolet-visible spectrum results in a transition of electrons from a lower energy occupied molecular orbital to a higher energy unoccupied molecular orbital. The energy of this radiation is generally insufficient to affect electrons in

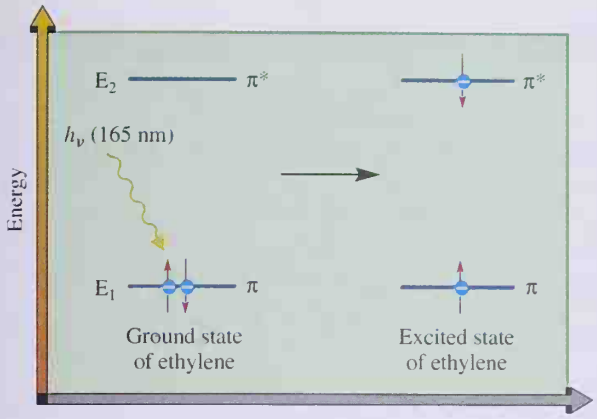


Figure 14.9
Electronic excitation of ethylene: a $\pi \rightarrow \pi^*$ transition. Absorption of ultraviolet radiation causes a transition of an electron from a pi bonding MO in the ground state to a pi antibonding MO in the excited state. There is no change in electron spin.

sigma bonding molecular orbitals but sufficient to effect $\pi \rightarrow \pi^*$ transitions of electrons in pi bonds, most particularly pi electrons of conjugated systems. Thus, ultraviolet-visible spectroscopy is an important experimental technique for the analysis of conjugated systems. As we shall see in Section 17.4, ultraviolet-visible radiation is also sufficient to affect $n \rightarrow \pi^*$ transitions of nonbonding electrons on oxygen in carbonyl groups.

As an example, consider ethylene. According to molecular orbital theory, the double bond in ethylene consists of one sigma bond formed by combination of sp^2 orbitals and one pi bond formed by combination of $2p$ orbitals. The relative energies of the pi bonding and antibonding molecular orbitals are shown schematically in Figure 14.9. The $\pi \rightarrow \pi^*$ transitions for simple, unconjugated alkenes occur below 200 nm (at 165 nm for ethylene). Because these transitions occur in the vacuum ultraviolet, they are not observed in conventional ultraviolet spectroscopy and, therefore, are not useful to us for determination of molecular structure.

For 1,3-butadiene, the difference in energy between the highest occupied pi molecular orbital and the lowest unoccupied pi molecular orbital is less than it is for ethylene, with the result that a $\pi \rightarrow \pi^*$ transition for butadiene (Figure 14.10) takes less energy (occurs at a longer wavelength) than that for ethylene. This transition for butadiene occurs at 217 nm.

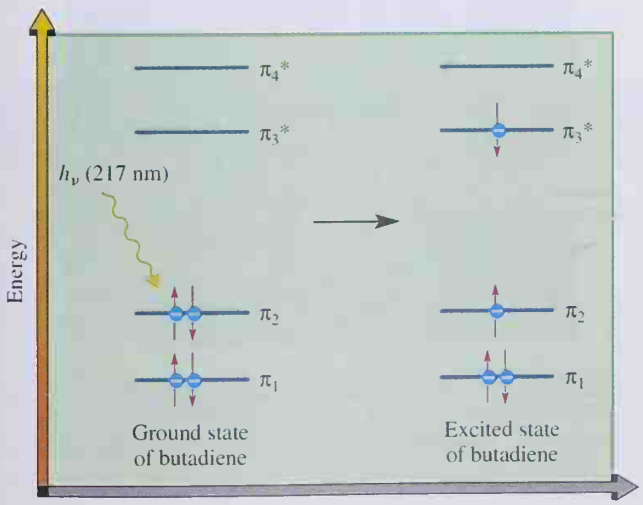


Figure 14.10
Electronic excitation of 1,3-butadiene: a $\pi \rightarrow \pi^*$ transition.

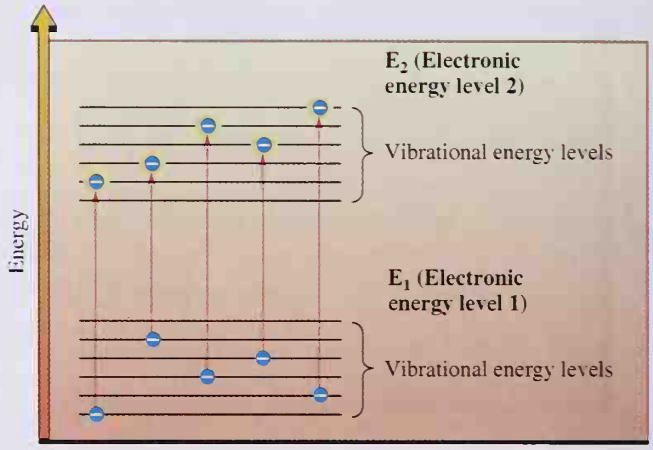


Figure 14.11
Electronic energy levels E_1 and E_2 with associated vibrational energy levels. Not shown are associated rotational energy levels.

Absorption of ultraviolet-visible radiation usually occurs over a relatively wide range of wavelengths because, at room temperature, many modes of both vibration and rotation are also excited. The energy levels for these excitations are quite closely spaced and considerably smaller than the energy differences between electronic excitations (Figure 14.11). Transitions between vibration and rotation energy levels are superposed on the electronic excitations, which results in a vast number of absorption peaks so closely spaced that the spectrophotometer cannot resolve them. For this reason, UV-visible absorption peaks are usually much broader than IR absorption peaks. Thus, the ultraviolet-visible spectrum of a compound consists of a band or bands of absorption with maxima corresponding to the major electronic transitions.

It has been found from analysis of spectral data that the greater the number of double bonds in conjugation, the longer the wavelength of ultraviolet radiation absorbed (the smaller the energy required for the $\pi \rightarrow \pi^*$ transition). Shown in Table 14.5 are wavelengths and energies required for $\pi \rightarrow \pi^*$ transitions in several conjugated alkenes.

Table 14.5 Wavelengths and energies required for $\pi \rightarrow \pi^*$ transitions of ethylene and several conjugated polyenes

Name	Structural Formula	λ_{max}	Energy (kcal/mol)
ethylene	$CH_2{=}CH_2$	165	173
1,3-butadiene	$CH_2{=}CHCH{=}CH_2$	217	132
trans-1,3,5-hexatriene	$CH_2{=}CHCH{=}CHCH{=}CH_2$	268	107
trans,trans-1,3,5,7-octatetraene	$CH_2{=}CHCH{=}CHCH{=}CHCH{=}CH_2$	290	92

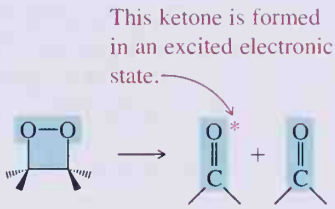
CHEMISTRY IN ACTION

Chemiluminescence

Spectroscopy deals with the interaction of electromagnetic radiation, in this case light, with matter. Some compounds can emit light as well as absorb it. Chemiluminescence occurs when a chemical reaction produces light as one of its products. For light to be emitted, the reaction must be highly exothermic.

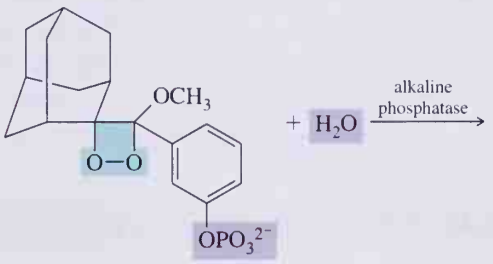
One class of molecules that exhibit chemiluminescence is the 1,2-dioxetanes. These molecules possess a strained, four-member ring and a weak oxygen-oxygen bond. At or above room temperature, 1,2-dioxetanes fragment into two ketones. The relief of ring strain and the generation of two strong carbon-oxygen double bonds liberate so much energy that one of the ketones is formed in an electronically excited state. The electronically excited ketone then gives off light and relaxes to its ground state.

Chemical reactions often release energy. The reaction in this tube and beaker releases energy in the form of light in a process called chemiluminescence. *(Charles D. Winters)*

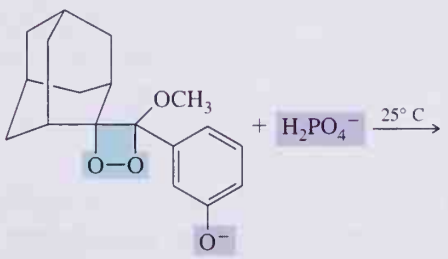


A 1,2-dioxetane

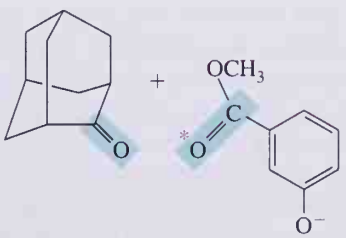
Recently new 1,2-dioxetanes have been synthesized, which are leading to new, ultrasensitive detection procedures. For example, the 1,2-dioxetane 1 is stable at room temperature and neutral pH.



(1)



(2)



(Box continued on p. 538.)

CHEMISTRY IN ACTION (Continued)

When (1) is treated with water in the presence of alkaline phosphatase, an enzyme which catalyzes hydrolysis of esters of phosphoric acid, the unstable dioxetane anion (2) is produced. Compound (2) undergoes rapid fragmentation, and light from the electronically excited ester is readily detected.

Research in clinical chemistry has now demonstrated that chemiluminescence has the potential to become a very useful noninvasive diagnostic technique. It can be used, for example, to detect antigens in the following way. First, the alkaline phosphatase enzyme is attached to a specific antibody and then mixed with serum or another clinical sample. If the corresponding antigen is present in the sample, an antibody-antigen complex is formed and then separated from unreacted antibody. To detect the complex, the 1,2-dioxetane (1) is added. Alkaline phosphatase catalyzes the hydrolysis of (1) to (2), the unstable dioxetane anion decomposes, and light is given off as the electronically excited ketone returns to its ground state. The amount of light generated is proportional to the amount of antigen in the sample. Because the enzyme can catalyze the destruction of many 1,2-dioxetane molecules, and because light is so easily detected, these enzyme-linked chemiluminescence reactions can detect as little as an attomole (10^{-18} mol) of antigen. Because these sensitivity limits equal or exceed the sensitivity of analytical techniques based on radioactivity, chemiluminescent assays may, in time, replace many assays that now rely on radioactivity for signal detection. Such a switch will lessen radioactive waste disposal problems and enhance safety for clinical workers.

See A. P. Schaap, H. Akhavan, and L. J. Romano, *Clin. Chem.*, **35:** 1863 (1989).

SUMMARY

The **vibrational infrared** spectrum (Section 14.1A) extends from 2.5 to 25μm. Radiation in this region can be referred to by its wavelength in micrometers or by its wavenumber $\bar{\nu}$ in reciprocal centimeters (cm^{-1}).

$$\bar{\nu} = \frac{1}{\lambda\ (\text{cm})} = \frac{10{,}000}{\lambda\ (\mu\text{m})}$$

where λ is the wavelength. Expressed as wavenumbers, the vibrational infrared extends from approximately 4000 to 400 cm^{-1}. To be **infrared-active** (Section 14.1B) a bond must be polar. There are $(3n - 6)$ allowed fundamental vibrations for a nonlinear molecule containing n atoms. The simplest vibrations that give rise to absorption of infrared radiation are **stretching** and **bending** vibrations. Stretching may be symmetrical or asymmetrical. Scissoring, rocking, wagging, and twisting are names given to types of bending vibrations.

The frequency of vibration for an infrared-active bond can be derived from Hooke's law for the vibration of a simple harmonic oscillator (Section 14.1C). From this equation, we can make the following correlations. The frequency of vibration increases when (1) bond strength increases, (2) the reduced mass of the vibrating system decreases. In addition to fundamental vibration peaks, infrared spectra also contain overtone and coupling peaks, which are usually much weaker.

A **correlation chart** is a list of the absorption patterns of characteristic functional groups. The intensity of a peak is referred to as strong (s), medium (m), or weak (w). Characteristic bending and stretching vibrations for most functional groups appear in the region 4000 to 1600 cm^{-1}. The region 1600 to 600 cm^{-1} is called the **fingerprint region** (Section 14.1D).

The region of the electromagnetic spectrum covered by most ultraviolet spectrophotometers runs from 200 to 400 nm, a region commonly referred to as the **near-ultraviolet** (Section 14.3A). Wavelengths and corresponding energies for near-ultraviolet and visible radiation are summarized in Table 14.4. Ultraviolet and visible spectral data are recorded as plots of wavelength versus **absorbance** (A). The relationship between absorbance, concentration, and length of sample cell is known as the **Beer-Lambert law.** The proportionality constant in this equation is given the name molar extinction coefficient, or, more simply, **extinction coefficient** (ϵ).

Beer-Lambert law: $A = \epsilon cl$

where A is the absorbance; ϵ is the extinction coefficient (in liters per centimeter per mole); c is the concentration of solute (in moles per liter); and l is the length of sample cell (in centimeters).

Absorption of radiation in the near-ultraviolet-visible spectrum is generally sufficient to effect $\pi \rightarrow \pi^*$ transitions of electrons in pi bonds, particularly pi electrons of conjugated systems. It is also sufficient to effect $n \rightarrow \pi^*$ transitions of nonbonding electrons associated with carbonyl groups. Absorption of ultraviolet-visible radiation usually occurs over a relatively wide range of wavelengths because transitions between vibrational and rotational energy levels are superposed on the electronic transitions. The result is a vast number of absorption peaks so closely spaced that the spectrophotometer cannot resolve them. Thus, the ultraviolet-visible spectrum of a compound consists of a band or small number of bands of absorption with maxima centered on the major electronic transitions.

ADDITIONAL PROBLEMS

Molecular Mechanics

14.5 In molecular mechanics calculations, the energy required to stretch or compress a bond is given by $E_b = k_b (r - r_0)^2$, where k_b is a constant for a given type of bond, r_0 is the equilibrium bond length, and r is the length of the bond in the stretched or compressed state. Values of these parameters for some common types of bonds are shown in the table. How much energy is required to stretch each type of bond by 5% of its length, by 10% of its length?

Bond Type	k_b (kcal/mol · nm²)	r_0 (nm)
C=O	57.9×10^3	0.123
$C(sp^3)$—$C(sp^3)$	20.0×10^3	0.153
$C(sp^3)$—H	30.0×10^3	0.108
O—H	45.1×10^3	0.096

14.6 In molecular mechanics calculations, the energy required to bend a bond is given by $E_q = k_q (q - q_0)^2$, where k_q is a constant for a given type of bond, q_0 is the equilibrium bond angle, and q is the angle of the bond in its bent state. Values of these parameters for some common types of bonds are shown in the table. How much energy is required to bend each type of bond by 5%, by 10%?

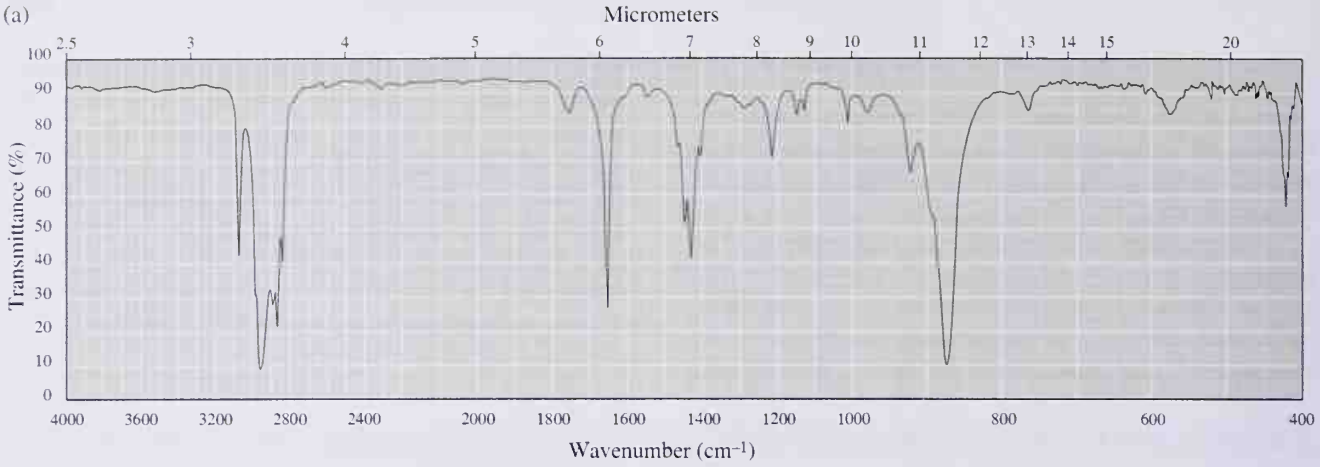
Bond Type	k_q (kcal/mol · radians²)	q_0 (degrees)
$C(sp^3)$—C=O	85.9	121.6
$C(sp^3)$—$C(sp^3)$—$C(sp^3)$	69.9	109.5
H—$C(sp^3)$—H	40.0	109.5
$C(sp^3)$—$C(sp^3)$—O	49.9	109.5

14.7 Given your answers to the two previous problems, is it easier to bend bonds or to stretch bonds?

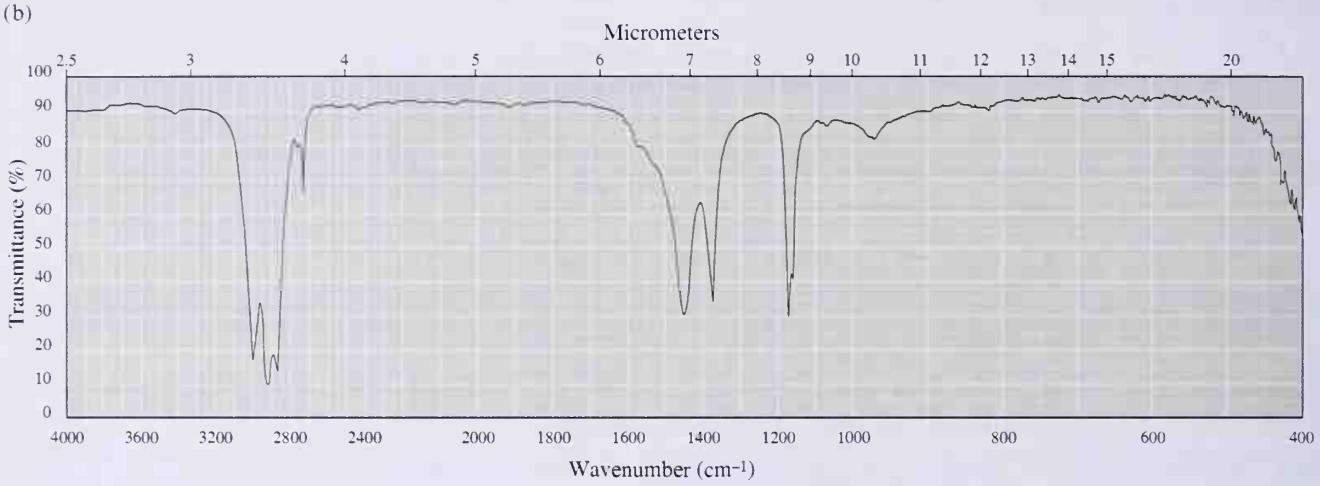
Infrared Spectra

14.8 Following are infrared spectra of methylenecyclopentane and 2,3-dimethyl-2-butene. Assign each compound its correct spectrum.

(a)

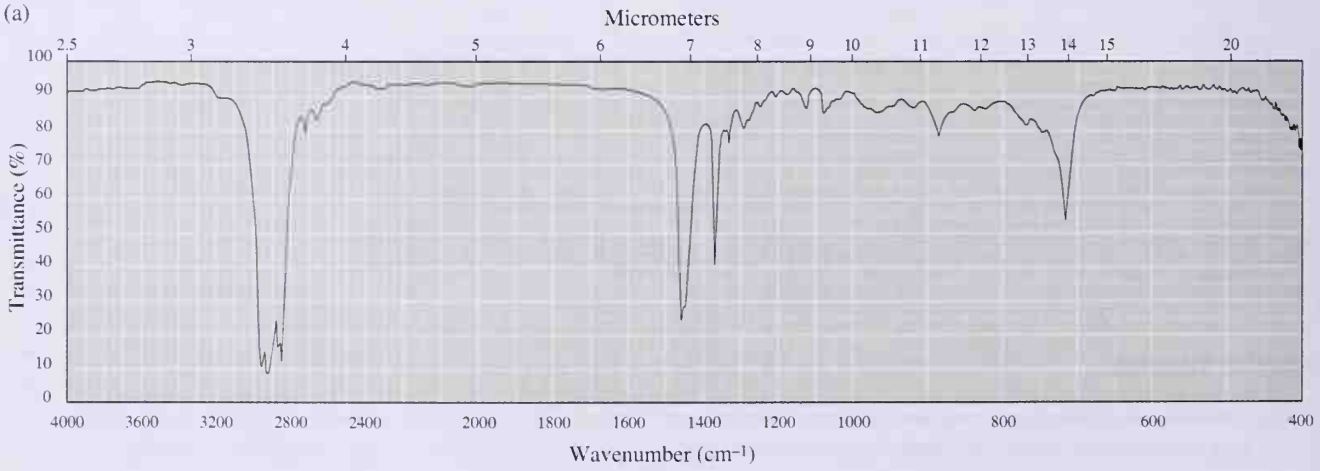


(b)

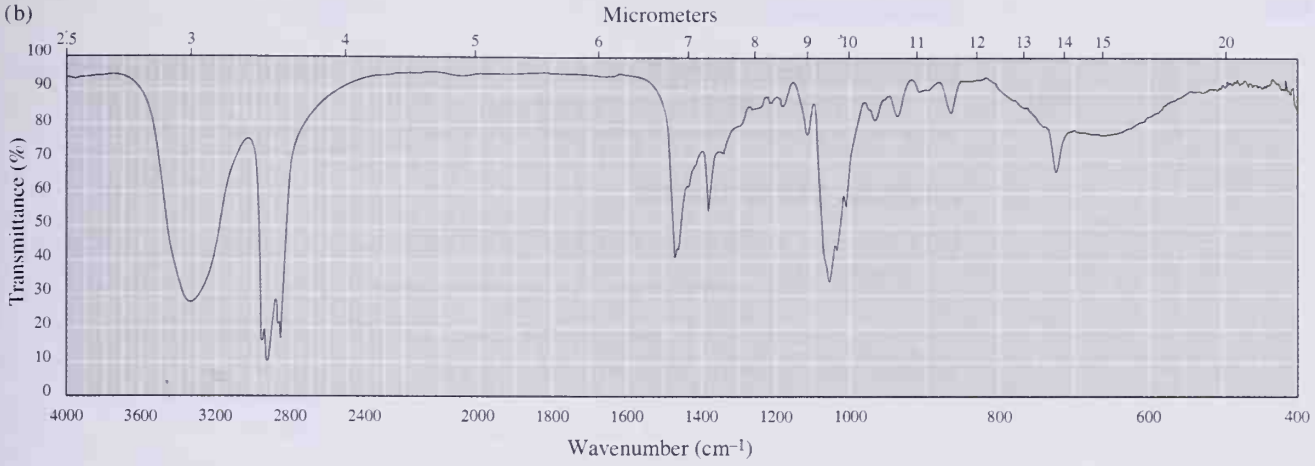


14.9 Following are infrared spectra of nonane and 1-hexanol. Assign each compound its correct spectrum.

(a)

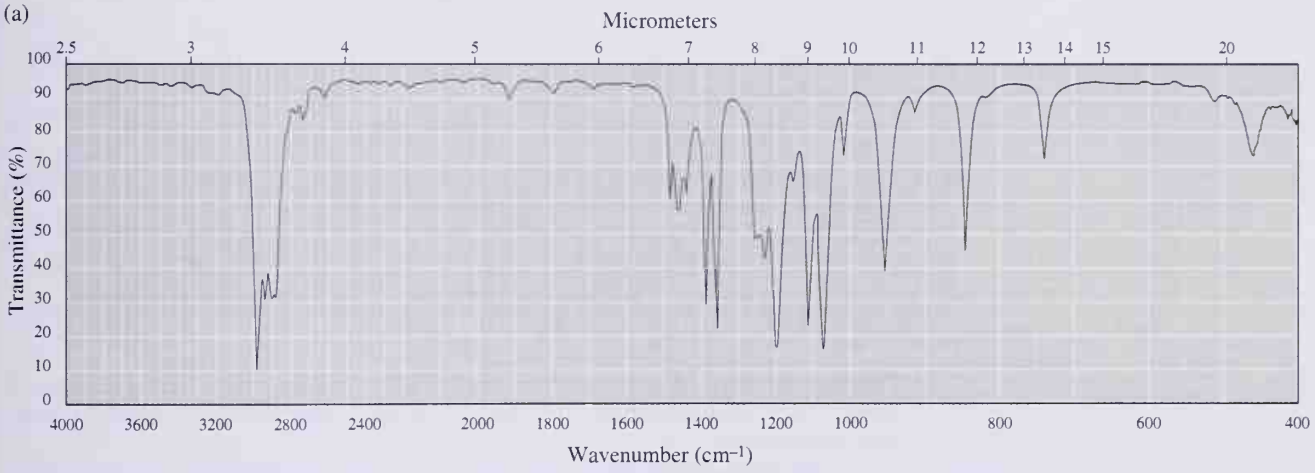


(b)

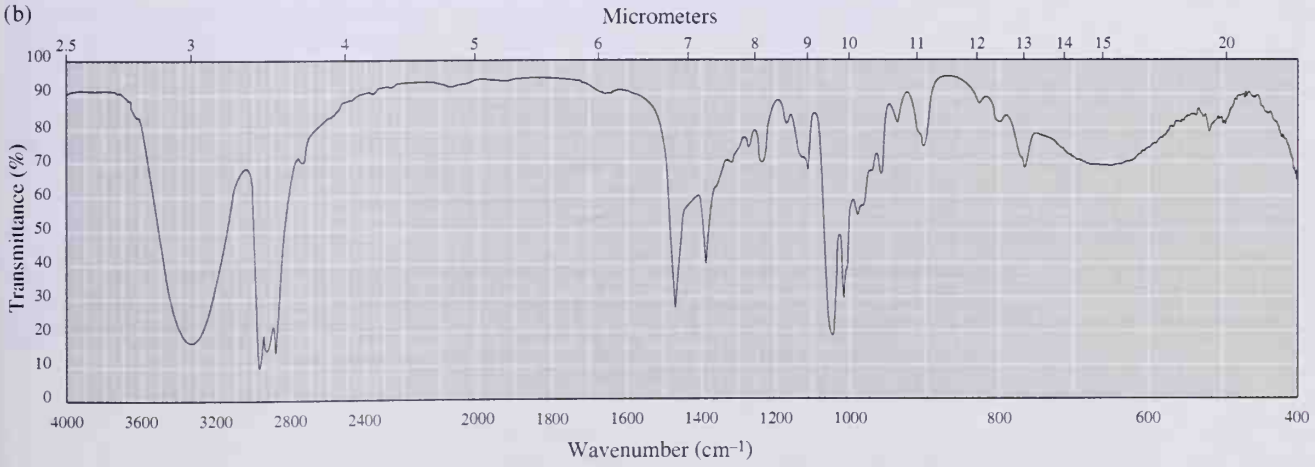


14.10 Following are infrared spectra of 2-methyl-1-butanol and *tert*-butyl ethyl ether. Assign each compound its correct spectrum.

(a)



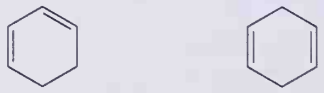
(b)



14.11 The IR intensity of the C≡C stretch in unsymmetrical internal alkynes is frequently very weak. Why is this?

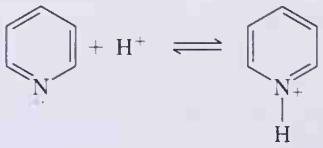
Ultraviolet-Visible Spectra

14.12 Show how to distinguish between 1,3-cyclohexadiene and 1,4-cyclohexadiene by ultraviolet spectroscopy.



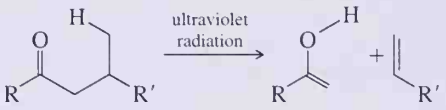
1,3-Cyclohexadiene 1,4-Cyclohexadiene

14.13 Pyridine exhibits a UV transition of the type $n \rightarrow \pi^*$ at 270 nm. In this transition, the unshared electron pair is promoted from a nonbonding MO to a pi antibonding MO. What is the effect on this UV peak if pyridine is protonated?



Pyridine Pyridinium ion

14.14 Many organic reactions occur on absorption of UV radiation. An important photochemical reaction of ketones is the Norrish Type II cleavage of ketones:



Compare this photochemical reaction to the McLafferty rearrangement seen in mass spectrometry. Why does absorption of UV light give reactions similar to fragmentations seen in mass spectrometry?

14.15 The weight of proteins or nucleic acids in solution is commonly determined by UV spectroscopy using the Beer-Lambert law. For example, the ϵ of double-stranded DNA at 260 nm is 6670. The formula weight of the repeating unit in DNA (650) can be used as the molecular weight. What is the weight of DNA in 2.0 mL of aqueous buffer if the absorbance, measured in a 1-cm cuvette, is 0.75?

14.16 A sample of adenosine triphosphate (ATP)(MW 507, ϵ = 14,700 at 257 nm) is dissolved in 5.0 mL of buffer. A 250-μL aliquot is removed and placed in a 1-cm cuvette with sufficient buffer to give a total volume of 2.0 mL. The absorbance of the sample at 257 nm is 1.15. Calculate the weight of ATP in the original 5.0-mL sample?

14.17 Biochemical molecules are frequently sold by optical density (OD) units, where one OD unit is the amount of compound that gives an absorbance of 1.0 at its UV maximum in 1.0 mL of solvent in a 1-cm cuvette. If the cost of 10.0 OD units of a DNA polymer, ϵ = 6600 at 262 nm, is $51, what is the cost per gram of this biochemical?

14.18 The Beer-Lambert law applies to IR spectroscopy as well as UV. Whereas ultraviolet spectra are a plot of absorbance (A) versus wavelength, IR spectra are a plot of percentage transmittance ($\%T$) versus wavenumber. Absorbance and percentage transmittance are related in the following way:

$$\text{Absorbance } (A) = \log \frac{T_0}{T}$$

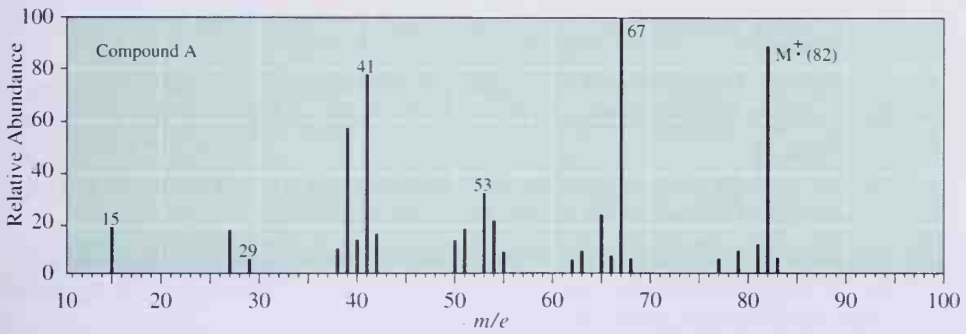
where T_0 is the baseline (100%) transmittance; and T is the transmittance of a peak.

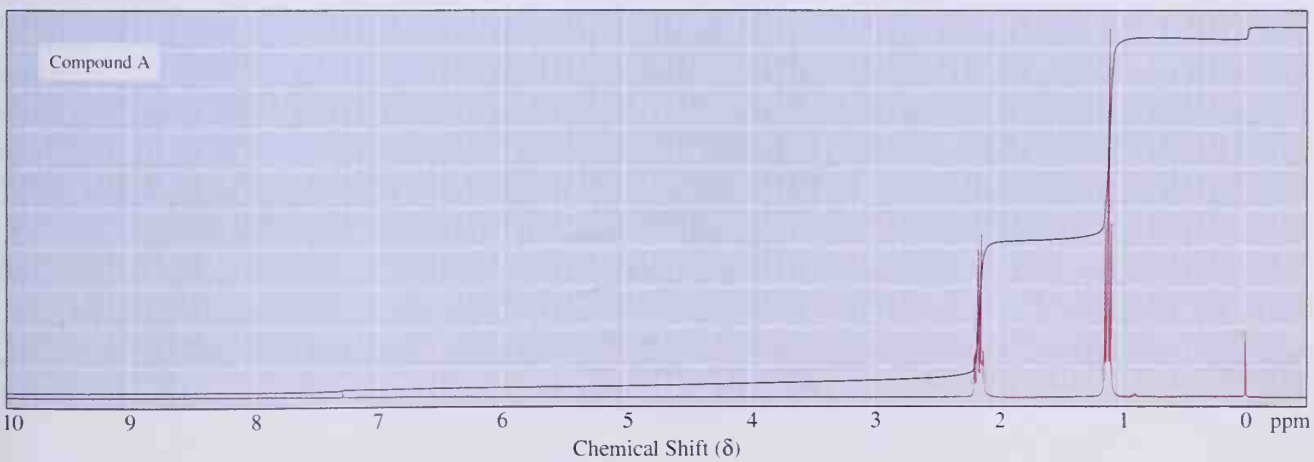
(a) What is the absorbance of a peak in an IR spectrum with 10% transmittance?

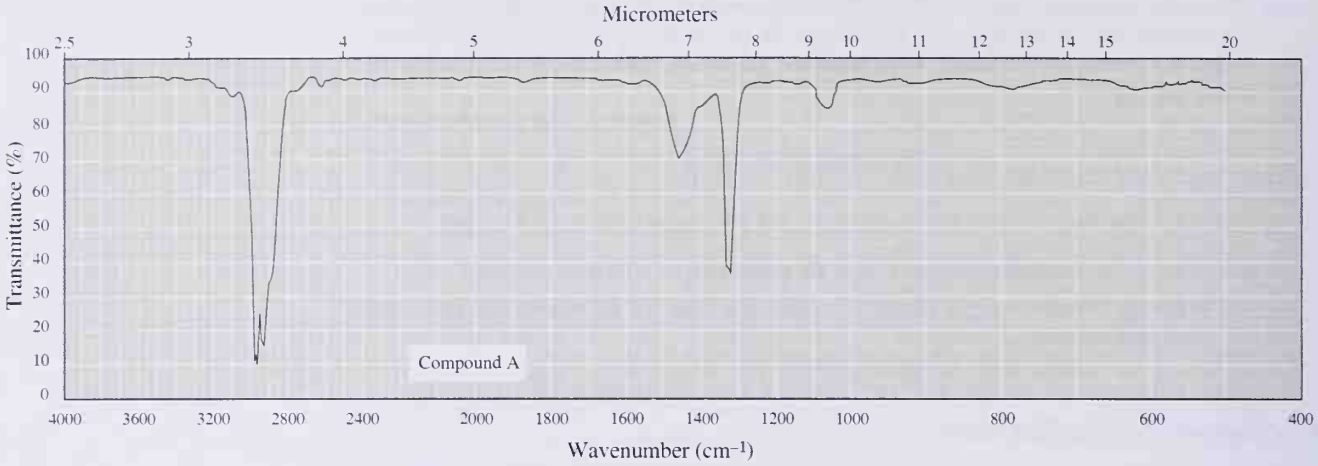
(b) If the concentration of this sample is halved, how does the absorbance and percentage transmittance change?

Combined Spectral Problems

14.19 Compound A, a hydrocarbon, bp 81°C, decolorizes a solution of bromine in carbon tetrachloride. Following are its mass spectrum, ^{1}H-NMR spectrum, and infrared spectrum. Compound A is transparent to ultraviolet-visible radiation.







(a) What is the molecular formula of compound A?

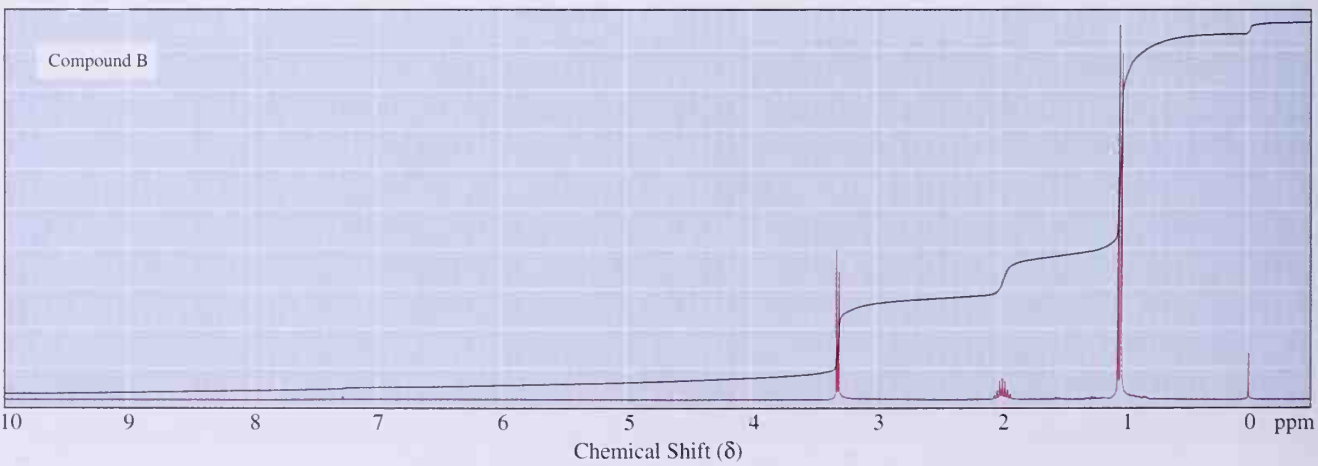
(b) From its molecular formula, calculate the index of hydrogen deficiency of compound A. How many rings are possible for this compounds? How many double bonds? How many triple bonds?

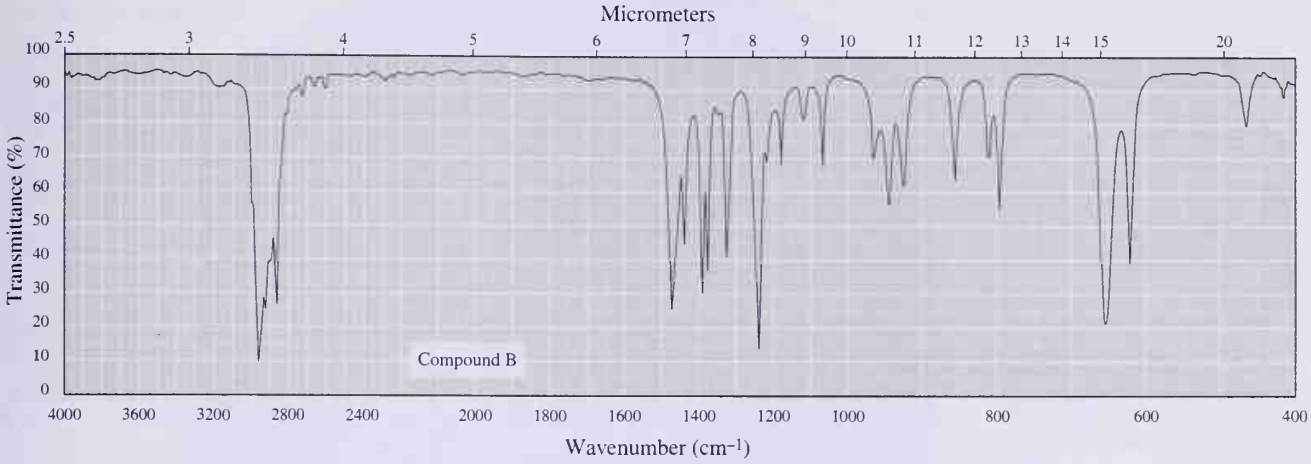
(c) Propose a structural formula for compound A consistent with the spectral information.

(d) Account for the presence of peaks in the mass spectrum of compound A at *m/e* 67, 53, 41, 29, and 15.

(e) The ^{13}C-NMR spectrum of compound A shows peaks at δ 12.4, 14.4, and 80.9. Assign each carbon in compound A its appropriate ^{13}C chemical shift.

14.20 Compound B is a liquid, bp 122°C. Following are its ^{1}H-NMR spectrum and infrared spectrum. Compound B shows a molecular ion peak, $M^{+\cdot}$, at *m/e* 136 and an $M^{+\cdot}$ + 2 peak of almost equal intensity at *m/e* 138.



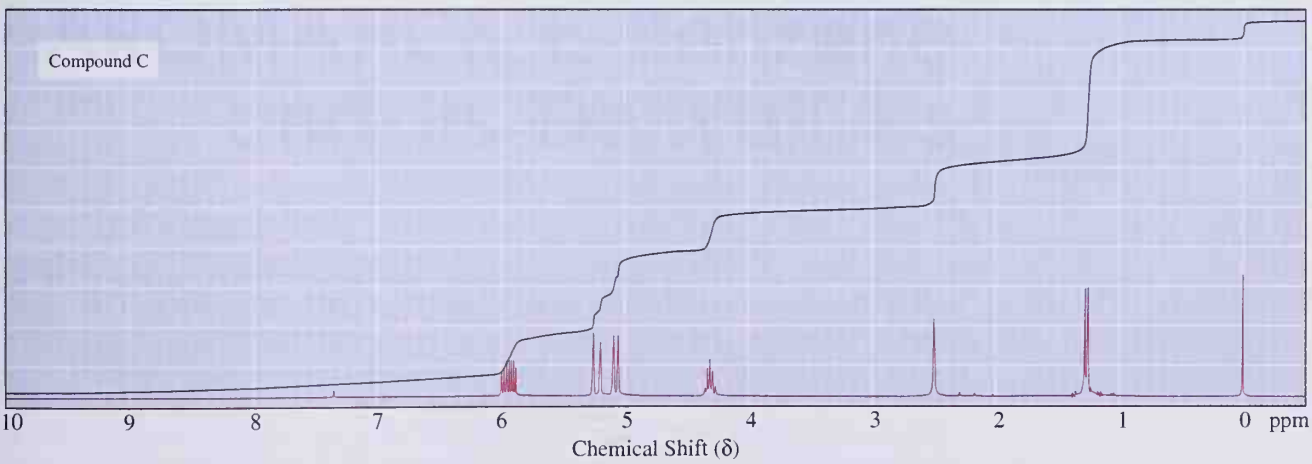


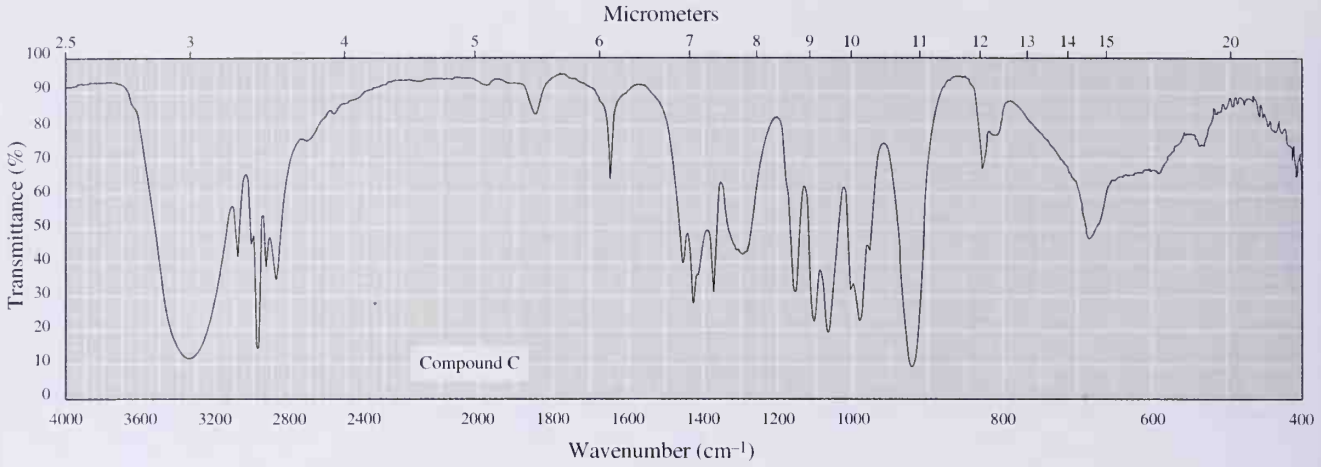
(a) From this information, deduce the structural formula of compound B.

(b) Account for the presence of peaks in its mass spectrum at *m/e* 138, 136, 123, 121, 43, and 41.

(c) The ^{13}C-NMR spectrum of compound B shows peaks at δ 21.0, 30.47, and 42.45. Assign each carbon in compound B its appropriate ^{13}C chemical shift.

14.21 Compound C, C_4H_8O, is a liquid, bp 97°C. Following are its ^{1}H-NMR spectrum and infrared spectrum.





(a) What is the index of hydrogen deficiency of compound C? How many rings or double bonds (or both) can it contain?

(b) What information can you learn from the infrared spectrum about the oxygen-containing functional group?

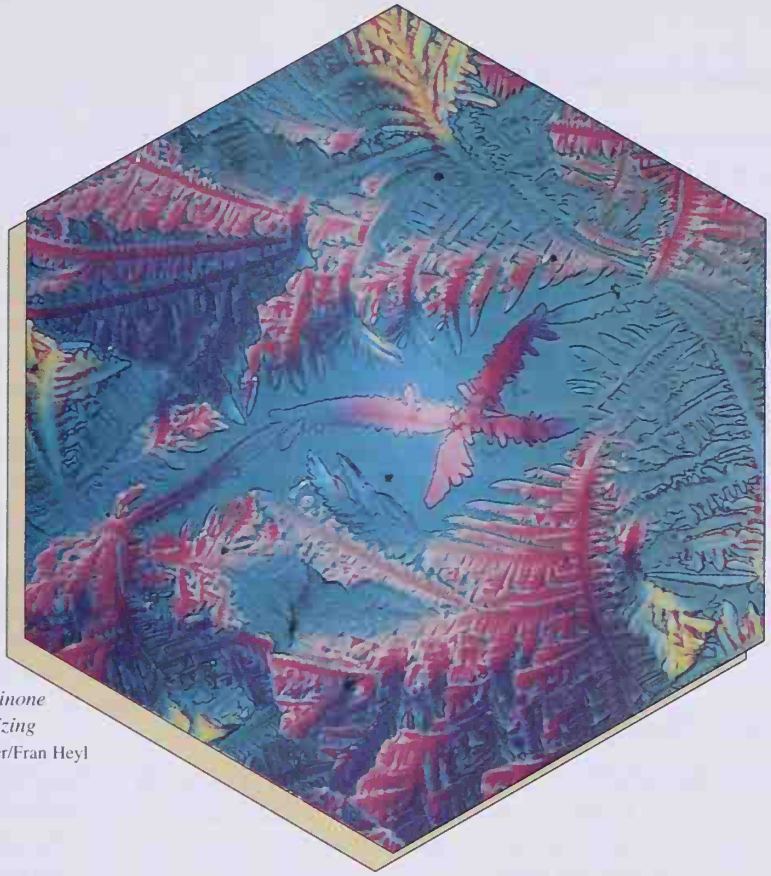
(c) What information can you learn from the ^{1}H-NMR spectrum about the presence or absence of vinylic hydrogens (hydrogens on a carbon-carbon double bond)?

(d) Propose a structural formula for compound C consistent with the spectral and chemical information.

(e) Account for the presence of peaks in the mass spectrum of compound C at *m/e* 71, 57, 45, 27, and 15.

(f) Account for the splitting patterns of single hydrogens at δ 5.1, 5.3, and 5.8. (*Hint:* Review the ^{1}H-NMR of vinyl acetate (Figure 13.17).

(g) The ^{13}C-NMR spectrum of compound C shows peaks at δ 23.1, 68.92, 113.5, and 143.3. Assign these peaks to the appropriate carbons in compound C.



Crystals of hydroquinone viewed under polarizing light. (© Mel Pollinger/Fran Heyl Associates)

15

AROMATICS I: Benzene and Its Derivatives

Benzene is a colorless compound with a melting point of 6°C and a boiling point of 80°C. It was first isolated by Michael Faraday in 1825 from the oily residue that collected in the illuminating gas lines of London. Benzene's molecular formula, C_6H_6, suggests a high degree of unsaturation. Compared with a saturated alkane of molecular formula C_6H_{14}, it has an index of unsaturation of four which can be met by an appropriate combination of rings, double bonds, and triple bonds. For example, a compound of molecular formula C_6H_6 might have four double bonds, or three double bonds and one ring, or two double bonds and two rings, or one triple bond and two rings, and so on. Considering benzene's high degree of unsaturation, it might be expected to show many of the reactions characteristic of alkenes and alkynes. Yet benzene is remarkably stable! It does not undergo addition, oxidation, and reduction reactions characteristic of these two types of compounds. For example, benzene does not react with bromine, hydrogen chloride, or other reagents that usually add to carbon-carbon double and triple bonds. It is not oxidized by potassium permanganate or chromic acid under conditions that readily oxidize

alkenes and alkynes. When benzene reacts, it does so by substitution in which a hydrogen atom is replaced by another atom or group of atoms.

With the discovery of benzene and its derivatives, chemists recognized marked distinctions between two broad classes of organic compounds: aliphatic compounds and aromatic compounds. Butane, butene, butanoic acid, ethanol, and their higher homologs consist of chains of carbon atoms, and because the chemical and physical properties of these compounds resemble those of oleic acid, stearic acid, and other substances derived from fats, they were named **aliphatic compounds** (Greek: *aleiphat,* fat or oil).

The term **aromatic compound** was used to classify benzene and its derivatives because many of them have distinctive odors. It became clear, however, that a sounder classification for these compounds should be based on structure and chemical reactivity, not aroma. The term "aromatic" has been retained but now refers to the fact that these compounds are highly unsaturated and unexpectedly stable toward reagents that attack alkenes and alkynes.

The term **arene** is used to describe an aromatic hydrocarbon. A group derived from an aromatic hydrocarbon is called an aryl group, and is given our symbol Ar. Benzene is the parent arene.

15.1 The Structure of Benzene

Let us put ourselves in the mid-19th century and examine the evidence on which chemists attempted to build a model for the structure of benzene. First, because the molecular formula of benzene is C_6H_6, it seemed clear that the molecule must be highly unsaturated. Yet benzene does not show the chemical properties of alkenes, the only unsaturated hydrocarbons known at that time. Benzene does undergo chemical reactions, but its characteristic reaction is substitution rather than addition. When benzene is treated with bromine in the presence of a ferric bromide catalyst, only one compound of molecular formula C_6H_5Br is formed.

$$\underset{\text{Benzene}}{C_6H_6} + Br_2 \xrightarrow{FeBr_3} \underset{\text{Bromobenzene}}{C_6H_5Br} + HBr$$

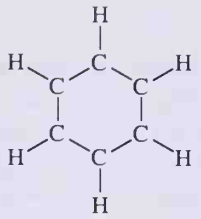
Chemists concluded, therefore, that all six hydrogens of benzene must be equivalent. When bromobenzene is treated with bromine in the presence of a ferric bromide catalyst, three isomeric dibromobenzenes are formed.

$$\underset{\text{Bromobenzene}}{C_6H_5Br} + Br_2 \xrightarrow{FeBr_3} \underset{\substack{\text{Three isomeric}\\ \text{dibromobenzenes}}}{C_6H_4Br_2} + HBr$$

For chemists in the mid-19th century, the problem was to incorporate these observations, along with the accepted tetravalence of carbon, into a structural formula for benzene. Before we examine these proposals, we should note that the problem of the structure of benzene and other aromatic hydrocarbons has occupied the efforts of chemists for over a century. Only since the 1930s has a general understanding of this problem been realized.

A. Kekulé's Model of Benzene

The first structure for benzene was proposed by August Kekulé in 1865 and consisted of a six-member ring with one hydrogen attached to each carbon.

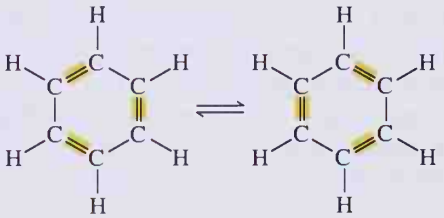


Structure for benzene
proposed by Kekulé in 1865

Now, more than 125 years after the time of Kekulé, we are apt to take for granted what scientists in his time knew and did not know. For example, it is a given to us that covalent bonds consist of one or more pairs of shared electrons. We must remember, however, that it was not until 1897 that J. J. Thomson, professor of physics at the Cavendish Laboratory at Cambridge University, discovered the electron. Thus, at the time Kekulé made his proposal for the structure of benzene, the existence of electrons and their role in chemical bonding was completely unknown.

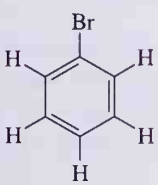
Thomson was awarded the Nobel Prize in physics in 1906.

Although Kekulé's structural formula provided for the equivalency of the C—H and C—C bonds, it was inadequate because all the carbon atoms were trivalent. To maintain the tetravalence of carbon, Kekulé proposed in 1872 that the ring contains three double bonds that shift back and forth so rapidly that the two forms cannot be separated. Each structure became known as a **Kekulé structure.**

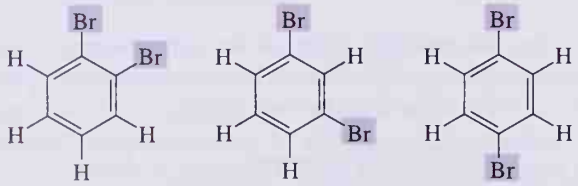


Two Kekulé structures for benzene,
proposed in 1872

This proposal accounted nicely for the fact that bromination of benzene gives only one bromobenzene, and bromination of bromobenzene gives three isomeric dibromobenzenes.



Bromobenzene

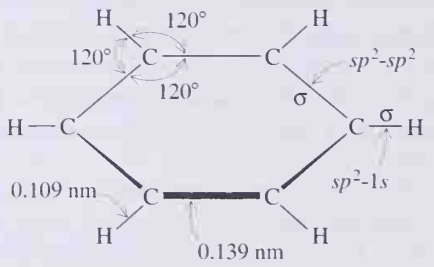


Three isomeric dibromobenzenes

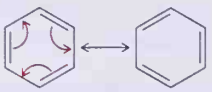
Although Kekulé's proposal was consistent with many experimental observations, it did not totally solve the problem and was contested for years. The major objection was that it did not account for the unusual chemical behavior of benzene. If benzene contains three double bonds, Kekulé's critics asked, why does it not show reactions typical of alkenes? Why, for example, does benzene not add 3 mol of bromine to form 1,2,3,4,5,6-hexabromocyclohexane?

B. The Valence Bond Model

The concepts of **hybridization of atomic orbitals** and **resonance,** developed by Linus Pauling in the 1930s, provided the first adequate description of the structure of benzene. The carbon skeleton of benzene forms a regular hexagon with C—C—C and H—C—C bond angles of 120°. For this type of bonding, carbon uses sp^2 hybrid orbitals. Each carbon forms sigma bonds to two adjacent carbons by overlap of sp^2-sp^2 hybrid orbitals, and one sigma bond to hydrogen by overlap of sp^2-1s orbitals. As determined experimentally, all carbon-carbon bonds are 0.139 nm in length, a value almost midway between that of a single bond between sp^3-hybridized carbons (0.147 nm) and a double bond between sp^2-hybridized carbons (0.133 nm).



Each carbon also has a single unhybridized 2p orbital perpendicular to the plane of the ring and containing one electron. These six parallel 2p orbitals overlap to form a continuous pi cloud encompassing all six carbon atoms. The electron density of the pi system of a benzene ring lies in one torus (a doughnut-shaped region) above the plane of the ring and a second torus below the plane of the ring (Figure 15.1). In the valence bond model, we show benzene as a resonance hybrid of two equivalent contributing structures, often referred to as Kekulé structures. Each Kekulé structure makes an equal contribution to the hybrid, and thus the C—C bonds are neither single nor double bonds but something intermediate.



Benzene as a hybrid of two equivalent contributing structures

We recognize full well that neither of these contributing structures exists; they are merely alternative ways to pair 2p orbitals with no reason to prefer one or the other. Nevertheless, chemists continue to use a single contributing structure to represent this molecule because it is as close as we can come to an accurate structure within the limitations of classical valence bond structures and the tetravalence of carbon.

The hybrid structure of benzene is also represented by a regular hexagon with an inscribed circle representing the six delocalized pi electrons.

A single Kekulé structure and a hexagon with an inscribed circle are widely used within the field as representations for benzene. In this textbook we use the Kekulé structure almost

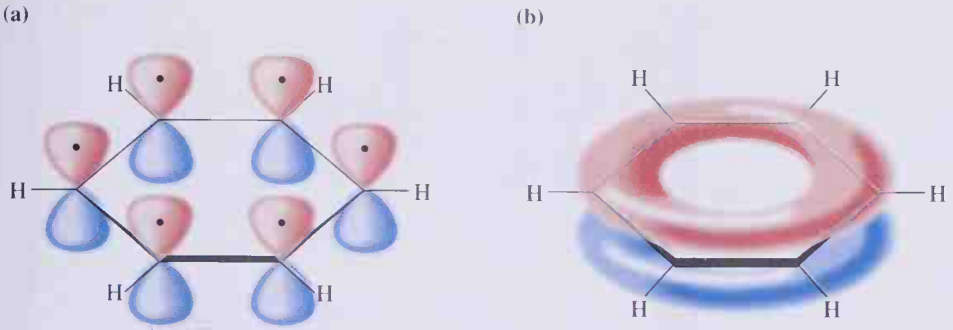


Figure 15.1
Valence bond model of bonding in benzene. (a) The carbon, hydrogen framework. The six $2p$ orbitals, each with one electron, are shown uncombined. (b) Overlap of parallel $2p$ orbitals to form a continuous pi cloud, shown by one torus above the plane of the ring and a second torus below the plane of the ring.

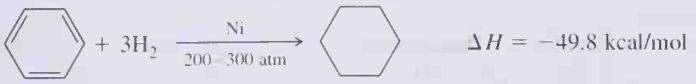
exclusively because, when dealing with reaction mechanisms of aromatic compounds, this representation makes it easier to count electrons and to do electron bookkeeping.

C. The Resonance Energy of Benzene

Resonance energy is the difference in energy between a resonance hybrid and its most stable contributing structure in which electron density is localized on particular atoms and in particular covalent bonds. The first experimental determination of the resonance energy of benzene was carried out by George Kistiakowski at Harvard University and involved comparison of the heats of hydrogenation of benzene and cyclohexene. Cyclohexene is readily reduced to cyclohexane by hydrogen in the presence of a transition metal catalyst (Section 5.8).

Cyclohexene Cyclohexane

Under these conditions, benzene is reduced only slowly to cyclohexane. It is reduced more rapidly when heated and under a pressure of several hundred atmospheres of hydrogen.



Benzene Cyclohexane

Catalytic hydrogenation of an alkene is an exothermic reaction. The heat of hydrogenation per double bond varies somewhat with the degree of substitution of the particular alkene; for cyclohexene, $\Delta H = -28.6$ kcal/mol. If we consider benzene to be 1,3,5-cyclohexatriene, a hypothetical unsaturated compound with alternating single and double bonds, we calculate that $\Delta H = 3(-28.6 \text{ kcal/mol}) = -85.8$ kcal/mol. Kistiakowski determined that ΔH for reduction of benzene to cyclohexane is only -49.8 kcal/mol, considerably less

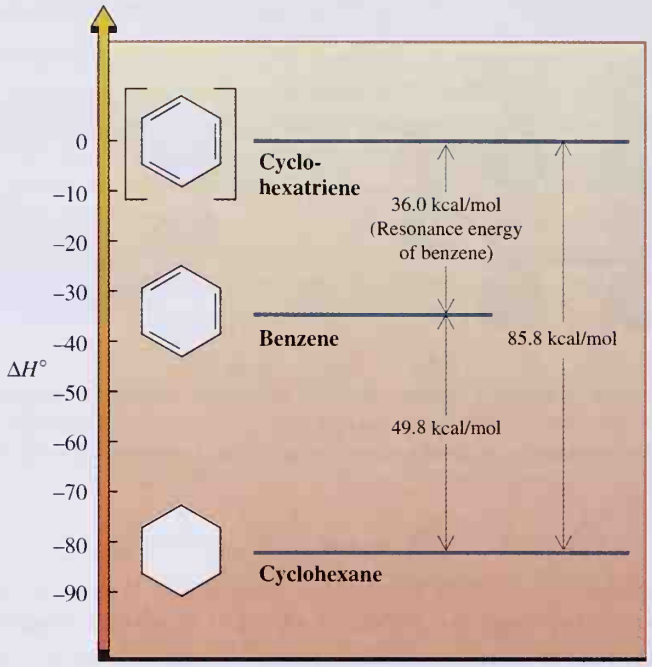
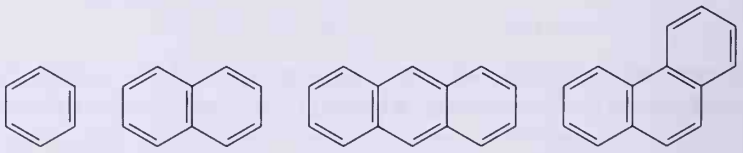


Figure 15.2
The resonance energy of benzene as determined by comparison of heats of hydrogenation of cyclohexene, benzene, and the hypothetical molecule 1,3,5-cyclohexatriene.

than that calculated for 1,3,5-cyclohexatriene. The difference between these values, 36.0 kcal/mol, is the **resonance energy of benzene.** These experimental results are shown graphically in Figure 15.2. There have been several other experimental determinations of the resonance energy of benzene using different model compounds, and although these determinations differ somewhat in their results, they all agree that the resonance stabilization of benzene is large. Following are resonance energies for several other aromatic hydrocarbons.



Resonance energy in kilocalories per mole:	Benzene	Naphthalene	Anthracene	Phenanthrene
	36	61	83	91

D. The Molecular Orbital Model of Benzene

According to molecular orbital theory, the skeletal framework of benzene consists of six carbons and six hydrogens arranged in a planar array. To simplify the discussion, we consider only the MOs formed by the uncombined $2p$ orbitals; the other MOs are not relevant at this point. Combination of six parallel $2p$ orbitals gives a set of six pi MOs.

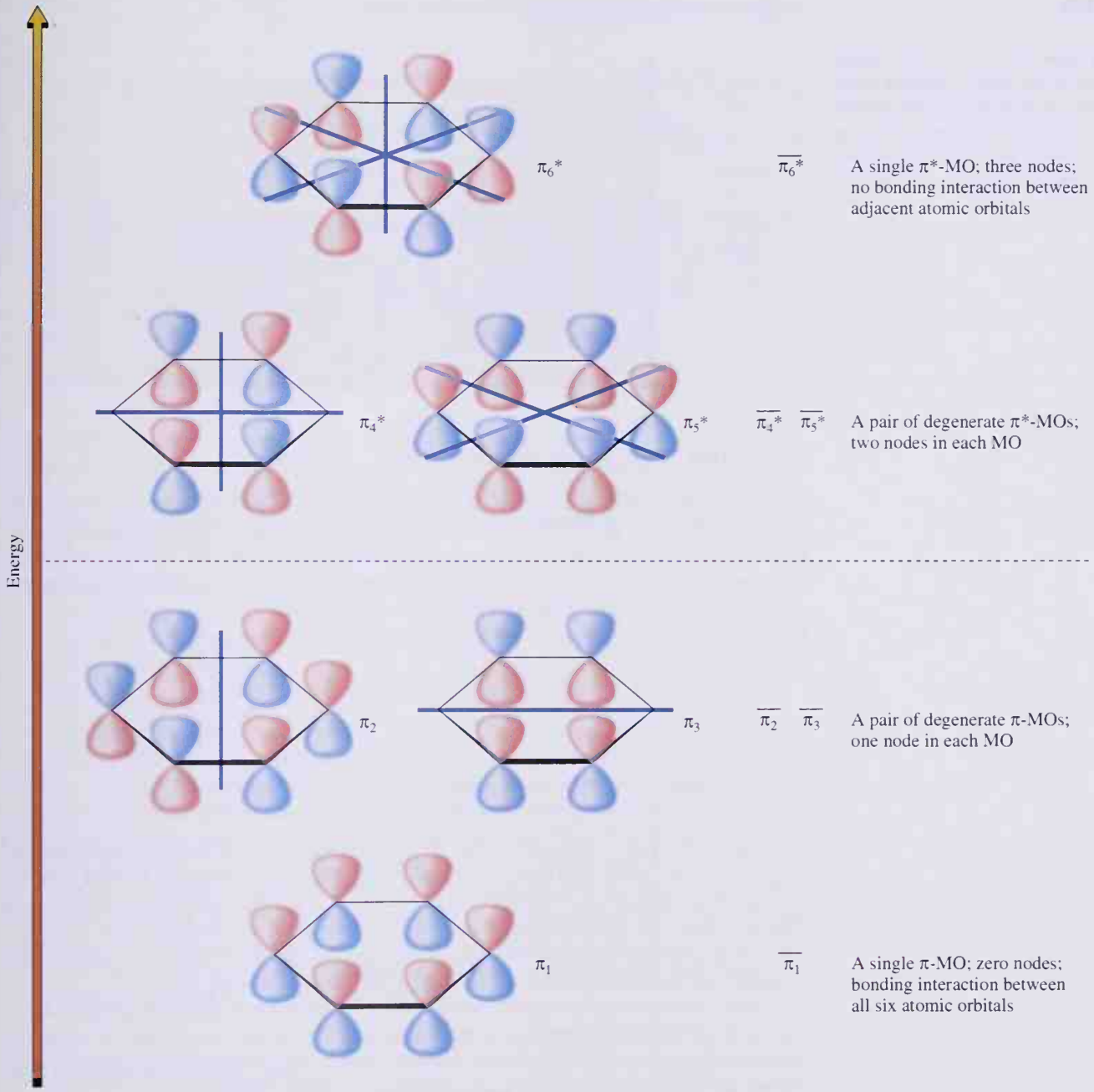


Figure 15.3
The molecular orbital representation of the pi bonding in benzene.

These orbitals along with their relative energies are shown in Figure 15.3. There are six electrons in the pi system of benzene, and in the ground state, these electrons occupy the three bonding MOs (Figure 15.4). The great stability of benzene results from the fact that these three bonding MOs are of much lower energy compared with the six uncombined $2p$ atomic orbitals.

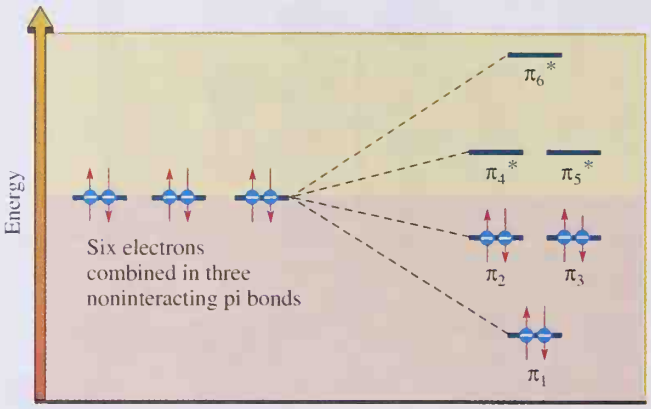
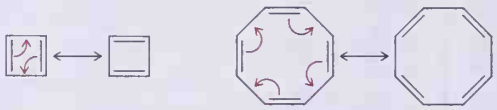


Figure 15.4
Molecular orbital energy diagram for benzene. In the ground state, only the three low-energy, pi bonding molecular orbitals are occupied.

15.2 The Concept of Aromaticity

Resonance theory is a powerful tool with which chemists can understand the unusual stability of benzene and its derivatives. According to resonance theory, benzene is best represented as a hybrid of two equivalent contributing structures. By analogy cyclobutadiene and cyclooctatetraene can also be drawn as hybrids of two contributing structures. Are either of these compounds aromatic?



Cyclobutadiene as a hybrid of two equivalent contributing structures

Cyclooctatetraene as a hybrid of two equivalent contributing structures

The answer for both compounds is no. Repeated attempts to synthesize cyclobutadiene failed. It was not until 1965 that it was finally synthesized and even then it could only be detected if trapped at 4 K (−269°C). Cyclobutadiene is a highly unstable compound and does not show any of the chemical and physical properties we associate with aromatic compounds. Cyclooctatetraene has chemical properties typical of alkenes. It reacts with halogens and halogen acids, as well as mild oxidizing and reducing agents.

Thus, while resonance theory is of great value in helping us to understand many of the chemical and physical properties of molecules and ions, it fails to provide an adequate understanding of aromaticity. Stated in broad terms, the question facing chemists was "What are the fundamental principles underlying aromatic character?"

A. Hückel's Criteria for Aromaticity

The underlying criteria for aromaticity were first recognized in the early 1930s by Erich Hückel, a German chemical physicist. He carried out MO energy calculations for cyclic, planar molecules in which each atom of the ring has one $2p$ orbital available for forming sets of molecular orbitals. His calculations demonstrated that cyclic, planar molecules with 2, 6, 10, 14, 18, and so on pi electrons in a fully conjugated system should be aromatic.

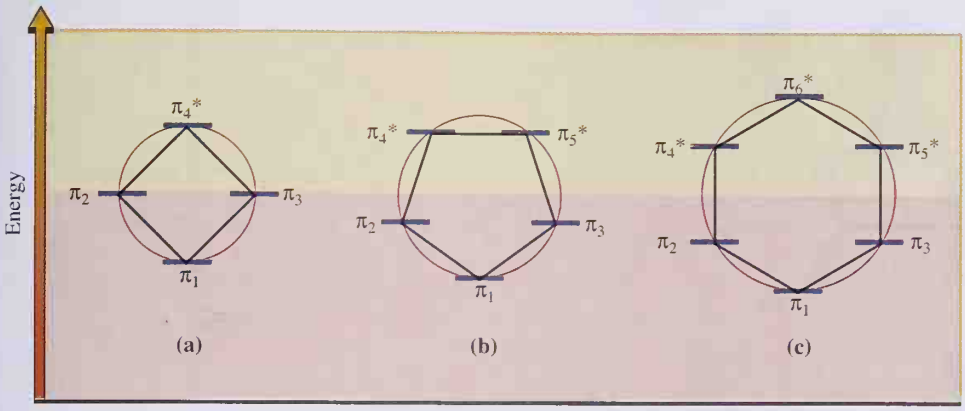


Figure 15.5
Frosti circles showing the number and relative energies of the molecular orbitals for planar, fully conjugated four-member, five-member, and six-member rings.

These numbers are generalized in the **(4*n* + 2) pi electron rule,** where *n* is a positive integer (0, 1, 2, 3, 4, . . .). Conversely, cyclic, planar molecules with 4*n* pi electrons (4, 8, 12, 16, 20, . . .) are especially unstable and are said to be antiaromatic. We have more to say about antiaromaticity shortly. Huckel's **criteria for aromaticity** are summarized as follows. To be aromatic, a compound must

1. Be cyclic
2. Have one *p* orbital on each atom of the ring
3. Be planar or nearly planar so that there is continuous or nearly continuous overlap of all *p* orbitals of the ring
4. Have 4*n* + 2 pi electrons in the cyclic arrangement of *p* orbitals

To determine whether a compound is aromatic or antiaromatic, it is necessary to construct an MO energy diagram of the molecule or ion. The patterns of MOs for planar, cyclic, conjugated systems can be constructed quite easily using the **Frosti circle,** or **inscribed polygon, method.** To construct such a diagram, draw a circle and then inscribe a polygon of the same number of atoms as the ring in question. Inscribe it in such a way that one point of the polygon is at the bottom of the circle. The relative energies of the MOs in the ring are then given by the points where the polygon touches the circle. Those MOs below the horizontal line through the center of the circle are bonding MOs. Those on the horizontal line are nonbonding MOs, and those above the line are antibonding MOs. Shown in Figure 15.5 are Frosti circles showing the MOs of cyclic, planar, and conjugated four-member, five-member, and six-member rings.

B. Antiaromatic Hydrocarbons

An **antiaromatic hydrocarbon** is one that is less stable than its acyclic analog of the same number of pi electrons. According to the Hückel criteria, cyclobutadiene is antiaromatic. To understand better why cyclobutadiene is not aromatic and the meaning of the term "antiaromatic," let us look at an MO energy diagram for this molecule. In constructing this diagram, we assume that cyclobutadiene is planar, that all carbon-carbon bond lengths are equal, that it contains four 2*p* atomic orbitals, and that these four atomic orbitals combine to give the set of four MOs shown in Figure 15.6. Let us now compare the electron configuration of planar cyclobutadiene with the electron configuration of planar 1,3-buta-

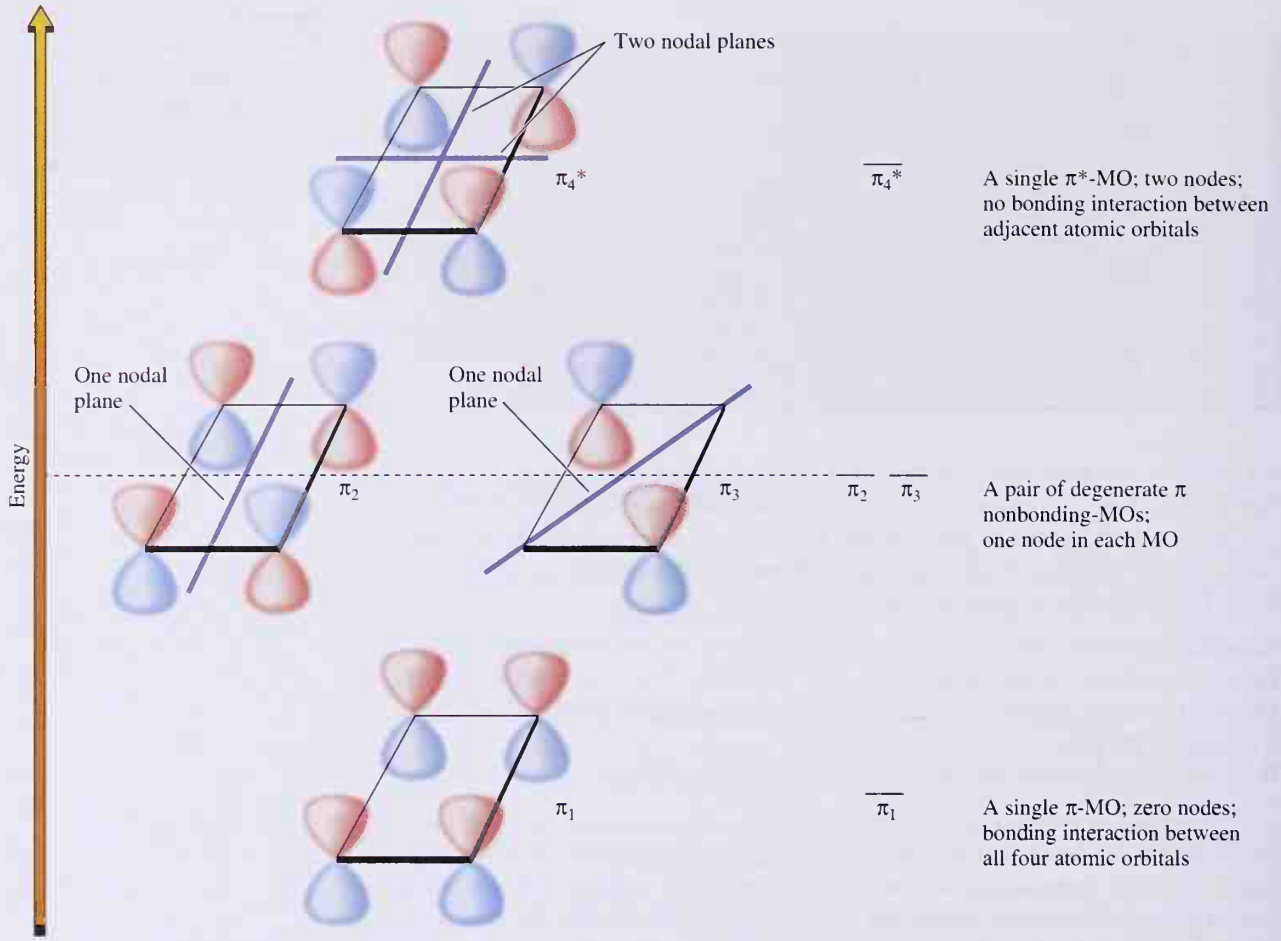


Figure 15.6
Pi molecular orbitals of cyclobutadiene: one bonding MO, a pair of degenerate nonbonding MOs, and one antibonding MO.

diene, the acyclic analog of cyclobutadiene. In the ground-state electron configuration of butadiene (Figure 7.3), the four electrons of the pi system lie in two low-lying bonding MOs. In the ground-state electron configuration of cyclobutadiene, two pi electrons fill the π_1 bonding MO. The third and fourth pi electrons are unpaired and lie in π_2 and π_3 nonbonding MOs (Figure 15.7). It is the existence of these two unpaired electrons in planar cyclobutadiene that makes this molecule so highly unstable and reactive compared with its acyclic analog that has conjugated double bonds.

Cyclooctatetraene is not aromatic for the following reason. X-ray studies show clearly that the most stable conformation for the molecule is a nonplanar tub conformation with two distinct types of carbon-carbon bonds, four longer carbon-carbon single bonds, and four shorter carbon-carbon double bonds. The four single bonds are equal in length to the single bonds in alkanes (approximately 0.147 nm), and the four double bonds are equal in length to double bonds in alkenes (approximately 0.133 nm). In the tub conformation, the overlap of 2*p* orbitals on carbons forming double bonds is excellent, but almost no overlap

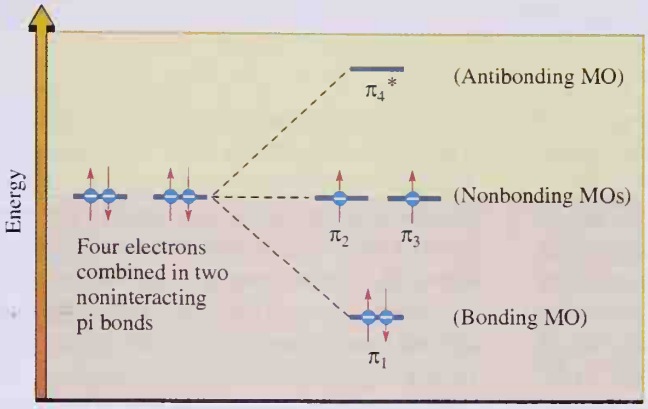
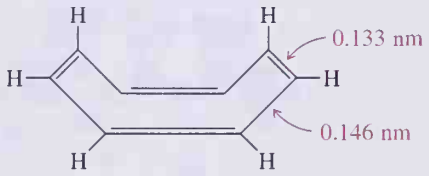


Figure 15.7
Molecular orbital energy diagram for cyclobutadiene. In the ground state, two electrons are in the low-lying π_1 bonding MO. The remaining two electrons are unpaired and occupy the degenerate π_2 and π_3 nonbonding MOs.

of $2p$ orbitals occurs on either end of carbon-carbon single bonds because the corresponding $2p$ orbitals are not parallel. Cyclooctatetraene shows reactions typical of alkenes and is classified as nonaromatic.



1,3,5,7-Cyclooctatetraene
(tub conformation with alternating
single and double bonds)

To appreciate why planar cyclooctatetraene would be classified as antiaromatic, we need to examine the MO energy diagram shown in Figure 15.8. (Note that the most stable conformation of this molecule is not planar, but if it were, Figure 15.8 would be its MO energy

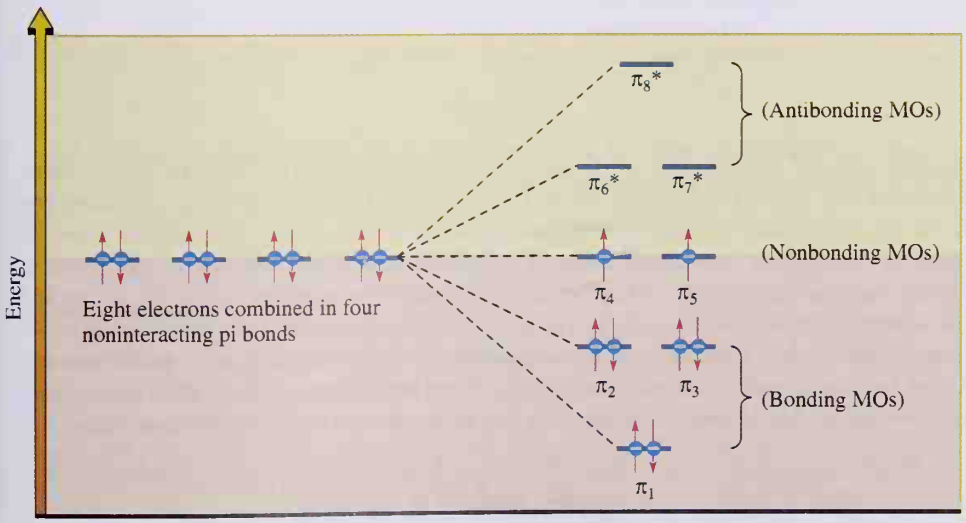


Figure 15.8
Molecular orbital energy diagram for a planar conformation of cyclooctatetraene. Three pairs of electrons fill the three low-lying bonding MOs. Two electrons are unpaired in degenerate pi nonbonding MOs.

CHEMISTRY IN ACTION

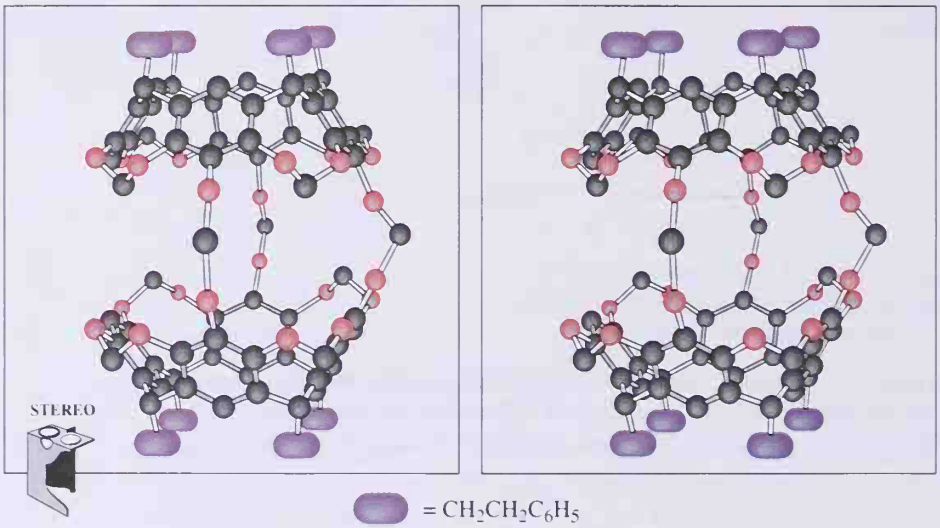
Isolation of Cyclobutadiene

Cyclobutadiene, an antiaromatic molecule, is one of the most reactive and unstable molecules in organic chemistry. One technique used for its study is matrix isolation. A precursor which gives cyclobutadiene on UV irradiation is mixed with some inert liquid or gas (for example argon or xenon) and the mixture is frozen near 4 K on a transparent support. Irradiation of the precursor generates cyclobutadiene, frozen in the matrix of inert gas. The product can then be characterized by IR and UV spectroscopy.

A second strategy has been to synthesize derivatives of cyclobutadiene with bulky substituents. This makes it impossible for the molecule to dimerize, which allows for the molecule to be handled in solution. Both the tri-*tert*-butyl and tetra-*tert*-butyl derivatives of cyclobutadiene have been made and are reasonably stable.

By far the most unusual approach to stabilizing cyclobutadiene came from the laboratories of D. J. Cram (University of California, Los Angeles), a pioneer in "host-guest chemistry." The host in host-guest chemis-

Compound 1



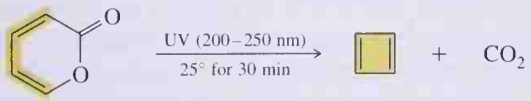
A hemicarcerand

diagram.) In the ground state of planar cyclooctatetraene, six pi electrons fill the three low-lying π_1, π_2, and π_3 bonding MOs. The remaining two pi electrons are unpaired and lie in the degenerate π_4 and π_5 nonbonding MOs. It is because of these two unpaired electrons that planar cyclooctatetraene, if it existed, would be classified as antiaromatic. Cyclooctatetraene, however, is large enough to pucker into a nonplanar conformation and become nonaromatic. We are now in a position to understand more fully the meaning of the term "antiaromatic." **Antiaromatic compounds** are cyclic, planar, have continuous overlap of $2p$ orbitals, and contain $4n$ pi electrons. When forced into a planar conformation with continuous overlap of $2p$ orbitals, the resulting structures are highly destabilized relative to

A noncyclic conjugated analog (compare 1,3-butadiene with all pi electrons paired versus cyclobutadiene with two unpaired pi electrons) or

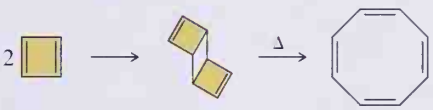
try is a relatively large molecule with an internal cavity which can serve as a host for a smaller, guest molecule. Compound 1 is an example of a recently prepared host molecule called a hemicarcerand (because it is capable of incarcerating guest molecules). Notice that in 1 there are two bands of four benzene rings, with three of the top benzene rings each linked to a different benzene ring along the bottom band. This molecule behaves like a clam shell. The three pairs of linked benzene rings act like hinges and the fourth benzene rings act as a mouth. At low temperatures, the mouth is closed, but as the temperature is raised to 100°C the molecule undergoes a conformational change, and the mouth opens. Molecules of the right size can enter into the cavity of the hemicarcerand, and as the temperature is reduced to room temperature, the mouth closes and the guest is trapped inside.

To trap cyclobutadiene inside 1, first a precursor molecule had to be introduced into the cavity. This was done by heating 1 with a large excess of α-pyrone. When α-pyrone is irradiated by UV light, it loses CO_2 and forms cyclobutadiene.



α-Pyrone Cyclobutadiene

The formation of the host-guest complex 1-(α-pyrone) was established by ^{1}H-NMR spectroscopy and elemental analysis. When the host-guest complex was irradiated with UV light at 25°C, the ^{1}H-NMR signals of the guest α-pyrone disappeared, and a signal for cyclobutadiene appeared at δ 2.35. Further evidence that cyclobutadiene was trapped inside the molecular cavity came when the product of irradiation was heated at 220°C. At this temperature, the mouth of the cavity opened, allowing the guest molecule to escape. Heating under these conditions gave 1 and cyclooctatetraene. Cyclooctatetraene is a major dimerization product of cyclobutadiene.



Cyclobutadiene Cyclooctatetraene

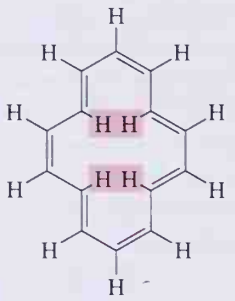
Additional spectroscopic and chemical evidence clearly established that the highly reactive cyclobutadiene had been trapped inside 1 and, in there, was stable at room temperature. Because unreactive C—C and C—O bonds lined its molecular cage, cyclobutadiene could undergo no chemical reactions with its surroundings. Like some vicious beast, it could now be studied without being a danger to itself or others.

A nonplanar conformation of the same molecule (compare tub-shaped cyclooctatetraene with all pi electrons paired versus planar cyclooctatetraene with two unpaired pi electrons).

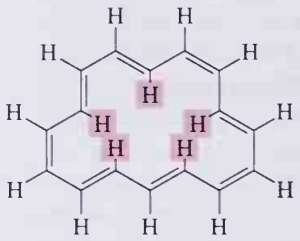
C. Annulenes

Cyclobutadiene, benzene, and cyclooctatetraene are the first members of a family of molecules called annulenes. An **annulene** is a cyclic hydrocarbon with continuous alternation of single and double bonds. The name of an annulene is derived by showing the number of atoms in the ring in brackets followed by the word annulene. Named as annulenes, cyclobutadiene, benzene, and cyclooctatetraene are [4]annulene, [6]annulene, and [8]annulene, respectively. These compounds, however, are rarely named as annulenes.

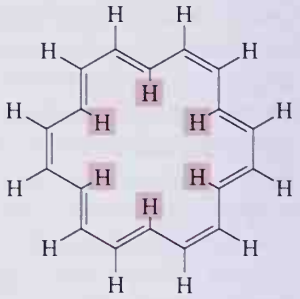
Beginning in the 1960s Franz Sondheimer and his colleagues, first at the Weizmann Institute in Israel and later at the University of London, synthesized a number of larger annulenes, primarily to test the validity of Hückel's criteria for aromaticity. They found, for example, that both [14]annulene and [18]annulene are aromatic, as predicted by Hückel. If [16]annulene were planar, it would be antiaromatic. The size of the ring, however, is large enough so it can pucker into a nonplanar conformation in which the double bonds are no longer in conjugation. [16]Annulene, therefore, is nonaromatic. [18]Annulene is aromatic, as predicted, and has a resonance energy of approximately 100 kcal/mol.



[14]Annulene
(aromatic)



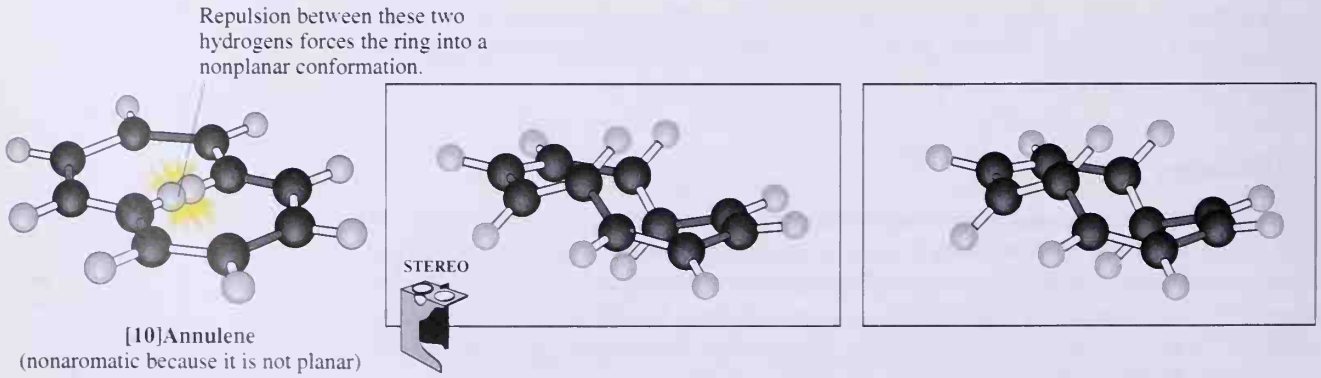
[16]Annulene
(nonaromatic)



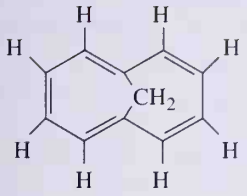
[18]Annulene
(aromatic)

Notice that in these larger annulenes, there are two sets of equivalent hydrogens: those that point outward from the ring and those that point inward to the center of the ring. As we see later in this chapter, these two sets of equivalent hydrogens have quite different ^{1}H-NMR chemical shifts.

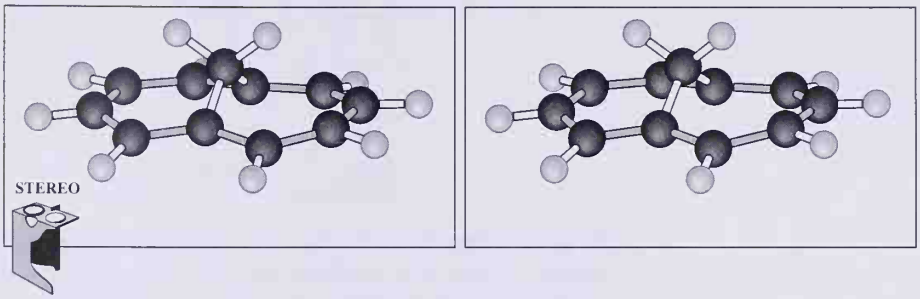
According to Hückel's criteria, [10]annulene should be aromatic; it is cyclic, has one $2p$ orbital on each carbon of the ring, and has $4(2) + 2 = 10$ electrons in the pi system. It has been found, however, that the molecule is not aromatic. The reason lies in the fact that the ring is too small to accommodate the two hydrogens that point inward toward the center of the ring. Repulsion between these two hydrogens forces the ring into a nonplanar conformation in which the overlap of all ten $2p$ orbitals is no longer continuous. Therefore, because [10]annulene is not planar, it is not aromatic. It shows reactions typical of alkenes and is classified as nonaromatic. What is remarkable is that if the two hydrogen atoms facing inward toward the center of the ring are replaced by a $—CH_2—$ group, the ring is now able to assume a conformation close enough to planar that it becomes aromatic.



[10]Annulene
(nonaromatic because it is not planar)

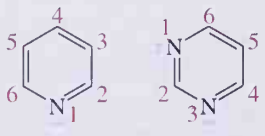


Bicyclo[4.4.1]undeca-1,3,5,7,9-pentaene



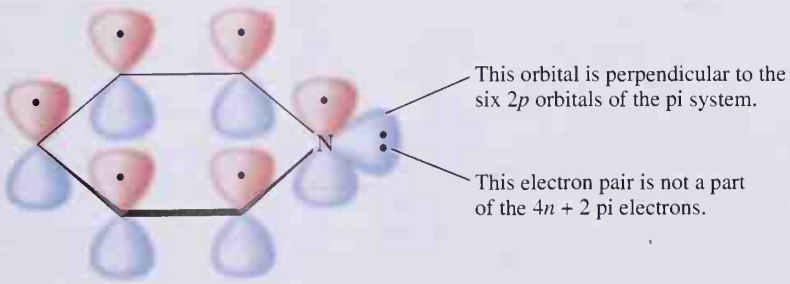
D. Heterocyclic Aromatic Compounds

Aromatic character is not limited to hydrocarbons but is found in heterocyclic compounds as well. A **heterocyclic compound** is one that contains more than one kind of atom in a ring. As the term is used in organic chemistry, it refers to a ring in which one or more of the atoms is other than carbon. Pyridine and pyrimidine are heterocyclic analogs of benzene. In pyridine, one CH unit of benzene is replaced by nitrogen and in pyrimidine, two CH units are replaced by nitrogens.



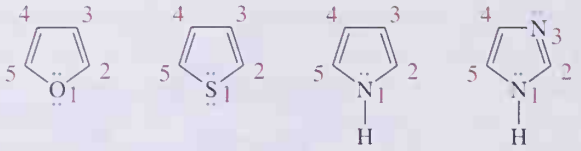
Pyridine Pyrimidine

Each molecule meets the Hückel criteria for aromaticity. Each is cyclic and planar, has one $2p$ orbital on each atom of the ring, and has six electrons in the pi system. In pyridine, nitrogen is sp^2-hybridized, and its unshared pair of electrons occupies an sp^2 orbital perpendicular to the $2p$ orbitals of the pi system, and thus is not a part of the pi system. In pyrimidine, neither unshared pair of electrons of nitrogen is part of the pi system. The resonance energy of pyridine is 32 kcal/mol, slightly less than that of benzene. The resonance energy of pyrimidine is 26 kcal/mol.



Pyridine

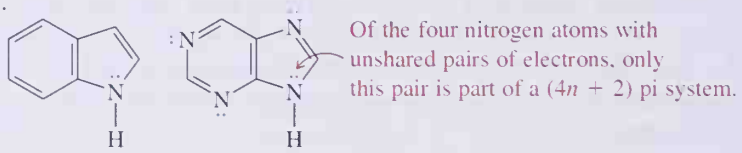
The five-member ring compounds furan, thiophene, pyrrole, and imidazole are also aromatic.



Furan Thiophene Pyrrole Imidazole

In these planar compounds, each heteroatom is sp^2-hybridized, and its unhybridized p orbital is part of a continuous cycle of five $2p$ orbitals. In furan and thiophene, one unshared pair of electrons of the heteroatom lies in the unhybridized $2p$ orbital and is a part of the pi system (Figure 15.9). The other unshared pair of electrons lies in an sp^2 hybrid orbital, perpendicular to the $2p$ orbitals, and is not a part of the pi system.

Nature abounds with compounds having a heterocyclic aromatic ring fused to one or more other rings. Two such compounds especially important in the biological world are indole and purine.



Indole Purine

Indole contains a pyrrole ring fused with a benzene ring. Compounds derived from indole include the essential amino acid L-tryptophan and the neurotransmitter serotonin. Purine contains a six-member pyrimidine ring fused with a five-member imidazole ring. Compounds derived from purine and pyrimidine are building blocks of deoxyribonucleic acids (DNA) and ribonucleic acids (RNA).

E. Aromatic Hydrocarbon Ions

Any neutral monocyclic unsaturated hydrocarbon with an odd number of carbons in the ring must of necessity have at least one —CH_2— group in the ring and, therefore, cannot

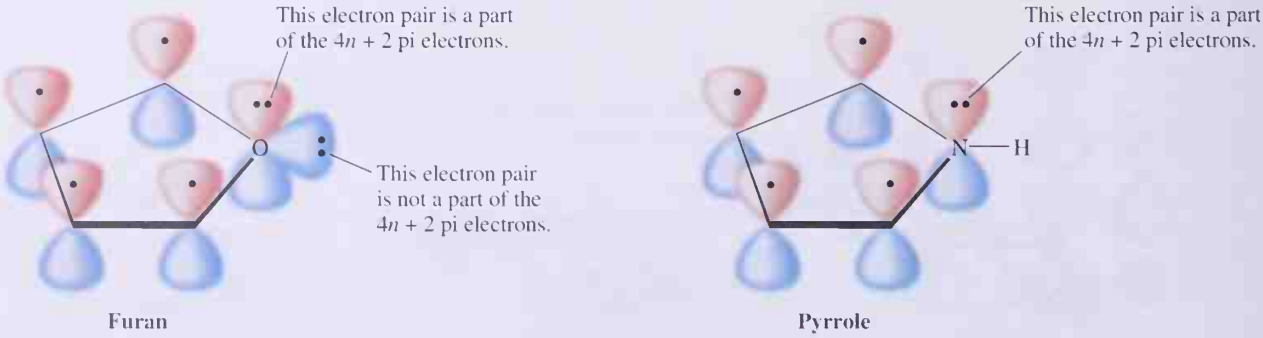
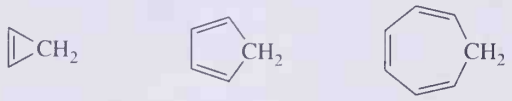


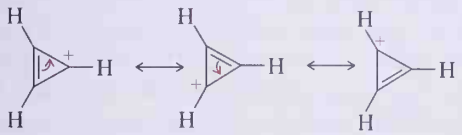
Figure 15.9
Origin of the $(4n + 2)$ pi electrons in furan and pyrrole. The resonance energy of furan is 16 kcal/mol; the resonance energy of pyrrole is 21 kcal/mol.

be aromatic. Examples of such hydrocarbons are cyclopropene, cyclopentadiene, and cycloheptatriene.

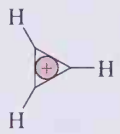


Cyclopropene Cyclopentadiene Cycloheptatriene

Cyclopropene has the correct number of pi electrons to be aromatic, namely $4(0) + 2 = 2$, but it does not have a continuous cycle of $2p$ orbitals. If, however, the $—CH_2—$ group becomes an sp^2-hybridized cation with a vacant $2p$ orbital, then the overlap of orbitals is continuous, and, according to molecular orbital theory, the **cyclopropenyl cation** should be aromatic. The cyclopropenyl cation can be drawn as a hybrid of three equivalent contributing structures. Note that the fact that we can draw three equivalent contributing structures is not the key to the aromaticity of this cation; the key is that it meets the Hückel criteria of aromaticity. Cyclopropenyl cation may also be represented by a triangle with an inscribed circle and a plus sign.

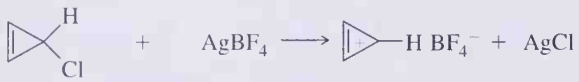


Cyclopropenyl cation represented as a hybrid of three equivalent contributing structures



Aromaticity of the cyclopropenyl cation shown by an inscribed circle and plus sign

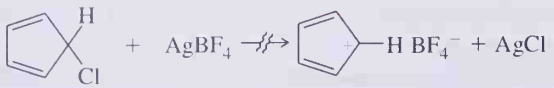
As an example of the aromatic stabilization of this cation, 3-chlorocyclopropene reacts readily with silver tetrafluoroborate to form a stable salt.



3-Chlorocyclopropene (Cyclopropenyl chloride)

Cyclopropenyl tetrafluoroborate

This chemical behavior is to be contrasted with that of 5-chloro-1,3-cyclopentadiene, which does not form a stable salt under these conditions. In fact, a cyclic, planar, conjugated cyclopentadienyl cation has four pi electrons, and, if formed, it would be antiaromatic.

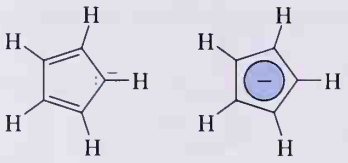


5-Chloro-1,3-cyclopentadiene

Cyclopentadienyl tetrafluoroborate

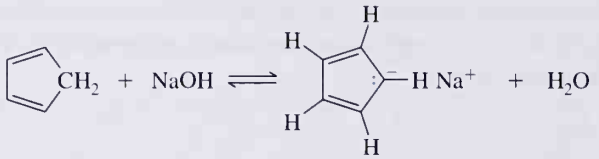
Note that it is possible to draw five equivalent contributing structures for the cyclopentadienyl cation. Yet this cation is not aromatic because it has only $4n$ pi electrons rather than the required $4n + 2$ pi electrons.

To form an aromatic ion from cyclopentadiene, it is necessary to convert the $—CH_2—$ group to an anion in which the $—CH—$ group becomes sp^2-hybridized and has two electrons in its unhybridized $2p$ orbital. The resulting **cyclopentadienyl anion** is aromatic.



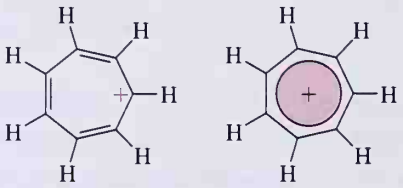
Cyclopentadienyl anion
(aromatic)

Evidence of the stability of this anion is the fact that cyclopentadiene has a pK_a of approximately 16.0 and is the most acidic hydrocarbon known. The acidity of cyclopentadiene is comparable to that of water (pK_a = 15.7). Consequently, when cyclopentadiene is treated with aqueous sodium hydroxide, an equilibrium is established in which some of the hydrocarbon is converted to its aromatic anion. K_{eq} for this equilibrium is approximately 0.5.



pK_a = 16.0			pK_a = 15.7
(weaker acid)	(weaker base)	(stronger base)	(stronger acid)

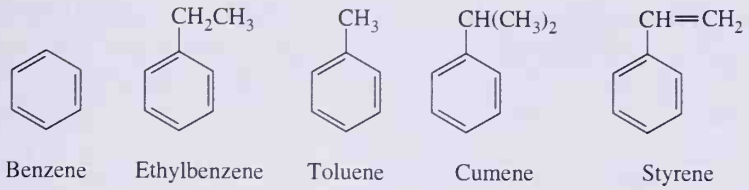
Cycloheptatriene forms an aromatic cation by conversion of its —CH_2— group to sp^2-hybridized carbon with a vacant 2*p* atomic orbital. The **cycloheptatrienyl cation (tropylium ion)** is planar and has six pi electrons in seven 2*p* orbitals, one from each atom of the ring. It can be drawn as a hybrid of seven equivalent contributing structures.



Cycloheptatrienyl cation
(Tropylium ion)
(aromatic)

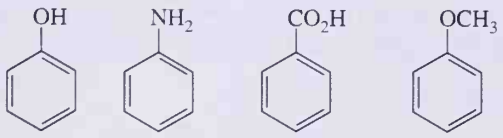
15.3 Nomenclature

The name **benzene** was given to the parent aromatic hydrocarbon because one of its sources was benzoic acid, which in turn, had been isolated from gum benzoin, a resin in certain trees in Sumatra and Java. Monosubstituted alkyl benzenes are named as derivatives of benzene, as for example, ethylbenzene. The IUPAC system also retains certain common names for several of the simpler monosubstituted alkyl benzenes. Examples are **toluene** (rather than methylbenzene), **cumene** (rather than isopropylbenzene), and **styrene.**



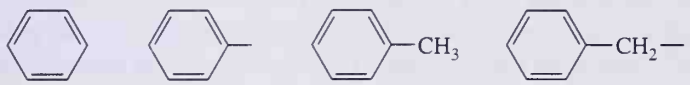
Benzene Ethylbenzene Toluene Cumene Styrene

Four other common names, **phenol, aniline, benzoic acid,** and **anisole,** are also retained by the IUPAC system.



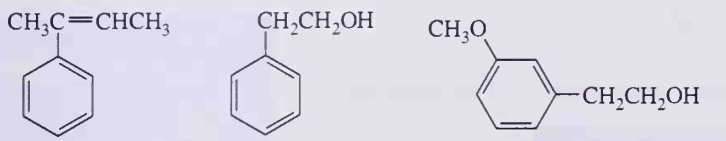
Phenol Aniline Benzoic acid Anisole

In more complex molecules, the benzene ring is often named as a substituent on a parent chain. In this case, the C_6H_5— group is given the name **phenyl.** You might think that when present as a substituent, benzene would become benzyl, just as ethane becomes ethyl. Not so! The name **benzyl** is used instead for $C_6H_5CH_2$—, a substituent group derived from toluene. "Phene" is a now-obsolete name for benzene and although this name is no longer used, a derivative has persisted in the name phenyl. Following are structural formulas for the phenyl group and the benzyl group:



Benzene Phenyl group Toluene Benzyl group

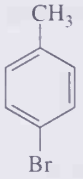
In molecules containing other functional groups, the phenyl group and its derivatives are named as substituents.



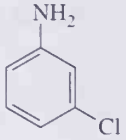
2-Phenyl-2-butene 2-Phenylethanol 2-(3-Methoxyphenyl)ethanol

When two substituents occur on a benzene ring, three constitutional isomers are possible. The substituents may be located by numbering the atoms of the ring or by using the locators **ortho, meta,** and **para.** 1,2- is equivalent to ortho (Greek: straight); 1,3- is equivalent to meta (Greek: after), and 1,4- is equivalent to para (Greek: beyond).

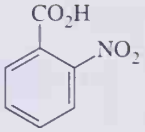
When one of the two substituents on the ring imparts a special name to the ring, as for example toluene, cumene, phenol, and aniline, then the compound is named as a derivative of that parent molecule. The special substituent is assumed to occupy ring position #1. The IUPAC system retains the common name **xylene** for the three isomeric dimethylbenzenes.



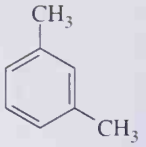
4-Bromotoluene
(*p*-Bromotoluene)



3-Chloroaniline
(*m*-Chloroaniline)

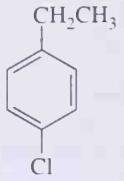


2-Nitrobenzoic acid
(*o*-Nitrobenzoic acid)

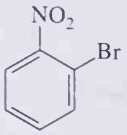


m-Xylene

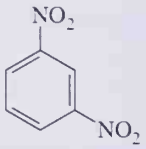
Where neither group imparts a special name, then the two substituents are located and listed in alphabetical order before the ending -benzene. The carbon of the benzene ring with the substituent of lower alphabetical ranking is numbered C-1.



1-Chloro-4-ethylbenzene
(*p*-Chloroethylbenzene)

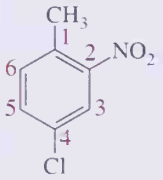


1-Bromo-2-nitrobenzene
(*o*-Bromonitrobenzene)

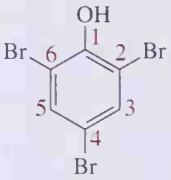


1,3-Dinitrobenzene
(*m*-Dinitrobenzene)

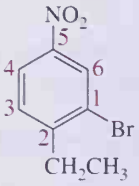
When three or more substituents are present on a ring, their locations are specified by numerals. If one of the substituents imparts a special name, then the molecule is named as a derivative of that parent name. If none of the substituents imparts a special name, then the substituents are located and listed in alphabetical order before the ending -benzene. In the following examples, the first compound is a derivative of toluene and the second a derivative of phenol. There is no special name for the third compound and, therefore, the three substituents are listed in alphabetical order.



4-Chloro-2-nitrotoluene



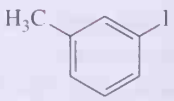
2,4,6-Tribromophenol

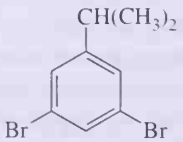


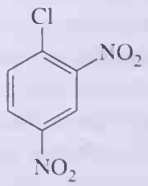
1-Bromo-2-ethyl-5-nitrobenzene

EXAMPLE 15.1

Write names for these molecules.

(a) 

(b) 

(c) 

Solution

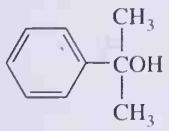
(a) This compound is a derivative of toluene, so the carbon bearing the methyl group is numbered C-1. Its name is 3-iodotoluene or *m*-iodotoluene.

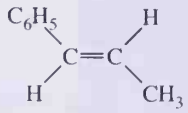
(b) This compound is a derivative of cumene, so the carbon bearing the isopropyl group is numbered C-1. Its name is 3,5-dibromocumene.

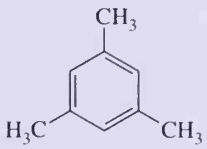
(c) 1-Chloro-2,4-dinitrobenzene.

PROBLEM 15.1

Write names for these molecules.

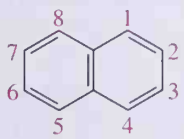
(a) 

(b) 

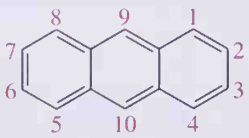
(c) 

Polynuclear aromatic hydrocarbons (PAHs) contain two or more benzene rings, each pair of which shares two ring carbon atoms. Naphthalene, anthracene, and phenanthrene, the most common PAHs, and other substances derived from them are found in coal tar and high-boiling petroleum residues. At one time, naphthalene was used as a moth repellant and insecticide in preserving linens, clothing, and furs, but its use has decreased due to the introduction of chlorinated hydrocarbons such as *p*-dichlorobenzene.

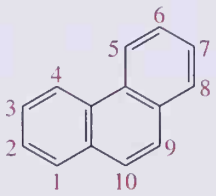
In numbering PAHs, carbon atoms common to two or more rings are not numbered because they have no replaceable hydrogens.



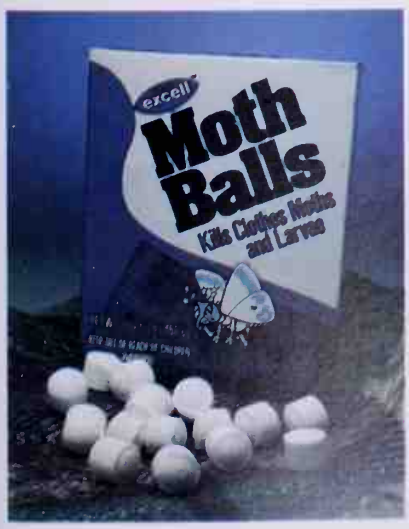
Naphthalene



Anthracene



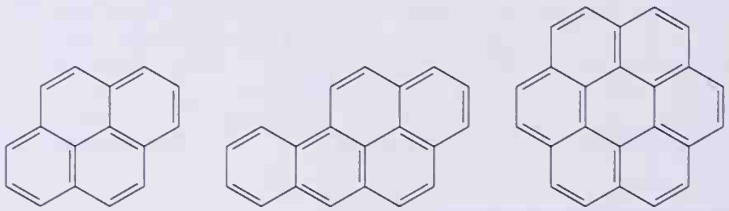
Phenanthrene



Naphthalene "moth balls." *(Charles D. Winters)*

Automobile exhaust and cigarette smoke both contain traces of benzo[a]pyrene, a potent carcinogen. It is estimated that approximately three thousand tons of benzo[a]pyrene are released into the atmosphere each year from these sources. *(© Martin Bough, 1992, Fundamental Photographs)*

Also found in petroleum and coal tar are lesser amounts of the following PAHs. These compounds can be found in the exhausts of gasoline-powered internal combustion engines (e.g., automobile engines) and in cigarette smoke. Benzo[a]pyrene has attracted particular interest because it is a very potent carcinogen (cancer-causing substance) and mutagen.



Pyrene Benzo[*a*]pyrene Coronene

15.4 Spectroscopic Properties

A. Mass Spectrometry

The mass spectra of most aromatic hydrocarbons show an intense molecular ion peak. The mass spectrum of toluene (Figure 15.10), for example, shows an intense molecular ion peak at *m/e* 92. The most characteristic cleavage pattern of alkyl-substituted aromatic hydrocarbons is at a benzylic carbon. The mass spectrum of toluene and most other alkyl-substituted aromatic hydrocarbons shows a fragment ion of *m/e* 91. Although it might seem that the most likely structure for the cation of *m/e* 91 is that of the benzyl cation, good experimental evidence suggests a molecular rearrangement to form the more stable tropylium ion (Section 15.3E). In the tropylium ion, the positive charge is delocalized equally over all seven carbon atoms of the cycloheptatrienyl ring.

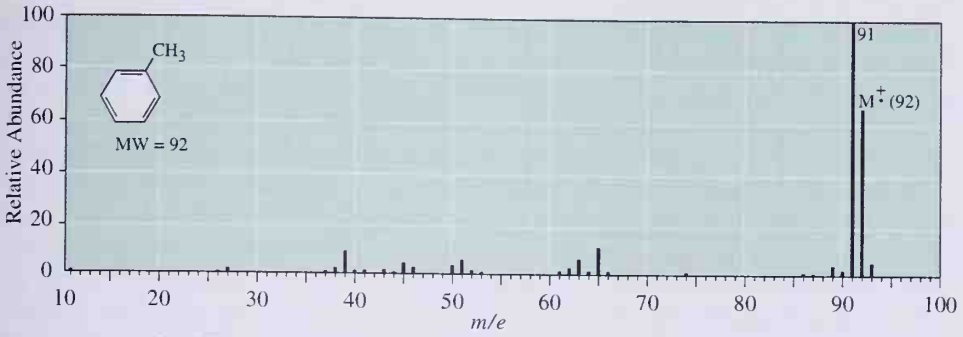
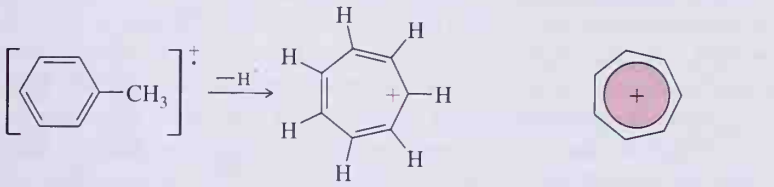


Figure 15.10
Mass spectrum of toluene. Prominent are the intense molecular ion peak at *m/e* 92 and the tropylium cation at *m/e* 91.



Toluene radical cation

Tropylium cation (*m/e* 91)

Tropylium cation (charge delocalized over all carbons of the ring)

The mass spectrum of butylbenzene (Figure 15.11) shows a molecular ion at *m/e* 134 and a peak at *m/e* 91 corresponding to cleavage at the benzyl carbon to form the tropylium cation. The prominent peak at *m/e* 92 in the mass spectrum of butylbenzene arises from a McLafferty rearrangement that occurs during the mass spectrometry of alkylbenzenes with at least one γ—H (gamma hydrogen) in the side chain.

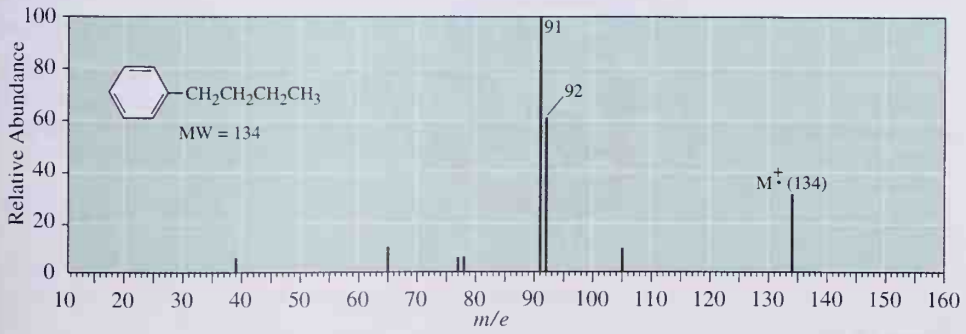
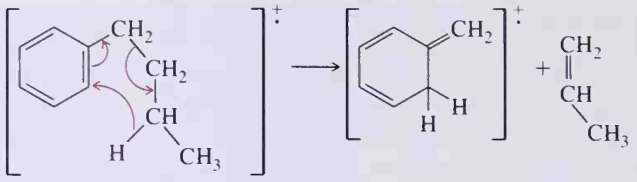


Figure 15.11
Mass spectrum of butylbenzene. Prominent are the molecular ion at *m/e* 134, the product of a McLafferty rearrangement at *m/e* 92, and the tropylium cation at *m/e* 91.



Butylbenzene (*m/e* 134) (*m/e* 92)

B. NMR Spectroscopy

All six hydrogens of benzene are equivalent and appear in the ^{1}H-NMR spectrum as a sharp singlet at δ 7.27. Hydrogens attached to a substituted benzene ring appear in the region δ 6.5 to δ 8.5. Few other hydrogens absorb in this region and, thus, aromatic hydrogens are quite easily identifiable by their distinctive chemical shifts.

Recall that vinylic hydrogens are in resonance at δ 4.6 to δ 5.7 (Section 13.14A). That aromatic hydrogens absorb even farther downfield than vinylic hydrogens is accounted for by **ring current,** a special property of aromatic rings (Figure 15.12). Recall that according to the valence bond model of benzene, the electron density of the pi system of a benzene ring lies in a torus (a doughnut-shaped region) above and below the plane of the ring (Figure 15.1). When the plane of an aromatic ring is oriented perpendicularly to an applied magnetic field, the applied field causes the pi electrons to circulate around the ring, which constitutes the so-called "ring current." This induced ring current has associated with it a closed-loop magnetic field that opposes the applied field in the middle of the ring but reinforces the applied field on the outside of the ring. Thus, given the position of aromatic hydrogens relative to the induced ring current, they come into resonance at a lower applied field, that is, at a larger chemical shift. Note that the increase in chemical shift of aromatic

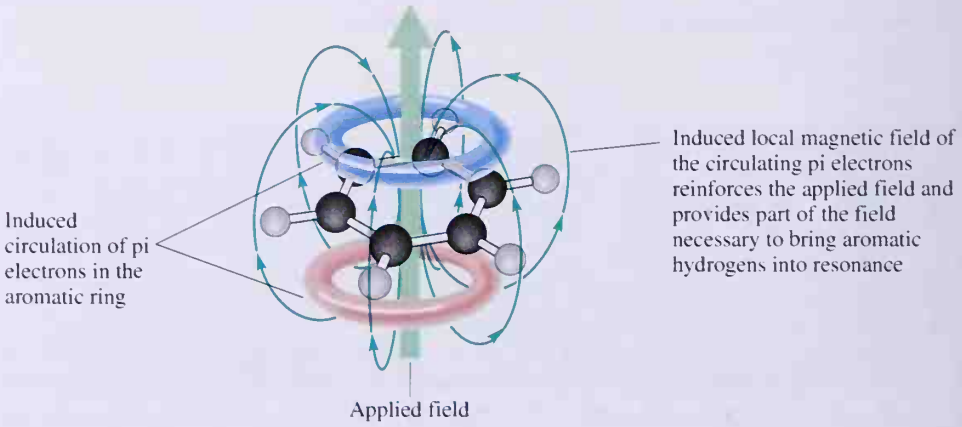
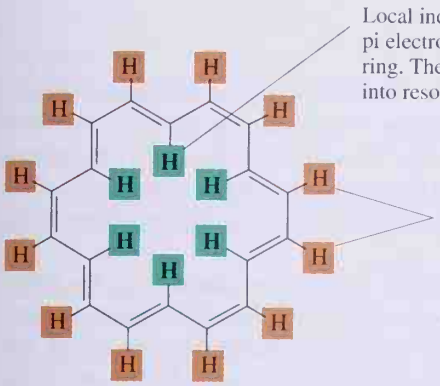


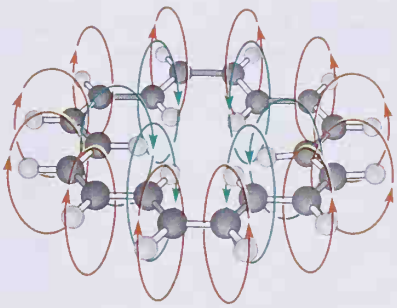
Figure 15.12
The magnetic field induced by circulation of pi electrons in the aromatic ring reinforces the applied field near aromatic hydrogens with the result that they come into resonance at a lower applied field (at a larger chemical shift relative to the TMS standard).

hydrogens arises in much the same way as the increase in chemical shift of vinylic hydrogens (Figure 13.11). The increase is larger for aromatic hydrogens, however, by approximately δ 1.5. The effect of induced ring current is characteristic not only of benzene and its derivatives, but also of all compounds that meet the Hückel criteria for aromaticity (Section 15.2A). Note that this concept of a circulating ring current and of an induced magnetic field correctly predicts that hydrogen atoms on the outside of the ring should come into resonance with a downfield shift. It also predicts that a hydrogen atom in the inside of the ring should come into resonance farther upfield. Of course, no hydrogens are on the inside of the ring in benzene, but with larger aromatic annulenes, as for example, [18]annulene, both "inside" and "outside" hydrogens occur. The degree of the upfield chemical shift of the inside hydrogens of [18]annulene is remarkable. They come into resonance at δ −3.00, that is, they come into resonance 3.00 δ units to the right of the TMS standard.



Local induced magnetic field of circulating pi electrons opposes applied field inside the ring. The six hydrogens inside the ring come into resonance at a greater applied field; at δ –3.00

Local induced magnetic field of circulating pi electrons reinforces applied field outside the ring. The twelve hydrogens outside the ring come into resonance at a smaller applied field; at δ 9.3



[18]Annulene
(aromatic)

EXAMPLE 15.2

Which hydrogens have a larger chemical shift, the six hydrogens of benzene or the eight hydrogens of cyclooctatetraene? Explain.

Solution

Benzene is an aromatic compound; its six equivalent hydrogens appear as a sharp singlet at δ 7.27. Cyclooctatetraene does not meet the Hückel criteria for aromaticity because it has $4n$ pi electrons and is nonplanar. Therefore, the eight equivalent hydrogens of the cyclooctatetraene ring appear as a singlet at δ 5.8 in the region of vinylic hydrogens (δ 4.5 – δ 6.5).

PROBLEM 15.2

Which compound gives a signal in the ^{1}H-NMR spectrum at a lower applied field (with a larger chemical shift), furan or cyclopentadiene? Explain.

In monosubstituted benzenes in which the ring substituent is neither strongly electron-withdrawing nor electron-releasing, as for example the alkyl benzenes, all ring hydrogens

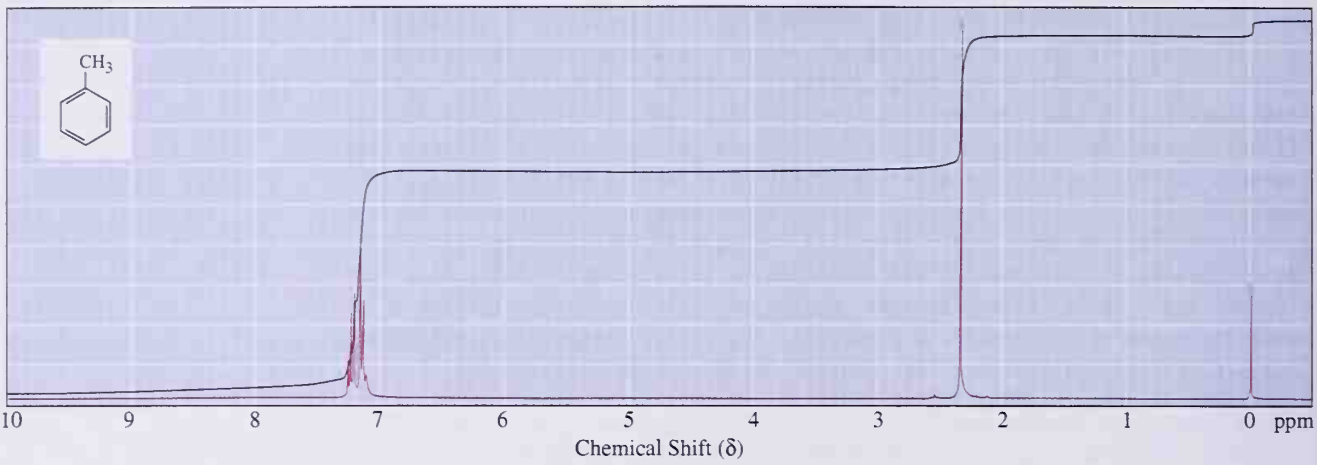
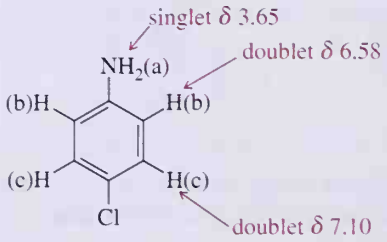


Figure 15.13
^{1}H-NMR spectrum of toluene.

have approximately the same chemical shift. The ^{1}H-NMR spectrum of toluene (Figure 15.13) shows a singlet at δ 2.3 for the three hydrogens of the methyl group and a multiplet at δ 7.2 for the five hydrogens of the aromatic ring. The signal for the methyl hydrogens appears at δ 2.3, about 1.4 farther downfield than the methyl hydrogens of an alkane. This downfield shift, like that of aromatic hydrogens, is due to the effect of the induced ring current and its associated magnetic field.

When a substituent is strongly electron-releasing or electron-withdrawing, the ortho, meta, and para hydrogens have different chemical shifts, and ^{1}H-NMR spectra become significantly more complex. The ^{1}H-NMR signal for the five aromatic hydrogens of anisole, for example, consists of two complex multiplets in the ratio of 3 : 2. The two ortho hydrogens and the one para hydrogen are more shielded and come into resonance at the higher applied field (smaller chemical shift); the two meta hydrogens are more deshielded and come into resonance at a lower applied field (larger chemical shift). We do not attempt to analyze these complex splitting patterns.

The splitting patterns of di-, tri-, and polysubstituted benzene rings are very complex. One splitting pattern, however, is quite easy to recognize, namely, that of a para-disubstituted benzene ring. If the two substituents are of sufficiently different electronegativity, then to a first approximation, the spectrum appears as a pair of doublets. Shown in Figure 15.14 is the ^{1}H-NMR spectrum of 4-chloroaniline. To a first approximation, the four aromatic hydrogens of 4-chloroaniline appear as a pair of doublets arising from coupling of hydrogens $H_{(b)}$ and $H_{(c)}$ with $J = 8$ Hz.



The higher field ^{1}H-NMR spectrum (200 MHz or higher) of 4-chloroaniline is considerably more complex than just a pair of doublets because of long range coupling. It is not our purpose in this text to deal with this level of complexity.

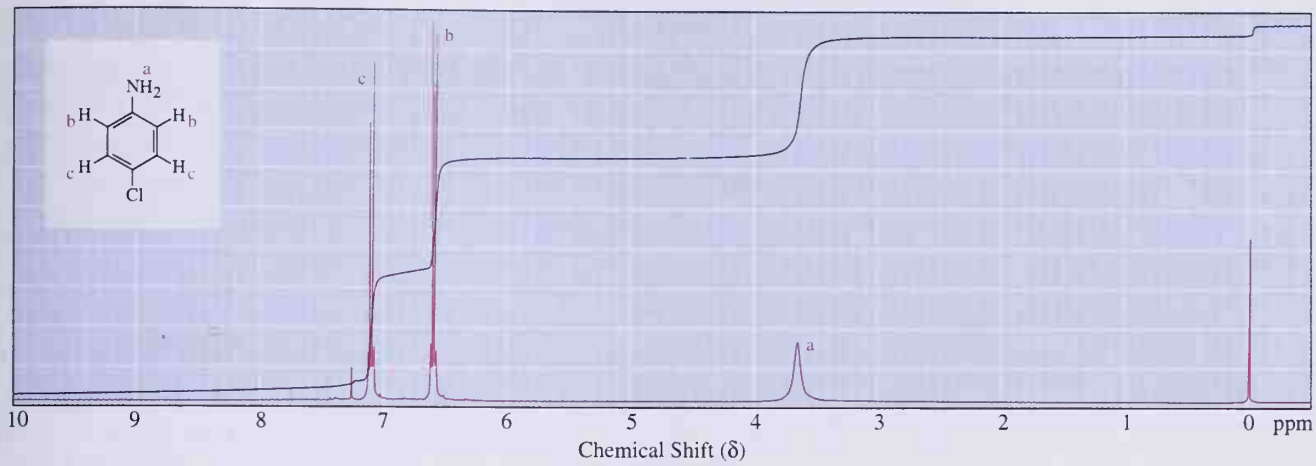


Figure 15.14
^{1}H-NMR spectrum of 4-chloroaniline.

In ^{13}C-NMR spectroscopy, carbon atoms of aromatic rings appear in the range δ 110 to δ 160. Benzene, for example, shows a single signal at δ 128. Because carbon-13 resonances for alkene carbons also appear in the range δ 110 to δ 160, it is generally not possible to establish the presence of an aromatic ring by ^{13}C-NMR spectroscopy alone. ^{13}C-NMR spectroscopy is particularly useful, however, in establishing substitution patterns of aromatic rings. The ^{13}C-NMR spectrum of 2-chlorotoluene (Figure 15.15) shows six signals in the aromatic region; its isomer 4-chlorotoluene (Figure 15.16) shows four signals in the aromatic region. Thus, all one needs do is count signals to distinguish between these constitutional isomers.

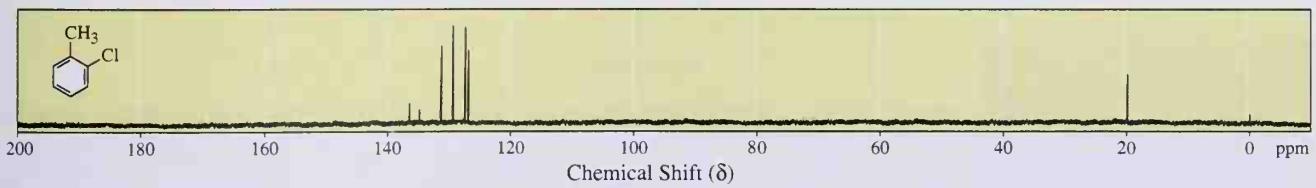


Figure 15.15
^{13}C-NMR spectrum of 2-chlorotoluene.

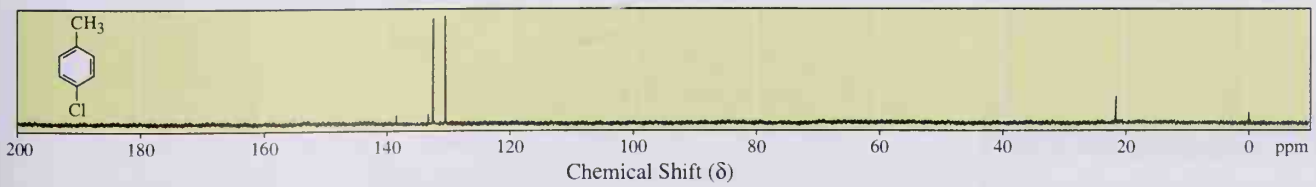


Figure 15.16
^{13}C-NMR spectrum of 4-chlorotoluene.

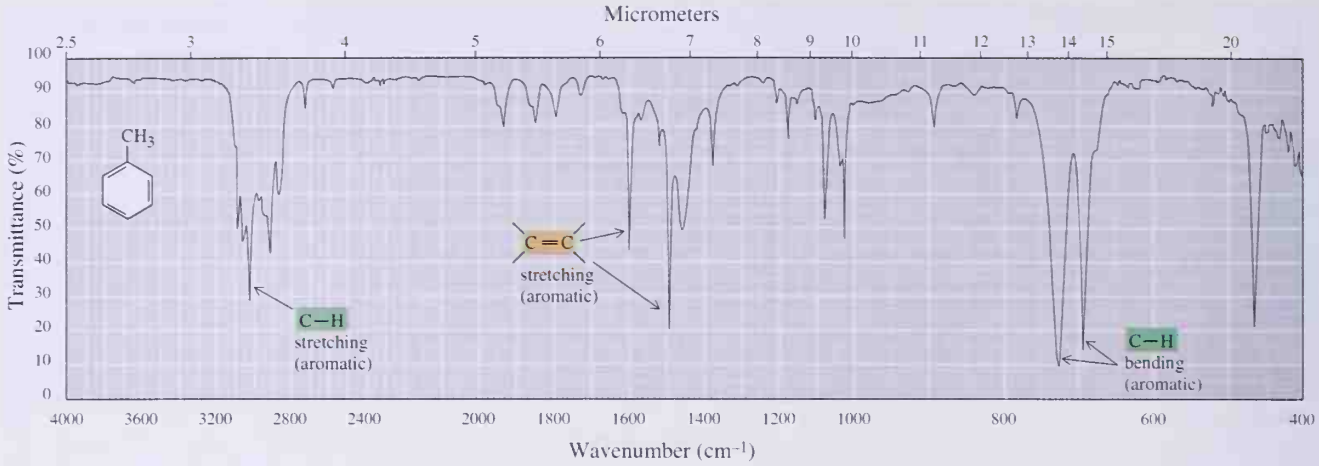


Figure 15.17
Infrared spectrum of toluene.

C. Intrared Spectroscopy

Aromatic rings show a moderate peak in the C—H stretching region at approximately 3030 cm^{-1}. In addition, aromatic rings show strong absorption in the region 690 to 900 cm^{-1} due to out-of-plane C—H bending. Finally, aromatic rings show absorptions due to carbon-carbon stretching typically at 1475 cm^{-1} and 1600 cm^{-1}. Each of these characteristic absorption patterns can be seen in the infrared spectrum of toluene (Figure 15.17).

Aromatic and vinyl ethers typically show two C—O stretching vibrations, one at either end of the range for C—O stretching. Anisole, for example, shows C—O stretching vibration at 1050 cm^{-1} and 1250 cm^{-1} (Figure 15.18).

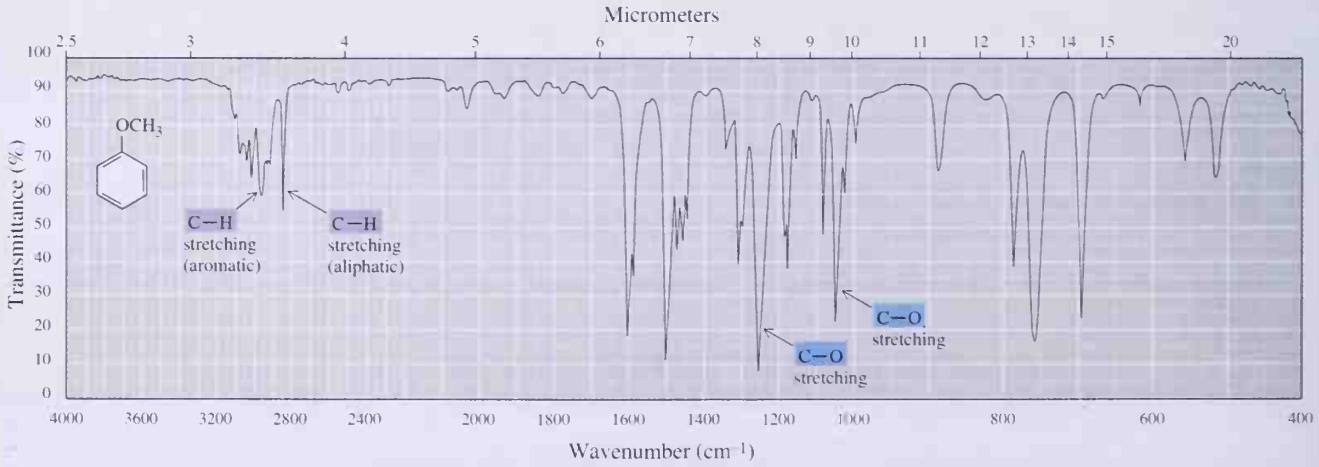


Figure 15.18
Infrared spectrum of anisole.

Table 15.1 Ultraviolet maxima for several aromatic compounds

	λ_{max} (nm)	ϵ	λ_{max} (nm)	ϵ
R = —H	203	7,400	254	204
—CH_3	207	7,000	261	225
—Cl	210	7,400	264	
—OH	211	6,200	270	1,450
—CO_2H	230	11,600	273	970

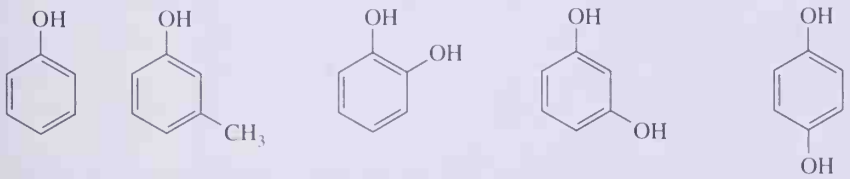
D. Ultraviolet-Visible Spectroscopy

Aromatic rings absorb radiation in the ultraviolet region of the spectrum as a result of $\pi \rightarrow \pi^*$ transitions (Figure 15.4). Most commonly two broad absorptions occur: the first of high intensity near 205 nm and a second, less intense absorption near 270 nm. The presence of these two absorptions in the ultraviolet spectrum is clear evidence for the presence of an aromatic ring. Shown in Table 15.1 are values of λ_{max} for benzene and several of its monosubstituted derivatives.

15.5 Phenols

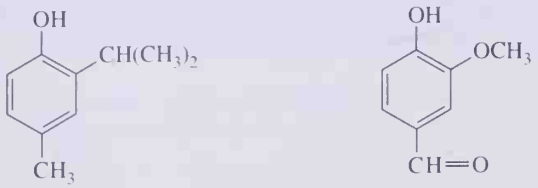
A. Structure and Nomenclature

The characteristic structural feature of a **phenol** is a hydroxyl group bonded directly to a benzene ring. Following is the structural formula of phenol, the simplest member of this class of compounds. Other phenols are named either as derivatives of the parent compound or by common names.



Phenol | 3-Methylphenol (*m*-Cresol) | 1,2-Benzenediol (Catechol) | 1,3-Benzenediol (Resorcinol) | 1,4-Benzenediol (Hydroquinone)

Phenols are widely distributed in nature. Phenol itself and the isomeric cresols (*o*-, *m*-, and *p*-cresol) are found in coal tar and petroleum. Thymol and vanillin are important constituents of thyme and vanilla beans.



2-Isopropyl-4-methylphenol (Thymol) | 4-Hydroxy-3-methoxybenzaldehyde (Vanillin)

Crystals of vanillin viewed under polarizing light. *(© Mel Pollinger/ Fran Heyl Associates)*

Text continued on p. 578.

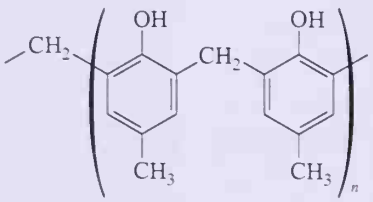
CHEMISTRY IN ACTION

Resists

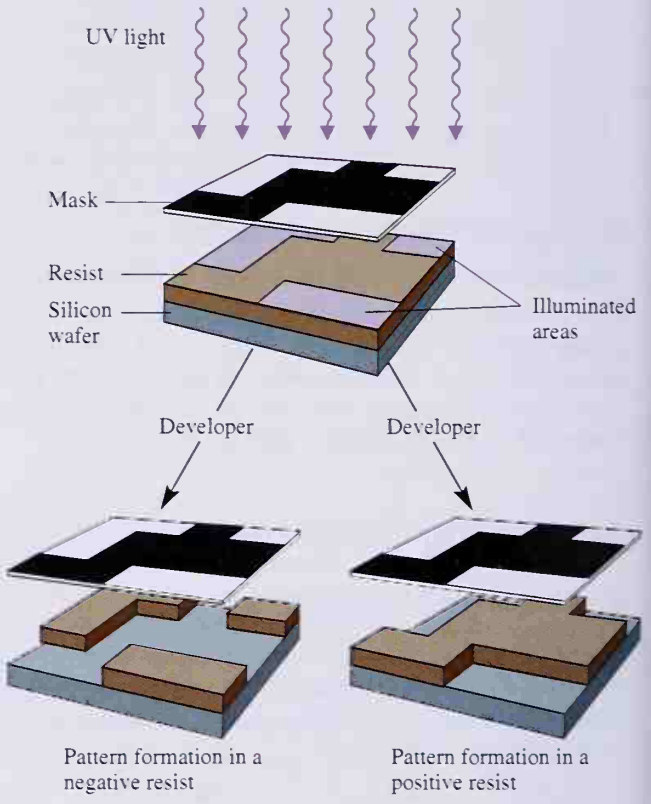
Some industries are obviously based on organic chemistry. The petroleum, pharmaceutical, and plastics industries, for example, all depend on the knowledge base of organic chemistry. Less well known is the vital role organic chemistry plays in the production of integrated circuits for the electronics industry. To make an integrated circuit, it is necessary to create exceptionally fine, complex patterns on a silicon wafer. These patterns have lines and spaces on the order of one micron (1×10^{-6} m) wide. The basis of this pattern-forming technology is the interaction of ultraviolet light with a special class of organic polymers.

A photoresist, or resist, as it is more commonly known, is a material that transfers an image from one medium to another. There are two kinds of resists: positive and negative. In a positive resist, the transferred image is the same as the original; in a negative resist, the image is the negative of the original (as in a photographic negative). The mask in the figure contains the master pattern, and ultraviolet light transfers this pattern to the polymeric resist that covers the silicon wafer. In a positive resist, the illuminated region becomes very soluble and can be washed away, exposing the silicon surface. In a negative resist, the light causes the polymer to become less soluble and the unilluminated regions can be washed away, producing a negative of the mask.

The most common positive photoresists used in the semiconductor industry are based on diazonapthoquinone and novolac resins. Novolacs are low-molecular-weight polymers of formaldehyde and phenols.



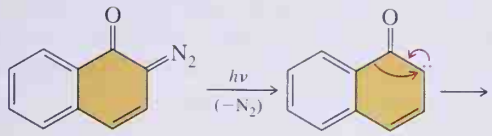
Novolac



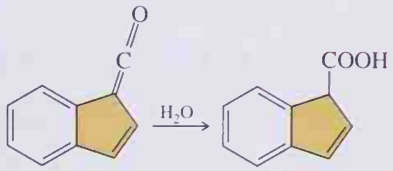
Pattern formation in a negative resist

Pattern formation in a positive resist

One type of mask is prepared by adding diazonapthoquinone to a novolac resin. When a mask prepared in this manner is irradiated with ultraviolet light, a series of chemical reactions follows: loss of N_2, rearrangement of the six-member ring to a five-member ring, and reaction with water to form a carboxylic acid. The product of these light-induced reactions is indenecarboxylic acid, a compound that is soluble in aqueous base.



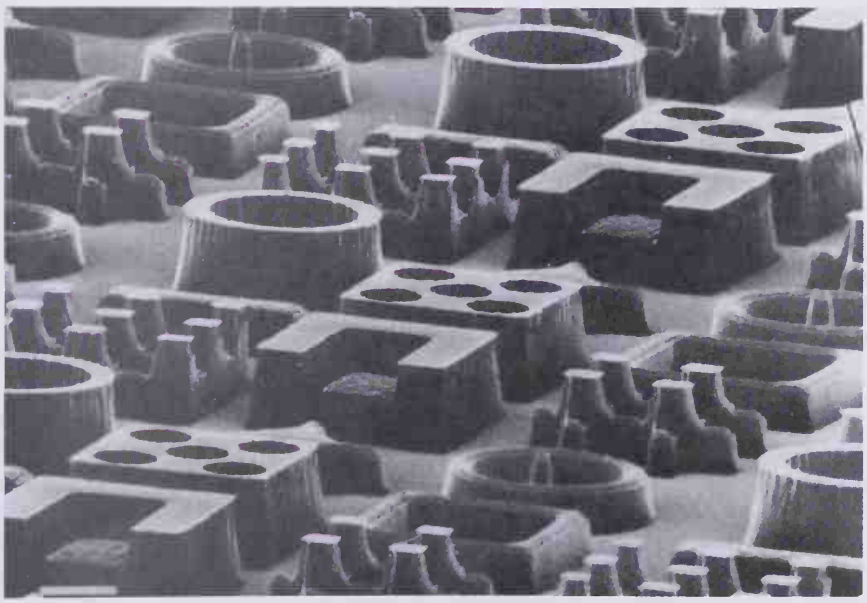
Diazonapthoquinone
(insoluble in base)



Indenecarboxylic
acid
(soluble in base)

Thus, the irradiated regions of the novolac mask are changed from hydrophobic (water-insoluble) to hydrophilic (water-soluble) and can be dissolved in base approximately 200 times more rapidly than unirradiated regions, thus providing the chemical basis for pattern transfer. With the proper masks, remarkably complex patterns can be produced, as can be seen in the accompanying illustration.

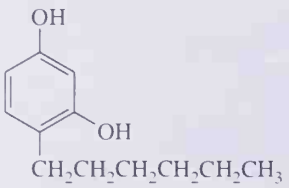
See A. Reifer, *Photoreactive Polymers* (John Wiley & Sons, New York, 1989), p. 178.



Scanning electron micrograph of three-dimensional shapes obtained from a novolac resist. From W. E. Feely et al., *Polymer Eng. Sci.*, **26,** 1101 (1968).

Thymol is a constituent of garden thyme, *Thymus vulgaris*. (© Connie Toops)

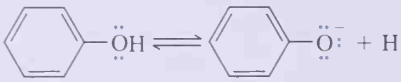
Phenol, or carbolic acid as it was once called, is a low-melting solid only slightly soluble in water. In sufficiently high concentrations, it is corrosive to all kinds of cells. In dilute solutions, it has some antiseptic properties, and was introduced into the practice of surgery by Joseph Lister who demonstrated his technique of aseptic surgery in the surgical theater of the University of Glasgow School of Medicine in 1865. Phenol's medical use is now limited. It has been replaced by antiseptics that are both more powerful and have fewer undesirable side effects. Among these are *n*-hexylresorcinol, which is widely used in nonprescription preparations as a mild antiseptic and disinfectant.



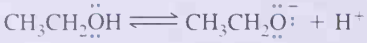
n-Hexylresorcinol

B. Acidity of Phenols

Phenols and alcohols both contain a hydroxyl group, —OH. However, phenols are grouped as a separate class of compounds because their chemical properties are quite different from those of alcohols. One of the most important of these differences is that phenols are significantly more acidic than alcohols. The acid ionization constant for phenol is approximately 10^6 times larger than that of ethanol.



$K_a = 1.1 \times 10^{-10}$ $pK_a = 9.95$



$K_a = 1.3 \times 10^{-16}$ $pK_a = 15.9$

Another way to compare the relative acid strengths of ethanol and phenol is to look at the hydrogen ion concentration and pH of a 0.1 *M* aqueous solution of each (Table 15.2). For comparison, the hydrogen ion concentration and pH of 0.1 *M* HCl are also included.

In aqueous solution, alcohols are neutral substances, and the hydrogen ion concentration of 0.1 *M* ethanol is the same as that of pure water. A 0.1 *M* solution of phenol is slightly acidic and has a pH of 5.4. By contrast, 0.1 *M* HCl, a strong acid (completely ionized in aqueous solution), has a pH of 1.0.

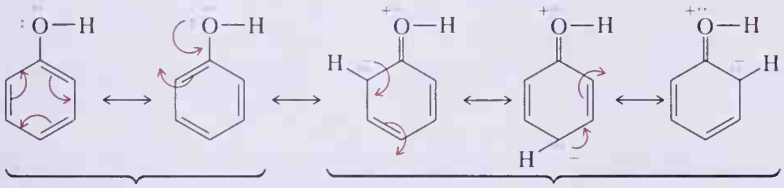
We can account for the enhanced acidity of phenols relative to alcohols by using the resonance model and looking at the stabilities of the ethoxide ion and phenoxide ion relative to the undissociated molecules. The principle we use in this analysis is the following: **when comparing the position of an equilibrium to that of a reference equilibrium, the position of the equilibrium in question is shifted toward the side favored by resonance stabilization.**

There is no possibility for resonance stabilization in either ethanol or ethoxide ion, and, therefore, we use this equilibrium as a reference. There is resonance stabilization for both phenol and phenoxide ion. For phenol two Kekulé structures can be drawn, which make equal contributions to the resonance hybrid. In addition, three structures can be drawn, which involve separation of unlike charge. Each places a positive charge on oxygen and a negative charge on an ortho or para position of the ring. Because these contributing

Table 15.2 Relative acidities of 0.1 *M* solutions of ethanol, phenol, and HCl

Acid Ionization Equation	$[H^+]$	pH
$CH_3CH_2OH \rightleftharpoons CH_3CH_2O^- + H^+$	1×10^{-7}	7.0
$C_6H_5OH \rightleftharpoons C_6H_5O^- + H^+$	3.3×10^{-6}	5.4
$HCl \rightleftharpoons Cl^- + H^+$	0.1	1.0

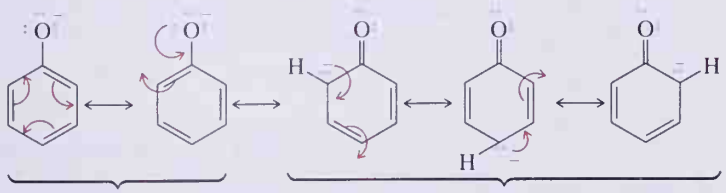
structures involve separation of unlike charge, their contribution to the hybrid is considerably less than that of the two equivalent Kekulé structures.



2 Kekulé structures

Contributing structures involving creation and separation of unlike charge

For phenoxide ion, two equivalent Kekulé structures also exist. In addition, three contributing structures place the negative charge on the ortho and para positions of the ring. These three contributing structures spread the negative charge of the phenoxide ion so that it is delocalized over four atoms. As we have seen already in this chapter, as well as in Section 1.8B, delocalization of electrons is of major importance in stabilizing molecules and ions.



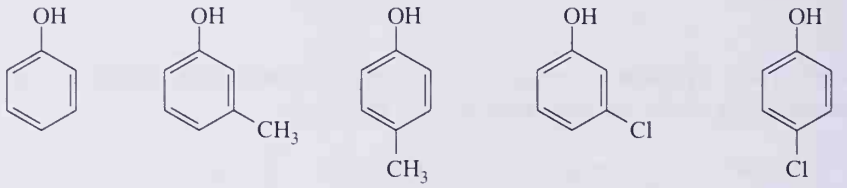
2 Kekulé structures

Contributing structures delocalizing negative charge on three carbon atoms of the ring

Because the phenoxide ion is stabilized more by resonance than is phenol, the equilibrium for the ionization of phenol is shifted to the right relative to the ionization of ethanol, which accounts for the fact that phenol is a stronger acid than ethanol. You should note that although the resonance model gives a way of understanding why phenol is a stronger acid than ethanol, it does not provide us with any quantitative means of predicting just how much stronger an acid it might be.

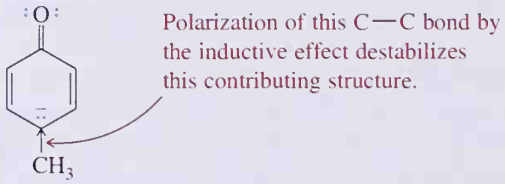
An alternative explanation for the greater acidity of phenols compared with alcohols lies in the greater electronegativity and, therefore, electron-withdrawing inductive effect of the sp^2-hybridized carbons of an aromatic ring relative to sp^3-hybridized carbons of an alkyl group. Because of this electron-withdrawing inductive effect, the O—H bond in a phenol is more polar and easier to break than the O—H bond of an alcohol.

Ring substituents have marked effects on the acidities of phenols by a combination of inductive and resonance effects. The **inductive effect** is due to electron polarization caused by differences in the relative electronegativities of bonded atoms and is relayed through sigma bonds. The inductive effect is often indicated by an arrow on the sigma bond with the head of the arrow pointing toward the more electronegative (polarizing) atom. We can interpret the relative acidities of alkyl phenols and the halophenols in terms of inductive effects. Both *m*-cresol and *p*-cresol are weaker acids than phenol itself; *m*-chlorophenol and *p*-chlorophenol are stronger acids than phenol.



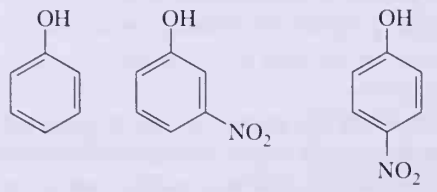
Phenol	*m*-Cresol	*p*-Cresol	*m*-Chlorophenol	*p*-Chlorophenol
pK_a 9.95	pK_a 10.01	pK_a 10.17	pK_a 8.85	pK_a 9.18

The acid-weakening effect of alkyl-substituted phenols can be understood in the following way. Each atom of the benzene ring is sp^2-hybridized, and the carbon of the alkyl substituent is sp^3-hybridized. As we saw in Section 4.2B, the greater the percentage of *s* character in a hybrid atomic orbital, the greater the effective electronegativity of the bonded atom. Therefore, the sp^2-hybridized carbon of an aromatic ring is more electronegative than the sp^3-hybridized atom of an alkyl substituent. Consequently, alkyl substituents are "electron-releasing" toward the aromatic ring. Because they are electron-releasing, they destabilize phenoxide ion-contributing structures and in effect reduce the acidity of substituted phenols.



The inductive effect of the halogens is opposite that of alkyl substituents. Because the halogens are more electronegative than carbon, they withdraw electron density from the aromatic ring and thereby stabilize the phenoxide ion. Fluorine, the most electronegative halogen, has the greatest acid-strengthening effect in halophenols; the effect is less for chlorophenols and still less for bromophenols.

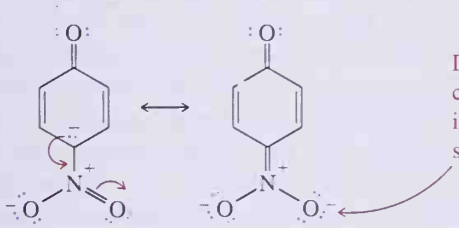
We find the operation of both the inductive effect and resonance effect in nitrophenols.



Phenol	*m*-Nitrophenol	*p*-Nitrophenol
pK_a 9.95	pK_a 8.28	pK_a 7.15

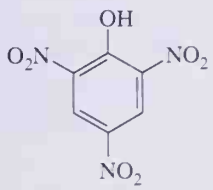
Both *m*-nitrophenol and *p*-nitrophenol are stronger acids than phenol. The acid-strengthening effect of the nitro group is greater in the para position even though in the para position it is farther away from the —OH group. Part of the acid-strengthening property of the nitro group is due to the inductive effect. Because of the electronegativity of the nitro group (in the Lewis structure of a nitro group, a positive charge occurs on nitrogen), both *m*-nitrophenol and *p*-nitrophenol are stronger acids than phenol.

We see operation of the **resonance effect** in nitrophenols in the following way. Nitro substitution in the ortho or para positions increases the acidity of phenols because the negative charge of the phenoxide ion can be further delocalized onto an oxygen of the nitro group as shown in the contributing structure on the right.



Delocalization of negative charge onto oxygen further increases the resonance stabilization of phenoxide ion.

The combined inductive and resonance acid-strengthening effects of nitro substituents are such that 2,4,6-trinitrophenol (picric acid) is a strong acid, stronger even than phosphoric acid or hydrogen sulfate ion (Table 3.2).



2,4,6-Trinitrophenol (Picric acid) pK_a 0.38

H_3PO_4

Phosphoric acid pK_1 2.1

HSO_4^-

Hydrogen sulfate anion pK 1.92

C. Acid-Base Reactions of Phenols

Phenols are weak acids and react with strong bases such as NaOH to form water-soluble salts.

Phenol $pK_a = 9.95$ (stronger acid)

Sodium hydroxide (stronger base)

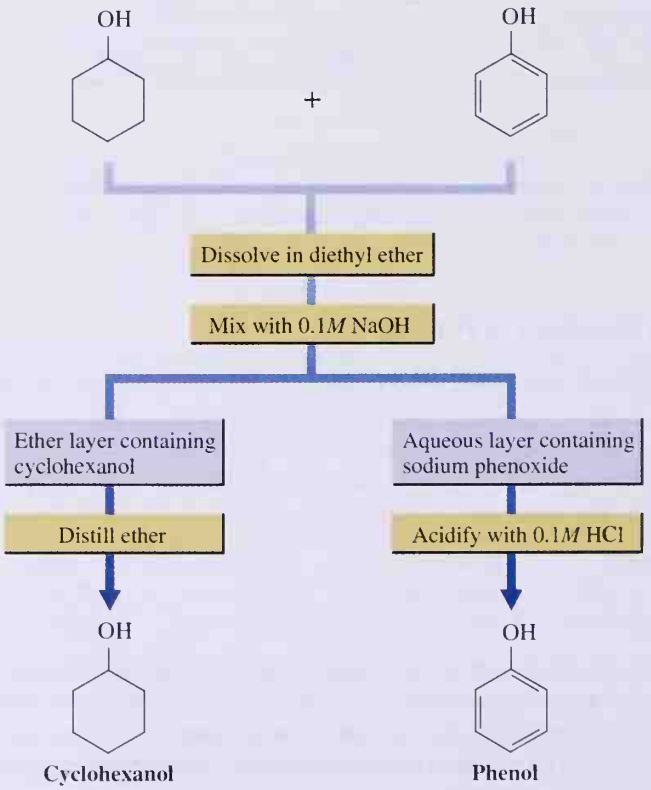
Sodium phenoxide (weaker base)

Water $pK_a = 15.7$ (weaker acid)

Most phenols do not react with weaker bases such as sodium bicarbonate; they do not dissolve in aqueous sodium bicarbonate. Carbonic acid is a stronger acid than phenol, and consequently the equilibrium for the reaction of phenol and bicarbonate ion lies far to the left. Most phenols, however, do form water-soluble salts with sodium carbonate, a stronger base than sodium bicarbonate.

Phenol	Sodium bicarbonate	Sodium phenoxide	Carbonic acid
$pK_a = 9.95$ (weaker acid)	(weaker base)	(stronger base)	$pK_a = 6.36$ (stronger acid)

That phenols are weakly acidic whereas alcohols are neutral provides a very convenient way to separate phenols from water-insoluble alcohols. Suppose we want to separate phenol from cyclohexanol. Each is only slightly soluble in water, and, therefore, they cannot be separated on the basis of their water solubility. However, they can be separated on the basis of their differences in acidity. First, the mixture of the two is dissolved in diethyl ether or some other water-immiscible solvent. Next, the ether solution is placed in a separatory funnel and shaken with dilute aqueous NaOH. Under these conditions, phenol reacts with NaOH and is converted to sodium phenoxide, a water-soluble salt. The upper layer in the separatory funnel is now diethyl ether (density 0.74 g/cm^3) containing only dissolved cyclohexanol. The lower aqueous layer contains dissolved sodium phenoxide. The layers are separated, and distillation of the ether (bp 35°C) leaves pure cyclohexanol (bp 161°C). Acidification of the aqueous phase with 0.1 *M* HCl or other strong acid converts sodium phenoxide to phenol, which is water-insoluble and can be separated and recovered in pure form. These experimental steps are summarized in the flow chart.



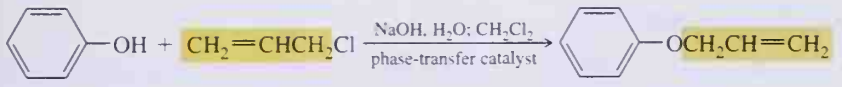
D. Preparation of Alkyl Aryl Ethers

Alkyl aryl ethers can be prepared by Williamson synthesis but with the very important limitation that aryl halides are quite unreactive under the conditions of Williamson synthesis; they do not undergo nucleophilic displacement by either S_N1 or S_N2 mechanisms.

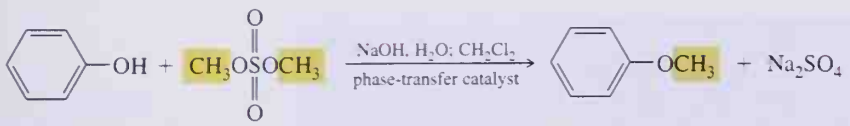
Williamson ether synthesis fails because aryl halides do not undergo S_N2 reactions.

The synthesis of alkyl aryl ethers by the Williamson method is limited to those ethers that can be synthesized from a phenoxide salt and an alkyl halide. Because phenols are weak acids, pK_a 9 to 10, phenoxide ions are easily prepared by reaction of a phenol with aqueous sodium hydroxide.

Aryl ethers are commonly synthesized by phase-transfer catalysis (Section 10.9). Both the alkyl halide and phenol are dissolved in dichloromethane, then the solution is mixed with an aqueous solution of sodium hydroxide and a phase-transfer catalyst is added. Phenol, a poor nucleophile, reacts with sodium hydroxide in the aqueous phase to form the phenoxide ion, an excellent nucleophile. The phase-transfer catalyst transports phenoxide ion to the dichloromethane phase where it reacts with the alkyl halide to form an ether. The following examples illustrate the Williamson synthesis of alkyl aryl ethers. The synthesis of allyl phenyl ether involves nucleophilic displacement on a primary halide; the synthesis of anisole illustrates the use of dimethyl sulfate to form an aryl methyl ether.

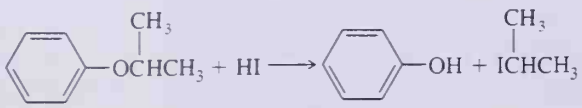


Phenol — 3-Chloropropene (Allyl chloride) — Phenyl 2-propenyl ether (Allyl phenyl ether)



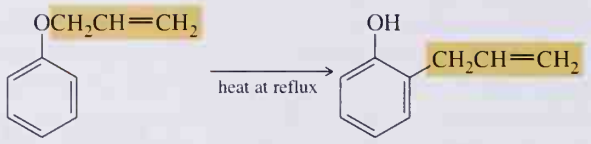
Phenol — Dimethyl sulfate — Methyl phenyl ether (Anisole)

Alkyl aryl ethers, ArOR, are cleaved to form RX and a phenol, ArOH. This illustrates the fact that nucleophilic substitution is not likely to occur at an aromatic carbon and that phenols, unlike alcohols, are not converted to aryl halides by treatment with concentrated HCl, HBr, or HI.



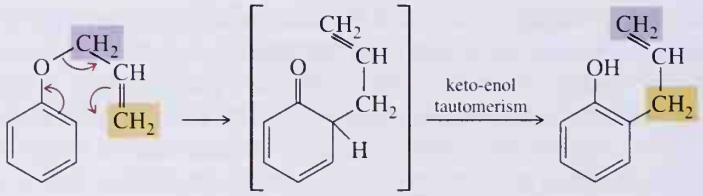
E. The Claisen Rearrangement of Allyl Phenyl Ethers

The Claisen rearrangement transforms allyl phenyl ethers to *o*-allylphenols as illustrated for the simplest member of this class of compounds, allyl phenyl ether. Because this rearrangement occurs to an ortho position of the aromatic ring, it is often called the ortho Claisen rearrangement.



Allyl phenyl ether 2-Allylphenol

Concerted intramolecular rearrangement involving simultaneous bond breaking and bond making gives a substituted cyclohexadienone intermediate, which then undergoes keto-enol tautomerism (Section 6.5B) to form the more stable aromatic ring.



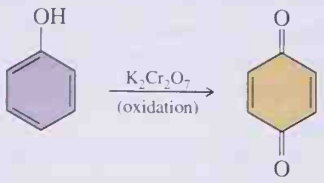
Allyl phenyl ether A cyclohexadienone intermediate 2-Allylphenol

F. Oxidation to Quinones

Because of the presence of the electron-donating —OH group on the ring, phenols are susceptible to oxidation by a variety of strong oxidizing agents. For example, oxidation of phenol itself by potassium dichromate gives 1,4-benzoquinone (*p*-quinone). By definition,

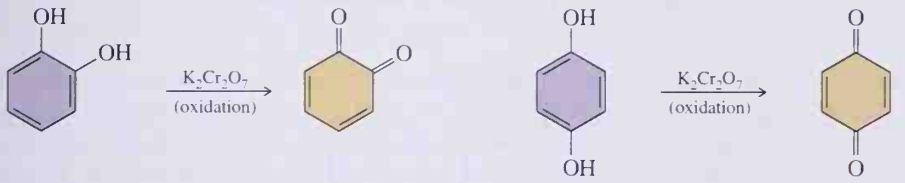
The bombardier beetle generates quinone, an irritating chemical, by the enzyme-catalyzed oxidation of hydroquinone using hydrogen peroxide as the oxidizing agent. Heat generated in this oxidation produces superheated steam which it ejects, along with *p*-quinone, with explosive force. *(Thomas Eisner and David Aneshansley, Cornell University)*

a quinone is a cyclohexadienedione. Quinones with carbonyl groups ortho to each other are called *o*-quinones; those with carbonyl groups para to each other are called *p*-quinones.



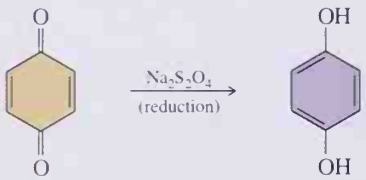
Phenol — 1,4-Benzoquinone (*p*-Quinone)

Quinones can also be obtained by oxidation of 1,2-benzenediol (catechol) or 1,4-benzenediol (hydroquinone).



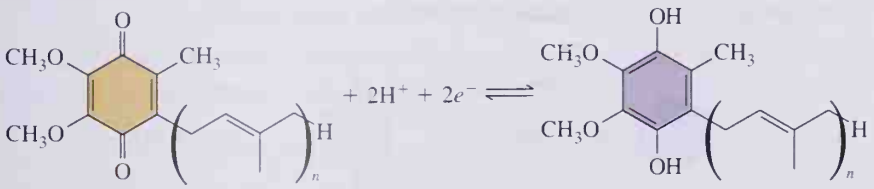
1,2-Benzenediol (Catechol) — 1,2-Benzoquinone (*o*-Quinone) — 1,4-Benzenediol (Hydroquinone) — 1,4-Benzoquinone (*p*-Quinone)

Perhaps the most important chemical property of quinones is that they are readily reduced to dihydroxybenzenes. For example, *p*-quinone is readily reduced to hydroquinone by sodium dithionite in neutral or alkaline solution.



1,4-Benzoquinone (*p*-Quinone) — 1,4-Benzenediol (Hydroquinone)

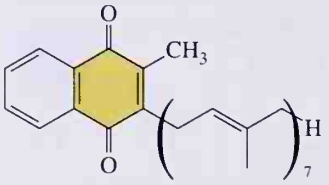
There are many examples in which the reversible oxidation-reduction of quinones or hydroquinones is important. One such example is coenzyme Q, alternatively known as ubiquinone. The name of this important biomolecule is derived from the Latin *ubique* (everywhere) plus quinone.



Coenzyme Q (oxidized form) — Coenzyme Q (reduced form)

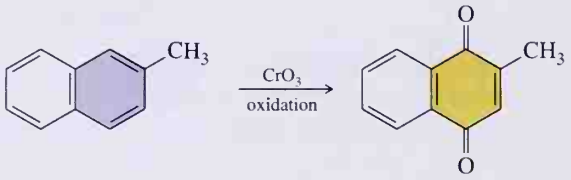
Coenzyme Q, a carrier of electrons in the respiratory chain, contains a long hydrocarbon chain of between six and ten isoprene units that serves to anchor it firmly in the nonpolar environment of the mitochondrial inner membrane. As can be seen from the balanced half-reaction, the oxidized form of coenzyme Q is a two-electron oxidizing agent. In subsequent steps of the respiratory chain, the reduced form of coenzyme Q transfers these two electrons to another link until they are eventually delivered to a molecule of oxygen which is in turn reduced to water.

Another quinone important in biological systems is vitamin K_2. This compound was discovered in 1935 as a result of a study of newly hatched chicks with a fatal disease in which their blood was slow to clot. It was later discovered that the delayed clotting time of blood was caused by a deficiency of prothrombin, and it is now known that vitamin K_2 is essential to the synthesis of prothrombin in the liver. The natural form of vitamin K_2 has a chain of from five to eight isoprene units attached to a 1,4-naphthoquinone ring. The following structure shows seven isoprene units in the side chain.



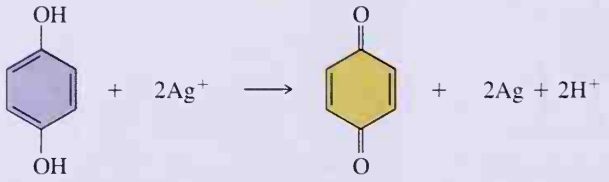
Vitamin K_2

The natural vitamins of the K family have for the most part been replaced by synthetic preparations. Menadione, one such synthetic material with vitamin K activity, has only hydrogen in place of the long alkyl side chain. Menadione is prepared by chromic acid oxidation of 2-methylnaphthalene under mild conditions.



2-Methylnaphthalene — 2-Methyl-1,4-naphthoquinone (Menadione)

A commercial process that uses a quinone is black-and-white photography. Black-and-white film is impregnated with silver bromide or silver iodide crystals, which become activated by exposure to light. The activated silver ions are reduced in the developing stage to metallic silver by hydroquinone, which at the same time is oxidized to quinone. Following is an equation showing the relationship between these species.

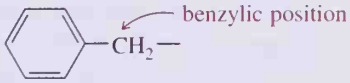


1,4-Benzenediol (Hydroquinone) — 1,4-Benzoquinone (*p*-Quinone)

All silver halide not reduced by light and interaction with hydroquinone is removed in the fixing process, and the result is a black image (a negative) left by deposited metallic silver where the film had been struck by light. Other compounds are now used to reduce "light-activated" silver bromide, but the result is the same, a deposit of metallic silver in response to exposure of black-and-white film to light.

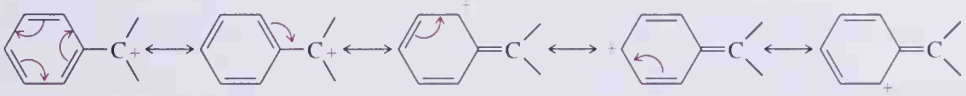
15.6 Reactions at a Benzylic Position

In this section we study two reactions of substituted aromatic hydrocarbons that occur preferentially at the **benzylic position.**



Benzyl group

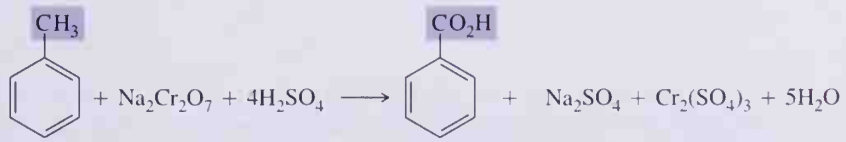
Reactions of aromatic compounds containing alkyl side chains occur preferentially at the benzylic position for two reasons. First, the benzene ring is especially resistant to reaction with many of the reagents that normally attack alkanes. Second, benzylic cations and benzylic radicals are easily formed because of resonance stabilization of these intermediates. A benzylic cation or radical is a hybrid of five contributing structures: two Kekulé structures and three that delocalize the positive charge (or the lone electron) onto carbons of the aromatic ring. Following are contributing structures for a benzyl cation. Similar contributing structures can be written for a benzyl radical.



The benzyl cation as a hybrid of five contributing structures

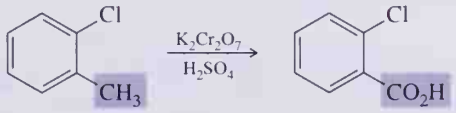
A. Oxidation

When treated with $KMnO_4$ in aqueous base or $Na_2Cr_2O_7$ in aqueous sulfuric acid, toluene is converted to benzoic acid, as shown in the following balanced equation:



Toluene Benzoic acid

Halogen and nitro substituents on an aromatic ring are unaffected by these oxidations. 2-Chlorotoluene, for example, is oxidized to 2-chlorobenzoic acid.



2-Chlorotoluene (*o*-Chlorotoluene)

2-Chlorobenzoic acid (*o*-Chlorobenzoic acid)

CHEMISTRY IN ACTION

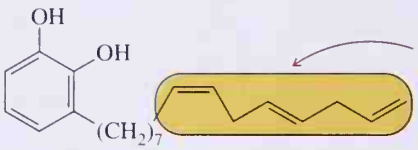
The Organic Chemistry of Lacquer

For over five thousand years, the sap of certain Japanese and Chinese trees has been used to make a durable and beautiful coating known in the western world as lacquer. Processing the sap is difficult because it is an extremely active allergen causing skin reactions similar to those caused by poison ivy and poison oak (other members of this genus). Nevertheless, craftsmen have developed techniques to process and use the sap as a coating for wood, bamboo, metal, shell, and other materials. A key to creating a clear, hard lacquer finish is a humid environment. Some artisans were said to transport their work by boat onto the ocean to provide the perfect damp, dust-free conditions required for proper hardening. As modern chemical methods have established the composition of the sap and its hardening mechanism, the reasons behind the artisan's trade secrets have been revealed.

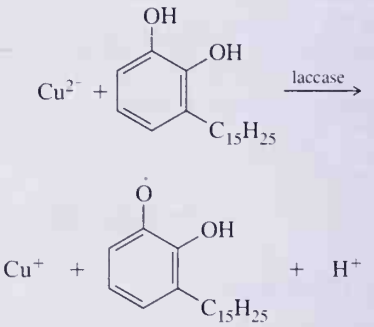
The sap from *Rhus verniciferum* Stokes, the oriental tree used for lacquer production, is an emulsion of oil in water. The major lacquer-forming components of the oil are derivatives of catechol with unsaturated side chains of 15 carbon atoms. Because the Japanese name for the processed sap used for lacquer is urushi, these compounds were named urushiols.

Components with three double bonds, one double bond, and a saturated side chain are also present in the sap. The compound with a saturated side chain is also present in poison ivy (*Rhus radicans* L.) and is responsible for that plant's irritant properties.

The hardening of the sap to produce lacquer results from the polymerization of the urushiol molecules. Polymerization is initiated by the enzyme laccase, also present in the sap. Laccase catalyzes the oxidation of the catechol by copper(II) ion to give a semiquinone radical. Recall that two-electron oxidations of hydroquinones give quinones.

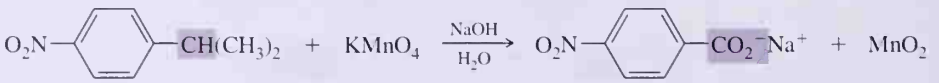


An urushiol



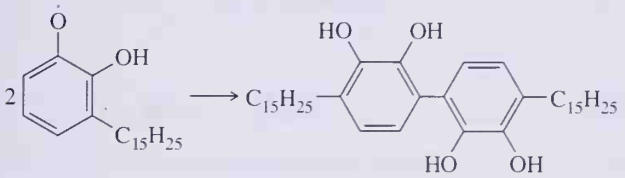
A semiquinone radical

Ethyl and isopropyl side chains are also oxidized to a carboxyl group. Oxidation of 4-nitrocumene gives 4-nitrobenzoic acid. Note that in oxidations by $KMnO_4$ in aqueous NaOH, the immediate product of oxidation is a water-soluble salt of the carboxylic acid and MnO_2 that precipitates as a brown solid. The solid MnO_2 is removed by filtration and the filtrate acidified, most commonly with aqueous HCl or H_2SO_4, to precipitate and isolate the carboxylic acid. A phase-transfer catalyst (Section 10.9) may be used to facilitate oxidation of water-insoluble aromatic compounds.



4-Nitrocumene (*p*-Nitrocumene) | Potassium permanganate | Sodium 4-nitrobenzoate (Sodium *p*-nitrobenzoate) | Manganese dioxide

This radical can react with a second radical to form a biphenyl derivative, a rigid unit that introduces rigidity into the lacquer film.

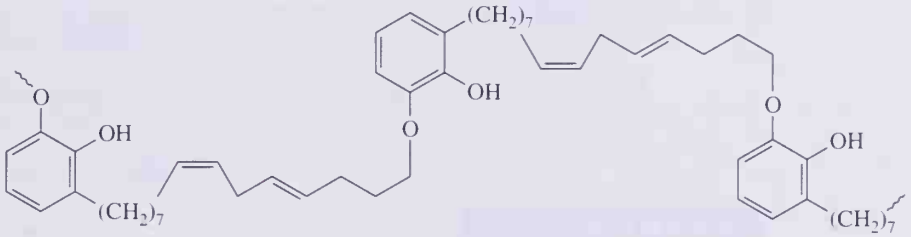


A biphenyl derivative

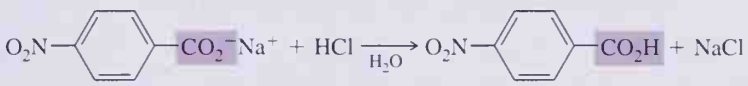
In addition, the radical can add to a double bond of the unsaturated side chain to generate a high-molecular-weight, tough, insoluble polymer.

Oxygen then oxidizes Cu^+ in laccase to Cu^{2+}, which then reacts with more urushiol to continue the hardening process. The amount of water in the film (which is a function of the air's relative humidity) affects the rate at which oxygen diffuses into the film to reoxidize Cu^+ to Cu^{2+}, thereby continuing polymerization. With too little water, polymerization does not take place; with too much water, polymerization is too rapid and leads to a rough surface. But artisans have known this for centuries!

See H. F. Jaeschke "Polymers in Conservation" Special Pub. #105, N. S. Allen, M. Edge, C. V. Horie (eds.), (Royal Society of Chemists, Cambridge, UK, 1992), 47.

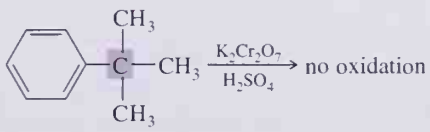


Urushiol polymer



4-Nitrobenzoic acid
(*p*-Nitrobenzoic acid)

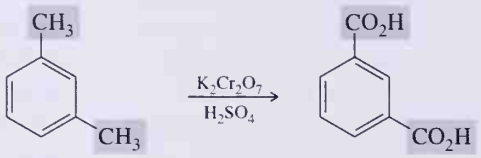
The side chain of *tert*-butylbenzene is not oxidized, however.



tert-Butylbenzene

From these observations, we conclude that if a benzylic hydrogen exists, then the benzylic carbon is oxidized to a carboxyl group and all other carbons of the side chain are removed. If no benzylic hydrogen exists, as in the case of *tert*-butylbenzene, no oxidation of the side chain occurs.

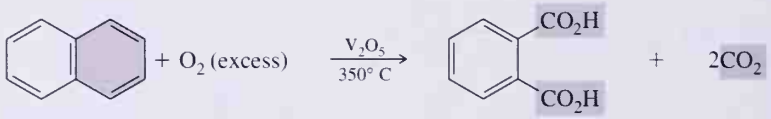
If more than one alkyl side chain exists, each is oxidized to $-CO_2H$. Oxidation of *m*-xylene gives 1,3-benzenedicarboxylic acid, more commonly named isophthalic acid.



m-Xylene — 1,3-Benzenedicarboxylic acid (Isophthalic acid)

It has been difficult to study these oxidations and to formulate mechanisms for them. Available evidence, however, supports the formation of unstable intermediates, which are either benzylic radicals or benzylic cations.

Naphthalene is oxidized to phthalic acid by molecular oxygen in the presence of a vanadium(V) oxide (vanadium pentoxide) catalyst. This conversion, which is the basis for an industrial synthesis of this aromatic dicarboxylic acid, illustrates the ease of oxidation of condensed benzene rings compared with benzene itself.



Naphthalene — 1,2-Benzenedicarboxylic acid (Phthalic acid)

EXAMPLE 15.3

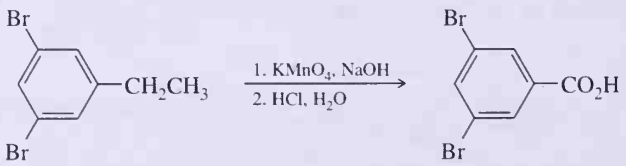
Draw structural formulas for the product of vigorous oxidation of

(a) 1,3-Dibromo-5-ethylbenzene by $KMnO_4$ in aqueous base followed by filtration and acidification of the filtrate with aqueous HCl

(b) 4-Isopropyltoluene by $K_2Cr_2O_7$ in aqueous H_2SO_4

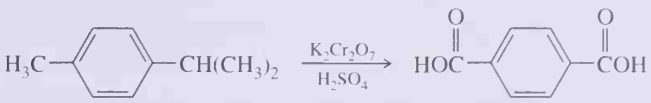
Solution

(a) The ethyl group is oxidized to $-CO_2H$; the bromine substituents are unaffected. The product is 3,5-dibromobenzoic acid.



3,5-Dibromoethylbenzene — 3,5-Dibromobenzoic acid

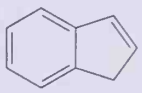
(b) Both alkyl groups are oxidized to $-CO_2H$ groups. The product is terephthalic acid, one of two monomers required for the synthesis of Dacron polyester and Mylar.

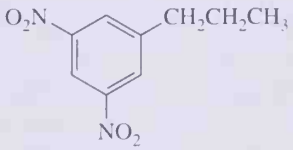


4-Isopropyl toluene — 1,4-Benzenedicarboxylic acid (Terephthalic acid)

PROBLEM 15.3

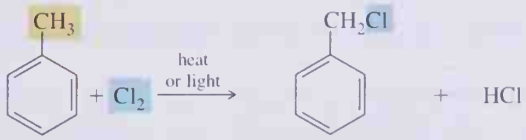
Predict the products resulting from vigorous oxidation of the following compounds by $K_2Cr_2O_7$ in aqueous H_2SO_4:

(a) 

(b) 

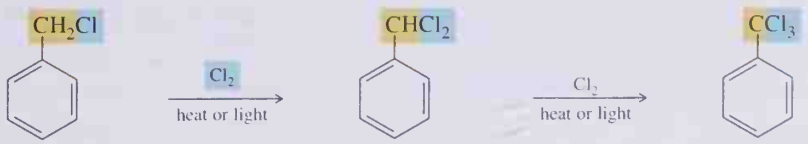
B. Halogenation

Reaction of toluene with chlorine in the presence of heat or light results in formation of chloromethylbenzene and HCl



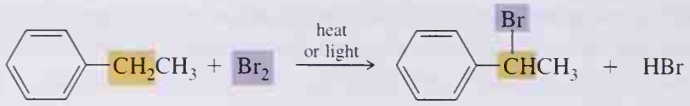
Toluene — Chloromethylbenzene (Benzyl chloride)

If the reaction is allowed to continue with excess chlorine, the second and finally the third benzylic hydrogen is replaced by chlorine to give dichloromethylbenzene and trichloromethylbenzene, respectively.



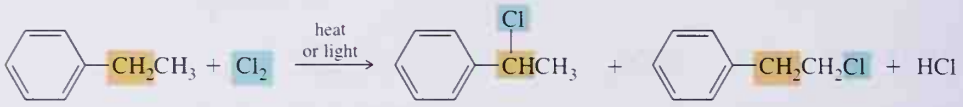
Chloromethylbenzene (Benzyl chloride) — Dichloromethylbenzene (Benzal chloride) — Trichloromethylbenzene (Benzotrichloride)

Halogenation of an alkyl side chain is highly regioselective, as illustrated by the halogenation of ethylbenzene. When treated with bromine, the only monobromo organic product formed is 1-bromo-1-phenylethane. This regioselectivity is dictated by resonance effects, namely, the resonance stabilization of the benzylic radical intermediate.



Ethylbenzene — 1-Bromo-1-phenylethane (only product)

When ethylbenzene is treated with chlorine under radical conditions, two products are formed in the ratio of 9 : 1.



Ethylbenzene — 1-Chloro-1-phenylethane (90%) — 1-Chloro-2-phenylethane (10%)

Thus, chlorination of alkyl side chains is also regioselective but not to the same high degree as bromination. Recall that we observed this same pattern in the regioselectivities of bromination and chlorination of alkanes (Section 2.9B).

Chlorination and bromination of alkyl side chains, catalyzed by heat, light, or other radical initiators, occur by a radical chain mechanism. Combining the information on product distribution for bromination and chlorination of hydrocarbons, we conclude that the order of stability of radicals is

methyl < 1° < 2° = 1° allylic = benzylic < 3° = 2° allylic < 3° allylic

Increasing radical stability

This order parallels the C—H bond dissociation energies (BDE) for formation of these radicals (Table 15.3).

Bromine is considerably more selective than chlorine in its abstraction of benzylic hydrogens, a fact that can be explained using the same argument we used in Section 5.6D

Table 15.3 C—H Bond dissociation energies for formation of selected radicals

Hydrocarbon	Radical	Type of Radical	BDE (kcal/mol)
$CH_2{=}CHCH_2{-}H$	$CH_2{=}CHCH_2\cdot$	allyl	77
$C_6H_5CH_2{-}H$	$C_6H_5CH_2\cdot$	benzyl	79
$(CH_3)_3C{-}H$	$(CH_3)_3C\cdot$	tertiary	92
$(CH_3)_2CH{-}H$	$(CH_3)_2CH\cdot$	secondary	95
$CH_3CH_2{-}H$	$CH_3CH_2\cdot$	primary	98
$CH_3{-}H$	$CH_3\cdot$	methyl	104

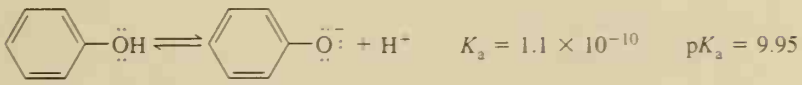
to account for the relative regioselectivities of bromine versus chlorine for 3° versus 2° versus 1° hydrogens.

In radical halogenation, the rate-determining step is hydrogen abstraction. According to the **Hammond postulate**, the higher the energy of activation for this step, the later in the course of the reaction the transition state is reached. As we demonstrated in Section 5.6D, abstraction of hydrogen by bromine has a higher energy of activation than abstraction by chlorine, and, therefore, the transition state for bromination is reached later in the reaction. This means that the transition state for bromination has considerably more radical character than that for chlorination, and thus the relative stabilities of radicals are more important for bromination than for chlorination. The result is that for both bromination and chlorination, the relative rates of hydrogen abstraction are in the order just given, but the effect is greater for bromination than for chlorination.

SUMMARY OF KEY REACTIONS

1. Acidity of Phenols (Section 15.5B)

Phenols are weak acids, pK_a approximately 10. Ring substituents may increase acidity by a combination of resonance and inductive effects.



$K_a = 1.1 \times 10^{-10}$ $pK_a = 9.95$

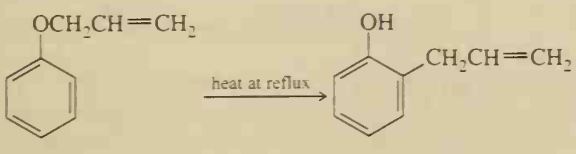
2. Reaction of Phenols with Strong Bases (Section 15.5C)

Water-insoluble phenols react quantitatively with strong bases to form water-soluble salts.

Phenol	Sodium hydroxide	Sodium phenoxide	Water
$pK_a = 9.95$			$pK_a = 15.7$
(stronger acid)	(stronger base)	(weaker base)	(weaker acid)

3. Claisen Rearrangement of Allyl Phenyl Ethers (Section 15.5D)

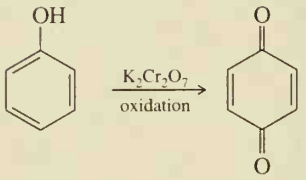
This concerted, intramolecular rearrangement occurs by a cyclic transition state to give a substituted cyclohexadienone, which then undergoes keto-enol tautomerism to regenerate the aromatic ring.



Allyn phenyl ether 2-Allylphenol

4. Oxidation of Phenols to Quinones (Section 15.5E)

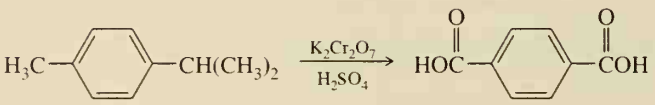
Oxidation by $K_2Cr_2O_7$ gives 1,2-quinones (*o*-quinones) or 1,4-quinones (*p*-quinones), depending on the structure of the particular phenol.



Phenol *p*-Benzoquinone

5. Oxidation at a Benzylic Position (Section 15.6)

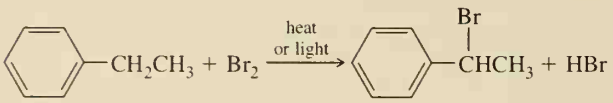
A benzylic carbon bonded to at least one hydrogen is oxidized to a carboxyl group. A phase-transfer catalyst may be used for oxidation of water-insoluble aromatic compounds.



4-Isopropyl toluene 1,4-Benzenedicarboxylic acid (Terephthalic acid)

6. Halogenation at a Benzylic Position (Section 15.6B)

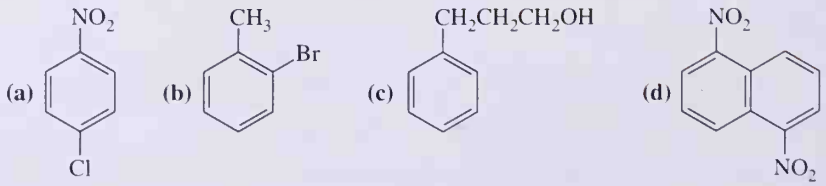
Halogenation is regioselective for a benzylic position and occurs by a radical chain mechanism. Bromination shows a higher regioselectivity for a benzylic position than chlorination does.

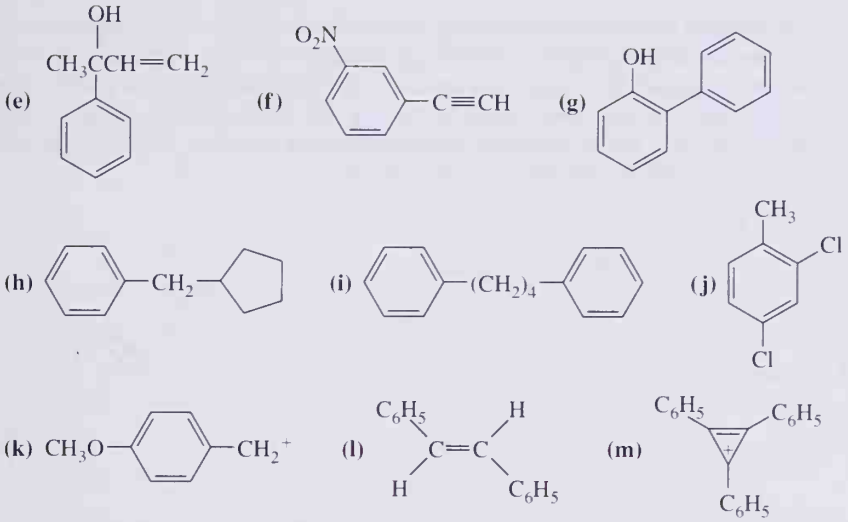


ADDITIONAL PROBLEMS

Nomenclature and Structural Formulas

15.4 Name the following molecules and ions:





15.5 Draw structural formulas for the following molecules:

(a) 1-Bromo-2-chloro-4-ethylbenzene **(b)** *m*-Nitrocumene

(c) 1,2-Dimethyl-4-iodobenzene **(d)** 3,5-Dinitrotoluene

(e) 2,4,6-Trinitrotoluene **(f)** 4-Phenyl-2-pentanol

(g) *p*-Cresol **(h)** Pentachlorophenol

(i) 1-Phenylcyclopropanol **(j)** Triphenylmethane

(k) Phenylethylene (styrene) **(l)** Benzyl bromide

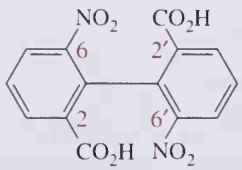
(m) 1-Phenyl-1-butyne **(n)** 3-Phenyl-2-propen-1-ol

15.6 Draw structural formulas for the following molecules:

(a) 1-Nitronaphthalene **(b)** 1,6-Dichloronaphthalene

(c) 9-Bromoanthracene **(d)** 2-Methylphenanthrene

15.7 Molecules of 6,6′-dinitrobiphenyl-2,2′-dicarboxylic acid have no tetrahedral stereocenter, and yet they can be resolved to a pair of enantiomers. Account for this chirality. *Hint:* It will help to build a model and study the ease of rotation about the single bond joining the two benzene rings.



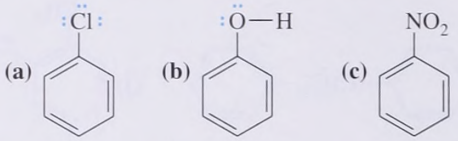
6,6-Dinitrobiphenyl-2,2′-dicarboxylic acid

Resonance in Aromatic Compounds

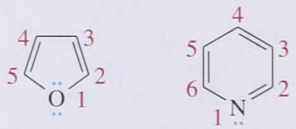
15.8 Following each name is the number of Kekulé structures that can be drawn for it. Draw these Kekulé structures, and show, using curved arrows, how the first contributing structure for each molecule is converted to the second, and so forth,

(a) Naphthalene-(3) **(b)** Phenanthrene-(4)

15.9 Each molecule below can be drawn as a hybrid of five contributing structures: two Kekulé structures and three that involve creation and separation of unlike charges. For (a) chlorobenzene and (b) phenol, the creation and separation of unlike charges place a positive charge on the substituent and a negative charge on the ring. For nitrobenzene (c) a positive charge is placed on the ring and an additional negative charge is placed on the $-NO_2$ group. Draw these five contributing structures for each molecule.



15.10 Following are structural formulas for furan and pyridine:



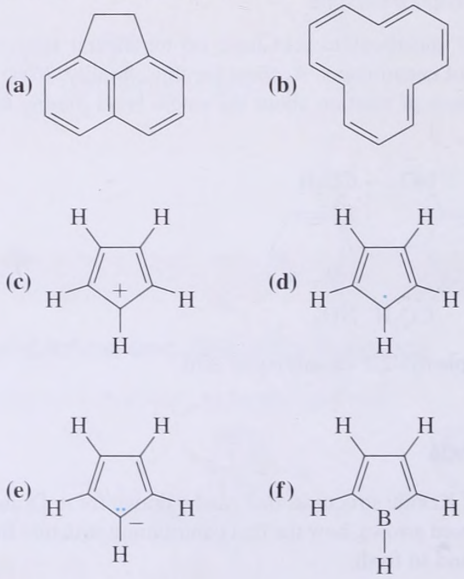
Furan Pyridine

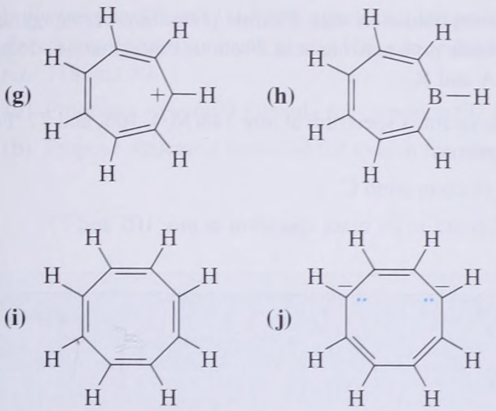
(a) Write four contributing structures for the furan hybrid that place a positive charge on oxygen and a negative charge first on carbon 3 of the ring and then on each other carbon of the ring.

(b) Write three contributing structures for the pyridine hybrid that place a negative charge on nitrogen and a positive charge on carbon 2, then on carbon 4, and then on carbon 6.

The Concept of Aromaticity

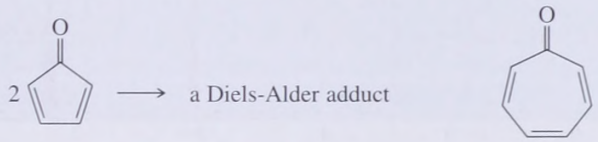
15.11 State the number of *p* orbital electrons in each of the following:





15.12 Which of the molecules and ions given in the previous problem are aromatic according to the Hückel criteria? Which, if planar, would be antiaromatic?

15.13 All attempts to synthesize cyclopentadienone yield only a Diels-Alder adduct. Cycloheptatrienone, however, has been prepared by several methods and is stable.



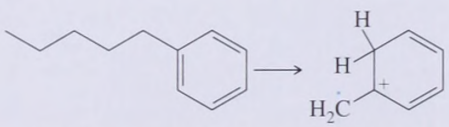
Cyclopentadienone Cycloheptatrienone

(a) Draw a structural formula for the Diels-Alder adduct formed by cyclopentadienone.

(b) How do you account for the marked difference in stability of these two ketones?

Spectroscopy

15.14 1-Phenylpentane shows a strong fragment ion at *m/e* 92, which has the following structure. How might this ion arise?



1-Phenylpentane *m/e* 92

15.15 Propose a structural formula consistent with each ^{1}H-NMR spectrum.

(a) $C_9H_{10}O$; δ 1.2 (t, 3H), 3.0 (q, 2H), 7.4–8.0 (m, 5H)

(b) $C_{10}H_{12}O_2$; δ 2.0 (s, 3H), 2.9 (t, 2H), 4.3 (t, 2H), and 7.3 (s, 5H)

(c) $C_{10}H_{14}$; δ 1.2 (d, 6H), 2.3 (s, 3H), 2.9 (septet, 1H), and 7.0 (s, 4H)

(d) C_8H_9Br; δ 1.8 (d, 3H), 5.0 (q, 1H), 7.3 (s, 5H)

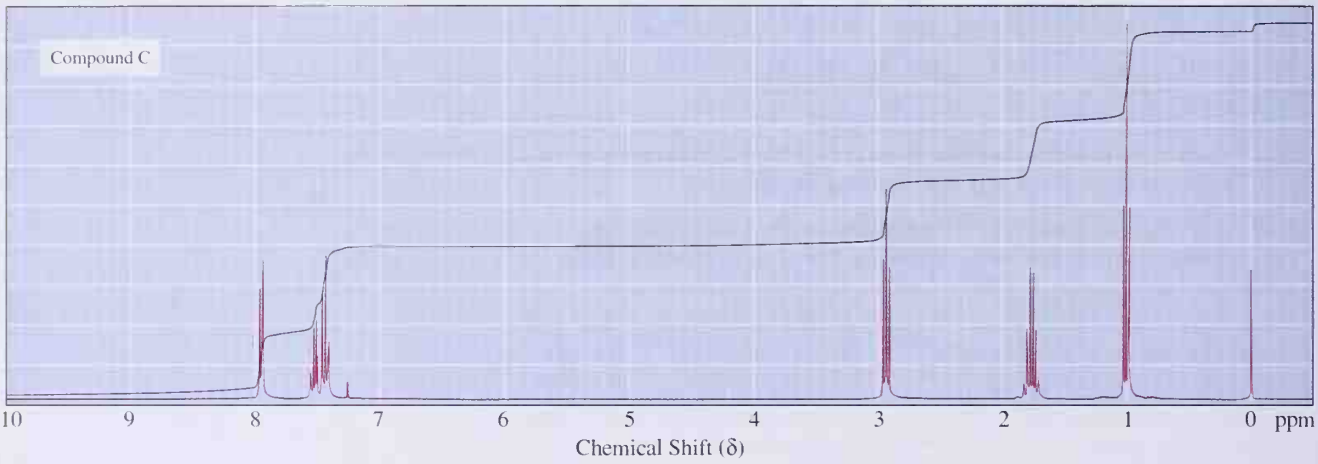
15.16 Compound A, molecular formula C_9H_{12}, shows prominent peaks in its mass spectrum at *m/e* 120($M^{+\cdot}$) and 105. Compound B, also of molecular formula C_9H_{12}, shows prominent peaks at

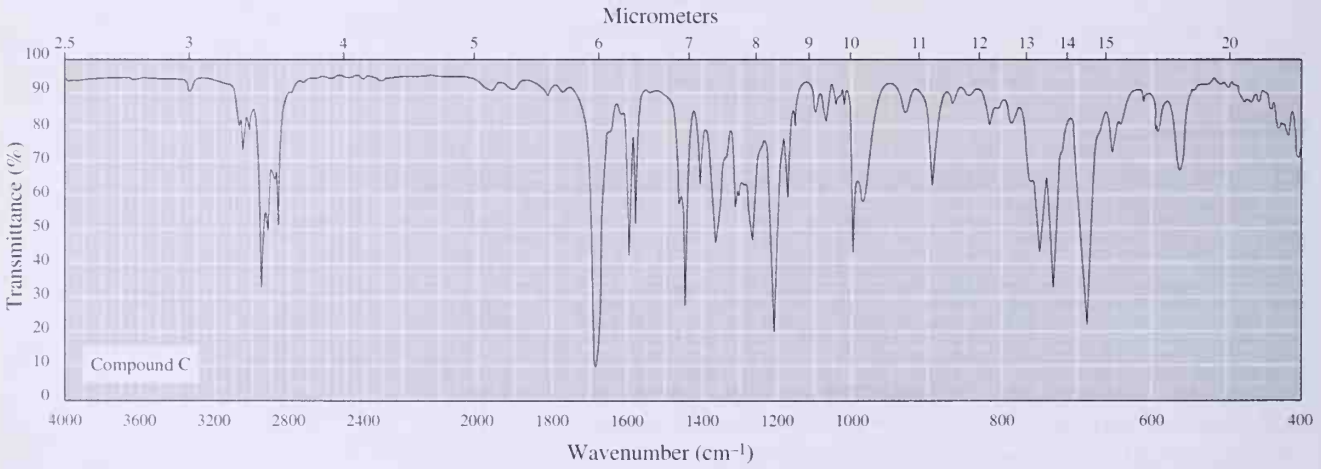
m/e 120($M^{+\cdot}$), 92, and 91. On vigorous oxidation with alkaline potassium permanganate followed by acidification, both compounds give benzoic acid. From this information, deduce the structural formulas of compounds A and B.

15.17 Compound C shows strong peaks in its mass spectrum at *m/e* 148($M^{+\cdot}$), 105, and 77. Following are its infrared and ^{1}H-NMR spectra.

(a) Deduce the structural formula of compound C.

(b) Account for the appearance of peaks in its mass spectrum at *m/e* 105 and 77.

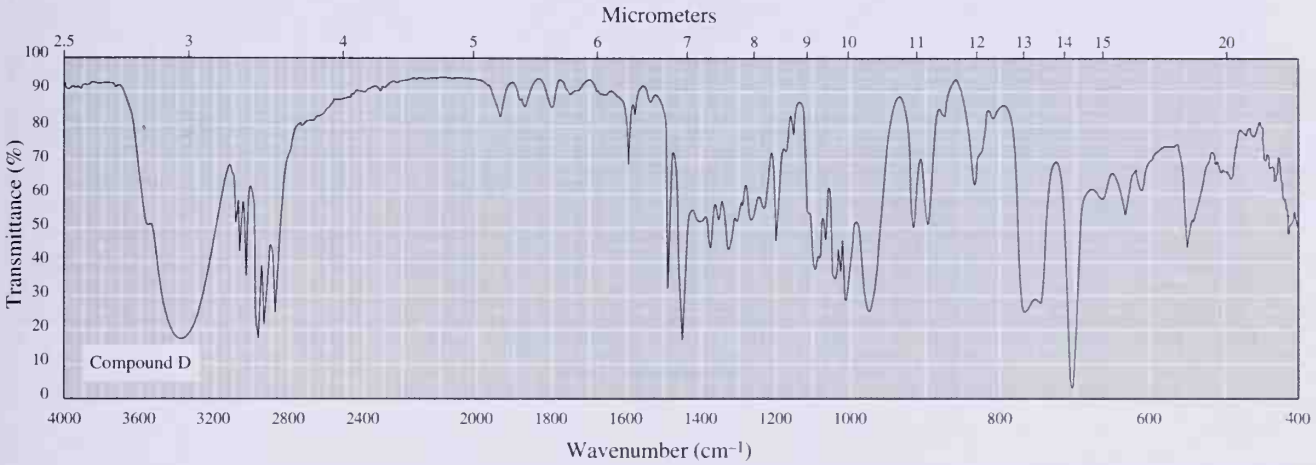


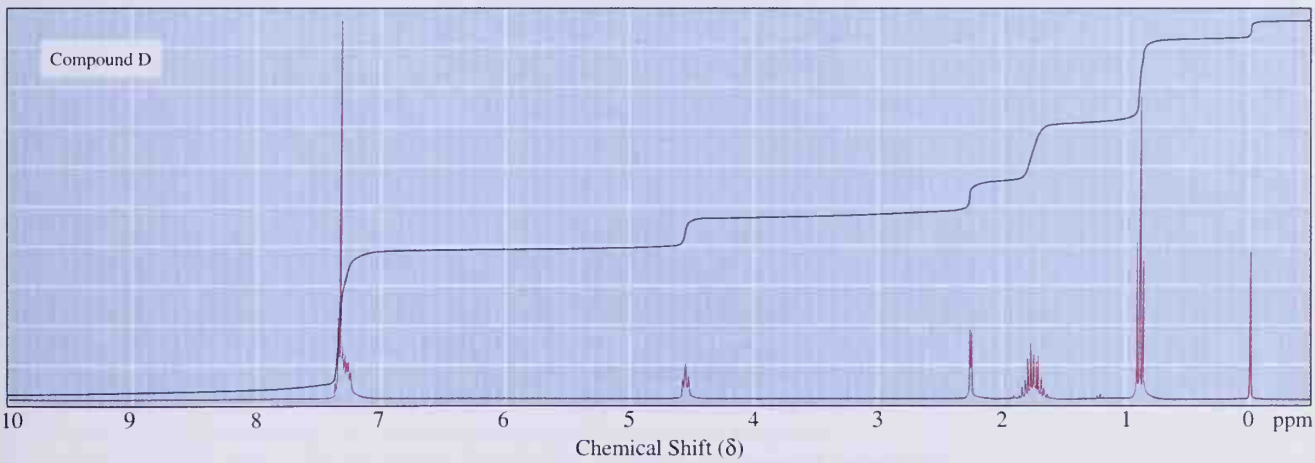


15.18 Following are IR and ^{1}H-NMR spectra of compound D. The mass spectrum of compound D shows a molecular ion peak at *m/e* 136, a base peak at *m/e* 107, and other prominant peaks at *m/e* 118 and 59.

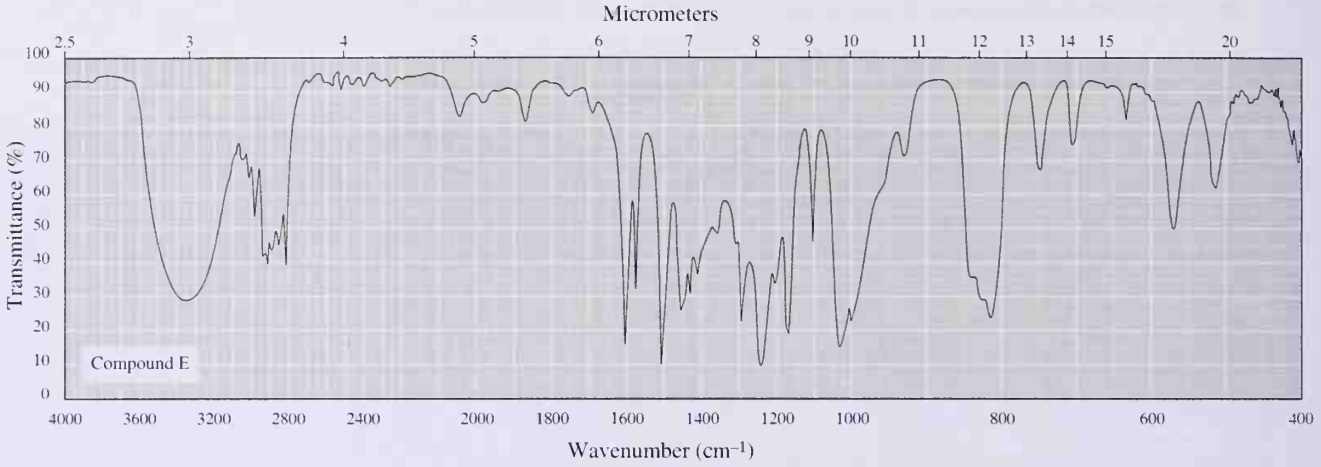
(a) Propose a structural formula for compound D based on this information.

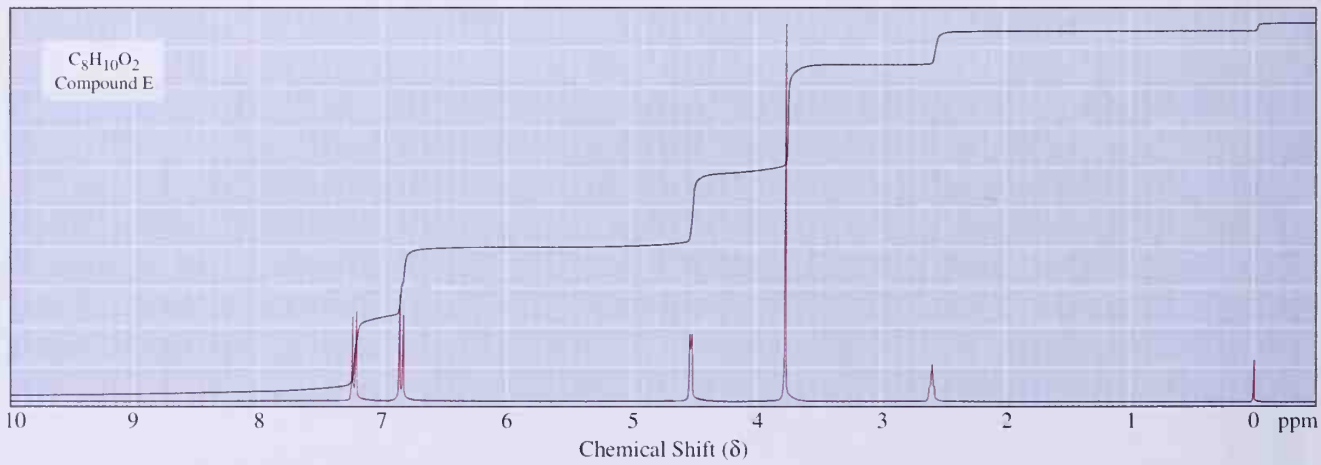
(b) Propose structural formulas for ions in the mass spectrum at *m/e* 118, 107, and 59.





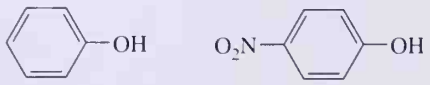
15.19 Compound E is a neutral solid of molecular formula $C_8H_{10}O_2$. Its mass spectrum shows a molecular ion at *m/e* 138 and significant peaks at M^+-1 and M^+-17. Following are IR and ^{1}H-NMR spectra of compound E. Deduce the structure of compound E.





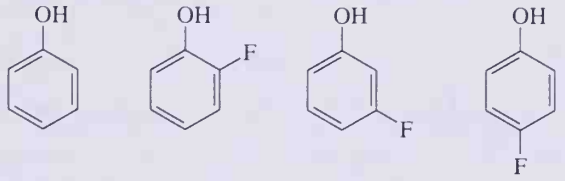
Acidity of Phenols

15.20 Use the resonance theory to account for the fact that *p*-nitrophenol is a stronger acid than phenol.



$K_a = 1.0 \times 10^{-10}$ $K_a = 7.0 \times 10^{-8}$

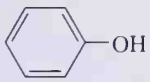
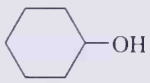
15.21 Explain the trends in the acidity of phenol and the monofluoro isomers of phenol.

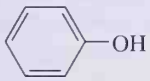


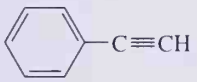
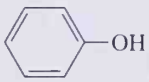
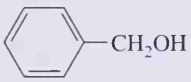
$pK_a = 10.0$ $pK_a = 8.81$ $pK_a = 9.28$ $pK_a = 9.81$

15.22 You wish to determine the inductive effects of a series of functional groups, for example Cl, Br, CN, CO_2H, and C_6H_5. Is it best to use a series of ortho-substituted, meta-substituted, or para-substituted phenols? Explain your answer.

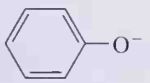
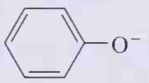
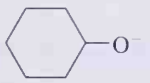
15.23 Arrange the molecules and ions in each set in order of increasing acidity (from least acidic to most acidic).

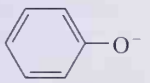
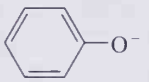
(a)   CH_3CO_2H

(b)  HCO_3^- H_2O

(c)   

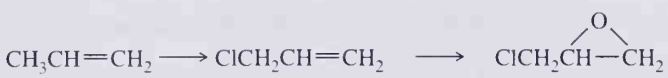
15.24 From each pair, select the stronger base.

(a)  or OH^- **(b)**  or 

(c)  or HCO_3^- **(d)**  or $CH_3CO_2^-$

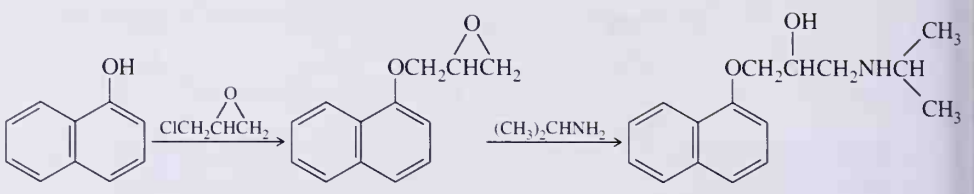
15.25 Propranolol is a β-adrenergic receptor antagonist. Members of this class have received enormous clinical attention because of their effectiveness in treating hypertension (high blood pressure), migraine headaches, glaucoma, ischemic heart disease, and certain cardiac arrhythmias. Starting materials for the synthesis of propranolol are propene, 1-naphthol, and isopropylamine. Show how to convert propene to epichlorohydrin in stage 1, and then complete the synthesis of propranolol in stage 2.

Stage 1: Synthesis of epichlorohydrin



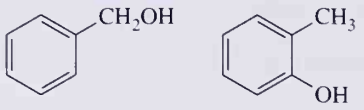
Propene	3-Chloropropene (Allyl chloride)	3-Chloro-1,2-epoxypropane (Epichlorohydrin)

Stage 2: Synthesis of propranolol



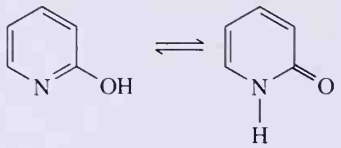
1-Naphthol Propranolol

15.26 Describe a procedure to separate a mixture of benzyl alcohol and *o*-cresol and recover each in pure form.



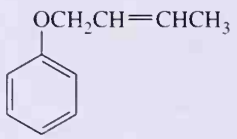
Benzyl alcohol (bp 205°C) *o*-Cresol (bp 191°C)

15.27 The molecule 2-hydroxypyridine, a derivative of pyridine, is in equilibrium with 2-pyridone. 2-Hydroxypyridine is aromatic. Does 2-pyridone have comparable aromatic character? Explain.



2-Hydroxypyridine 2-Pyridone

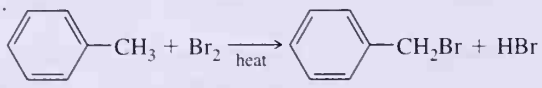
15.28 Draw the structural formula of the product you expect from Claisen rearrangement of the following allyl phenyl ether:



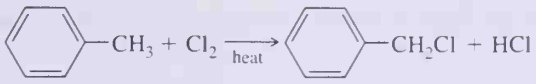
Reactions at the Benzylic Position

15.29 Write a balanced equation for the oxidation of *p*-xylene to 1,4-benzenedicarboxylic acid (terephthalic acid) using potassium permanganate in aqueous sodium hydroxide. How many milligrams of $KMnO_4$ is required to oxidize 250 mg of *p*-xylene to terephthalic acid?

15.30 Each of the following reactions occurs by a radical chain mechanism:



Toluene Benzyl bromide



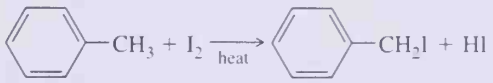
Toluene Benzyl chloride

(a) Calculate the enthalpy change, ΔH, in kilocalories per mole for each reaction.

(b) Write a pair of chain propagation steps for each mechanism, and show that the net result of the chain propagation steps is the observed reaction.

(c) Calculate ΔH for each chain propagation step, and show that the sum for each pair of chain propagation steps is identical with the value of ΔH calculated in part (a).

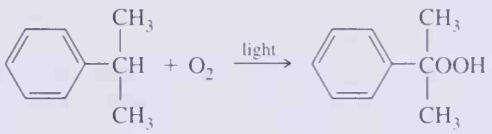
15.31 Following is an equation for iodination of toluene:



Toluene Benzyl iodide

This reaction does not take place. All that happens under experimental conditions for the formation of radicals is initiation to form iodine radicals, I·, followed by termination to reform I_2. How do you account for these observations?

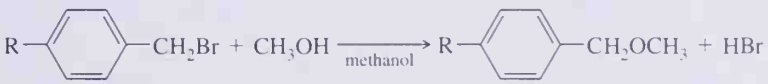
15.32 Following is an equation for hydroperoxidation of cumene:



Cumene Cumene hydroperoxide

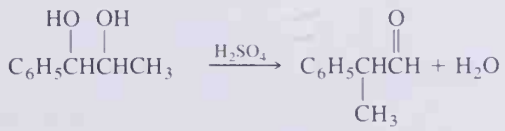
Propose a radical chain mechanism for this reaction. Assume that initiation is by reaction of cumene with molecular oxygen, a diradical (Section 1.9).

15.33 Para-substituted benzyl halides undergo reaction with methanol by an S_N1 mechanism to give a benzyl ether. Account for the following order of reactivity under these conditions.



Rate of S_N1 reaction: R = CH_3O— > CH_3— > H— > NO_2—

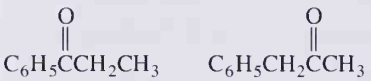
15.34 When warmed in dilute sulfuric acid, 1-phenyl-1,2-propanediol undergoes dehydration and rearrangement to give 2-phenylpropanal.



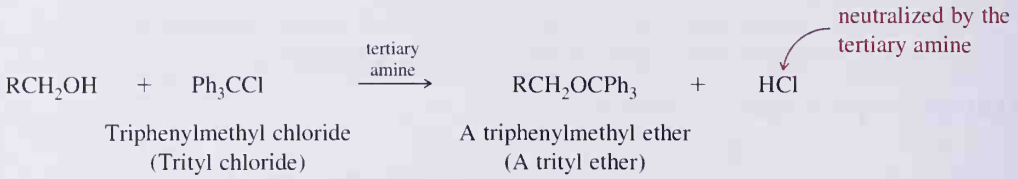
1-Phenyl-1,2-propanediol 2-Phenylpropanal

(a) Propose a mechanism for this example of a pinacol rearrangement (Section 9.5F).

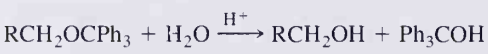
(b) Account for the fact that 2-methylpropanal is formed rather than either of the following ketones:



15.35 In the chemical synthesis of DNA and RNA, hydroxyl groups are normally converted to triphenylmethyl (trityl) ethers to protect the hydroxyl group from reaction with other reagents.



Triphenylmethyl ethers are stable to aqueous base but are rapidly cleaved in aqueous acid.

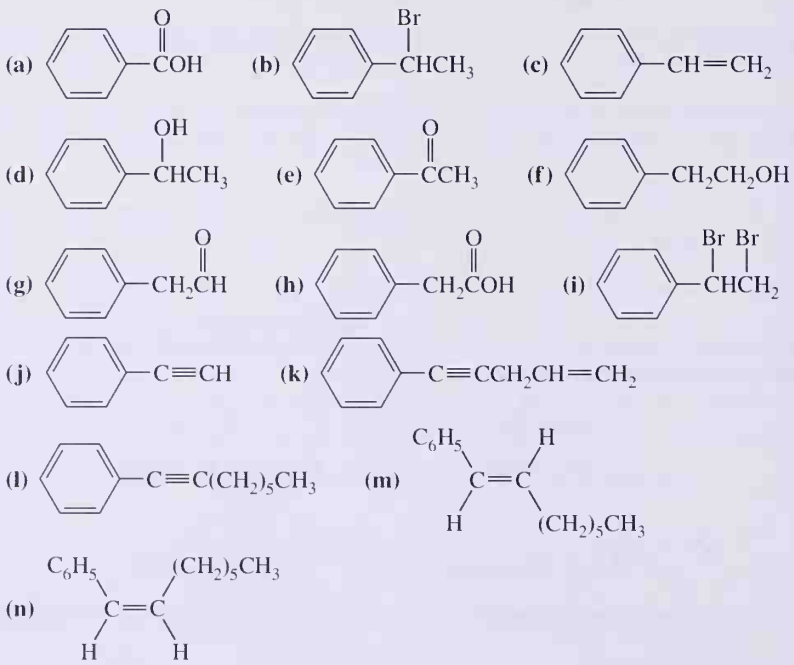


(a) Why are triphenylmethyl ethers so readily hydrolyzed by aqueous acid?

(b) How might the structure of the triphenylmethyl group be modified to increase or decrease its acid sensitivity?

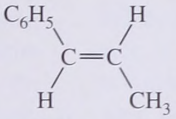
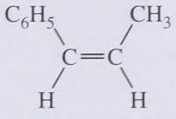
Synthesis

15.36 Using ethylbenzene as the only aromatic starting material, show how to synthesize the following compounds. In addition to the indicated starting material, use any other necessary organic or inorganic chemicals. Note that any compound already synthesized in one part of this problem may then be used to make any other compound in the problem.



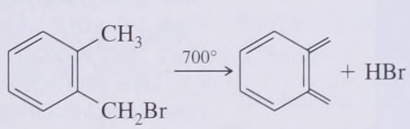
15.37 Show how to convert 1-phenylpropane into each of the following. In addition to this starting material, use any necessary inorganic reagents. Any compound synthesized in one part of this problem may then be used to make any other compound in the problem.

(a) $C_6H_5\underset{\displaystyle Br}{\underset{|}{C}}HCH_2CH_3$ **(b)** $C_6H_5CH{=}CHCH_3$ **(c)** $C_6H_5\underset{\displaystyle Cl\ Cl}{\underset{|\ \ |}{CH}}CHCH_3$

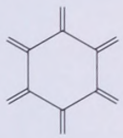
(d) $C_6H_5C{\equiv}CCH_3$ **(e)**  **(f)** 

(g) $C_6H_5\underset{\displaystyle HO\ OH}{\underset{|\ \ |}{CH}}CHCH_3$ **(h)** $C_6H_5\underset{\displaystyle OH}{\underset{|}{C}}HCH_2CH_3$ **(i)** $C_6H_5\overset{\displaystyle O}{\overset{\|}{C}}CH_2CH_3$

15.38 Benzylic bromination followed by loss of HBr by heating at high temperatures can be used to generate reactive intermediates such as (1). How do you take advantage of this observation to synthesize hexaradialene? (See L. G. Harruff, M. Brown, and V. Boekelheide, *J. Am. Chem. Soc.*, **100,** 2893 (1978).)



(1)



Hexaradialene

JACQUELINE K. BARTON

Jacqueline K. Barton is a native New Yorker and was educated in that city. She received her B.A. degree from Barnard College in 1974 and her Ph.D. from Columbia University in 1979. While at Columbia she worked in an area of platinum chemistry. Following her Ph.D. work, Dr. Barton did further research at Yale University and Bell Laboratories and then joined the faculty of Hunter College. In 1983 she returned to Columbia University where she rose rapidly to the rank of full professor. In the fall of 1989 she assumed her present position as Professor of Chemistry at the California Institute of Technology.

Dr. Barton has done outstanding research in the field of biochemistry, particularly in the design of simple molecular probes to explore the variations in structure and conformation along the DNA helix (the subject of Chapter 25). In spite of having been a research scientist for a relatively short time, she has done important new work and has received many honors. In 1985 she received the Alan T. Waterman Award of the National Science Foundation as the outstanding young scientist in the United States. In 1987 she was the recipient of the American Chemical Society's Eli Lilly Award in Biological Chemistry, and the following year she received the Society's Award in Pure Chemistry. That same year, 1988, she also received the Mayor of New York's Award of Honor in Science and Technology.

Like so many chemists, she is interested in art and has a painting by the Spanish artist Miro on her office wall as well as a print by the French artist Vasareley. This interest in form and color in art carries over into her research.

A Background in Math—But No Chemistry

"I never took chemistry in high school. Maybe one shouldn't publicize that, but it's the truth. However, I was always very interested in mathematics, so I took a lot of calculus when I was in high school. I also took a course in geometry, and that interest in geometry has carried over into my research, since the sort of science I do now is very much governed by structures and shapes.

"When I went to college I thought that, in addition to taking math, I should take some science courses. I walked into the freshman chemistry class, and there were about 150 people there. However, there was also a small honors class with about 10 students. Even though I hadn't had chemistry before I

thought I would try it—and I loved it. What chemistry allowed me to do was to combine the abstract and the real. I was very excited by it."

But, Dr. Barton says it was really the experience of the laboratory that got her interested in chemistry. Like many of us in chemistry, she was fascinated by color changes in reactions and the significance of these observations. However, she was also interested in trying to predict what would happen in a reaction, and, if her prediction was not correct, to try to explain this and then to do more experiments that would solve the puzzle. As she said, "That's really what got me started in science."

> "The bottom line is that chemistry is fun, it's addictive, and, if one has a sense of curiosity, it can be tremendously entertaining and appealing."

In addition, Dr. Barton also had an inspirational teacher and role model, Bernice Segal. "She was an absolute inspiration to me. She gave a magnificent course, and she was a very tough lady who asked a lot of you—and you did it!"

The Platinum Blues

Dr. Barton's Ph.D. thesis research was mostly on compounds known to chemists for years as the "platinum blues."

"Most platinum compounds are orange or red and yet there are these magnificient blue complexes. What are they? What are their structures, and why are they blue? I made one of these complexes, and it was indeed blue. It's an absolutely beautiful molecule. We solved the structure of the molecule and found that it contains four platinum atoms in a line. We also found that it's mixed-valent, where the platinum has an average oxidation number of $2\frac{1}{4}$, a fact that helps to explain its blue color."

Research in Bioinorganic Chemistry

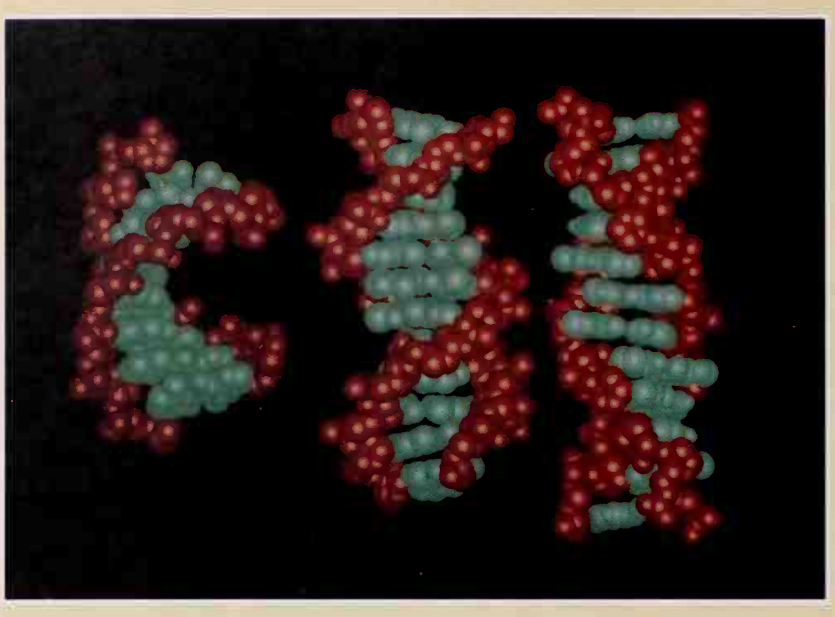
Dr. Barton's current research is in the area of bioinorganic chemistry, the role of metals in biological systems.

"The interest of my group is to exploit inorganic chemistry as a tool to ask questions of biological interest and to explore biological molecules. A lot of the work in bioinorganic chemistry thus far has been the exploration of metal centers in biology. Why is blood red? Why does the iron [in heme] do what it does? That's just one example, but there are hundreds of others. Many enzymes and proteins within the body in fact contain metals, and the reason we've looked at blood and then the heme center within it has been because it's colored. An obvious tool that transition metal chemistry provides is color, and so things change color when reactions occur. That is one of the things that fascinated me in the first place.

"Another wonderful thing about transition metal chemistry is that it allows us to build molecules that have interesting shapes and structures depending upon the coordination geometry. In fact, you can create a wealth of different shapes, several of which are chiral, and that's something we take advantage of in particular. What we want to do is make a variety of molecules of different shapes, target these molecules to sites on a DNA strand, and then ask questions such as 'Does DNA vary in its shape as a function of sequence? If we think about how proteins bind to DNA, do they also take advantage of shape recognition in binding to one site to activate one gene or turn off another gene? When scientists first wondered about these and other such problems, they would write down a one-dimensional sequence of DNA and would think about it in one-dimensional terms. How does the protein recognize a particular DNA sequence? DNA is clearly not one dimensional. It has a three-dimensional structure, and different sequences of bases will generate different shapes and different forms. Therefore, we think we can build transition metal complexes of particular shapes, target them to particular sequences of bases in DNA, and then use these complexes to plot out the topology of DNA. We can then ask how nature takes advantage of this topology. We want to develop a true molecular understanding, a three-dimensional understanding, of the structure and the shapes of biologically important molecules such as DNA and RNA."

A Revolution in Chemistry in the Last Ten Years

"I think our work may be an example of where chemistry is going in general. I think there has been a revolution in chemistry in the past 10 years. The revolution is at the inter-



Double helical conformations of DNA: A (left), B (center), and Z (right). *(Jacqueline Barton)*

face between chemistry and biology where we can now ask chemical questions about biological molecules. First of all, we can make biological molecules that are pure. I can now go to a machine called a DNA synthesizer,[1] and I can type in a sequence of DNA; from that sequence I can synthesize a pure material, with full knowledge of where all of the bonds are. Then I can run it through a HPLC and get it 100% pure.[2] Therefore, I can now talk about these biopolymers in chemical terms as molecules rather than as impure cellular extracts. I couldn't do that before."

Not only do we have the ability to prepare biological molecules in pure form, but Dr. Barton stressed that we have the techniques to characterize them in ways that we chemists think about molecules. "The development of new techniques allows us to make a bridge between chemistry and biology and ask chemical questions with molecular detail. It's an exciting time to be doing chemistry, and that is why I see it as a new frontier area."

New Chemistry Curricula

Dr. Barton stressed the point that it is chemists who are "making new materials and making and exploring biological systems. It's the chemist who looks at questions of molecular detail and asks about structure and its relationship to function." Since this involves so many areas of chemistry, she believes that "we are going to have to stop making divisions between inorganic, physical, analytical, and organic chemistry. We must all do a little bit of each." This is an attitude shared by many in chemical education today, and it means that we should perhaps rethink the curriculum in chemistry in particular and science in general.

No matter what the curricular structure, however, she believes what is important in the education of scientists is "to get across the excitement that now we can know what biologically important molecules look like. And, from knowing what they look like, we can manipulate them and change them a little. Then we can ask how those changes affect the function, so we can relate the structure of the molecule and its macroscopic function."

"A protein molecule of average size is so small you could put more than a billion billion of them on the head of a pin. We now know we can

[1] The chemical synthesis of DNA is discussed in Chapter 25.

[2] An HPLC is a "high pressure liquid chromatograph," an instrument capable of separating one type of molecule from another.

manipulate molecules that are of those dimensions and can know exactly what they look like. I can't imagine that we can't get people interested in chemistry if we can get across the excitement that comes from the realization that we are looking at things so small and yet can do surgery on them."

Chemistry Is Fun

"The bottom line is that chemistry is fun, it's addictive, and, if one has a sense of curiosity, it can be tremendously entertaining and appealing. And it is not so difficult. It's difficult when one thinks about it as rote memorization, which *is* difficult and boring. But that isn't what chemistry is. Chemistry is trying to understand the world around us in some detail. For example, we are interested in knowing such things as what makes skin soft, what makes things different in color, why sugar is sweet, or why a particular pharmaceutical agent makes us feel better."

Women in Science

"Because I am a woman, and there are so few women currently in professional positions in chemistry, I'm asked those questions often. First of all, I am not an expert on the subject. What I like to think my best contribution to women in chemistry can be is to do the best science I can, and to be recognized for my science, not for being a woman in science. I think that it is generally important when women go into science that they should appreciate that there are no special opportunities; that is, you will be treated like any other person doing science. But just as there should be no special opportunities in that respect, happily —maybe this is naive of me—I think there are also no special detriments or obstacles that one need consider in this day and age. One shouldn't think that 'because I am a woman I can't do it.' That's patently false. In fact, everyone is extremely supportive of women who do science. However, I remember talking to Bernice Segal, my former teacher at Barnard College, and having her explain to me that when she was a graduate student she had to do things behind a curtain, because the women weren't supposed to be doing chemistry. Mildred Cohn, another one of my role models, took over 20 years to have her own independent position as a professor, as opposed to being a laboratory assistant working for someone else. The bottom line is that I don't have a story like that to tell. That's the good news. In my generation there are few such stories of blatant discrimination. Now the world is a much better place for a woman to do science."

Dr. Barton's enthusiasm for her work and for chemistry in general is obvious. It is evident that she will continue to do some of the most important work in science and that her infectious enthusiasm for chemistry will bring many more young people into our profession.

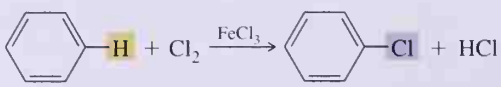
16

Buckyball. (Richard E. Smalley, Rice University)

AROMATICS II: Reactions of Benzene and Its Derivatives

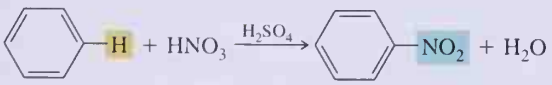
By far the most characteristic reaction of aromatic compounds is substitution at a ring carbon. Some groups that can be introduced directly on the ring are the halogens (except fluorine), the nitro ($-NO_2$) group, the sulfonic acid ($-SO_3H$) group, alkyl ($-R$) groups, and acyl ($RCO-$) groups. Each of these substitution reactions is represented in the following equations:

Halogenation:



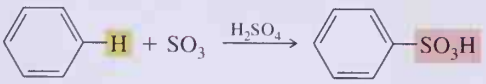
Chlorobenzene

Nitration:



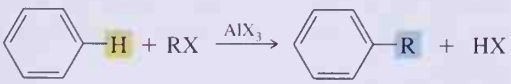
Nitrobenzene

Sulfonation:



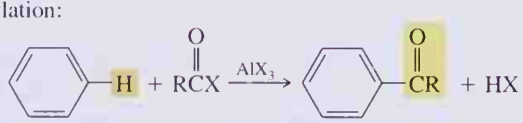
Benzenesulfonic acid

Alkylation:



An alkylbenzene

Acylation:

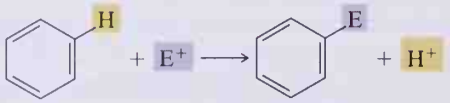


An acylbenzene

Considerable experimental evidence suggests that a key step in these substitutions is attack by an electrophile on the aromatic ring. We take these reactions one at a time and examine their common mechanistic theme.

16.1 Electrophilic Aromatic Substitution

An electrophile is a positive ion (E^+) or some other electron-deficient species. Electrophiles can attack an aromatic ring and replace one of the hydrogen atoms on the ring in a reaction called electrophilic aromatic substitution.

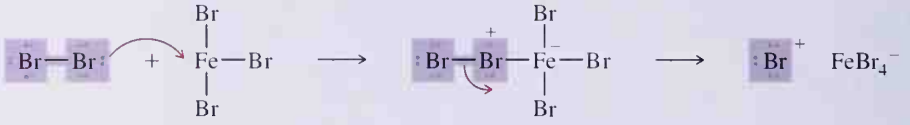


In this and the following sections we study several common types of electrophiles, how they are generated, and the mechanisms by which they replace hydrogen on an aromatic ring.

A. Bromination and Chlorination

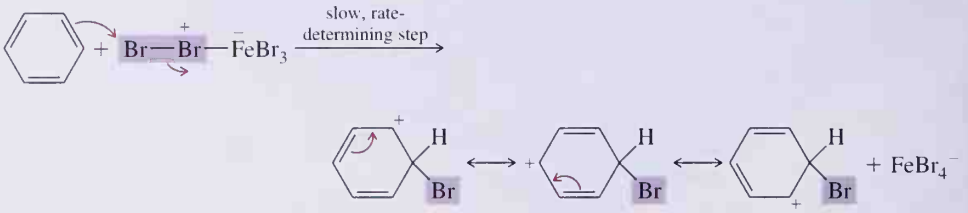
Bromine does not react with benzene alone (in contrast to the instantaneous addition of bromine to cyclohexene). In the presence of a Lewis acid catalyst, however, a reaction does take place; it is not addition but substitution of a bromine atom for a hydrogen atom.

The first step in this reaction involves interaction of bromine and the Lewis acid catalyst, as, for example, ferric bromide or aluminum bromide. A bromine atom of Br_2 donates a pair of electrons to the Lewis acid to form a molecular complex with positive charge on bromine and negative charge on the metal. Rearrangement of electrons in this complex generates a **bromonium ion** as part of an ion pair.



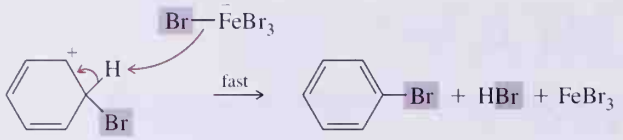
Bromine (a Lewis base) | Ferric bromide (a Lewis acid) | A molecular complex with a positive charge on bromine and a negative charge on iron | An ion pair containing the bromonium ion

Reaction of the Br_2—$FeBr_3$ complex with the pi electron cloud of benzene (a Lewis base) forms a resonance-stabilized cation intermediate, here represented as a hybrid of three contributing structures.



(Resonance-stabilized cation intermediate)

Proton transfer from the cation intermediate to $FeBr_4^-$ forms HBr, regenerates the Lewis acid catalyst, and gives bromobenzene.



Cation intermediate | Bromobenzene

At this point, we should stop to compare and contrast the reaction of bromine and benzene (an aromatic hydrocarbon) with that of bromine and cyclohexene (an alkene). Both benzene and cyclohexene are electron-rich compounds and, therefore, react with electron-deficient (electrophilic) species. In the case of cyclohexene, reaction with Br_2 leads to a bridged bromonium ion intermediate (Section 5.3D). With benzene in the presence of a Lewis acid catalyst, reaction with Br_2 leads to a resonance-stabilized cation intermediate. From this point, however, the two reactions are fundamentally different. The bridged bromonium ion intermediate undergoes a reaction with Br^- to yield an addition product.

A bridged bromonium ion intermediate | *trans*-1,2-Dibromocyclohexane

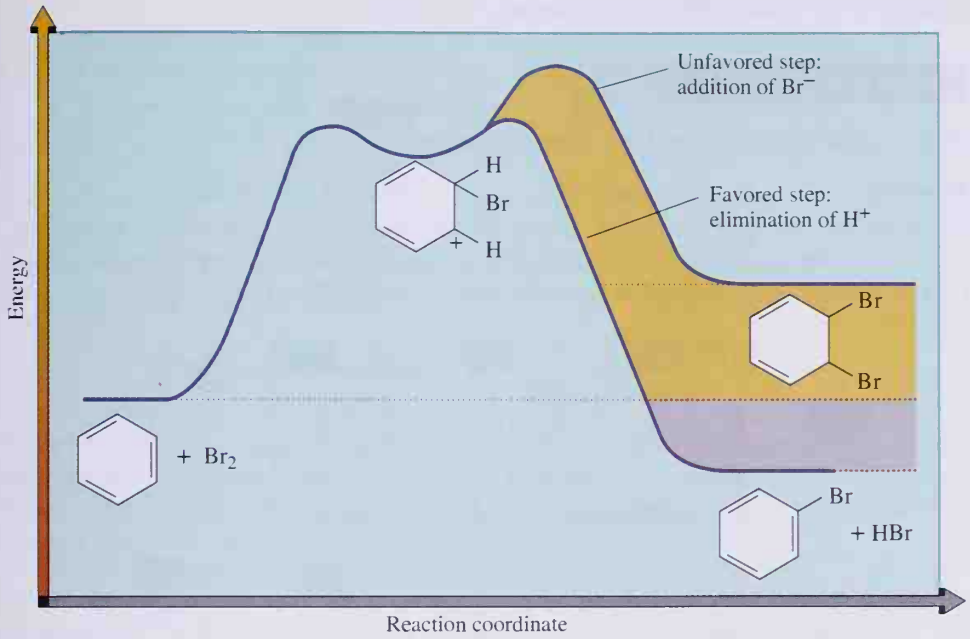
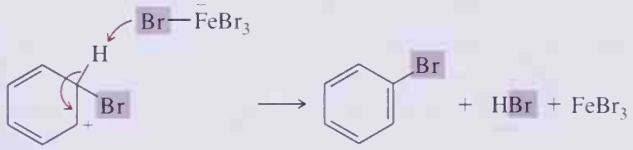


Figure 16.1
Reaction of benzene with bromine. Energy diagram for substitution versus addition.

The cation intermediate from benzene loses a proton to regenerate the aromatic ring and yield a substitution product

Proton transfer to regenerate the aromatic ring:

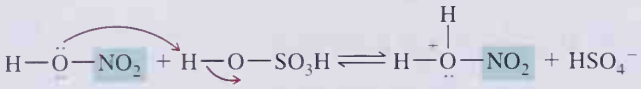


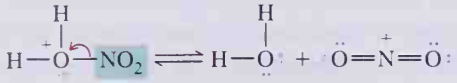
Bromobenzene

The energy diagram in Figure 16.1 shows both addition and substitution reactions of benzene. Reaction of the cation intermediate to form an addition product results in loss of the resonance stabilization of the aromatic ring. Reaction of the cation intermediate to form a substitution product regenerates the resonance stabilized aromatic ring.

B. Nitration and Sulfonation

The sequence of steps for electrophilic nitration and sulfonation of benzene is similar to that for bromination. For nitration, the electrophile is the **nitronium ion,** NO_2^+, generated by reaction of nitric acid and sulfuric acid.





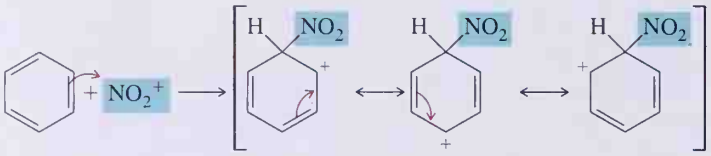
Nitronium ion

EXAMPLE 16.1

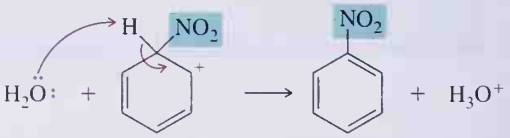
Write a stepwise mechanism for nitration of benzene.

Solution

The nitronium ion (a Lewis acid) attacks the benzene ring (a Lewis base) to form a resonance-stabilized cation intermediate. Proton transfer from this intermediate to either H_2O or HSO_4^- regenerates the aromatic ring and gives nitrobenzene.

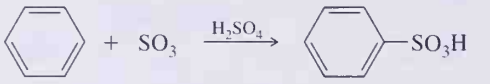


Resonance-stabilized cation intermediate



Nitrobenzene

Sulfonation of benzene is carried out using concentrated sulfuric acid, often saturated with sulfur trioxide. In the following equation, the sulfonating agent is shown as sulfur trioxide.



Benzene Sulfur trioxide Benzenesulfonic acid

PROBLEM 16.1

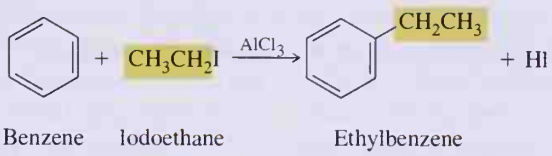
Write the stepwise mechanism for sulfonation of benzene. In this reaction, the electrophile is SO_3 formed as shown in the following equation:

$$H_2SO_4 \rightleftharpoons SO_3 + H_2O$$

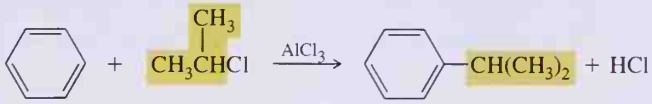
Hint: In thinking about a mechanism for this reaction, consider formal charges on sulfur and oxygen in the Lewis structure of sulfur trioxide.

C. Friedel-Crafts Alkylation and Acylation

Alkylation of aromatic hydrocarbons was discovered in 1877 by the French chemist, Charles Friedel, and a visiting American chemist, James Crafts. They discovered that mixing benzene, an alkyl halide, and $AlCl_3$ results in formation of an alkylbenzene and HX. **Friedel-Crafts alkylation** forms a new carbon-carbon bond between benzene and an alkyl group, as illustrated by reactions of benzene with iodoethane and with 2-chloropropane, each in the presence of aluminum chloride.

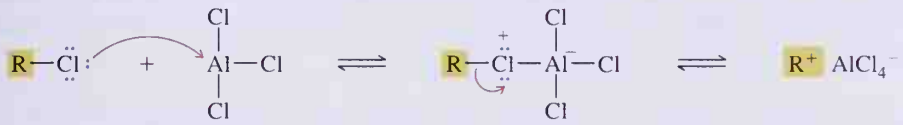


Benzene Iodoethane Ethylbenzene



Benzene 2-Chloropropane Cumene (Isopropylbenzene)

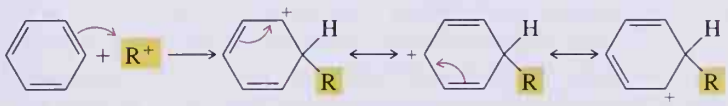
Friedel-Crafts alkylation is among the most important methods for forming new carbon-carbon bonds to aromatic rings. It begins with formation of a complex between the alkyl halide and aluminum chloride. In this complex, aluminum has a negative charge, and the halogen of the alkyl halide has a positive charge.



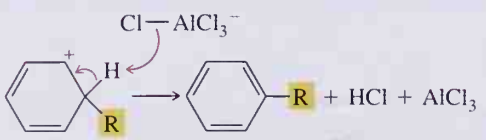
Alkyl chloride (a Lewis base) Aluminum chloride (a Lewis acid) A molecular complex with a positive charge on chlorine and a negative charge on aluminum An ion pair containing a carbocation

The alkyl group can also be written as a carbocation, although it is unlikely that a free carbocation is actually formed, especially in the case of the relatively unstable primary and secondary carbocations. Nonetheless, we very often write the reactive intermediate as a carbocation to simplify the mechanism.

Reaction of an alkyl carbocation with an aromatic ring gives a resonance-stabilized carbocation intermediate, which then loses a hydrogen to give an alkylbenzene.



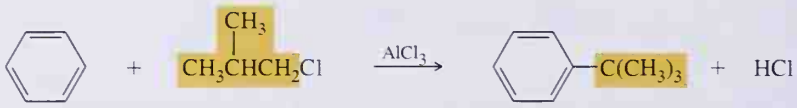
A resonance-stabilized cation intermediate



Vinylic halides and aryl halides generally do not react under conditions of the Friedel-Crafts alkylation because of the high energy of activation required to form vinylic and aryl carbocations.

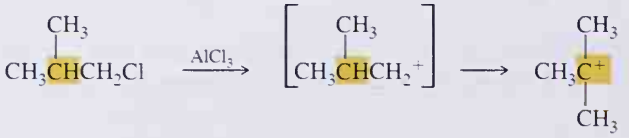
There are three major limitations on Friedel-Crafts alkylation. First, the possibility for rearrangement of the alkyl group; second, overalkylation of the aromatic ring; and third, failure of reaction altogether on aromatic rings bearing one or more strong electron-withdrawing groups. We deal with the first of these limitations in this section and with the second and third limitations in the following section.

Friedel-Crafts alkylation involves the generation of a carbocation and as we have already seen, carbocations may undergo any of three different reactions: (1) reaction with a nucleophile, (2) loss of H^+ to form an alkene, and (3) rearrangement followed by reactions (1) or (2) or both (1) and (2). Rearrangements are especially likely when a less stable carbocation can rearrange to a more stable one. **Carbocation rearrangements** are common in Friedel-Crafts alkylations. For example, reaction of benzene with 1-chloro-2-methylpropane (isobutyl chloride) gives only 2-methyl-2-phenylpropane (*tert*-butylbenzene).



Benzene 1-Chloro-2-methylpropane 2-Methyl-2-phenylpropane (*tert*-Butylbenzene)

In this case, the less stable primary isobutyl cation quickly rearranges to the more stable *tert*-butyl cation, which then has a sufficient lifetime to serve as the electrophile in this example of Friedel-Crafts alkylation.



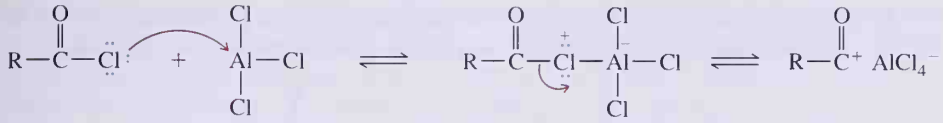
1-Chloro-2-methylpropane Isobutyl cation *tert*-Butyl cation

In practice, alkylation with primary halides is not useful, and alkylbenzenes containing a primary alkyl group other than $—CH_2CH_3$ must be prepared by other means. Alkylation is useful for introducing isopropyl, *tert*-butyl, and other alkyl groups, the cations of which do not tend to rearrange.

Friedel and Crafts also discovered that treatment of an aromatic hydrocarbon with an acyl halide in the presence of aluminum chloride gives a ketone. An **acyl halide** is a derivative of a carboxylic acid in which the —OH of the carboxyl group is replaced by a halogen, most commonly chlorine. Acyl halides are also referred to as acid halides. An RCO— group is known as an acyl group; hence, reaction of an acyl halide with an aromatic hydrocarbon is known as **Friedel-Crafts acylation,** as illustrated by reaction of benzene and acetyl chloride in the presence of aluminum chloride to form acetophenone.

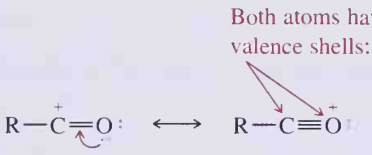
Benzene Acetyl chloride (an acyl halide) Acetophenone (a ketone)

Friedel-Crafts acylation begins with donation of a pair of electrons from the halogen of the acyl halide to aluminum to form a molecular complex similar to what we already saw for Friedel-Crafts alkylations.



Acyl chloride (a Lewis base) | Aluminum chloride (a Lewis acid) | A molecular complex with a positive charge on chlorine and a negative charge on aluminum | An ion pair containing an acyl cation

Of the two major contributing structures that can be drawn for the **acyl cation,** the one with complete valence shells for both carbon and oxygen makes the greater contribution to the hybrid. It is unlikely, however, that a free cation is formed.



(more important contributing structure)

Friedel-Crafts acylation is free of two of the major limitations on Friedel-Crafts alkylations. First, acyl cations do not undergo rearrangement. Thus, the carbon skeleton of an acyl halide is transferred unchanged to the aromatic ring. Second, overacylation does not occur.

EXAMPLE 16.2

Write structural formulas for the products you expect from Friedel-Crafts alkylation or acylation of benzene with

(a) $C_6H_5CH_2Cl$

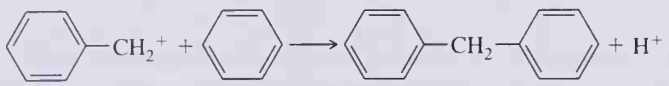
Benzyl chloride

(b) $C_6H_5\overset{\overset{O}{\|}}{C}Cl$

Benzoyl chloride

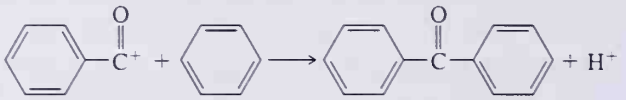
Solution

(a) Benzyl chloride in the presence of a Lewis acid catalyst gives the benzyl cation, which then attacks benzene followed by loss of H^+ to give diphenylmethane. In this example, the benzyl cation, although primary, cannot rearrange.



Benzyl cation | Diphenylmethane

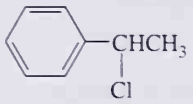
(b) Treatment of benzoyl chloride with aluminum chloride gives an acyl cation, an electrophile, which then attacks benzene to give benzophenone, a ketone.



Benzoyl cation Benzophenone

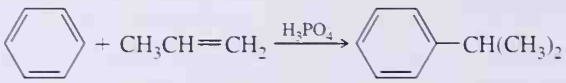
PROBLEM 16.2

Write structural formulas for the products you expect from Friedel-Crafts alkylation or acylation of benzene with

(a) $(CH_3)_3CCCl$ (with O) (b) $CH_3CH_2CH_2Cl$ (c) 

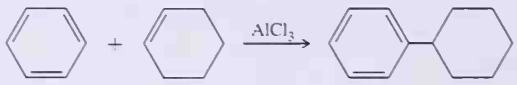
D. Other Electrophilic Aromatic Alkylations

Once it was discovered that Friedel-Crafts alkylations and acylations involve cation electrophiles, it was realized that the same reactions can be accomplished by other combinations of reagents and catalysts. We study two of these in this section: generation of carbocations from alkenes and from alcohols. As we saw in Section 5.3, treatment of an alkene with a strong acid, most commonly H_2SO_4, H_3PO_4, or HF/BF_3, generates a carbocation. Cumene is synthesized industrially (over 4.5 billion pounds in 1993) by reaction of benzene with propene in the presence of an acid catalyst.



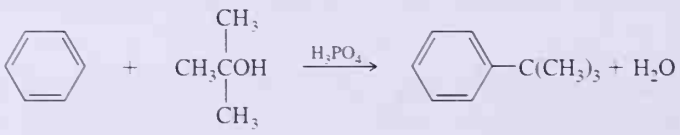
Benzene Propene (Propylene) Cumene

Alkylation with an alkene can also be carried out with a Lewis acid catalyst. Treatment of benzene with cyclohexene in the presence of aluminum chloride gives cyclohexylbenzene.



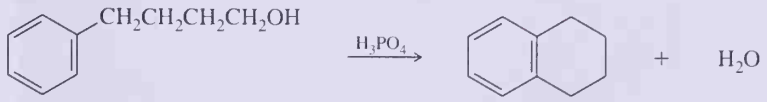
Benzene Cyclohexene Cyclohexylbenzene

Carbocations can also be generated by treatment of an alcohol with H_2SO_4, H_3PO_4, or HF (Section 9.5D).



Benzene 2-Methyl-2-propanol (*tert*-Butyl alcohol) *tert*-Butylbenzene

The following example of electrophilic aromatic alkylation involves intramolecular alkylation to form a six-member ring. The product of this reaction is a derivative of naphthalene in which hydrogens have been added to carbons 1, 2, 3, and 4. Hence the name 1,2,3,4-tetrahydronaphthalene.



4-Phenyl-1-butanol — 1,2,3,4-Tetrahydronaphthalene (Tetralin)

16.2 Disubstitution and Polysubstitution

A. Effects of a Substituent Group on Further Substitution

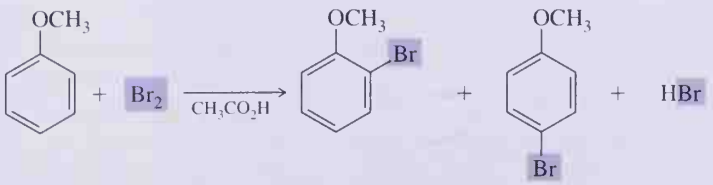
Electrophilic aromatic substitution of benzene itself gives only one product. In electrophilic aromatic substitution of a monosubstituted benzene, three products are possible: substitution ortho, meta, or para to the existing group on the ring. We can make the following generalization about the manner in which existing groups influence the **position** of further substitution.

1. Some groups direct an incoming group preferentially to the ortho and para positions; other groups direct it preferentially to the meta position. In other words, groups on the benzene ring can be classified as **ortho-para directors** or as **meta directors.**

We can make the following generalization about the manner in which existing groups influence the **rate** of further substitution.

2. Some groups cause the rate of a second substitution to be greater than that for benzene itself, whereas other groups cause the rate of a second substitution to be smaller than that for benzene. In other words, groups on a benzene ring can be classified as **activating** or **deactivating** toward further substitution.

These directing and activating-deactivating effects can be seen by comparing the products of bromination of anisole and nitration of nitrobenzene. Bromination of anisole proceeds at a rate considerably greater than that for bromination of benzene (the methoxy group is activating), and the product is a mixture of *o*-bromoanisole and *p*-bromoanisole (the methoxy group is ortho-para directing).



Anisole — *o*-Bromoanisole (4%) — *p*-Bromoanisole (96%)

Quite another situation is seen in nitration of nitrobenzene. First, the reaction requires fuming nitric acid and a higher temperature. Because nitration of nitrobenzene proceeds much more slowly than nitration of benzene itself, we say that a nitro group is strongly

Text continued on p. 622

CHEMISTRY IN ACTION

Buckyball: A New Form of Carbon

Spaceship Earth at Disney's Epcot Center is an example of a geodesic dome. *(John Madere © All rights reserved)*

A favorite chemistry question is: What are the elemental forms of carbon? The usual answer is that pure carbon is found in two forms: graphite and diamond. These allotropes have been known for centuries, and it was generally believed that they are the only forms of carbon having extended networks of C atoms in well-defined structures.

But not so! The scientific world was startled in 1985 when Richard E. Smalley of Rice University, Houston, Texas, and Harry W. Kroto of the University of Sussex, UK, and their coworkers announced that they had isolated microscopic quantities of a new form of carbon from soot, the black material that collects when carbon-containing materials are burned in limited quantities of oxygen.

This new form of carbon has the molecular formula C_{60} and a structure that resembles a soccer ball. It has 60 vertices and 32 faces, 12 of them pentagons and 20 of them hexagons. The molecule reminded its discoverers of a geodesic dome, a structure invented by the innovative American engineer and philosopher R. Buckminster Fuller. Therefore, the official name of this allotrope of carbon has become buckminsterfullerene, and chemists refer to C_{60} simply as "buckyball."

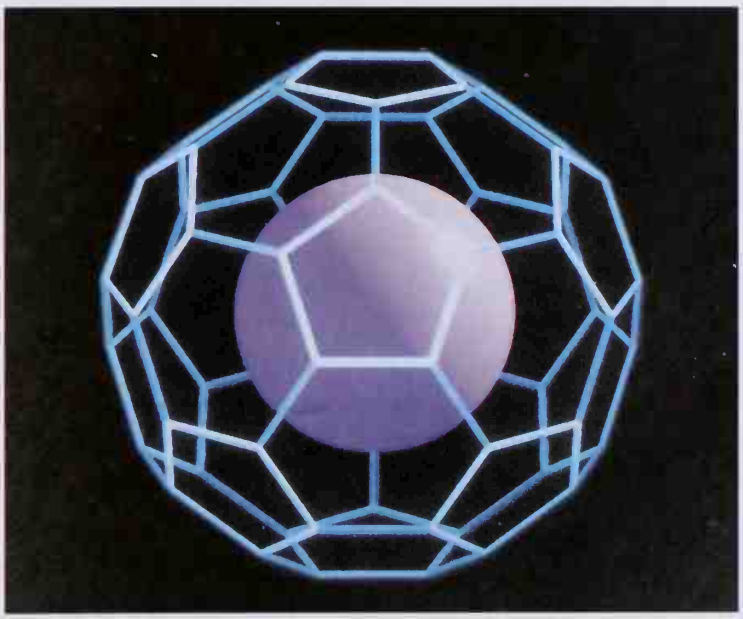
Fullerenes are now made in larger quantities by a process developed by physicists Donald R. Huffman of the University of Arizona and Wolfgang Krätschmer of the Max Planck Institute for Nuclear Physics, Heidelberg, Germany. In their process, carbon is vaporized from graphite electrodes in an atmosphere of helium gas

at a pressure of 100 torr. The soot that forms in this environment contains about 5% C_{60} by mass. In addition, it also contains C_{70} with a fullerene shape similar to that of C_{60} except that the extra carbon atoms lead to an egg-shaped structure. More recently, both smaller and larger fullerenes have been discovered but buckyball, the first discovered, remains the most readily available and fully studied.

Buckyball was initially thought to be chemically inert because of the unique stability of its icosahedral framework, but now chemists realize that it is quite reactive, particularly with radicals. C_{60} has in effect 30 carbon-carbon double bonds to which radicals can add. In addition, $AlCl_3$ and strong acids catalyze addition of benzene and other aromatics to fullerenes.

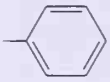
Among the derivatives receiving particular interest are metallofullerenes, compounds consisting of fullerenes containing one or more atoms of metal encapsulated within the fullerene cage. According to the notation introduced by Smalley, the symbol "@" designates the entity encapsulated by the carbon cage. Thus, C_{60} containing a single lanthanum atom is represented by $La@C_{60}$. $La@C_{60}$ and $La@C_{82}$, the first metal-encapsulated fullerenes discovered, are generated by vaporization of graphite impregnated with lanthanum oxide, La_2O_3. Since their discovery, metallofullerenes containing uranium and other transition metals have also been prepared. One of the remarkable findings is that fullerenes doped with alkali metal ions are superconductors at relatively high temperatures. $Rb_3@C_{60}$, for example, becomes superconducting at 28K.

The fullerenes are remarkable molecules, have remarkable properties, and are the subject of intense research in laboratories around the world. Reports of new fullerene research appear quite often in journals, such as *Science, Nature, Journal of the American Chemical Society, Chemical & Engineering News,* and others. In what ways will this research become commercially useful? It is not yet clear, but there is every expectation that it will become clearer soon.

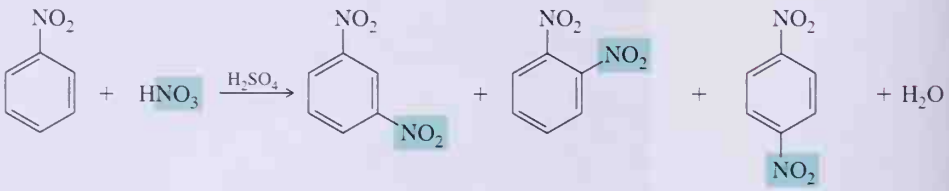


The structure of a metallofullerene. *(Richard E. Smalley, Rice University)*

Table 16.1 Effects of substituents on further electrophilic aromatic substitution

Ortho-para Directing	Meta Directing
Strongly Activating	**Moderately Deactivating**
$-\ddot{N}H_2$ $-\ddot{N}HR$ $-\ddot{N}R_2$ $-\ddot{O}H$	$-CH(=O)$ $-CR(=O)$ $-CAr(=O)$ $-COH(=O)$ $-COR(=O)$ $-CNH_2(=O)$ $-SOH(=O)(=O)$ $-C\equiv N$
Moderately Activating	
$-\ddot{N}HCR(=O)$ $-\ddot{N}HCAr(=O)$ $-\ddot{O}CH_3$ $-\ddot{O}R$ $-\ddot{O}CR(=O)$ $-\ddot{O}CAr(=O)$	
Weakly Activating	**Strongly Deactivating**
$-CH_3$ $-CH_2CH_3$ $-R$ 	$-NO_2$ $-NH_3^+$ $-\overset{+}{N}HR_2$ $-\overset{+}{N}H_2R$ $-\overset{+}{N}R_3$ $-CF_3$ $-CCl_3$
Weakly Deactivating	
$-\ddot{F}:$ $-\ddot{Cl}:$ $-\ddot{Br}:$ $-\ddot{I}:$	

deactivating. Second, the product formed consists of approximately 93% of the meta isomer and less than 7% of the ortho and para isomers combined.



Nitrobenzene — *m*-Dinitrobenzene (93%) — *o*-Dinitrobenzene — *p*-Dinitrobenzene

less than 7% combined

Substitution reactions such as these have been studied for a wide variety of monosubstituted derivatives of benzene, and the directing and activating-deactivating influences of various functional groups have been determined. Listed in Table 16.1 are the directing and activating-deactivating influences for the major functional groups with which we are concerned in this text.

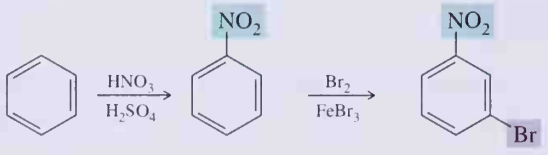
If we compare these ortho-para and meta directors for structural similarities and differences, we can make the following generalizations:

1. Except for alkyl and phenyl groups, all groups in which the atom bonded to the ring has an unshared pair of electrons are ortho-para directing. Groups in which the atom bonded to the aromatic ring bears a partial or full positive charge are meta directing.

2. Groups that are activating toward further substitution are also ortho-para directors. The one exception to this generalization is the halogens; they are weakly deactivating but still ortho-para directing.

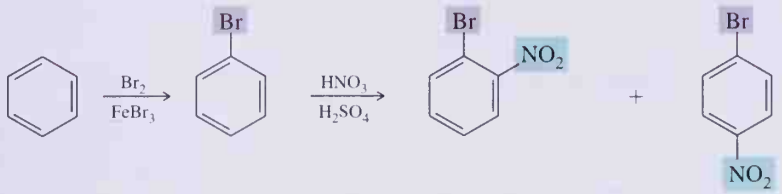
These are, of course, empirical generalizations. In Section 16.2B, we provide a sound mechanism-based rationale for them.

We can illustrate the usefulness of these generalizations by considering the synthesis of two different disubstituted derivatives of benzene. Suppose we wish to prepare *m*-bromonitrobenzene from benzene. Such a conversion can be done in two steps: nitration and bromination. If the steps are carried out in just that order, the major product is indeed *m*-bromonitrobenzene. The nitro group is a meta director and, therefore, directs bromination to the meta position.



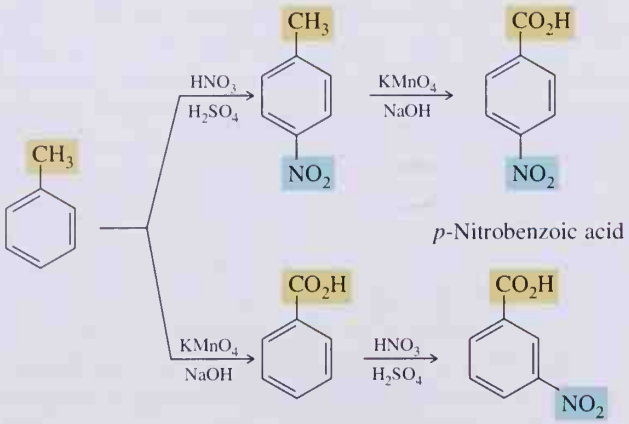
Nitrobenzene *m*-Bromonitrobenzene

If, however, we reverse the order of the steps and first form bromobenzene, we now have on the ring an ortho-para directing group, and nitration takes place preferentially at the ortho and para positions.



Bromobenzene *o*-Bromonitrobenzene *p*-Bromonitrobenzene

As another example of the importance of order in successive electrophilic aromatic substitutions, consider the conversion of toluene to *p*-nitrobenzoic acid. The nitro group can be introduced with a nitrating mixture of nitric and sulfuric acids. The carboxyl group can be produced by oxidation of the methyl group of toluene (Section 15.6A).

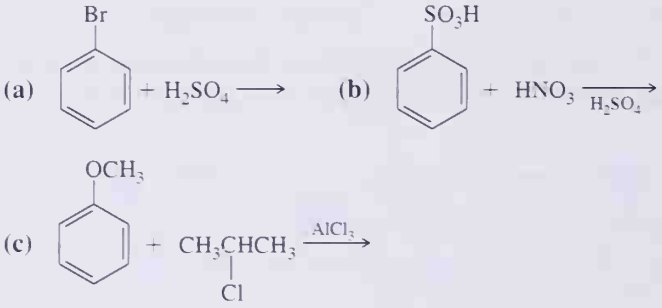


Nitration of toluene yields a product with the two substituents in the desired para relationship. Nitration of benzoic acid, on the other hand, yields a product with the substituents meta to each other. Again, we see that the order in which the steps are performed is critical.

Note that in this last example we showed nitration of toluene producing only the para isomer. Because methyl is an ortho-para directing group, both ortho and para isomers are formed. In problems of this type in which you are asked to prepare one or the other of these isomers, we assume that they are both formed but that there are physical methods by which they can be separated and the desired isomer obtained.

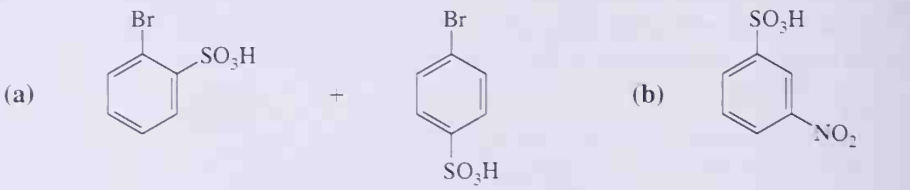
EXAMPLE 16.3

Complete the following electrophilic aromatic substitution reactions. Where you predict meta substitution, show only the meta product. Where you predict ortho-para substitution, show both products.

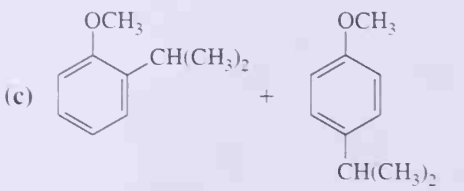


Solution

Bromine in (a) is ortho-para directing and weakly deactivating. The sulfonic acid group in (b) is meta directing and moderately deactivating. The methoxy group in (c) is ortho-para directing and moderately activating.



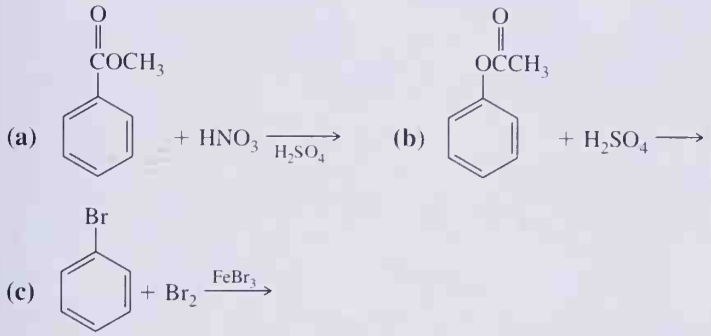
o-Bromobenzenesulfonic acid | *p*-Bromobenzenesulfonic acid | *m*-Nitrobenzenesulfonic acid



o-Methoxycumene | *p*-Methoxycumene

PROBLEM 16.3

Complete the following electrophilic aromatic substitution reactions. Where you predict meta substitution, show only the meta product. Where you predict ortho-para substitution, show both products.



B. Theory of Directing Effects

We have seen that a group on a benzene ring exerts a major effect on further substitution. We can account for patterns of orientation by starting with the general mechanism first presented in Section 16.1 for electrophilic aromatic substitution and carrying it a step further to consider how groups already present on the ring affect the energetics of further substitution. Specifically, we need to consider both resonance and inductive effects and the relative importance of each.

First let us consider nitration of anisole. The rate of electrophilic aromatic substitution is determined by the slowest step in the mechanism. For nitration of anisole, and in fact for almost every other substitution we consider, the slow and rate-determining step is attack of the electrophile on the aromatic ring. Electrophilic attack of a nitronium ion on the ring produces a resonance-stabilized cation intermediate. Shown in Figure 16.2 is the cation intermediate formed by attack of the electrophile meta to the methoxy group. Also shown in Figure 16.2 is the cation intermediate formed by attack para to the methoxy group. Note that in terms of electronic effects, structural formulas for the cation formed by attack ortho to the methoxy are essentially the same as those for para attack, so, for convenience, we deal only with para attack. The cation intermediate formed by meta attack is a hybrid of three major contributing structures: (a), (b), and (c). The cation intermediate formed by para attack is a hybrid of four major contributing structures: (d), (e), (f), and (g). Note that for each orientation, we can draw three contributing structures that place the positive charge on carbon atoms of the benzene ring. These three structures are the only important ones that can be drawn for meta attack. However, for para attack (and for ortho attack as well), a fourth contributing structure, (f), can be drawn that involves an unshared pair of electrons on the oxygen atom of the methoxy group and places a positive charge on this oxygen. Contributing structure (f) is more stable than contributing structures (d), (e), or (g) because in cation (f) all atoms have complete octets. Because the cation formed by ortho-para attack on anisole has a greater degree of resonance stabilization and hence a lower energy of activation for its formation, nitration of anisole occurs preferentially in the ortho and para positions.

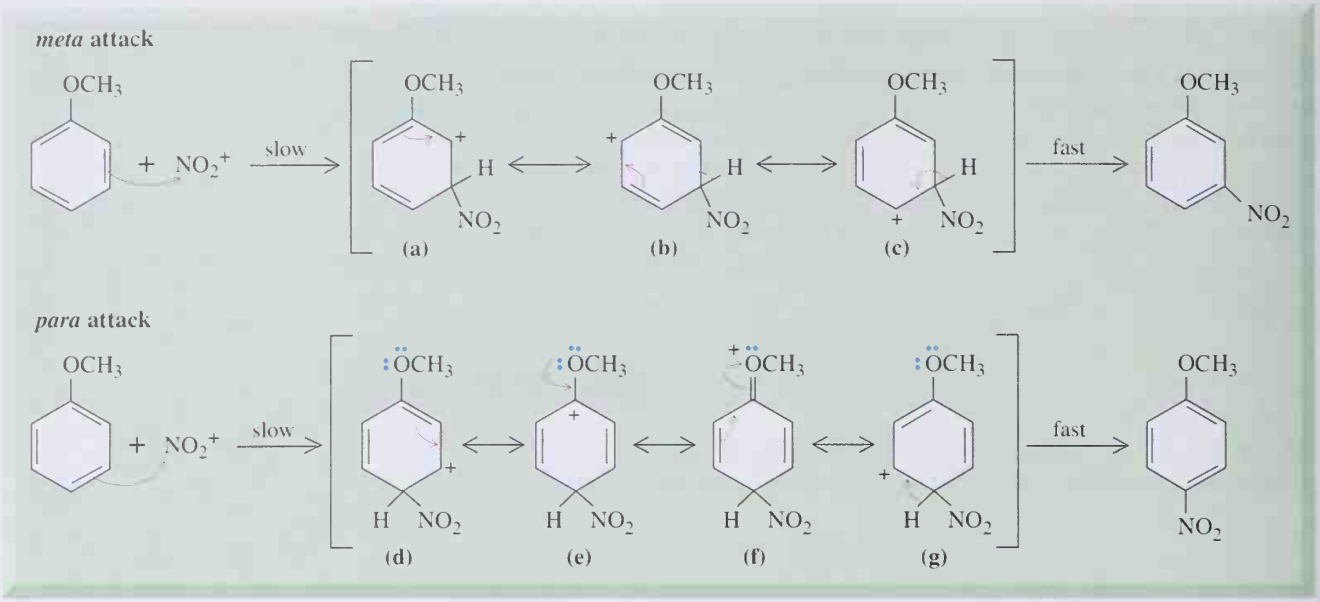
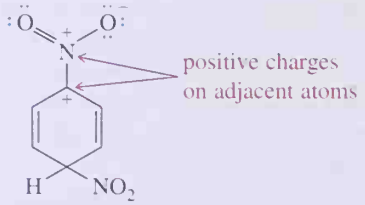


Figure 16.2
Nitration of anisole. Electrophilic attack meta and para to the methoxy group.

Now let us examine the meta directing influence of the nitro group by the same pattern of analysis. Shown in Figure 16.3 are resonance-stabilized cation intermediates formed by attack of the nitronium ion meta to the nitro group and then para to it. Each cation in Figure 16.3 is a hybrid of three contributing structures; no additional important ones can be drawn. Now we need to compare the relative resonance stabilization of each hybrid. If we draw a Lewis structure for the nitro group showing the positive charge on nitrogen, we see at once that contributing structure (e) in Figure 16.3 places positive charges on adjacent atoms. Because of the electrostatic repulsion thus generated, this structure makes only a negligible contribution to the hybrid.



None of the contributing structures for meta attack places positive charges on adjacent atoms. As a consequence, resonance stabilization of the cation for meta attack is greater than that for para (or ortho) attack. Stated alternatively, the energy of activation for meta attack is less than that for para attack.

Comparison of the entries in Table 16.1 shows that almost all of the ortho-para directing groups have an unshared pair of electrons on the atom bonded to the aromatic ring. Thus, the directing effect of most of the ortho-para directing groups given in Table 16.1 is due primarily to the ability of the atom bonded to the ring to further delocalize the positive charge on the aromatic ring in the cation intermediate.

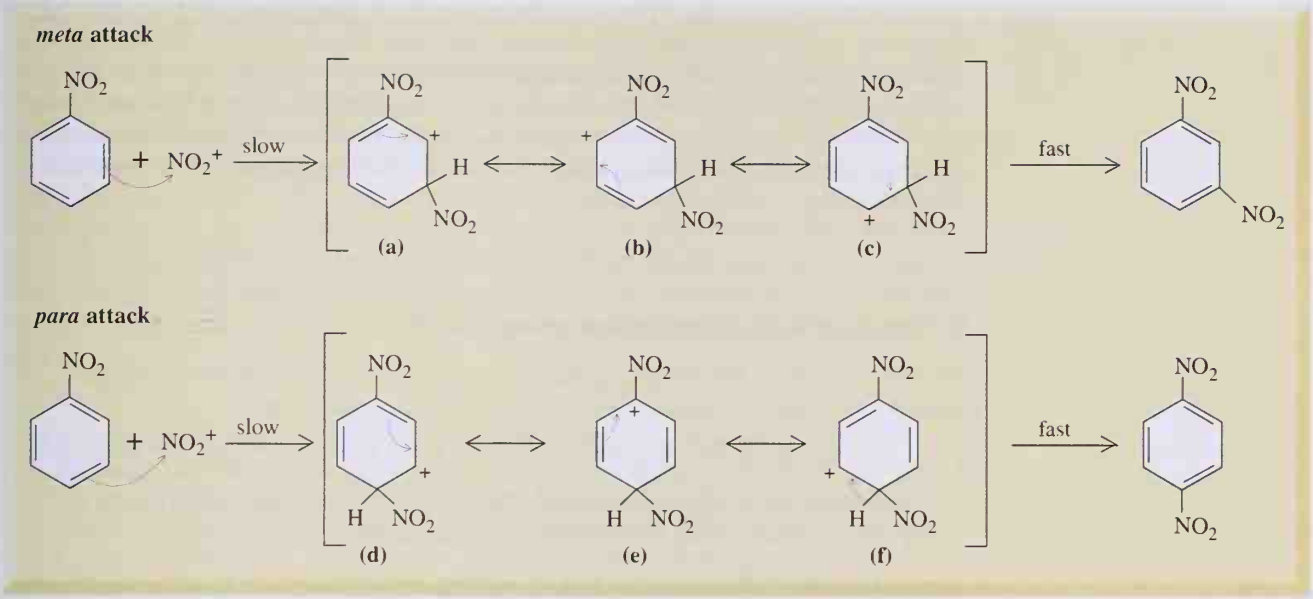
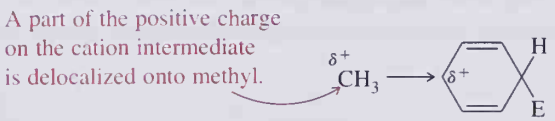


Figure 16.3
Nitration of nitrobenzene. Electrophilic attack meta and para to the nitro group.

To account for the fact that methyl, ethyl, and other alkyl groups are also ortho-para directing, we need to consider their inductive effect. The inductive effect results from differences in electronegativity in bonded atoms and is transmitted primarily through sigma bonds. In the case of methyl, ethyl, or other alkyl groups bonded to an aromatic ring, the carbon of the alkyl group is sp^3-hybridized, whereas those of the aromatic ring are sp^2-hybridized. Because of the greater degree of *s* character, an sp^2-hybridized carbon atom (33% *s* character) has a greater effective electronegativity than an sp^3-hybridized carbon atom (25% *s* character), and consequently an inductive polarization of electrons occurs from the alkyl substituent toward the aromatic ring. We used the electron-releasing inductive effect of alkyl groups in Section 5.3D to account for the relative stabilities of methyl, primary, secondary, and tertiary carbocations, and again in Section 15.5B to account for the decreased acidity of alkylphenols compared with phenol itself. In Section 15.5B we used the electron-withdrawing inductive effect of the halogens to explain the increased acidity of halophenols relative to phenol.

Operation of the electron-releasing inductive effect of alkyl groups in electrophilic aromatic substitution is indicated for a methyl substituent by an arrow on the sigma bond between methyl and the ring, indicating an inductive polarization of electrons toward the ring. The net effect of inductive polarization of electrons from alkyl groups is to delocalize further the positive charge of the cation intermediate and, therefore, to give it greater stabilization (a lower energy of activation for its formation).



As expected from this explanation, the greater the electron-releasing ability of an alkyl group, the greater the overall rate of electrophilic aromatic substitution. In practice, it is found that the rate of electrophilic aromatic substitution of *tert*-butylbenzene is greater than that for isopropylbenzene, which is in turn greater than that for ethylbenzene and toluene. Thus, the inductive effect, the same factor that stabilizes alkyl-substituted carbocations, is also responsible for determining the relative rates of electrophilic aromatic substitution of alkylbenzenes.

C. Theory of Activating-Deactivating Effects

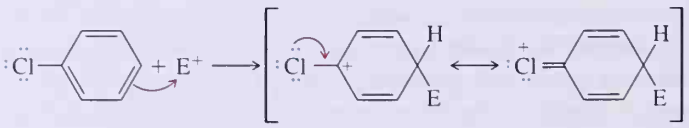
We can account for the activating-deactivating effect of substituent groups by much the same combination of resonance and inductive effects. Briefly stated,

1. Any resonance effect (such as that of $-NH_2$, $-OH$, or $-OR$) that stabilizes the intermediate cation lowers the energy of activation for its formation and has an activating effect toward further electrophilic aromatic substitution.
2. Any resonance effect (such at that of $-NO_2$, $-C{\equiv}N$, $>C{=}O$, or $-SO_3H$) that decreases electron density on the ring deactivates the ring to further substitution.
3. Any inductive effect (such as that of $-CH_3$ or other alkyl group) that releases electron density toward the ring activates the ring toward further substitution.
4. Any inductive effect (such as that of halogen, trialkylammonium ions, $-CCl_3$, or $-CF_3$) that decreases electron density on the ring deactivates the ring to further substitution.

The halogens represent an interesting combination of the resonance and inductive effects, the two operating in opposite directions. Recall from Table 16.1 that halogens are ortho-para directing, but quite unlike other ortho-para directors listed in that table, the halogens are weakly deactivating. These observations can be accounted for in the following way:

The inductive effect of halogens. The halogens are more electronegative than carbon and have an electron-withdrawing inductive effect. Aryl halides therefore react more slowly toward electrophilic aromatic substitution than benzene.

The resonance effect of halogens. When the aromatic ring is attacked by an electrophile to form a cation intermediate, a halogen on the ring can contribute to resonance stabilization of the cation intermediate and thus is ortho-para directing.



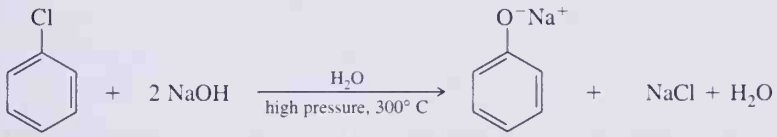
Thus, the inductive and resonance effects of the halogens are counter to each other. The net effect of this opposition is that the halogens are weakly deactivating but ortho-para directing.

16.3 Nucleophilic Aromatic Substitution

One of the important chemical characteristics of aryl halides is that they undergo relatively few reactions involving the carbon-halogen bond. Simple aryl halides, for example, do not undergo nucleophilic substitution by either S_N1 or S_N2 pathways. Two exceptions to this generalization are nucleophilic substitution by way of a benzyne intermediate and nucleophilic substitution of nitro-substituted aryl halides. Nucleophilic aromatic substitutions of these types are far less common than the electrophilic aromatic substitutions we just discussed, and, therefore, they have only limited usefulness in the synthesis of organic compounds. We study these reactions not for their synthetic usefulness but rather for the additional insights they give us into the unique chemical properties of aromatic compounds.

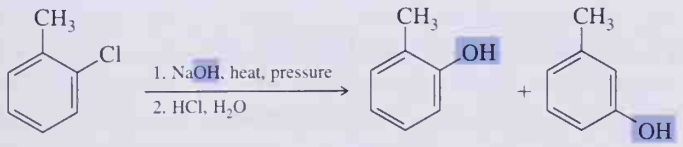
A. Nucleophilic Substitution by Way of a Benzyne Intermediate

An apparent exception to the generalization about the lack of reactivity of aryl halides to nucleophilic substitution is the industrial process developed in 1924 for the synthesis of phenol from chlorobenzene. When heated at 300°C under high pressure with aqueous NaOH, chlorobenzene is converted to sodium phenoxide. Neutralization of this salt with aqueous acid gives phenol.



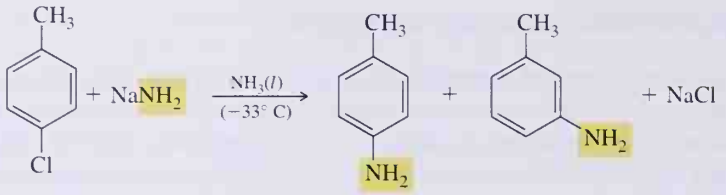
Chlorobenzene Sodium phenoxide

In later technological developments, it was discovered that chlorobenzene could be hydrolyzed to phenol by steam under pressure at 500°C. Each of these reactions appears to involve nucleophilic substitution of —OH for —Cl on the benzene ring. However, this reaction is not as simple as it might seem, as illustrated by the reaction of substituted halobenzenes with NaOH. For example, *o*-chlorotoluene under these conditions gives a mixture of 2-methylphenol (*o*-cresol) and 3-methylphenol (*m*-cresol).



2-Methylphenol (*o*-Cresol) 3-Methylphenol (*m*-Cresol)

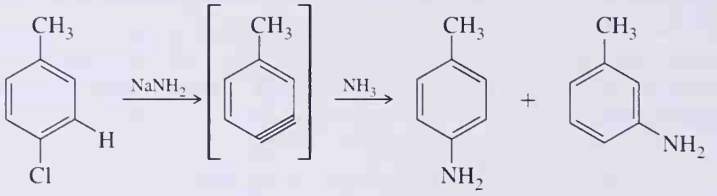
The same type of reaction can be brought about by the use of sodium amide in liquid ammonia. Under these conditions, for example, *p*-chlorotoluene gives a mixture of 4-methylaniline (*p*-toluidine) and 3-methylaniline (*m*-toluidine) in approximately equal amounts.



4-Methylaniline (*p*-Toluidine) 3-Methylaniline (*m*-Toluidine)

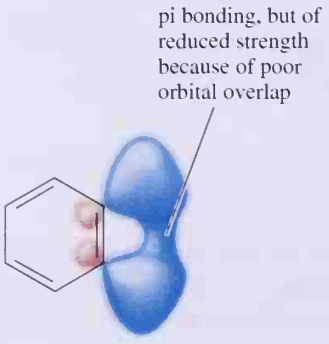
The difference in this reaction compared with other substitution reactions we have dealt with so far is that the entering group appears not only at the position occupied by the leaving group but also at a position adjacent to it.

To account for these experimental observations, it has been proposed that an elimination of HX occurs to form a **benzyne** intermediate, which then undergoes addition to the triple bond to give the products observed.



A benzyne intermediate 4-Methylaniline (*p*-Toluidine) 3-Methylaniline (*m*-Toluidine)

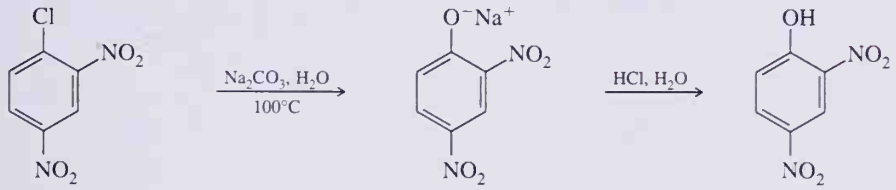
The bonding in a benzyne intermediate and also the reason for its extremely reactive nature can be pictured in the following way. According to valence bond theory, the benzene ring retains its coplanarity, pi-bonding, and aromatic character. The adjacent sp^2 orbitals formerly bonding to halogen and a hydrogen atom now contain one electron each and overlap to form the second pi bond of the benzyne triple bond. The problem is that the atomic orbitals forming this pi bond are not parallel as is the case in acetylene and unstrained alkynes, but rather they lie at angles of 120° to the bond axis connecting them. Consequently, the overlap between these orbitals is reduced. Reduced overlap in turn means a weaker and more reactive pi bond. Therefore, the second pi bond of the benzyne intermediate undergoes addition very readily to reform two new and stronger sigma bonds.



A benzyne intermediate

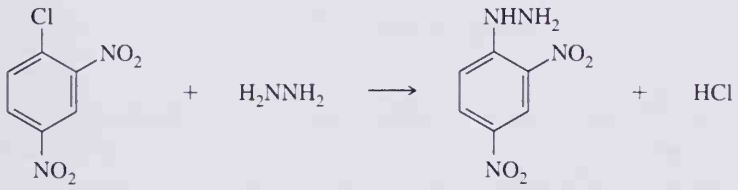
B. Nucleophilic Substitution by Addition-Elimination

Aromatic halides are normally quite inert to the types of nucleophiles that readily displace halide ions from alkyl halides. However, when an aromatic ring contains strong electron-withdrawing nitro groups ortho or para to the halogen (or both), **nucleophilic aromatic substitution** occurs quite readily. For example, when 2,4-dinitrochlorobenzene is heated at reflux in aqueous sodium carbonate followed by treatment with aqueous acid, it is converted in nearly quantitative yield to 2,4-dinitrophenol.



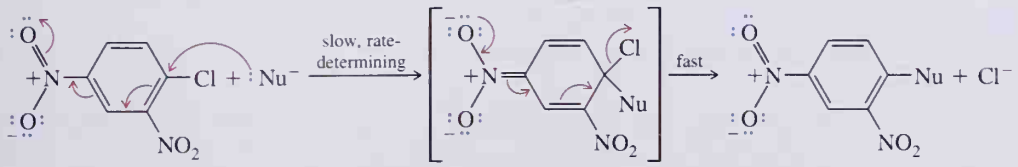
2,4-Dinitrochlorobenzene Sodium 2,4-dinitrophenoxide 2,4-Dinitrophenol

One application of this reaction is the synthesis of 2,4-dinitrophenylhydrazine, a common reagent used to prepare derivatives of aldehydes and ketones (Section 17.11B).



2,4-Dinitrochlorobenzene Hydrazine 2,4-Dinitrophenylhydrazine

This type of nucleophilic aromatic substitution for halogen has been studied extensively, and it has been determined that reaction occurs in two steps: nucleophilic addition followed by elimination. In Step 1, the nucleophile adds to the aromatic ring at the carbon bearing the halogen. This addition places a negative charge on the ring, which is stabilized by resonance interaction with the nitro or other strong electron-withdrawing groups in the ortho or para positions (or both ortho and para) to the halogen. In certain cases, addition compounds have been isolated and are named **Meisenheimer complexes** after the German chemist who first isolated them. In Step 2, halide ion is eliminated to regenerate the aromatic ring. For the majority of reactions of this type, addition of the nucleophile in Step 1 is the slow, rate-determining step.

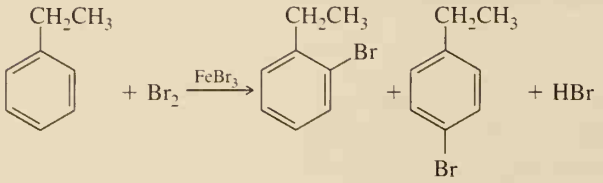


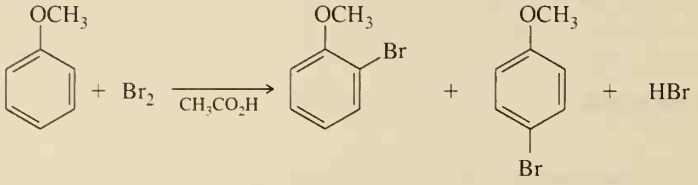
Meisenheimer complex

SUMMARY OF KEY REACTIONS

1. Halogenation (Section 16.1A)

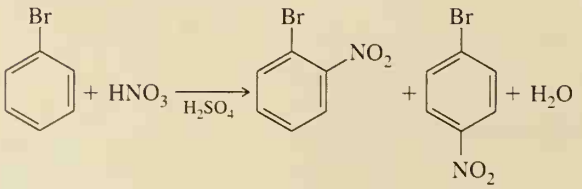
The electrophile is a halonium ion formed as an ion pair by treatment of chlorine or bromine with a Lewis acid. Halogenation of an aromatic ring substituted by strongly activating groups (such as —OH, —OR, and —NH_2) does not require a Lewis acid catalyst.





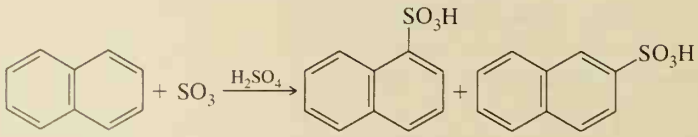
2. Nitration (Section 16.1B)

The attacking electrophile is a nitronium ion, NO_2^+, formed by treatment of nitric acid with sulfuric acid.



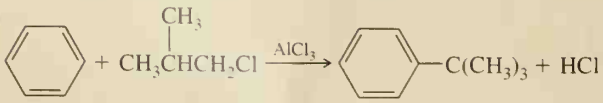
3. Sulfonation (Section 16.1B)

The electrophile in sulfonation is sulfur trioxide, SO_3.



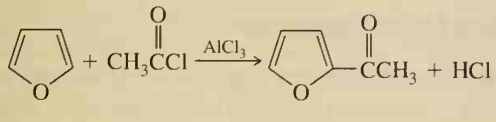
4. Friedel-Crafts Alkylation (Section 16.1C)

The attacking electrophile is a carbocation formed as an ion pair by treatment of an alkyl halide with a Lewis acid. Rearrangements from a less stable carbocation to a more stable carbocation are common.



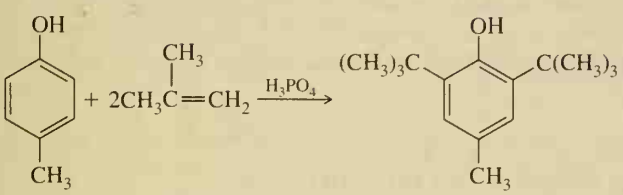
5. Friedel-Crafts Acylation (Section 16.1C)

The attacking electrophile is an acyl cation formed as an ion pair by treatment of an acyl halide with a Lewis acid.



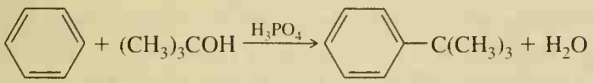
6. Alkylation Using an Alkene (Section 16.1D)

The attacking electrophile is a carbocation formed by treatment of the alkene with a proton acid or with a Lewis aid.



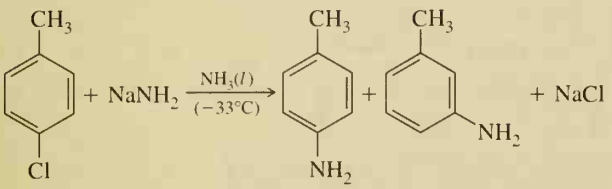
7. Alkylation Using an Alcohol (Section 16.1D)

The attacking electrophile is a carbocation formed by treatment of the alcohol with a proton acid or with a Lewis acid.



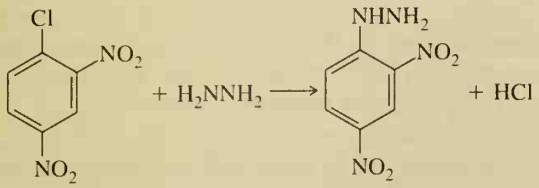
8. Nucleophilic Aromatic Substitution: A Benzyne Intermediate (Section 16.3A)

Elimination of the elements of HX from an aryl halide by strong base forms a benzyne intermediate, which undergoes nonregioselective nucleophilic addition to give the substitution product(s).



9. Nucleophilic Aromatic Substitution: Addition-Elimination (Section 16.3B)

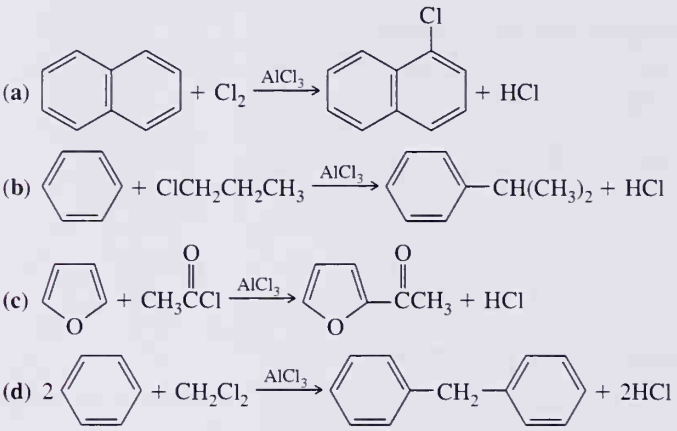
Addition of the nucleophile to the carbon bearing the leaving group forms a tetrahedral intermediate from which halide ion is lost to regenerate the aromatic ring. This type of aromatic substitution is facilitated by strong electron-withdrawing nitro groups located ortho and para to the halogen.



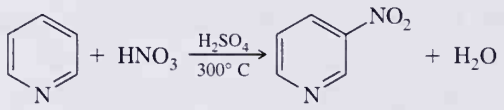
ADDITIONAL PROBLEMS

Electrophilic Aromatic Substitution: Monosubstitution

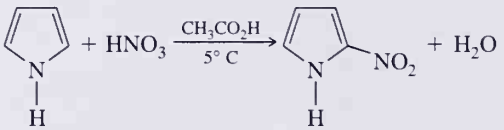
16.4 Write a stepwise mechanism for each of the following reactions. Used curved arrows to show the flow of electrons in each step.



16.5 Pyridine undergoes electrophilic aromatic substitution preferentially at the 3 position as illustrated by the synthesis of 3-nitropyridine. Pyrrole undergoes electrophilic aromatic substitution preferentially at the 2 position as illustrated by the synthesis of 2-nitropyrrole.



Pyridine 3-Nitropyridine



Pyrrole 2-Nitropyrrole

(a) Write resonance contributing structures for the intermediate formed by attack of NO_2^+ at the 2, 3, and 4 positions of pyridine. From examination of these intermediates, offer an explanation for preferential nitration at the 3 position.

(b) Write resonance contributing structures for the intermediate formed by attack of NO_2^+ at the 2 and 3 positions of pyrrole. From examination of these intermediates, offer an explanation for preferential nitration at the 2 position.

16.6 Addition of *m*-xylene to the strongly acidic solvent HF/SbF_5 at $-45°$ gives a new compound, which shows ^{1}H-NMR resonances at δ 2.88 (3H), 3.00 (3H), 4.67 (2H), 7.93 (1H), 7.83 (1H), and 8.68 (1H). Assign a structure to the compound giving this spectrum.

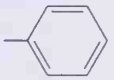
16.7 Addition of *tert*-butylbenzene to the strongly acidic solvent HF/SbF_5 followed by aqueous work-up gives benzene. Propose a mechanism for this dealkylation reaction.

16.8 What product do you predict from the reaction of SCl_2 with benzene in the presence of $AlCl_3$? What product results if diphenyl ether is treated with SCl_2 and $AlCl_3$?

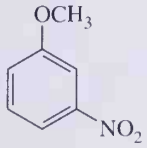
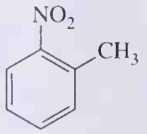
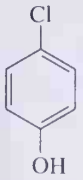
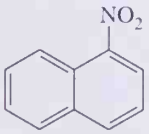
16.9 Other groups besides H^+ can act as leaving groups in electrophilic aromatic substitution. One of the best leaving groups is the trimethylsilyl group (Me_3Si—). For example, treatment of $Me_3SiC_6H_5$ with CF_3CO_2D rapidly forms DC_6H_5. What are the properties of a silicon-carbon bond that allows you to predict this kind of reactivity?

Disubstitution and Polysubstitution

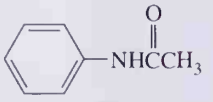
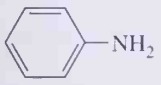
16.10 The following groups are ortho-para directors. Draw a contributing structure for the resonance-stabilized aryl cation formed during electrophilic aromatic substitution that shows the role of each group in stabilizing the intermediate by further delocalizing its positive charge.

(a) —OH **(b)** —OCCH$_3$ **(c)** —N(CH$_3$)$_2$ **(d)** —NHCCH$_3$ **(e)** 

16.11 Predict the major product from treatment of each compound with HNO_3, H_2SO_4.

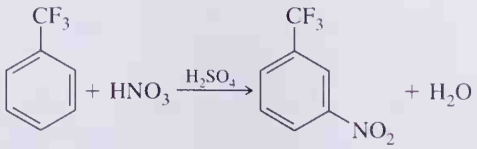
(a)  **(b)**  **(c)**  **(d)** 

16.12 How do you account for the fact that *N*-phenylacetamide (acetanilide) is less reactive toward electrophilic aromatic substitution than aniline?

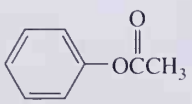
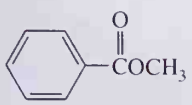
N-Phenylacetamide (Acetanilide) Aniline

16.13 The trifluoromethyl group is almost exclusively meta directing as shown in the following example:

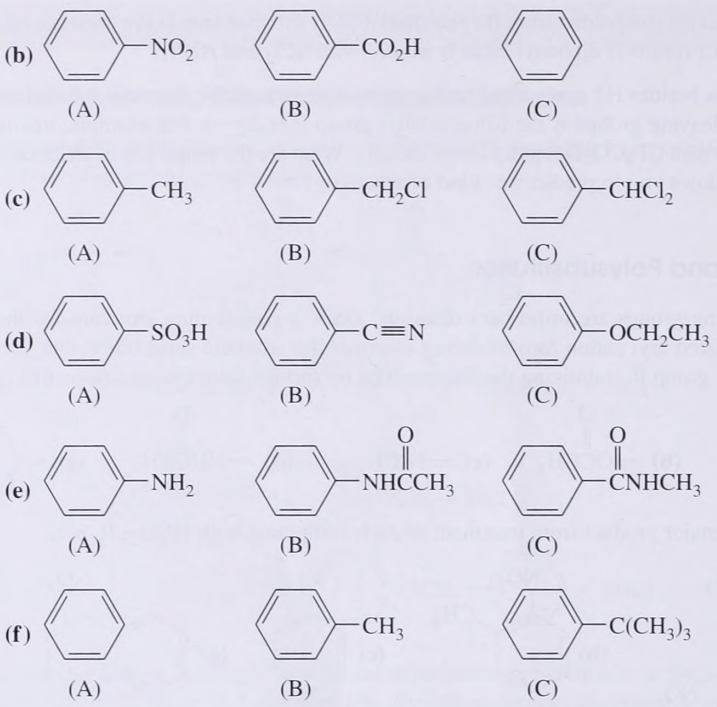


Draw contributing structures for the aryl cation intermediate formed during nitration. First assume para attack and then meta attack. By reference to contributing structures you have drawn, account for the fact that nitration is essentially 100% in the meta position.

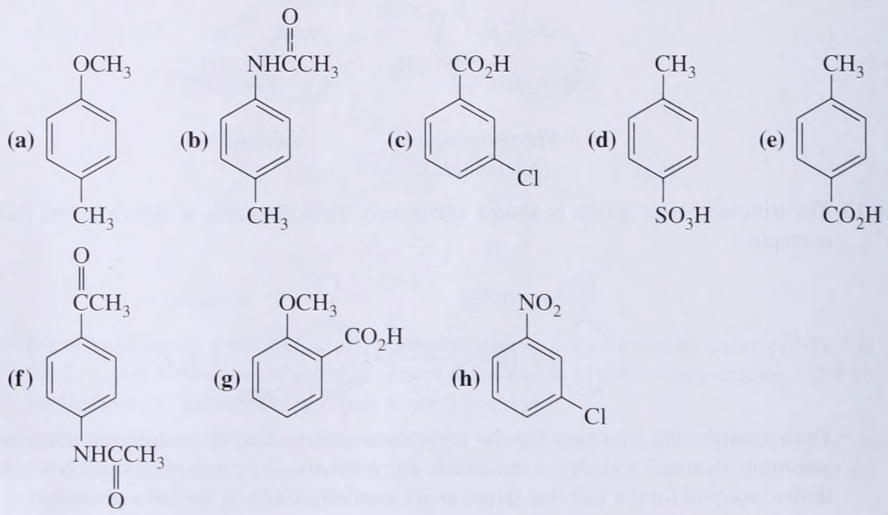
16.14 Arrange the following in order of decreasing reactivity (fastest to slowest) toward electrophilic aromatic substitution:

(a)   

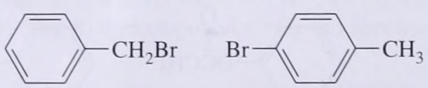
(A) (B) (C)



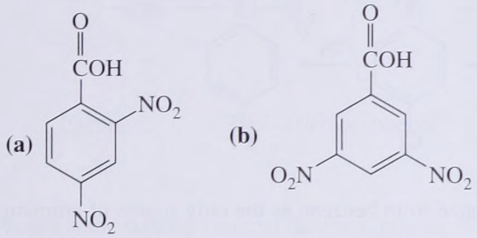
16.15 For each compound, indicate which group on the ring is the more strongly activating and then draw the structural formula of the major product formed by nitration of that ring.



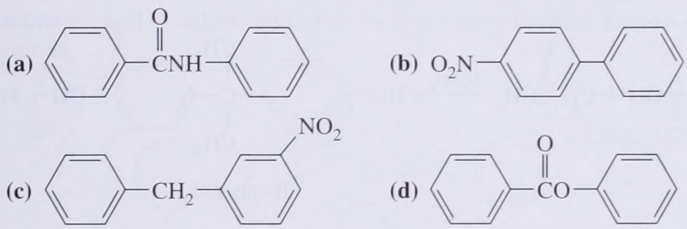
16.16 Show how to convert toluene to each of the following:



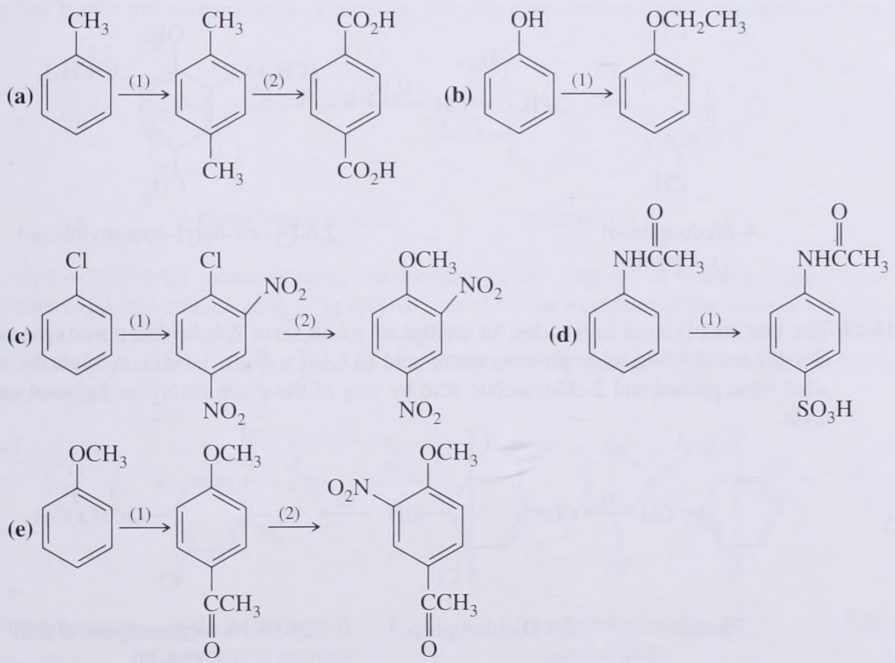
16.17 Show how to convert toluene to the following carboxylic acids.

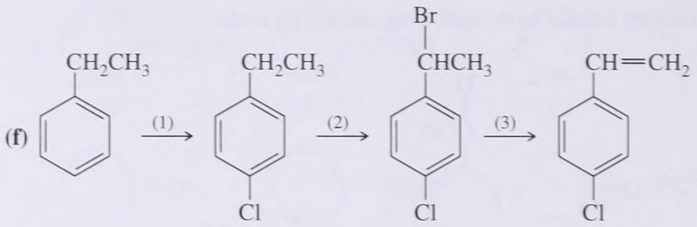


16.18 The following molecules each contain two rings. Which of the two rings undergoes electrophilic aromatic substitution more readily? Draw the major product formed on nitration.



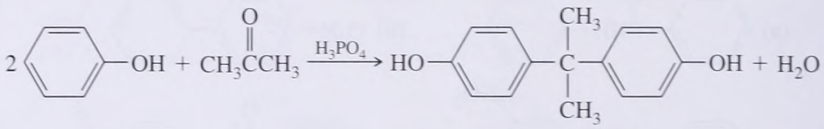
16.19 Show reagents and conditions to bring about the following conversions. Each reaction arrow indicates one step; the numbers over the arrows are to number successive steps.





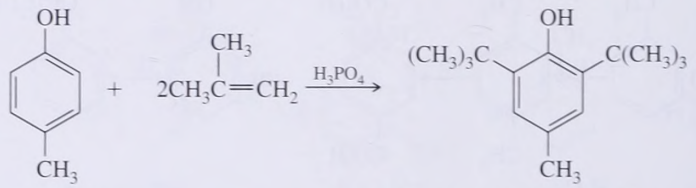
16.20 Propose a synthesis of triphenylmethane from benzene as the only source of aromatic rings, and any other necessary reagents.

16.21 Reaction of phenol with acetone in the presence of an acid catalyst gives a compound known as bisphenol A. Bisphenol A is used in the production of epoxy resins and polycarbonate resins. Propose a mechanism for the formation of bisphenol A.



Bisphenol A

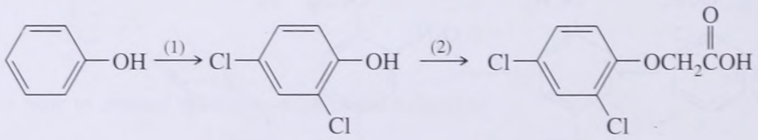
16.22 2,6-Di-*tert*-butyl-4-methylphenol, alternatively known as butylated hydroxytoluene (BHT), is used as an antioxidant in foods to "retard spoilage." BHT is synthesized industrially from 4-methylphenol (*p*-cresol) by reaction with 2-methylpropene in the presence of phosphoric acid. Propose a mechanism for this reaction.



4-Methylphenol (*p*-Cresol)

2,6-Di-*tert*-butyl-4-methylphenol

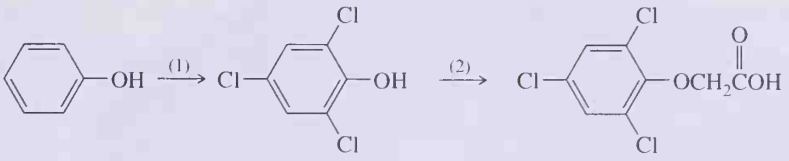
16.23 The first widely used herbicides for control of weeds were 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,6-trichlorophenoxyacetic acid (2,4,6-T). Show how each might be synthesized from phenol and 2-chloroacetic acid by way of the given chlorinated phenol intermediate.



Phenol

2,4-Dichlorophenol

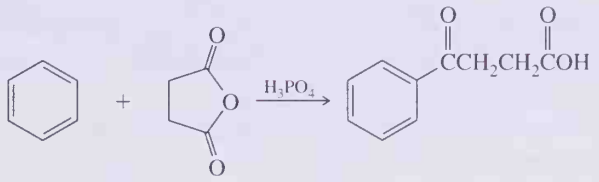
2,4-Dichlorophenoxyacetic acid (2,4-D)



Phenol 2,4,6-Trichlorophenol 2,4,6-Trichlorophenoxyacetic acid (2,4,6-T)

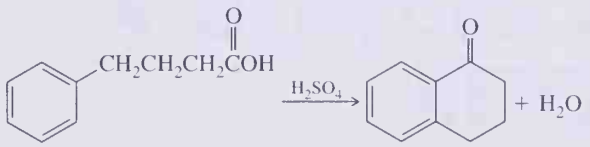
16.24 Phenol is the starting material for the synthesis of 2,3,4,5,6-pentachlorophenol, known alternatively as pentachlorophenol or more simply as "penta." At one time, penta was widely used as a wood preservative for decks, siding, and outdoor wood furniture. Draw the structural formula for pentachlorophenol and describe its synthesis from phenol.

16.25 Treatment of benzene with succinic anhydride in the presence of an acid catalyst, most often phosphoric acid or sulfuric acid, gives the following γ-ketoacid. Propose a mechanism for this reaction.



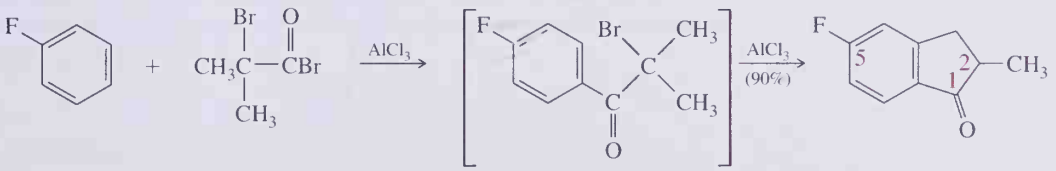
Succinic anhydride 4-Oxo-4-phenylbutanoic acid

16.26 Reaction of 4-phenylbutanoic acid in the presence of concentrated sulfuric acid gives a compound known most commonly as α-tetralone. Propose a mechanism for this cyclodehydration.



4-Phenylbutanoic acid α-Tetralone

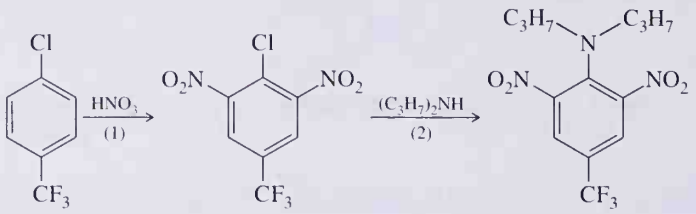
16.27 5-Fluoro-2-methyl-1-indanone is an intermediate in the synthesis of sulindac (Clinoril), a nonsteroidal anti-inflammatory drug (NSAID) used for the treatment of rheumatoid arthritis, osteoarthritis, and gout. It is formed by treatment of fluorobenzene with 2-bromo-2-methylpropanoyl bromide in the presence of aluminum chloride. Propose a mechanism for this transformation.



Fluorobenzene 2-Bromo-2-methylpropanoyl bromide (an intermediate; not isolated) 5-Fluoro-2-methyl-1-indanone

Nucleophilic Aromatic Substitution

16.28 Following are the final steps in the synthesis of trifluralin, a pre-emergent herbicide.



Trifluralin B

(a) Account for the orientation of nitration in Step (1).

(b) Propose a mechanism for the substitution reaction in Step (2).

Syntheses

16.29 Starting with benzene, toluene, or phenol as the only sources of aromatic rings, show how to synthesize the following. Assume in all syntheses that ortho-para mixtures can be separated into the desired isomer.

(a) *m*-Nitrobromobenzene

(b) *p*-Nitrobromobenzene

(c) 2,4,6-Trinitrotoluene (TNT)

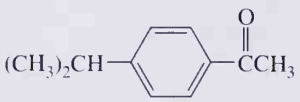
(d) *m*-Chlorobenzoic acid

(e) *p*-Chlorobenzoic acid

(f) *p*-Dichlorobenzene

(g) *m*-Nitrobenzenesulfonic acid

16.30 Following is the structure of the orris odor ketone. Describe its synthesis from benzene.



4-Isopropylacetophenone

16.31 Following is the structural formula of musk ambrette, a synthetic musk, essential in perfumes to enhance and retain odor. Describe its synthesis from *m*-cresol (3-methylphenol).

Cinnamon sticks and almonds. (Charles D. Winters)

17

ALDEHYDES AND KETONES

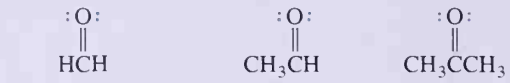
In this and several following chapters, we study the physical and chemical properties of compounds containing the **carbonyl group, C=O.** Because the carbonyl group is the central structural feature of aldehydes, ketones, carboxylic acids, and their functional derivatives, it is one of the most important functional groups in organic chemistry. The chemical properties of this functional group are straightforward, and an understanding of its few characteristic reaction themes leads very quickly to an understanding of a wide variety of reactions.

17.1 Structure

A. Characteristic Structural Features

The characteristic structural feature of an **aldehyde** is a carbonyl group bonded to a hydrogen atom and a carbon atom (Section 1.4B). In methanal, the simplest aldehyde, the carbonyl group is bonded to two hydrogen atoms. In other aldehydes, it is bonded to one

hydrogen atom and one carbon atom. Following are Lewis structures for methanal and ethanal. Under each in parentheses is its common name. The characteristic structural feature of a **ketone** is a carbonyl group bonded to two carbon atoms (Section 1.4B). Following is a Lewis structure for propanone, the simplest ketone.



Methanal (Formaldehyde) | Ethanal (Acetaldehyde) | Propanone (Acetone)

B. Covalent Bonding

Covalent bonding in the carbonyl group can be described in terms of the valence bond model and also in terms of the molecular orbital model.

Valence Bond Model

The carbon-oxygen double bond consists of one sigma bond formed by overlap of sp^2 hybrid orbitals of carbon and oxygen and one pi bond formed by the overlap of parallel $2p$ orbitals. The two nonbonding pairs of electrons on oxygen lie in its remaining sp^2 hybrid orbitals (see Figure 1.20).

Molecular Orbital Model

According to the molecular orbital model, combination of two atomic orbitals from carbon and four atomic orbitals from oxygen gives six molecular orbitals: a set of sigma bonding and sigma antibonding MOs, a set of pi bonding and pi antibonding MOs, and a set of two

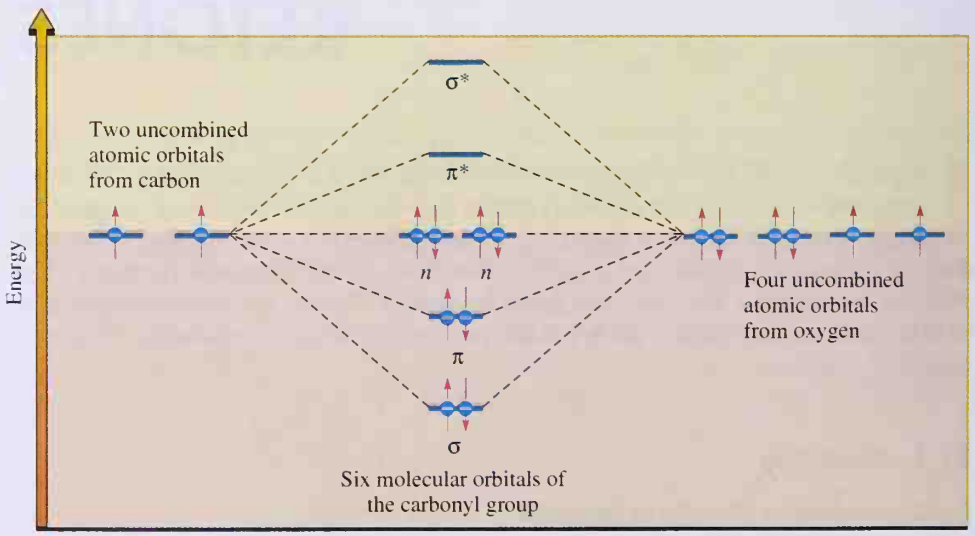


Figure 17.1
Molecular orbital description of covalent bonding in a carbonyl group.

nonbonding MOs. The sigma bonding and antibonding MOs are formed by combination of $2p$ atomic orbitals lying along a common axis; the pi bonding and antibonding MOs are formed by combination of parallel $2p$ atomic orbitals. The relative energies of the uncombined atomic orbitals and these three sets of MOs are shown in Figure 17.1. In the ground state, the eight electrons of the uncombined atomic orbitals fill the sigma and pi bonding MOs and the two nonbonding MOs.

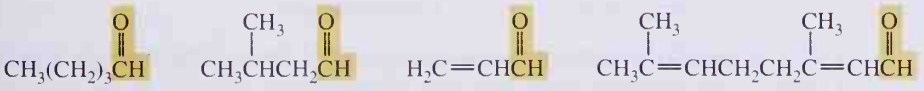
The highest occupied MOs are the two nonbonding MOs, and the lowest unoccupied MO is the pi antibonding MO. When the carbonyl group enters into a chemical reaction as an electron-pair donor (a Lewis base), it donates a pair of electrons from a nonbonding MO on oxygen. When a carbonyl group enters into a chemical reaction as an electron-pair acceptor (a Lewis acid), the pi antibonding MO is the electron-pair acceptor. As we see in Section 17.4, the lowest energy electronic transition for a carbonyl group is an n to π^* transition.

17.2 Nomenclature

A. IUPAC Nomenclature

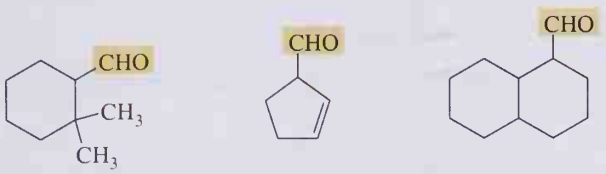
The IUPAC system of nomenclature for aldehydes and ketones follows the familiar pattern of selecting as the parent alkane the longest chain of carbon atoms that contains the functional group. The aldehyde group is shown by changing the suffix -e of the parent alkane to -al (Section 2.5). Because the carbonyl group of an aldehyde can only appear at the end of a parent chain and because numbering must start with it as carbon 1, its position is unambiguous, and, therefore, there is no need to use a number to locate it.

For **unsaturated aldehydes,** the presence of a carbon-carbon double or triple bond is indicated by the infix -en- or -yn- as shown in the following examples. As with other molecules with both an infix and a suffix, the location of the suffix determines the numbering pattern.



Pentanal | 3-Methylbutanal | 2-Propenal | 3,7-Dimethyl-2,6-octadienal

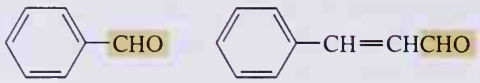
For cyclic molecules in which —CHO is attached directly to the ring, the molecule is named by adding the suffix **-carbaldehyde** to the name of the ring. The atom of the ring to which the aldehyde group is attached is numbered 1 unless the ring (as for example a bicyclic ring) has some other fixed numbering pattern, in which case the —CHO group is given a number as low as possible.



2,2-Dimethylcyclohexanecarbaldehyde | 2-Cyclopentenecarbaldehyde | Bicyclo[4.4.0]decane-2-carbaldehyde

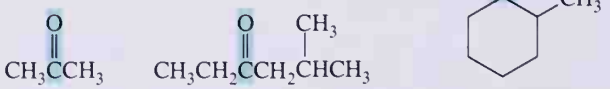
Among the aldehydes for which the IUPAC system retains common names are benzaldehyde and cinnamaldehyde.

Benzaldehyde is found in the kernels of bitter almonds. Cinnamaldehyde is found in Ceylon and Chinese cinnamon oils. *(Charles D. Winters)*

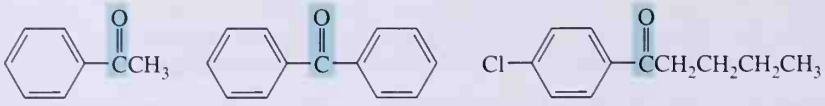


Benzaldehyde Cinnamaldehyde

In the IUPAC system, ketones are named by selecting as the parent alkane the longest chain that contains the carbonyl group and then indicating the presence of the carbonyl group by changing the suffix from -e to -one (Section 2.5). The parent chain is numbered from the direction that gives the carbonyl carbon the lowest number. The IUPAC system retains the common names acetone, acetophenone, and benzophenone.



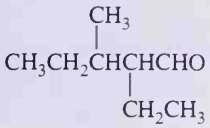
Propanone (Acetone) 5-Methyl-3-hexanone 2-Methylcyclohexanone

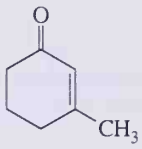


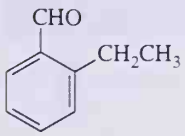
Acetophenone Benzophenone 1-(4-Chlorophenyl)-1-pentanone

EXAMPLE 17.1

Give IUPAC names for the following compounds:

(a) 

(b) 

(c) 

Solution

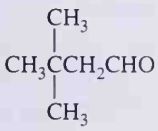
(a) The longest chain is six carbons, but the longest chain that contains the aldehyde group is five carbons. Therefore the parent chain is pentane. The name is 2-ethyl-3-methylpentanal.

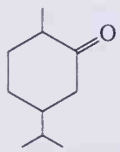
(b) Number the six-member ring beginning with the carbonyl carbon. The IUPAC name is 3-methyl-2-cyclohexenone.

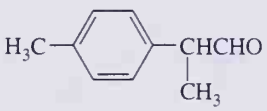
(c) This molecule is derived from benzaldehyde. Its IUPAC name is 2-ethylbenzaldehyde.

PROBLEM 17.1

Give IUPAC names for the following compounds:

(a) 

(b) 

(c) 

B. IUPAC Names for More Complex Aldehydes and Ketones

In naming compounds that contain more than one functional group that might be indicated by a suffix, the IUPAC system has established an **order of precedence of functions.** The order of precedence for the functional groups we have studied so far is given in Table 17.1.

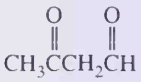
17.1 Decreasing order of precedence of several functional groups

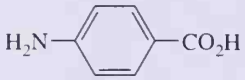
Functional Group	Suffix if Higher Precedence	Prefix if Lower Precedence
$-CO_2H$	-oic acid	—
$-CHO$	-al	oxo-
$>C=O$	-one	oxo-
$-OH$	-ol	hydroxy-
$-NH_2$	-amine	amino-
$-SH$	-thiol	mercapto-

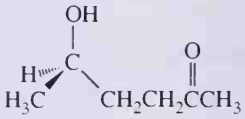
The table details how to indicate a given functional group if it has the highest precedence and how to show its presence if it has a lower precedence.

EXAMPLE 17.2

Give IUPAC names for the following compounds, each of which contains two functional groups:

(a) 

(b) 

(c) 

Solution

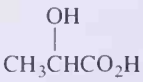
(a) An aldehyde is of higher precedence than a ketone. The presence of the ketone is indicated by the prefix oxo-. The IUPAC name of this compound is 3-oxobutanal.

(b) The carboxyl group is of higher precedence. The presence of the amine group is indicated by the prefix amino-. The IUPAC name of this compound is 4-aminobenzoic acid. Alternatively, it may be named *p*-aminobenzoic acid, abbreviated PABA. PABA, a growth factor of microorganisms, is required for the synthesis of folic acid and its derivatives.

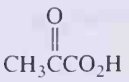
(c) The presence of the —OH group is indicated by the prefix hydroxy-. The IUPAC name of this compound is (R)-5-hydroxy-2-hexanone.

PROBLEM 17.2

Give IUPAC names for the following compounds, each of which is important in intermediary metabolism. Below each compound is given the name by which it is more commonly known in the biological sciences.

(a) 

Lactic acid (product of anaerobic glycolysis)

(b) 

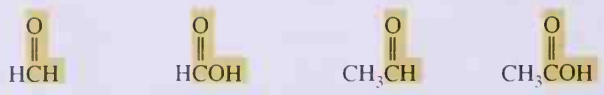
Pyruvic acid (product of anaerobic glycolysis)

(c) $H_2NCH_2CH_2CH_2CO_2H$

γ-Aminobutyric acid (a neurotransmitter in the central nervous system)

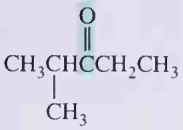
C. Common Names

The common name for an aldehyde is derived from the common name of the corresponding carboxylic acid by changing the suffix -ic or -oic to -aldehyde. Because we have not yet studied common names for carboxylic acids, we are not in a position to discuss common names for aldehydes. However, we can illustrate how they are derived by reference to a few common names with which you are familiar. The name formaldehyde is derived from formic acid; the name acetaldehyde is derived from acetic acid.

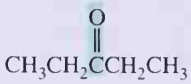


Formaldehyde Formic acid Acetaldehyde Acetic acid

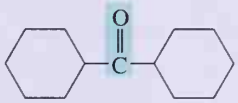
Common names for ketones are derived by naming the two alkyl or aryl groups attached to the carbonyl group, followed by the word "ketone" as shown in the following examples. Note that each alkyl or aryl group is listed as a separate word followed by the word "ketone."



Ethyl isopropyl ketone



Diethyl ketone



Dicyclohexyl ketone

17.3 Physical Properties

Oxygen is more electronegative than carbon (3.5 compared with 2.5); therefore, a carbon-oxygen double bond is polar, with oxygen bearing a partial negative charge and carbon bearing a partial positive charge.

Polarity of a carbonyl group

Because of the polarity of the carbonyl group, aldehydes and ketones are polar compounds and interact in the pure state by dipole-dipole interactions; they have higher boiling points than nonpolar compounds of comparable molecular weight. Table 17.2 lists boiling points of six compounds of comparable molecular weight.

Diethyl ether has the lowest boiling point. Diethyl ether is a polar molecule, but because of steric hindrance, only a weak dipole-dipole interaction exists between its molecules (Section 11.3). The boiling point of pentane, a nonpolar hydrocarbon, is only slightly

Table 17.2 Boiling points of six compounds of comparable molecular weight

Name	Structural Formula	Molecular Weight	bp (°C)
pentane	$CH_3CH_2CH_2CH_2CH_3$	72	36
diethyl ether	$CH_3CH_2OCH_2CH_3$	74	34
butanal	$CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}H$	72	76
2-butanone	$CH_3CH_2\overset{\overset{O}{\|}}{C}CH_3$	72	80
1-butanol	$CH_3CH_2CH_2CH_2OH$	74	117
propanoic acid	$CH_3CH_2\overset{\overset{O}{\|}}{C}OH$	72	141

Table 17.3 Physical properties of selected aldehydes and ketones

IUPAC Name	Common Name	Structural Formula	bp (°C)	Solubility (g/100 g water)
methanal	formaldehyde	HCHO	−21	infinite
ethanal	acetaldehyde	CH_3CHO	20	infinite
propanal	propionaldehyde	CH_3CH_2CHO	49	16
butanal	butyraldehyde	$CH_3CH_2CH_2CHO$	76	7
hexanal	caproaldehyde	$CH_3(CH_2)_4CHO$	129	slightly
propanone	acetone	CH_3COCH_3	56	infinite
2-butanone	ethyl methyl ketone	$CH_3COCH_2CH_3$	80	26
3-pentanone	diethyl ketone	$CH_3CH_2COCH_2CH_3$	101	5

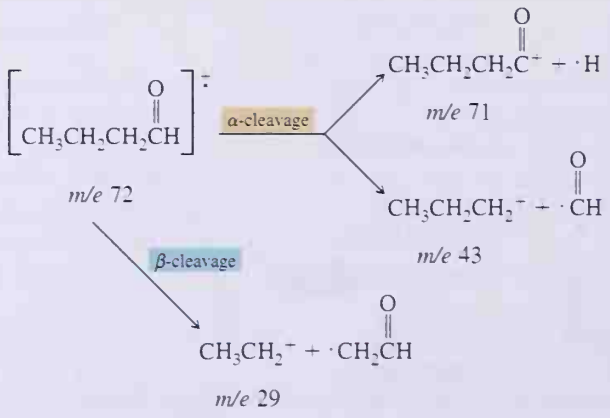
higher than that of diethyl ether. Both butanal and 2-butanone are polar compounds and, because of the intermolecular association between carbonyl groups, their boiling points are higher than those of pentane and diethyl ether. Aldehydes and ketones have no partially positive hydrogen atom attached to oxygen and cannot associate by hydrogen bonding. Therefore, the boiling points of aldehydes and ketones are lower than those of alcohols (Section 9.3A) and carboxylic acids (Section 19.3)—compounds that can associate by hydrogen bonding.

The carbonyl groups of aldehydes and ketones interact with water molecules as hydrogen bond acceptors, and, therefore, low-molecular-weight aldehydes and ketones are more soluble in water than are nonpolar compounds of comparable molecular weight. Listed in Table 17.3 are boiling points and solubilities in water for several low-molecular-weight aldehydes and ketones.

17.4 Spectroscopic Properties

A. Mass Spectrometry

Two characteristic fragmentation patterns of aliphatic aldehydes are cleavage of one of the bonds to the carbonyl group (α-cleavage) and cleavage of a C—C bond adjacent to the carbonyl group (β-cleavage). Each of these patterns can be seen in the mass spectrum of butanal (Figure 17.2).



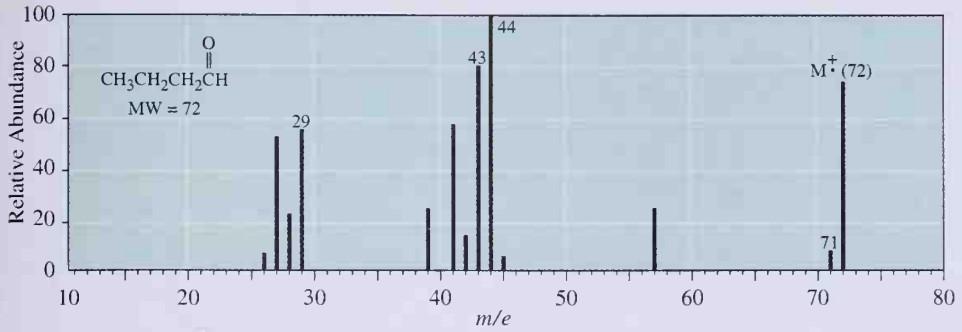
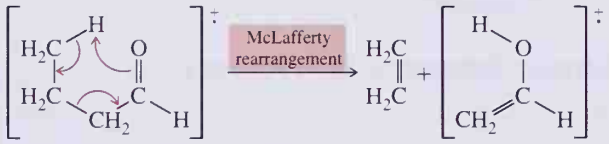


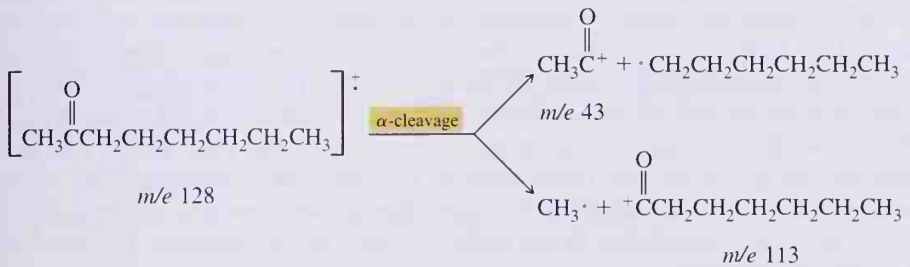
Figure 17.2
Mass spectrum of butanal. Characteristic fragmentation patterns for aliphatic aldehydes are α-cleavage, β-cleavage, and McLafferty rearrangement.

Aliphatic aldehydes with at least one γ-hydrogen also undergo fragmentation by McLafferty rearrangement.



m/e 44

The characteristic fragmentation patterns for aliphatic ketones, namely α-cleavage and McLafferty rearrangement, can be seen in the mass spectrum of 2-octanone (Figure 17.3).



m/e 128

m/e 43

m/e 113

m/e 58

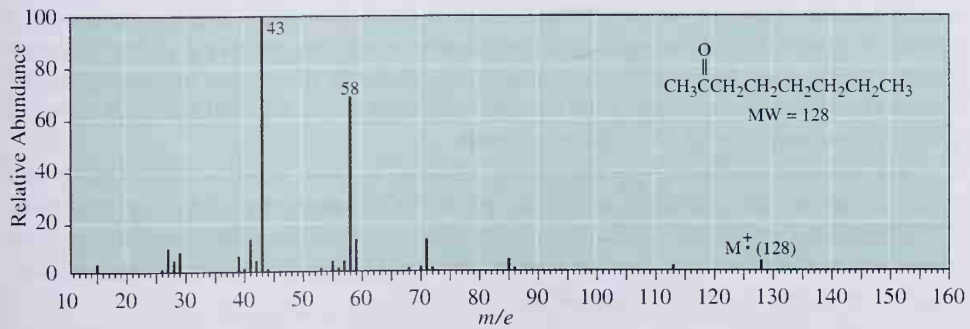


Figure 17.3
Mass spectrum of 2-octanone. Characteristic fragmentation patterns for aliphatic ketones are α-cleavage and McLafferty rearrangement.

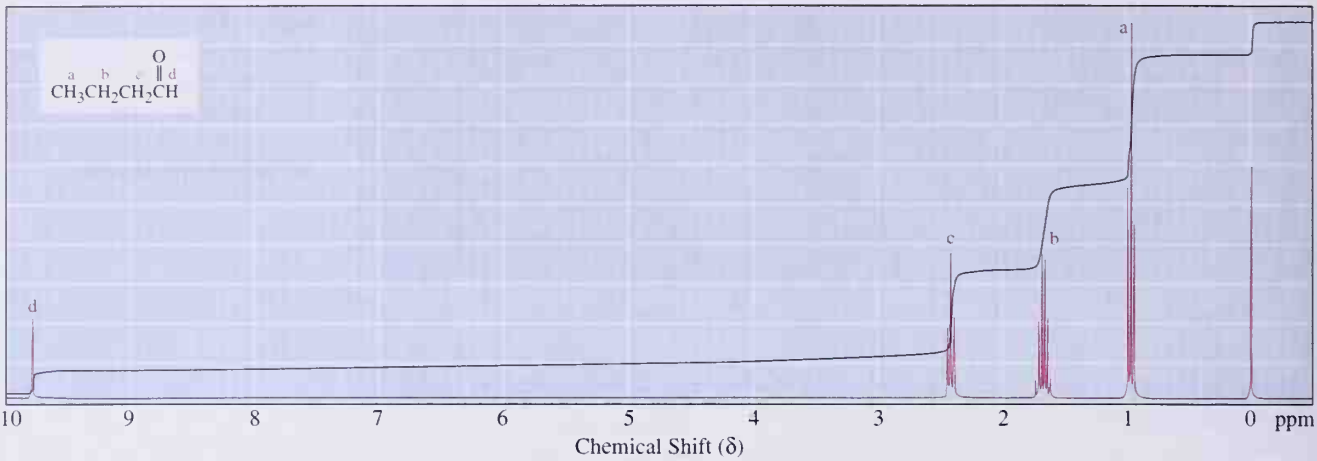


Figure 17.4
^{1}H-NMR spectrum of butanal.

B. Nuclear Magnetic Resonance Spectroscopy

^{1}H-NMR spectroscopy is an important means for identifying aldehydes and for distinguishing between aldehydes and other carbonyl-containing compounds. Just as a carbon-carbon double bond causes a downfield shift in the signal of a vinylic hydrogen (Figure 13.11), a carbon-oxygen double bond also causes a downfield shift in the signal of an aldehyde hydrogen, typically to between δ 9.4 and δ 9.8. The spectrum of butanal, for example, shows a singlet at δ 9.78 for the aldehyde hydrogen (Figure 17.4). Coupling constants between this hydrogen and those on the adjacent α-carbon are small (approximately 1 to 3 Hz) and, consequently, the aldehyde hydrogen signal often appears as a singlet rather than a doublet or triplet as the case may be. Hydrogens on an α-carbon to an aldehyde or ketone typically appear around δ 2.2 to 2.5. Those in butanal appear at δ 2.42, split into a triplet by the two hydrogens of the adjacent methylene group. Just as the aldehyde hydrogen is not split by the adjacent nonequivalent α-hydrogens, the α-hydrogens are not split by the aldehyde hydrogen. The carbonyl carbons of aldehydes and ketones are readily identifiable by the position of their signal between δ 190 and 210 in ^{13}C-NMR spectroscopy.

C. Infrared Spectroscopy

Aldehydes and ketones show characteristic strong infrared absorption between 1680 and 1750 cm^{-1} associated with the stretching vibration of the carbon-oxygen double bond. The stretching vibration for the carbonyl group of menthone occurs at 1711 cm^{-1} (Figure 17.5).

Because few other bond vibrations absorb energy between 1680 and 1750 cm^{-1}, absorption in this region of the spectrum is a reliable means for confirming the presence of a carbonyl group. Because several different functional groups contain a carbonyl group, however, it is often not possible to tell from absorption in this region alone whether the carbonyl-containing compound is an aldehyde, a ketone or, as we shall see in Chapters 19 and 20, a carboxylic acid, an ester, or an amide.

The position of the C=O stretching vibration is quite sensitive to the molecular environment of the carbonyl group, in particular to ring size and to conjugation. Cyclohexanone and larger cyclic ketones in which little or no ring strain occurs show absorption at 1715 cm^{-1}. As ring strain increases, C=O absorption shifts to a higher wavenumber as shown in the following series:

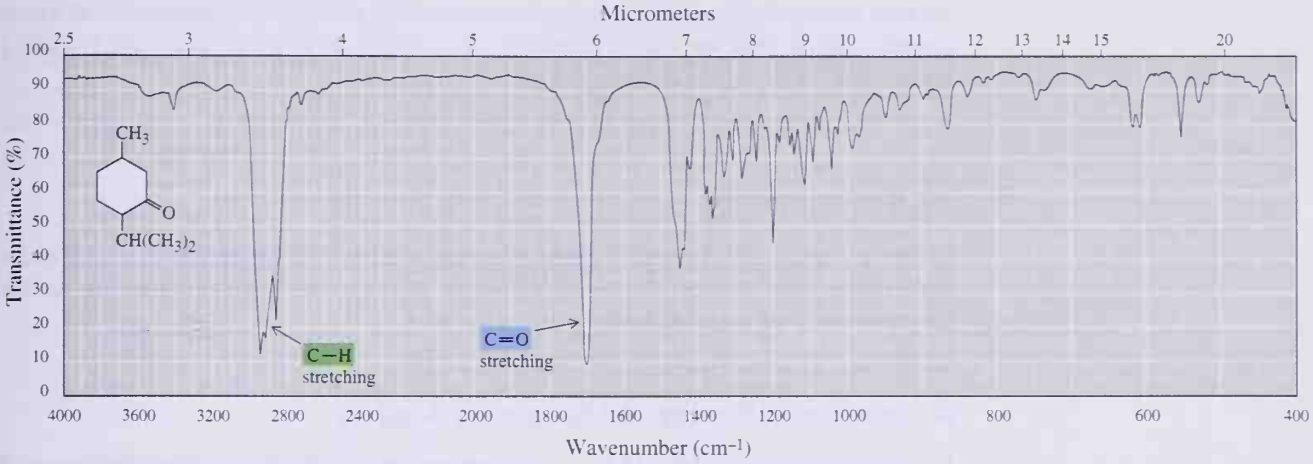
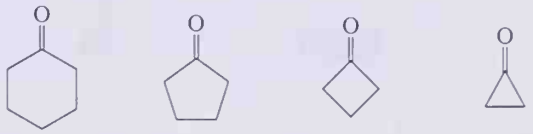
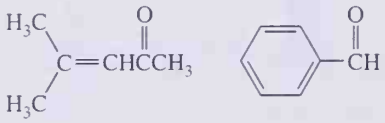


Figure 17.5
Infrared spectrum of menthone.



1715 cm^{-1} 1745 cm^{-1} 1780 cm^{-1} 1850 cm^{-1}

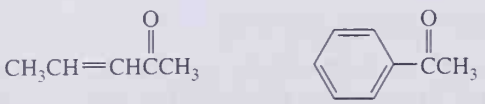
The presence of a carbon-carbon double bond in conjugation with the carbonyl group results in a shift of the C=O absorption to a lower wavenumber as seen in the following α,β-unsaturated ketone and aromatic aldehyde.



1690 cm^{-1} 1700 cm^{-1}

D. Ultraviolet-Visible Spectroscopy

Simple aldehydes and ketones show only weak absorption in the ultraviolet region of the spectrum due to an n to π^* electronic transition of the carbonyl group. If, however, the carbonyl group is conjugated with one or more carbon-carbon double bonds, intense absorption (ε = 8,000–20,000) occurs due to a π to π^* transition; the position of absorption shifts to longer wavelengths, and the extinction coefficient of the absorption maximum increases sharply. For the α,β-unsaturated ketone 3-penten-2-one, for example, λ_{max} = 224 nm (log ε 4.10).



3-Penten-2-one
λ_{max} 224 nm (log ε 4.10)

Acetophenone
λ_{max} 246 nm (log ε 3.99)

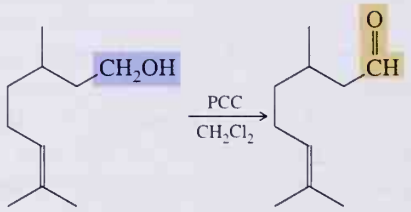
As with alkenes and aromatic hydrocarbons, the greater the extent of conjugation of unsaturated systems with the carbonyl group, the more the absorption maximum is shifted toward the visible region of the spectrum.

17.5 Preparation

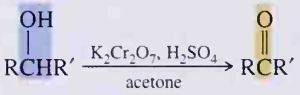
We have already seen several of the most common methods for preparation of aldehydes and ketones from alkenes, alkynes, and primary and secondary alcohols. Here we review the most useful of these methods.

A. Oxidation of Primary and Secondary Alcohols

Pyridinium chlorochromate (PCC) is the most commonly used reagent for oxidation of a primary alcohol (Section 9.5G) to an aldehyde. Under these conditions, carbon-carbon double bonds are normally not oxidized.

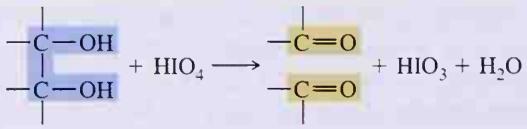


PCC, chromic acid, and various other forms of Cr(VI), as well as potassium permanganate, may be used to oxidize a secondary alcohol to a ketone.



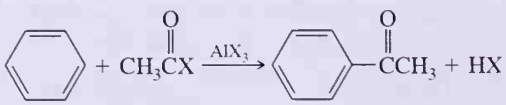
B. Oxidation of 1,2-Glycols by Periodic Acid or Lead Tetraacetate

The product may be two ketones, two aldehydes, or one aldehyde and one ketone depending on the substitution pattern of the glycol (Section 9.5H).



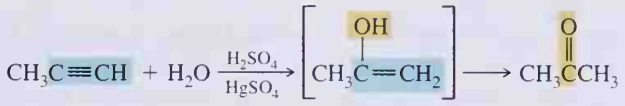
C. Friedel-Crafts Acylation of Aromatic Rings

The Friedel-Crafts acylation process is detailed in Section 16.1C.



D. Acid-Catalyzed Hydration of Alkynes

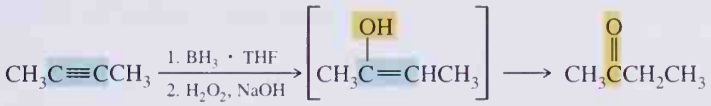
Addition follows Markovnikov's rule (Section 6.5C): hydrogen adds to the carbon of the triple bond bearing the greater number of hydrogens. The resulting enol is in equilibrium with a keto form. Hydration of acetylene gives acetaldehyde. Hydration of any other alkyne gives a ketone.



Propyne — Propen-2-ol (an enol) — Propanone

E. Hydroboration-Oxidation of Alkynes

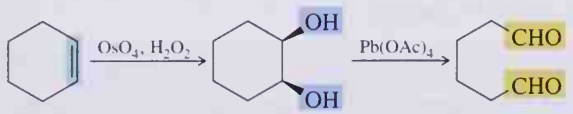
Treatment of a disubstituted carbon-carbon triple bond with diborane yields a trialkenylborane (Section 6.5B), which, on oxidation with hydrogen peroxide in aqueous sodium hydroxide, gives an enol. The enol is in tautomeric equilibrium with a ketone. Hydroboration of a terminal alkyne using disiamylborane, $(sia)_2BH$, followed by oxidation with alkaline hydrogen peroxide gives an aldehyde.



2-Butyne — 2-Buten-2-ol (an enol) — 2-Butanone

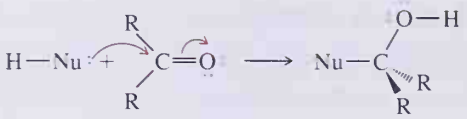
F. Oxidation of Alkenes: Cleavage of the Carbon-Carbon Double Bond

The most effective oxidative cleavage of a carbon-carbon double bond (Section 5.7) is a two-stage sequence: (1) oxidation of the alkene to a glycol using potassium permanganate or hydrogen peroxide and a catalytic amount of osmium tetroxide followed by (2) oxidation of the glycol using either periodic acid or lead tetraacetate.



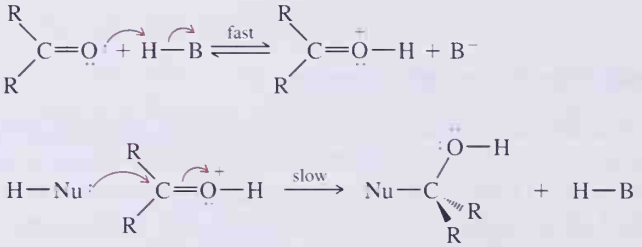
17.6 Reactions

One of the most common reaction themes of a carbonyl group is addition of a nucleophile to form a **tetrahedral carbonyl addition compound.** In the following general reaction, the nucleophilic reagent is written as H—Nu: to emphasize the presence of the unshared pair of electrons on the nucleophile.



Tetrahedral carbonyl addition compound

A second common reaction theme of a carbonyl group is reaction with a proton or other Lewis acid to form a resonance-stabilized cation. Protonation increases the electron deficiency of the carbonyl carbon and makes it even more reactive toward nucleophiles. This cation then reacts with a nucleophile to give a tetrahedral carbonyl addition compound like that just shown.



Tetrahedral carbonyl addition compound

17.7 Addition of Carbon Nucleophiles

In this section, we examine reactions of carbonyl groups with the following types of carbon nucleophiles:

RMgX	RLi	$RC{\equiv}C:^-$	$:C{\equiv}N:^-$
A Grignard reagent	An organolithium reagent	Anion of a terminal alkyne	Cyanide ion

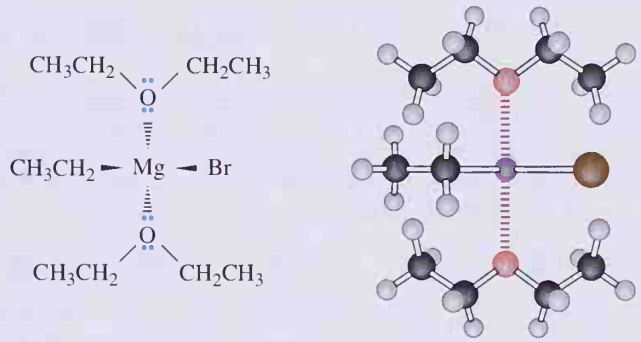
From the perspective of the organic chemist, addition of a carbon nucleophile is one of the most important types of nucleophilic additions to a carbonyl group because, in the process, a new carbon-carbon bond is formed.

A. Formation and Structure of Organometallic Compounds

Alkyl and aryl halides react with Group I, Group II, and certain other metals to form organometallic compounds. An **organometallic compound** is one that contains a carbon-metal bond. Organomagnesium compounds are called **Grignard reagents** after their discoverer, Victor Grignard, who was awarded a Nobel Prize in chemistry in 1912 for this discovery and its application to organic synthesis. Butylmagnesium chloride, for example, is prepared by treating 1-chlorobutane dissolved in diethyl ether with magnesium metal.

$$\underset{\text{1-Chlorobutane}}{CH_3CH_2CH_2CH_2Cl} + Mg \xrightarrow{\text{ether}} \underset{\text{Butylmagnesium chloride}}{CH_3CH_2CH_2CH_2MgCl}$$

Grignard reagents form on the surface of the metal and dissolve as coordination compounds consisting of one molecule of Grignard reagent and two molecules of ether. In this coordination compound, Mg is surrounded by four groups in a tetrahedral arrangement. Two of the four groups are ether molecules.



Ethylmagnesium bromide diethyrate

Organolithium reagents are formed by reaction of an alkyl or aryl halide with two equivalents of lithium metal as illustrated by the preparation of butyllithium. In this reaction, a solution of 1-chlorobutane dissolved in pentane is added to lithium wire at −10°C. Yields of alkyl or aryllithium compounds are typically 80% to 90%.

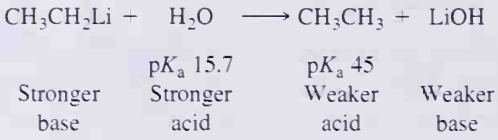
$$\underset{\text{1-Chlorobutane}}{CH_3CH_2CH_2CH_2Cl} + 2Li \xrightarrow{\text{pentane}} \underset{\text{Butyllithium}}{CH_3CH_2CH_2CH_2Li} + LiCl$$

Carbon-metal bonds in organometallics are best described as polar covalent, with carbon bearing a partial negative charge and the metal bearing a partial positive charge. Shown in Table 17.4 are electronegativity differences (Pauling scale, Table 1.3) between carbon and various metals. From the difference in electronegativity, we can calculate a percent ionic character using the formula presented in Section 1.2B. Organolithium and organomagnesium bonds have the highest partial ionic character and behave as strong nucleophiles in their reactions with carbonyl-containing compounds. Organozinc and organocadmium compounds have lesser partial ionic character and are weaker nucleophiles in their reactions with carbonyl-containing compounds.

Table 17.4 Percent ionic character of some C—M bonds

C—M Bond	Difference in Electronegativity	Percent Ionic Character
C—Li	2.5 − 1.0 = 1.5	60
C—Mg	2.5 − 1.2 = 1.3	52
C—Al	2.5 − 1.5 = 1.0	40
C—Zn	2.5 − 1.6 = 0.9	36
C—Cd	2.5 − 1.7 = 0.8	32
C—Sn	2.5 − 1.8 = 0.7	28
C—Hg	2.5 − 1.9 = 0.6	24

Because these organometallic compounds are also very strong bases, they react with any acid stronger than the alkane from which they are derived. Ethyllithium, for example, reacts with water to give ethane and lithium hydroxide. This reaction, like others discussed in Section 3.3, is an example of a stronger acid and a stronger base reacting to give a weaker acid and a weaker base.



Following are several other classes of proton donors that react readily with organometallics derived from Group I and Group II metals.

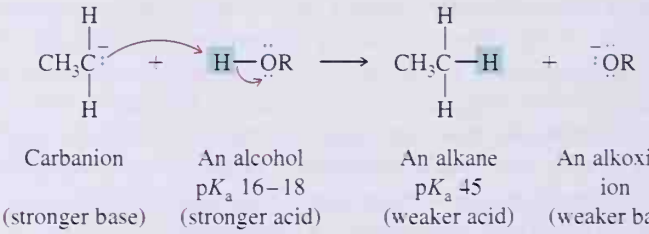
R_2NH	$RC{\equiv}CH$	ROH	HOH	ArOH	RSH	RCO_2H
pK_a 30–35 Amines	pK_a 25 Terminal alkynes	pK_a 16–18 Alcohols	pK_a 15.7 Water	pK_a 9–10 Phenols	pK_a 8–9 Thiols	pK_a 4–5 Carboxylic acids

EXAMPLE 17.3

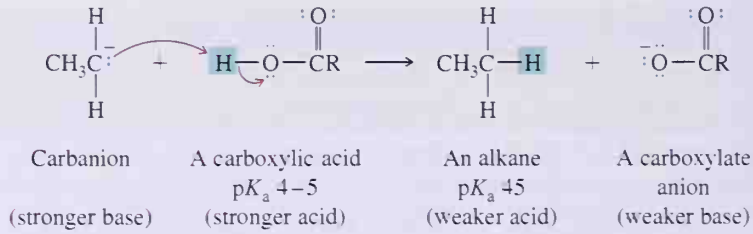
Write acid-base reactions between ethyllithium and (a) an alcohol and (b) a carboxylic acid. Use curved arrows to show the flow of electrons in each reaction. In addition show that each reaction is an example of a stronger acid and stronger base reacting to form a weaker acid and weaker base.

Solution

(a) The alcohol is the stronger acid, and ethyl carbanion is the stronger base.

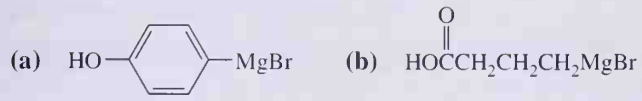


(b) The carboxylic acid is the stronger acid, and ethyl carbanion the stronger base.



PROBLEM 17.3

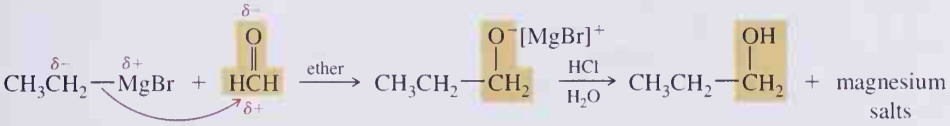
Explain why these Grignard reagents cannot be used as synthetic intermediates.



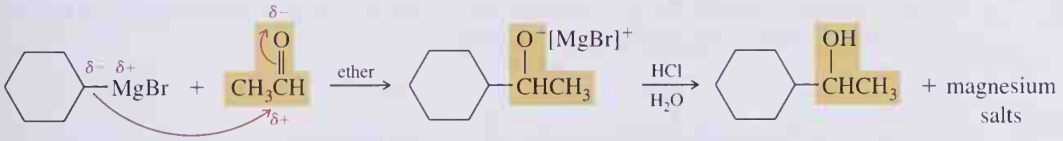
B. Addition of Grignard Reagents

Carbanions derived from Grignard reagents are good nucleophiles and add to carbonyl groups to form tetrahedral carbonyl addition compounds. In the case of a Grignard reagent, the tetrahedral carbonyl addition compound is a **magnesium alkoxide** (the magnesium salt of an alcohol). In the following examples, the magnesium oxygen bond is written $-O^-[MgBr]^+$ to emphasize its ionic character. An alkoxide ion is a strong base and, when treated with aqueous acid, forms an alcohol.

Treatment of formaldehyde with a Grignard reagent followed by hydrolysis in aqueous acid gives a primary alcohol; treatment of any other aldehyde with a Grignard reagent followed by hydrolysis gives a secondary alcohol. The driving force for these reactions is the attraction of the partial negative charge on the carbon of the organometallic for the partial positive charge of the carbonyl carbon.

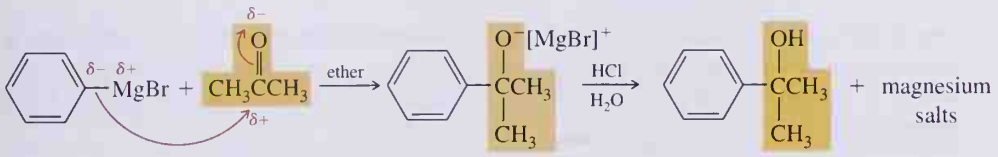


Methanal — A magnesium alkoxide — 1-Propanol (a primary alcohol)



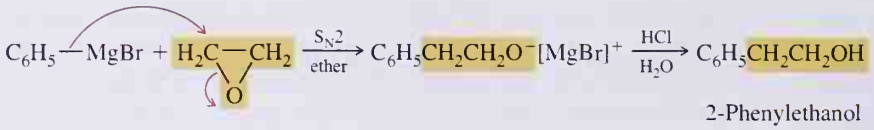
Ethanal (an aldehyde) — A magnesium alkoxide — 1-Cyclohexylethanol (a secondary alcohol)

Treatment of a ketone with a Grignard reagent followed by hydrolysis in aqueous acid gives a tertiary alcohol.



Acetone (a ketone) — A magnesium alkoxide — 2-Phenyl-2-propanol (a tertiary alcohol)

Grignard reagents also add to epoxides by nucleophilic substitution. As you would predict for an S_N2 reaction, the organometallic compound attacks the less hindered carbon of the highly strained epoxide ring and displaces alkoxide ion. Treatment of ethylene oxide with a Grignard reagent is a very convenient way to lengthen a carbon chain by two atoms as illustrated by the reaction of phenylmagnesium bromide with ethylene oxide.



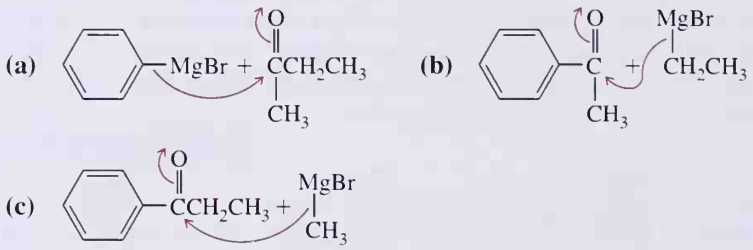
2-Phenylethanol

EXAMPLE 17.4

2-Phenyl-2-butanol can be synthesized by three different combinations of a Grignard reagent and a ketone. Show each combination.

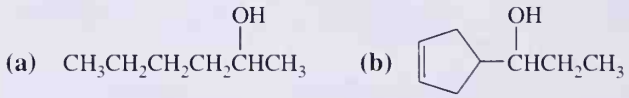
Solution

In each solution, curved arrows show formation of the new carbon-carbon bond and the alkoxide ion.



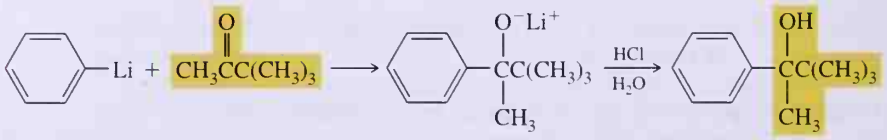
PROBLEM 17.4

Write structural formulas for all combinations of Grignard reagent and aldehyde or ketone that might be used to synthesize these alcohols.



C. Addition of Organolithium Compounds

Organolithium compounds are generally more reactive in carbonyl addition reactions than organomagnesium compounds and typically give higher yields of products. Following is a synthesis illustrating the use of an organolithium reagent to form a sterically hindered tertiary alcohol.

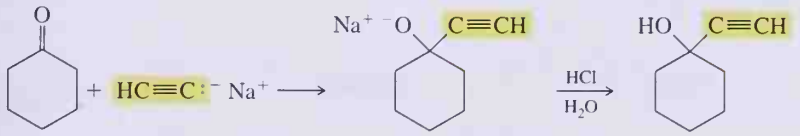


3,3-Dimethyl-2-butanone

3,3-Dimethyl-2-phenyl-2-butanol

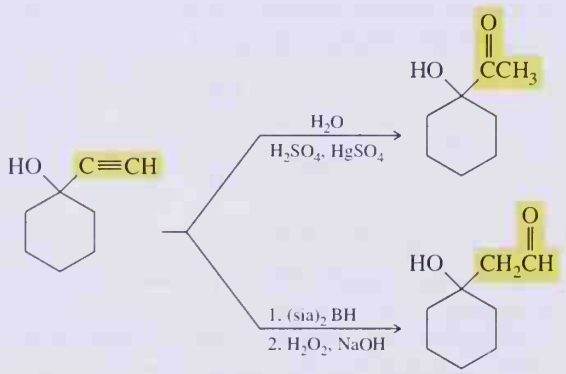
D. Addition of Salts of Terminal Alkynes

The anion of a terminal alkyne is a nucleophile and adds to the carbonyl group of an aldehyde or ketone to form a tetrahedral carbonyl addition compound. These addition compounds contain both a hydroxyl group and a carbon-carbon triple bond, each of which can be further modified. In the following example, addition of sodium acetylide to cyclohexanone followed by hydrolysis in aqueous acid gives 1-ethynylcyclohexanol.



A sodium alkoxide 1-Ethynylcyclohexanol

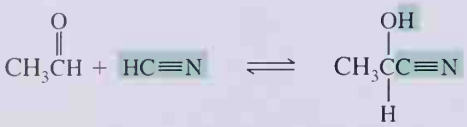
Acid-catalyzed hydration of this hydroxyalkyne (Section 6.5C) gives an α-hydroxy methyl ketone. Alternatively, hydroboration followed by oxidation with alkaline hydrogen peroxide (Section 6.5B) gives a β-hydroxyaldehyde.



This example illustrates two of the most valuable reactions of acetylenes: (1) addition of the anion of a terminal alkyne to the carbonyl group of an aldehyde or ketone to form an alkynyl alcohol and (2) hydration of an alkyne to give either an aldehyde or ketone depending on the substitution pattern of the alkyne and the method of hydration.

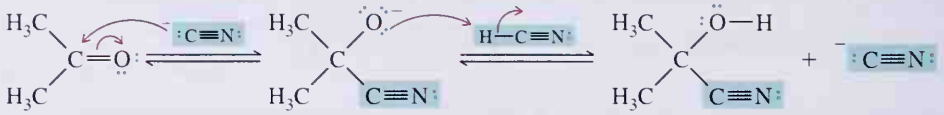
E. Addition of Hydrogen Cyanide

Hydrogen cyanide, HCN, adds to the carbonyl group of an aldehyde or ketone to form a tetrahedral carbonyl addition compound called a cyanohydrin. The characteristic structural feature of a **cyanohydrin** is an —OH group and a —CN group bonded to the same carbon. For example, HCN adds to acetaldehyde to form acetaldehyde cyanohydrin in 75% yield.



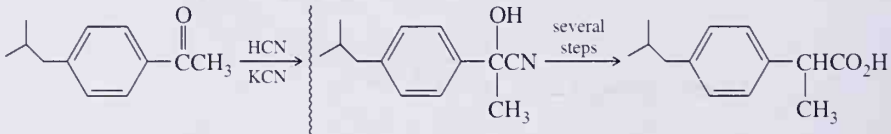
Acetaldehyde cyanohydrin

Addition of hydrogen cyanide is catalyzed by cyanide ion. Because HCN is a weak acid, pK_a 9.31, the concentration of cyanide ion in aqueous HCN is too low for cyanohydrin formation to proceed at a reasonable rate. Cyanohydrin formation, therefore, is generally carried out by dissolving NaCN or KCN in water and adding acid to adjust the pH of the solution to approximately 10.0, giving a solution in which HCN and CN^- are present in approximately equal concentrations. Reaction is initiated by nucleophilic addition of cyanide ion to the carbonyl group to form an alkoxide that in turn reacts with HCN to form a cyanohydrin and CN^-.



Acetone Acetone cyanohydrin

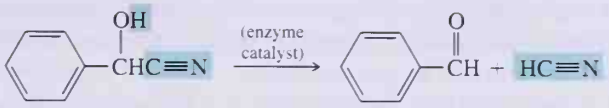
For aldehydes and most aliphatic ketones, the position of equilibrium favors cyanohydrin formation. For many aryl ketones and sterically hindered aliphatic ketones, however, the position of equilibrium favors starting materials, and for these types of molecules, cyanohydrin formation is not a useful reaction. The following synthesis of ibuprofen, for example, failed because the cyanohydrin was formed only in low yield.



4-Isobutylacetophenone A cyanohydrin Ibuprofen

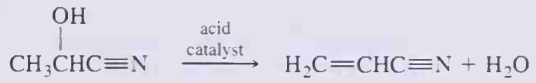
Benzaldehyde cyanohydrin (mandelonitrile) provides an interesting example of a chemical defense mechanism in the biological world. This substance is synthesized by millipedes *(Apheloria corrigata)* and stored in special glands. When a millipede is attacked, the cyanohydrin is released from the storage gland, undergoes enzyme-catalyzed dissociation to produce HCN, and is then released to ward off predators. The quantity of HCN emitted by a single millipede is sufficient to kill a small mouse.

When the millipede *Apheloria corrigata* is attacked, benzaldehyde cyanohydrin is released from storage glands. It then undergoes enzyme-catalyzed hydrolysis to benzaldehyde and HCN and is emitted as a spray to ward off predators. *(© Michael J. Doolittle, Rainbow)*



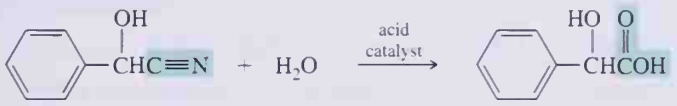
Benzaldehyde cyanohydrin Benzaldehyde

The main value of cyanohydrins lies in the new functional groups into which they can be converted. First, the secondary or tertiary alcohol of the cyanohydrin may undergo acid-catalyzed dehydration to form an unsaturated nitrile. For example, acid-catalyzed dehydration of acetaldehyde cyanohydrin gives acrylonitrile, the monomer from which polyacrylonitrile (Orlon, Table 5.4) is made.

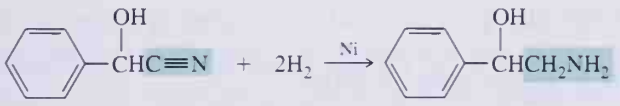


Acetaldehyde cyanohydrin Acrylonitrile

Second, acid-catalyzed hydrolysis of the nitrile group (Section 20.4E) gives a carboxylic acid. For example, hydrolysis of benzaldehyde cyanohydrin gives 2-hydroxy-2-phenylethanoic acid. Third, a nitrile is reduced to a primary amine by hydrogen over a nickel or other transition metal catalyst (Section 22.9). Catalytic reduction of benzaldehyde cyanohydrin, for example, gives 2-amino-1-phenylethanol.



Benzaldehyde cyanohydrin 2-Hydroxy-2-phenylethanoic acid



Benzaldehyde cyanohydrin 2-Amino-1-phenylethanol

17.8 The Wittig Reaction

In 1954, Georg Wittig reported a method for the synthesis of alkenes from aldehydes and ketones using compounds called phosphonium ylides (Chemistry in Action: The Octet Rule, Chapter 1). An **ylide** is a molecule which, when written in a Lewis structure showing all atoms with complete octets, has positive and negative charges on adjacent atoms. For his pioneering study and development of this reaction into a major synthetic tool, Professor Wittig shared the Nobel Prize in chemistry in 1979. A Wittig synthesis is illustrated by the conversion of cyclohexanone to methylenecyclohexane.

A phosphonium ylide Methylene-cyclohexane Triphenyl-phosphine oxide

We study the Wittig reaction in two stages: first, the formation and structure of phosphonium ylides themselves and second, the reaction of a phosphonium ylide with the carbonyl group of an aldehyde or ketone to give an alkene.

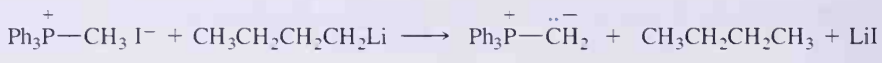
Phosphorus is the second element in Group VA of the periodic table and, like nitrogen, has five electrons in its valence shell. Examples of trivalent phosphorus compounds are phosphine and triphenylphosphine. Phosphine is a highly toxic, flammable gas. Triphenylphosphine is a colorless, odorless solid.

Phosphine (bp −87°C) Triphenylphosphine (mp 81°C)

Because phosphorus is below nitrogen in the periodic table, trivalent compounds of phosphorus are weaker bases than trivalent compounds of nitrogen and also better nucleophiles (Section 10.7B). Treatment of a trivalent phosphorus compound with a primary or secondary alkyl halide gives a phosphonium salt by an S_N2 pathway. Because trivalent phosphorus compounds are also weak bases, treatment of a tertiary halide with a trivalent phosphorus compound gives largely an alkene by an E2 pathway.

Triphenylphosphine — Methyltriphenylphosphonium iodide (an alkyltriphenylphosphonium salt)

α-Hydrogen atoms on the alkyl group of an alkyltriphenylphosphonium salt are weakly acidic and can be removed by reaction with a very strong base, typically butyllithium, sodium hydride (NaH), or sodium amide ($NaNH_2$).

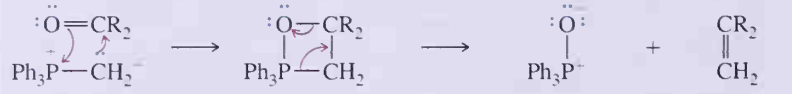


Butyllithium — A phosphonium ylide — Butane

The product of removal of hydrogen from an alkyltriphenylphosphonium salt is a phosphonium ylide.

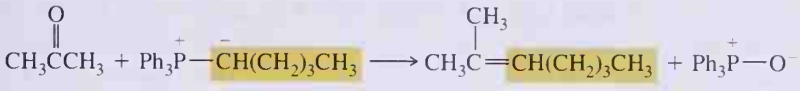
Phosphonium ylides react with the carbonyl groups of aldehydes and ketones by a cycloaddition reaction to form a four-member ring called an **oxaphosphetane.** The name for this ring system is derived by combination of the following units: oxa- to show that it contains oxygen, -phosph- to show that it contains phosphorus, -et- to show that it is a four-member ring, and -ane to show only carbon-carbon single bonds in the ring.

Oxaphosphetanes can be isolated at low temperature. On warming to room temperature, they fragment to give triphenylphosphine oxide and an alkene.

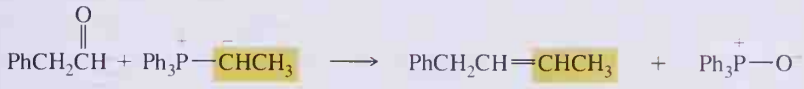


An oxaphosphetane — Triphenylphosphine oxide — An alkene

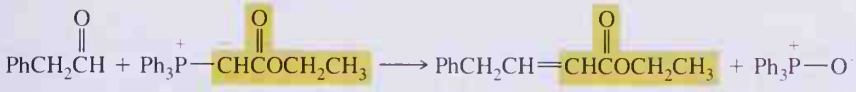
The Wittig reaction is effective with a wide variety of aldehydes and ketones and with ylides derived from a wide variety of primary, secondary, and allylic halides as shown by the following examples:



2-Methyl-2-heptene



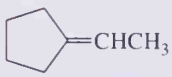
1-Phenyl-2-butene
(87% Z isomer; 13% E isomer)



Ethyl 4-phenyl-2-butenoate
(only the E isomer formed)

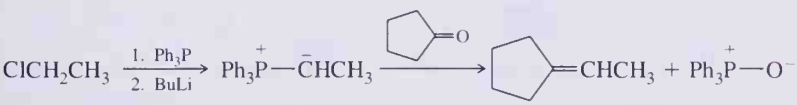
EXAMPLE 17.5

Show how the following alkene can be synthesized by a Wittig reaction:

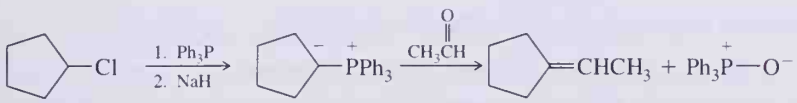


Solution

Starting materials are either cyclopentanone and the triphenylphosphonium ylide derived from chloroethane, or acetaldehyde and the triphenylphosphonium ylide derived from chlorocyclopentane.



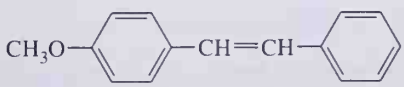
Chloroethane

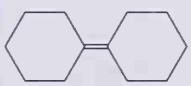


Chlorocyclopentane

PROBLEM 17.5

Show how the following alkenes can be synthesized by a Wittig reaction:

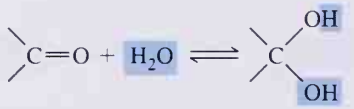
(a) 

(b) 

17.9 Addition of Oxygen Nucleophiles

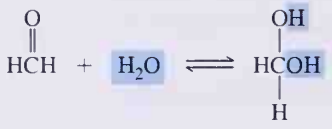
A. Addition of Water

Addition of water (hydration) to a carbonyl group of an aldehyde or ketone forms a 1,1-diol. Note that here, numbers 1,1 do not refer to an IUPAC numbering system, but rather to the fact that the two hydroxyl groups are on the same carbon. A 1,1-diol is commonly referred to as the hydrate of the corresponding aldehyde or ketone. These compounds are unstable and are rarely isolated.



A 1,1-diol
(a hydrate)

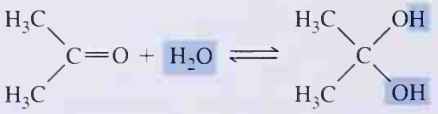
When methanal (formaldehyde), bp −21°C, is dissolved in water at 20°C, the position of equilibrium is such that formaldehyde is more than 99% hydrated. The hydration constant for this equilibrium is approximately 2.2×10^3. Formalin, a solution commonly used for preservation of biological specimens, is 37% methanal by weight in water.



$$K_h = K_{eq}[H_2O] = \frac{[CH_2(OH)_2]}{[CH_2O]} = 2.2 \times 10^3$$

Methanal Methanediol

Hydration constants for most ketones and for aromatic aldehydes are considerably smaller than that for methanal. The hydration constant for acetone is 2×10^{-3}. Thus, except for the simplest aldehydes, very little of the hydrated form is present at equilibrium in aqueous solution.

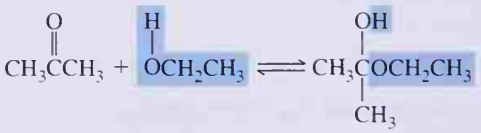


$$K_h = 2 \times 10^{-3}$$

Acetone 2,2-Propanediol

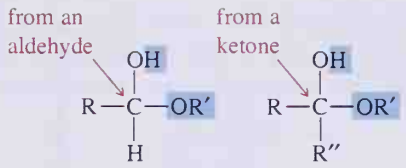
B. Addition of Alcohols: Formation of Acetals

Alcohols add to aldehydes and ketones in the same manner as described for water. Addition of one molecule of alcohol to the carbonyl group of an aldehyde or ketone forms a **hemiacetal** (a half-acetal).



(A hemiacetal)

Following are the characteristic structural features of a hemiacetal. In each instance, the R groups may be alkyl or aryl.



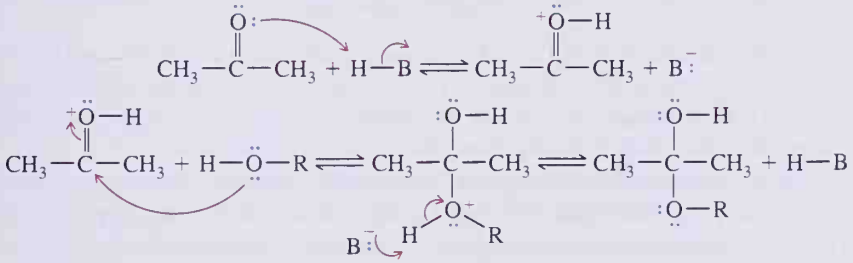
Characteristic structural features of a hemiacetal

Hemiacetals are only minor components of an equilibrium mixture except in one very important type of molecule. When a hydroxyl group is part of the same molecule that contains the carbonyl group, and a five- or six-member ring can form, the compound exists almost entirely in the cyclic hemiacetal form. We have much more to say about cyclic hemiacetals when we consider the chemistry of carbohydrates in Chapter 18.

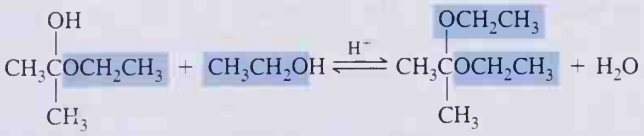
4-Hydroxypentanal

A cyclic hemiacetal
(the major form present at equilibrium)

Formation of hemiacetals is catalyzed by acid, most commonly sulfuric acid or *p*-toluenesulfonic acid. The function of the acid catalyst is to protonate the carbonyl oxygen, thus rendering the carbonyl carbon more susceptible to attack by the nucleophilic oxygen atom of the alcohol.



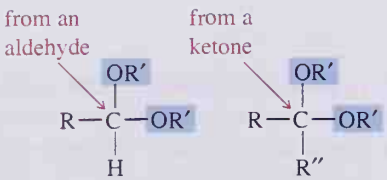
Hemiacetals react further with alcohols to form **acetals** plus a molecule of water. This reaction is acid-catalyzed.



(A hemiacetal)

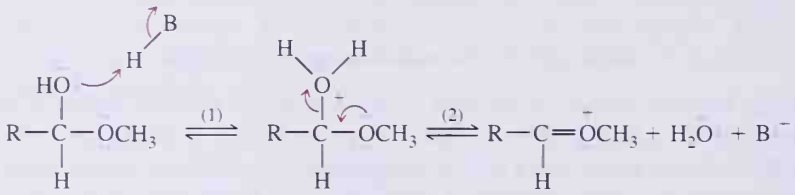
(A diethyl acetal)

Following are general formulas showing the characteristic structural feature of an acetal:



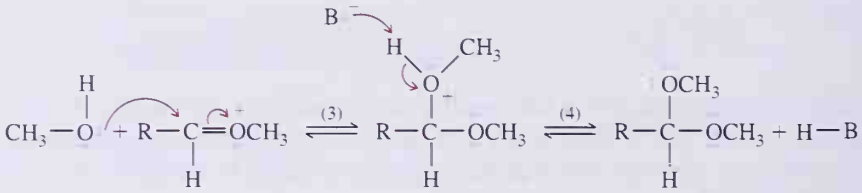
Characteristic structural features of an acetal

The mechanism for the acid-catalyzed conversion of a methyl hemiacetal into a dimethyl acetal is divided into two steps. In Step 1, H^+, an electrophile and Lewis acid, reacts with —OH of the hemiacetal to form an oxonium ion, which, in Step 2, loses a molecule of water to form a cation.



An oxonium ion

The cation is an electrophile and in Step 3 reacts with a nucleophile (in this case, a second molecule of alcohol) to form a new oxonium ion. Loss of a proton in Step 4 completes the reaction. Note that the acid HB is a true catalyst in this reaction. It is used in Step 1 but is regenerated in Step 4.



A new oxonium ion

Formation of acetals is often carried out using the alcohol as the solvent and dissolving either dry HCl (hydrogen chloride gas) or *p*-toluenesulfonic acid in the alcohol. Because the alcohol is both a reactant and solvent, it is present in large molar excess, which forces the position of equilibrium to the right and favors acetal formation.

As another experimental technique to favor acetal formation, water is removed from the reaction vessel by azeotropic distillation using a **Dean-Stark trap** (Figure 17.6). An **azeotrope** is a liquid mixture with a constant boiling point that is different from that of any of its components. An azeotropic mixture boils at a constant temperature without change in composition.

In this method for preparing an acetal, the aldehyde or ketone, alcohol, acid catalyst, and benzene are brought to reflux. The component with the lowest boiling point is an azeotrope, bp 69°C, consisting of 91% benzene and 9% water. This vapor is condensed and collected in a side trap where it separates into two layers. At room temperature, the composition of the upper, less dense layer is 99.94% benzene and 0.06% water. The composition of the lower, more dense layer is almost the reverse, 0.07% benzene and 99.93% water. As reflux continues, benzene from the top layer is returned to the refluxing mixture, and water is drawn off at the bottom through a stopcock.

EXAMPLE 17.6

Show the reaction of the carbonyl group of each aldehyde or ketone with one molecule of alcohol to form a hemiacetal, and then with a second molecule of alcohol to form an acetal. Note that in part (c), ethylene glycol is a diol, and one molecule provides both —OH groups.

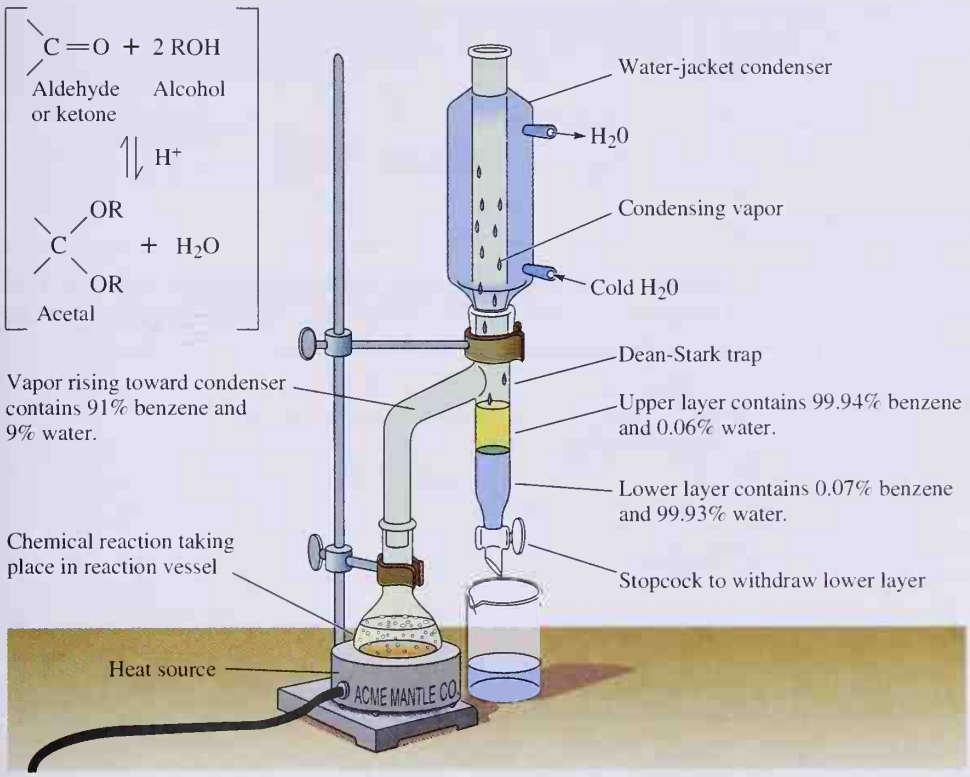
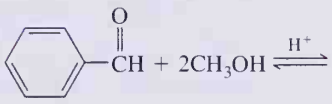


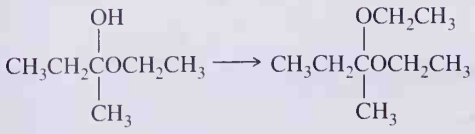
Figure 17.6
A Dean-Stark trap for removing water by azeotropic distillation.

(a) $CH_3CH_2CCH_3 + 2CH_3CH_2OH \overset{H^+}{\rightleftharpoons}$ **(b)**  $\overset{H^+}{\rightleftharpoons}$

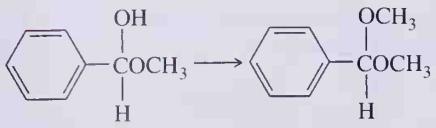
(c) 

Solution

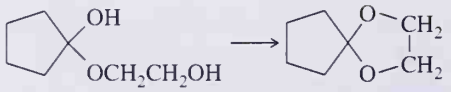
Given are formulas of the hemiacetal, and then the acetal:

(a) 

A hemiacetal An acetal

(b) 

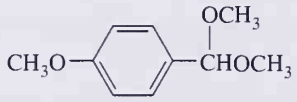
A hemiacetal An acetal

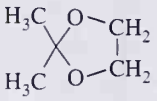
(c) 

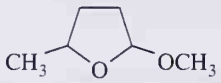
A hemiacetal A cyclic acetal

PROBLEM 17.6

Hydrolysis of an acetal forms an aldehyde or ketone and two molecules of alcohol. Following are structural formulas for three acetals. Draw the structural formulas for the products of hydrolysis of each in aqueous acid.

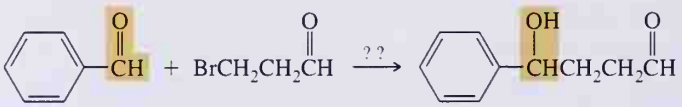
(a) 

(b) 

(c) 

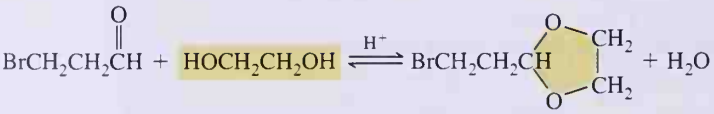
C. Acetals as Carbonyl-Protecting Groups

Acetals are valuable in synthetic organic chemistry as protecting groups as illustrated by the synthesis of 4-hydroxy-4-phenylbutanal from benzaldehyde and 3-bromopropanal.



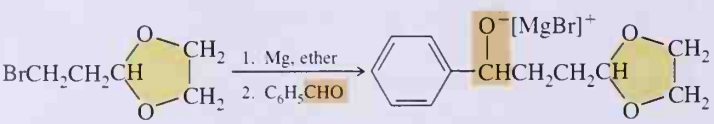
Benzaldehyde 3-Bromopropanal 4-Hydroxyl-4-phenylbutanal

One obvious way to form a new carbon-carbon bond between these two molecules is to treat benzaldehyde with a Grignard reagent from 3-bromopropanal. Any Grignard reagent formed from 3-bromopropanal, however, reacts immediately with the carbonyl group of another molecule of 3-bromopropanal, and, in effect, the Grignard reagent self-destructs during preparation. A way to avoid this problem is to protect the carbonyl group of 3-bromopropanal by conversion to an acetal.

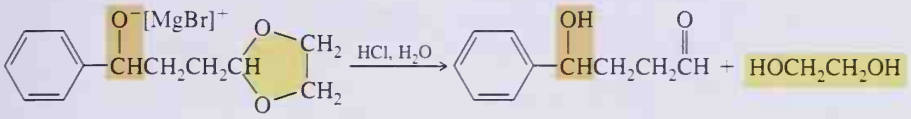


A cyclic acetal

Treatment of the protected bromoaldehyde with magnesium in diethyl ether followed by addition of benzaldehyde gives a magnesium alkoxide.

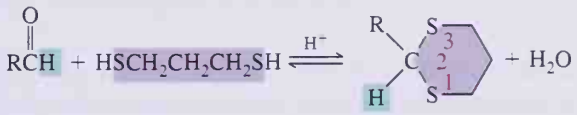


Treatment of the magnesium alkoxide with aqueous acid accomplishes two things. First, protonation of the alkoxide gives the desired alcohol and second, hydrolysis of the cyclic acetal regenerates the aldehyde.



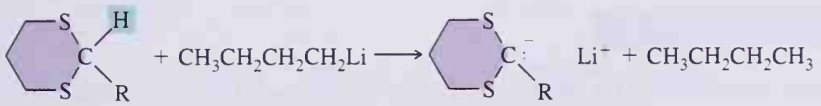
17.10 Addition of Sulfur Nucleophiles

The sulfur atom of a thiol is a far better nucleophile than the oxygen atom of an alcohol (Section 10.7B). Thiols, like alcohols, add to the carbonyl group of aldehydes and ketones to form tetrahedral carbonyl addition compounds. A common sulfur nucleophile used for this purpose is 1,3-propanedithiol. The carbonyl groups of both aldehydes and ketones react with this compound in the presence of an acid catalyst to form cyclic thioacetals. Products of this reaction are also called **1,3-dithianes;** "1,3-dithi-" to indicate that atoms of sulfur occur at positions 1 and 3 of the ring, and "-ane" to indicate that the ring is saturated (contains only carbon-carbon single bonds). Following is an equation for formation of a 1,3-dithiane from an aldehyde.



A 1,3-dithiane
(a thioacetal)

The special value of 1,3-dithianes derived from an aldehyde is that the hydrogen atom on carbon 2 of the ring is weakly acidic; it has a pK_a of approximately 31. In the presence of an alkane-derived base such as butyllithium, a 1,3-dithiane derived from an aldehyde is converted into a lithium salt.



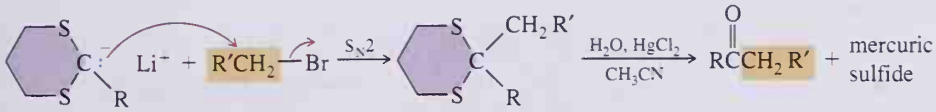
Stronger acid
pK_a 31

Stronger base

Weaker base

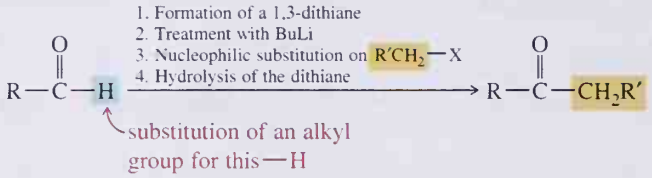
Weaker acid
pK_a 45

A 1,3-dithiane anion is an excellent nucleophile and reacts by an S_N2 pathway with primary alkyl halides to give a disubstituted dithiane. Treatment of this product with mercuric chloride, $HgCl_2$, in aqueous acetonitrile brings about hydrolysis of the dithiane to give a ketone.

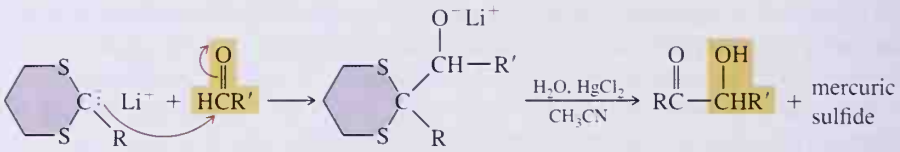


Lithium salt of
a 1,3-dithiane

The result of this series of reations is conversion of an aldehyde to a ketone.



Anions derived from 1,3-dithianes also add to the carbonyl groups of aldehydes and ketones to form tetrahedral carbonyl addition compounds. Acid-catalyzed hydrolysis of the initially formed lithium salt gives an α-hydroxyketone. Following is the reaction of a dithiane anion with the carbonyl group of an aldehyde:



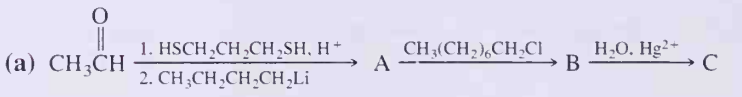
Lithium salt of a 1,3-dithiane

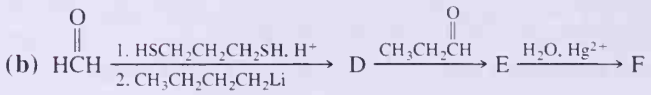
The result of this series of reactions is replacement of the hydrogen atom of the original aldehyde by either a secondary alcohol or, if carbonyl addition takes place with a ketone, a tertiary alcohol.

These two important reactions of 1,3-dithianes provide an example of what is called reversal of polarity. Under normal circumstances, the carbon atom of a carbonyl group bears a partial positive charge and is, therefore, an electrophile. When converted to a 1,3-dithiane and then treated with butyllithium, the same carbon becomes an anion and, therefore, a nucleophile.

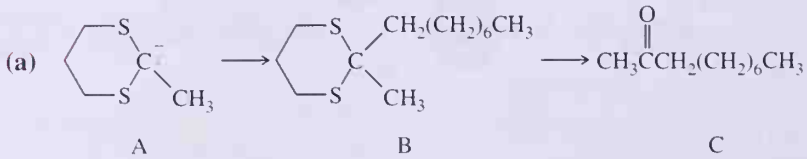
EXAMPLE 17.7

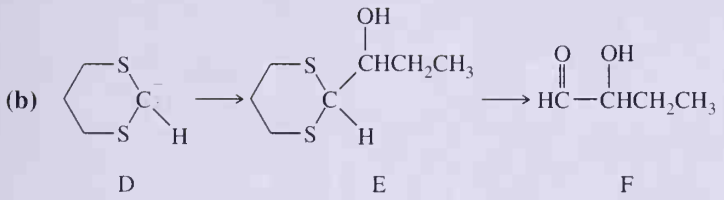
Give structural formulas for the lettered compounds in each reaction sequence.





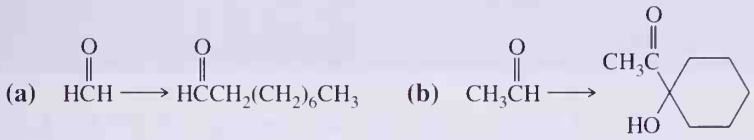
Solution





PROBLEM 17.7

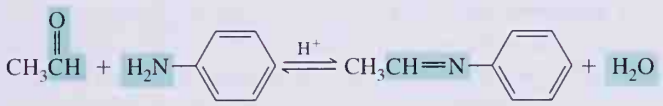
Show how to convert the given starting material into the indicated product using a 1,3-dithiane as an intermediate.



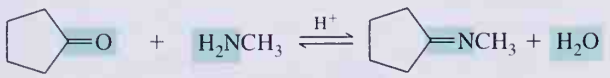
17.11 Addition of Nitrogen Nucleophiles

A. Ammonia and Its Derivatives

Ammonia, primary aliphatic amines (RNH_2), and primary aromatic amines ($ArNH_2$) react with the carbonyl group of aldehydes and ketones in the presence of an acid catalyst to give a product that contains a carbon-nitrogen double bond. A molecule containing a carbon-nitrogen double bond is called an **imine** or, alternatively, a **Schiff base.**

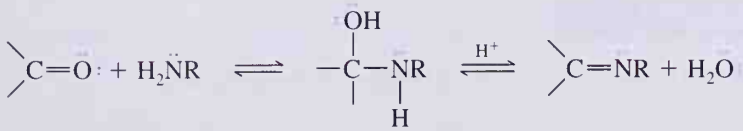


Ethanal Aniline An imine

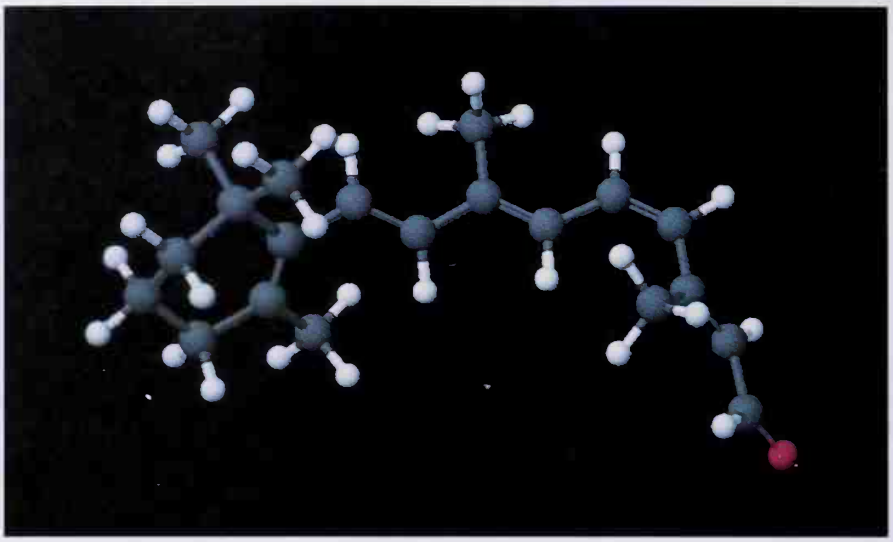


Cyclopentanone Methylamine An imine

The mechanism of imine formation can be divided into two steps. In Step 1, the nitrogen atom of ammonia or the primary amine, both good nucleophiles, adds to the carbonyl carbon to form a tetrahedral carbonyl addition compound. Acid-catalyzed dehydration of this addition compound in Step 2 is the slow, rate-determining step.

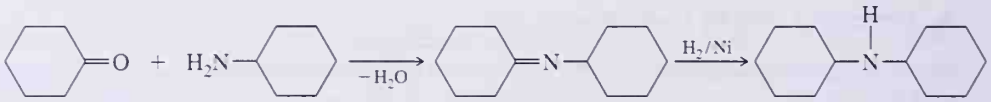


A tetrahedral carbonyl addition compound An imine



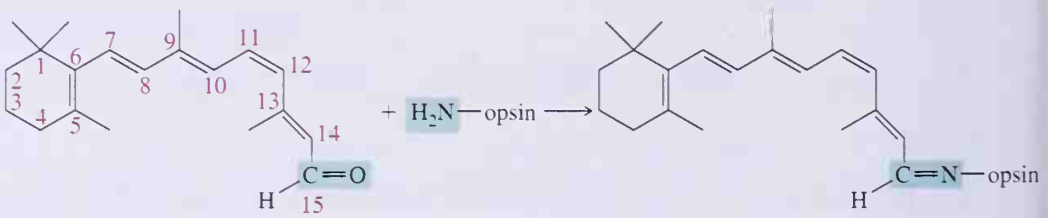
A ball-and-stick model of 11-*cis*-retinal. *(Charles D. Winters)*

One of the chief values of imines is that the carbon-nitrogen double bond can be reduced by hydrogen in the presence of a nickel or other transition metal catalyst to a carbon-nitrogen single bond. Thus, a primary amine is converted to a secondary amine by way of an imine as illustrated by the conversion of cyclohexylamine to dicyclohexylamine. We discuss this synthesis of amines in more detail in Chapter 22.



Cyclohexanone Cyclohexylamine An imine Dicyclohexylamine

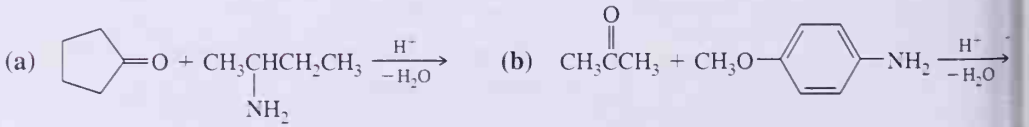
To give but one example of the importance of imines in biological systems, the active form of **vitamin A aldehyde** (retinal) is bound to the protein **opsin** of the human retina in the form of an imine. The primary amino group for this reaction is provided by the side chain of the amino acid, lysine (Section 24.1). This imine is called **rhodopsin**, or **visual purple.**



11-*cis*-Retinal Rhodopsin (Visual purple)

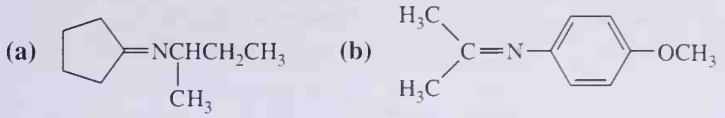
EXAMPLE 17.8

Write structural formulas for the imines formed in these reactions:



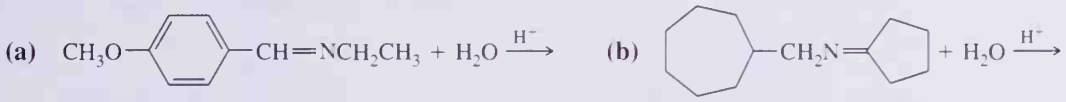
Solution

Given are structural formulas for each imine:

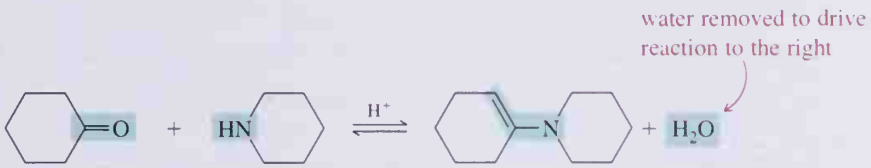


PROBLEM 17.8

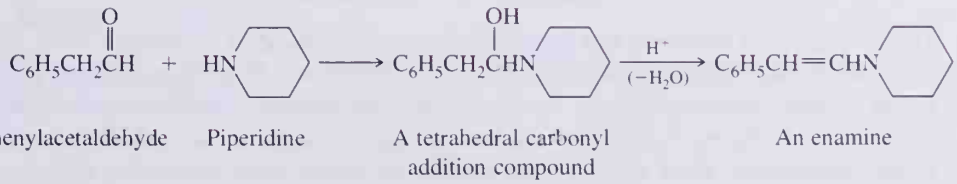
Acid-catalyzed hydrolysis of an imine gives an amine salt and an aldehyde or ketone. Write structural formulas for the products of hydrolysis of the following imines:



Secondary amines react with aldehydes and ketones to form enamines. The name **enamine** is derived from en- to indicate the presence of a carbon-carbon double bond and -amine to indicate the presence of an amino group. Following is enamine formation between cyclohexanone and piperidine, a cyclic secondary amine.



The mechanism for formation of an enamine is very similar to that for formation of an imine. In Step 1, nucleophilic addition of the secondary amine to the carbonyl carbon of the aldehyde or ketone followed by migration of a proton from nitrogen to oxygen gives a tetrahedral carbonyl addition compound. Acid-catalyzed dehydration in Step 2 gives the enamine. It is at this stage that enamine formation differs from imine formation. Nitrogen has no proton to be lost. Instead a proton is lost from the α-carbon of the ketone or aldehyde portion of the molecule.

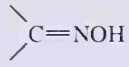
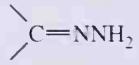
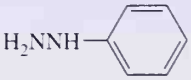
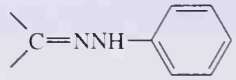
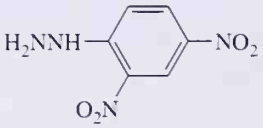
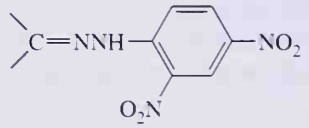
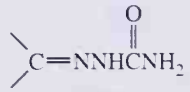


We return to the chemistry of enamines and their use in synthesis in Section 21.3.

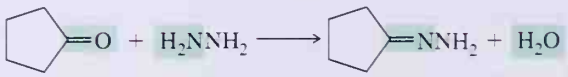
B. Hydrazine and Related Compounds

Aldehydes and ketones react with hydrazine to form compounds called hydrazones as illustrated by the treatment of cyclopentanone with hydrazine. A common use of hydra-

Table 17.5 Derivatives of ammonia and hydrazine used for forming imines

Amine or Hydrazine Reagent	Name Given to Type of Derivative Formed
H_2NOH Hydroxylamine	 An oxime
H_2NNH_2 Hydrazine	 A hydrazone
 Phenylhydrazine	 A phenylhydrazone
 2,4-Dinitrophenylhydrazine	 A 2,4-Dinitrophenylhydrazone (a 2,4-DNP)
 Semicarbazide	 A semicarbazone

zones is as intermediates in the reduction of carbonyl groups to methylene groups (Section 17.16C).



Hydrazine A hydrazone

The derivatives of ammonia and hydrazine most commonly used for reaction with aldehydes and ketones are shown in Table 17.5. The chief value of these nitrogen nucleophiles is that oximes, phenylhydrazones, 2,4-dinitrophenylhydrazones (2,4-DNP), and semicarbazones formed by most aldehydes and ketones are crystalline solids with sharp melting points. Historically, these aldehyde and ketone derivatives often provided a convenient way to identify liquid aldehydes or ketones. Recorded in the following table are boiling points of 2-, 3-, and 4-methylcyclohexanone and of 2,6-dimethyl-4-heptanone. It is extremely difficult if not impossible to distinguish between these four compounds by boiling point alone. The melting points of their 2,4-DNPs, however, are sufficiently far apart that identification is easily possible. Given advances in instrumental methods of analysis, compounds such as these are now more easily distinguished by spectroscopic means.

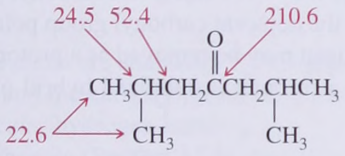
Compound	bp (°C)	mp of 2,4-DNP (°C)
2-methylcyclohexanone	163	137
2,6-dimethyl-4-heptanone	168	92
3-methylcyclohexanone	169	155
4-methylcyclohexanone	169	130

EXAMPLE 17.9

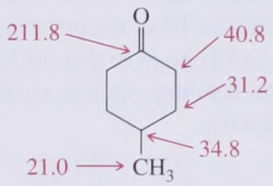
Show how to distinguish between 2,6-dimethyl-4-heptanone and 4-methylcyclohexanone based on the number of signals in the ^{13}C-NMR spectrum of each.

Solution

The ^{13}C-NMR spectrum of the first compound shows four signals, that of the second compound shows five signals.



2,6-Dimethyl-4-heptanone
(four signals)



4-Methylcyclohexanone
(five signals)

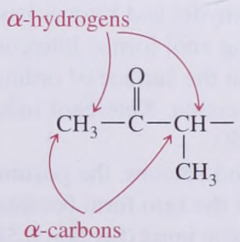
PROBLEM 17.9

Sketch the ^{1}H-NMR spectrum of 2,6-dimethyl-4-heptanone.

17.12 Keto-Enol Tautomerism

A. Acidity of α-Hydrogens

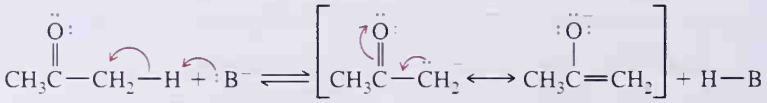
A carbon atom adjacent to a carbonyl group is called an α-carbon, and hydrogen atoms attached to it are called α-hydrogens.



Because carbon and hydrogen have comparable electronegatives, a C—H bond normally has little polarity, and a hydrogen atom bonded to carbon shows low acidity. The situation is different, however, for hydrogens alpha to a carbonyl group. α-Hydrogens are more acidic than acetylenic hydrogens, vinylic hydrogens, and alkane hydrogens but less acidic than alcohols.

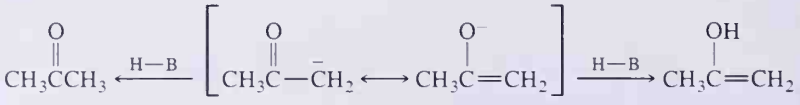
Type of Bond	pK_a
$CH_3CH_2O—H$	16
$CH_3\overset{\overset{O}{\|}}{C}CH_2—H$	20
$CH_3C{\equiv}C—H$	25
$CH_2{=}CH—H$	36
$CH_3CH_2—H$	45

Two factors contribute to the increased acidity of a C—H bond α to a carbonyl group relative to other C—H bonds. First, the presence of the adjacent carbonyl group polarizes the electron pair of the C—H bond so that the hydrogen may be removed as a proton by a strong base. Second, the resulting enolate anion is a resonance-stabilized hybrid of two major contributing structures.



Resonance-stabilized enolate anion

When the resonance-stabilized anion reacts with a proton donor, it may do so either on oxygen or on the α-carbon. Protonation on the α-carbon gives the original molecule in what is called the keto form. Protonation on oxygen gives an enol (en- to show that it is an alkene plus -ol to show that it is an alcohol). Keto and enol forms are constitutional isomers.



Keto form Enolate anion Enol form

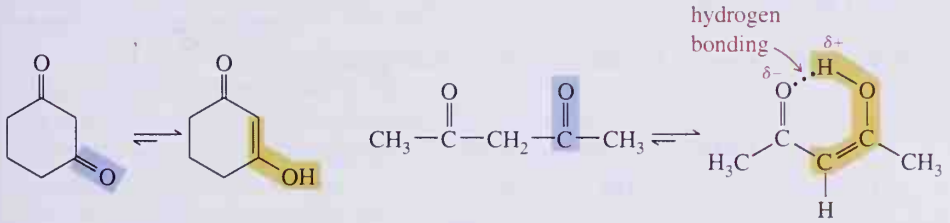
B. Keto-Enol Tautomerism

Under ordinary conditions, all aldehydes and ketones having at least one α-hydrogen are in equilibrium with the corresponding enol forms. Interconversion of these isomers is catalyzed by acids and bases, but even the surface of ordinary laboratory glassware is acidic enough to catalyze this interconversion. Keto-enol interconversion is the most common form of tautomerism (Section 6.5B).

For most simple aldehydes and ketones, the position of the equilibrium in keto-enol tautomerism lies far on the side of the keto form because a carbon-oxygen double bond is stronger than a carbon-carbon double bond (Section 6.5B). For acetaldehyde and acetone, the keto form predominates by better than 99% at equilibrium.

(Approx. 100%) (Approx. 99%)

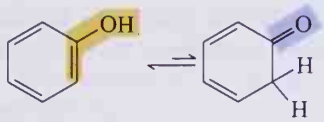
For certain types of molecules, the enol form may be the major form and in some cases the only form present at equilibrium. In 1,3-cyclohexanedione and 2,4-pentanedione and other β-diketones where an α-carbon is substituted with two carbonyl groups, the position of equilibrium shifts in favor of the enol form.



1,3-Cyclohexanedione 2,4-Pentanedione
(Acetylacetone)

These enols are stabilized by conjugation of the pi systems of the carbon-carbon double bond and the carbonyl group. The enol of 2,4-pentanedione is further stabilized by intramolecular hydrogen bonding.

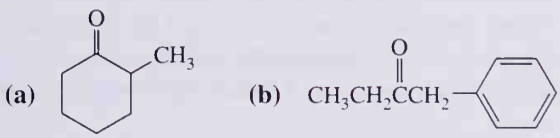
Phenols (Section 15.5) may be viewed as highly stable enols. The enol form in this equilibrium is of course favored by resonance stabilization of the aromatic ring.



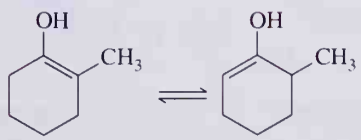
Enol form Keto form

EXAMPLE 17.10

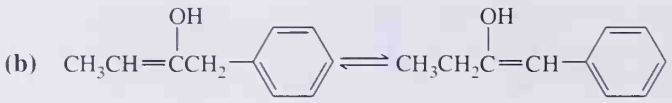
Write two enol structures for each of the following compounds. Which enol do you predict to predominate at equilibrium?



Solution



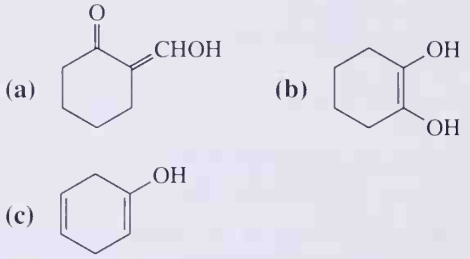
Major enol form
(more substituted
double bond)



Major enol form (the double bond of the enol is conjugated with the aromatic ring)

PROBLEM 17.10

Draw a structural formula for the keto form of each enol.

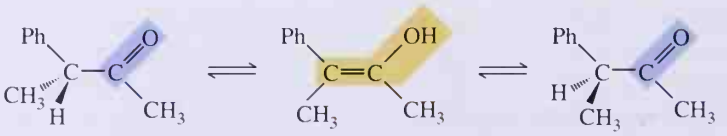


17.13 Reactions at the α-Carbon

Because of keto-enol tautomerism and its catalysis by both acids and bases, a carbon atom α to a carbonyl group is unique in its chemical reactivity compared with a β-carbon and other carbons in a hydrocarbon chain.

A. Racemization

When enantiomerically pure (either the R or the S) 3-phenyl-2-butanone is dissolved in ethanol, no change occurs in the optical activity of the solution over time. If, however, a trace of either acid (for example, aqueous or gaseous HCl) or base (for example, sodium ethoxide) is added, the optical activity of the solution begins to decrease and gradually drops to zero. When 3-phenyl-2-butanone is isolated from this solution, it is found to be a racemic mixture (Section 8.5C). Furthermore, the rate of racemization is proportional to the concentration of acid or base. These observations can be explained by a rate-determining acid- or base-catalyzed formation of an achiral enol intermediate. Tautomerism of the achiral enol to the chiral keto form generates the R and S enantiomers with equal probability.



(R)-3-Phenyl-2-butanone An achiral enol (S)-3-Phenyl-2-butanone

Racemization by this mechanism occurs only at α-carbon stereocenters with at least one α-hydrogen.

CHEMISTRY IN ACTION

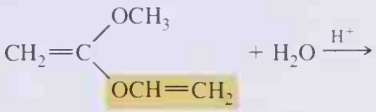
Synthesis of Simple Enols

Enols are perhaps the most useful and common reactive intermediates in organic chemistry. For many years, enols of acetaldehyde, acetone, and other simple aldehydes and ketones were thought to be too unstable to isolate or observe. However, recent work has demonstrated that enols can be made in sufficient amounts for NMR and other studies.

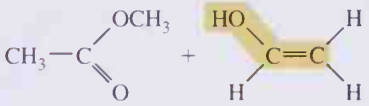
Vinyl alcohol is the simplest enol. Both acid and base catalyze its conversion by keto-enol tautomerism to acetaldehyde. However, it was theorized that if a precursor could be found that rapidly hydrolyzes to vinyl alcohol under almost neutral conditions, tautomerization might be slow enough to permit detection and observation of the enol. B. Capon and his students discovered that the class of compounds called ketene acetals are suitable precursors for this type of reaction.

Ketenes are molecules that contain the $R_2C{=}C{=}O$ functional group. Molecules with the grouping $R_2C{=}C(OR)_2$ are thus acetals of ketenes. A ketene acetal that hydrolyzes to vinyl alcohol was prepared in the following way. Treatment of the dimethylacetal of chloroacetaldehyde with 2-chloroethanol in the presence of an acid catalyst resulted in exchange of one of the $-OCH_3$ groups of the acetal. Treatment of this compound with 2 mol of sodium *tert*-butoxide resulted in a double dehydrohalogenation to form the ketene acetal.

Hydrolysis of this ketene acetal is rapid with only 10^{-4} *M* HCl, and a mixture of vinyl alcohol and methyl acetate is formed.



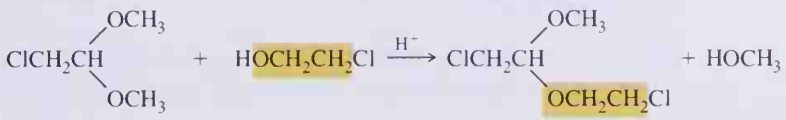
A ketene acetal



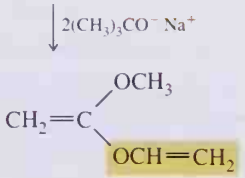
Methyl acetate Vinyl alcohol (an enol)

At −10°C, the vinyl alcohol product is stable for several hours. As shown in the ^{1}H-NMR spectrum of vinyl alcohol prepared in this way, the hydrogen exchange among —OH groups is slow, leading to spin-spin splitting with the adjacent =CH.

See B. Capon et al., *Accts. Chem. Res.*, **21:** 135 (1988).



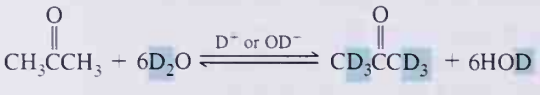
Dimethylacetal of chloroacetaldehyde 2-Chloroethanol



A ketene acetal

B. Deuterium Exchange

When an aldehyde or ketone with one or more α-hydrogens is dissolved in an aqueous solution enriched with D_2O and also containing catalytic amounts of either D^+ or OD^-, exchange of α-hydrogens occurs at a rate proportional to the concentration of the acid or base catalyst. The degree of enrichment in α-hydrogens is proportional to the percentage of D_2O in the original solution. If D_2O (99.9 atom % D) is used, then it is possible to exchange α-hydrogens completely for deuterium as illustrated for acetone. In naming compounds, the presence of deuterium is shown by the symbol "d," and the number of deuterium atoms is shown by a subscript following the symbol "d." Acetone-d_6 is available commercially in over 99.8 atom % D.

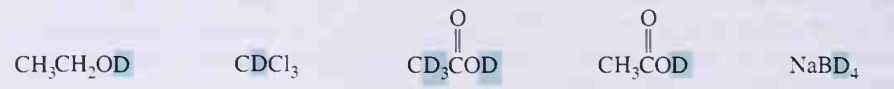


Acetone Acetone-d_6

We account for these results by proposing acid- or base-catalyzed enolization followed by incorporation of deuterium as the enol form converts to the keto form.

Deuterium exchange has two values. First, by observing changes in hydrogen to carbon ratios before and after deuterium exchange, it is possible to determine the number of exchangeable α-hydrogens in a molecule.

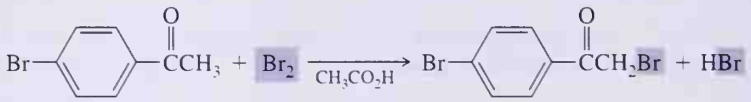
Second, exchange of α-hydrogens is a convenient way to introduce an isotopic label into molecules. At present, more than 225 deuterium-labeled compounds are available commercially, generally in isotopic enrichments of up to 99.5+ atom % D. Among these are:



Ethyl alcohol-d | Chloroform-d | Acetic-d_3 acid-d | Acetic acid-d | Sodium borodeuteride

C. Halogenation

Aldehydes and ketones react at an α-carbon with bromine and chlorine to form α-haloaldehydes and α-haloketones as illustrated by bromination of *p*-bromoacetophenone.

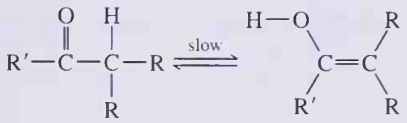


p-Bromoacetophenone

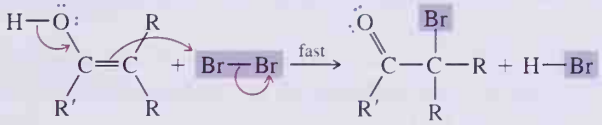
Bromination or chlorination at an α-carbon is catalyzed by both acid and base. For acid-catalyzed halogenation, acid generated by the reaction catalyzes further reaction. For base-catalyzed halogenation, it is necessary to add slightly more than one mole of base per mole of halogen to neutralize the HX formed and thus keep the solution basic.

The slow step of acid-catalyzed halogenation is formation of an enol. This is followed by rapid reaction of halogen with the double bond to give the α-haloketone.

Step 1: Acid-catalyzed enolization

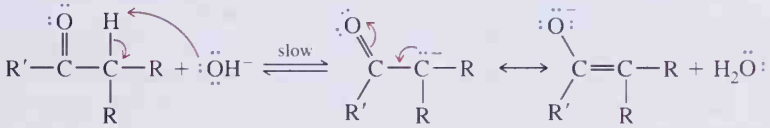


Step 2: Nucleophilic attack of the enol on halogen



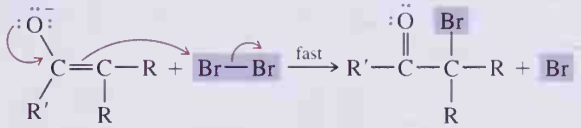
In base-catalyzed halogenation, the slow step is formation of an **enolate anion,** which then reacts with halogen by nucleophilic displacement to form the final product.

Step 1: Formation of resonance-stabilized enolate anion



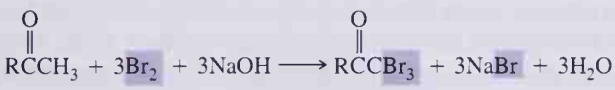
Resonance-stabilized enolate anion

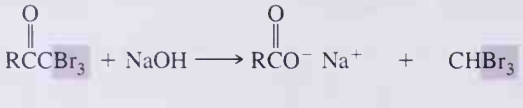
Step 2: Nucleophilic attack of the enolate anion on halogen



A major difference exists between acid-catalyzed and base-catalyzed halogenation. In principle, both can lead to polyhalogenation. In practice, the rate of acid-catalyzed introduction of a second halogen is considerably less than the rate of the first halogenation because introduction of an electronegative α-halogen atom destabilizes the enol. Thus, it is generally possible to stop acid-catalyzed halogenation at a single substitution. For base-catalyzed halogenation, each successive halogenation is more rapid than the first because introduction of an electronegative halogen atom on an α-carbon further increases the acidity of remaining α-hydrogens, and, thus, each successive α-hydrogen is removed more rapidly than the previous one. For this reason, base-catalyzed halogenation is generally not a useful synthetic reaction.

However, one circumstance in which base-catalyzed halogenation is useful is base-catalyzed halogenation of methyl ketones. In the presence of base, a methyl ketone reacts with three equivalents of halogen to form a 1,1,1-trihaloketone which then reacts with an additional mole of hydroxide ion to form a carboxylic salt and a trihalomethane. Reaction of the carboxylic salt with aqueous HCl or other strong acid gives the carboxylic acid.

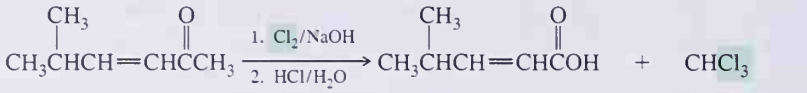




Tribromomethane
(Bromoform)

Common names for the trihalomethanes are chloroform, bromoform, and iodoform. For this reason, reaction of a methyl ketone with a halogen in base is called the **haloform reaction.**

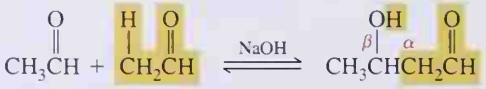
The haloform reaction is an indirect way to oxidize a methyl ketone to a carboxylic acid as illustrated by the oxidation of the following unsaturated methyl ketone to an unsaturated carboxylic acid.



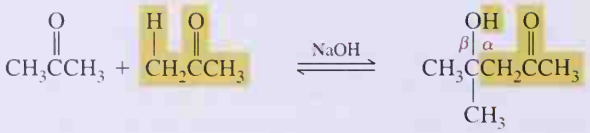
5-Methyl-3-hexen-2-one — 4-Methyl-2-pentenoic acid — Trichloromethane (Chloroform)

17.14 The Aldol Reaction

Unquestionably the most important reaction of enolate anions is nucleophilic addition to the carbonyl group of a molecule of the same or a different compound as illustrated by the following reactions. Although such reactions may be catalyzed by either acid or base, base catalysis is more common.



3-Hydroxybutanal
(a β-hydroxyaldehyde)

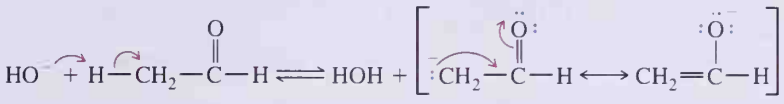


4-Hydroxy-4-methyl-2-pentanone
(a β-hydroxyketone)

The common name of the product derived from reaction of acetaldehyde in base is aldol, a name derived from the fact that it is both an aldehyde (ald-) and an alcohol (-ol). Aldol is also the generic name given to any product formed in this type of reaction. The characteristic structural feature of the product of an **aldol reaction** is the presence in it of a β-hydroxyaldehyde or a β-hydroxyketone.

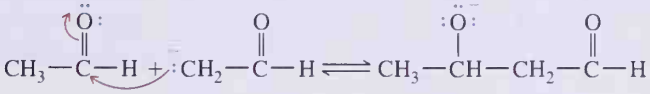
The key step for base-catalyzed aldol reactions is nucleophilic addition of the enolate anion from one carbonyl-containing molecule to the carbonyl group of another to form a tetrahedral carbonyl addition compound. This mechanism is illustrated by the aldol reaction between two molecules of acetaldehyde.

Step 1: Formation of a resonance-stabilized enolate anion



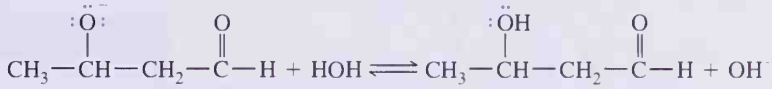
(Enolate anion)

Step 2: Nucleophilic addition of the enolate anion to a carbonyl carbon

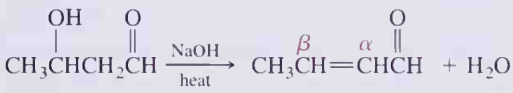


(An alkoxide ion)

Step 3: Reaction of the alkoxide ion with a proton donor to form the aldol product

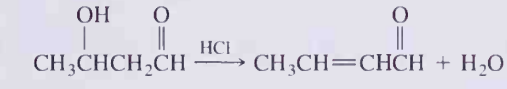


β-Hydroxyaldehydes and β-hydroxyketones are very easily dehydrated, and often the conditions necessary to bring about an aldol reaction are sufficient to cause dehydration. The major product from dehydration of an aldol reaction product is one in which the carbon-carbon double bond is conjugated with the carbonyl group, that is, the product is an α,β-unsaturated aldehyde or α,β-unsaturated ketone. Conjugation of unsaturation imparts added stability to molecules compared with unconjugated unsaturation (Section 7.2).



An α,β-unsaturated aldehyde

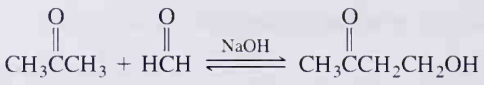
Alternatively, warming the aldol product in dilute mineral acid leads to dehydration.



3-Hydroxybutanal (Aldol) 2-Butenal (Crotonaldehyde)

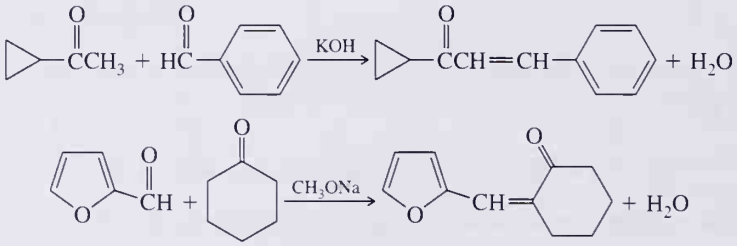
Equilibrium constants for aldol reactions are generally small, meaning that at equilibrium, often little aldol product is present. However, equilibrium constants for dehydration are generally large so that if reaction conditions are sufficiently vigorous to bring about dehydration, good yields of product can be obtained.

The ingredients in the key step of an aldol reaction are an enolate anion and an enolate anion acceptor. In self-reactions, both roles are played by one kind of molecule. **Mixed aldol reactions** are also possible, as for example the mixed aldol reaction between acetone and formaldehyde. Formaldehyde cannot provide an anion because it has no α-hydrogen, but it can function as a particularly good anion acceptor because its carbonyl group is unhindered. Acetone forms an anion, but its carbonyl group, bonded to two alkyl groups, is a poorer anion acceptor than that of formaldehyde. Consequently, the mixed aldol reaction between acetone and formaldehyde gives 4-hydroxy-2-butanone.



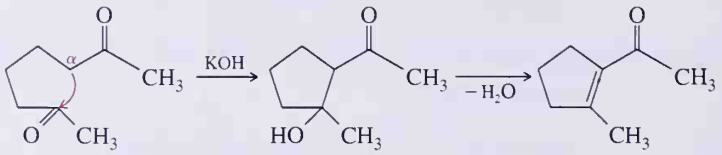
4-Hydroxy-2-butanone

In the case of mixed aldol reactions in which no appreciable difference in reactivity exists between the two carbonyl-containing compounds, mixtures of products result. Following are two examples of mixed aldol reactions in which one of the carbonyl-containing compounds is an aldehyde without α-hydrogens and the other carbonyl-containing compound is a ketone. Ketones with α-hydrogens provide good enolate anions, whereas aldehydes with no α-hydrogens provide good enolate anion acceptors.

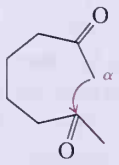


Furfural

When both the enolate anion and the carbonyl group to which it adds are in the same molecule, aldol reaction results in formation of a ring. This type of intramolecular aldol reaction is particularly useful for formation of five- and six-member rings. Intramolecular aldol reaction of 2,7-octanedione gives a five-member ring. Note that in this molecule, two enolate anions are possible: one of which leads to a seven-member ring, the other to a five-member ring. Formation of five-member and six-member rings is favored over formation of four-member and seven-member rings.

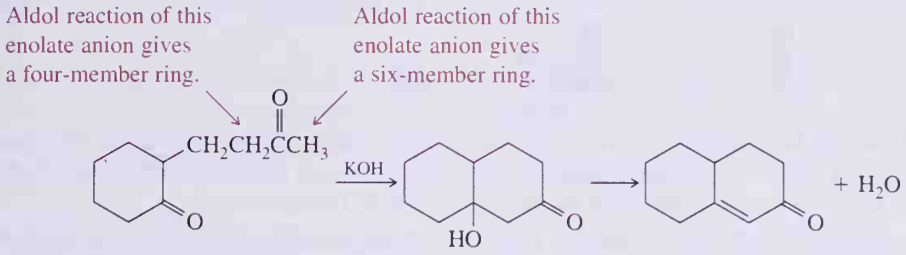


2,7-Octanedione
(aldol reaction of this enolate anion gives a five-member ring)



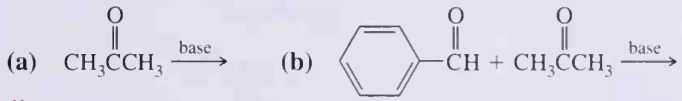
2,7-Octanedione
(aldol reaction of this enolate anion gives a seven-member ring)

Following is another example in which either a four-member ring or a six-member ring can be formed, depending on which enolate anion reacts with the carbonyl group of the substituted cyclohexanone. Because of the greater stability of six-member rings relative to four-member rings, it is the six-member ring that is formed in this intramolecular aldol reaction.

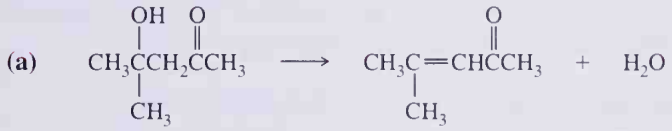


EXAMPLE 17.11

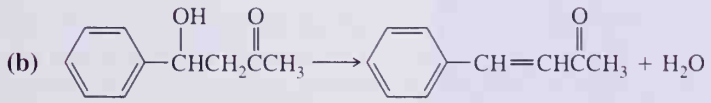
Name and draw structural formulas for the products of the following aldol reactions and for the unsaturated compounds produced by dehydration.



Solution



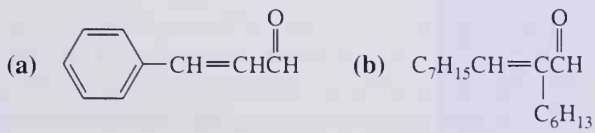
4-Hydroxy-4-methyl-2-pentanone — 4-Methyl-3-penten-2-one



4-Hydroxy-4-phenyl-2-butanone — 4-Phenyl-3-buten-2-one

PROBLEM 17.11

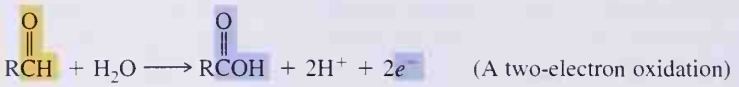
Draw structural formulas for the two carbonyl-containing compounds which, on aldol reaction followed by dehydration, give the following:



17.15 Oxidation

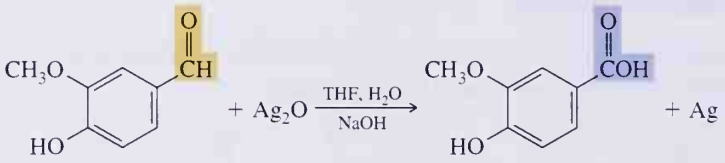
A. Oxidation of Aldehydes

Oxidation of an aldehyde to a carboxylic acid is a two-electron oxidation as shown by the following balanced half-reaction:



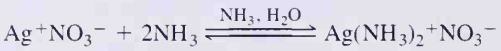
Aldehydes are oxidized to carboxylic acids by a variety of common oxidizing agents, including nitric acid, aqueous potassium permanganate, and aqueous chromic acid. In fact, aldehydes have one of the most easily oxidized of all functional groups.

Aldehydes are also oxidized to carboxylic acids by Ag(I) ion. One laboratory procedure is to shake a solution of the aldehyde dissolved in aqueous ethanol or in aqueous tetrahydrofuran (THF) with a slurry of Ag_2O.



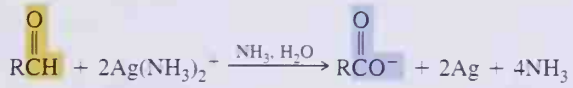
Vanillin Vanillic acid

Tollens' reagent, another form of Ag(I), is prepared by dissolving silver nitrate in water, adding sodium hydroxide to precipitate silver(I) as Ag_2O, and then adding aqueous ammonia to redissolve silver(I) as the silver-ammonia complex ion.



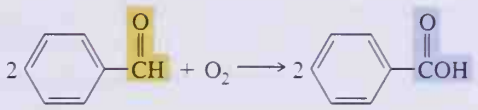
A silver mirror has been deposited in the inside of this flask. *(Charles D. Winters)*

When Tollens' reagent is added to an aldehyde, the aldehyde is oxidized to a carboxylic anion and silver(I) is reduced to metallic silver. If this reaction is done properly, silver precipitates as a smooth, mirror-like deposit, hence the name **silver-mirror test.** Silver(I) is rarely used at the present time for the oxidation of aldehydes because of the expense of silver and because other, more convenient methods exist for this oxidation. This reaction, however, is still used for silvering mirrors.

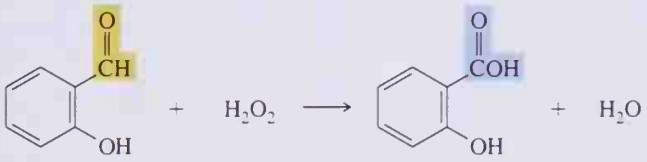


Precipitates as a silver mirror

Aldehydes are oxidized to carboxylic acids by molecular oxygen and hydrogen peroxide.



Benzaldehyde Benzoic acid

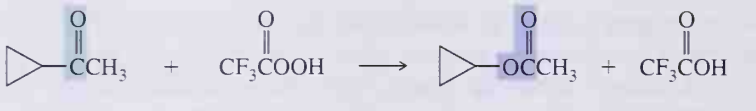


2-Hydroxybenzaldehyde (Salicylaldehyde) 2-Hydroxybenzoic acid (Salicylic acid)

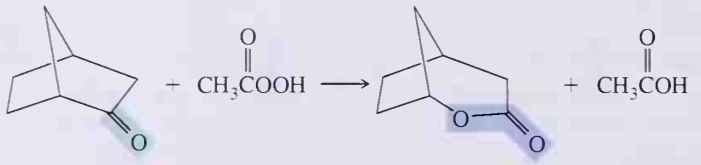
Molecular oxygen is one of the least expensive and most readily available oxidizing agent, and on an industrial scale air oxidation of organic molecules, including aldehydes, is very common. Air oxidation of aldehydes can also be a problem. Aldehydes that are liquid at room temperature are so sensitive to oxidation by molecular oxygen that they must be protected from contact with air during storage. Often this is done by sealing the aldehyde in a container under an atmosphere of nitrogen.

B. Oxidation of Ketones

Ketones, in contrast to aldehydes, are oxidized only under rather special conditions. For example, they are not normally oxidized by Mn(VII) or Cr(VI). In fact these reagents are used routinely to oxidize secondary alcohols to ketones in good yield. Ketones are oxidized to esters by peroxyacids. The net effect of this oxidation is to insert an oxygen atom between the carbonyl carbon and an α-carbon of the ketone as illustrated for the following compounds. Reagents most commonly used for this purpose are peroxybenzoic acid, peroxyacetic acid, and trifluoroperoxyacetic acid. Oxidation of ketones by peroxyacids is often called **Baeyer-Villiger oxidation** after the chemists (J. F. W. Baeyer and V. Villiger) who developed this reaction as a useful synthetic technique.

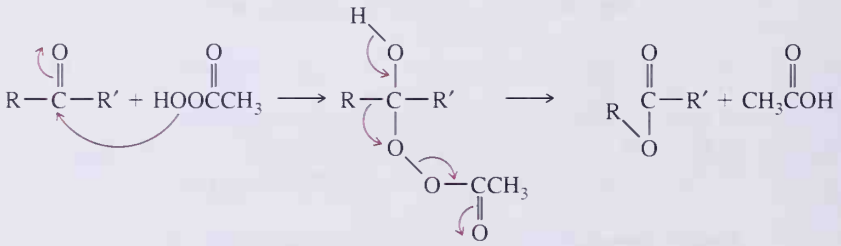


Trifluoroperoxyacetic acid | Trifluoroacetic acid



Peroxyacetic acid | Acetic acid

The mechanism of Baeyer-Villiger oxidation is thought to involve addition of the peroxyacid to the ketone carbonyl to form a tetrahedral carbonyl addition compound. Decomposition by migration of a group attached to the carbonyl carbon completes the reaction. This sequence of steps is illustrated by reaction of an unsymmetrical ketone with peroxyacetic acid.

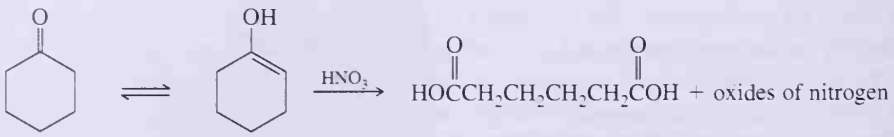


A tetrahedral carbonyl addition intermediate

With symmetrical ketones, no ambiguity arises about which group migrates from carbon to oxygen during Baeyer-Villiger oxidation. With unsymmetrical ketones, the following migratory aptitudes have been observed.

$$3^\circ \text{ alkyl} > 2^\circ \text{ alkyl} > \text{benzylic} = \text{aryl} > 1^\circ \text{ alkyl} > \text{methyl}$$

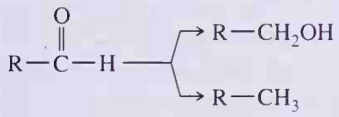
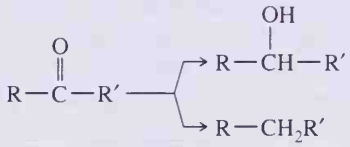
Ketones are also oxidized, via their enol form, by potassium dichromate and potassium permanganate at higher temperatures and higher concentrations of acid or base. The carbon-carbon double bond of the enol is cleaved to form two carboxyl groups. An important industrial application of this reaction is oxidation of cyclohexanone to hexanedioic acid (adipic acid), one of the two monomers required for the synthesis of the polymer nylon 66 (Section 20.12). In the industrial process, the oxidizing agent is nitric acid.



Cyclohexanone (keto form) | Cyclohexanone (enol form) | Hexanedioic acid (Adipic acid)

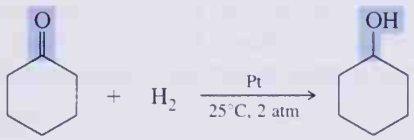
17.16 Reduction

Aldehydes are reduced to primary alcohols and ketones to secondary alcohols. In addition, both aldehyde and ketone carbonyl groups can be reduced to $-CH_2-$ groups.

Aldehydes	Can be Reduced to	Ketones	Can be Reduced to
			

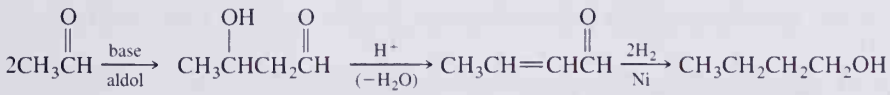
A. Catalytic Reduction

The carbonyl group of an aldehyde or ketone is reduced to an alcohol group by hydrogen in the presence of a transition metal catalyst, most commonly finely divided palladium, platinum, nickel, ruthenium, or a copper-chromium complex. Reductions are generally carried out at temperatures from 25 to 100°C and at pressures of hydrogen from 1 to 5 atm. Under suitable conditions, cyclohexanone is reduced to cyclohexanol.



Cyclohexanone Cyclohexanol

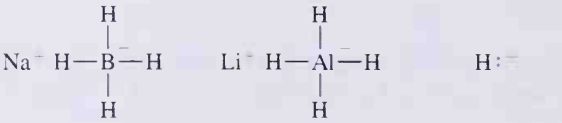
Catalytic reduction of aldehydes and ketones is simple to carry out, yields are generally very high, and isolation of the final product is very easy. A disadvantage is that some other functional groups are also reduced under these conditions, for example, carbon-carbon double and triple bonds, as can be seen in the commercial synthesis of 1-butanol from acetaldehyde. This conversion involves three stages: (1) base-catalyzed aldol reaction, (2) dehydration, and (3) catalytic reduction of both double bonds.



3-Hydroxybutanal 2-Butenal 1-Butanol

B. Metal Hydride Reductions

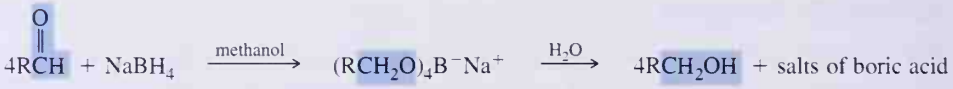
By far the most common laboratory reagents for reduction of the carbonyl group of an aldehyde or ketone to an alcohol group are sodium borohydride, lithium aluminum hydride (LAH), and their derivatives. These compounds behave as sources of hydride ion, a very strong nucleophile.



Sodium borohydride | Lithium aluminum hydride (LAH) | Hydride ion

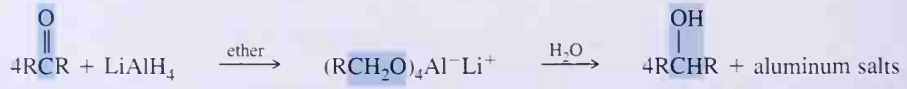
Lithium aluminum hydride is a very powerful reducing agent; it reduces not only the carbonyl groups of aldehydes and ketones rapidly but also those of carboxylic acids (Section 19.8A) and their functional derivatives (Section 20.10). Sodium borohydride is a much more selective reagent, reducing only aldehydes and ketones rapidly.

Sodium borohydride is soluble in water and in low-molecular-weight alcohols. Reductions using this reagent are most commonly carried out in aqueous methanol, in methanol, or in ethanol. The initial product of reduction is a tetraalkoxyborate, which, on treatment with water, is converted to an alcohol and boric acid salts. One mole of sodium borohydride reduces four moles of aldehyde or ketone.



(A sodium tetraalkoxyborate)

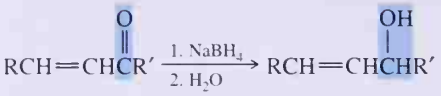
Unlike sodium borohydride, LAH reacts violently with water, methanol, and other protic solvents to liberate hydrogen gas and form metal hydroxides. Therefore, reductions of aldehydes and ketones using this reagent must be carried out in aprotic solvents, most commonly diethyl ether or tetrahydrofuran. The stoichiometry for LAH reductions is the same as that for sodium borohydride reductions: 1 mol of LAH per 4 mol of aldehyde or ketone.



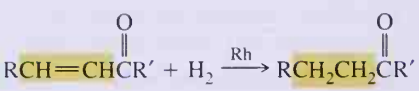
(A lithium tetraalkoxyaluminate)

Both LAH and sodium borohydride are selective in that neither reduces isolated carbon-carbon double bonds. For molecules in which the carbon-carbon double bond is conjugated with the carbonyl group, however, it is sometimes observed that both functional groups are reduced. Results depend very much on the particular molecule and reactions conditions. Reduction of both functional groups is more common with $LiAlH_4$ than with $NaBH_4$.

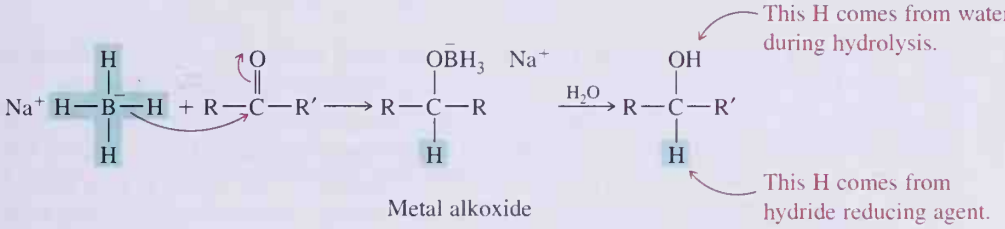
Selective reduction of the carbonyl group:



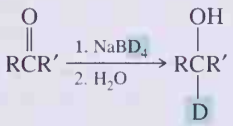
Selective reduction of the carbon-carbon double bond:



The key step in the metal hydride reduction of an aldehyde or ketone is transfer of a hydride ion from the reducing agent to the carbonyl carbon to form a tetrahedral carbonyl addition compound. Hydride transfer from boron or aluminum is repeated three more times until all reducing equivalents have been used. In reduction of an aldehyde or ketone to an alcohol, only the hydrogen atom attached to carbon comes from the hydride reducing agent; the hydrogen atom attached to oxygen comes from hydrolysis of the metal alkoxide salt.

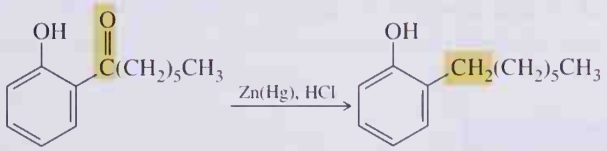


By using deuterated hydride reducing agents, it is possible to prepare primary and secondary alcohols containing an atom of deuterium on the carbon bearing the —OH group.



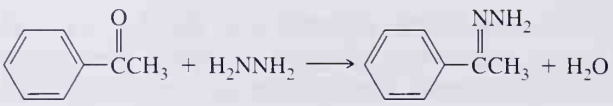
C. Reduction of a Carbonyl Group to a Methylene Group

Several methods are available for reducing the carbonyl group of an aldehyde or ketone to a methylene group (—CH_2—). One of the first discovered involves refluxing the aldehyde or ketone with amalgamated zinc (zinc with a surface layer of mercury) in concentrated HCl. This reaction is known as the **Clemmensen reduction** after the German chemist, E. Clemmensen, who developed it in 1912.

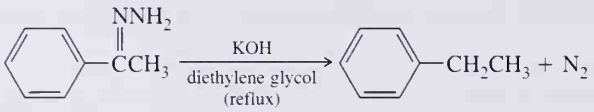


Because the Clemmensen reduction requires the use of concentrated HCl, it cannot be used to reduce a carbonyl group in a molecule that also contains acid-sensitive groups, as, for example, a tertiary alcohol that might undergo dehydration or an acetal that is hydrolyzed and the resulting carbonyl group also reduced. The mechanism of Clemmensen reduction is not well understood.

The **Wolff-Kishner reduction,** discovered independently by L. Wolff and N. Kishner and reported within months of Clemmensen's discovery, is an alternative method for reduction of a carbonyl group to a methylene group. In this reduction, the aldehyde or ketone is treated with hydrazine to form a hydrazone which is then heated with concentrated sodium hydroxide in a high-boiling solvent such as diethylene glycol (bp 245°C).



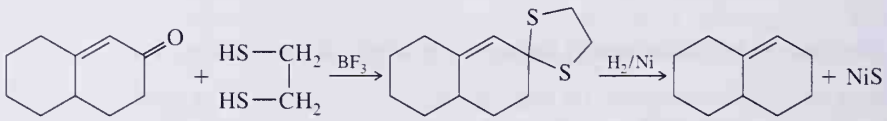
Hydrazine A hydrazone



More recently it is has been found possible to bring about the same reaction in dimethyl sulfoxide (DMSO) with potassium *tert*-butoxide and hydrazine at room temperature.

Still another means of reducing the carbonyl group of an aldehyde or ketone to a methylene group involves what is called **Raney nickel desulfurization.** In this process, the aldehyde or ketone is first converted to a thioacetal (Section 17.10) which is then treated with Raney nickel. Raney nickel itself is prepared by treating a nickel-aluminum alloy with aqueous NaOH. Aluminum is oxidized to Al(III) and dissolves; water is reduced to hydrogen, H_2. Through this process, nickel is left as a finely divided suspension impregnated with hydrogen gas. Thus, Raney nickel is a means of catalytic hydrogenation.

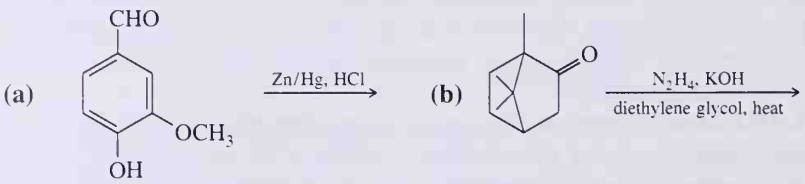
When a thioacetal is treated with Raney nickel, each carbon-sulfur bond is cleaved, and sulfur is replaced by hydrogen. Atoms of sulfur from the thioacetal are converted to nickel sulfide, NiS. Note that under these conditions, a carbon-carbon double bond is not affected. Raney nickel desulfurization is an example of **hydrogenolysis,** cleavage of a covalent bond (in this case, a carbon-sulfur bond) by H_2.



Each of the reductions presented in this section has its special conditions, advantages, and disadvantages. The Clemmensen reduction cannot be used in the presence of groups sensitive to concentrated acid, the Wolff-Kishner reduction cannot be used in the presence of groups sensitive to concentrated base, and Raney nickel desulfurization cannot be used in the presence of groups sensitive to catalytic hydrogenation. However, the carbonyl group of almost any aldehyde or ketone can be reduced to a methylene group by one of these methods.

EXAMPLE 17.12

Complete the following reactions:

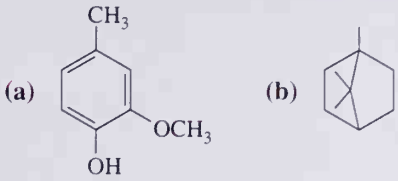


Vanillin
(from vanilla beans)

Camphor

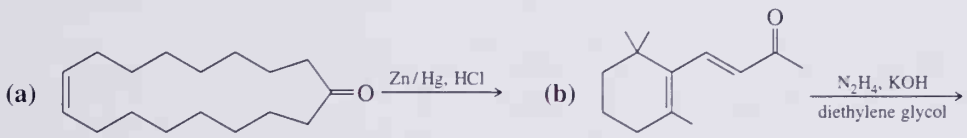
Solution

(a) The reaction is an example of Clemmensen reduction.
(b) This reaction is an example of a Wolff-Kishner reduction.



PROBLEM 17.12

Complete the following carbonyl reduction reactions:



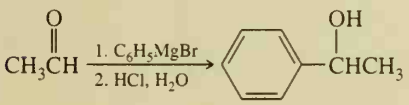
Civetone
(from the civet cat; used as a fixative in perfumery)

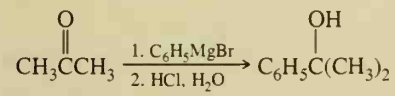
δ-Ionone
(odor of violets; a key intermediate in the commercial synthesis of vitamin A)

SUMMARY OF KEY REACTIONS

1. Reaction with Grignard Reagents (Section 17.7B)

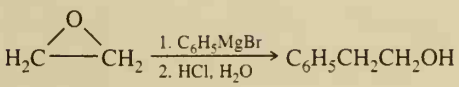
Treatment of formaldehyde with a Grignard reagent followed by hydrolysis gives a primary alcohol. Similar treatment of any other aldehyde gives a secondary alcohol. Treatment of a ketone gives a tertiary alcohol.





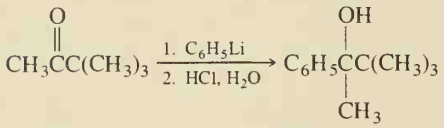
2. Reaction of a Grignard Reagent with an Epoxide (Section 17.7B)

Treatment of an epoxide with a Grignard reagent followed by hydrolysis gives an alcohol.



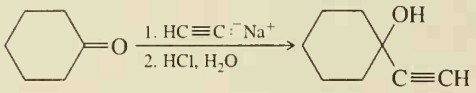
3. Reaction with Organolithium Reagents (Section 17.7C)

Reactions of aldehydes and ketones with organolithium reagents are similar to those with Grignard reagents. Organolithium compounds are more polar, more reactive, and generally give higher yields.



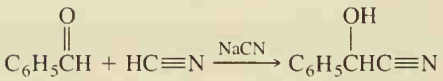
4. Reaction with Alkali Metal Salts of Terminal Alkynes (Section 17.7D)

Treatment of an aldehyde or ketone with an alkali metal salt of a terminal alkyne followed by hydrolysis gives an α-hydroxyalkyne.



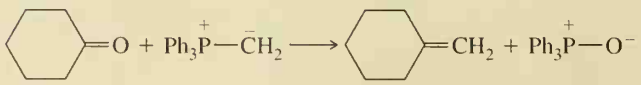
5. Reaction with HCN to Form Cyanohydrins (Section 17.7E)

For aldehydes and most sterically unhindered aliphatic ketones, equilibrium favors formation of the cyanohydrin. For aryl ketones, equilibrium favors starting materials, and little cyanohydrin is obtained.



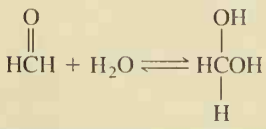
6. The Wittig Reaction (Section 17.8)

Treatment of an aldehyde or ketone with a triphenylphosphonium ylide gives an oxaphosphetane intermediate, which fragments to give triphenylphosphine oxide and an alkene.



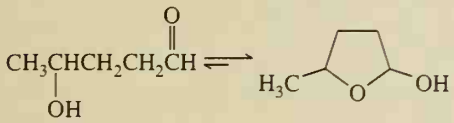
7. Hydration (Section 17.9A)

The degree of hydration is greater for aldehydes than for ketones.



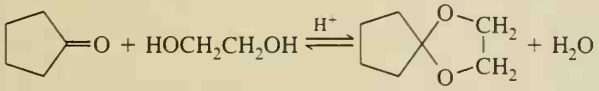
8. Addition of Alcohols to Form Hemiacetals (Section 17.9B)

Hemiacetals are only minor components of an equilibrium mixture of aldehyde or ketone and alcohol, except where the —OH and C=O are parts of the same molecule and a five- or six-member ring can form.



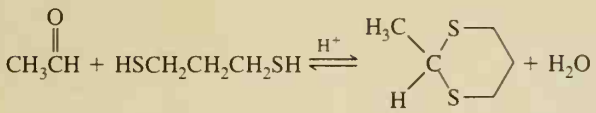
9. Addition of Alcohols to Form Acetals (Section 17.9B)

Formation of acetals is catalyzed by acid. Acetals are stable to water and aqueous base but are hydrolyzed in aqueous acid. Acetals are valuable as carbonyl-protecting groups.



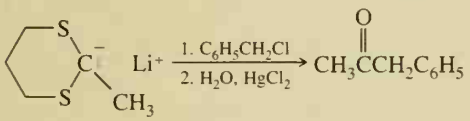
10. Addition of Sulfur Nucleophiles: Formation of 1,3-Dithianes (Section 17.10)

The most commonly used thiol for preparing thioacetals is 1,3-propanedithiol. The product is called a 1,3-dithiane.



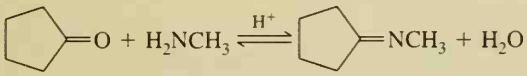
11. Alkylation of Aldehyde 1,3-Dithiane Anions (Section 17.10)

Treatment of an aldehyde 1,3-dithiane (pK_a 31) with butyllithium gives an anion. This anion can enter into substitution reactions with primary alkyl halides and addition reactions with the carbonyl group of aldehydes and ketones.



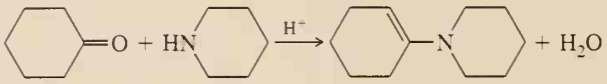
12. Addition of Ammonia and Its Derivatives: Formation of Imines (Section 17.11A)

Addition of ammonia or a primary amine to the carbonyl group an aldehyde or ketone forms a tetrahedral carbonyl addition compound. Loss of water from this intermediate gives an imine.



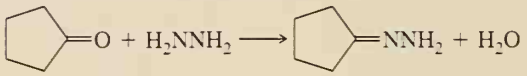
13. Addition of Secondary Amines: Formation of Enamines (Section 17.11A)

Addition of a secondary amine to the carbonyl group of an aldehyde or ketone forms a tetrahedral carbonyl addition intermediate. Acid-catalyzed dehydration of this intermediate gives an enamine.



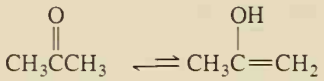
14. Addition of Hydrazine and Its Derivatives (Section 17.11B)

Treatment of an aldehyde or ketone with hydrazine gives a hydrazone. Derivatives of hydrazine react similarly.



15. Keto-Enol Tautomerism (Section 17.12A)

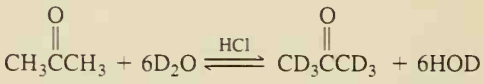
The keto form predominates at equilibrium, except for those aldehydes and ketones in which the enol is stabilized by resonance or hydrogen bonding.



(approx. 99%)

16. Deuterium Exchange at the α-Carbon (Section 17.13B)

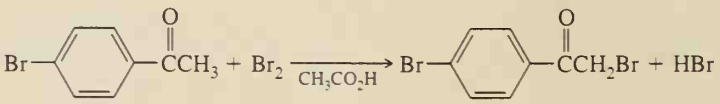
Acid or base-catalyzed deuterium exchange at an α-carbon involves formation of an enol or enolate anion intermediate.



Acetone Acetone-d_6

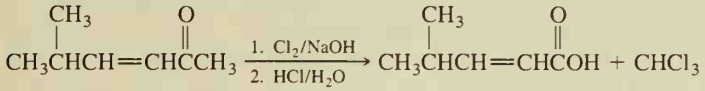
17. Halogenation at the α-Carbon (Section 17.13B)

The rate-determining step in halogenation at an α-carbon is acid- or base-catalyzed formation of an enol or enolate anion intermediate.



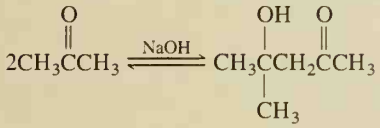
18. The Haloform Reaction (Section 17.13B)

The haloform reaction oxidizes a methyl ketone to a carboxylic acid.



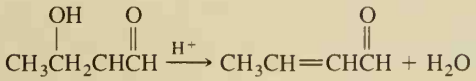
19. The Aldol Reaction (Section 17.14)

The aldol reaction involves nucleophilic attack by an enolate anion from one aldehyde or ketone on the carbonyl group of another aldehyde or ketone. The product of an aldol reaction is a β-hydroxyaldehyde or a β-hydroxyketone.



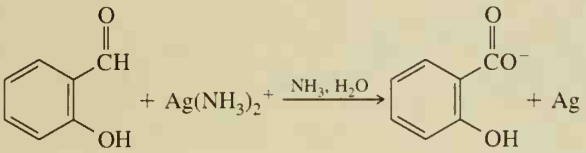
20. Dehydration of the Product of an Aldol Reaction (Section 17.14)

Dehydration of the β-hydroxyaldehyde or ketone from an aldol reaction occurs very readily under acidic or basic conditions and gives an α,β-unsaturated aldehyde or ketone.



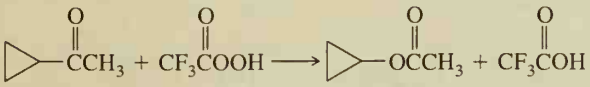
21. Oxidation of an Aldehyde to a Carboxylic Acid (Section 17.15A)

The aldehyde group is among the most easily oxidized functional groups. Oxidizing agents include $KMnO_4$, $K_2Cr_2O_7$, Tollens' reagent, H_2O_2, and O_2.



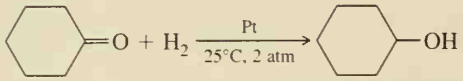
22. Oxidation of a Ketone to an Ester: The Baeyer-Villager Oxidation (Section 17.15B)

Oxidation of a ketone by a peroxyacid involves nucleophilic addition to the carbonyl group of the ketone to form a tetrahedral carbonyl addition intermediate followed by molecular rearrangement to give an ester.



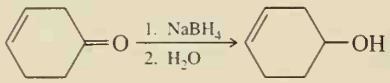
23. Catalytic Reduction (Section 17.16A)

Catalytic reduction of the carbonyl group of an aldehyde or ketone to an alcohol group is simple to carry out, and yields are high. A disadvantage of this method is that some other functional groups, including carbon-carbon double and triple bonds, may also be reduced. Selectivity is often possible with proper choice of transition metal catalyst and reaction conditions.



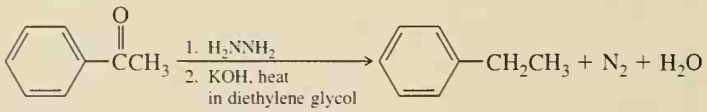
24. Metal Hydride Reduction (Section 17.16B)

Both $LiAlH_4$ and $NaBH_4$ are selective in that neither reduces isolated carbon-carbon double or triple bonds.



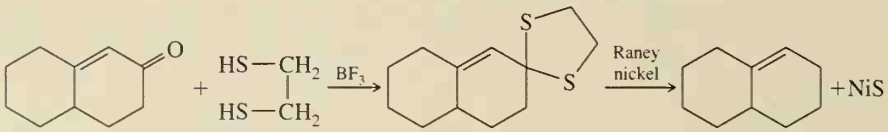
25. Wolff-Kishner Reduction of an Aldehyde or Ketone (Section 17.16C)

Formation of a hydrazone followed by treatment with base, commonly KOH in diethylene glycol or potassium *tert*-butoxide in dimethyl sulfoxide, reduces the carbonyl group of an aldehyde or ketone to a methylene group.



26. Raney-Nickel Reduction of a Thioacetal (Section 17.16C)

Formation of a thioacetal followed by Raney nickel desulfurization reduces the carbonyl group of an aldehyde or ketone to a methylene group.



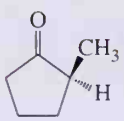
ADDITIONAL PROBLEMS

Structure and Nomenclature

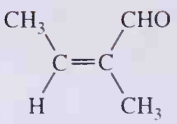
17.13 Name the following compounds:

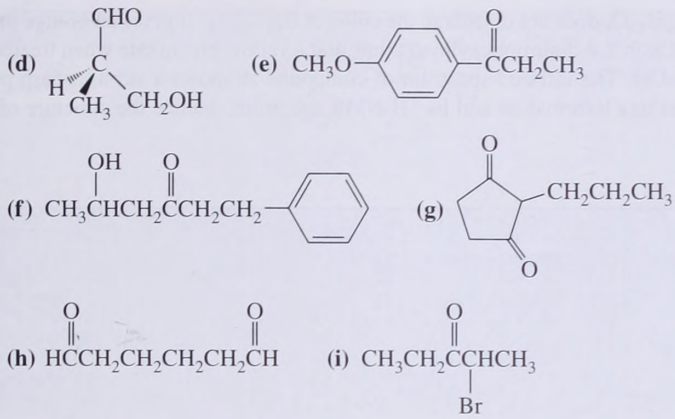
(a) $(CH_3CH_2CH_2)_2C{=}O$

(b)



(c)

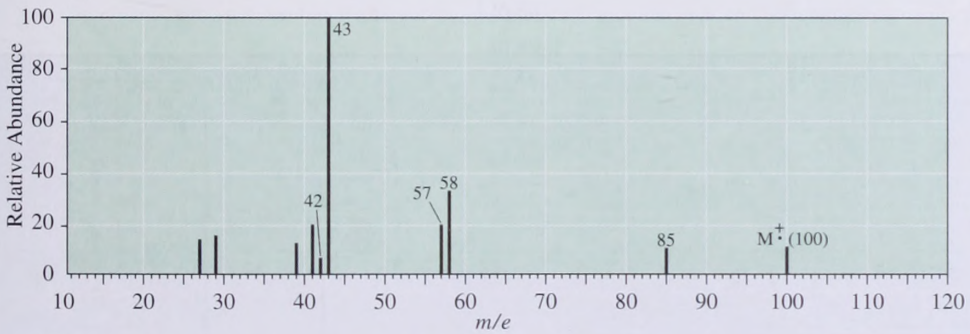




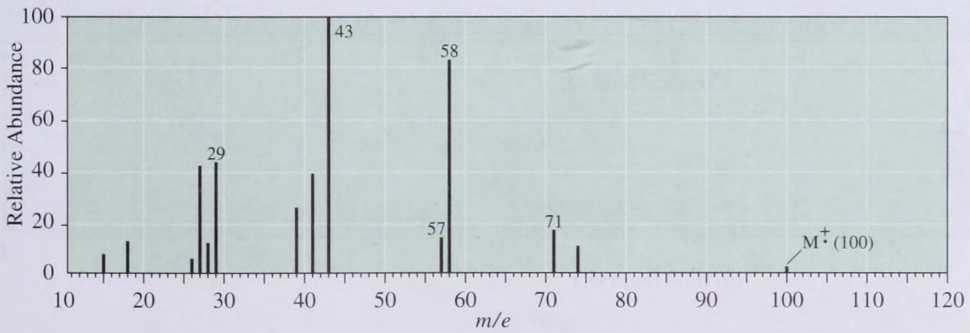
Spectroscopy

17.14 2-Methylpentanal and 4-methyl-2-pentanone are constitutional isomers of molecular formula $C_6H_{12}O$. Following are two mass spectra. Which is the mass spectrum of 2-methylpentanal, and which is the mass spectrum of 4-methyl-2-pentanone? Assign all labeled peaks and explain your reasoning.

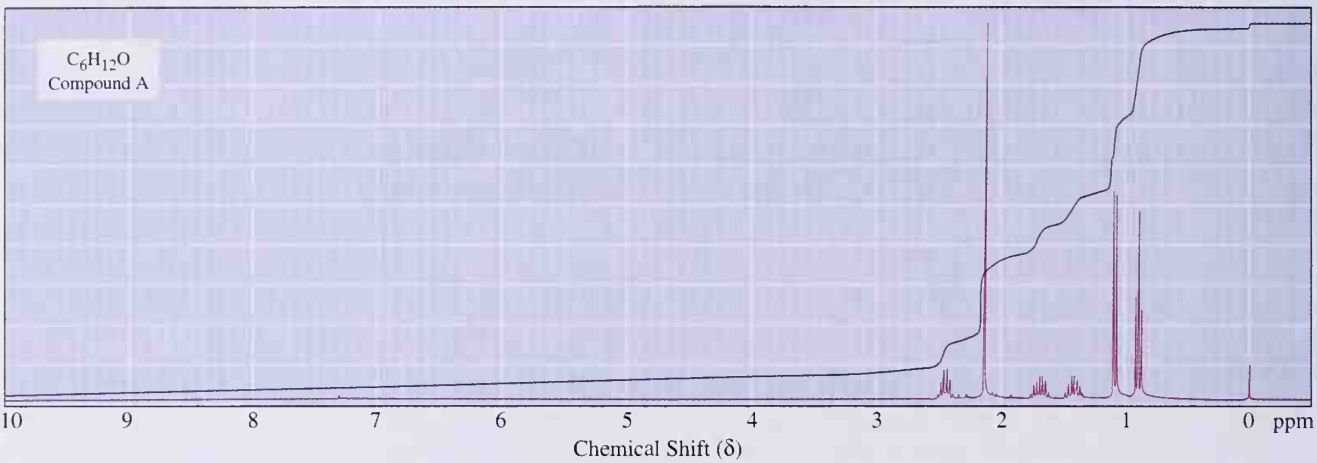
(a)



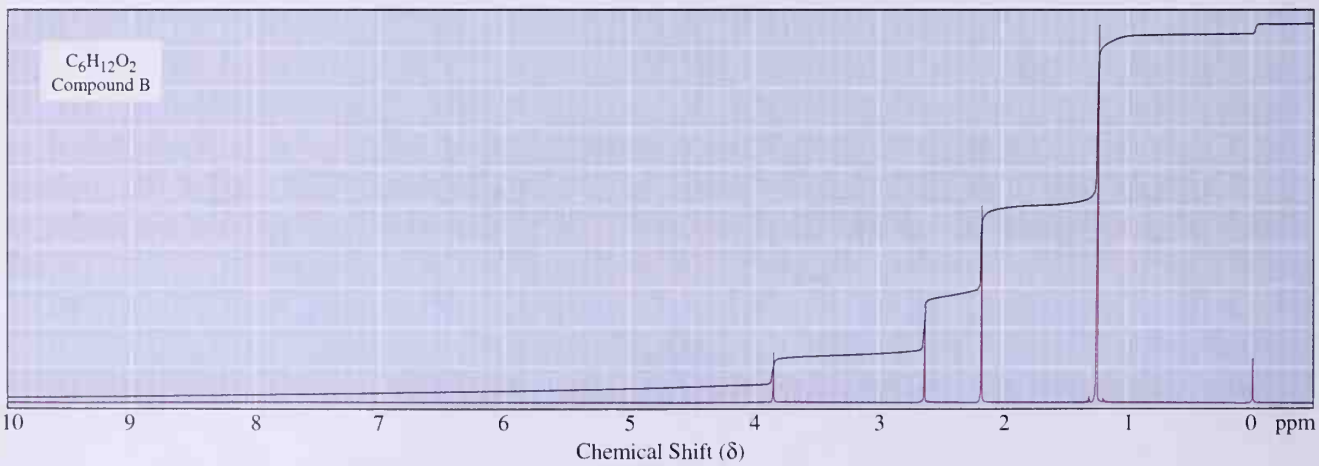
(b)

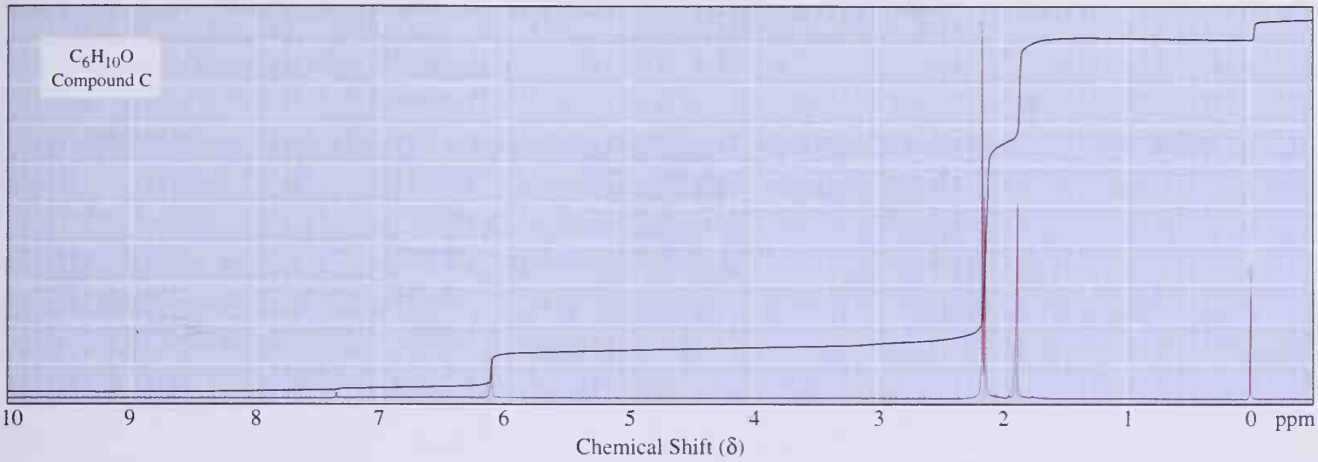


17.15 Compound A, $C_6H_{12}O$, does not discharge the color of Br_2/CCl_4. It gives an orange precipitate when treated with 2,4-dinitrophenylhydrazine, and a yellow precipitate when treated with I_2 in aqueous NaOH. The infrared spectrum of compound A shows a strong, sharp peak at 1724 cm^{-1}. From this information and its ^1H-NMR spectrum, deduce the structure of compound A.



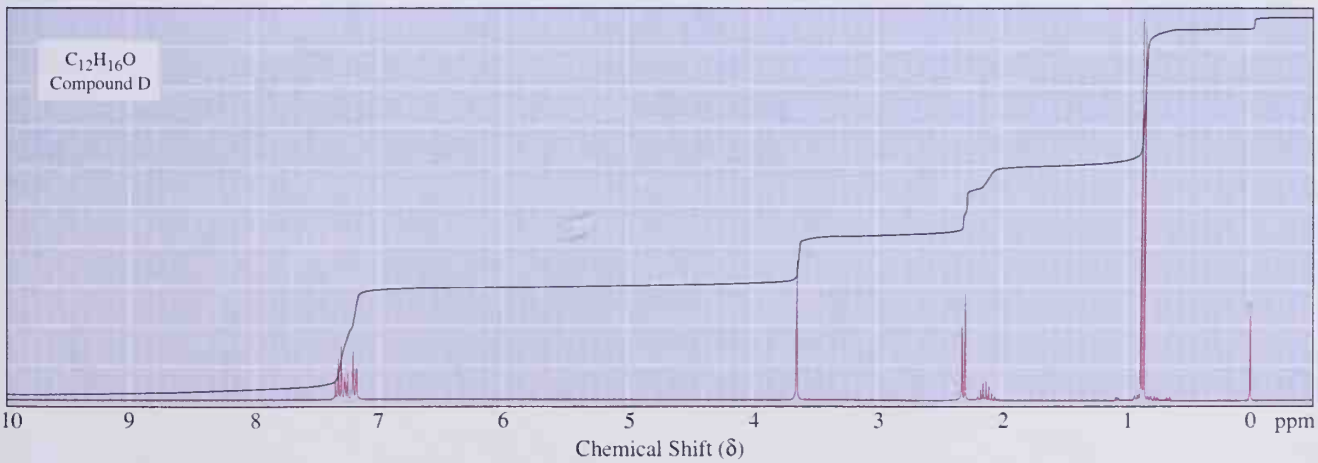
17.16 Following are ^1H-NMR spectra for compounds B, $C_6H_{12}O_2$, and C, $C_6H_{10}O$. On warming in dilute acid, compound B is converted to compound C. Deduce the structural formulas for compounds C and D.





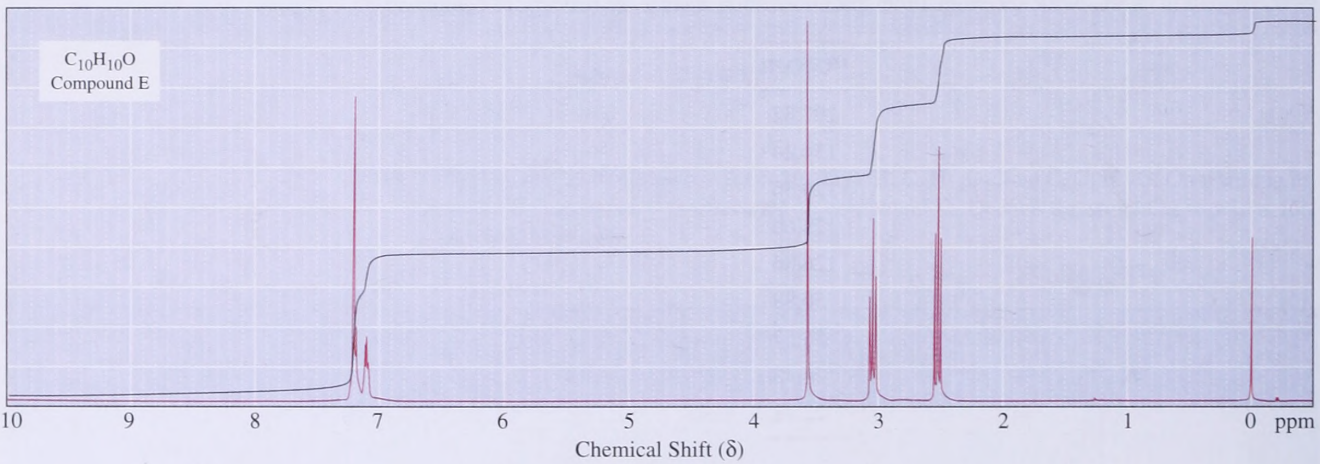
17.17 Following is the ^{1}H-NMR-spectrum of compound D, $C_{12}H_{16}O$. Also given are positions of signals in its ^{13}C-NMR spectrum. From this information, deduce the structure of compound D.

^{13}C-NMR
207.82
134.24
129.36
128.60
126.86
50.88
50.57
24.43
22.48

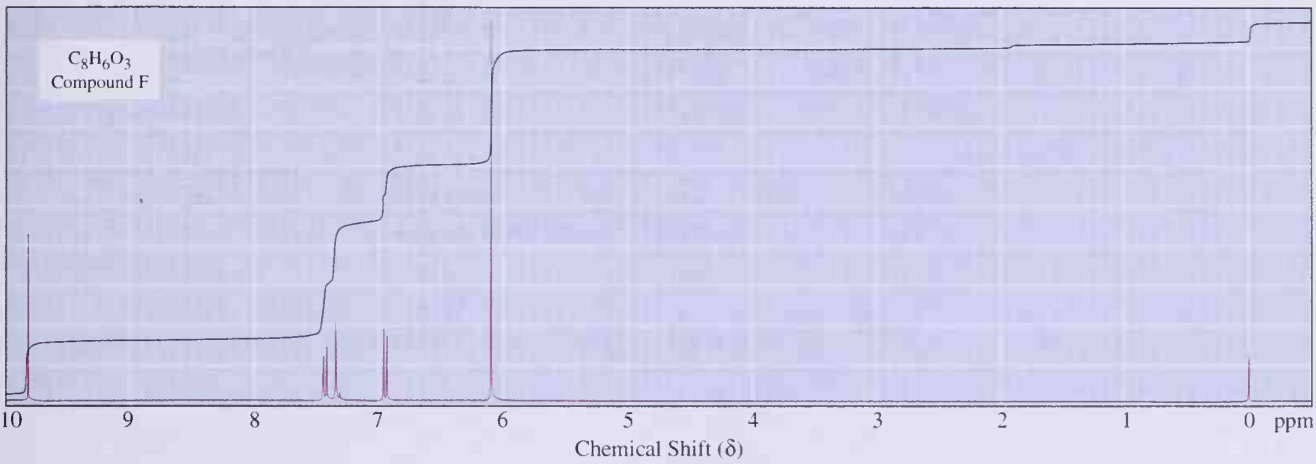


17.18 Following is the ^{1}H-NMR-spectrum of compound E, $C_{10}H_{10}O$. Also given are positions of signals in its ^{13}C-NMR spectrum. From this information, deduce the structure of compound E.

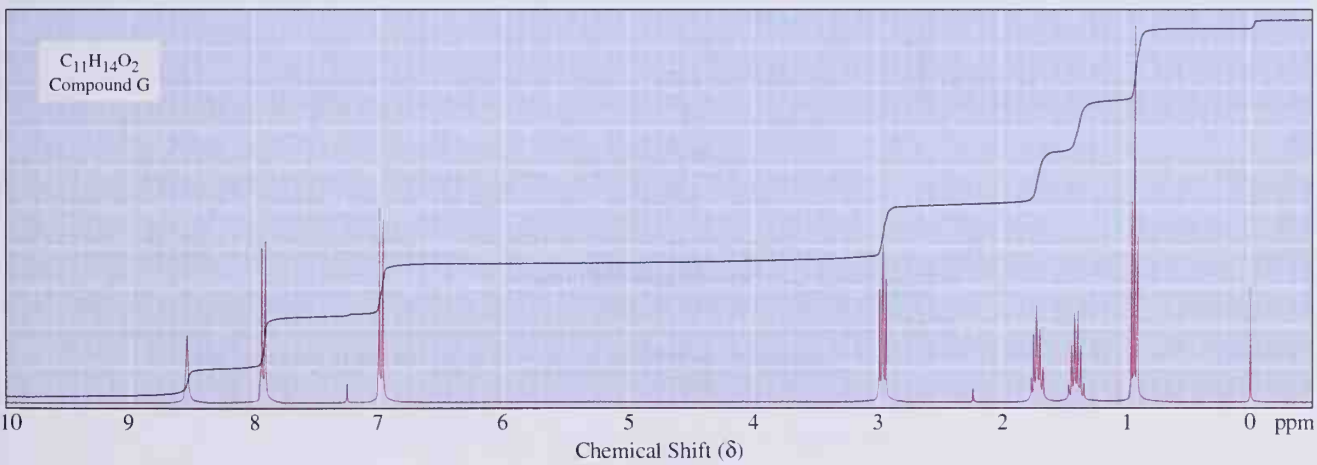
^{13}C-NMR
210.19
136.64
133.25
128.14
127.52
126.82
126.75
45.02
38.11
28.34



17.19 Compound F, $C_8H_6O_3$, gives a precipitate when treated with hydroxylamine in aqueous ethanol, and a silver mirror when treated with Tollens' solution. Following is its ^{1}H-NMR spectrum. Deduce the structure of compound F.

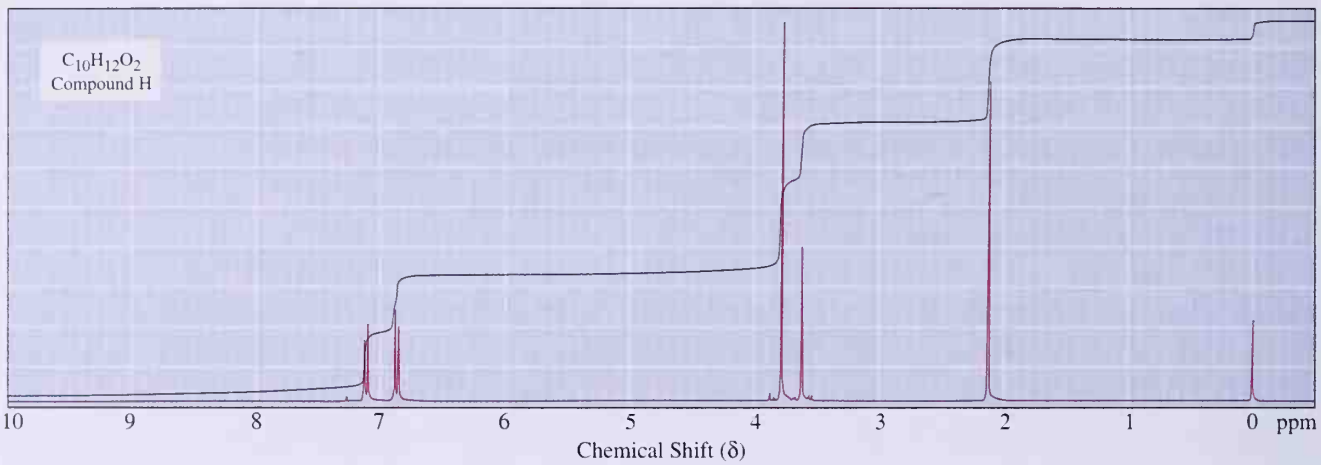


17.20 Compound G, $C_{11}H_{14}O_2$, is insoluble in water, aqueous acid, and aqueous $NaHCO_3$ but dissolves readily in 10% Na_2CO_3 and 10% NaOH. When these alkaline solutions are acidified with 10% HCl, compound G is recovered unchanged. Given this information and the ^{1}H-NMR spectrum, deduce the structure of compound G.



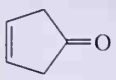
17.21 Following is the ^{1}H-NMR spectrum of compound H, $C_{10}H_{12}O_2$, and signals in its ^{13}C-NMR spectrum. Compound H is insoluble in water, 10% NaOH, and 10% HCl. Deduce the structural formula of compound H.

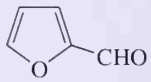
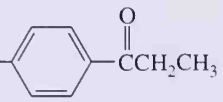
^{13}C-NMR
206.51
158.67
130.33
126.31
114.17
55.21
50.07
29.03



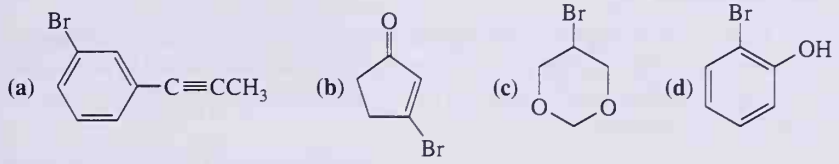
Addition of Carbon Nucleophiles

17.22 Draw structural formulas for the product formed by treatment of the following compounds with propylmagnesium bromide followed by hydrolysis in aqueous acid.

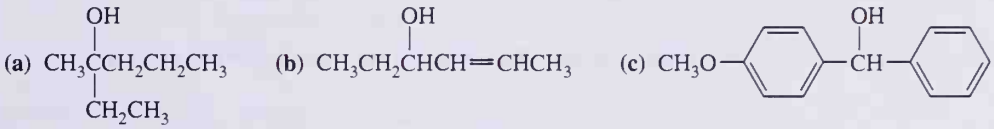
(a) CH_2O (b) $H_2C-CHCH_3$ (O) (c) $CH_3CH_2\overset{O}{\overset{\|}{C}}CH_2CH_3$ (d) 

(e)  (f) CH_3O–  –$\overset{O}{\overset{\|}{C}}CH_2CH_3$ (g) $CH_3CH_2OCH_2CH_2\overset{O}{\overset{\|}{C}}H$

17.23 Organic halides that possess a functional group that reacts with a Grignard reagent cannot themselves form a Grignard reagent. Indicate which of the following bromides needs to have its other functional groups protected in order to generate RMgBr.

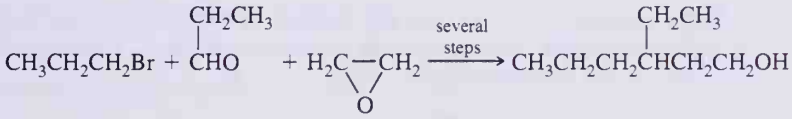


17.24 Suggest a synthesis for the following alcohols starting from an aldehyde, ketone, or epoxide and an appropriate Grignard reagent. In parentheses below each target molecule is shown the number of combinations of Grignard reagent and aldehyde, ketone, or epoxide that might be used.

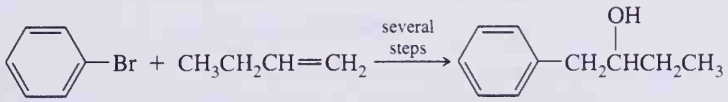


(5 combinations) (3 combinations) (2 combinations)

17.25 Show how to synthesize the following alcohol using 1-bromopropane, propanal, and ethylene oxide as the only sources of carbon atoms. It can be done using each given compound only once. (*Hint:* Do one Grignard reaction to form an alcohol, convert the alcohol to an alkyl halide, and then do a second Grignard reaction.)

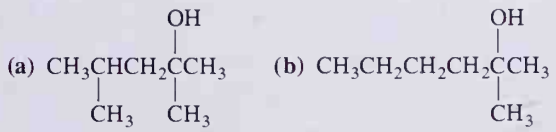


17.26 1-Phenyl-2-butanol is used in perfumery. Show how to synthesize this alcohol from bromobenzene, 1-butene, and any necessary inorganic reagents.



Bromobenzene 1-Butene 1-Phenyl-2-butanol

17.27 Show how to synthesize the following isomeric alcohols by treatment of acetone with a Grignard reagent.

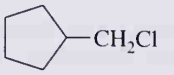
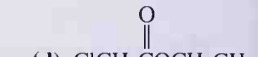


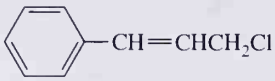
17.28 With organolithium and organomagnesium compounds, approach to the carbon atom from the less hindered direction is generally preferred. Assuming this is the case, predict the stereochemistry of the major product formed by reaction of methylmagnesium bromide with 4-*tert*-butylcyclohexanone.

Wittig Reaction

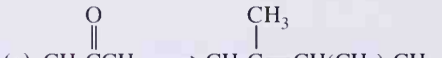
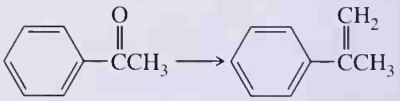
17.29 Why is triphenylphosphine used in the Wittig reaction instead of a trialkylphosphine, such as triethylphosphine?

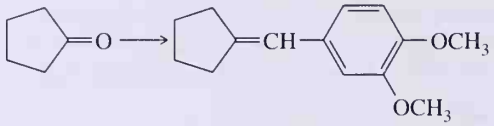
17.30 Draw structural formulas for (1) the triphenylphosphonium salt formed by treatment of each haloalkane with triphenylphosphine, (2) the phosphonium ylide formed by treatment of each phosphonium salt with butyllithium, and (3) the alkene formed by treatment of each phosphonium ylide with acetone.

(a) $(CH_3)_2CHBr$ **(b)** $CH_2{=}CHCH_2Br$ **(c)**  **(d)** 

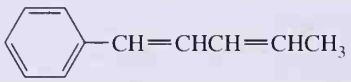
(e) $CH_3CH_2CH_2CH_2Br$ **(f)** 

17.31 Show how to bring about the following conversions using a Wittig reaction:

(a)  **(b)** 

(c) 

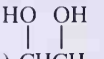
17.32 The Wittig reaction can be used for the synthesis of conjugated dienes, as for example, 1-phenyl-1,3-pentadiene. Propose two sets of reagents that might be combined in a Wittig reaction to give this conjugated diene.



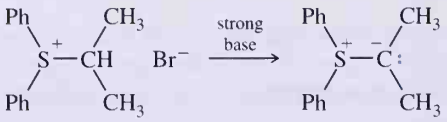
1-Phenyl-1,3-pentadiene

17.33 Show how to convert heptanal into the following:

(a) $CH_3(CH_2)_5CH{=}CH_2$ **(b)**  **(c)** $CH_3(CH_2)_5CH{=}CHCH{=}CH_2$

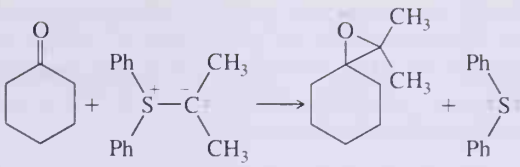
(d)  **(e)**  **(f)** $CH_3(CH_2)_5CH_2CH_2CH_2OH$

17.34 It is possible to generate sulfur ylides in a manner similar to that used to produce phosphonium ylides. For example, treating a sulfonium salt with a strong base gives the sulfur ylide



A sulfonium bromide

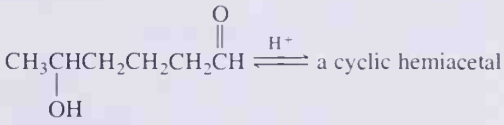
Sulfur ylides react with ketones to give, not alkenes, but epoxides. Suggest a mechanism for this reaction.



A sulfur ylide

Addition of Oxygen Nucleophiles

17.35 5-Hydroxyhexanal forms a six-member cyclic hemiacetal, which predominates at equilibrium in aqueous solution.



5-Hydroxyhexanal

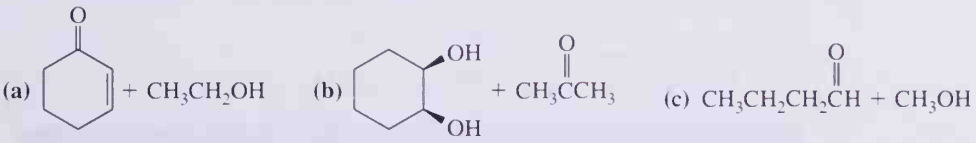
(a) Draw a structural formula for this cyclic hemiacetal.

(b) How many stereoisomers are possible for 5-hydroxyhexanal?

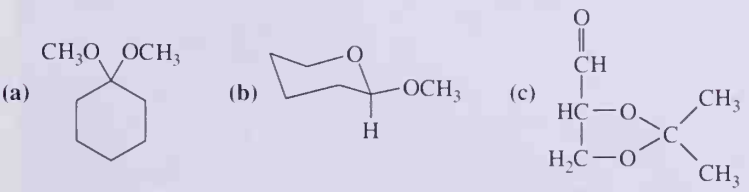
(c) How many stereoisomers are possible for this cyclic hemiacetal?

(d) Draw alternative chair conformations for each stereoisomer of the cyclic hemiacetal, and label groups axial or equatorial. Also predict which of the alternative chair conformations for each stereoisomer is the more stable.

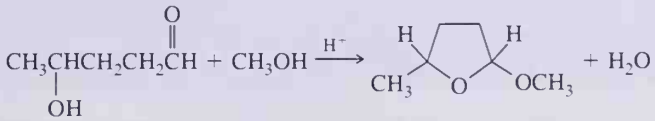
17.36 Draw structural formulas for the hemiacetal and then the acetal formed from each pair of reactants in the presence of an acid catalyst.



17.37 Draw structural formulas for the products of hydrolysis of the following acetals:



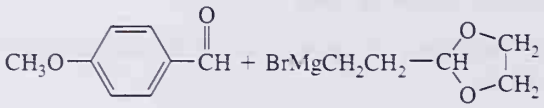
17.38 Propose a mechanism to account for the formation of a cyclic acetal from 4-hydroxypentanal and one equivalent of methanol. If the carbonyl oxygen of 4-hydroxypentanal is enriched with oxygen-18, do you predict that the oxygen label appears in the cyclic acetal or in the water?



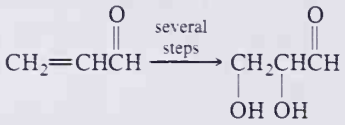
4-Hydroxypentanal

17.39 In Section 11.6A we saw that ethers, such as diethyl ether and tetrahydrofuran, are quite resistant to the actions of all acids except hot concentrated HI or HBr. Acetals, however, in which two ether groups are linked to the same carbon undergo hydrolysis readily even in dilute aqueous acid. How do you account for this marked difference in chemical reactivity toward dilute aqueous acid between ethers and acetals?

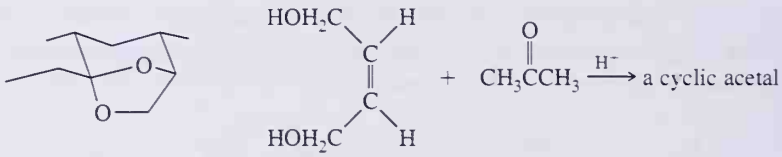
17.40 Draw a structural formula for the magnesium alkoxide formed in the following Grignard reaction and then the product formed on hydrolysis of the magnesium alkoxide with aqueous acid.



17.41 Show how to bring about the following conversion:



17.42 Multistriatin is a component of the aggregating pheromone of the European elm bark beetle, the insect vector of Dutch elm disease. In one laboratory synthesis of this molecule, (Z)-2-butene-1,4-diol was used as a starting material. Because of the requirements of subsequent steps, it was necessary to protect the two —OH groups of this molecule, which was done by making a cyclic acetal with acetone.



Multistriatin (Z)-2-Butene-1,4-diol

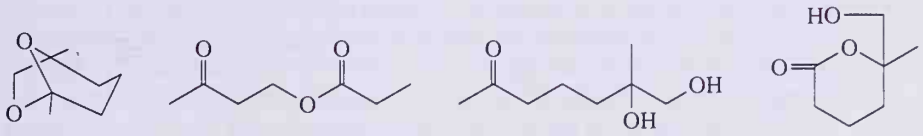
European elm bark beetle, the vector for Dutch elm disease. *(© Stephen Dalton, Photo Researchers, Inc.)*

(a) Draw the structural formula of the cyclic acetal formed by reaction of acetone and (Z)-2-butene-1,4-diol.

(b) The cyclic acetal was next treated with 3-chloroperoxybenzoic acid to form an epoxide. This product was then treated with methylmagnesium iodide followed by hydrolysis in aqueous acid. Draw the structural formula for the product formed after each of these reactions.

(c) Explain why it was necessary to protect the —OH groups in the starting diol.

17.43 Which of these molecules will cyclize to give the insect pheromone frontalin?



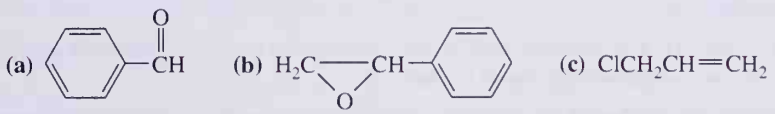
Frontalin A B C

Addition of Sulfur Nucleophiles

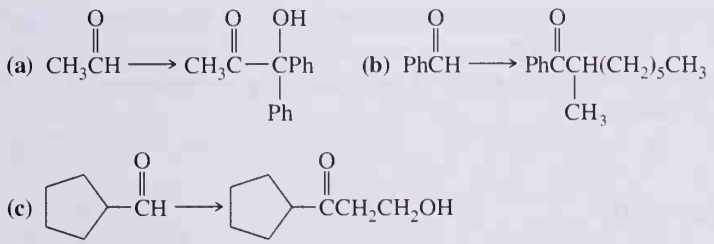
17.44 Draw a structural formula for the product of reaction of benzaldehyde with the following dithiols in the presence of an acid catalyst:

(a) 1,2-Ethanedithiol (b) 1,3-Propanedithiol

17.45 Draw a structural formula for the product formed by treating each of these compounds with (1) the lithium salt of the 1,3-dithiane derived from acetaldehyde and then (2) H_2O, $HgCl_2$.



17.46 Show how to bring about the following conversions using a 1,3-dithiane:



Addition of Nitrogen Nucleophiles

17.47 Draw structural formulas for the products of the following acid-catalyzed reactions:

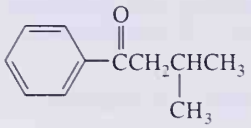
(a) Phenylacetaldehyde + hydrazine →

(b) Cyclopentanone + semicarbazide →

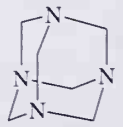
(c) Acetophenone + 2,4-dinitrophenylhydrazine →

(d) *p*-Bromoacetophenone + hydroxylamine →

17.48 The following ketone reacts with hydroxylamine to form a pair of isomeric oximes related in the same manner that *cis* and *trans* alkenes are related. Draw structural formulas for these isomeric oximes, and specify the configuration of each using the E-Z convention.



17.49 Methenamine (hexamethylenetetramine), a product of the reaction of formaldehyde and ammonia, is an example of a prodrug, a compound that is inactive itself but is converted to an active drug by a biochemical transformation. The strategy behind use of methenamine as a prodrug is that nearly all bacteria are sensitive to formaldehyde at concentrations of 20 mg/mL or higher. Formaldehyde cannot be used directly in medicine, however, because an effective concentration in plasma cannot be achieved with safe doses. Methenamine is stable at pH 7.4 (the pH of blood plasma) but undergoes acid-catalyzed hydrolysis to formaldehyde and ammonium ion under the acidic conditions of renal tubules and the urinary tract. Thus, methenamine can be used as a site-specific drug to treat urinary infections.



Methenamine
(Hexamethylenetetramine)

(a) Write a balanced equation for the hydrolysis of methenamine to formaldehyde and ammonium ion.

(b) Does the pH of an aqueous solution of methenamine increase, remain the same, or decrease as a result of hydrolysis? Explain.

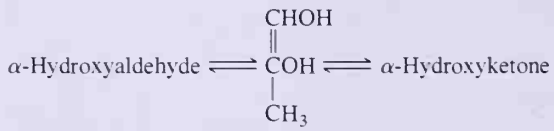
(c) Explain the meaning of the following statement: The functional group in methenamine is the nitrogen analog of an acetal.

(d) Account for the observation that methenamine is stable in blood plasma but undergoes hydrolysis in the urinary tract.

(e) Propose a mechanism for the acid-catalyzed hydrolysis of methenamine to formaldehyde and ammonium ion.

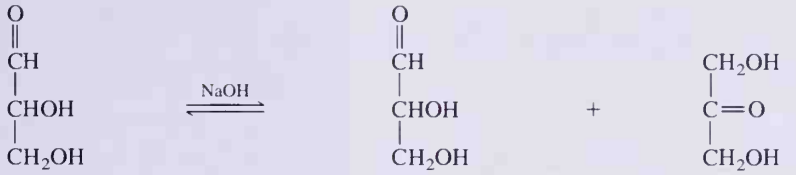
Keto-Enol Tautomerism

17.50 The following molecule belongs to a class of compounds called enediols; each carbon of the double bond carries an —OH group. Draw structural formulas for the α-hydroxyketone and the α-hydroxyaldehyde with which this enediol is in equilibrium.



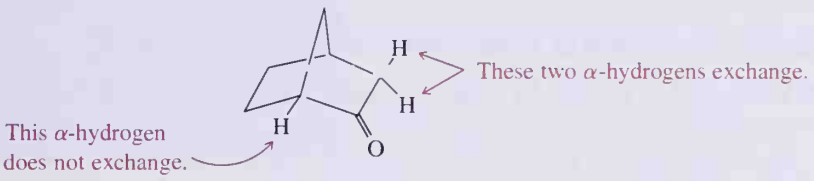
An enediol

17.51 Account for the fact that in dilute aqueous base, (R)-glyceraldehyde is converted into an equilibrium mixture of (R,S)-glyceraldehyde and dihydroxyacetone.



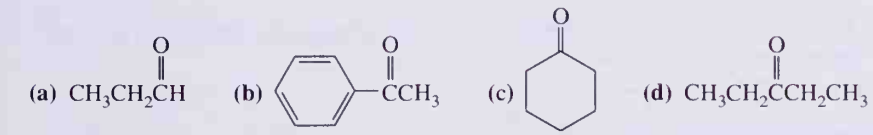
(R)-Glyceraldehyde (R,S)-Glyceraldehyde Dihydroxyacetone

17.52 The following bicyclic ketone has two α-carbons and three α-hydrogens. When this molecule is treated with D_2O in the presence of an acid catalyst, only two α-hydrogens exchange with deuterium. The α-hydrogen at the bridgehead does not exchange. How do you account for the fact that two α-hydrogens do exchange but the third does not? You will find it helpful to build a model of this molecule and of the enols by which exchange of α-hydrogens occurs.

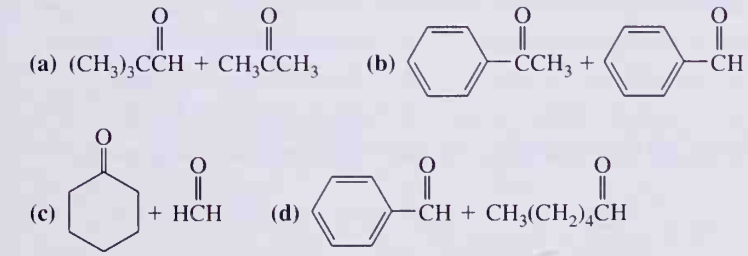


The Aldol Reaction

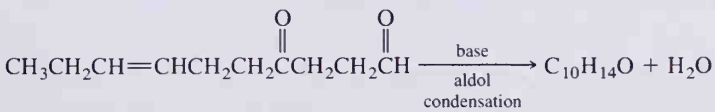
17.53 Draw structural formulas for the products of aldol reactions of the following compounds and for the α,β-unsaturated aldehyde or ketone formed from dehydration of each aldol product:



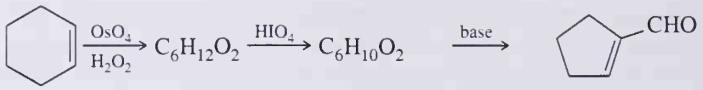
17.54 Draw structural formulas for the products of the following mixed aldol reactions and for the compound formed by dehydration of each aldol product:



17.55 When treated with base, the following compound undergoes an intramolecular aldol reaction to give a product containing a ring (yield 78%). Propose a structural formula for this product.

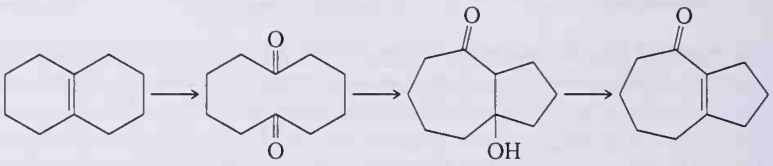


17.56 Cyclohexene can be converted to 1-cyclopentenecarbaldehyde by the following series of reactions. Propose a structural formula for each intermediate compound.



1-Cyclopentenecarbaldehyde

17.57 How might you bring about the following conversions?



Oxidation/Reduction of Aldehydes and Ketones

17.58 Draw structural formulas for the products formed by treatment of butanal with the following reactants:

(a) $LiAlH_4$ followed by H_2O
(b) $NaBH_4$ in CH_3OH/H_2O
(c) H_2/Pt
(d) $Ag(NH_3)_2^+$ in NH_3/H_2O
(e) $KMnO_4$, H_3O^+, warm
(f) $HOCH_2CH_2OH$, HCl
(g) Zn(Hg)/HCl
(h) $HSCH_2CH_2SH$, H^+
(i) Compound (h) + Raney nickel
(j) N_2H_4, KOH at 250°C
(k) $C_6H_5NH_2$
(l) $C_6H_5NHNH_2$
(m) Pyrrolidine

17.59 Draw structural formulas for the products for the reaction of *p*-bromoacetophenone with the reagents given in the previous problem.

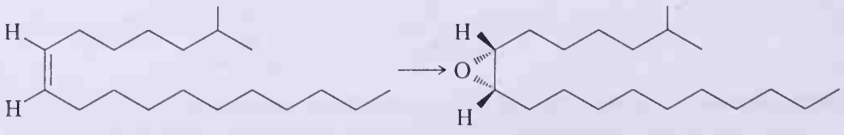
Qualitative Organic Analysis

17.60 Describe a simple chemical test to distinguish between the members in each set. Describe what you expect to observe, and write an equation for each positive test.

(a) Cyclohexanol and cyclohexanone
(b) Benzaldehyde and acetophenone
(c) Benzaldehyde and benzyl alcohol
(d) 2-Hexanone and 3-hexanone
(e) Benzaldehyde and its dimethyl acetal
(f) 2-Hexanone and 2-hexanol
(g) Cyclohexene and cyclohexanone
(h) Cyclohexene and cyclohexanol

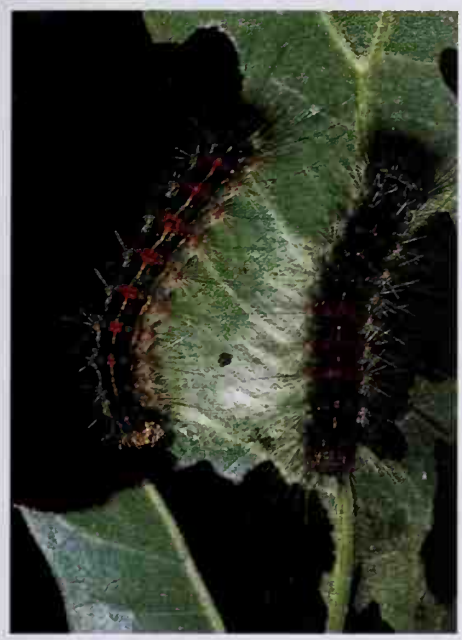
Synthesis

17.61 Disparlure is a sex attractant of the gypsy moth *(Porthetria dispar)*. It has been synthesized in the laboratory from the following (Z)-alkene:



(Z)-2-Methyl-7-octadecene

Disparlure



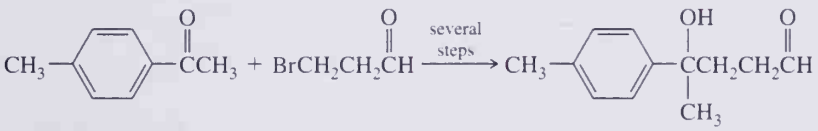
Gypsy moth, *Porthetria dispar*. *(Animals, Animals © William D. Griffin)*

(a) Propose two sets of reagents that might be combined in a Wittig reaction to give the indicated (Z)-alkene. Note that at least for simple phosphonium ylides, the product of a Wittig reaction is a (Z)-alkene.

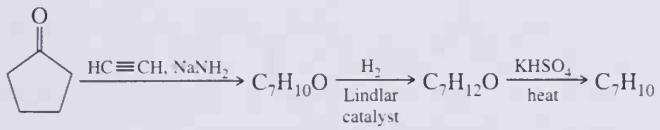
(b) How might the (Z)-alkene be converted to disparlure?

(c) How many stereoisomers are possible for disparlure? How many are formed in the sequence you chose?

17.62 Starting with the given two compounds and any other necessary organic or inorganic reagents, show how to make the compound shown at the right.

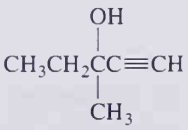


17.63 Propose structural formulas for compounds A, B, and C in the following conversion. Show also how to prepare compound C by a Wittig reaction.



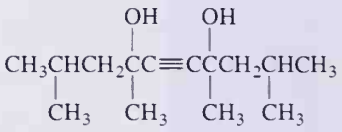
(A) (B) (C)

17.64 Following is the structural formula of the tranquilizer Oblivon (meparfynol). Propose a synthesis for this molecule starting with acetylene and a ketone.



Oblivon

17.65 Following is the structural formula of Surfynol, a defoaming surfactant. Describe the synthesis of this molecule from acetylene and a ketone. You may wish to look up surfactant in a science reference work and find out what surfactants are, how they work, and what they are used for.



Surfynol

17.66 Starting with acetylene and 1-bromobutane as the only sources of carbon atoms, show how to synthesize the following:

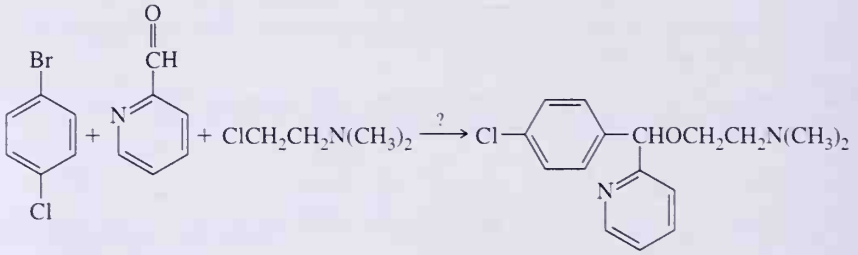
(a) meso-5,6-Decanediol **(b)** Racemic 5,6-decanediol

(c) 5-Decanone **(d)** 5,6-Epoxydecane

(e) 5-Decanol **(f)** Decane

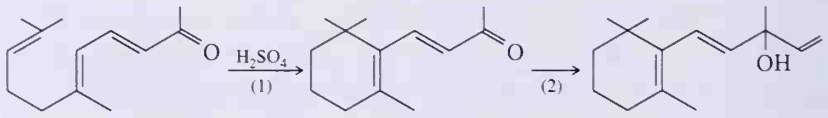
(g) 6-Methyl-5-decanol **(h)** 6-Methyl-5-decanone

17.67 Carbinoxamine is a histamine antagonist, specifically an H_1-antagonist. The maleic acid salt of the levorotatory isomer is sold as the prescription drug rotoxamine. Propose a synthesis of carbinoxamine from the three compounds shown on the left of the reaction arrow. *Note:* Aryl bromides form Grignard reagents much more readily than aryl chlorides do.

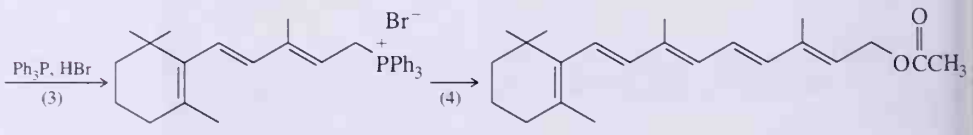


Carbinoxamine

17.68 Following are the final steps in one industrial synthesis of vitamin A acetate:



Pseudo-ionone β-ionone



Vitamin A acetate

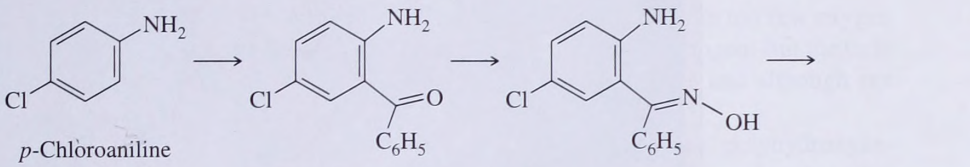
(a) Propose a mechanism for the acid-catalyzed cyclization in Step 1.

(b) Propose reagents to bring about Step 2.

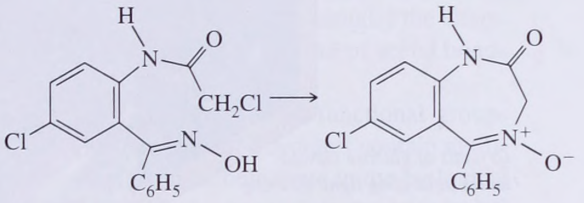
(c) Propose a mechanism for formation of the phosphonium salt in Step 3.

(d) Show how Step 4 can be completed by a Wittig reaction.

17.69 Following is a synthesis of diazepam, a prescription tranquilizer sold under several trade names, the most well known of which is Valium. This drug may well be the most commercially successful of all synthetic drugs!



p-Chloroaniline



Diazepam

Show reagents and conditions for the synthesis of diazepam from *p*-chloroaniline. (*See* Sternbach, L. H., and Reeder, E., *J. Org. Chem.*, **26,** 4936(1961).)

18

Crystals of glucose viewed under polarizing light. (© Philip A. Harrington/Fran Heyl Associates).

CARBOHYDRATES

Carbohydrates are the most abundant organic molecules in the world. Among their many vital functions, they are storehouses of chemical energy (glucose, starch, glycogen); components of supportive structures in plants (cellulose) and bacterial cell walls (mucopolysaccharides); and essential components of nucleic acids (D-ribose and 2-deoxy-D-ribose) and thereby of the mechanisms for the genetic control of development and growth of living organisms. Furthermore, bound to plasma membranes of animal cells are large numbers of relatively small carbohydrates that mediate interactions between cells. For example, A, B, and O blood types are determined by specific membrane-bound carbohydrates.

The simpler members of the carbohydrate family are often referred to as **saccharides** because of the sweet taste of sugars (Latin: *saccharum*, sugar). The name "carbohydrate," or "hydrate of carbon," derives from the formula for many members of this class: $C_n(H_2O)_m$. Two examples of carbohydrates with molecular formulas that can be written alternatively as hydrates of carbon are shown in the table.

Carbohydrate	Molecular Formula	Molecular Formula as Hydrate of Carbon
glucose (blood sugar)	$C_6H_{12}O_6$	$C_6(H_2O)_6$
sucrose (table sugar)	$C_{12}H_{22}O_{11}$	$C_{12}(H_2O)_{11}$

Not all carbohydrates, however, have this general formula. Some contain too few oxygen atoms to fit this formula, some contain too many. Some also contain nitrogen. But the term "carbohydrate" has become firmly rooted in chemical nomenclature, and although not completely accurate, it persists as the name of this class of compounds.

At the molecular level, **carbohydrates** are polyhydroxyaldehydes, polyhydroxyketones, or compounds that yield either polyhydroxyaldehydes or polyhydroxyketones after hydrolysis. Complex carbohydrates are polymers of monosaccharides joined by acetal bonds (Section 17.9B). Therefore, the chemistry of carbohydrates is essentially the chemistry of two functional groups: hydroxyl groups and carbonyl groups, and of acetal bonds formed between these two functional groups.

However, the notion that carbohydrates have only two types of functional groups belies the complexity of their chemistry. All but the simplest carbohydrates contain multiple stereocenters. For example, glucose, the most abundant carbohydrate in the biological world, contains one aldehyde group, four secondary alcohol groups, one primary alcohol group, and four stereocenters. Working with molecules of this complexity presents enormous challenges to organic chemists and biochemists alike.

18.1 Monosaccharides

A. Structure

Monosaccharides are the monomers from which more complex carbohydrates are constructed. They have the general formula $C_nH_{2n}O_n$, where n varies from three to eight. The suffix **-ose** indicates that a molecule is a carbohydrate and the prefixes tri-, tetr-, pent-, and so forth, indicate the number of carbon atoms in the chain. Monosaccharides derived from an aldehyde are classified as **aldoses;** those derived from a ketone are classified as **ketoses.**

Monosaccharides classified by number of carbon atoms

Name	Formula
triose	$C_3H_6O_3$
tetrose	$C_4H_8O_4$
pentose	$C_5H_{10}O_5$
hexose	$C_6H_{12}O_6$
heptose	$C_7H_{14}O_7$
octose	$C_8H_{16}O_8$

There are only two trioses: glyceraldehyde, which is an aldotriose, and dihydroxyacetone, which is a ketotriose.

Glyceraldehyde (an aldotriose) Dihydroxyacetone (a ketotriose)

Often the designations aldo- and keto- are omitted, and these molecules are referred to simply as trioses, tetroses, and so forth. Although these designations do not tell the nature of the carbonyl group, at least they indicate that the monosaccharide contains three or four carbon atoms, respectively.

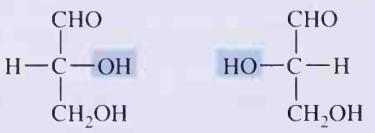
B. Nomenclature

Glyceraldehyde is a common name; the IUPAC name for this monosaccharide is 2,3-dihydroxypropanal. Similarly, dihydroxyacetone is a common name; its IUPAC name is 1,3-dihydroxypropanone. However, the common names for these and other monosaccharides are so firmly rooted in the literature of organic chemistry and biochemistry, that they are used almost exclusively whenever these compounds are referred to. Therefore, throughout our discussions of the chemistry of carbohydrates, we use the names most common in the literature of chemistry and biochemistry.

C. Stereoisomerism

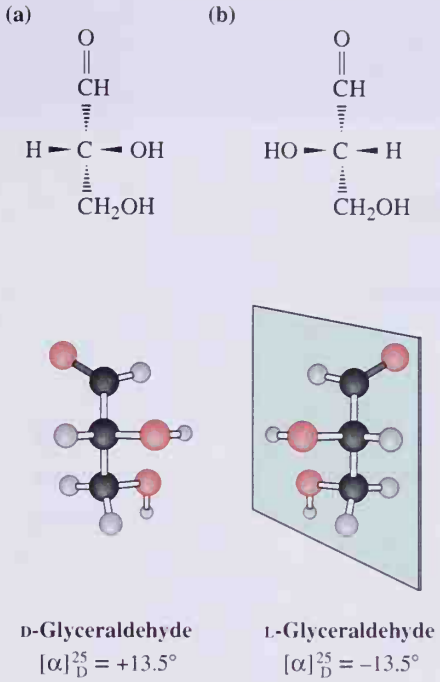
Dihydroxyacetone does not contain stereocenters and, therefore, does not show stereoisomerism. Glyceraldehyde, however, has one stereocenter and does show enantiomerism (Figure 18.1). The configuration in Figure 18.1(a) is named D-glyceraldehyde, and its enantiomer in part (b) is named L-glyceraldehyde.

The structural formulas in Figure 18.1 show the configuration of each stereocenter by a combination of dashed and solid wedges. Structural formulas for monosaccharides can also be drawn as Fischer projections (Section 8.4). In a **Fischer projection,** the carbon chain is written vertically with the carbon bearing the carbonyl group toward the "top." Horizontal lines represent groups projecting above the plane of the page; vertical lines show groups projecting behind the plane of the page. Application of these rules gives the following Fischer projections for the enantiomers of glyceraldehyde:



D-Glyceraldehyde L-Glyceraldehyde

At times confusion may arise about whether a structural formula is or is not a Fischer projection. The problem arises because Fischer projections can be mistaken for Lewis

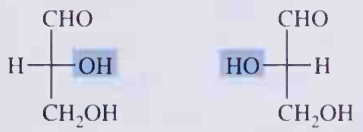


D-Glyceraldehyde
$[\alpha]_D^{25} = +13.5°$

L-Glyceraldehyde
$[\alpha]_D^{25} = -13.5°$

Figure 18.1
The enantiomers of glyceraldehyde.

structures, and whereas Fischer projection formulas do show the configuration about each stereocenter, Lewis structures do not. Therefore, the original Fischer convention has been modified to avoid this potential problem. In a **modified Fischer projection,** all stereocenters are represented by the crossing points of bonds; carbon atoms at these stereocenters are not shown. We use the modified Fischer projection convention throughout the text.



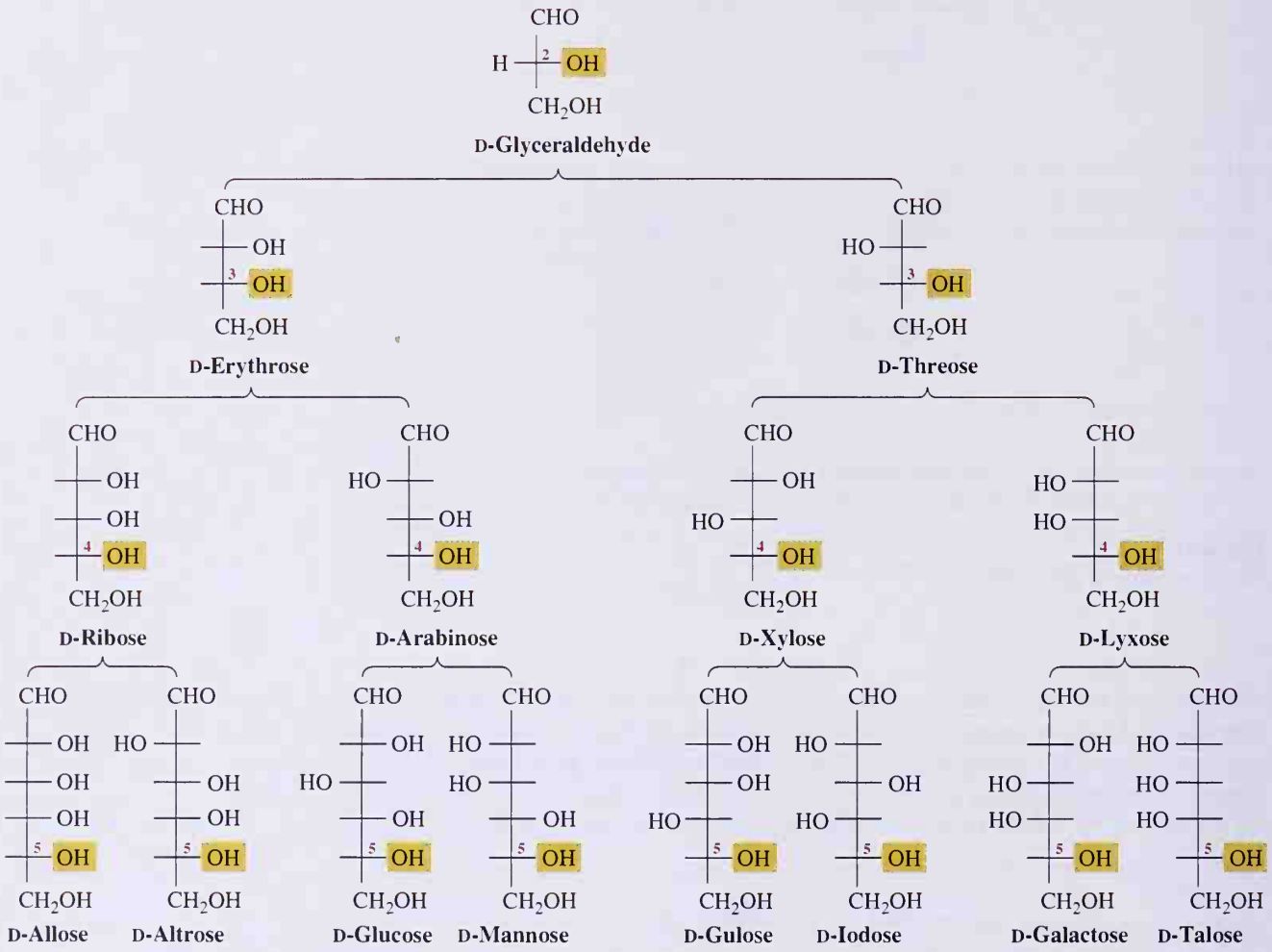
D-Glyceraldehyde L-Glyceraldehyde

(drawn according to the modified Fischer convention)

D-Glyceraldehyde and L-glyceraldehyde serve as reference points for the assignment of relative configuration to all other aldoses and ketoses. The reference point is the stereocenter farthest from the carbonyl group. Because this stereocenter is the next to the last carbon on the chain, it is called the **penultimate carbon.** A monosaccharide that has the same configuration as D-glyceraldehyde about the penultimate carbon is called a **D-monosaccharide;** a monosaccharide that has the same configuration as L-glyceraldehyde about the penultimate carbon is called an **L-monosaccharide.**

In 1891, when Emil Fischer proposed the use of D and L to specify absolute configurations in monosaccharides, it was known that glyceraldehyde exists as a pair of enan-

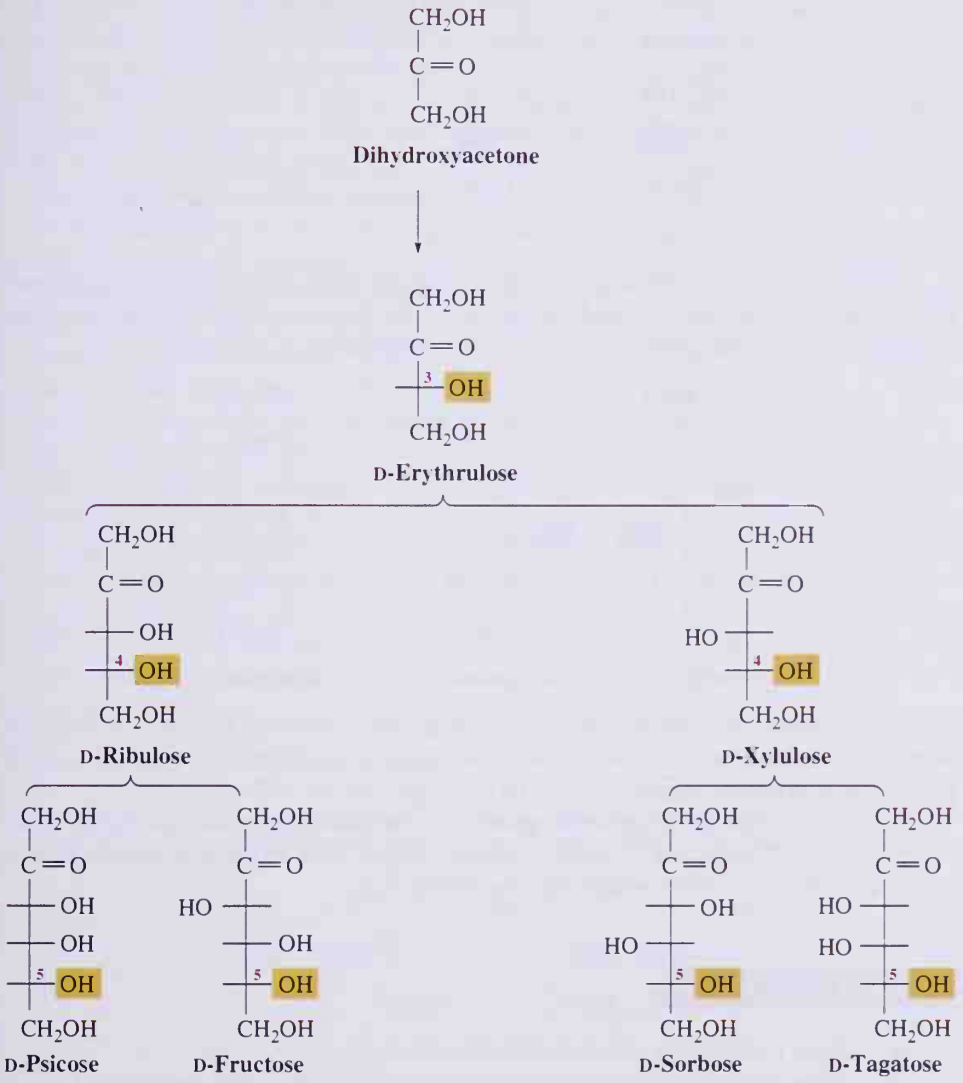
Table 18.1 Configurational relationships between the isomeric D-aldotetroses, D-aldopentoses, and D-aldohexoses derived from D-glyceraldehyde*



* The configuration of the reference —OH on the penultimate carbon is shown in color.

tiomers, and that one of them has a specific rotation of +13.5°; the other a specific rotation of −13.5°. The question Fischer and others faced was, which enantiomer has which specific rotation? Is the specific rotation of D-glyceraldehyde +13.5°, or is it −13.5°? Because there was no experimental way to answer the question at that time, Fischer did the only possible thing—he guessed. He guessed that Figure 18.1(a) is the absolute configuration of the dextrorotatory enantiomer and named it D-glyceraldehyde (D for dextrorotatory). He named its enantiomer L-glyceraldehyde (L for levorotatory). Fischer could have been wrong, but by a stroke of good fortune, he wasn't. In 1952, his assignment of absolute configuration was proven correct by a special application of x-ray crystallography. Thus, Fischer projections of monosaccharides give absolute configurations of all stereocenters.

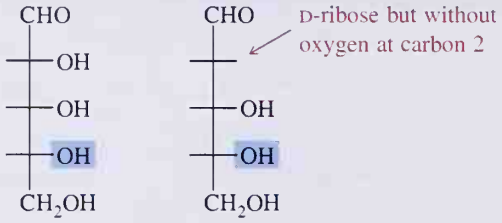
Table 18.2 Configurational relationships among the D-ketopentoses and D-ketohexoses derived from dihydroxyacetone and D-erythrulose*



* The configuration of the reference —OH on the penultimate carbon is shown in color.

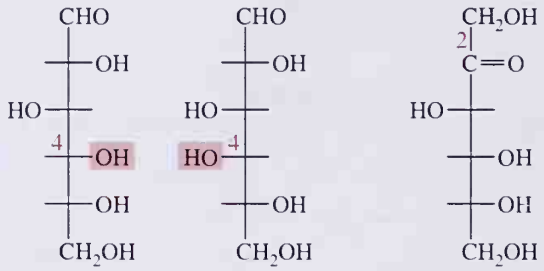
Shown in Tables 18.1 and 18.2 are names and Fischer projection formulas for all D-tetroses, D-pentoses, and D-hexoses. Each name consists of three parts. The letter "D" specifies the absolute configuration at the stereocenter farthest from the carbonyl group. Prefixes, such as rib-, arabin-, and gluc-, are common or trivial names given to these compounds without regard to configuration. The suffix -ose shows that the molecule belongs to the class of molecules called carbohydrates.

D-Ribose and 2-deoxy-D-ribose, the most abundant pentoses in the biological world, are essential building blocks of nucleic acids; D-ribose in ribonucleic acids (RNA) and 2-deoxy-D-ribose in deoxyribonucleic acids (DNA).



D-Ribose 2-Deoxy-D-ribose

The three most abundant hexoses in the biological world are D-glucose, D-galactose, and D-fructose. The first two are D-aldohexoses; the third is a D-ketohexose. Note that D-galactose differs from D-glucose only in the configuration at carbon-4.



D-Glucose D-Galactose D-Fructose

Glucose, by far the most common hexose, is also known as dextrose because it is dextrorotatory. Other names for this monosaccharide are grape sugar, blood sugar, and corn sugar. Human blood normally contains 65 to 110 mg of glucose per 100 mL.

Fructose is found combined with glucose in the disaccharide, sucrose (table sugar, Section 18.7C). D-Galactose is found combined with glucose in the disaccharide lactose (milk sugar, Section 18.7B), which appears only in milk.

EXAMPLE 18.1

(a) Draw Fischer projections for all aldotetroses.
(b) Show which are D-monosaccharides, which are L-monosaccharides, and which are enantiomers.
(c) Refer to Table 18.1, and write names for the aldotetroses you have drawn.

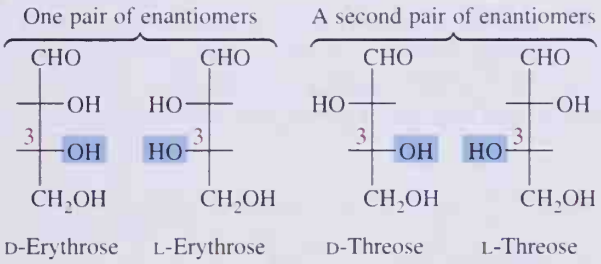
Solution

Following are Fischer projections for the four possible aldotetroses. D- and L- refer to the arrangement of groups attached to the penultimate carbon, which, in the case of aldotetroses, is carbon 3. In the Fischer projection of a D-aldotetrose, the —OH on carbon 3 is on the right, and in an L-aldotetrose it is on the left.

CHEMISTRY IN ACTION

The Genius of Emil Fischer

Just a little more than 100 years ago Emil Fischer made one of the key discoveries in the history of chemistry. Fischer was born in a German village near Cologne in 1852. He was educated in German public schools and continued on to the University of Berlin, where, against the wishes of his businessman father, he entered a degree program in the sciences. He graduated with a doctorate in chemistry in 1874. Among his first accomplishments were the synthesis of phenylhydrazine, and the discovery that when carbohydrates are treated with this compound, they give crystalline derivatives. The importance of this discovery was that until that time carbohydrates had been very difficult to work with because of their tendency to form syrupy mixtures. With the use of the phenylhydrazine reaction along with reaction sequences by which carbohydrate chains can be extended by one carbon at a time, Fischer was able to assign relative configurations to each of the stereocenters in glucose. He published his results in 1891. Underlying Fischer's work was the theory proposed in 1874 by the Dutch physical chemist, Jacobus H. van't Hoff, and the French organic chemist, Joseph-Achille Le Bel, that carbon is tetrahedral and that a compound containing a carbon atom bonded to four different groups can exist in enantiomeric forms. By no means was this theory universally accepted. Fischer's establishing of the structure of glucose, however, based as it was on the concept of a tetrahedral carbon atom, offered proof of the theory of van't Hoff and Le Bel, and moved it quickly to general acceptance. Thus, in establishing the relative configurations of the stereocenters of glucose, Fischer helped unravel the complexities of carbohydrate structure and at the same time helped establish the validity of a tetrahedral carbon atom. Each accomplishment was as significant as the other. In 1902, Fischer was awarded the Nobel Prize for his work on the chemistry of carbohydrates and of purines. Fischer is quoted as saying that his goal was to be the first to synthesize an "artificial ferment" (what we today call an enzyme) and with that accomplishment he would consider his mission in life fulfilled. He did not reach that goal, nor could he have realized the difficulties and the decades of research it would take before it was attained.

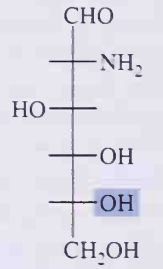


PROBLEM 18.1

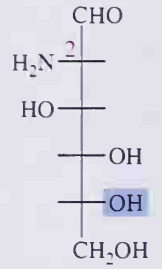
(a) Draw Fischer projections for all 2-ketopentoses.
(b) Show which are D-ketopentoses, which are L-ketopentoses, and which are enantiomers.
(c) Refer to Table 18.2, and write names for the ketopentoses you have drawn.

D. Amino Sugars

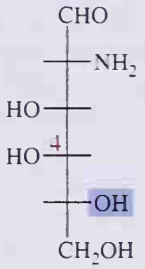
Amino sugars contain an $-NH_2$ group in place of an $-OH$ group. Only three amino sugars are common in nature: D-glucosamine, D-mannosamine, and D-galactosamine.



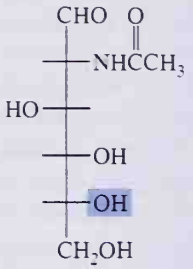
D-Glucosamine



D-Mannosamine (C-2 isomer of D-glucosamine)



D-Galactosamine (C-4 isomer of D-glucosamine)

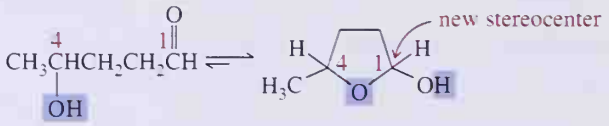


N-Acetyl-D-glucosamine

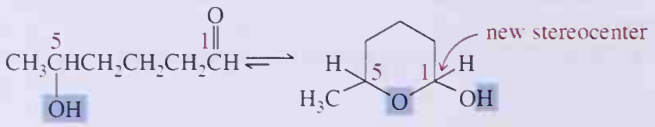
N-Acetyl-D-glucosamine, a derivative of D-glucosamine, is a component of many polysaccharides, including chitin, the hard shelllike exoskeleton of lobsters, crabs, shrimp, and other crustaceans.

18.2 The Cyclic Structure of Monosaccharides

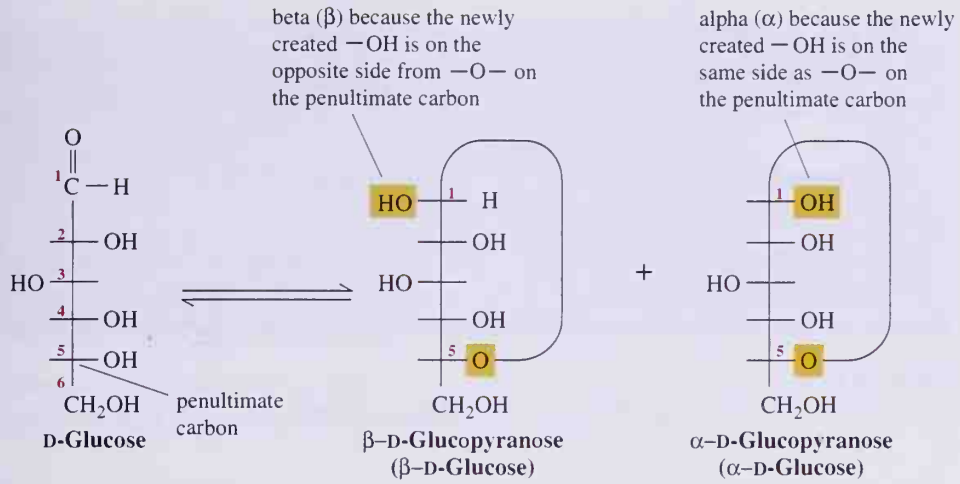
We saw in Section 17.9B that aldehydes and ketones react with alcohols to form hemiacetals. We also saw that cyclic hemiacetals form very readily when (1) hydroxyl and carbonyl groups are parts of the same molecule and (2) their interaction can form a five-member or six-member ring. For example, 4-hydroxypentanal forms a five-member cyclic hemiacetal. Note that 4-hydroxypentanal contains one stereocenter and that a second stereocenter is generated at carbon 1 as a result of hemiacetal formation. Similarly, 5-hydroxyhexanal forms a six-member cyclic hemiacetal in which a new stereocenter is also generated at carbon 1.



4-Hydroxypentanal A cyclic hemiacetal



5-Hydroxyhexanal A cyclic hemiacetal



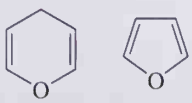
Monosaccharides have hydroxyl and carbonyl groups in the same molecule, and they exist almost exclusively as cyclic hemiacetals.

A. Fischer Projections

D-Glucose can be isolated in two crystalline forms called α-D-glucose and β-D-glucose, which have different chemical and physical properties. One of the most easily measured physical properties of these stereoisomers is their optical rotation. One form has a specific rotation of +112°, the other a specific rotation of +18.7°. These α- and β-isomers are formed by reaction between the —OH on carbon 5 and the carbonyl group at position 1 to give a pair of six-member cyclic hemiacetals. The new stereocenter resulting from hemiacetal formation is referred to as the **anomeric carbon.** The diastereomers thus formed are given the special name **anomers.**

In the terminology of carbohydrate chemistry, the symbol α indicates that in the Fischer projection, —OH on the anomeric carbon is on the same side as the —O— on the penultimate carbon, that is, —OH on the anomeric carbon is on the same side as the —O— by which D or L configuration is determined. The symbol β indicates that —OH on the anomeric carbon is on the opposite side from the —O— by which D or L configuration is determined.

The size of a monosaccharide hemiacetal ring is shown by reference to the heterocyclic molecules pyran and furan.



Pyran Furan

Six-member hemiacetal rings are shown by the infix **-pyran-,** and five-member hemiacetal rings are shown by the infix **-furan-.** Thus, the α- and β-anomers of D-glucose are properly named α-D-glucopyranose and β-D-glucopyranose. However, for convenience they are often named simply α-D-glucose and β-D-glucose.

In aqueous solution, the equilibrium constant for hemiacetal formation from D-glucose is greater than 200, which means that at equilibrium, only traces of aldehyde are present.

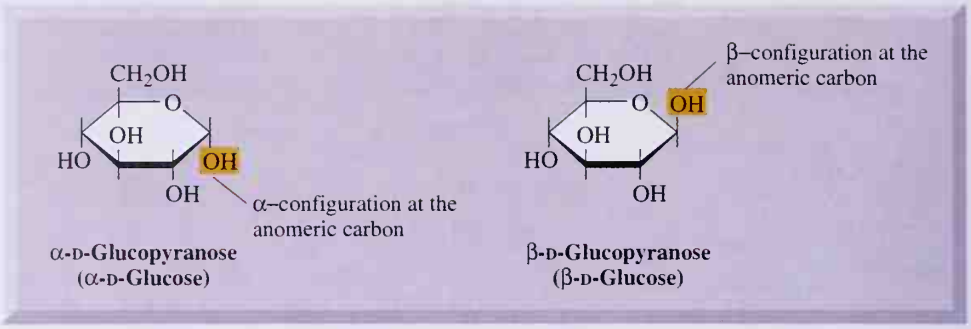


Figure 18.2
Haworth projections for α-D-glucopyranose and β-D-glucopyranose.

B. Haworth Projections

An alternative convention for representing the cyclic structure of monosaccharides is the **Haworth projection,** named after the English chemist, Sir Walter N. Haworth (Nobel laureate, 1937). In Haworth projections, five-member and six-member cyclic hemiacetals are represented as planar pentagons or hexagons, as the case may be, lying perpendicular to the plane of the paper. Groups attached to the carbons of the ring then lie either above or below the plane of the ring and parallel to the plane of the paper. Haworth projections are most commonly written with the anomeric carbon to the right and the hemiacetal oxygen to the back. Haworth projections for the α- and β-pyranose forms of D-glucose are shown in Figure 18.2.

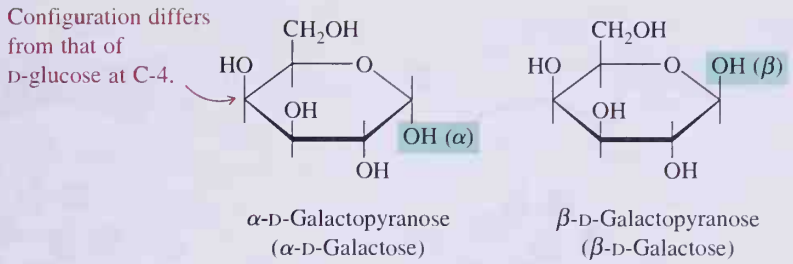
Perhaps the simplest way to arrive at the correct configuration of groups on a Haworth projection is to build a molecular model of the open-chain form of the monosaccharide and then to create the cyclic hemiacetal. Notice that in the Fischer projection of β-D-glucopyranose, groups on carbons 1, 2, 3, and 4 are left, right, left, right, respectively. In the Haworth projection of the same molecule, these groups are up, down, up, down, respectively. Furthermore, you will find it helpful to remember that the $-CH_2OH$ of all D-monosaccharides is above the plane of the ring. You would do well to remember the configuration of groups on the Haworth projection of both α-D-glucopyranose and β-D-glucopyranose as reference structures. By knowing how the open-chain configuration of any other monosaccharide differs from that of D-glucose, you can then construct its Haworth projection by reference to the Haworth projection of D-glucose.

EXAMPLE 18.2

Draw Haworth projections for the α- and β-anomers of D-galactopyranose.

Solution

One way to arrive at the structures for the α- and β-anomers of D-galactopyranose is to use the α and β forms of D-glucopyranose as reference and to remember, or discover by looking at Table 18.1, that D-galactose differs from D-glucose only in the configuration at carbon 4. Following are Haworth projections for α-D-galactopyranose and β-D-galactopyranose:



PROBLEM 18.2

Mannose exists in aqueous solution as a mixture of α-D-mannopyranose and β-D-mannopyranose. Draw Haworth projections for these molecules.

The most prevalent forms of D-ribose and other pentoses in the biological world are furanoses. Shown in Figure 18.3 is a structural formula for α-D-ribofuranose (α-D-ribose) drawn first in a Fischer projection and then in a Haworth projection. Also shown is a Haworth projection for β-2-deoxy-D-ribofuranose (β-2-deoxy-D-ribose). Units of D-ribose and 2-deoxy-D-ribose in nucleic acids and most other biological molecules are found almost exclusively in the β-configuration.

C. Conformation Representations

A five-member ring is sufficiently close to being planar that Haworth projections are adequate to represent furanoses. For pyranoses, however, the six-member ring is more accurately represented as a strain-free chair conformation. Structural formulas for α-D-glucopyranose and β-D-glucopyranose are drawn in Figure 18.4 as strain-free **chair conformations.** There is 64% β-form and 36% α-form present at equilibrium in

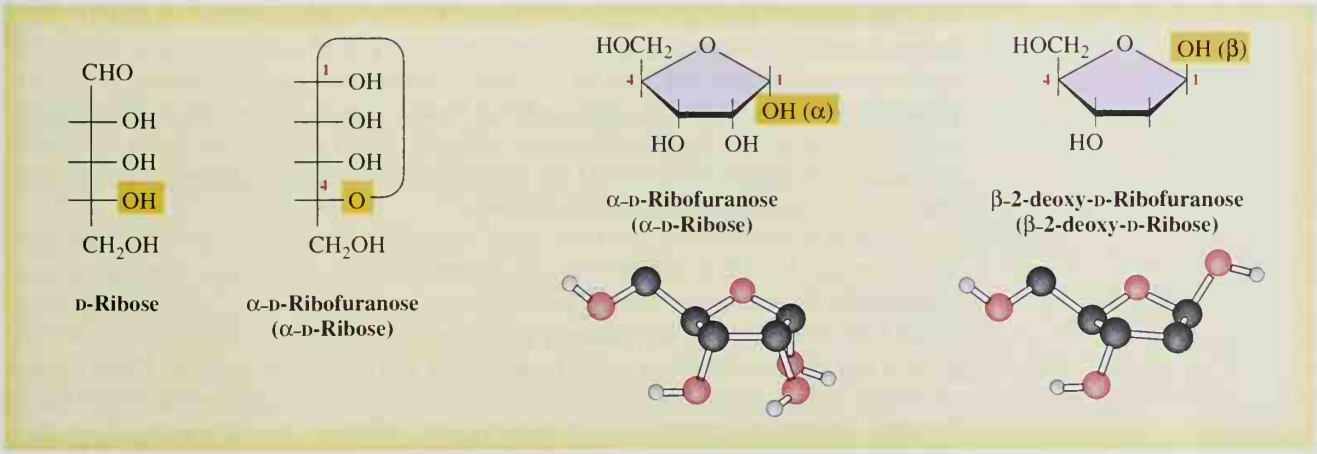


Figure 18.3
Fischer and Haworth projection formulas for D-ribofuranoses.

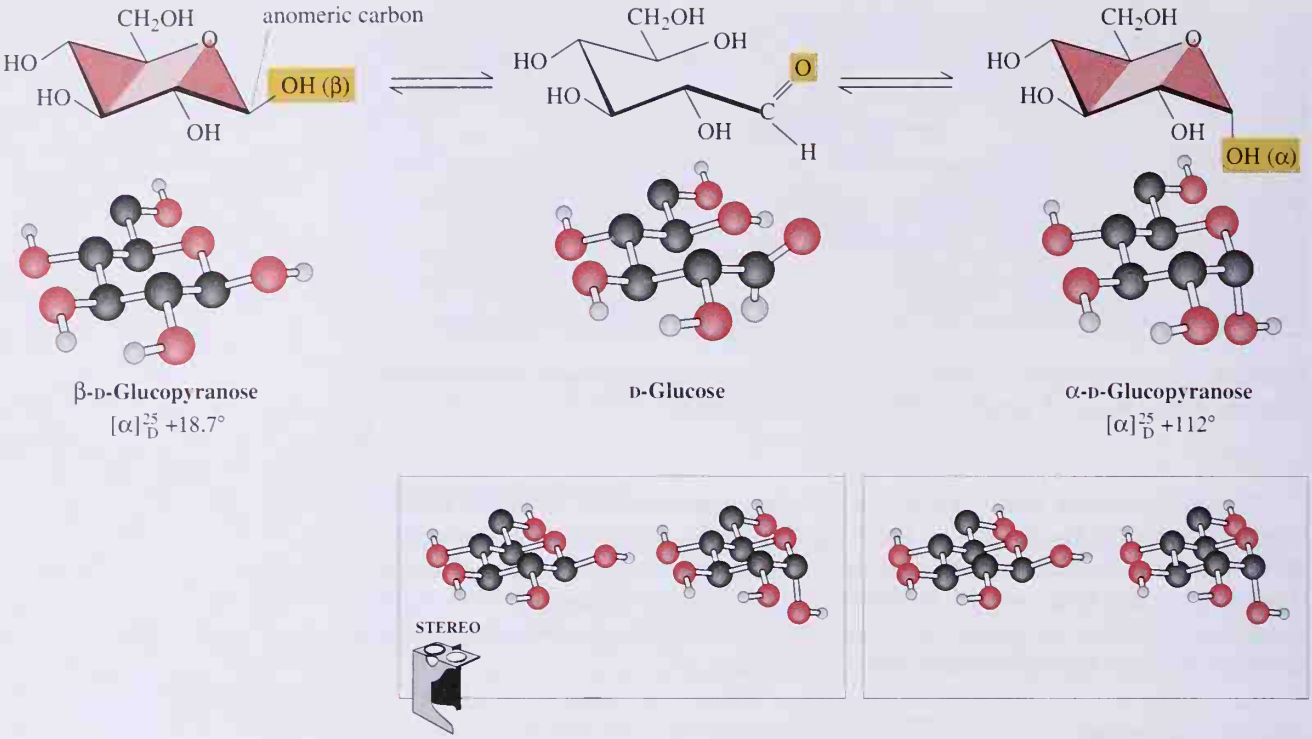


Figure 18.4
Chair conformations of α-D-glucopyranose and β-D-glucopyranose.

aqueous solution. Also drawn is the open-chain or free aldehyde form with which the cyclic hemiacetal forms are in equilibrium in aqueous solution.

At this point, you should compare the relative orientations of groups on D-glucopyranose rings in the Haworth projections and chair conformations. Notice, for example, that the orientations of groups on carbons 1 through 5 in the Haworth projection of β-D-glucopyranose are up, down, up, down, and up, respectively. The same is the case in the chair conformation. Furthermore, each of the groups on the chair conformation of β-D-glucopyranose drawn in Figure 18.4 is equatorial. Finally, notice that —OH on the anomeric carbon is equatorial in β-D-glucopyranose and axial in α-D-glucopyranose. Because of the equatorial orientation of the —OH on its anomeric carbon, β-D-glucopyranose is more stable and predominates in aqueous solution.

Other monosaccharides also form cyclic hemiacetals. Shown in Figure 18.5 are structural formulas for the cyclic hemiacetals formed by D-fructose along with approximate percentages of each form present at equilibrium in aqueous solution. Cyclization by hemiacetal formation between the carbonyl group on carbon 2 and the hydroxyl on carbon 5 gives a pair of anomers called α-D-fructofuranose and β-D-fructofuranose. These isomers are drawn as Haworth projections. Fructose also forms a pair of pyranoses by cyclization between the carbonyl group and the hydroxyl on carbon 6. Structural formulas of these compounds are drawn as chair conformations. In the furanose forms of fructose, the most common in the biological world, the —OH on the anomeric carbon is below the plane of the ring, by definition, in the α-anomer and above the plane of the ring in the β-anomer.

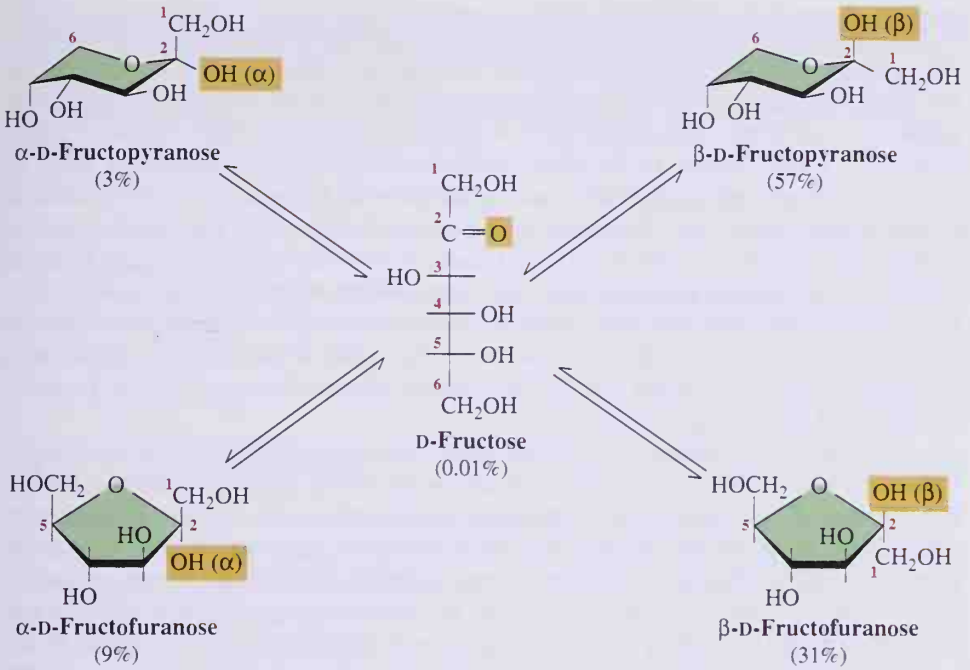


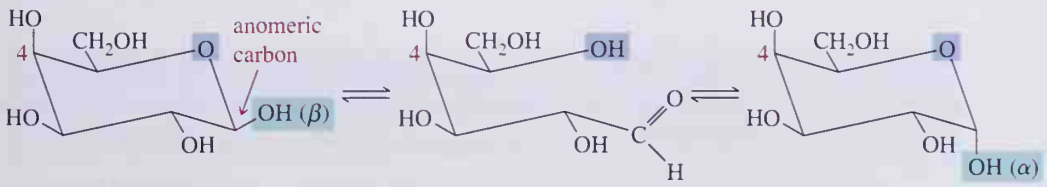
Figure 18.5
The major forms of D-fructose in equilibrium in aqueous solution.

EXAMPLE 18.3

Draw chair conformations for α-D-galactopyranose and β-D-galactopyranose. Label the anomeric carbon in each cyclic hemiacetal.

Solution

D-Galactose differs in configuration from D-glucose only at carbon 4. Therefore, draw the α and β forms of D-glucopryanose, and then invert the configurations of the —OH groups on carbon 4.



PROBLEM 18.3

Draw chair conformations for α-D-mannopyranose and β-D-mannopyranose. Label the anomeric carbon atom in each.

D. Mutarotation

The α- and β-anomers of monosaccharides are interconvertible in aqueous solution, and the change in specific rotation that accompanies this interconversion is known as **mutarotation.** As an example, a freshly prepared solution of α-D-glucopyranose shows an initial rotation of $+112°$ (Figure 18.4), which gradually decreases to an equilibrium value of $+52.7°$ as α-D-glucopyranose reaches an equilibrium with β-D-glucopyranose. A solution of β-D-glucopyranose also undergoes mutarotation, during which the specific rotation changes from an initial value of $+18.7°$ (Figure 18.4) to the same equilibrium value of $+52.7°$. Furthermore, it has been determined with modern techniques, most notably ^{13}C-NMR spectroscopy, that only traces of the furanose forms and the free aldehyde are present at equilibrium in aqueous solution. Thus, from the value of the specific rotation after mutarotation, we can calculate that the equilibrium mixture consists of 64% β-D-glucopyranose and 36% α-D-glucopyranose.

Mutarotation is common to all carbohydrates that exist in hemiacetal and open-chain forms. Shown in Table 18.3 are specific rotations for freshly prepared solutions of the α and β forms of D-glucopyranose, D-galactopyranose, and D-mannopyranose, along with equilibrium values for the specific rotation of each after equilibration. For these three monosaccharides, only traces of furanose forms and of the aldehyde are present at equilibrium in aqueous solution. Given also in Table 18.3 are percentages of the α-pyranose and β-pyranose forms of each monosaccharide present at equilibrium. From analyses of the composition of the equilibrium mixtures of monosaccharides in water, we can make the following generalizations. For most monosaccharides in aqueous solution

1. Little free aldehyde or ketone is present.
2. Pyranose forms predominate over furanose forms. It is important not to confuse this statement of the form present at equilibrium in aqueous solution with a statement of the form that predominates in a biological system. They may be quite different. For example, although D-ribose and 2-deoxy-D-ribose exist in aqueous solution mainly in the pyranose form, each is found in nucleic acids exclusively in the β-furanose form.
3. In pyranose forms, the diastereomer in which the larger group on the anomeric carbon is equatorial predominates. Note that in the case of 2-ketohexoses (for example, fructopyranose), the larger group on the anomeric carbon is $—CH_2OH$. In the case of aldohexoses (for example, D-glucose), the larger group on the anomeric carbon is —OH.

Table 18.3 Specific rotations for α- and β-anomers of D-glucopyranose, D-galactopyranose, and D-mannopyranose before and after mutarotation

Monosaccharide	Specific Rotation (Degrees °)	Specific Rotation After Mutarotation (Degrees °)	Percentage Present at Equilibrium (%)
α-D-glucose	+112.0	+52.7	36
β-D-glucose	+18.7	+52.7	64
α-D-galactose	+190.7	+80.2	28
β-D-galactose	+52.8	+80.2	72
α-D-mannose	+29.3	+14.5	68
β-D-mannose	−16.3	+14.5	32

Table 18.4 Relative sweetness of some carbohydrate sweetening agents

Monosaccharide		Disaccharide		Other Carbohydrate Sweetening Agent	
D-fructose	174	sucrose* (table sugar)	100	honey	97
D-glucose	74	lactose (milk sugar)	0.16	molasses	74
D-xylose	0.40			corn syrup	74
D-galactose	0.22				

* Sucrose is taken as a standard for relative sweetness and it is arbitrarily assigned a value of 100.

18.3 Physical Properties

Monosaccharides are colorless, crystalline solids and because hydrogen bonding is possible between polar —OH groups and water, all monosaccharides are very soluble in water. They are only slightly soluble in alcohol and are insoluble in nonpolar solvents, such as diethyl ether, chloroform, and benzene.

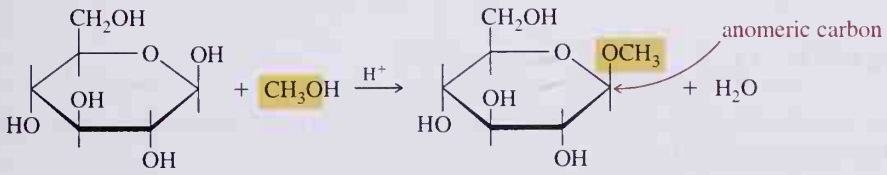
Although all monosaccharides are sweet to the taste, some are sweeter than others (Table 18.4). D-Fructose tastes the sweetest, even more than sucrose (table sugar). In the production of table sugar, sugar cane or sugar beet is boiled with water and the resulting solution cooled. As the mixture cools, sucrose crystals separate and are collected. Subsequent boilings and coolings of the filtrate yield a dark, thick syrup known as molasses. The sweet taste of honey is due largely to D-fructose, and that of corn syrup to D-glucose.

18.4 Reactions of Monosaccharides

In this section we discuss the reaction of monosaccharides with alcohols, with reducing agents, and with oxidizing agents.

A. Formation of Glycosides

Reaction of a monosaccharide hemiacetal with an alcohol forms an acetal as illustrated by the reaction of β-D-glucopyranose (β-D-glucose) with methanol.



β-D-Glucopyranose (β-D-Glucose)

Methyl β-D-glucopyranoside (Methyl β-D-glucoside)

A cyclic acetal derived from a monosaccharide is called a **glycoside,** and the bond from the anomeric carbon to the —OR group is called a **glycoside bond.** As we shall see in Sections

18.7 and 18.8, di-, tri-, and polysaccharides are examples of glycosides. In these molecules, monosaccharide units are joined by glycoside bonds formed between the anomeric carbon of one monosaccharide unit and an —OH of another monosaccharide unit.

Glycosides are named by listing the alkyl or aryl group attached to oxygen followed by the name of the carbohydrate involved in which the terminal -e is replaced by -ide. For example, glycosides derived from β-D-glucopyranose are named β-D-glucopyranosides; those derived from β-D-ribofuranose are named β-D-ribofuranosides.

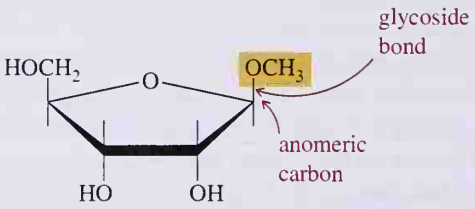
EXAMPLE 18.4

Draw structural formulas for the following glycosides. In each, label the anomeric carbon and the glycoside bond.

(a) Methyl β-D-ribofuranoside (methyl β-D-riboside)
(b) Methyl α-D-galactopyranoside (methyl α-D-galactoside)

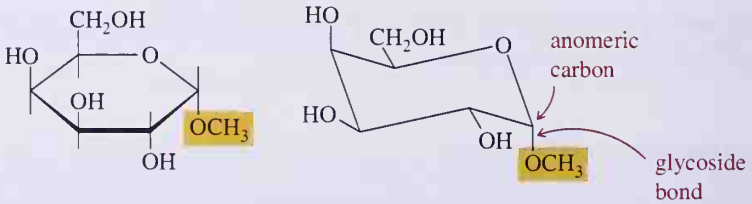
Solution

(a)



Methyl β-D-ribofuranoside
(Methyl β-D-riboside)

(b) The methyl glycoside is drawn both as a Haworth projection and in a chair conformation.



Methyl α-D-galactopyranoside
(Methyl α-D-galactoside)

PROBLEM 18.4

Draw structural formulas for the following glycosides. In each, label the anomeric carbon and the glycoside bond.

(a) Methyl β-D-fructofuranoside (methyl β-D-fructoside)
(b) Methyl α-D-mannopyranoside (methyl α-D-mannoside)

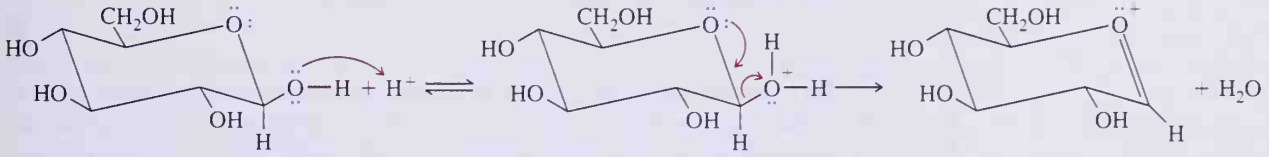
Glycosides are stable in water and aqueous base, but like other acetals (Section 17.9B), they are hydrolyzed in aqueous acid to an alcohol and a monosaccharide.

EXAMPLE 18.5

Propose a mechanism for the reaction of β-D-glucopyranose with methanol in the presence of a mineral acid to give a mixture of methyl α-D-glucopyranoside and methyl β-D-glucopyranoside. In writing this mechanism, show the pyranose ring in a chair conformation.

Solution

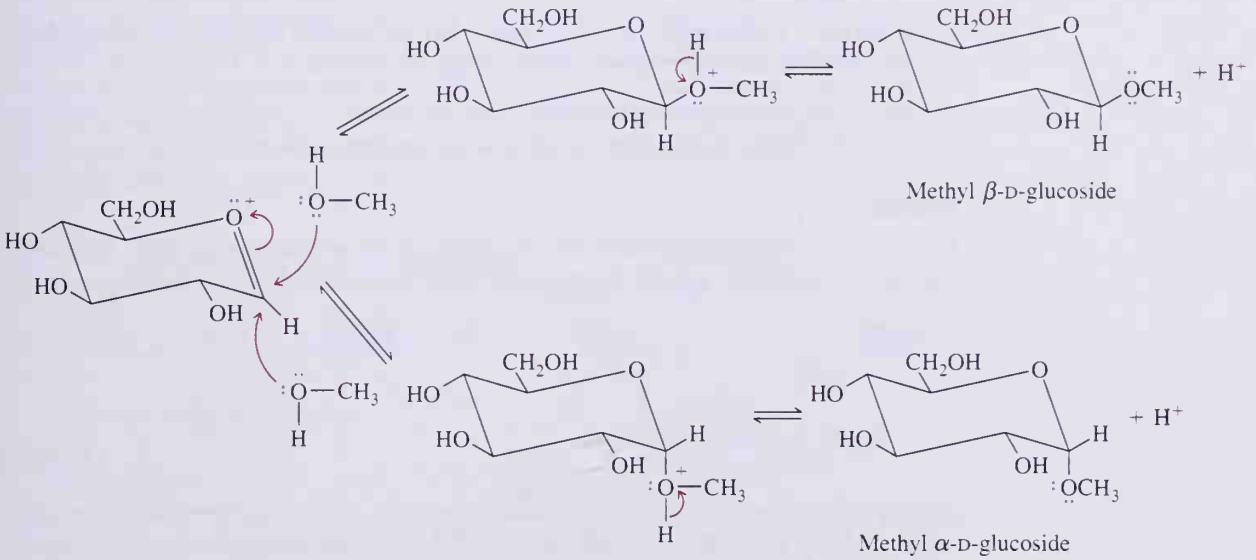
Refer to Section 17.9B and the mechanism presented for acid-catalyzed formation of an acetal. Apply the same mechanistic reasoning to this problem. Begin by proton transfer to the anomeric —OH and formation of an oxonium ion. Loss of H_2O from this oxonium ion gives a resonance-stabilized cation.



An oxonium ion

A resonance-stabilized cation

Reaction of the resonance-stabilized cation (an electrophile and Lewis acid) with methanol (a nucleophile and a Lewis base) from one face of the cation followed by loss of a proton gives the β-glycoside; reaction from the other face gives the α-glycoside.



Methyl β-D-glucoside

Methyl α-D-glucoside

Notice that each of these steps is reversible, and according to the **principle of microscopic reversibility** (Section 9.5E), the mechanism for hydrolysis of a glycoside is the reverse of the mechanism for its formation.

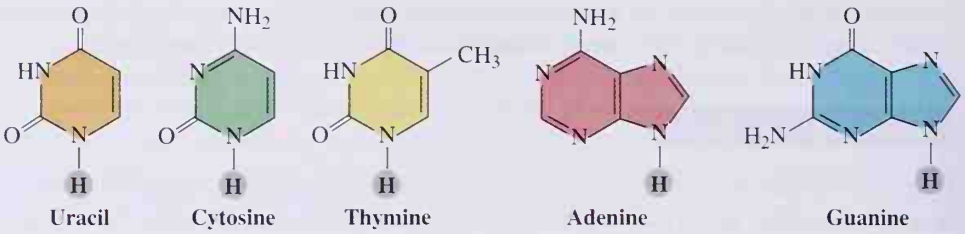


Figure 18.6
Structural formulas of the most important purine and pyrimidine bases found in DNA and RNA. The hydrogen atom shown in color is lost in forming an *N*-glycoside.

PROBLEM 18.5

Suppose that a β-D-glycopyranose is treated with methanol enriched in oxygen-18. Is the isotopic label found in the resulting methyl glycoside, in the water produced in the reaction, or in both the methyl glycoside and in water? Explain.

■

Just as the anomeric carbon of a cyclic hemiacetal undergoes reaction with R—OH to form a glycoside, it also undergoes reaction with an N—H group to form an *N*-glycoside. Especially important in the biological world are the *N*-glycosides formed between D-ribose and 2-deoxy-D-ribose, each as a furanose, and the heterocyclic aromatic amines, uracil, cytosine, thymine, adenine, and guanine (Figure 18.6). *N*-Glycosides of these purine and pyrimidine bases are structural units of nucleic acids (Chapter 25).

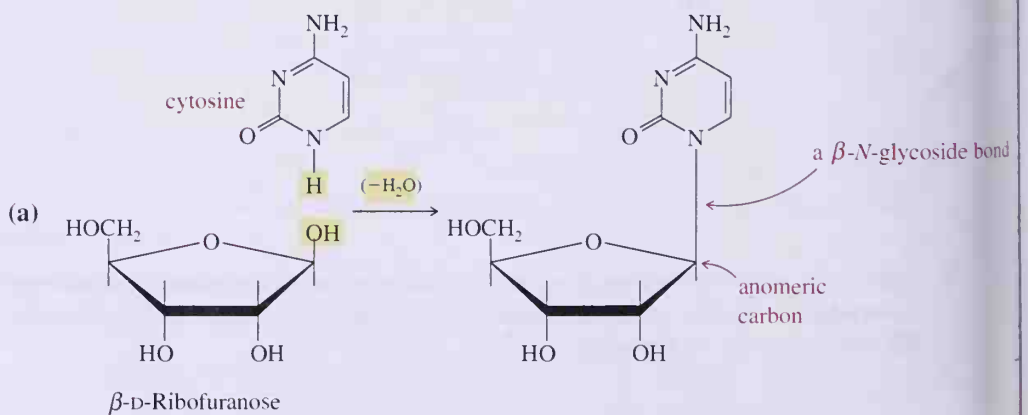
EXAMPLE 18.6

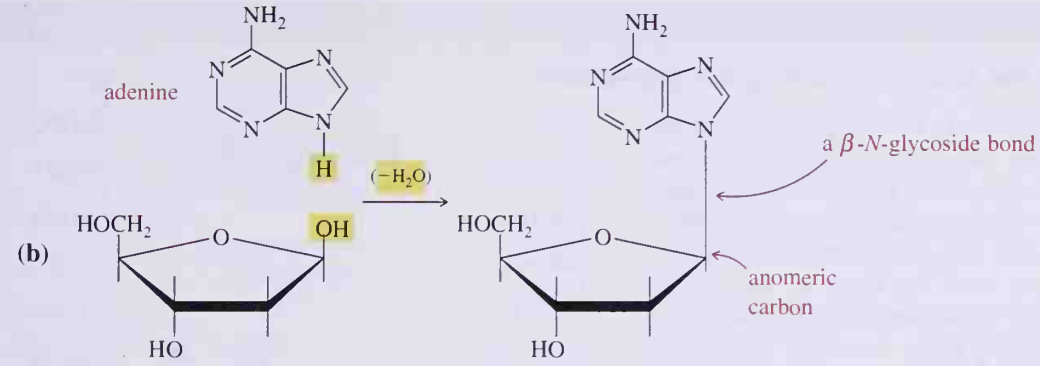
Draw structural formulas for the *N*-glycosides formed between the following compounds. In each, label the anomeric carbon and the *N*-glycoside bond.

(a) β-D-Ribofuranose (β-D-ribose) and cytosine
(b) β-2-Deoxy-D-ribofuranose (β-2-deoxy-D-ribose) and adenine

Solution

Following are structural formulas for each heterocyclic aromatic amine base, the monosaccharide hemiacetal, and the *N*-glycoside. Each *N*-glycoside bond is labeled.





β-2-Deoxy-D-ribofuranose

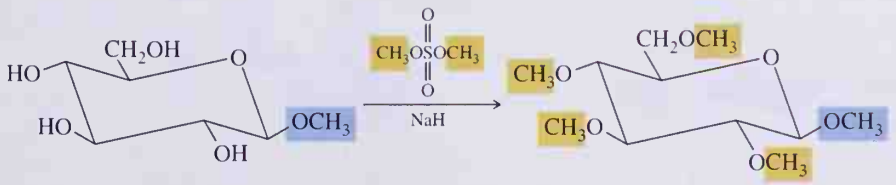
PROBLEM 18.6

Draw structural formulas for the *N*-glycosides formed between the following compounds. In each, label the anomeric carbon and the *N*-glycoside bond.

(a) β-2-Deoxy-D-ribofuranose (β-2-deoxy-D-ribose) and uracil
(b) β-D-Ribofuranose (β-D-ribose) and guanine

B. Formation of Methyl Ethers

Treatment of a monosaccharide with methanol or another alcohol in the presence of an acid catalyst converts it into a mixture of α- and β-glycosides. All remaining —OH groups can be converted to methyl ether groups by treatment of the glycoside with dimethyl sulfate in the presence of a strong base such as sodium hydride, NaH. In this reaction, the function of sodium hydride is to convert —OH (a poor nucleophile) into $—O^-$ (a good nucleophile), which then participates in an S_N2 reaction by attacking a carbon of dimethyl sulfate and displacing sulfate ion (a good leaving group).



Methyl β-D-glucopyranoside

Methyl 2,3,4,6-tetra-*O*-methyl-β-D-glucopyranoside

Because all free —OH groups on the monosaccharide are converted to $—OCH_3$ groups, the process is called **permethylation.** In naming these compounds, each $—OCH_3$, other than that on the anomeric carbon, is named as an *O*-methyl group.

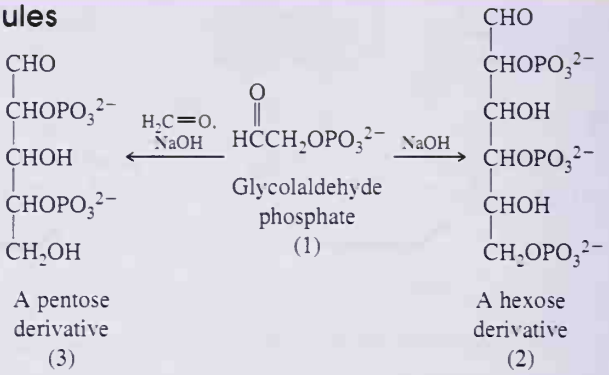
Treatment of a permethylated glycoside with dilute aqueous acid results in hydrolysis of the methyl glycoside bond (acetals are hydrolyzed in dilute aqueous acid; Section 17.9B), but other $—OCH_3$ groups are unaffected (ethers are stable under these conditions; Section 11.6A).

(Text continued on p. 738)

CHEMISTRY IN ACTION

Understanding the Shapes of Biological Molecules

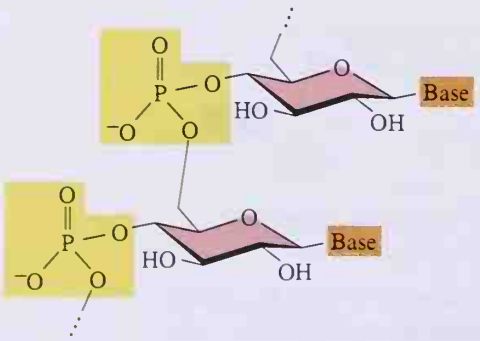
The late politician, Robert F. Kennedy, was known for saying "Some people see things as they are and ask why. Others see things as they could be and ask why not." This approach can be applied to science as well as to politics. The Swiss chemist, Albert Eschenmoser, asked why DNA and RNA are based on five-carbon sugars (pentoses) and not six-carbon sugars (hexoses). Both kinds of sugars are easily formed in abiological reactions of the kind that might have taken place at the origin of life. The reaction of the two-carbon molecule glycolaldehyde phosphate (1) in the presence of sodium hydroxide gives hexose derivatives (2). If the same reaction conditions also include the one-carbon compound formaldehyde, pentose derivatives are the major products (3).



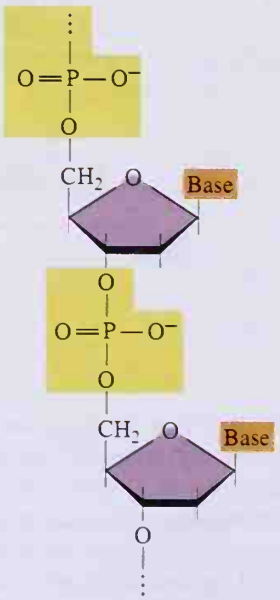
A pentose derivative (3)

A hexose derivative (2)

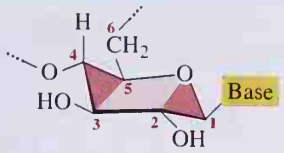
The double-helix structure of DNA is now well known, thanks to the brilliant deductions of Watson and Crick. A strand of DNA consists of pentoses in a five-member cyclic acetal form joined by phosphate ester groups and having a heterocyclic aromatic amine base bonded to each sugar by a nitrogen-containing acetal bond. Because six-carbon sugars are so prevalent, Eschenmoser asked what kind of structure a hexose-based DNA molecule might have. He discovered that if all the groups in a hexose-based DNA strand were in their lowest energy conformation, the hexose DNA would have a three-dimensional shape very different from that of naturally occurring ribose-based DNA. There would be no helix. Instead, the strands would be linear. The reason for this difference between natural DNA and the hypothetical hexose-based DNA lies in the conformation of six-member rings. In the chair conformation of lowest energy, all the bonds in the six-member ring are perfectly staggered as can be seen in a Newman projection. Notice that in the Newman projection, the dihedral angle between oxygen on carbon 4 and the CH_2 group on carbon 5 is 60°. Another way to visualize this geometry is to picture the numbers on a clock face. If oxygen bonded to carbon 4 is placed at 12 o'clock, then CH_2 bonded to carbon 5 is at 10 o'clock. The dihedral angle

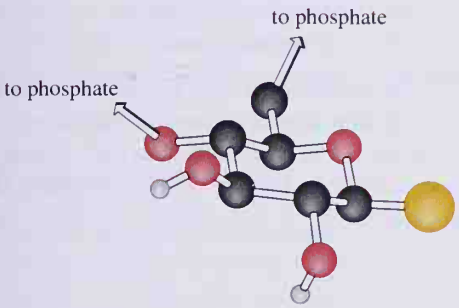


A hexose-based nucleic acid

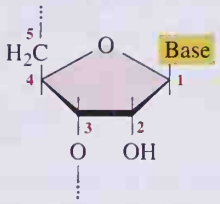


A pentose-based nucleic acid

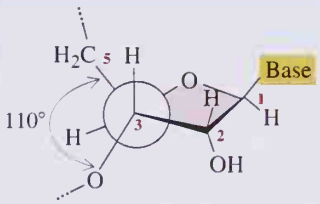




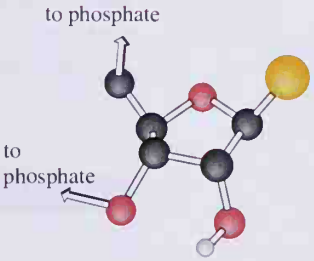
Chair conformation of a hexose in a hexose-based nucleic acid

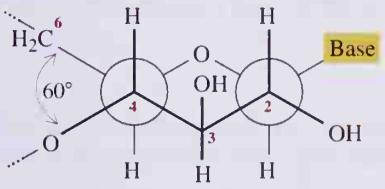


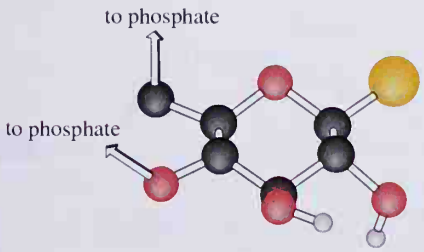
Conformation of a pentose in a pentose-based nucleic acid



Newman projection of a pentose in a pentose-based nucleic acid. View is along bond 3–4.







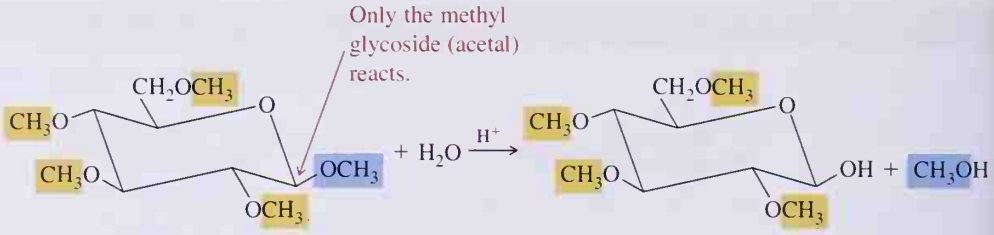
Newman projection of hexose in a hexose-based nucleic acid. Views are along bonds 2–1 and 4–5.

is 60° in the clockwise direction, or +60°. If the Newman projection were made along any other bond of the hexose-based DNA backbone, we would see dihedral angles of 60° as well. For some of these groups, if we place the front atom at 12 o'clock, the back atom is at 10 o'clock. The dihedral angle is 60° in a counterclockwise direction, or −60°. When we make Newman projections for all the bonds in the backbone of hexose-based DNA, we find that the sum of all dihedral angles, including plus and minus signs, is zero. In other words, every time one bond twists right, another bond twists left. This cancellation explains why the hexose DNA would be linear, instead of helical.

If we do the same Newman projection analysis for naturally occurring ribose-based DNA, we find that groups on the five-member ring are not perfectly staggered as they are on a six-member ring. The five-member ring is more nearly planar, and some dihedral angles are very close to 110°. If we sum these angles, we get a value of 36°. This means that each time a unit of ribose is added to a pentose-based DNA chain, the structure is extended and twisted by 36° relative to the lower unit. It is this twisting that produces a helical structure.

Eschenmoser's insights into the nature of hexose-based DNAs show that they would have very different three-dimensional structures from natural ribose-based DNAs. This fact by itself, however, does not explain why DNA is based on a pentose rather than a hexose. Instead, it makes us ask new questions, such as, are helical structures better storehouses of genetic information than linear structures?

See Eschenmoser, A., and M. Dobler, *Helv. Chim. Acta* **75**:218 (1992).



Methyl 2,3,4,6-tetra-*O*-methyl-*β*-D-glucopyranoside

2,3,4,6-Tetra-*O*-methyl-*β*-D-glucopyranose

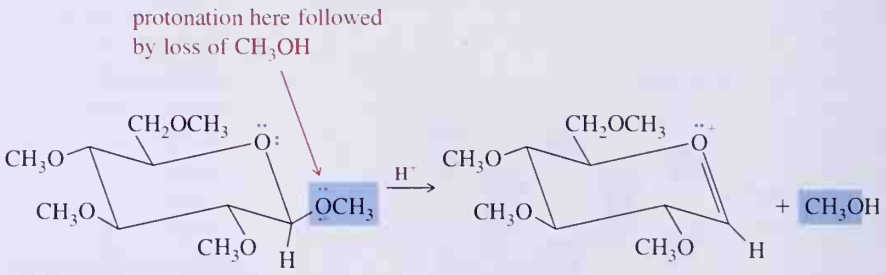
Permethylation followed by acid-catalyzed hydrolysis of the glycoside bond is an important experimental method for determining the ring size of a monosaccharide glycoside. For example, the fact that the preceding reaction of permethylated methyl- *β*-D-glucoside gives 2,3,4,6-tetra-*O*-methyl-D-glucose demonstrates that the cyclic structure in the glycoside must have been formed between the carbonyl group at position 1 and the —OH on carbon 5.

EXAMPLE 18.7

How do you account for the observation that an $-OCH_3$ glycoside bond is hydrolyzed in dilute HCl, but other $-OCH_3$ bonds in a permethylated monosaccharide are not hydrolyzed under these conditions?

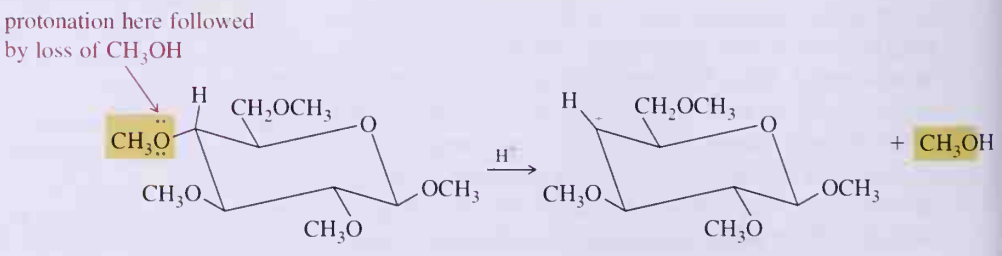
Solution

The slow, rate-determining step in this hydrolysis is formation of a cation. Protonation of the glycoside oxygen followed by loss of methanol gives a resonance-stabilized cation.



A resonance-stabilized cation

Protonation of any other of the methylated oxygens followed by loss of methanol gives an ordinary primary carbocation or secondary carbocation, depending on which carbon loses methanol.



A secondary carbocation

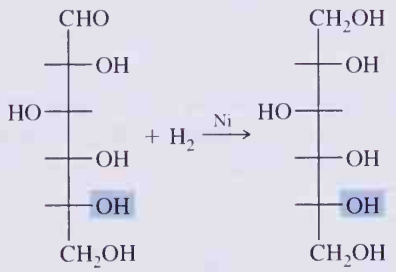
The resonance-stabilized cation formed by loss of the glycoside oxygen is more stable (has a lower energy of activation for its formation) than any of the alternative cations. Recall from Section 11.6A that hydrolysis of a primary or secondary alkyl ether requires hot concentrated acid and a strong nucleophile, both of which are present in concentrated HBr and HI.

PROBLEM 18.7

Suppose it were possible to convert D-glucose to a permethylated D-glucofuranoside. Draw an open-chain formula for the tetra-*O*-methyl-D-glucose that would be isolated after this permethylated derivative is treated with dilute aqueous HCl.

C. Reduction

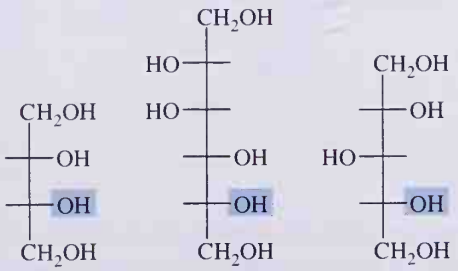
The carbonyl group of a monosaccharide can be reduced to an alcohol group by a variety of reducing agents, including $NaBH_4$ and hydrogen in the presence of a transition metal catalyst. The reduction products are known as **alditols.** Reduction of D-glucose gives D-glucitol, more commonly known as D-sorbitol. Note that D-glucose is shown here in the open-chain form. Only a small amount of this form is present in solution, but as it is reduced, the equilibrium between cyclic hemiacetal forms and the open-chain form shifts to replace it.



D-Glucose D-Glucitol (D-Sorbitol)

Sorbitol is found in the plant world in many berries (except grapes) and in cherries, plums, pears, apples, seaweed, and algae. It is about 60% as sweet as sucrose (table sugar) and has been used in the manufacture of candies and as a sugar substitute for diabetics. Approximately 70% of orally ingested sorbitol is metabolized to CO_2 in the body without appearance as glucose in the blood.

Also common in the biological world are erythritol and D-mannitol.



Erythritol D-Mannitol Xylitol

At one time, xylitol was used as a sweetening agent in "sugarless" gum, candy, and sweet cereals. However, it has been removed from the market because tests showed it to be potentially carcinogenic.

EXAMPLE 18.8

D-Glucose is reduced by $NaBH_4$ to D-glucitol. Do you expect the alditol formed under these conditions to be optically active or optically inactive? Explain.

Solution

D-Glucitol is a chiral substance. Given the fact that reduction by $NaBH_4$ does not affect any of the stereocenters, predict the product to be optically pure and optically active.

PROBLEM 18.8

D-Erythrose is reduced by $NaBH_4$ to erythritol. Do you expect the alditol formed under these conditions to be optically active or optically inactive? Explain.

D. Oxidation

Cu(II) and Ag(I)

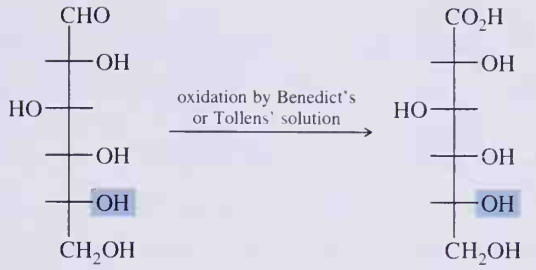
The aldehyde group of an aldose is oxidized to a carboxyl group by solutions of silver ion in aqueous ammonia (Tollens' solution, Section 17.15A) or cupric ion (Benedict's or Fehling's reagent). A positive Tollens' test is indicated by precipitation of metallic silver in the form of a silver mirror.

$$\underset{\text{RCH}}{\overset{\text{O}}{\overset{\|}{\text{C}}}}\text{H} + 2\text{Ag(NH}_3)_2^+ + 3\text{OH}^- \longrightarrow \underset{\text{RCO}^-}{\overset{\text{O}}{\overset{\|}{\text{C}}}} + \underset{\text{Precipitates as a silver mirror}}{2\text{Ag}} + 2\text{H}_2\text{O} + 4\text{NH}_3$$

Benedict's and Fehlings' solutions are prepared by adding copper(II) sulfate to a solution of sodium carbonate in either a citrate buffer (**Benedict's solution**) or tartrate buffer (**Fehling's reagent**). The function of citrate or tartrate is to buffer the pH of the solution and to form a complex ion with copper(II). A positive test is indicated by formation of copper(I) oxide, which precipitates as a red solid.

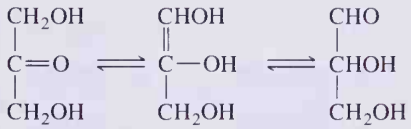
$$\underset{\text{RCH}}{\overset{\text{O}}{\overset{\|}{\text{C}}}}\text{H} + 2\text{Cu}^{2+} + 5\text{OH}^- \xrightarrow[\text{tartrate buffer}]{\text{citrate or}} \underset{\text{RCO}^-}{\overset{\text{O}}{\overset{\|}{\text{C}}}} + 3\text{H}_2\text{O} + \underset{\text{Precipitates as a brick-red solid}}{\text{Cu}_2\text{O}}$$

Oxidation of an aldose or 2-ketose by Benedict's or Tollens' solutions yields a monocarboxylic acid known as an **aldonic acid.** For example, D-glucose is oxidized to D-gluconic acid.



D-Glucose D-Gluconic acid

Ketoses also reduce these solutions. Carbon 1 of a ketose is not oxidized directly. Rather, the basic conditions of the test catalyze isomerization of a 2-ketose to an aldose by way of an enediol intermediate. The aldose then gives the positive test with Tollens', Fehling's, and Benedict's solutions.

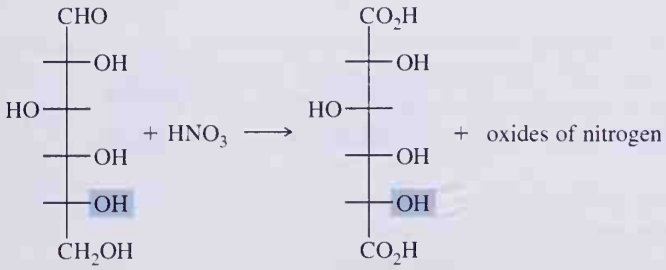


A ketose An enediol An aldose

Carbohydrates that reduce copper(II) ion to Cu_2O or silver(I) to metallic silver are classified as **reducing sugars.** Those that do not reduce these reagents are classified as **nonreducing sugars.** The chemical basis for this classification depends on two features: first, all reducing sugars are hemiacetals in equilibrium with small amounts of open-chain aldoses or ketoses; second, in dilute base, the condition of these tests, ketoses are in equilibrium with aldoses via enediol intermediates.

Nitric Acid

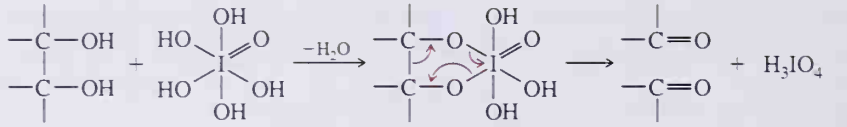
Warm nitric acid oxidizes the —CHO group of an aldose to a $—CO_2H$ group and also oxidizes the terminal $—CH_2OH$ to $—CO_2H$. A dicarboxylic acid derived from an aldose is called an **aldaric acid.** For example, oxidation of D-glucose by nitric acid yields D-glucaric acid.



D-Glucose D-Glucaric acid

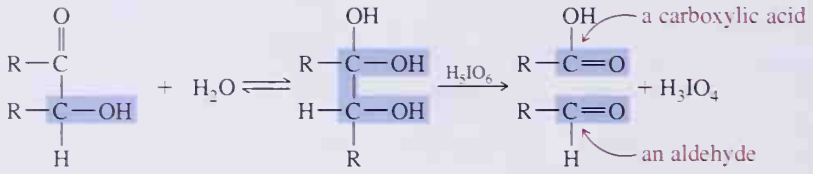
Periodic Acid

Periodic acid, H_5IO_6, cleaves carbon-carbon bonds of a **1,2-diol (glycol,** Section 17.5B) in a reaction that proceeds through a cyclic periodate ester. In this reaction, iodine(VII) of periodic acid is reduced to iodine (V) of iodic acid.

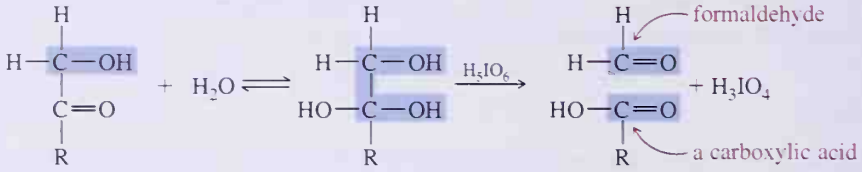


A 1,2-diol | Periodic acid | A cyclic periodate ester | Iodic acid

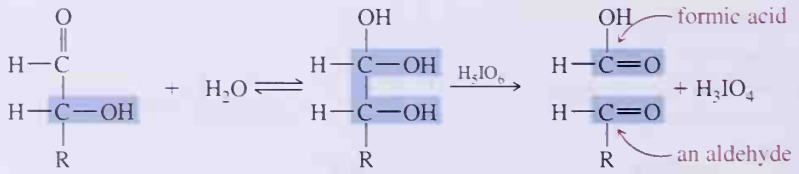
Periodic acid also cleaves carbon-carbon bonds of other oxidizable groups including α-hydroxyketone groups and α-hydroxyaldehyde groups by a similar mechanism. Following are abbreviated structural formulas for these combinations of functional groups and the products of their oxidative cleavage by periodic acid. As a way to help you understand how each set of products is formed, each carbonyl in a starting material is shown as a hydrated intermediate which then is oxidized. In this way, each oxidation can be viewed as analogous to oxidation of a glycol.



α-Hydroxyketone | Hydrated intermediate

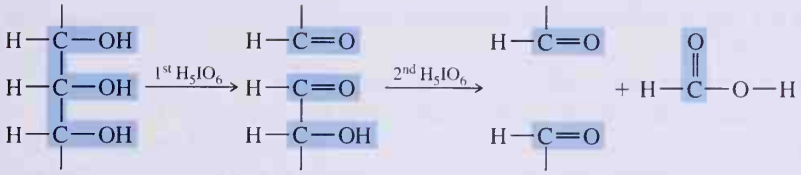


α-Hydroxyketone | Hydrated intermediate

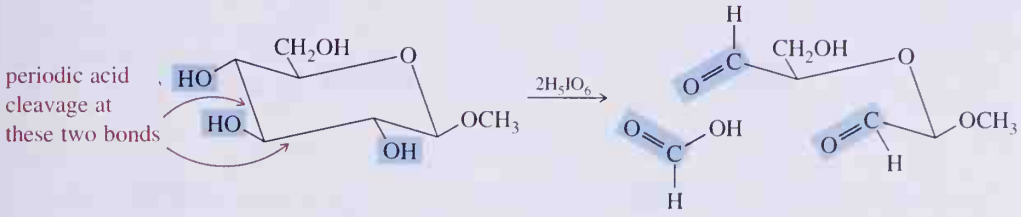


α-Hydroxyaldehyde | Hydrated intermediate

Periodic acid oxidation has proven useful in structure determinations of carbohydrates, particularly in determining the size of glycoside rings. For example, methyl β-D-glucoside consumes 2 mol of periodic acid and produces 1 mol of formic acid. This stoichiometry and the formation of formic acid is possible only if —OH groups are on three adjacent carbon atoms.

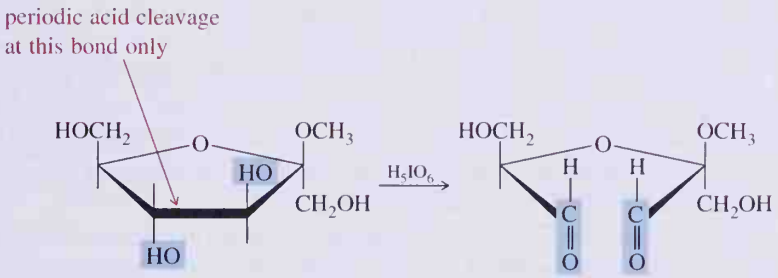


This is evidence that methyl β-D-glucoside is indeed a pyranoside.



Methyl β-D-glucopyranoside

Methyl β-D-fructoside consumes only one mole of periodic acid and produces neither formaldehyde nor formic acid. Thus, oxidizable groups exist on adjacent carbons at only one site in the molecule. The fructoside, therefore, must be a five-member ring (a fructofuranoside).



Methyl β-D-fructofuranoside

18.5 Glucose Assays: The Search for Specificity

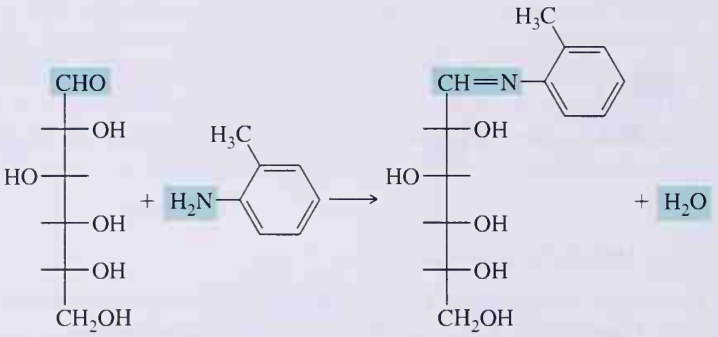
The analytical procedure most often performed in the clinical chemistry laboratory is the determination of glucose in blood, urine, or other biological fluid. The need for a rapid and reliable test for glucose stems from the high incidence of diabetes mellitus. Approximately 2 million known diabetics live in the United States, and it is estimated that another million diabetics are undiagnosed.

Diabetes mellitus is characterized by insufficient blood levels of the polypeptide hormone, insulin (Section 24.7). If the concentration of insulin is insufficient, muscle and liver cells do not absorb glucose, which in turn leads to increased levels of blood glucose (hyperglycemia), impaired metabolism of fats and proteins, ketosis, and possible diabetic coma. Thus, a rapid and reliable procedure for the determination of blood glucose levels is critical for early diagnosis and effective management of this disease.

During the past 70 years, many such tests have been developed. We discuss three of these, each chosen to illustrate some of the problems involved in developing suitable clinical laboratory tests and how these problems can be solved. Furthermore, these tests

illustrate the use of both chemical and enzymatic techniques in the modern clinical chemistry laboratory.

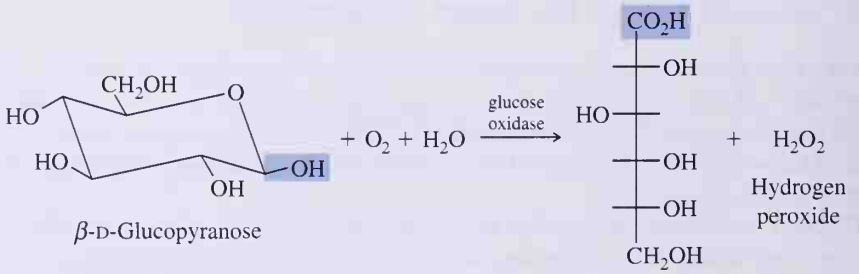
One of the most successful and widely used glucose assays is based on the fact that aldehydes react with primary aliphatic and aromatic amines to form imines (Section 17.11A). Specifically, when glucose is treated with *o*-toluidine (2-methylaniline), it forms an imine with a blue-green color and with an absorption at 625 nm, the intensity of which is directly proportional to glucose concentration.



D-Glucose 2-Methylaniline (*o*-Toluidine) An imine (blue-green)

The *o*-toluidine method can be applied directly to serum, plasma, cerebrospinal fluid, and urine, and to samples as small as 20 μL (20×10^{-6} L). Although this method can be used to measure glucose concentrations, it has the disadvantage that galactose and mannose, and to a lesser extent lactose and xylose, also react with *o*-toluidine to give colored imines and, therefore, are potential sources of false-positive results. This, however, is generally not a problem because these mono- and disaccharides are normally present in serum and plasma only in very low concentrations.

In recent years, the search for even greater specificity in glucose determinations led to the introduction of enzyme-based assay procedures. What was needed was an enzyme that catalyzes a specific reaction of glucose but not comparable reactions of any other substance normally present in biological fluids. The enzyme glucose oxidase meets these requirements. It catalyzes the oxidation of β-D-glucose to D-gluconic acid.



β-D-Glucopyranose

D-Gluconic acid

Glucose oxidase is specific for β-D-glucose. Therefore, complete oxidation of any sample containing both β-D-glucose and α-D-glucose requires conversion of the α form to the β form. Fortunately, this interconversion is rapid and complete in the short time required for the test. Molecular oxygen, O_2, is the oxidizing agent in this reaction and is reduced to hydrogen peroxide, H_2O_2, the concentration of which can be determined spec-

trophotometrically. In one procedure, hydrogen peroxide is reacted with iodide ion to form molecular iodine.

$$2I^- + H_2O_2 + 2H^+ \longrightarrow I_2 + 2H_2O$$

$$I_2 + I^- \longrightarrow I_3^-$$

The absorption of triiodide ion at 420 nm is used to calculate iodine concentration from which the concentration of glucose can be determined. In another procedure, hydrogen peroxide formed in the glucose oxidase-catalyzed reaction is used to oxidize *o*-toluidine to a colored product in a reaction catalyzed by the enzyme, peroxidase. The concentration of the colored oxidation product is determined spectrophotometrically and is proportional to the concentration of glucose in the test solution.

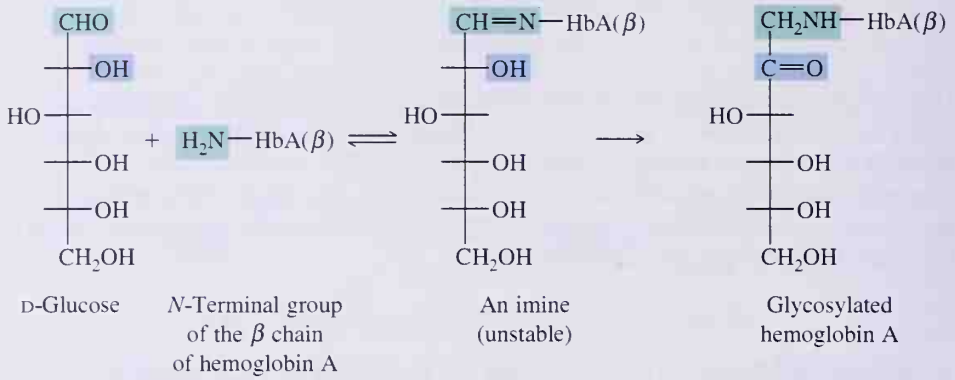
$$o\text{-Toluidine} + H_2O_2 \xrightarrow{\text{peroxidase}} \text{colored product} + H_2O$$

Several commercially available test kits use the glucose oxidase reaction for qualitative determination of glucose in urine. One of these, Clinistix (produced by the Ames Co., Elkhart, Ind.), consists of a filter paper strip impregnated with glucose oxidase, peroxidase, and *o*-toluidine. The test end of the paper is dipped into a urine sample, removed, and examined after 10 s. A blue color develops if the concentration of glucose in the urine exceeds about 1 mg/mL.

Any determination of glucose in blood reflects glucose levels during the sampling period only. There is now a simple, convenient laboratory method that can be used to monitor long-term glucose levels. This method depends on the measurement of the relative amounts of hemoglobin and certain hemoglobin derivatives normally present in blood. Hemoglobin A (HbA) is the main type of hemoglobin present in normal red blood cells. In addition, several lesser components are present, including glycosylated hemoglobins (HbA_1). Glycosylated hemoglobins are synthesized within red blood cells in two steps. In Step 1, the free $—NH_2$ group of the β chain of hemoglobin reacts with the carbonyl group

Chemstrip kit for blood glucose test. *(Charles D. Winters)*

of glucose to form an imine. Step 1 is reversible. In a slower, irreversible second step, the imine undergoes a type of keto-enol tautomerism to form a glycosylated hemoglobin.



D-Glucose | *N*-Terminal group of the β chain of hemoglobin A | An imine (unstable) | Glycosylated hemoglobin A

Because this slow, irreversible second step occurs continuously throughout the 120-day life span of a typical red blood cell population, levels of glycosylated hemoglobin within this population reflect the average blood glucose levels during that period.

Normal levels of glycosylated hemoglobins fall within the range of 4.5% to 8.5% of total hemoglobin. In cases of uncontrolled or poorly controlled diabetes, the percentage of glycosylated hemoglobins may rise to two or three times these values. Thus, the level of glycosylated hemoglobin can be used to give a picture of the average blood glucose level over the previous 8 to 10 weeks.

18.6 L-Ascorbic Acid (Vitamin C)

The structural formula of L-ascorbic acid (vitamin C) resembles that of a monosaccharide. In fact, this vitamin is synthesized both biochemically and commercially from D-glucose. The biosynthetic route is an example of highly selective enzyme-catalyzed reactions, and the chemical (industrial) synthesis is an example of a creative blend of synthetic organic chemistry and microbiology.

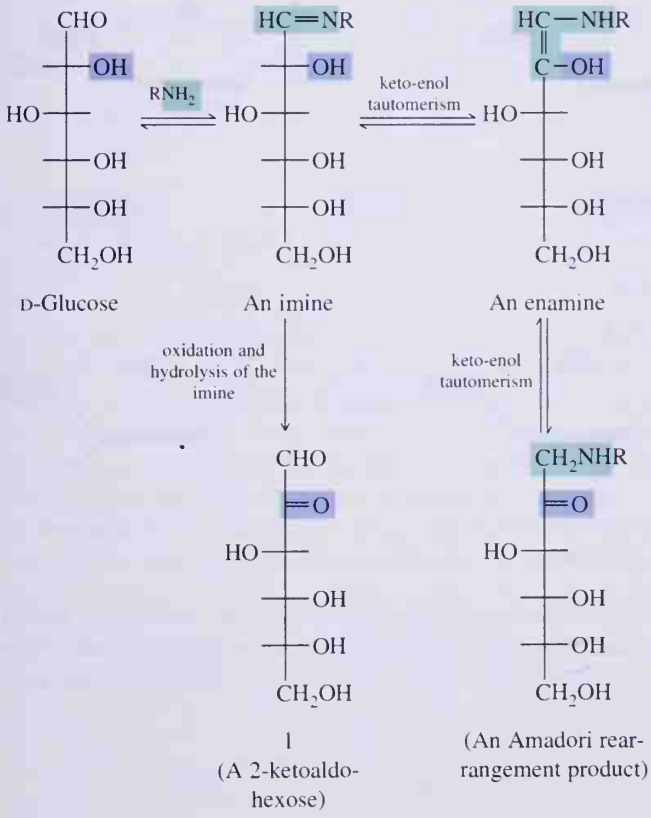
A. Biosynthesis

All steps in the biochemical synthesis of L-ascorbic acid are enzyme-catalyzed. As we look at them, our concern is only to recognize the types of reactions involved, not the particular enzymes or oxidizing and reducing agents. Step 1 in the biochemical synthesis of L-ascorbic acid is oxidation of carbon 6 of D-glucose followed in Step 2 by reduction of the aldehyde group at position 1 to give L-gulonic acid. This acid is of the L series, not because of inversion of configuration at the penultimate carbon of D-glucose but rather because of the rules for writing Fischer projections. Carbon 1 of what was D-glucose is now $-CH_2OH$, and carbon 6 is now $-CO_2H$. According to the Fischer convention, the carbon chain must be turned in the plane of the paper and renumbered so that the carboxyl group (the most highly oxidized carbon) is uppermost and appears as carbon 1. When this is done, the —OH group on the penultimate carbon is now on the left, and, therefore, the resulting monosaccharide belongs to the L series.

CHEMISTRY IN ACTION

The Maillard Reaction

A common complication in diabetes is cataracts. Glycosylated hemoglobin can be used to measure long-term blood glucose levels. The connection between these two statements is a very general and important reaction, the **Maillard reaction.** This reaction, sometimes called nonenzymatic browning, is a series of reactions, beginning with the formation of an imine, between the carbonyl group of the sugar and an NH_2 group of an amino acid or protein. Keto-enol tautomerism of the imine gives an enamine (Section 17.11A). A second keto-enol tautomerism gives a stable aminoketone called an Amadori rearrangement product. The imine may also undergo oxidation and hydrolysis to give a 2-ketoaldohexose.



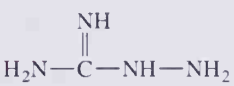
I
(A 2-ketoaldohexose)

(An Amadori rearrangement product)

Many proteins in the body with long half-lives are modified by the Maillard reaction. In the case of the proteins in the lens of the eye, reaction of sugar groups with their amine substituents (a process called glycosylation) changes the proteins' shape, causing them to aggregate and thus leading to the opaqueness of cataracts. Because most diabetics do, from time to time, have higher than normal blood sugar levels, their lens proteins are more prone to cataract formation due to glycosylation.

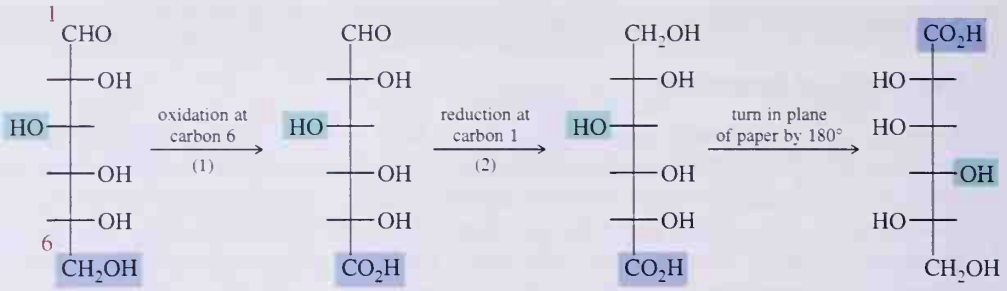
The oxygen transport protein, hemoglobin, which is present in red blood cells, is another example of a protein that reacts with glucose to give Amadori rearrangement products. Over the lifetime of a red blood cell, glucose reacts with an NH_2 group of hemoglobin to form a glycosylated hemoglobin designated HbA_{1c} (Section 18.5). The amount of HbA_{1c} in the blood is a measure of how well diabetic patients are controlling their glucose levels over a period of 8–10 weeks.

With time, the glycosylated hemoglobin undergoes further reactions to produce fluorescent compounds of unknown structure, named advanced glycosylation hemoglobin end products (Hb-AGEs). This type of Maillard reaction adduct is formed with many long-lived proteins in the body. It is associated with the arterial rigidity common in old age. Such rigidity is also seen, at an accelerated rate, in many diabetic patients. The formation Hb-AGE is a useful marker for this type of harmful adduct of bodily proteins in general. Normal patients average 0.42% of their hemoglobin as Hb-AGE; with diabetic patients the average is 0.75%. The experimental drug, aminoguanidine, lowers the proportion of Hb-AGE in diabetics' blood substantially.



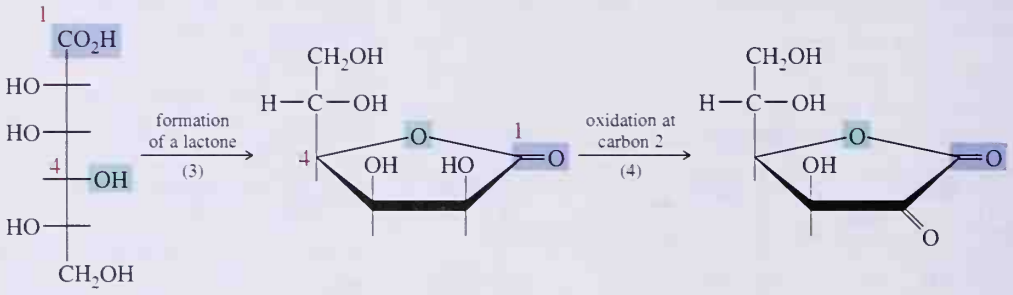
Aminoguanidine

Perhaps by interfering with the Maillard reaction, a drug of this type may be able to prevent some of the complications of diabetes and even slow some of the complications of aging.



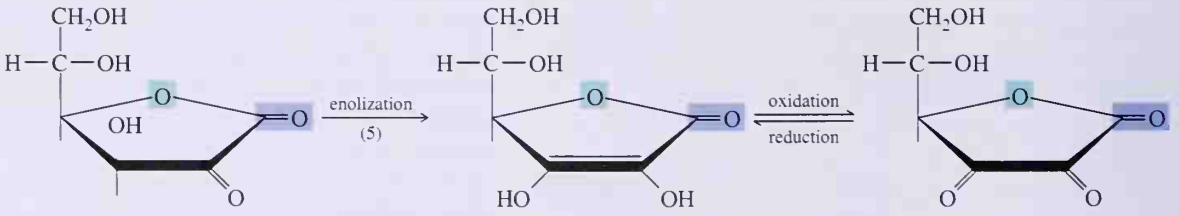
D-Glucose D-Glucuronic acid L-Gulonic acid

In Step 3, L-gulonic acid is converted to L-gulonolactone (lactone is a name given to a cyclic ester). Because humans lack the enzyme system necessary to convert L-gulonic acid to L-gulonolactone, we, along with other primates and guinea pigs, are unable to synthesize ascorbic acid. Oxidation in Step 4 converts the secondary alcohol group at carbon 2 to a ketone.



L-Gulonic acid L-Gulonolactone

Enolization of the carbonyl group at position 2 in Step 5 forms L-ascorbic acid.



L-Ascorbic acid (Vitamin C) L-Dehydroascorbic acid

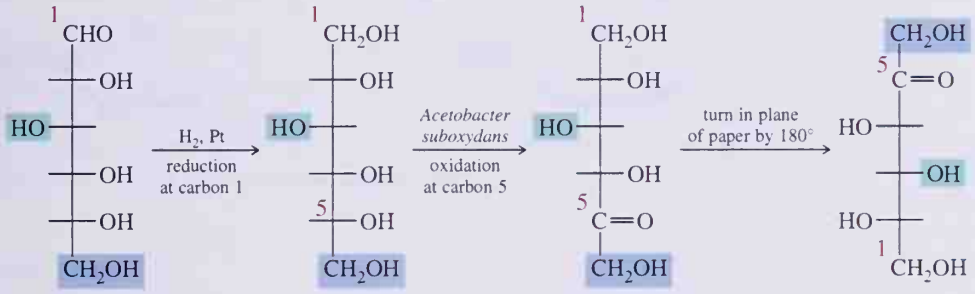
L-Ascorbic acid is very easily oxidized to L-dehydroascorbic acid, a diketone. Both L-ascorbic acid and L-dehydroascorbic acid are physiologically active and are found together in most body fluids. Activity is lost if the lactone group of either molecule is hydrolyzed to a carboxyl group and a hydroxyl group.

B. Industrial Synthesis

Approximately 30 million pounds of vitamin C is synthesized every year in the United States, and its synthesis illustrates the use of microbiological fermentation as a synthetic tool where no purely chemical method can carry out a particular step or steps in a regioselective or stereoselective manner. When supplied with suitable nutrients, single-cell orga-

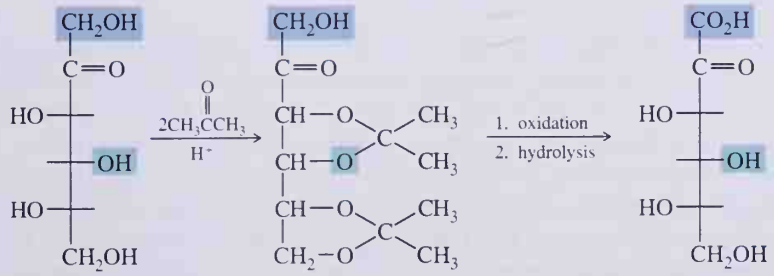
nisms, such as yeast, mold, and bacteria, multiply, and as they do so, waste products from their metabolism accumulate. Under favorable circumstances, these wastes can be concentrated for other uses. For example, among the most common modern antibiotics, the penicillins, streptomycins, tetracyclines, and cephalosporins are all made by microbiological fermentation.

A classic example of the blend of chemistry and microbiological fermentation is the industrial synthesis of vitamin C. It begins with a readily available and very inexpensive raw material, D-glucose, which is reduced by catalytic hydrogenation to D-sorbitol. Selective oxidation of the secondary alcohol group on carbon 5 of the sorbitol chain is the next step. There is no known way to bring about this selective oxidation economically by purely chemical means. Success of the synthesis depends on the fact the bacterium *Acetobacter suboxydans* catalyzes this oxidation and converts D-sorbitol to L-sorbose. Note that as in the biochemical synthesis, the monosaccharide is now of the L series, not because of inversion of configuration at any stereocenter, but because of the rules of the Fischer convention. The carbon chain must be turned so that the more highly oxidized end is toward the top, in which case, the chiral carbon farthest from the carbonyl group has an L configuration. Thus, oxidation of D-sorbitol catalyzed by the enzyme systems of *Acetobacter suboxydans* gives L-sorbose.



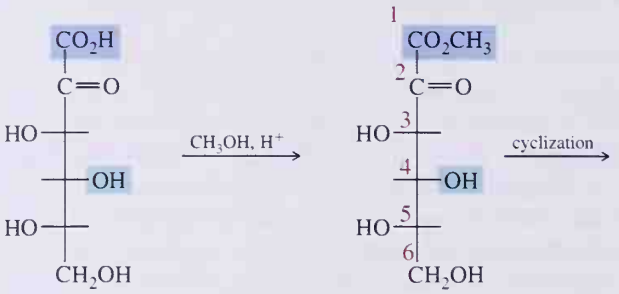
D-Glucose — D-Glucitol (D-Sorbitol) — L-Sorbose

At this stage, the chemist takes over to complete the synthesis of vitamin C. The first task is to protect all but one of the remaining —OH groups so that the primary alcohol adjacent to the carbonyl group can be oxidized to a carboxyl group. Protection is achieved by treating L-sorbose with 2 mol of acetone in the presence of an acid catalyst. Two five-member cyclic acetals form: one by the —OH groups on carbons 3 and 4, the other by the —OH groups on carbons 5 and 6. Note that no attempt is made in the structural formula of the diacetal to show the stereochemistry of each chiral carbon. Oxidation of the remaining primary alcohol followed by hydrolysis of the cyclic acetals gives 2-keto-L-gulonic acid.



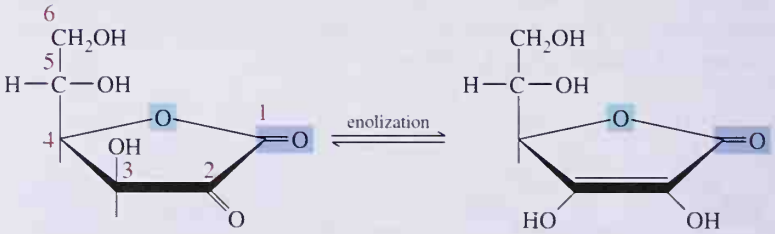
L-Sorbose — 2-Keto-L-gulonic acid

2-Keto-L-gulonic acid is then converted to a methyl ester by reaction with methanol in the presence of an acid catalyst (Section 19.9A) followed by cyclization to form L-ascorbic acid.



2-Keto-L-gulonic acid

Methyl ester of
2-keto-L-gulonic acid



L-Ascorbic acid
(Vitamin C)

18.7 Disaccharides and Oligosaccharides

Most carbohydrates in nature contain more than one monosaccharide unit. Those that contain two units are called **disaccharides,** those that contain three are called **trisaccharides,** as so forth. The more general term, **oligosaccharide,** is often used for carbohydrates that contain from four to ten monosaccharides. Carbohydrates containing larger numbers of monosaccharides are called **polysaccharides.**

In a disaccharide, two monosaccharide units are joined together by a glycoside bond between the anomeric carbon of one unit and an —OH of the other. Three important disaccharides are maltose, lactose, and sucrose.

A. Maltose

Maltose derives its name from its presence in malt, the juice from sprouted barley and other cereal grains. Maltose consists of two molecules of D-glucopyranose joined by a glycoside bond between carbon 1 (the anomeric carbon) of one glucose unit and carbon 4 of the second glucose unit. Because the oxygen atom on the anomeric carbon of the first glucose unit is alpha, the bond joining the two glucose units is called an α-1,4-glycoside bond. Shown in Figure 18.7 are Haworth and chair formulas for β-maltose, so named because the —OH on the anomeric carbon of the rightmost glucose unit is beta. Maltose is a reducing sugar because the hemiacetal group on the right-hand unit of D-glucose is in equilibrium with the free aldehyde and can be oxidized to a carboxylic acid.

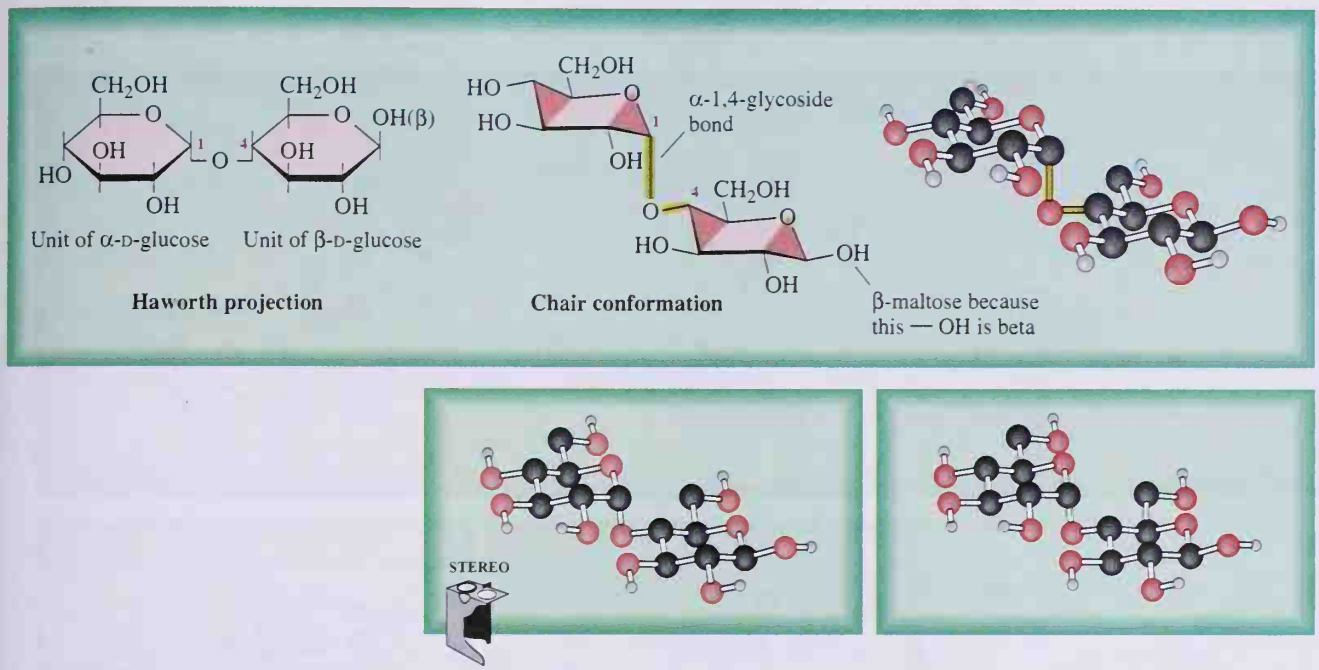


Figure 18.7
β-Maltose (derived from hydrolysis of starch). *Note:* The 1,4-glycoside bond shown in the Haworth structure is C-1—O—C-4, not C-1—CH_2—O—CH_2—C-4 as the intersections of lines on either side of oxygen might suggest. These line intersections are unavoidable consequences of the Haworth practice of drawing monosaccharide rings parallel to one another.

B. Lactose

Lactose (Figure 18.8) is the principal sugar present in milk. It makes up about 5% to 8% of human milk and 4% to 6% of cow's milk. Hydrolysis of lactose yields D-glucose and D-galactose. In lactose, D-galactopyranose is joined by a β-glycoside bond to carbon 4 of D-glucopyranose. Lactose is a reducing sugar.

Persons who are intolerant of milk and milk products have a deficiency in lactase, the enzyme normally present in the intestinal villi that catalyzes the hydrolysis of lactose to galactose and glucose. This disorder affects about 10% of the white population in the United States, and occurs more commonly among African-Americans, Asians, Native Americans, and Hispanics.

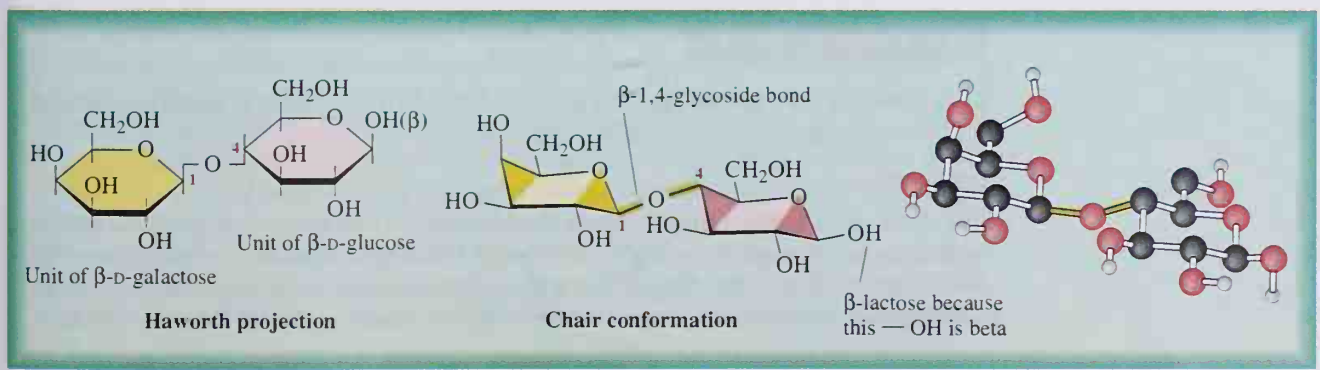


Figure 18.8
Lactose (from the milk of mammals).

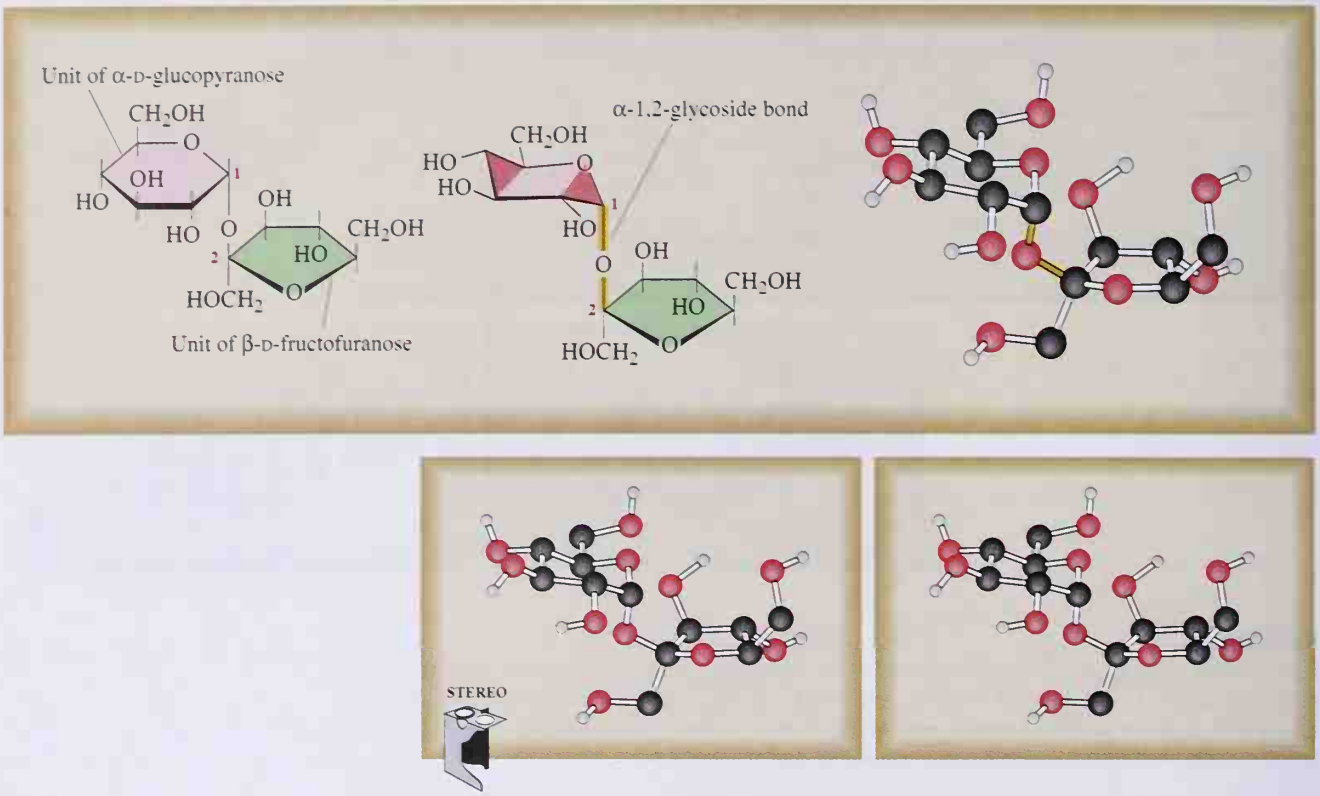


Figure 18.9
Sucrose (from sugar cane and sugar beet).

C. Sucrose

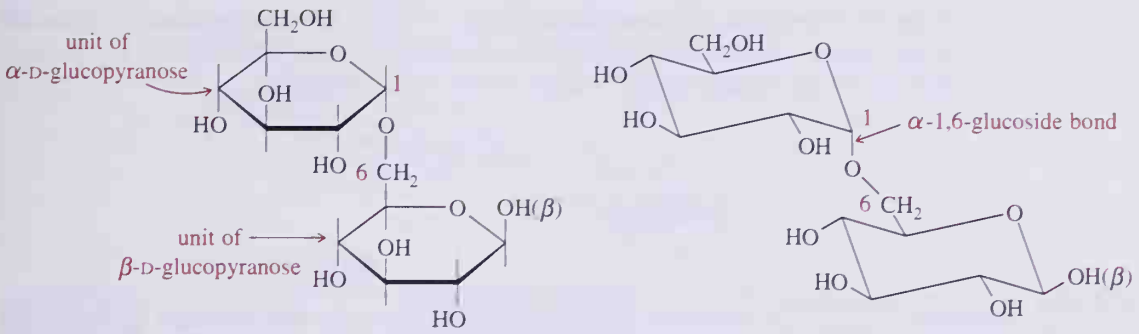
Sucrose (table sugar) is the most abundant disaccharide in the biological world (Figure 18.9). It is obtained principally from the juice of sugar cane and sugar beets. In sucrose, carbon 1 of D-glucose is joined to carbon 2 of D-fructose by an α-1,2-glycoside bond. Glucose is in a six-member (pyranose) ring form, whereas fructose is in a five-member (furanose) ring form. Because the anomeric carbons of both glucose and fructose are involved in formation of the glycoside bond, sucrose is a nonreducing sugar.

EXAMPLE 18.9

Draw Haworth and chair formulas for the β-anomer of a disaccharide in which two units of D-glucopyranose are joined by an α-1,6-glycoside bond.

Solution

First draw the structural formula of α-D-glucopyranose. Then connect the anomeric carbon of this monosaccharide to carbon 6 of a second D-glucopyranose unit by an α-glycoside bond. The resulting molecule is either alpha or beta, depending on the orientation of the —OH group on the reducing end of the disaccharide. The disaccharide shown here is beta.

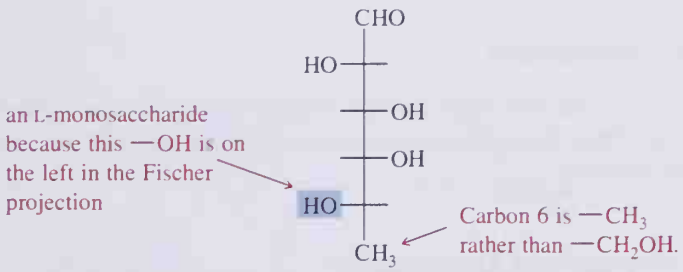


PROBLEM 18.9

Draw Haworth and chair formulas for the α form of a disaccharide in which two units of D-glucopyranose are joined by an β-1,3-glycoside bond.

D. Blood Group Substances

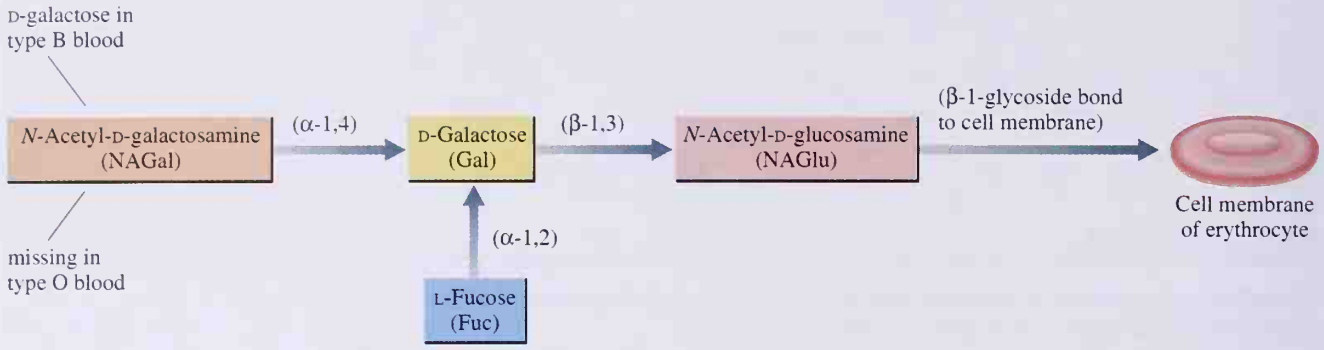
Membranes of animal plasma cells have large numbers of relatively small carbohydrates bound to them. In fact, it appears that the outsides of most plasma cell membranes are literally "sugar-coated." These membrane-bound carbohydrates are part of the mechanism by which cell types recognize each other, and in effect act as biochemical markers **(antigenic determinants).** Typically, these membrane-bound carbohydrates contain from 4 to 17 units composed of a relatively few monosaccharides, including D-galactose (Gal), D-mannose (Man), L-fucose (Fuc), *N*-acetyl-D-glucosamine (NAGlu), and *N*-acetyl-D-galactosamine (NAGal). L-Fucose is a 6-deoxyaldohexose.



L-Fucose

Among the first discovered and best understood of these membrane-bound carbohydrates are the **blood group substances.** Although blood group substances are found chiefly on the surface of erythrocytes (red blood cells), they are also found on proteins and lipids in other parts of the body. In the ABO system, first described in 1900, individuals are classified according to four blood types: A, B, AB, and O. Blood from individuals of the same type can be mixed without clumping (agglutination) of erythrocytes. However, if serum of type A blood is mixed with type B blood, or vice versa, the erythrocytes clump. Serum from a type O individual is compatible with types A, B, and AB blood. At the cellular level, the chemical basis for this classification is a group of relatively small, membrane-bound carbohydrates. Following is the composition of the tetrasaccharide found on the cell mem-

brane of erythrocytes of individuals with type A blood. The configurations of glycoside bonds between the monosaccharide units and of the glycoside bond between the tetrasaccharide and the erythrocyte cell wall are shown in parentheses.



This tetrasaccharide has several distinctive features. First, it contains a monosaccharide of the "unnatural," or L, series, namely L-fucose. Second, it contains D-galactose to which two other monosaccharides are bonded, one by an α-1,2-glycoside bond, the other by an α-1,4-glycoside bond. This last monosaccharide is what determines the ABO classification. In blood of type A, the chain terminates in *N*-acetyl-D-galactosamine (NAGal); in type B blood, it terminates instead in D-galactose (Gal), and in type O blood, the fourth monosaccharide is missing completely. The saccharides of type AB blood contain both A and B tetrasaccharides in the erythrocyte membrane.

18.8 Polysaccharides

Polysaccharides consist of a large number of monosaccharide units joined together by glycoside bonds. Three important polysaccharides all made up of glucose units, are starch, glycogen, and cellulose.

A. Starch: Amylose and Amylopectin

Starch is the carbohydrate used for energy storage in plants. This polysaccharide is found in all plant seeds and tubers and is the form in which glucose is stored for later use by plants. Starch can be separated into two principal polysaccharides: amylose and amylopectin. Although the starch from each plant is unique, most starches contain 20% to 25% amylose and 75% to 80% amylopectin. Complete hydrolysis of both amylose and amylopectin yields only D-glucose. X-ray diffraction studies show that amylose is composed of continuous, unbranched chains of up to 4000 D-glucose units joined by α-1,4-glycoside bonds (Figure 18.10).

Amylopectin has a highly branched structure and contains two types of glycoside bonds. This polymer contains the same type chains of D-glucose joined by α-1,4-glycoside

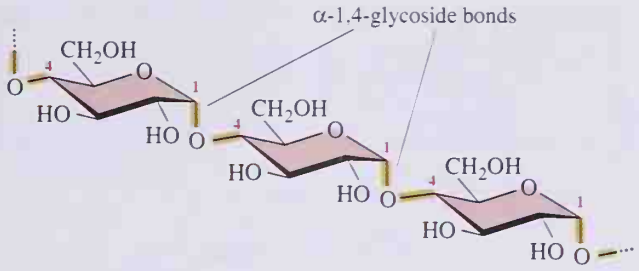


Figure 18.10
Amylose, a linear polymer of up to 4000 units of D-glucopyranose joined by α-1,4-glycoside bonds.

bonds as amylose does, but polymer chains vary in length from only 24 to 30 units (Figure 18.11). In addition, considerable branching occurs from this linear network. At branch points, new chains are started by α-1,6-glycoside bonds between carbon 1 of one glucose unit and carbon 6 of another. In fact amylopectin has such a highly branched structure that it is hardly possible to distinguish between main chains and branch chains.

Why are carbohydrates stored in plants as polysaccharides rather than monosaccharides, a more directly useable form of energy? The answer has to do with osmotic pressure which is proportional to the molar concentration, not the molecular weight, of a solute. If 1000 molecules of glucose are assembled into one starch macromolecule, then a solution containing 1 g of starch per 10 mL will have only 1/1000 the osmotic pressure relative to a solution of 1 g of glucose in the same volume. This feat of packaging is of tremendous advantage because it reduces the strain on various membranes enclosing solutions of such macromolecules.

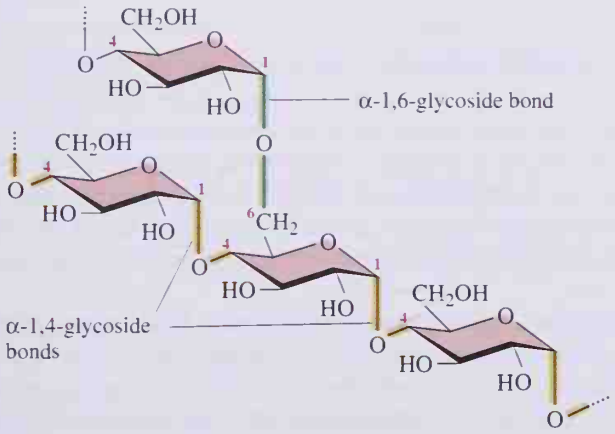


Figure 18.11
Amylopectin is a highly branched polymer of D-glucose. Chains consist of 24–30 units of D-glucose joined by α-1,4-glycoside bonds and branches created by α-1,6-glycoside bonds.

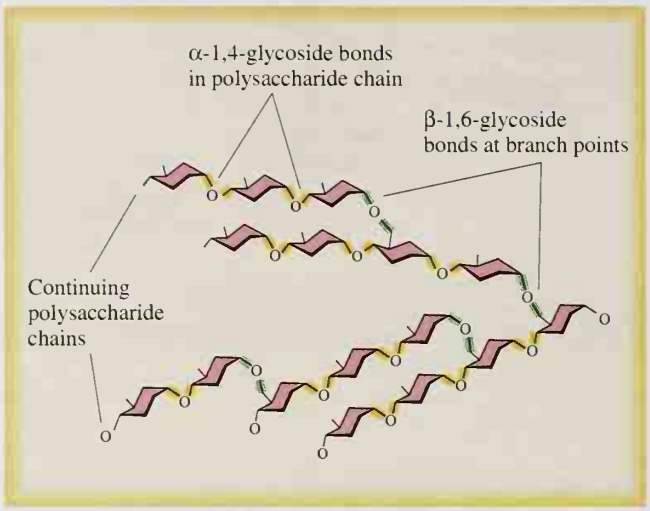


Figure 18.12
Glycogen is a highly branched polymer of D-glucose joined by α-1,4-glycoside bonds. Branches created by α-1,6-glycoside bonds contain 12–18 units of glucose.

B. Glycogen

Glycogen (Figure 18.12) is the reserve carbohydrate for animals. Like amylopectin, glycogen is a nonlinear polymer of D-glucose joined by α-1,4- and α-1,6-glycoside bonds, but it has a lower molecular weight and an even more highly branched structure. The total amount of glycogen in the body of a well-nourished adult is about 350 g, divided almost equally between liver and muscle.

C. Cellulose

Cellulose, the most widely distributed plant skeletal polysaccharide, constitutes almost half of the cell wall material of wood. Cotton is almost pure cellulose. Cellulose is a linear polymer of D-glucose units joined by β-1,4-glycoside bonds (Figure 18.13). It has an average molecular weight of 400,000, corresponding to approximately 2800 glucose units. Cellulose fibers consist of bundles of parallel polysaccharide chains held together by hydrogen bonding between hydroxyl groups on adjacent chains. This arrangement of parallel chains in bundles due to hydrogen bonding gives cellulose fibers their high mechanical strength.

Humans and other animals cannot use cellulose as food because our digestive systems do not contain β-glucosidases, enzymes that catalyze hydrolysis of β-glucoside bonds. Instead we have only α-glucosidases; hence, the polysaccharides we use as sources of glucose are starch and glycogen. On the other hand, many bacteria and microorganisms do contain β-glucosidases and can digest cellulose. Termites are fortunate (much to our regret) to have such bacteria in their intestines and can use wood as their principal food. Ruminants (cud-chewing animals) can also digest grasses and hay because β-glucosidase-containing microorganisms are present within their alimentary systems.

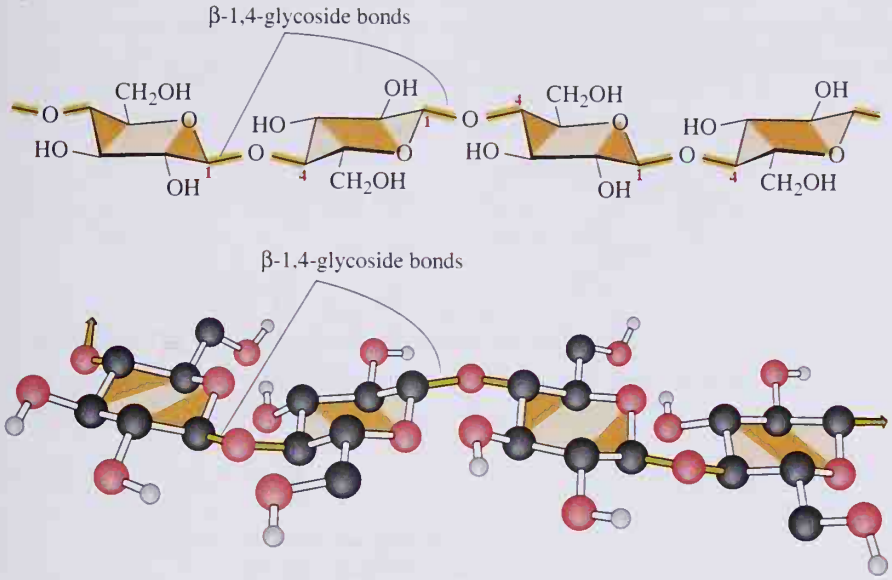


Figure 18.13
Cellulose is a linear polymer of up to 3000 units of D-glucose joined by β-1,4-glycoside bonds.

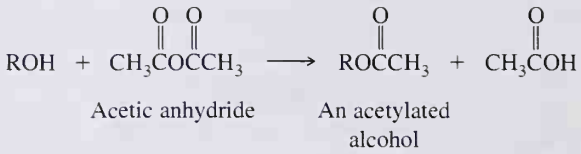
D. Textile Fibers from Cellulose

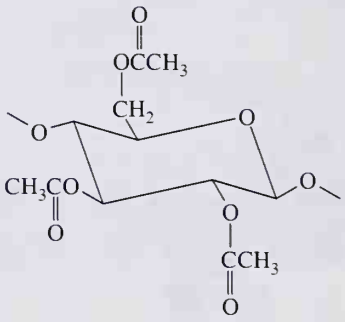
Cotton, an important textile fiber, is almost pure cellulose. Both rayon and acetate rayon are made from chemically modified and regenerated cellulose and were the first synthetic textile fibers to become commercially important.

In the production of rayon, cellulose is treated with carbon disulfide to form alkali-soluble xanthate ester groups. A solution of cellulose xanthate is then extruded through a spinneret, a metal disc with many tiny holes, into dilute sulfuric acid to hydrolyze the xanthate ester groups and precipitate free or "regenerated" cellulose. Regenerated cellulose extruded as a filament is called "viscose rayon" thread; extruded as a sheet, it is called cellophane.

$$\underset{}{\text{ROH}} + \underset{\text{Carbon disulfide}}{\text{CS}_2} + \text{NaOH} \longrightarrow \underset{\text{Sodium salt of a xanthate ester}}{\text{ROC}(=\text{S})\text{S}^-\text{Na}^+}$$

In the industrial synthesis of acetate rayon, cellulose is acetylated with acetic anhydride. Acetylated cellulose is then dissolved in a suitable solvent, precipitated, and drawn into fibers known as acetate rayon. Cellulose acetate, acetylated to the extent of about 80%, became commercial in Europe about 1920 and in the United States a few years later. Cellulose triacetate, which has about 97% of the hydroxyls converted to acetate ester groups, became commercial in the United States in 1954. Today, acetate fibers rank fourth in production in the United States, surpassed only by Dacron polyester, nylon, and rayon fibers.



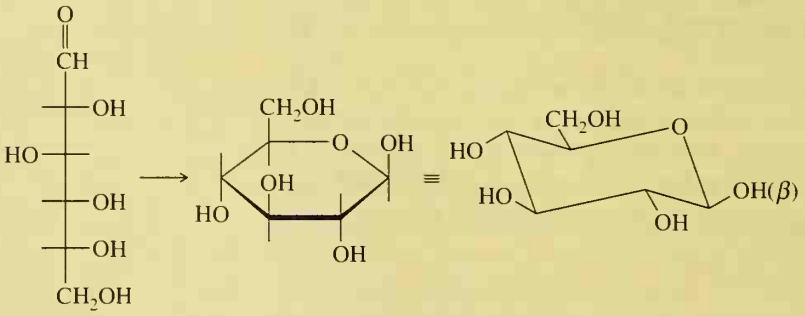


One glucose unit of a fully acetylated cellulose

SUMMARY OF KEY REACTIONS

1. Formation of Cyclic Hemiacetals (Section 18.2)

A five-member cyclic hemiacetal of monosaccharide is a furanose; a six-member cyclic hemiacetal is a pyranose. A pyranose is most commonly drawn as a Haworth projection or as a chair conformation.

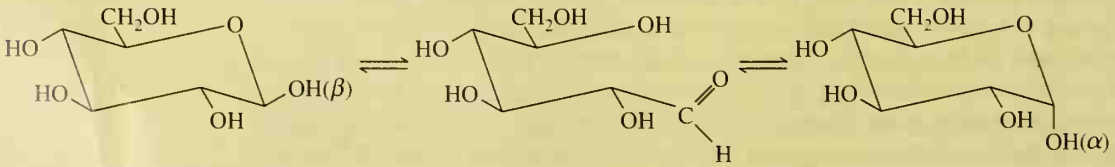


D-Glucose

β-D-Glucopyranose (β-D-Glucose)

2. Mutarotation (Section 18.2D)

Anomeric forms of a monosaccharide are in equilibrium in aqueous solution. Mutarotation is the change in specific rotation that accompanies this equilibration.



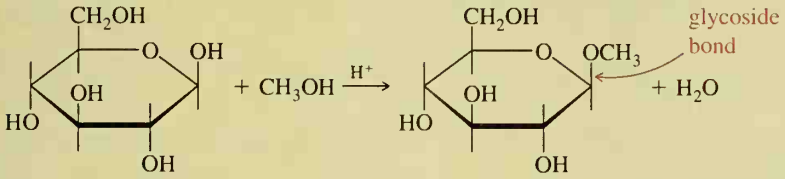
β-D-Glucopyranose
$[\alpha]_D^{25}$ + 18.7°

D-Glucose

α-D-Glucopyranose
$[\alpha]_D^{25}$ + 112°

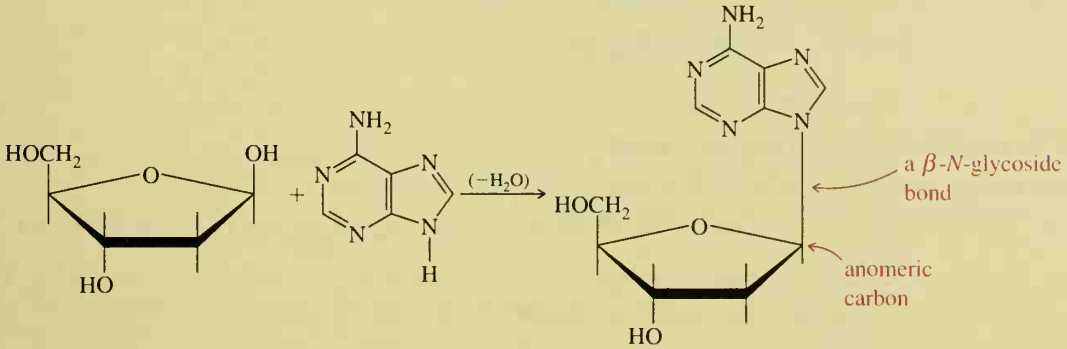
3. Formation of Glycosides (Section 18.4A)

Treatment of a monosaccharide with an alcohol in the presence of an acid catalyst forms a cyclic acetal called a glycoside. The bond to the new —OR group is called a glycoside bond.



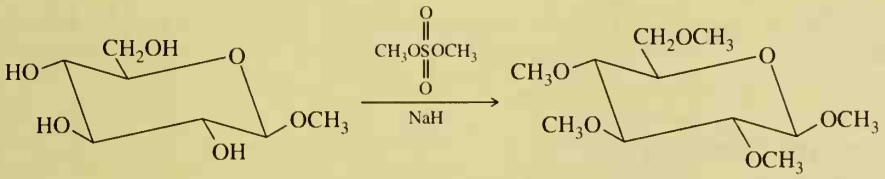
4. Formation of *N*-Glycosides (Section 18.4A)

The *N*-glycosides formed between a monosaccharide and a heterocyclic aromatic amine are especially important in the biological world.



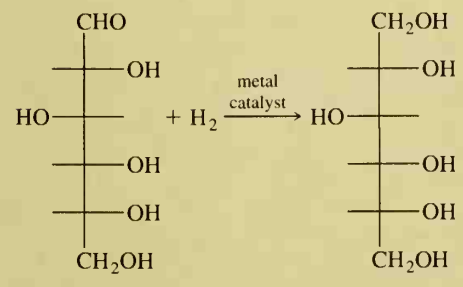
5. Formation of Methyl Ethers (Section 18.4B)

All —OH groups of a carbohydrate can be converted to methyl ether groups by reaction with dimethyl sulfate in the presence of sodium hydride.



6. Reduction (Section 18.4C)

Reduction of the carbonyl group of an aldose or ketose to a hydroxyl group yields a polyhydroxy compound called an alditol.

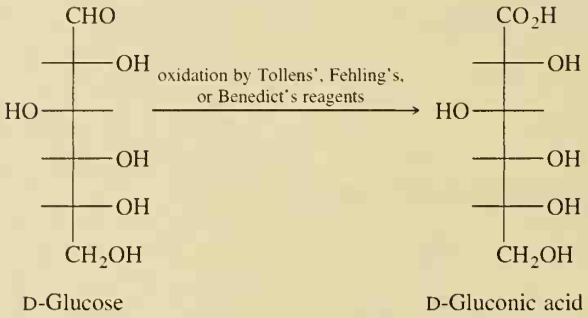


D-Glucose

D-Glucitol (D-Sorbitol)

7. Oxidation to an Aldonic Acid (Section 18.4D)

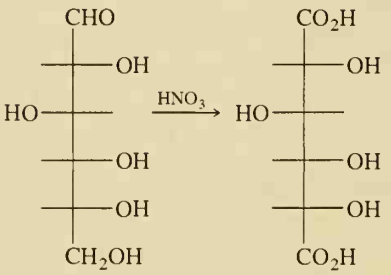
Oxidation of the aldehyde group of an aldose to a carboxyl group by Tollens' reagent, Fehling's reagent, or other mild oxidizing agents gives a polyhydroxycarboxylic acid called an aldonic acid.



D-Glucose D-Gluconic acid

8. Oxidation to an Aldaric Acid (Section 18.4D)

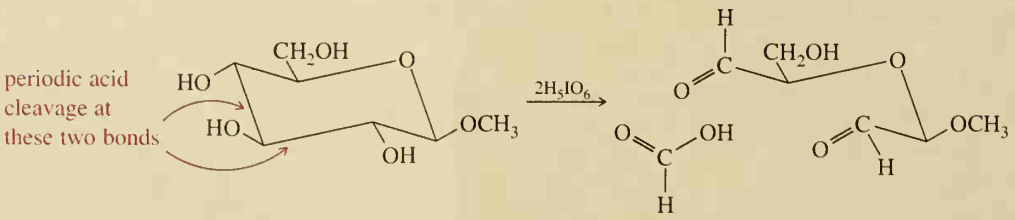
Nitric acid oxidation of both the aldehyde group and the primary alcohol group of an aldose gives a polyhydroxydicarboxylic acid called an aldaric acid.



D-Glucose D-Glucaric acid

9. Oxidation by Periodic Acid (Section 18.4D)

Periodic acid oxidizes and cleaves carbon-carbon bonds of 1,2-glycol, α-hydroxyketone, and α-hydroxyaldehyde groups.



ADDITIONAL PROBLEMS

Monosaccharides

18.10 Explain the meaning of the designations D and L as used to specify the configuration of carbohydrates.

18.11 List the rules for drawing Fischer projections.

18.12 What is the meaning of the prefix deoxy- as it is used in carbohydrate chemistry?

18.13 2,6-Dideoxy-D-altrose, known alternatively as D-digitoxose, is a monosaccharide obtained on hydrolysis of digitoxin, a natural product extracted from foxglove *(Digitalis purpurea)*. Digitoxin has found wide use in cardiology because it reduces pulse rate, regularizes heart rhythm, and strengthens heart beat. Draw the structural formula of 2,6-dideoxy-D-altrose.

18.14 Give L-fucose a name incorporating the prefix "deoxy-" that shows its relationship to galactose.

18.15 Table 18.1 shows a Fischer projection of D-arabinose. Draw a Fischer projection for L-arabinose.

The Cyclic Structure of Monosaccharides

18.16 Build a molecular model of D-glucose and show that its six-member hemiacetals (α-D-glucopyranose and β-D-glucopyranose) have the absolute configurations shown in Figure 18.2 and not the mirror images of these structures.

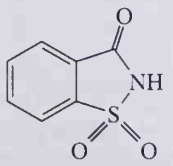
18.17 Explain the conventions of using α and β to designate the configuration of cyclic forms of monosaccharides.

18.18 Explain the phenomenon of mutarotation with reference to carbohydrates. By what means is it detected?

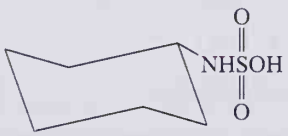
18.19 The table shows specific rotations for the anomers of D-mannose and the value after mutarotation. Calculate the percentage of each anomer present at equilibrium.

	Specific Rotation (Degrees °)	Specific Rotation After Mutarotation (Degrees °)
α-D-mannose	+29.3	+14.5
β-D-mannose	−16.3	+14.5

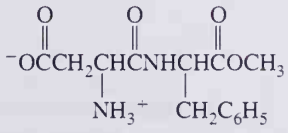
18.20 It has been proposed that structural characteristics of sweet-tasting compounds are (1) a hydrogen bond donating group, AH, (2) a hydrogen bond accepting group, B, and (3) that atoms A and B are separated by between 0.25 and 0.4 nm. Identify the A and B units in these non-nutritive sweeteners.

(a) 

Saccharin
(500× sucrose)

(b) 

Cyclamic acid
(30× sucrose)

(c) 

Aspartame
(160× sucrose)

18.21 It has been observed that sugars that can form one or more strong intramolecular hydrogen bonds are less sweet than sugars which cannot form such hydrogen bonds. Draw chair conformations of β-D-galactose and β-D-mannose and identify one strong intramolecular hydrogen bond in each molecule.

Reactions of Monosaccharides

18.22 Draw Fischer projections for the product(s) formed by reaction of D-galactose with the following. In addition state whether each product is optically active or inactive.

(a) $NaBH_4$ in H_2O **(b)** H_2/Pt **(c)** HNO_3, warm **(d)** $AgNO_3$ in NH_3, H_2O
(e) H_5IO_6 **(f)** $C_6H_5NH_2$

18.23 An important technique for establishing relative configurations among isomeric aldoses and ketoses is to convert both terminal carbon atoms to the same functional group. This can be done either by selective oxidation or reduction. As a specific example, nitric acid oxidation of D-erythrose gives meso-tartaric acid. Similar oxidation of D-threose gives (S,S)-tartaric acid.

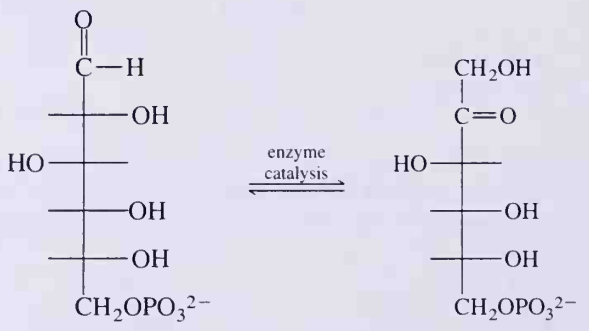
Tartaric acid

Given this information and the fact that D-erythrose and D-threose are diastereomers of each other, draw Fischer projections for D-erythrose and D-threose. Check your answers against Table 18.1.

18.24 There are four D-aldopentoses (Table 18.1). If each is reduced with $NaBH_4$, which yield optically active alditols? Which yield optically inactive alditols?

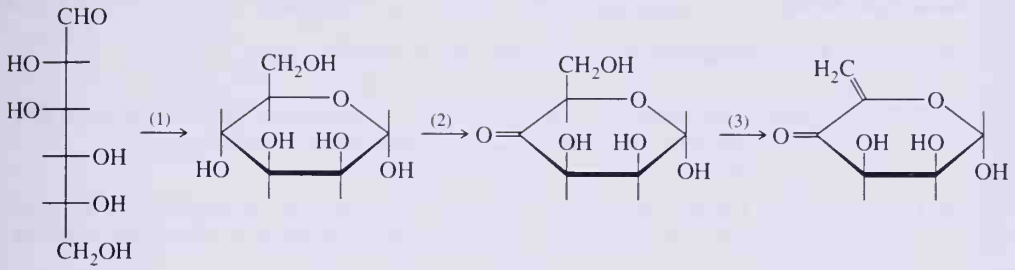
18.25 Name the two alditols formed by $NaBH_4$ reduction of D-fructose.

18.26 One pathway for the metabolism of glucose-6-phosphate is its enzyme-catalyzed conversion to fructose-6-phosphate. Show that this transformation can be regarded as two enzyme-catalyzed keto-enol tautomerism steps.

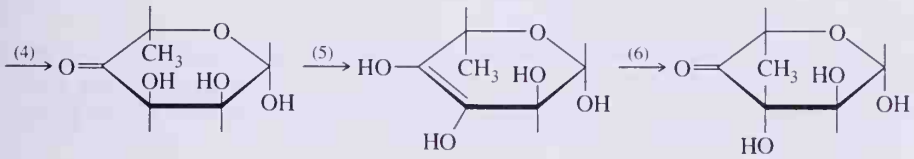


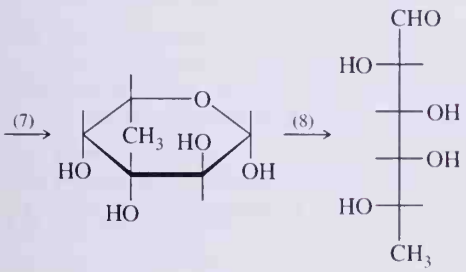
D-Glucose-6-phosphate D-Fructose-6-phosphate

18.27 L-Fucose is one of several monosaccharides commonly found in the surface polysaccharides of animal cells. This 6-deoxyaldohexose is synthesized biochemically from D-mannose in the following eight steps:



D-Mannose





L-Fucose

(a) Describe the type of reaction (i.e., oxidation, reduction, hydration, dehydration, etc.) involved in each step.

(b) Explain why it is that this monosaccharide derived from D-mannose now belongs to the L series.

18.28 **(a)** Draw a structural formula for the compound formed when D-ribose is converted to methyl β-D-ribofuranoside and then permethylated with sodium hydride and dimethyl sulfate.

(b) Draw the structural formula for the product of mild acid-catalyzed hydrolysis of the permethylated compound formed in part (a).

(c) With how many moles of periodic acid does the compound in part (b) react?

18.29 Repeat the preceding problem for 2-deoxy-D-ribose.

18.30 Account for the fact that when permethylated monosaccharides are treated with warm aqueous acid, only the methyl glycoside bond is hydrolyzed.

18.31 Treatment of methyl β-D-glucopyranoside with benzaldehyde forms a six-member cyclic acetal. Draw the most stable conformation of this acetal. Identify each new stereocenter in the acetal? *Hint:* There are free —OH groups on carbons 2, 3, 4, and 6 of methyl β-D-glucopyranoside. Only two of these —OH groups are properly positioned to give a six-member cyclic acetal with benzaldehyde.

Ascorbic Acid

18.32 Assign R or S configurations to each chiral carbon in ascorbic acid.

18.33 Write a balanced half-reaction to show that conversion of ascorbic acid to dehydroascorbic acid is an oxidation. How many electrons are involved in this oxidation?

18.34 Given the fact that ascorbic acid and dehydroascorbic acid are the physiologically active forms of vitamin C, is ascorbic acid a biological oxidizing agent or a biological reducing agent? Explain.

18.35 Ascorbic acid is a diprotic acid with the following acid ionization constants:

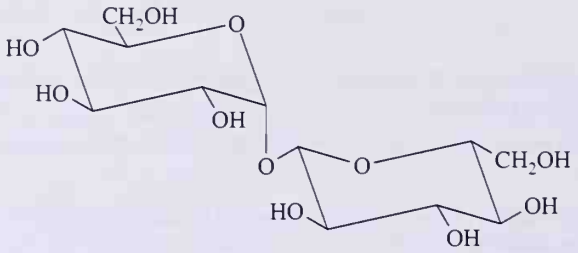
$$pK_{a1} = 4.10 \qquad pK_{a2} = 11.79$$

The two acidic protons are those connected with the enediol part of the molecule. Which proton has which ionization constant? (*Hint:* Draw separately the anion derived by loss of one of these protons and that formed by loss of the other proton. Which anion has the greater degree of resonance stabilization?)

Disaccharides and Oligosaccharides

18.36 In making candy or sugar syrups, sucrose is boiled in water with a little acid, such as lemon juice. Why does the product mixture taste sweeter than the starting sucrose solution?

18.37 Trehalose is found in young mushrooms and is the chief carbohydrate in the blood of certain insects. Trehalose is a disaccharide consisting of two units of D-glucose joined by an α-1,1-glycoside bond.



Trehalose

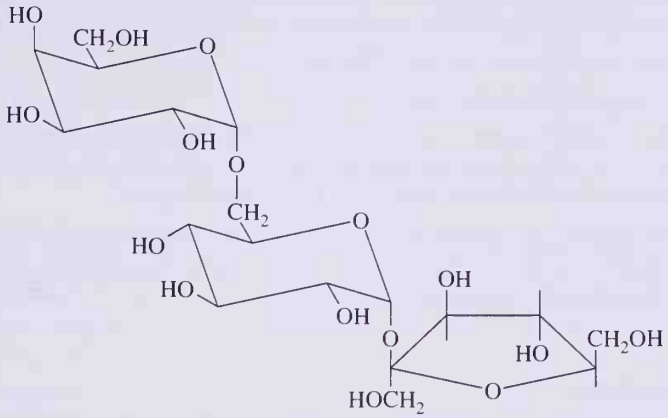
(a) Is trehalose a reducing sugar?

(b) Does trehalose undergo mutarotation?

(c) With how many moles of periodic acid does trehalose react? How many moles of formaldehyde are formed? How many moles of formic acid are formed?

(d) Draw structural formulas for the two *O*-methylated monosaccharides formed when trehalose is permethylated with dimethyl sulfate and sodium hydride and then warmed in dilute aqueous acid to hydrolyze the glycoside bond.

18.38 The trisaccharide raffinose occurs principally in cottonseed meal.



Raffinose

(a) Name the three monosaccharide units in raffinose.

(b) Describe each glycoside bond in this trisaccharide.

(c) Is raffinose a reducing sugar?

(d) With how many moles of periodic acid does raffinose react?

Gentian plant. *(© Larry Ulrich)*

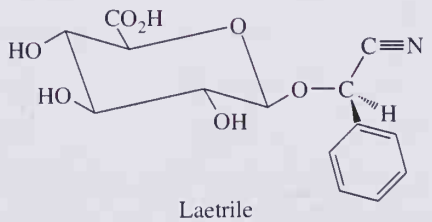
18.39 Gentiobiose is a disaccharide found in a number of natural products, including gentian plants *(Gentiana lutea)*. It is a reducing sugar and is hydrolyzed by β-glycosidases, (enzymes with catalytic activity limited to hydrolysis of β-glycoside bonds). Reaction of gentiobiose with dimethyl sulfate in the presence of sodium hydride yields an octamethyl derivative, which, when hydrolyzed in warm aqueous acid, gives equimolar amounts of 2,3,4,6-tetra-*O*-methyl-D-glucose and 2,3,4-tri-*O*-methyl-D-glucose. Propose a structural formula for gentiobiose.

18.40 Hot water extracts of ground willow bark are an effective pain reliever. Unfortunately, the liquid is so bitter that most persons refuse it. The pain reliever in these infusions is salicin, a glycoside of glucose and 2-(hydroxymethyl)phenol.

(a) Given this information, what four structures are possible for salicin?

(b) A dilute aqueous solution of salicin is neutral. Which structures are now possible for salicin?

18.41 Following is the structural formula of laetrile:



Laetrile

(a) Assign an R or S configuration to the stereocenter bearing the nitrile (—CN) group.

(b) Account for the fact that on hydrolysis in warm aqueous acid, laetrile liberates benzaldehyde and HCN.

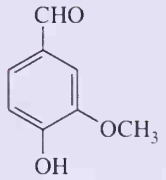
18.42 Amygdalin is a disaccharide glycoside isolated from pits of plants of the genus *Prunus*, which includes plums, apricots, cherries, and peaches. It is called a cyanogenic (cyanide-producing) glycoside because it, like laetrile, releases HCN when hydrolyzed either by warm aqueous acid or by specific enzymes. Hence, amygdalin and other cyanogenic glycosides are poten-

tially very toxic. Complete hydrolysis of amygdalin in warm aqueous acid gives HCN, benzaldehyde, and 2 mol of D-glucose. Partial hydrolysis of amygdalin catalyzed by a specific β-glycosidase gives gentiobiose (see Problem 18.39), HCN, and benzaldehyde.

(a) Propose a structural formula for amygdalin.

(b) Is amygdalin a reducing sugar?

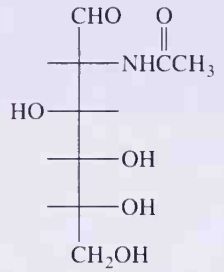
(c) The "natural" isomer of amygdalin has the R configuration on the stereocenter bearing the —CN group. In the presence of dilute base, this stereocenter is racemized to an R,S configuration. Propose a mechanism for this racemization.



Vanillin

18.43 Vanillin, the principal component of vanilla, occurs in vanilla beans and other natural sources as a β-D-glucopyranoside. Draw a structural formula for this glycoside. Draw the D-glucose unit in this glycoside as a chair conformation.

Polysaccharides



N-Acetyl-D-glucosamine

18.44 At left is the Fischer projection for *N*-acetyl-D-glucosamine.

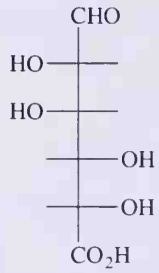
(a) Draw Haworth and chair structures for the α- and β-pyranose forms of this monosaccharide.

(b) Draw Haworth and chair structures for the disaccharide formed by joining two units of the pyranose form of *N*-acetyl-D-glucosamine by a β-1,4-glycoside bond. If you drew this correctly, you drew the structural formula for the repeating dimer of chitin, the structural polysaccharide component of the shell of lobster and other crustaceans.

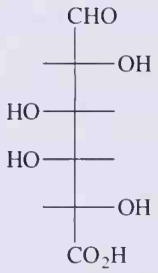
18.45 Propose structural formulas for the following polysaccharides:

(a) Alginic acid, isolated from seaweed, is used as a thickening agent in ice cream and other foods. Alginic acid is a polymer of D-mannuronic acid in the pyranose form joined by β-1,4-glycoside bonds.

(b) Pectic acid is the main component of pectin, which is responsible for the formation of jellies from fruits and berries. Pectic acid is a polymer of D-galacturonic acid in the pyranose form joined by α-1,4-glycoside bonds.



D-Mannuronic acid



D-Galacturonic acid

18.46 Certain types of streptococci found in the mouth, especially *Streptococcus mutans*, have an enzyme system that uses sucrose as a starting material for the synthesis of high-molecular-weight polysaccharides known as **dextrans.** About 10% of the dry weight of dental plaque is composed of dextran. In one study of the dextran composition of dental plaque, dextran was methylated with methyl iodide in the presence of NaH and then the permethylated polysaccharide was hydrolyzed in dilute aqueous acid. The only monosaccharides obtained were the following four *O*-methyl derivatives of D-glucose.

Methylated D-glucose	Mole (%)
2,3,4,6-tetra-*O*-methyl-D-glucose	14.6
2,4,6-tri-*O*-methyl-D-glucose	50.5
2,3,4-tri-*O*-methyl-D-glucose	20.9
2,4-di-*O*-methyl-D-glucose	14.0

(a) Draw the structural formula of the open-chain form of each of these derivatives of D-glucose.

(b) The isolation of one of these derivatives is evidence that one group of glucose units in this dextran participates in only 1,3-glycoside bonds. Explain. What is the percentage of 1,3-glycoside bonds?

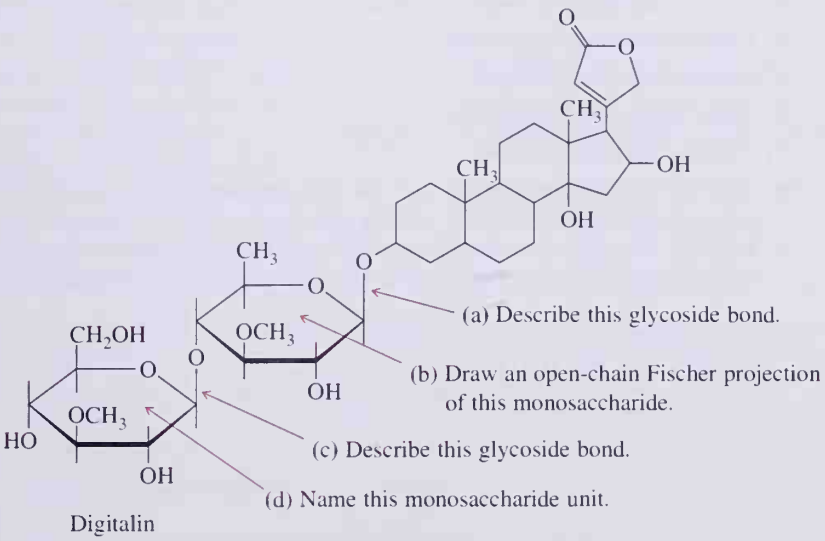
(c) The isolation of a second derivative of D-glucose is evidence that another group of glucose units participates in only 1,6-glycoside bonds. Explain. What is the percentage of 1,6-glycoside bonds?

(d) The isolation of a third glucose derivative is evidence that a third group of glucose units participates in both 1,3- and 1,6-glycoside bonds and, therefore, serves as branchpoints in the polysaccharide chain. Explain. What is the percentage of chain branching?

(e) The fourth derivative of D-glucose represents the glucose units at the end of branched chains. Compare the percentage of this terminal glucose unit with the percentage of chain branching you determined in part (d).

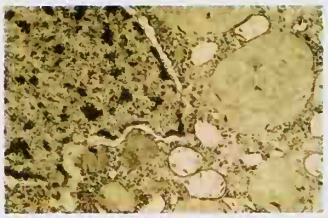
(f) From all of this evidence, sketch the polysaccharide of dextran in the same manner as glycogen is sketched in Figure 18.12.

18.47 Digitalis is a preparation made from the dried seeds and leaves of the foxglove plant, *Digitalis purpurea*. The plant is native to southern and central Europe and cultivated in the United States. The preparation is a mixture of several active components, including digitalin. Digitalis is used in medicine to increase the force of myocardial contraction and as a conduction depressant to decrease heart rate (the heart pumps more forcefully but less often).



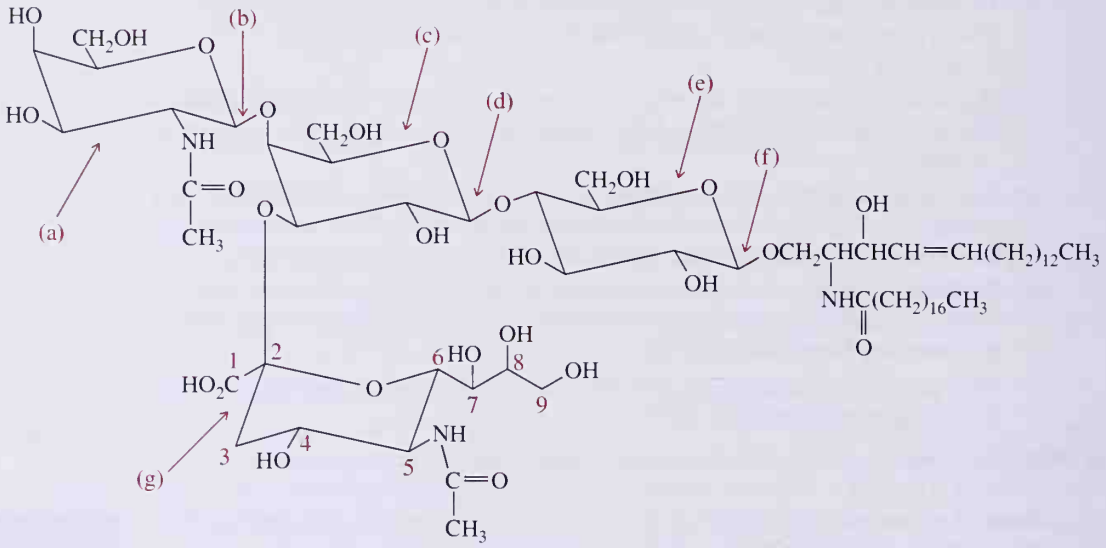
Digitalin

The foxglove plant produces the important cardiac medication digitalis. *(© Lois Moulton, Tony Stone Images)*



Tay-Sachs disease cerebral sphingolipidosis. *(© IMS Creative. All rights reserved. Custom Medical Stock)*

18.48 Following is the structural formula of ganglioside GM_2, a macromolecular glycolipid (meaning that it contains a lipid and monosaccharide units joined by glycoside bonds). In normal cells, this and other gangliosides are synthesized continuously and degraded by lysosomes, which are cell organelles containing digestive enzymes. If pathways for the degradation of gangliosides are inhibited, the gangliosides accumulate in the central nervous system, causing all sorts of life-threatening consequences. In inherited diseases of ganglioside metabolism, death usually occurs at an early age. Diseases of ganglioside metabolism include Gaucher's disease, Niemann-Pick disease, and Tay-Sachs disease. Tay-Sachs disease is a hereditary defect that is transmitted as an autosomal recessive gene. The concentration of ganglioside GM_2 is abnormally high in this disease because the enzyme responsible for catalyzing the hydrolysis of glycoside bond (b) is absent.



Ganglioside GM_2 (Tay-Sachs ganglioside)

(a) Name this monosaccharide unit.

(b) Describe this glycoside bond (α or β, and between which carbons of each unit).

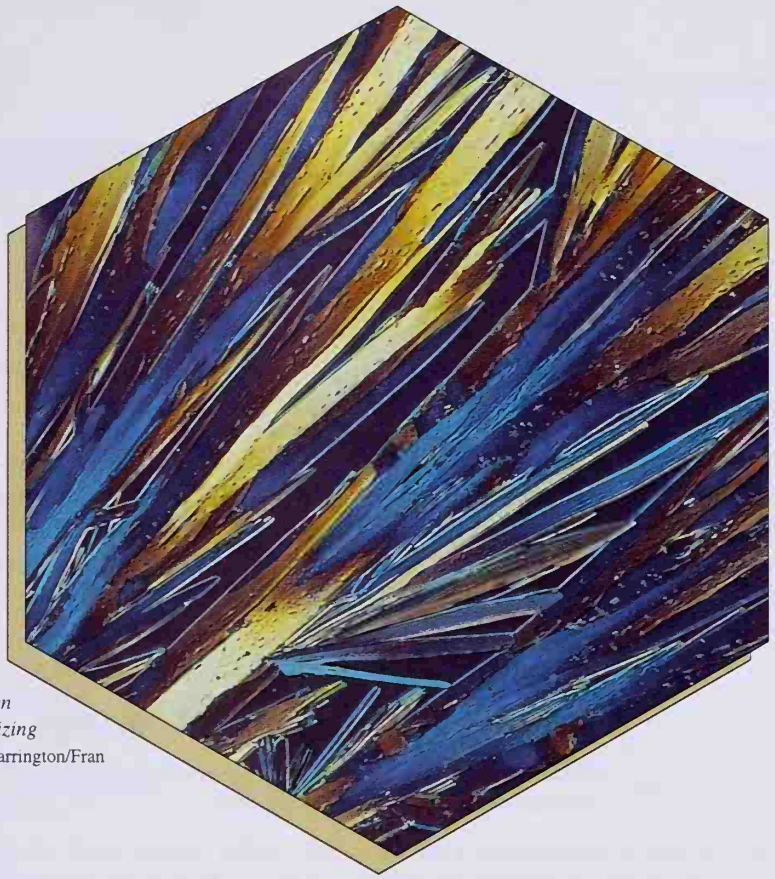
(c) Name this monosaccharide unit.

(d) Describe this glycoside bond.

(e) Name this monosaccharide unit.

(f) Describe this glycoside bond.

(g) This unit is *N*-acetylneuraminic acid, the most abundant member of a family of amino sugars containing nine or more carbons and distributed widely throughout the animal kingdom. Draw the open-chain form of this amino sugar. Do not be concerned with the configuration of the five tetrahedral stereocenters in the open-chain form.



Crystals of ibuprofen viewed under polarizing light. (© Phillip A. Harrington/Fran Heyl Associates)

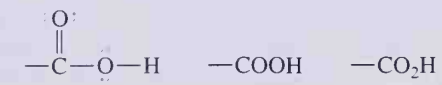
19

CARBOXYLIC ACIDS

The most important chemical property of carboxylic acids, another class of organic compounds containing the carbonyl group, is their acidity. Furthermore, carboxylic acids form numerous important derivatives, including esters, amides, anhydrides, and acid halides. In this chapter we study carboxylic acids themselves; in Chapter 20, we study derivatives of carboxylic acids.

19.1 Structure

The characteristic structural feature of a carboxylic acid is a **carboxyl group,** so named because it is made up of a **carb**onyl group and a hydr**oxyl** group. Following is a Lewis structure of the carboxyl group as well as two alternative representations for it:



Alternative representations of a carboxyl group

The general formula of an aliphatic carboxylic acid is R—CO_2H; the general formula for an aromatic carboxylic acid is Ar—CO_2H.

RCO_2H	$ArCO_2H$
An aliphatic carboxylic acid	An aromatic carboxylic acid

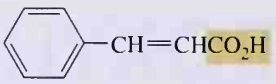
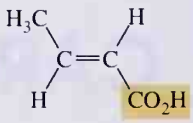
19.2 Nomenclature

A. IUPAC System

The IUPAC name for a carboxylic acid is derived from the name of the longest carbon chain that contains the carboxyl group by dropping the final **-e** from the name of the parent alkane and adding the suffix **-oic** followed by the word **acid** (Section 2.5). The chain is numbered beginning with the carbon of the carboxyl group. The carboxyl carbon is understood to be carbon 1. The IUPAC system retains the common names formic acid and acetic acid.

HCO_2H	CH_3CO_2H	$CH_3CHCH_2CO_2H$ (with CH_3 branch)
Methanoic acid (Formic acid)	Ethanoic acid (Acetic acid)	3-Methylbutanoic acid

If the carboxylic acid contains a carbon-carbon double or triple bond, change the infix from -an to **-en-** or **-yn-** to indicate the presence of the multiple bond, and show the location of the multiple bond by a number.

$H_2C{=}CHCO_2H$		
Propenoic acid (Acrylic acid)	3-Phenylpropenoic acid (Cinnamic acid)	(E)-2-Butenoic acid (*trans*-Crotonic acid)

In the IUPAC system, a carboxyl group takes precedence over most other functional groups (Table 17.1), including hydroxyl groups and amino groups, as well as the carbonyl groups of aldehydes and ketones. As illustrated in the following examples, an —OH group is indicated by the prefix hydroxy-, an —NH_2 group is indicated by the prefix amino-, and an aldehyde or ketone C=O group is indicated by the prefix oxo-.

$CH_3CHCH_2CH_2CH_2CO_2H$ (with OH)	$H_2NCH_2CH_2CH_2CO_2H$	$CH_3CCH_2CH_2CH_2CO_2H$ (with O)
5-Hydroxyhexanoic acid	4-Aminobutanoic acid	5-Oxohexanoic acid

Dicarboxylic acids are named by adding the suffix **-dioic acid** to the name of the parent alkane that contains both carboxyl groups. The numbers of the carboxyl carbons are not indicated because they can only be on the ends of the alkane chain. The IUPAC system retains the common names oxalic, malonic, succinic, and tartaric acids. Listed in Table 19.1 are IUPAC names and common names for several important aliphatic dicarboxylic acids. The name of oxalic acid is derived from one of its sources in the biological world,

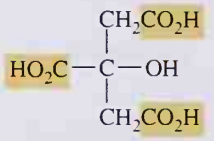
Table 19.1 Some aliphatic dicarboxylic acids

Structural Formula	IUPAC Name	Common Name
$HOC{-}COH$ (O, O)	ethanedioic acid	oxalic acid
$HOCCH_2COH$ (O, O)	propanedioic acid	malonic acid
$HOCCH_2CH_2COH$ (O, O)	butanedioic acid	succinic acid
$HOCCHCHCOH$ (O, O; HO, OH)	2,3-dihydroxybutanedioic acid	tartaric acid
$HOCCH_2CH_2CH_2COH$ (O, O)	pentanedioic acid	glutaric acid
$HOCCH_2CH_2CH_2CH_2COH$ (O, O)	hexanedioic acid	adipic acid

namely, plants of the genus *Oxalis*, one of which is rhubarb. Tartaric acid is a byproduct of fermentation of D-glucose in grape juice to produce wine. It is collected as the potassium hydrogen salt and sold as "cream of tartar." Adipic acid is one of the two monomers required for the synthesis of the polymer nylon 66. In 1993, the U.S. chemical industry produced 1.6 billion pounds of adipic acid, solely for the synthesis of nylon 66.

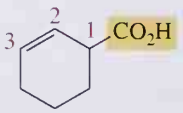
Leaves of the rhubarb plant contain the poison oxalic acid. *(© Ann Reilly: PHOTO/NATS)*

Name tri- and higher carboxylic acids by using the suffixes **-tricarboxylic acid, -tetracarboxylic acid,** and so on. An example of a tricarboxylic acid is 2-hydroxy-1,2,3-propanetricarboxylic acid, whose common name (citric acid) the IUPAC retains. Citric acid can be extracted from citrus juices; lemon juice, for example contains 5% to 8% citric acid. Citric acid is important in a metabolic pathway known alternatively as the tricarboxylic acid (TCA) cycle, or Krebs cycle.

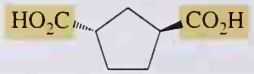


2-Hydroxy-1,2,3-propanetricarboxylic acid
(Citric acid)

A carboxylic acid containing a carboxyl group attached to a cycloalkane ring is named by giving the name of the ring and adding the suffix -carboxylic acid. The atoms of the ring are numbered beginning with the carbon bearing the $—CO_2H$ group.

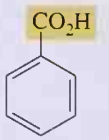


2-Cyclohexenecarboxylic acid

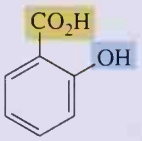


trans-1,3-Cyclopentanedicarboxylic acid

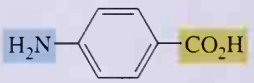
The simplest aromatic carboxylic acid is benzoic acid. Derivatives are named by using numbers and prefixes to show the presence and location of substituents relative to the carboxyl group. Certain aromatic carboxylic acids have common names by which they are more usually known. For example, 2-hydroxybenzoic acid is more often called salicylic acid, a name derived from the fact that this aromatic carboxylic acid was first isolated from the bark of the willow, a tree of the genus *Salix*. 4-Aminobenzoic acid, more commonly named *p*-aminobenzoic acid (PABA), is a growth factor required by microorganisms for the synthesis of folic acid. At the molecular level, sulfa drugs function as antibiotics by virtue of their ability to inhibit the enzyme system in bacteria that catalyzes the incorporation of PABA into folic acid (Section 20.15).



Benzoic acid



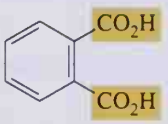
2-Hydroxybenzoic acid
(Salicylic acid)



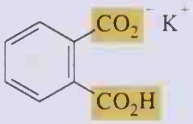
4-Aminobenzoic acid
(PABA)

Aromatic dicarboxylic acids are named by adding the words dicarboxylic acid to "benzene." Following are structural formulas for 1,2-benzenedicarboxylic acid and 1,4-benzenedicarboxylic acid. Each is more usually known by its common name: phthalic acid and terephthalic acid. The monopotassium salt of phthalic acid (potassium hydrogen phthalate, or KHP) is widely used as a primary standard in preparing solutions for acid-base titrations. Terephthalic acid is one of the two organic components required for the synthesis of the textile fiber known as Dacron polyester, or Dacron.

Bark of the willow, *Salix alba*, is a source of salicylic acid. *(© William H. Allen, Jr.)*



1,2-Benzenedicarboxylic acid
(Phthalic acid)



Potassium hydrogen phthalate
(KHP)

1,4-Benzenedicarboxylic acid
(Terephthalic acid)

B. Common Names

Aliphatic carboxylic acids, many of which were known long before the development of structural theory and IUPAC nomenclature, are named according to their source or for some characteristic property. Table 19.2 lists several of the unbranched aliphatic carboxylic acids found in the biological world along with the common name of each. Those of 16, 18, and 20 carbon atoms are particularly abundant in fats and oils, and the phospholipid components of biological membranes. Formic acid was so named because it was first isolated from ants (Latin: *formica*). Acetic acid is a component of vinegar (Latin: *acetum*). Propionic acid was the first acid to be classified as a fatty acid (Greek: *pro*, first and *pion*, fat). Butyric acid was first isolated from butter (Latin: *butyrum*). Valeric acid was first isolated from garden heliotrope, a plant of the genus *Valeriana* and native to Europe and Asia.

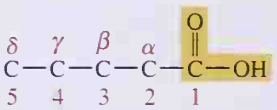
When common names are used, the Greek letters α, β, γ, and δ are often attached to locate substituents. The α-position in a carboxylic acid is the one next to the carboxyl group; an α-substituent in a common name is equivalent to a 2-substituent in an IUPAC

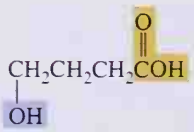
Garden heliotrope, a plant of the genus *Valeriana*, is source of valeric acid. *(© Ann Reilly: PHOTO/NATS)*

Table 19.2 Several aliphatic carboxylic acids and their common names and derivations

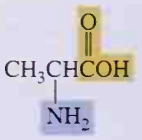
Structure	IUPAC Name	Common Name	Derivation
HCO_2H	methanoic acid	formic acid	Latin: *formica*, ant
CH_3CO_2H	ethanoic acid	acetic acid	Latin: *acetum*, vinegar
$CH_3CH_2CO_2H$	propanoic acid	propionic acid	Greek: *propion*, first fatty acid
$CH_3(CH_2)_2CO_2H$	butanoic acid	butyric acid	Latin: *butyrum*, butter
$CH_3(CH_2)_3CO_2H$	pentanoic acid	valeric acid	Latin: *valeriana*, a flowering plant
$CH_3(CH_2)_4CO_2H$	hexanoic acid	caproic acid	Latin: *caper*, goat
$CH_3(CH_2)_6CO_2H$	octanoic acid	caprylic acid	Latin: *caper*, goat
$CH_3(CH_2)_8CO_2H$	decanoic acid	capric acid	Latin: *caper*, goat
$CH_3(CH_2)_{10}CO_2H$	dodecanoic acid	lauric acid	Latin: *laurus*, laurel
$CH_3(CH_2)_{12}CO_2H$	tetradecanoic acid	myristic acid	Greek: *myristikos*, fragrant
$CH_3(CH_2)_{14}CO_2H$	hexadecanoic acid	palmitic acid	Latin: *palma*, palm tree
$CH_3(CH_2)_{16}CO_2H$	octadecanoic acid	stearic acid	Greek: *stear*, solid fat
$CH_3(CH_2)_{18}CO_2H$	eicosanoic acid	arachidic acid	Greek: *arachis*, peanut

name. Following are two examples of the use of Greek letters in common names to show the position of substituents:



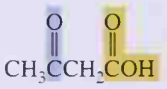


4-Hydroxybutanoic acid
(γ-Hydroxybutyric acid)



2-Aminopropanoic acid
(α-Aminopropionic acid; Alanine)

In common names, the presence of a ketone carbonyl in a substituted carboxylic acid is indicated by the prefix keto-, illustrated by the common name β-ketobutyric acid.



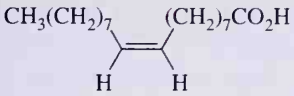
3-Oxobutanoic acid
(β-Ketobutyric acid; Acetoacetic acid)

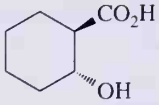
Acetyl (aceto) group

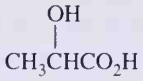
This substituted carboxylic acid is also named acetoacetic acid. In deriving this name, which is more common in the biological literature, 3-oxobutanoic acid is regarded as a substituted acetic acid, and the name of the substituent group, CH_3CO—, is aceto-.

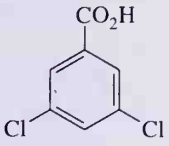
EXAMPLE 19.1

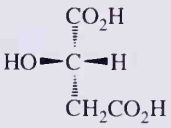
Write IUPAC names for the following carboxylic acids:

(a) 

(b) 

(c) 

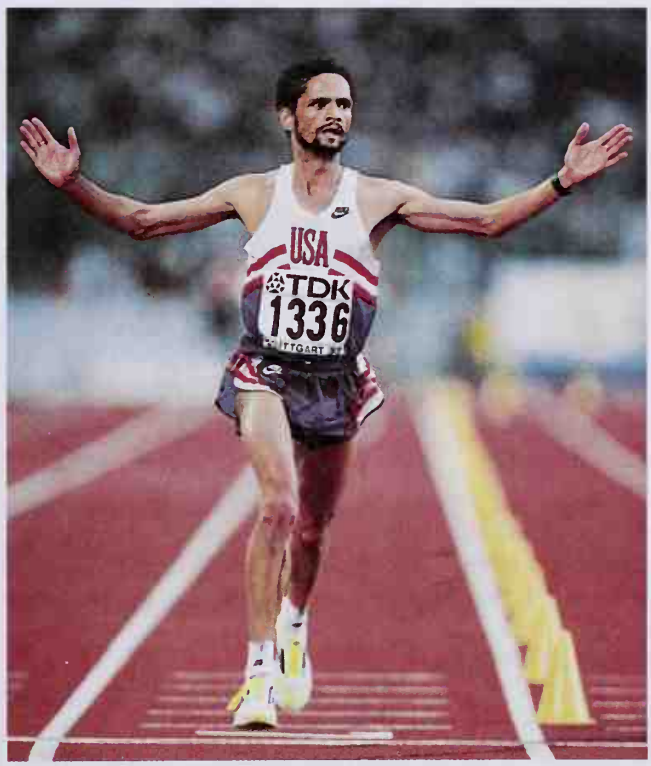
(d) 

(e) 

(f) $ClCH_2CO_2H$

Solution

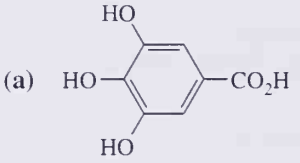
(a) (Z)-9-Octadecenoic acid
(b) *trans*-2-Hydroxycyclohexanecarboxylic acid
(c) 2-Hydroxypropanoic acid (lactic acid)
(d) 3,5-Dichlorobenzoic acid
(e) (S)-2-Hydroxybutanedioic [(S)-malic acid]
(f) Chloroethanoic acid (chloroacetic acid)



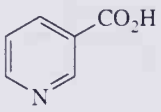
Lactic acid, a product of anaerobic glycolysis, causes painful muscle contractions. *(© ALLSPORT USA/Gray Mortimore)*

PROBLEM 19.1

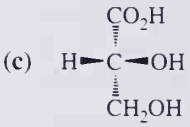
Each of the following compounds has a well-recognized common name (at least well recognized in certain subspecialities of chemistry, biochemistry, and biology). A derivative of glyceric acid is a key intermediate in glycolysis. Maleic acid is a key intermediate in the TCA cycle. Mevalonic acid is a key intermediate in the biosynthesis of steroids. Write IUPAC names for these compounds. Be certain to show configuration for the stereoisomers drawn in (c), (d), and (e).



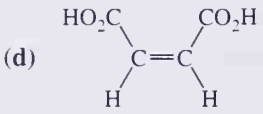
Gallic acid



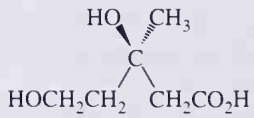
Nicotinic acid



Glyceric acid



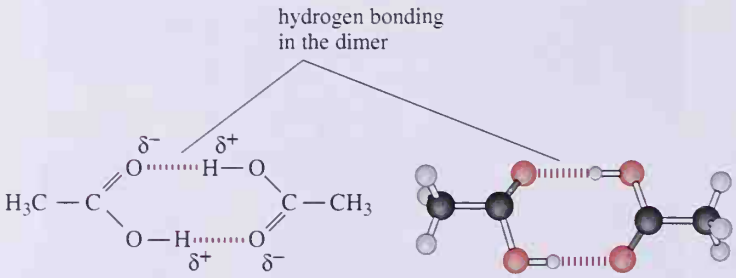
Maleic acid



Mevalonic acid

19.3 Physical Properties

In the liquid and solid states, carboxylic acids are associated by hydrogen bonding into dimeric structures as shown for acetic acid in the liquid state.



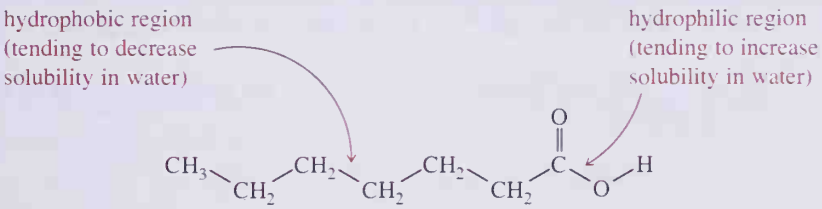
Because of their polarity and association by intermolecular hydrogen bonding, carboxylic acids have higher boiling points than those of alcohols and aldehydes of comparable molecular weight. For example, because of hydrogen bonding resulting in dimer formation, butanoic acid has a higher boiling point than either 1-pentanol (also hydrogen-bonded in the pure liquid) or pentanal (Table 19.3).

Carboxylic acids also interact with water molecules by hydrogen-bonding through both the carbonyl and hydroxyl groups. Because of these hydrogen-bonding interactions, carboxylic acids are more soluble in water than alcohols, ethers, aldehydes, and ketones of comparable molecular weight. We account for this trend of solubility in water for carboxylic acids in the following way. A carboxylic acid consists of two regions of distinctly different polarity: a polar hydrophilic carboxyl group and, except for formic acid, a nonpo-

Table 19.3 Boiling points of selected carboxylic acids, alcohols, and aldehydes of comparable molecular weight

Structure	Name	Molecular Weight	Boiling Point (°C)
CH_3CO_2H	acetic acid	60.5	118
$CH_3CH_2CH_2OH$	1-propanol	60.1	97
CH_3CH_2CHO	propanal	58.1	48
$CH_3(CH_2)_2CO_2H$	butanoic acid	88.1	163
$CH_3(CH_2)_3CH_2OH$	1-pentanol	88.1	137
$CH_3(CH_2)_3CHO$	pentanal	86.1	103
$CH_3(CH_2)_4CO_2H$	hexanoic acid	116.2	205
$CH_3(CH_2)_5CH_2OH$	1-heptanol	116.2	176
$CH_3(CH_2)_5CHO$	heptanal	114.1	153

lar hydrophobic group. The hydrophilic carboxyl group increases water solubility; the hydrophobic hydrocarbon chain decreases water solubility.



The first four aliphatic carboxylic acids are infinitely soluble in water because the hydrophobic character of the hydrocarbon chain is more than offset by the hydrophilic character of the carboxyl group. As the size of the hydrocarbon chain increases relative to the size of the hydrophilic group, water solubility decreases. The solubility of hexanoic acid in water is 1.0 g/100 g water. That of decanoic acid is only 0.2 g/100 g water.

19.4 Acidity

A. Acid Ionization Constants

Carboxylic acids are weak acids and ionize in water according to the following equation:

$$\underset{\text{Acid}}{RCO_2H} + \underset{\text{Base}}{H_2O} \rightleftharpoons \underset{\text{Conjugate base}}{RCO_2O^-} + \underset{\text{Conjugate acid}}{H_3O^+}$$

The equilibrium constant, K_{eq}, for this acid ionization is given by the expression (Section 3.2).

$$K_{eq} = \frac{[RCO_2^-][H_3O^+]}{[RCO_2H][H_2O]}$$

For dilute solutions of carboxylic acids in water, the concentration of water, $[H_2O]$, does not change appreciably and is approximately 55.5 mol/L. Combining the concentration of water with the equilibrium expression gives the more usual form of the acid ionization constant.

$$K_a = K_{eq}[H_2O] = \frac{[RCO_2^-][H^+]}{[RCO_2H]}$$

Values of K_a for most unsubstituted aliphatic, as well as aromatic, carboxylic acids fall within the range 10^{-4} to 10^{-5}. The value of K_a for acetic acid, for example, is 1.74×10^{-5}.

$$CH_3CO_2H \rightleftharpoons CH_3CO_2^- + H^+ \qquad K_a = 1.74 \times 10^{-5}$$

It is generally more convenient to refer to pK_a values for acids, where $pK_a = -\log K_a$. Thus, pK_a values for most unsubstituted carboxylic acids fall within the range 4 to 5. The value of pK_a for acetic acid is 4.76.

Before we go on to compare the relative strengths of carboxylic acids, we must ask: Why are carboxylic acids so much more acidic than alcohols, compounds that also contain an —OH group? Values of pK_a for most alcohols fall within the range 15 to 19; the value of pK_a for ethanol is 15.9. Thus, alcohols are slightly weaker acids than water (pK_a = 15.7).

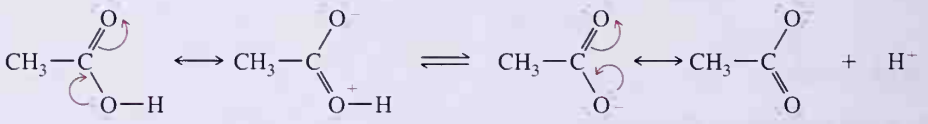
The structural feature responsible for the greater acidity of carboxylic acids compared with alcohols is the carbonyl group. To account for the acid-strengthening effect of the carbonyl group, we use the resonance theory, just as we did in Section 15.5B to account for the greater acidity of phenols relative to alcohols. Our guideline is: The more stable the products compared with the reactants, the further the position of equilibrium is shifted toward the right.

In comparing alcohols and carboxylic acids, we take the acid ionization of an alcohol as a reference equilibrium.

$$CH_3CH_2O{-}H \rightleftharpoons CH_3CH_2O^- + H^+$$

No resonance stabilization occurs in either the undissociated alcohol or the anion, and, therefore, no significant force drives an alcohol to act as an acid.

We can write two contributing structures for the un-ionized carboxylic acid. One of these structures involves creation and separation of unlike charge and, therefore, makes little contribution to the hybrid.

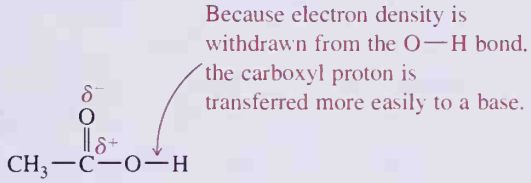


This contributing structure involves separation of unlike charges.

Contributing structures are equivalent; the carboxylate anion is stabilized by delocalization of the negative charge.

Ionization of a carboxylic acid gives an anion for which we can write two equivalent contributing structures. Because these contributing structures are equivalent, there is significant resonance stabilization of the carboxylic acid anion compared with an alkoxide anion, and, therefore, the equilibrium for ionization of a carboxylic acid is shifted to the right relative to the ionization of an alcohol.

An alternative way to account for the acid-strengthening effect of the carbonyl group is to recognize that because of the difference in electronegativity between carbon and oxygen, there is a partial positive charge on the carbonyl carbon, which, in turn, induces a polarization of electrons in the O—H bond away from hydrogen. This electron-withdrawing inductive effect of the carbonyl group weakens the O—H bond and facilitates ionization of a carboxylic acid compared with an alcohol.



Electron-withdrawing substituents near the carboxyl group increase the acidity of carboxylic acids, often by several orders of magnitude. Compare, for example, the acidities of acetic acid and the halogen-substituted acetic acids. As the electronegativity of the halogen increases, its inductive effect increases, and the strength of the halogen-substituted acid increases. Fluoroacetic acid is the strongest of the monohalogenated acetic acids.

Formula:	CH_3CO_2H	ICH_2CO_2H	$BrCH_2CO_2H$	$ClCH_2CO_2H$	FCH_2CO_2H
Name:	Acetic acid	Iodoacetic acid	Bromoacetic acid	Chloroacetic acid	Fluoroacetic acid
pK_a:	4.76	3.18	2.90	2.86	2.59

Increasing strength

To see the effects of multiple halogen substitution, compare the values of pK_a for the mono-, di-, and trichloroacetic acids. Trichloroacetic acid, the strongest of the three acids, is a stronger acid than H_3PO_4.

Formula:	$ClCH_2CO_2H$	Cl_2CHCO_2H	Cl_3CCO_2H
Name:	Chloroacetic acid	Dichloroacetic acid	Trichloroacetic acid
pK_a:	2.86	1.48	0.70

Increasing strength

The inductive effect of halogen substitution falls off rather rapidly when distance from the carboxyl group increases. Although the acid ionization constant for 2-chlorobutanoic acid is 100 times that for butanoic acid, the acid ionization constant for 4-chlorobutanoic is only about 2 times that for butanoic acid.

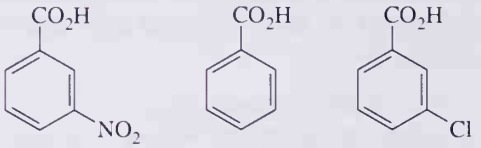
Formula:	$CH_3CH_2CH_2CO_2H$	$CH_2(Cl)CH_2CH_2CO_2H$	$CH_3CH(Cl)CH_2CO_2H$	$CH_3CH_2CH(Cl)CO_2H$
Name:	Butanoic acid	4-Chlorobutanoic acid	3-Chlorobutanoic acid	2-Chlorobutanoic acid
pK_a:	4.82	4.52	3.98	2.83

Increasing strength

Increase in acidity due to the inductive effect of electron-withdrawing groups can also be seen by comparing the acidities of *p*-chlorobenzoic acid (pK_a 3.98) and *p*-nitrobenzoic acid (pK_a 3.41) with benzoic acid (pK_a 4.19).

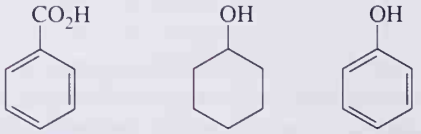
EXAMPLE 19.2

Match each acid with its appropriate pK_a value.

(a) 

m-Nitrobenzoic acid | Benzoic acid | *m*-Chlorobenzoic acid

pK_a values = 4.19, 3.82, and 3.47

(b) 

Benzoic acid | Cyclohexanol | Phenol

pK_a values = 18.0, 9.95, and 4.19

Solution

(a) Both nitro and chloro substituents are electron-withdrawing and increase the acidity of substituted benzoic acids. Because of the positive charge on nitrogen and because of its two electronegative oxygen atoms, the nitro group has a stronger inductive effect than chlorine. Therefore, in order of increasing acidity, these acids are

Benzoic acid pK_a 4.19 — *m*-Chlorobenzoic acid pK_a 3.82 — *m*-Nitrobenzoic acid pK_a 3.47

Increasing acid strength

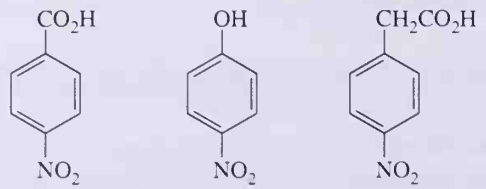
(b) pK_a values for unsubstituted aliphatic alcohols are in the range 15 to 18 (Section 9.5B); the pK_a values for phenols not substituted by electron-withdrawing groups are in the range 9 to 10 (Section 15.5B), and the pK_a values for unsubstituted aliphatic and aromatic carboxylic acids are in the range 4 to 5. Therefore, in order of increasing acidity, these acids are

Cyclohexanol pK_a 18 — Phenol pK_a 9.95 — Benzoic acid pK_a 4.19

Increasing acid strength

PROBLEM 19.2

Match each acid with the appropriate pK_a value.

(a) 

p-Nitrobenzoic acid | *p*-Nitrophenol | *p*-Nitophenylacetic acid

pK_a values = 7.15, 3.85, and 3.43

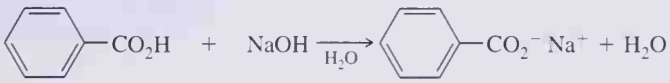
(b)

CH_3CCO_2H (with CH_3 above and below)	CF_3CO_2H	CH_3CHCO_2H (with OH)
2,2-Dimethylpropanoic acid	Trifluoroacetic acid	2-Hydroxypropanoic acid (Lactic acid)

pK_a values = 5.03, 3.08, and 0.22

B. Reaction with Bases

All carboxylic acids, whether soluble or insoluble in water, react with NaOH, KOH, and other strong bases to form water-soluble salts.

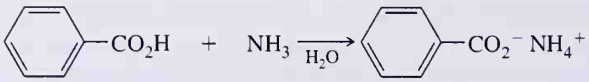


Benzoic acid (slightly soluble in water) — Sodium benzoate (60 g/100 mL water)

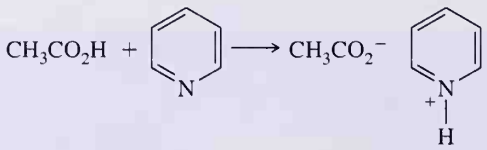
Sodium benzoate is often added to baked goods "to retard spoilage." The Food and Drug Administration limit on use of this food additive is 0.1% by weight. Calcium propanoate is also used for the same purpose. Carboxylic acids also form water-soluble salts with ammonia and with aliphatic and aromatic amines.

Sodium benzoate and calcium propanoate are used as preservatives in baked goods. *(Charles D. Winters)*

A commercial remedy for excess stomach acid. The bubbles are carbon dioxide, CO_2, from reaction between citric acid, $C_6H_8O_7$, and sodium bicarbonate, $NaHCO_3$. *(Charles D. Winters)*



Benzoic acid (slightly soluble in water) — Ammonium benzoate (20 g/100 mL water)



Acetic acid Pyridine Pyridinium acetate

As described in Section 3.3, carboxylic acids react with sodium bicarbonate and sodium carbonate to form water-soluble sodium salts and carbonic acid (a weaker acid). Carbonic acid, in turn, decomposes to give water and carbon dioxide, which evolves as a gas.

$$CH_3CO_2H + Na^+ HCO_3^- \longrightarrow CH_3CO_2^- Na^+ + CO_2 + H_2O$$

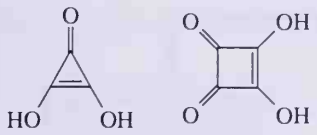
Salts of carboxylic acids are named in the same manner as the salts of inorganic acids; the cation is named first and then the anion. The name of the anion is derived from the name of the carboxylic acid by dropping the suffix **-ic acid** and adding the suffix **-ate.**

Carboxylic Acid	Anion	Salt
$CH_3CH_2CO_2H$ Propanoic acid (Propionic acid)	$CH_3CH_2CO_2^-$ Propanoate (Propionate)	$(CH_3CH_2CO_2^-)_2\ Ca^{2+}$ Calcium propanoate (Calcium propionate)
$CH_3(CH_2)_{14}CO_2H$ Hexadecanoic acid (Palmitic acid)	$CH_3(CH_2)_{14}CO_2^-$ Hexadecanoate (Palmitate)	$CH_3(CH_2)_{14}CO_2^-\ Na^+$ Sodium hexadecanoate (Sodium palmitate)

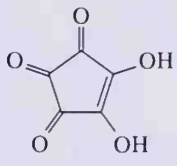
CHEMISTRY IN ACTION

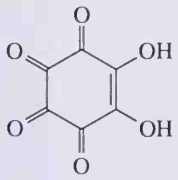
New Organic Acids

Carboxylic acids are the major type of organic acids. Delocalization of the negative charge in a carboxylate anion between two electronegative oxygen atoms provides the driving force for ionization. The same kind of charge delocalization, but on a different carbon framework, can produce exceptionally strong organic acids. The following organic acids all have the formula $(C_nO_n)H_2$.



	Deltic acid	Squaric acid
pK_{a1}	2.5	0.5
pK_{a2}	6.0	3.5

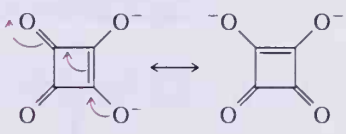




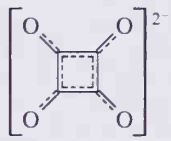
	Croconic acid	Rhodizonic acid
pK_{a1}	0.8	
pK_{a2}	2.2	

Although croconic acid and rhodizonic acid have been known for almost 100 years, squaric acid and deltic acid were first made in 1959 and 1976, respectively. On loss of its two protons, each acid produces an anion with a highly delocalized charge. The pK_{a1} values of deltic, squaric, and croconic acids are comparable to those of phosphoric acid (H_3PO_4, pK_{a1} 2.1), trichloroacetic acid (CCl_3CO_2H, pK_a 0.7), and trifluoroacetic acid (CF_3CO_2H, pK_a 0.2).

Structural studies of squaric acid indicate that the dianion is highly symmetrical, with equal C—C bond lengths and equal C—O bond lengths. The dotted lines in the structure on the right represent the extensive delocalization of electrons.



Two of several equivalent contributing structures



Resonance-stabilized dianion; equal C—C bond lengths and C—O bond lengths

Recently, these acids, especially deltic acid, have been used in a novel way by inorganic chemists. In the solid state, molecules of deltic acid exist as layered sheets, stacked one upon another. Many useful inorganic materials also exist in the solid state as layered sheets. In attempts to make new layered structures, salts of various metal cations and deltic acid anions have been prepared to determine if the flat deltic acid anion can promote the crystallization of new layered materials.

A consequence of the water solubility of carboxylic acid salts is that water-insoluble carboxylic acids can be converted to water-soluble ammonium or alkali metal salts and then extracted into aqueous solution. The salt, in turn, can be transformed into the free carboxylic acid by addition of HCl, H_2SO_4, or other strong acid.

Shown in Figure 19.1 is a flowchart for separation of benzoic acid, a water-insoluble carboxylic acid, from benzyl alcohol, a water-insoluble nonacidic compound. First, the mixture of benzoic acid and benzyl alcohol is dissolved in diethyl ether. When the ether solution is shaken with aqueous NaOH or other strong base, benzoic acid is converted to its water-soluble salt. Then the ether and aqueous phases are separated. The ether solution is distilled, yielding first diethyl ether (bp 35°C) and then benzyl alcohol (bp 205°C). The aqueous solution is acidified with HCl, and benzoic acid precipitates as a water-insoluble solid (mp 122°C) and is recovered by filtration.

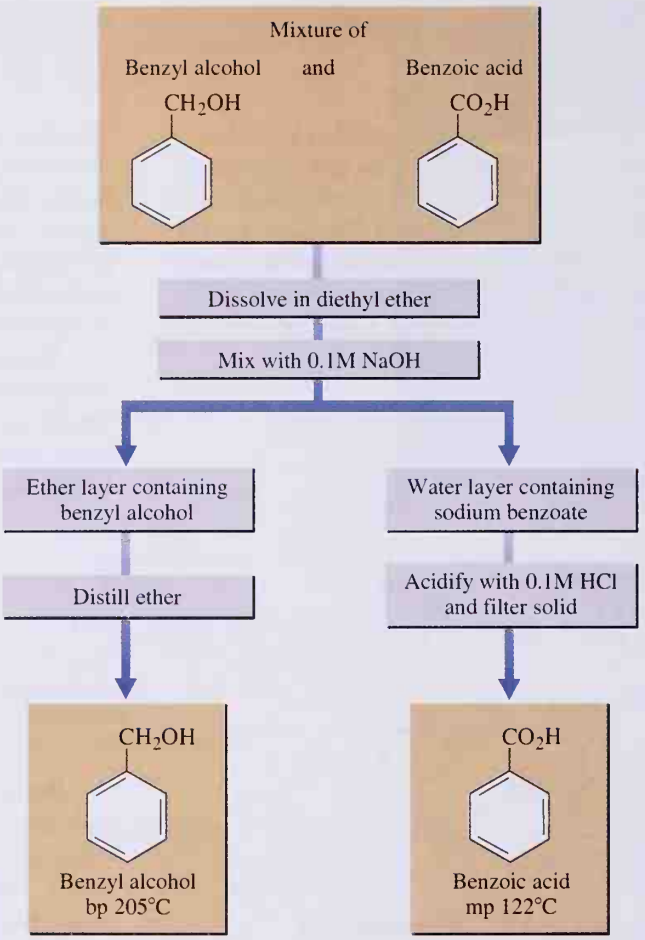
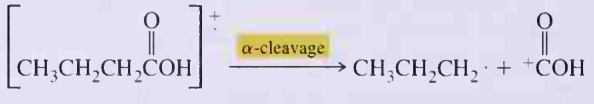


Figure 19.1
Flowchart for separation of benzoic acid from benzyl alcohol.

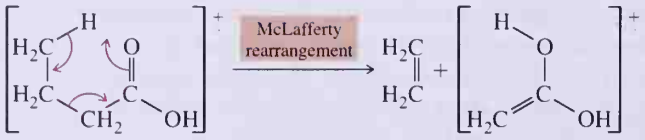
19.5 Spectroscopic Properties

A. Mass Spectrometry

The molecular ion peak from a carboxylic acid is generally observed, although it is often very weak. The most common fragmentation patterns are α-cleavage of the carboxyl group to give the ion $[CO_2H]^+$ of *m/e* 45 and McLafferty rearrangement. The base peak is very often that due to McLafferty rearrangement. Each of these patterns is seen in the mass spectrum of butanoic acid (Figure 19.2).



m/e 45



m/e 60

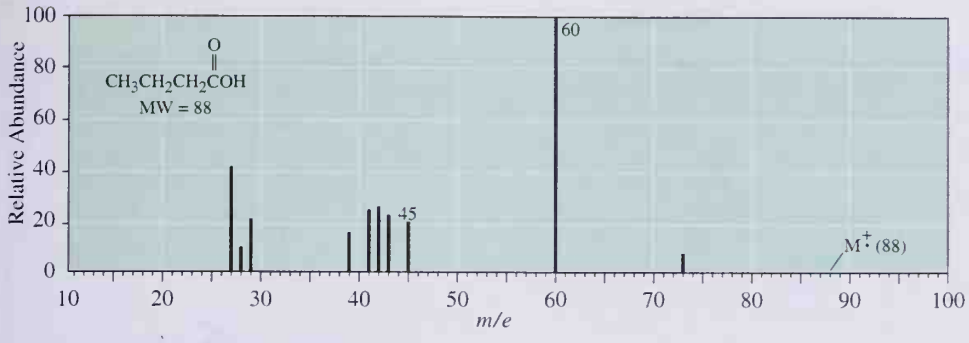


Figure 19.2
Mass spectrum of butanoic acid. Common fragmentation patterns of carboxylic acids are α-cleavage to give the ion $[CO_2H]^+$ of *m/e* 45 and McLafferty rearrangement.

B. Nuclear Magnetic Resonance Spectroscopy

Hydrogens on the α-carbon to a carboxyl group give rise to a signal in the ^{1}H-NMR spectrum in the range δ 2.0 to 2.5. The hydrogen of the carboxyl group gives a signal in the range δ 10 to 13. The chemical shift of the carboxyl hydrogen is so large, even larger than the chemical shift of an aldehyde hydrogen, that it serves to distinguish carboxyl hydrogens from most other types of hydrogens. The ^{1}H-NMR signal for carboxyl hydrogens falls off the scale of chart papers, most of which are calibrated from δ 0 to 10. The signal for the carboxyl hydrogen of 2-methylpropanoic acid appears at the left of the spectrum in Figure 19.3 and has been offset by δ 2.4 ppm. Thus, the chemical shift of this hydrogen is δ 12.2.

C. Infrared Spectroscopy

The carboxyl group of a carboxylic acid gives rise to two characteristic absorptions in the infrared spectrum. One of these occurs in the region 1700 to 1725 cm^{-1} and is associated with the stretching vibration of the carbonyl group. This is essentially the same range of absorption as that for the carbonyl group of simple aldehydes and ketones. The other infrared absorption characteristic of the carboxyl group is a peak between 2500 and 3300

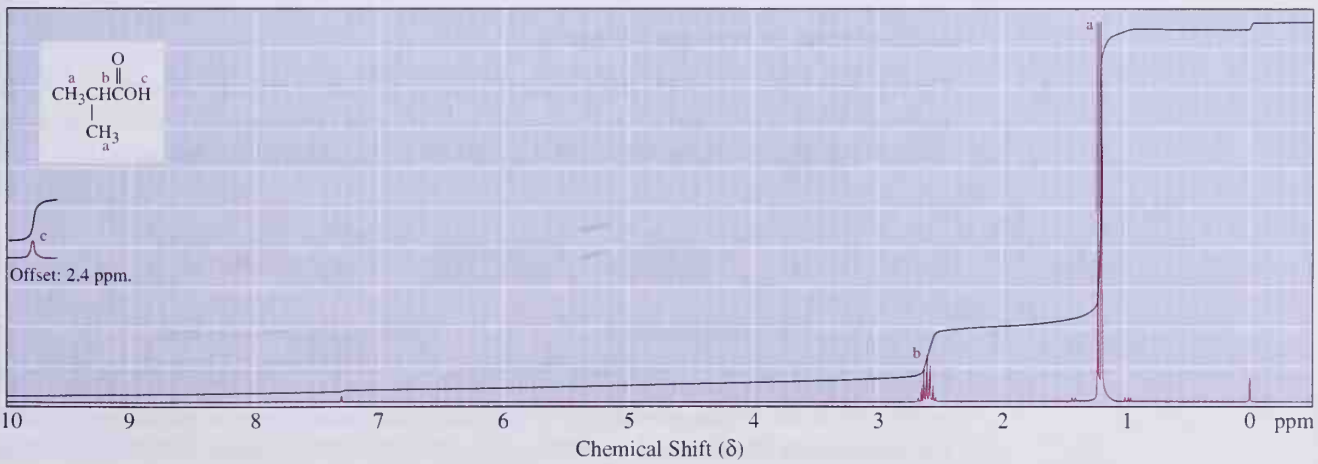


Figure 19.3
^{1}H-NMR spectrum of 2-methylpropanoic acid (isobutyric acid).

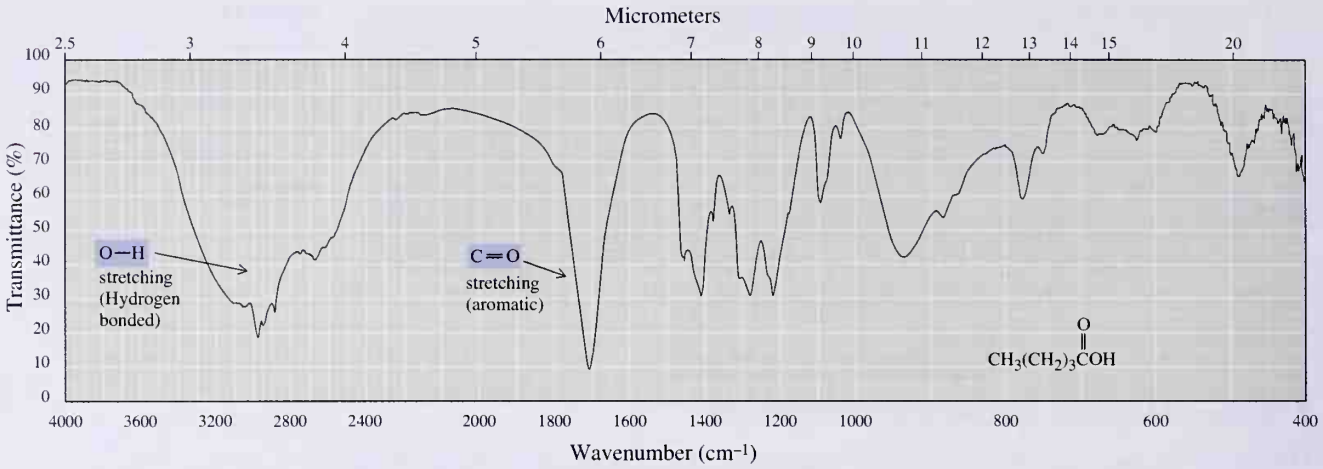


Figure 19.4
IR spectrum of pentanoic acid.

cm^{-1} due to the stretching vibration of the O—H group. This absorption is generally very broad due to hydrogen bonding between molecules of the carboxylic acid. Both C=O and O—H stretching bands can be seen in the infrared spectrum of pentanoic acid in Figure 19.4.

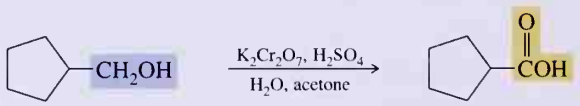
D. Ultraviolet Spectroscopy

Like aldehydes and ketones, an unconjugated carboxyl group shows only weak absorption in the ultraviolet spectrum.

19.6 Preparation

A. Oxidation of Primary Alcohols

The reagents most commonly used in the laboratory to oxidize primary alcohols to carboxylic acids are $K_2Cr_2O_7$ and CrO_3 in aqueous sulfuric acid (Section 9.5G). Water-insoluble alcohols are dissolved in acetone and the aqueous and nonaqueous solutions mixed.

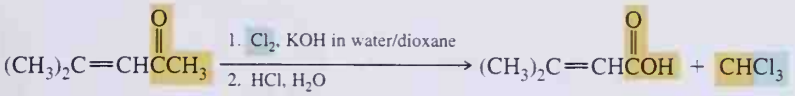


Cyclopentylmethanol Cyclopentanecarboxylic acid

Potassium permanganate in alkaline solution is also used to oxidize primary alcohols to carboxylic acids. Permanganate ion is reduced to manganese dioxide which precipitates and is removed by filtration. Acidification of the aqueous solution with HCl or other mineral acid converts the potassium salt of the carboxylic acid to the free acid.

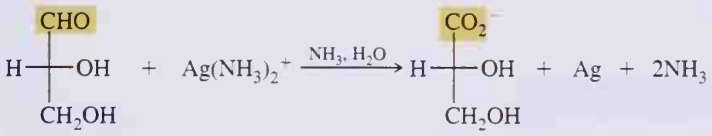
B. Oxidation of Methyl Ketones by the Haloform Reaction

The haloform reaction is an indirect way to oxidize a methyl ketone to a carboxylic acid (Section 17.13C). In the following example, an unsaturated methyl ketone is oxidized to an unsaturated carboxylic acid.



C. Oxidation of Aldehydes

Oxidation of an aldehyde affords a carboxylic acid. Oxidizing agents commonly used for this purpose are $KMnO_4$, CrO_3 in aqueous sulfuric acid (Jones' reagent), and HNO_3. In addition, Ag(I) in aqueous ammonia (Tollens' reagent) is highly selective for the oxidation of an aldehyde to a carboxylic acid.



D-Glyceraldehyde

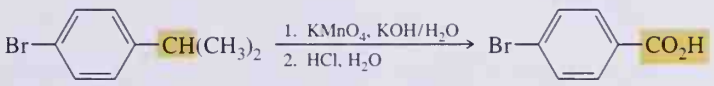
D-Glycerate anion

Silver mirror

The usefulness of this route to carboxylic acids depends on the availability of aldehydes. Although aldehydes are available, carboxylic acids are usually more readily available, and it is more often the case that it is necessary to convert a carboxylic acid to an aldehyde rather than vice versa.

D. Oxidation of Arene Side Chains

Side chains in arenes are oxidized by strong oxidizing agents to carboxyl groups (Section 15.6A). This reaction is, therefore, a general route to substituted benzoic acids. The oxidizing agent most commonly used is alkaline potassium permanganate, often with the aromatic compound dissolved in a nonpolar organic solvent and use of a phase-transfer catalyst. Under these conditions, *p*-bromocumene is oxidized to *p*-bromobenzoic acid.



1-Bromo-4-isopropylbenzene (*p*-Bromocumene)

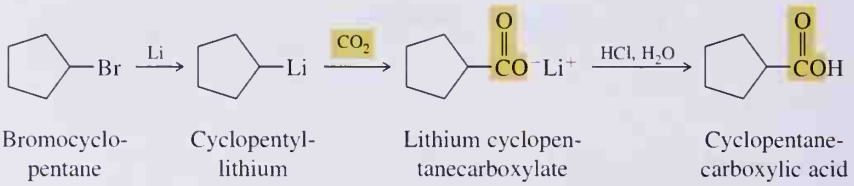
4-Bromobenzoic acid

E. Carbonation of Organolithium or Organomagnesium Reagents

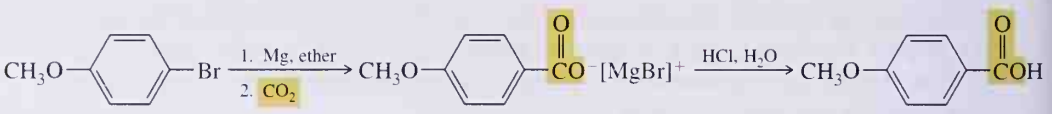
Organolithium and organomagnesium compounds (Section 17.7A) react with carbon dioxide by nucleophilic addition to the carbonyl carbon to form lithium and magnesium salts of carboxylic acids. Carbon dioxide is added in the form of dry ice, which both adds

carbon dioxide to the reaction mixture and cools it. The carboxylate anion is then converted to the carboxylic acid by acidification with HCl or other mineral acid.

Examples of this synthetic method are the preparation of cyclopentanecarboxylic acid from bromocyclopentane, and the preparation of 4-methoxybenzoic acid from 4-bromoanisole.



Bromocyclopentane — Cyclopentyllithium — Lithium cyclopentanecarboxylate — Cyclopentanecarboxylic acid



4-Bromoanisole — 4-Methoxybenzoic acid

EXAMPLE 19.3

Show how to bring about each conversion in good yield.

(a) $PhCH_2CH_2OH \longrightarrow PhCH_2CO_2H$

(b) $PhCH_2CH_2OH \longrightarrow PhCH_2CH_2CO_2H$

Solution

(a) Oxidation of this primary alcohol with chromic acid at room temperature gives phenylacetic acid. Note that if oxidation is carried out at too high a temperature, the two-carbon side chain is oxidized to give benzoic acid.

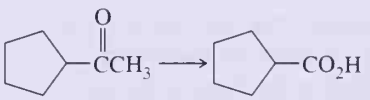
$$PhCH_2CH_2OH \xrightarrow[H_2SO_4]{K_2Cr_2O_7} PhCH_2CO_2H$$

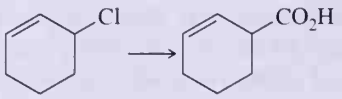
(b) The target acid contains one more carbon than the starting alcohol. To extend the chain by one carbon, first convert the alcohol to a haloalkane and then to an organolithium or organomagnesium intermediate. Carbonation of the organometallic intermediate followed by acidification with aqueous HCl gives 3-phenylpropanoic acid.

$$PhCH_2CH_2OH \xrightarrow[2.\ Mg,\ ether]{1.\ SOCl_2} PhCH_2CH_2MgCl \xrightarrow[2.\ HCl,\ H_2O]{1.\ CO_2} PhCH_2CH_2CO_2H$$

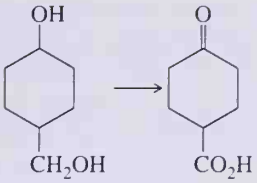
PROBLEM 19.3

Show how to bring about each conversion in good yield.

(a) 

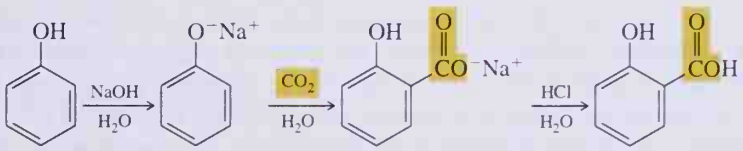
(b) 

(c)



F. Kolbe Carboxylation: Synthesis of Salicylic Acid

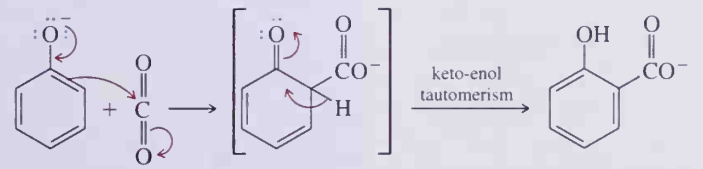
Phenoxide ions are analogous to Grignard and organolithium compounds in that they react with carbon dioxide to give a carboxylic acid salt as shown by the industrial synthesis of salicylic acid, the starting material for the synthesis of aspirin (Section 20.5B). Phenol is dissolved in aqueous NaOH, and this solution is then saturated with CO_2 under pressure to give sodium salicylate. This process is referred to as high-pressure carboxylation of sodium phenoxide. On acidification of the alkaline solution, salicylic acid is isolated as a solid, mp 157 to 159°C.



Phenol | Sodium phenoxide | Sodium salicylate | Salicylic acid

The importance of salicylic acid in industrial organic chemistry is demonstrated by the fact that over 3 million pounds of aspirin are synthesized in the United States each year.

Reaction between sodium phenoxide and carbon dioxide begins by nucleophilic attack of a phenoxide anion on the carbonyl of carbon dioxide to give a cyclohexadienone intermediate, which then undergoes keto-enol tautomerism (Section 17.12B) to give salicylate anion.



Sodium phenoxide | A cyclohexadienone intermediate | Salicylate anion

19.7 Industrial Synthesis of Acetic Acid

In 1993, acetic acid production in the United States totaled 3.7 billion pounds, a volume that ranked it 20th in the list of all organics manufactured by the U.S. chemical industry. The first industrial synthesis of acetic acid was commercialized in 1916 in Canada and Germany, using acetylene as a feedstock. The process involved two stages: (1) hydration of acetylene to acetaldehyde followed by (2) oxidation of acetaldehyde to acetic acid by molecular oxygen, catalyzed by cobalt(III) acetate.

The light of one kind of headlamp used by miners and cave explorers is given off by the combustion of acetylene, which is produced by the slow addition of water to calcium carbide. *(Charles D. Winters)*

$$HC{\equiv}CH + H_2O \xrightarrow[HgSO_4]{H_2SO_4} [CH_2{=}CHOH] \longrightarrow CH_3\overset{O}{\overset{\|}{C}}H \xrightarrow[Co^{3+}]{O_2} CH_3\overset{O}{\overset{\|}{C}}OH$$

Acetylene — Enol of acetaldehyde — Acetaldehyde — Acetic acid

The technology of producing acetic acid from acetylene is simple, and yields are high—factors that made this the major route to acetic acid for over 50 years. Acetylene was prepared by reaction of calcium carbide with water. Calcium carbide, in turn, was prepared by heating calcium oxide (from limestone, $CaCO_3$) with coke (from coal) to between 2000 and 2500°C in an electric furnace.

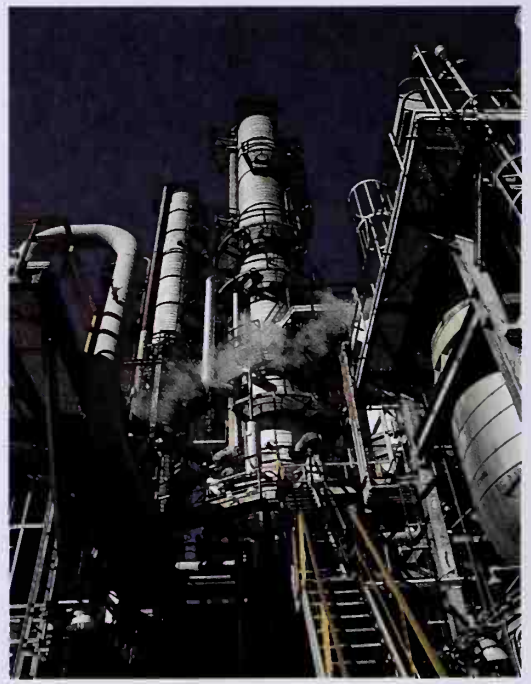
$$CaO + 3C \xrightarrow[-CO]{2500°C} CaC_2 \xrightarrow{2H_2O} HC{\equiv}CH + Ca(OH)_2$$

Calcium oxide — Calcium carbide — Acetylene

This procedure required enormous amounts of energy and, as the cost of energy rose, acetylene ceased to be an economical feedstock from which to manufacture acetic acid.

As an alternative feedstock, chemists and chemical engineers turned to ethylene, already available in huge quantities from the refining of natural gas and petroleum. The process of producing acetic acid from ethylene depends on the fact, known since 1894, that in the presence of catalytic amounts of Pd^{2+} and Cu^{2+} salts, ethylene is oxidized by molecular oxygen to acetaldehyde.

$$2H_2C{=}CH_2 + O_2 \xrightarrow[\text{(Wacker process)}]{Pd^{2+},\ Cu^{2+}} 2CH_3\overset{O}{\overset{\|}{C}}H$$



A plant for the production of acetic acid from methanol and carbon monoxide. *(Courtesy of B. P. America)*

The first chemical plant to use ethylene oxidation for the manufacture of acetaldehyde was built in Germany by Wacker-Chemie in 1959, and the process itself became known as the **Wacker process.**

In 1973, the Monsanto Company developed an entirely new synthesis for acetic acid based on the reaction of methanol and carbon monoxide in presence of small amounts of soluble rhodium(III) salts, HI, and H_2O.

$$CH_3OH + CO \xrightarrow[\text{(Monsanto process)}]{Rh^{3+},\ HI,\ H_2O} CH_3\overset{\overset{O}{\|}}{C}OH$$

The **Monsanto process** for low-pressure carbonylation is based on methanol, a compound readily available by catalytic reduction of carbon monoxide. Carbon monoxide and hydrogen, as **synthesis gas,** are in turn available from the reaction of water with methane, coal, and various petroleum products. Synthesis gas is now the major source of both methanol and acetic acid, and it is likely that synthesis gas will be a major feedstock for the production of other organics in the decades ahead.

19.8 Reduction

A. Lithium Aluminum Hydride

The carboxyl group is one of the organic functional groups most resistant to reduction. It is not affected by catalytic hydrogenation under conditions that easily reduce aldehydes and ketones to alcohols and that reduce alkenes and alkynes to alkanes. Thus, it is possible to reduce these functional groups to alcohols or alkanes in the presence of carboxyl groups.

$$CH_3\overset{\overset{O}{\|}}{C}CH_2CH_2CH_2\overset{\overset{O}{\|}}{C}OH + H_2 \xrightarrow[25°C,\ 2\ atm]{Pt} CH_3\overset{\overset{OH}{|}}{C}HCH_2CH_2CH_2\overset{\overset{O}{\|}}{C}OH$$

5-Oxohexanoic acid 5-Hydroxyhexanoic acid

With lithium aluminum hydride ($LiAlH_4$, abbreviated LAH) it is possible to reduce a carboxylic acid to a primary alcohol in excellent yield. Lithium aluminum hydride cannot be used in the presence of water or other protic solvents because it reacts violently with these proton acids to form lithium and aluminum salts and hydrogen gas. Reduction, therefore, is carried out in diethyl ether, tetrahydrofuran (THF), or some other nonreactive, aprotic solvent. The initial product is an aluminum alkoxide, which is then treated with water to give the primary alcohol and lithium and aluminum hydroxides. These hydroxides are insoluble in diethyl ether or THF and are removed by filtration. Evaporation of the solvent yields the primary alcohol.

$$R\overset{\overset{O}{\|}}{C}OH \xrightarrow[2.\ H_2O]{1.\ LiAlH_4,\ \text{ether or THF}} RCH_2OH + LiOH + Al(OH)_3$$

In the reduction of a carboxyl group, two hydrogens from $LiAlH_4$ are delivered to the carbonyl group. The hydrogen on the hydroxyl group of the product is provided by water or by aqueous acid during work-up.

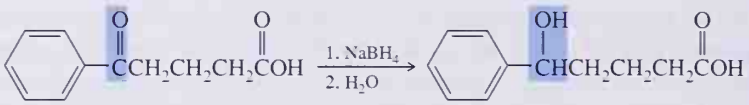
Following are balanced equations for treatment of a carboxylic acid with LAH to form a tetraalkoxylaluminate ion followed by its hydrolysis in water:

$$4RCOH + 3LiAlH_4 \longrightarrow [(RCH_2O)_4Al]Li + 2LiAlO_2 + 4H_2$$

$$[(RCH_2O)_4Al]Li + 4H_2O \longrightarrow 4RCH_2OH + LiOH + Al(OH)_3$$

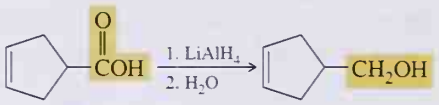
The less reactive sodium borohydride does not reduce carboxylic acids.

We saw in Section 17.16B that aldehydes and ketones are reduced to alcohols by both $LiAlH_4$ and $NaBH_4$. Only $LiAlH_4$, however, reduces carboxyl groups. Thus, it is possible to reduce the carbonyl group of an aldehyde or ketone selectively in the presence of a carboxyl group by using the less reactive $NaBH_4$ as the reducing agent. An example is the selective reduction of the following ketoacid to a hydroxyacid:



5-Oxo-5-phenylpentanoic acid 5-Hydroxy-5-phenylpentanoic acid

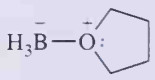
Alkenes are generally not affected by hydride reducing reagents. These reagents function as hydride ion donors, that is, as nucleophiles, and alkenes are not attacked by nucleophiles. Thus, it is possible to reduce the carbonyl group of an aldehyde, a ketone, or a carboxylic acid in the presence of a carbon-carbon double bond. Reduction of the following unsaturated carboxylic acid with lithium aluminum hydride gives an unsaturated primary alcohol:



As we shall see in Chapter 20, $LiAlH_4$ is a powerful and nonselective reducing agent. In addition to reducing the carbonyl groups of aldehydes, ketones, and carboxylic acids, it also reduces functional derivatives of carboxylic acids, including esters, acid halides, acid anhydrides, and amides. Furthermore, it reduces nitriles (RCN) and nitro groups (RNO_2) to primary amines (RCH_2NH_2 and RNH_2, respectively). We take up the reduction of these functional groups in Chapter 20.

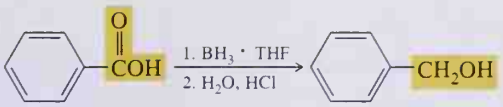
B. Reduction by Diborane

A carboxylic acid is also reduced to a primary alcohol by diborane, B_2H_6. Diborane reductions are most commonly carried out using a solution of diborane in tetrahydrofuran. In this case, the reducing agent is best represented as a 1 : 1 complex between borane and the ether. This is the same reagent used for hydroboration of alkenes (Section 5.4).

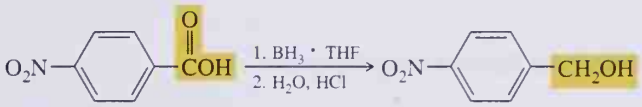


$BH_3 \cdot$ THF complex

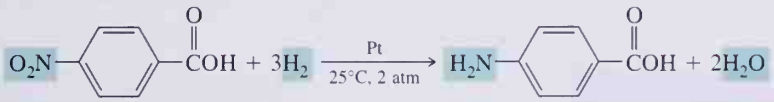
Reduction of a carboxylic acid with diborane gives first a boron alkoxide and a mole of hydrogen gas per mole of carboxyl group. Hydrolysis of the boron alkoxide in aqueous acid gives the primary alcohol and boric acid.



Although lithium aluminum hydride is by far the more common reagent for the reduction of simple carboxylic acids, diborane has a major advantage in dealing with carboxylic acids containing other functional groups. The rate at which diborane reduces carboxylic acids is greater than the rate at which it reduces nitriles, nitro groups, esters, and several other carbonyl-containing functional groups. Thus, it is possible to reduce a carboxyl group selectively in the presence of these other functional groups. In the following example, the carboxyl group is reduced selectively in the presence of a nitro group. Note that $LiAlH_4$ reduces both of these functional groups.



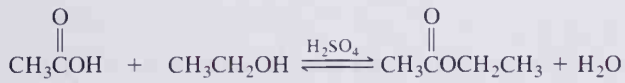
It is possible to achieve the alternative selectivity, namely, to reduce the nitro group selectively in the presence of the carboxyl group. Catalytic hydrogenation at room temperature and 2 atm pressure reduces the nitro group to a primary amine but has no effect on either the aromatic ring or the carboxylic acid.



19.9 Esterification

A. Fischer Esterification

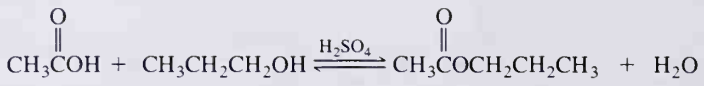
Esters can be prepared by treatment of a carboxylic acid with an alcohol in the presence of an acid catalyst, most commonly sulfuric acid or gaseous HCl. Conversion of a carboxylic acid and alcohol to an ester is given the special name **Fischer esterification,** after the German chemist, Emil Fischer (1852–1919), whose name is also firmly established in the chemistry of carbohydrates and in the designation Fischer projection formula. As an example of Fischer esterification, treatment of acetic acid with ethanol in the presence of concentrated sulfuric acid gives ethyl acetate and water.



Ethanoic acid (Acetic acid)	Ethanol (Ethyl alcohol)	Ethyl ethanoate (Ethyl acetate)

Acid-catalyzed esterification is reversible, and generally at equilibrium the quantities of both ester and alcohol are appreciable. If, for example, 60.1 g (1.00 mol) of acetic acid and 60.1 g (1.00 mol) of 1-propanol are heated under reflux in the presence of a few drops of concentrated sulfuric acid until equilibrium is reached, the reaction mixture contains approximately 0.67 mol each of propyl acetate and water and 0.33 mol each of acetic acid and 1-propanol. Thus, at equilibrium, about 67% of the carboxylic acid and alcohol are converted to the desired ester.

Ethyl acetate-containing household products include nail polish, nail polish remover, and airplane glue. *(Charles D. Winters)*



	Acetic acid	1-Propanol	Propyl acetate	
Initial:	1.00 mol	1.00 mol	0.00 mol	0.00 mol
Equilibrium:	0.33 mol	0.33 mol	0.67 mol	0.67 mol

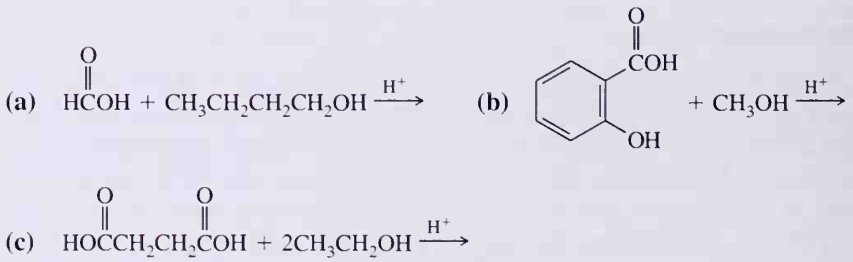
By control of reaction conditions, it is possible to use Fischer esterification to prepare esters in high yields. If the alcohol is inexpensive compared with the carboxylic acid, a large excess of it can be used to drive the equilibrium to the right and achieve a high conversion of carboxylic acid to its ester. Alternatively, water can be removed by azeotropic distillation and a Dean-Stark trap (Figure 17.6).

B. The Mechanism of Fischer Esterification

A mechanism for Fischer esterification consistent with all of our experimental observations about this reaction is given in Figure 19.5. It is important that you understand this mechanism thoroughly because it is a model for many other reactions of carboxylic acids presented in this chapter, as well as for the functional derivatives of carboxylic acids presented in Chapter 20.

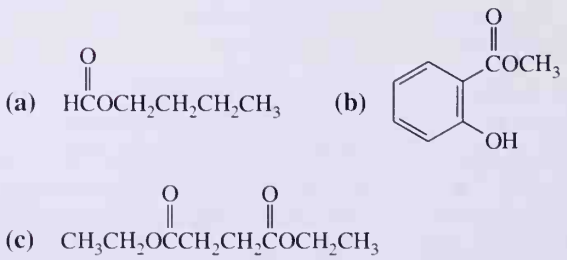
EXAMPLE 19.4

Complete these Fischer esterifications.



Solution

Following is a structural formula for the ester produced in each reaction:



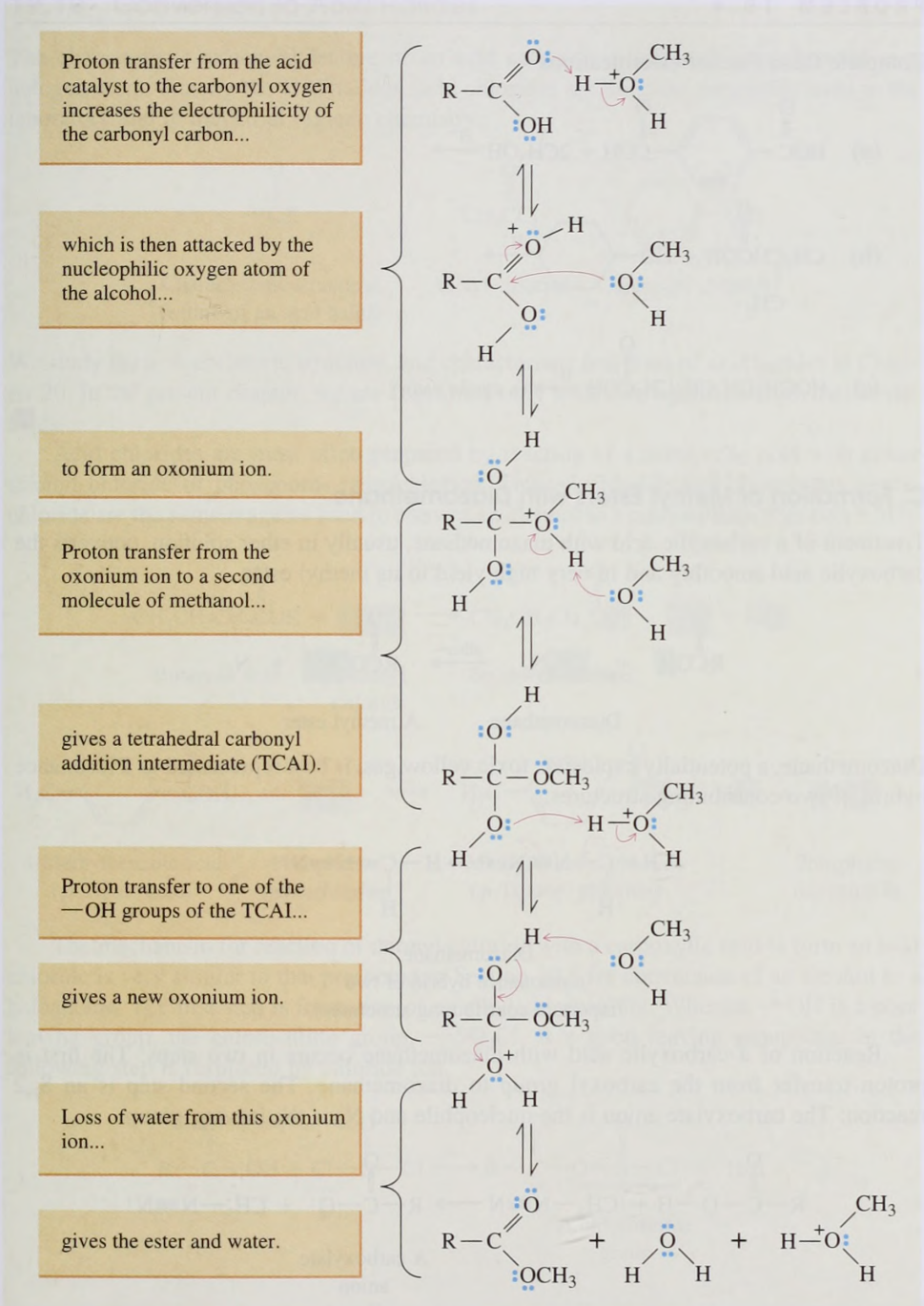
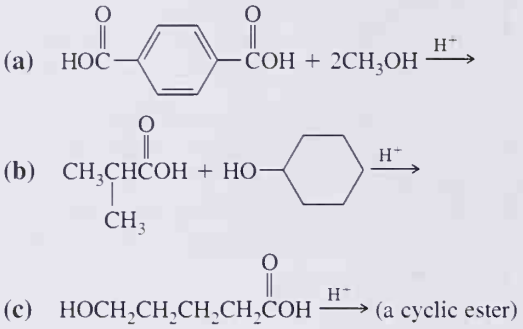


Figure 19.5
A mechanism for Fischer esterification.

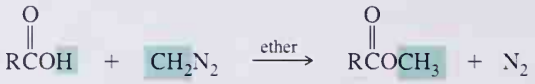
PROBLEM 19.4

Complete these Fischer esterifications.



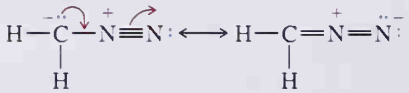
C. Formation of Methyl Esters with Diazomethane

Treatment of a carboxylic acid with diazomethane, usually in ether solution, converts the carboxylic acid smoothly and in very high yield to its methyl ester.



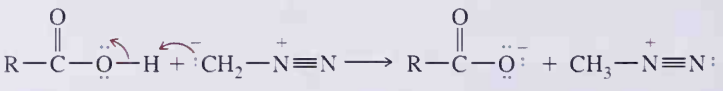
Diazomethane A methyl ester

Diazomethane, a potentially explosive, toxic yellow gas, is best represented as a resonance hybrid of two contributing structures.

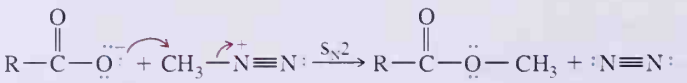


Diazomethane
(a resonance hybrid of two
important contributing structures)

Reaction of a carboxylic acid with diazomethane occurs in two steps. The first is proton transfer from the carboxyl group to diazomethane. The second step is an S_N2 reaction: The carboxylate anion is the nucleophile and N_2 is the leaving group.



A carboxylate
anion



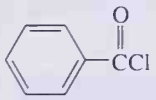
Because of the hazards associated with its use, diazomethane is used only where other means of preparation of methyl esters are not suitable, and even then diazomethane is used only in small quantities.

19.10 Conversion to Acid Halides

The characteristic structural feature of an acid halide is a carbonyl group bonded to a halogen atom. Among the acid halides, acid chlorides are the most frequently used in the laboratory and in industrial organic chemistry.

Characteristic structural feature of an acid halide

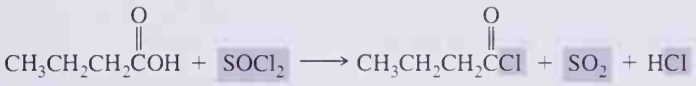
Acetyl chloride



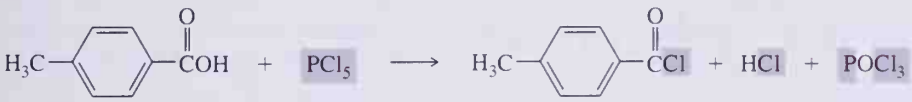
Benzoyl chloride

We study the nomenclature, structure, and characteristic reactions of acid halides in Chapter 20. In the present chapter, we are concerned only with their synthesis from carboxylic acids.

Acid chlorides are most often prepared by reaction of a carboxylic acid with either thionyl chloride or phosphorus pentachloride. Thionyl chloride and phosphorus pentachloride are the same reagents used to convert an alcohol to a chloroalkane (Section 9.5D).

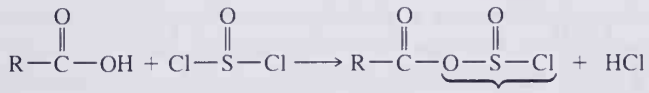


Butanoic acid — Thionyl chloride — Butanoyl chloride

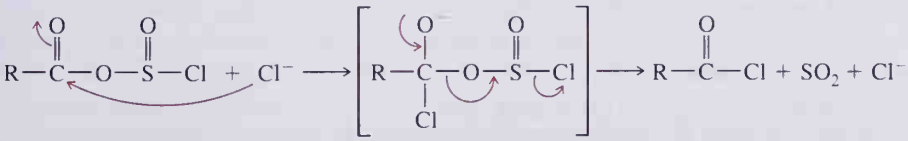


4-Methylbenzoic acid (*p*-Toluic acid) — Phosphorus pentachloride — 4-Methylbenzoyl chloride (*p*-Toluoyl chloride) — Phosphorus oxychloride

The mechanism for reaction of thionyl chloride with a carboxylic acid to form an acid chloride is very similar to that presented in Section 10.8 for conversion of an alcohol to a haloalkane. The first step is formation of an alkyl chlorosulfite. Whereas —OH is a poor leaving group, the chlorosulfite group, $-SO_2Cl$, is a good leaving group, and in the following step is displaced by chloride ion.



A chlorosulfite group

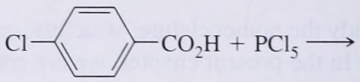
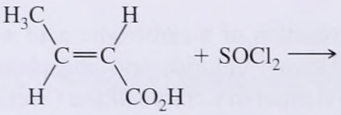


A tetrahedral carbonyl addition intermediate

Note that in the second step of this mechanism, chloride ion adds to the carbonyl carbon to form a tetrahedral carbonyl addition intermediate, which then collapses by loss of the chlorosulfite group to give the acid chloride. Addition to a carbonyl carbon to form a tetrahedral carbonyl addition intermediate followed by its collapse is a theme common to a great many reactions of carboxylic acids and their derivatives, and we see much more on this theme in the following chapter.

EXAMPLE 19.5

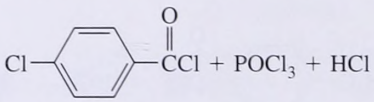
Complete the following equations:

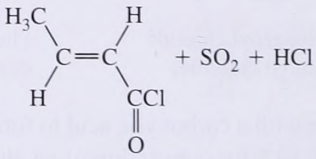
(a) $CH_3(CH_2)_6CO_2H + SOCl_2 \longrightarrow$ **(b)**  **(c)** 

Solution

Following are the products for each reaction:

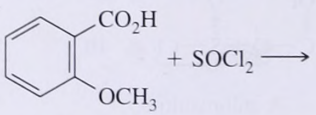
(a) $CH_3(CH_2)_6\overset{\displaystyle O}{\overset{\|}{C}}Cl + SO_2 + HCl$

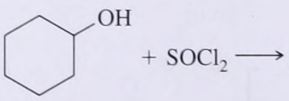
(b) 

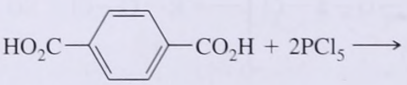
(c) 

PROBLEM 19.5

Complete the following equations:

(a) 

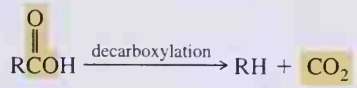
(b) 

(c) 

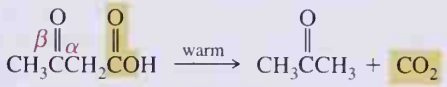
19.11 Decarboxylation

A. Decarboxylation of β-Ketoacids

Decarboxylation is the loss of CO_2 from the carboxyl group of a molecule.



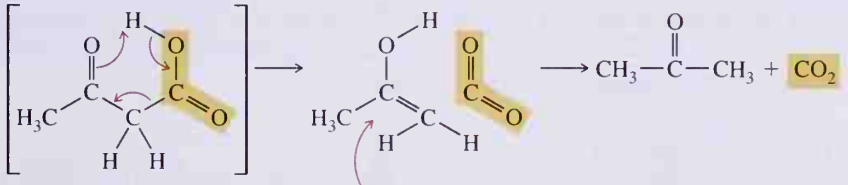
Almost any carboxylic acid, heated to a very high temperature, undergoes thermal decarboxylation. Most carboxylic acids, however, are quite resistant to moderate heat and melt or even boil without decarboxylation. An exception is carboxylic acids that have a carbonyl group on the carbon atom beta to the carboxyl group. This type of carboxylic acids undergoes decarboxylation quite readily in acid solution at room temperature or on mild heating. For example, when 3-oxobutanoic acid (acetoacetic acid) is heated, it undergoes decarboxylation to give acetone and carbon dioxide.



3-Oxobutanoic acid (Acetoacetic acid) — Acetone

Decarboxylation on mild heating is a unique property of 3-oxocarboxylic acids (β-ketoacids) and is not observed with other classes of ketoacids.

The mechanism for decarboxylation of a β-ketoacid involves an "aromatic transition state," that is, it involves rearrangement of six electrons in a cyclic six-member transition state to give carbon dioxide and an enol. The enol is then in equilibrium with the keto form by keto-enol tautomerism (Section 17.12).

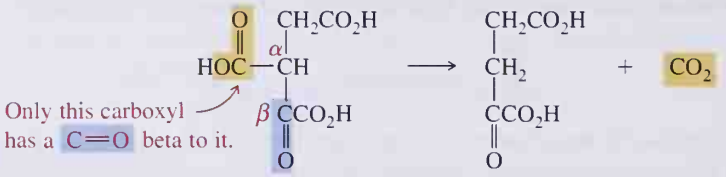


(A cyclic six-member transition state) — Enol of a ketone

3-Oxobutanoic acid (acetoacetic acid) and its reduction product, 3-hydroxybutanoic acid are synthesized in the liver from acetyl-CoA, a product of the metabolism of fatty acids and certain amino acids. 3-Hydroxybutanoic acid and acetoacetic acid are known collectively as ketone bodies. The concentration of ketone bodies in the blood of healthy, well-fed humans is approximately 0.01 m*M*/L. However, in persons suffering from starvation or diabetes mellitus, the concentration of ketone bodies may increase to as much as 500 times normal. Under these conditions, the concentration of acetoacetic acid increases to the point where it undergoes spontaneous decarboxylation to form acetone and carbon dioxide. Acetone is not metabolized by humans and is excreted through the kidneys and the lungs. The odor of acetone is responsible for the characteristic "sweet smell" on the breath of severely diabetic patients.

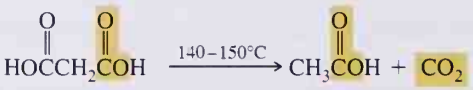
Another important example of decarboxylation of a β-ketoacid in the biological world occurs during the oxidation of foodstuffs in the TCA cycle. One of the intermediates in this

cycle is oxalosuccinic acid, which undergoes spontaneous decarboxylation to produce α-ketoglutaric acid. Only one of the three carboxyl groups of oxalosuccinic acid has a carbonyl group in the β-position to it, and it is this carboxyl group that is lost as CO_2.

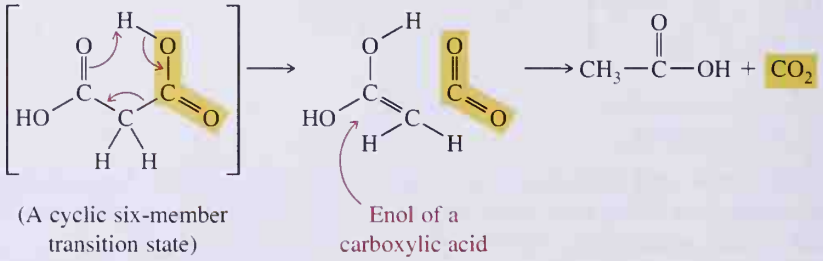


B. Decarboxylation of Malonic Acid and Substituted Malonic Acids

The presence of a carbonyl group of a ketone or aldehyde on the carbon beta to the carboxyl group is sufficient to facilitate decarboxylation. In the more general reaction, decarboxylation is facilitated by the presence of any carbonyl group on the β-carbon, including that of a carboxyl group or ester. Malonic acid and substituted malonic acids, for example, undergo decarboxylation on heating, as illustrated by the thermal decarboxylation of malonic acid when it is heated slightly above its melting point of 135 to 137°C.

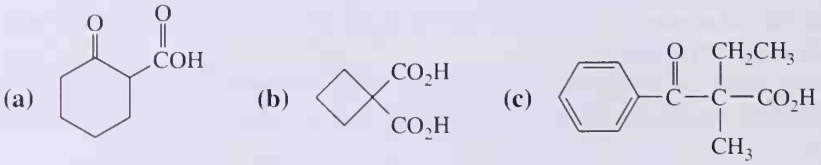


The mechanism for decarboxylation of malonic acids is very similar to that which we just studied for the decarboxylation of β-ketoacids. Formation of a cyclic, six-member transition state involving rearrangement of electron pairs gives the enol form of a carboxylic acid, which is in turn isomerized to the carboxylic acid.



EXAMPLE 19.6

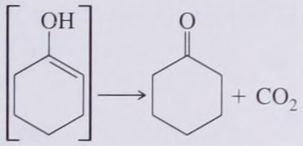
Each of these carboxylic acids undergoes thermal decarboxylation. Draw a structural formula for the enol intermediate and final product formed in each reaction.



Solution

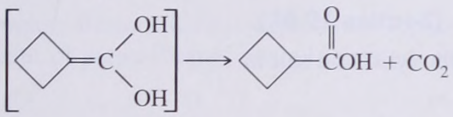
Following is a structural formula for the enol intermediate and the final product of each decarboxylation:

(a)



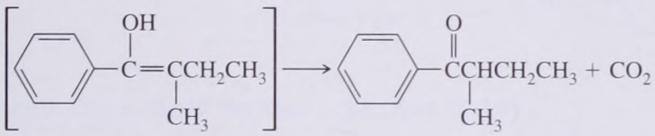
Enol intermediate

(b)



Enol intermediate

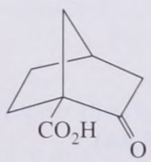
(c)



Enol intermediate

PROBLEM 19.6

Account for the observation that the following β-ketoacid is stable to thermal decarboxylation. It can be heated for an extended time at temperatures above its melting point without noticeable decomposition.

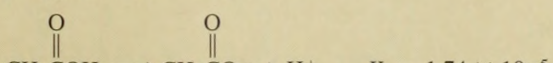


2-Oxobicyclo[2.2.1]heptane-1-carboxylic acid

SUMMARY OF KEY REACTIONS

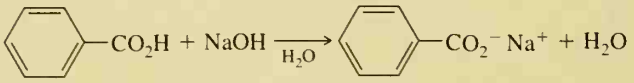
1. Acidity of Carboxylic Acids (Section 19.4A)

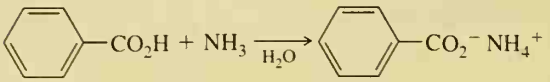
Values of pK_a for most unsubstituted aliphatic and aromatic carboxylic acids are within the range pK_a 4 to 5. Substitution by electron-withdrawing groups decreases pK_a (increases acidity).



2. Reaction of Carboxylic Acids with Bases (Section 19.4B)

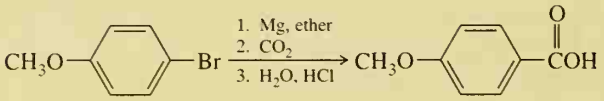
Carboxylic acids form water-soluble salts with alkali metal hydroxides and bicarbonates as well as ammonia and aliphatic and aromatic amines.

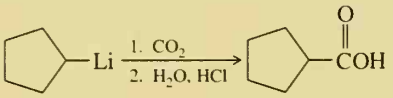




3. Carbonation of Grignard and Organolithium Reagents (Section 19.6F)

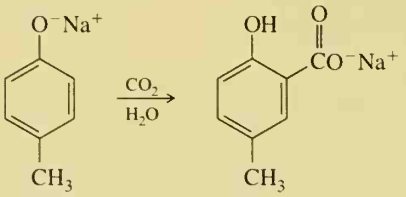
Reaction with carbon dioxide followed by hydrolysis of the carboxylic acid salt in aqueous acid gives a carboxylic acid.





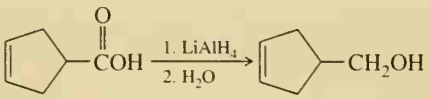
4. Kolbe Synthesis: Carboxylation of Phenols (Section 19.6F)

Nucleophilic addition of a phenoxide ion to carbon dioxide gives a substituted cyclohexadienone, which then undergoes keto-enol tautomerism to regenerate the aromatic ring.



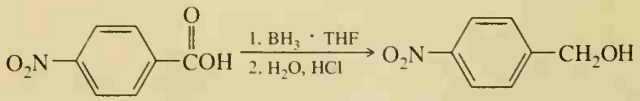
5. Reduction by Lithium Almunimum Hydride (Section 19.8A)

Sodium borohydride does not reduce carboxylic acids. Lithium aluminum hydride, a more powerful hydride reducing agent, reduces a carboxylic acid to a primary alcohol. These hydride reducing agents do not reduce isolated carbon-carbon double or triple bonds.



6. Reduction by Diborane (Section 19.8B)

A carboxylic acid is reduced to a primary alcohol by diborane.



7. Fischer Esterification (Section 19.9A)

Fischer esterification is reversible and in order to achieve high yields of ester, it is necessary to force the equilibrium to the right. One way to accomplish this is to add an excess of alcohol; another is to remove water by azeotropic distillation using a Dean-Stark trap.

$$CH_3\overset{O}{\overset{\|}{C}}OH + CH_3CH_2CH_2OH \overset{H_2SO_4}{\rightleftharpoons} CH_3\overset{O}{\overset{\|}{C}}OCH_2CH_2CH_3 + H_2O$$

8. Reaction with Diazomethane (Section 19.9C)

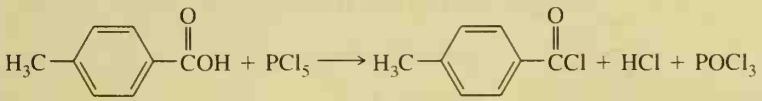
Because diazomethane is explosive and poisonous, it is used only when other means of preparation of methyl esters are not suitable.

$$CH_3(CH_2)_4CH{=}CH\overset{O}{\overset{\|}{C}}OH + \underset{\text{Diazomethane}}{CH_2N_2} \xrightarrow{\text{ether}} CH_3(CH_2)_4CH{=}CH\overset{O}{\overset{\|}{C}}OCH_3 + N_2$$

9. Conversion to Acid Halides (Section 19.10)

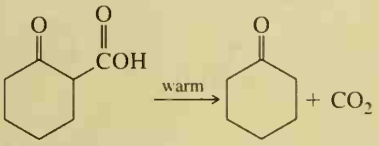
Acid chlorides, the most common and widely used of the acid halides, are prepared by treatment of carboxylic acids with either thionyl chloride or phosphorus pentachloride.

$$CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}OH + SOCl_2 \longrightarrow CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}Cl + SO_2 + HCl$$



10. Decarboxylation of β-Ketoacids (Section 19.11A)

The mechanism of decarboxylation involves redistribution of bonding electrons in a cyclic, six-member transition state.



11. Decarboxylation of β-Dicarboxylic Acids (Section 19.11B)

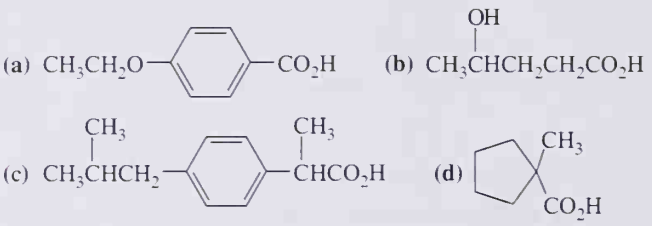
The mechanism of decarboxylation of a β-dicarboxylic acid is similar to that for decarboxylation of a β-ketoacid.

$$HO\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OH \xrightarrow{\text{heat}} CH_3\overset{O}{\overset{\|}{C}}OH + CO_2$$

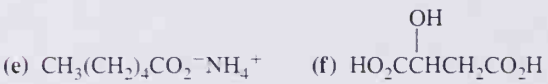
ADDITIONAL PROBLEMS

Structure and Nomenclature

19.7 Give the IUPAC name for each compound.



Ibuprofen



19.8 Draw structural formulas for the following.

(a) 4-Nitrophenylacetic acid
(b) 4-Aminobutanoic acid
(c) 3-Chloro-4-phenyl-butanoic acid
(d) 5-Nitrosalicylic acid
(e) (Z)-3-Hexenedioic acid
(f) 2-Pentynoic acid
(g) Potassium phenylacetate
(h) Sodium oxalate
(i) 2-Oxocyclohexanecarboxylic acid
(j) 2,2-Dimethylpropanoic acid
(k) Potassium 2,4-hexadienoate (the food preservative potassium sorbate)

A black carpet beetle. *(Animals, Animals © Oxford Scientific Films)*

19.9 Megatomoic acid, the sex attractant of the female black carpet beetle, has the structure:

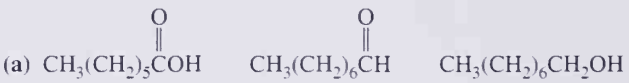
Megatomoic acid

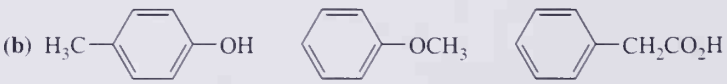
(a) What is its IUPAC name?

(b) State the number of stereoisomers possible for this compound.

Physical Properties

19.10 Arrange the following in order of increasing boiling point:





Spectroscopy

19.11 Account for the presence of peaks at *m/e* 135 and 107 in the mass spectrum of 4-methoxybenzoic acid (*p*-anisic acid).

19.12 Account for the presence of the following peaks in the mass spectrum of hexanoic acid.

(a) *m/e* 60

(b) A series of peaks differing by 14 mass units at *m/e* 45, 59, 73, and 87.

(c) A series of peaks differing by 14 mass units at *m/e* 29, 43, 57, and 71.

19.13 Given here are ^{1}H-NMR and ^{13}C-NMR spectral data for twelve compounds. In addition to the given data, each shows strong, sharp absorption between 1720 and 1700 cm^{-1}, and strong, broad absorption over the region 2500–3000 cm^{-1}. Propose a structural formula for each compound.

(a) $C_5H_{10}O_2$

^{1}H-NMR	^{13}C-NMR
0.94 (t, 3H)	180.71
1.39 (m, 2H)	33.89
1.62 (m, 2H)	26.76
2.35 (t, 2H)	22.21
12.0 (s, 1H)	13.69

(b) $C_6H_{12}O_2$

^{1}H-NMR	^{13}C-NMR
1.08 (s, 9H)	179.29
2.23 (s, 2H)	47.82
12.1 (s, 1H)	30.62
	29.57

(c) $C_5H_8O_4$

^{1}H-NMR	^{13}C-NMR
0.93 (t, 3H)	170.94
1.80 (m, 2H)	53.28
3.10 (t, 1H)	21.90
12.7 (s, 2H)	11.81

(d) $C_5H_8O_4$

^{1}H-NMR	^{13}C-NMR
1.29 (s, 6H)	174.01
12.8 (s, 2H)	48.77
	22.56

(e) $C_4H_6O_2$

^{1}H-NMR	^{13}C-NMR
1.91 (d, 3H)	172.26
5.86 (d, 1H)	147.53
7.10 (m, 1H)	122.24
12.4 (s, 1H)	18.11

(f) $C_3H_4Cl_2O_2$

^{1}H-NMR	^{13}C-NMR
2.34 (s, 3H)	171.82
11.3 (s, 1H)	79.36
	34.02

(g) $C_5H_8Cl_2O_2$

^{1}H-NMR	^{13}C-NMR
1.42 (s, 6H)	180.15
6.10 (s, 1H)	77.78
12.4 (s, 1H)	51.88
	20.71

(h) $C_5H_9BrO_2$

^{1}H-NMR	^{13}C-NMR
0.97 (t, 3H)	176.36
1.50 (m, 2H)	45.08
2.05 (m, 2H)	36.49
4.25 (t, 1H)	20.48
12.1 (s, 1H)	13.24

(i) $C_4H_8O_3$

^{1}H-NMR	^{13}C-NMR
2.62 (t, 2H)	177.33
3.38 (s, 3H)	67.55
3.68 (t, 2H)	58.72
11.5 (s, 1H)	34.75

(j) $C_6H_{10}O_3$

^{1}H-NMR	^{13}C-NMR
1.90 (m, 2H)	208.44
2.16 (s, 3H)	179.08
2.40 (t, 2H)	42.29
2.55 (t, 2H)	32.93
11.4 (s, 1H)	29.91
	18.84

(k) $C_{10}H_{12}O_3$

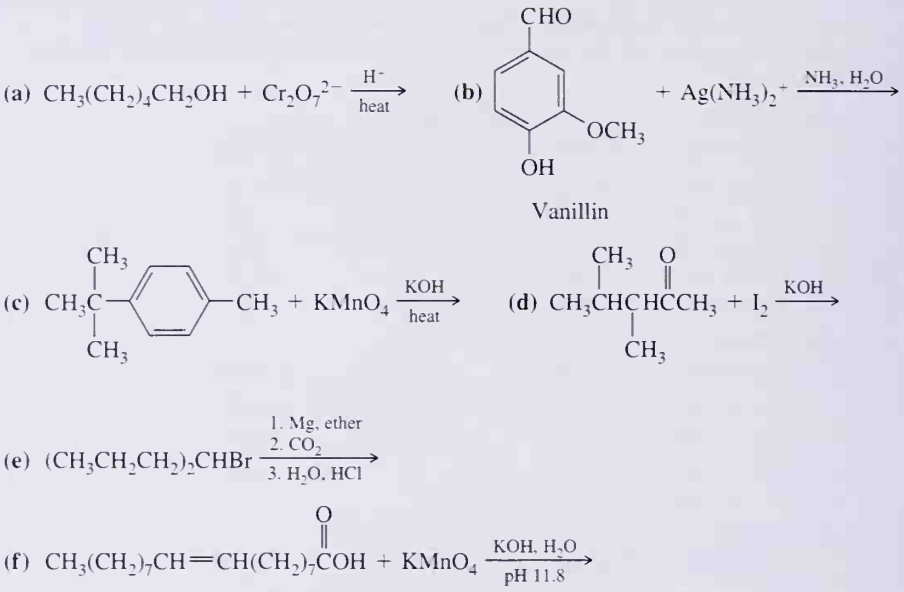
^{1}H-NMR	^{13}C-NMR
2.49 (t, 2H)	173.89
2.80 (t, 2H)	157.57
3.72 (s, 3H)	132.62
6.78 (d, 2H)	128.99
7.11 (d, 2H)	113.55
12.4 (s, 1H)	54.84
	35.75
	29.20

(l) $C_{10}H_{10}O_2$

^{1}H-NMR	^{13}C-NMR
2.34 (s, 3H)	167.82
6.38 (d, 1H)	143.82
7.18 (d, 1H)	139.96
7.44 (d, 2H)	131.45
7.56 (d, 2H)	129.37
12.0 (s, 1H)	127.83
	111.89
	21.13

Preparation of Carboxylic Acids

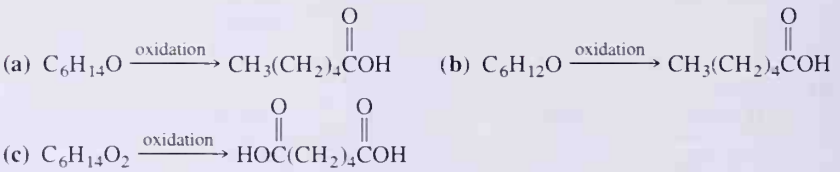
19.14 Complete the following reactions:



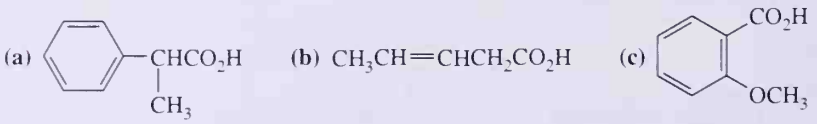
19.15 Show how to prepare pentanoic acid from the following compounds:

(a) 1-Pentanol **(b)** Pentanal **(c)** 1-Pentene **(d)** 1-Butanol
(e) 1-Bromopropane **(f)** 2-Hexanone **(g)** 1-Hexene

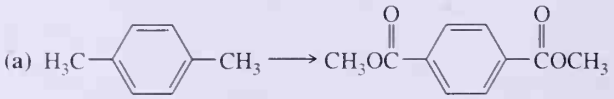
19.16 Draw the structural formula of a compound of the given molecular formula, which on oxidation by potassium permanganate in aqueous KOH followed by acidification with aqueous HCl gives the carboxylic acid or dicarboxylic acid shown.

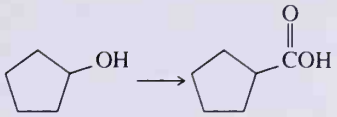


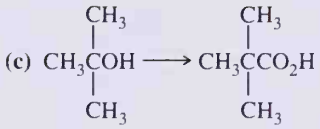
19.17 Show how to synthesize each carboxylic acid starting from an alkyl halide or aryl halide.

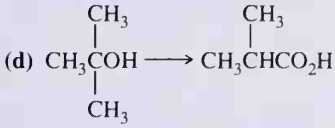


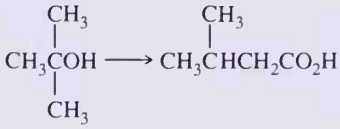
19.18 Each compound can be prepared in 2 or 3 sequential steps from the given starting material. Show the reagents and experimental conditions necessary to bring about each conversion in good yield.



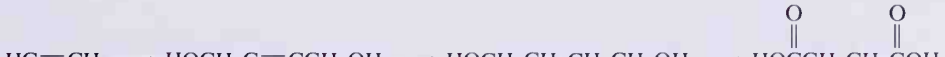
(b) 

(c) 

(d) 

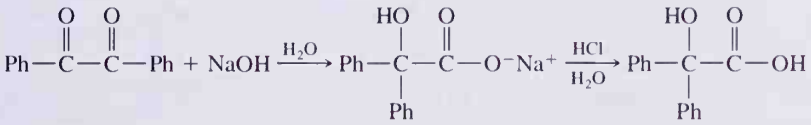
(e) 

19.19 Succinic acid can be synthesized by the following series of reactions from acetylene. Show the necessary reagents and experimental conditions to carry out this synthesis in good yield.



Acetylene — 2-Butyne-1,4-diol — 1,4-Butanediol — Butanedioic acid (Succinic acid)

19.20 The reaction of an α-diketone with concentrated sodium or potassium hydroxide to give the salt of an α-hydroxyacid is given the general name benzil-benzilic acid rearrangement. It is illustrated by the conversion of benzil to sodium benzilate and then to benzilic acid.

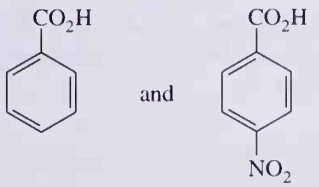


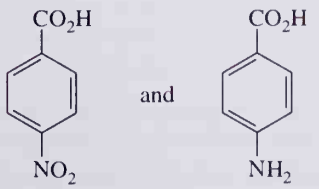
Benzil (an α-diketone) — Sodium benzilate — Benzilic acid

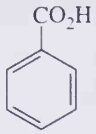
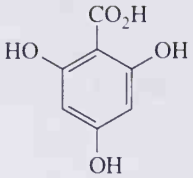
Propose a mechanism for this base-catalyzed rearrangement of benzil to sodium benzilate.

Acidity of Carboxylic Acids

19.21 Assign the acid in each set its appropriate pK_a.

(a)  (pK_a 4.19 and 3.14)

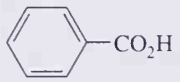
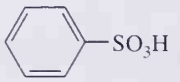
(b)  (pK_a 4.92 and 3.14)

(c)  and  (pK_a 4.19 and 1.68)

(d) $CH_3CCH_2CO_2H$ and CH_3CCO_2H (pK_a 3.58 and 2.49)

(e) CH_3CHCO_2H and $CH_3CH_2CO_2H$ (pK_a 4.78 and 3.08)

(f) $CH_3CH_2CO_2H$ and $N{\equiv}CCH_2CO_2H$ (pK_a 4.78 and 2.45)

(g)  and  (pK_a 4.19 and 0.70)

19.22 Low-molecular-weight dicarboxylic acids normally exhibit two different pK_a values. Ionization of the first carboxyl group is easier than the second. This effect diminishes with molecular size, and for adipic acid and longer chain dicarboxylic acids the two acid ionization constants differ by about one pK unit.

Dicarboxylic Acid	Structural Formula	pK_{a1}	pK_{a2}
oxalic	HO_2CCO_2H	1.23	4.19
malonic	$HO_2CCH_2CO_2H$	2.83	5.69
succinic	$HO_2C(CH_2)_2CO_2H$	4.16	5.61
glutaric	$HO_2C(CH_2)_3CO_2H$	4.31	5.41
adipic	$HO_2C(CH_2)_4CO_2H$	4.43	5.41

Why do the two pK_a values differ more for the shorter chain dicarboxylic acids than for the longer chain dicarboxylic acids?

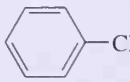
19.23 Calculate $[H^+]$ and pH of the following solutions:

(a) 0.20 *M* HCl **(b)** 0.20 *M* Phenol (pK_a 9.95)

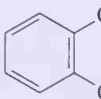
(c) 0.20 *M* CH_3CO_2H (pK_a 4.76) **(d)** 0.20 *M* *o*-Cresol (pK_a 10.2)

19.24 Account for the fact that water-insoluble carboxylic acids (pK_a 4–5) dissolve in 10% aqueous sodium bicarbonate (pH 8.5) with the evolution of a gas but water-insoluble phenols (pK_a 9.5–10.5) do not dissolve in 10% sodium bicarbonate.

19.25 Complete the following acid-base reactions:

(a)  $+ NaOH \longrightarrow$

(b) $CH_3CH{=}CHCH_2CO_2H + NaHCO_3 \longrightarrow$

(c)  $+ NaHCO_3 \longrightarrow$

(d) $CH_3\underset{\displaystyle OH}{\underset{|}{C}}HCO_2H + H_2NCH_2CH_2OH \longrightarrow$

(e) $CH_3CH{=}CHCH_2CO_2^-Na^+ + HCl \longrightarrow$

(f) $CH_3CH_2CH_2CH_2Li + CH_3CO_2H \longrightarrow$

(g) $CH_3CH_2CH_2CH_2MgBr + CH_3CH_2OH \longrightarrow$

Reactions of Carboxylic Acids

19.26 Using your knowledge of resonance, predict which atom(s) in each molecule undergoes reaction with electrophiles such as H^+ to give the most stable cation.

(a) $CH_3-\ddot{O}-CH{=}CH_2$ (b) $CH_2{=}CH-CH{=}CH_2$ (c) $CH_3-\overset{\displaystyle \ddot{O}:}{\overset{\|}{C}}-CH_3$

(d) $CH_3-\overset{\displaystyle \ddot{O}:}{\overset{\|}{C}}-\ddot{O}-H$ (e) $CH_3-\overset{\displaystyle \ddot{O}:}{\overset{\|}{C}}-\underset{\displaystyle H}{\underset{|}{\ddot{N}}}-H$

(f) $H-\underset{\displaystyle H}{\underset{|}{\ddot{N}}}-\overset{\displaystyle \ddot{N}-H}{\overset{\|}{C}}-\underset{\displaystyle H}{\underset{|}{\ddot{N}}}-H$

19.27 Give the expected organic products when $PhCH_2CO_2H$, phenylacetic acid, is treated with each of the reagents.

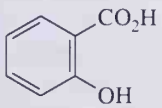
(a) $SOCl_2$ (b) PCl_5 (c) NaOH, H_2O

(d) CH_3MgBr (1 equivalent) (e) $LiAlH_4$ followed by H_2O

(f) $BH_3 \cdot THF$, followed by HCl, H_2O (g) $CH_3OH + H_2SO_4$ (catalyst) (h) CH_2N_2

19.28 Draw a structural formula for the ester formed in the following examples of Fischer esterification:

(a) $H_2N-C_6H_4-CO_2H + CH_3CH_2OH \xrightarrow[2.\ NaOH]{1.\ H_2SO_4}$ Benzocaine (a topical anesthetic)

(b)  $+ CH_3OH \xrightarrow{H_2SO_4}$ Oil of wintergreen

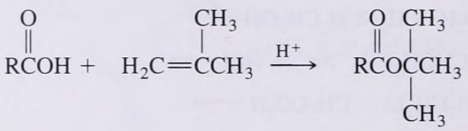
(c) $CH_3CO_2H + CH_3\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2CH_2OH \xrightarrow{H_2SO_4}$ Isopentyl acetate (a component of artificial banana flavor)

19.29 When a carboxylic acid is dissolved in $H_2{}^{18}O$, the oxygen-18 label, ^{18}O, appears equally distributed in both oxygen atoms of acid molecules that have undergone isotopic exchange. Why should this be so?

19.30 Fischer esterification cannot be used to prepare *tert*-butyl esters. Instead, carboxylic acids are treated with 2-methylpropene with an acidic catalyst to generate them.

(a) Why does the Fischer esterification fail for the synthesis of *tert*-butyl esters?

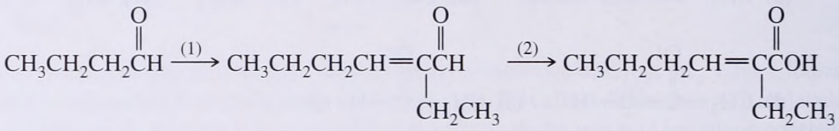
(b) Propose a mechanism for the 2-methylpropene method.



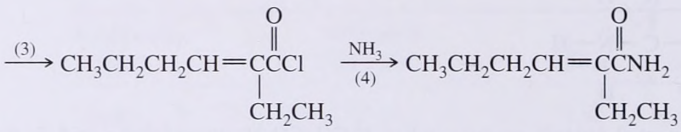
2-Methylpropene (Isobutylene) (A *tert*-butyl ester)

Synthesis

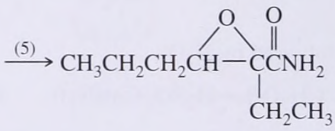
19.31 Quiactin is a mild sedative belonging to a class of molecules called oxanamides (it contains an *oxi*r*ane* or epoxide ring and an *amide* group). Quiactin is synthesized from butanal in the following five steps.



Butanal 2-Ethyl-2-hexenal 2-Ethyl-2-hexenoic acid



2-Ethyl-2-hexenoyl chloride 2-Ethyl-2-hexenamide



2-Ethyl-2,3-epoxyhexanamide (Quiactin)

(a) Show how to bring about the transformations in Steps 1, 2, 3, and 5.

(b) How many stereocenters are there in Quiactin? How many stereoisomers are possible for this compound?

Nylon fibers viewed under polarized light. (© Herb Charles Ohlmeyer/Fran Heyl Associates)

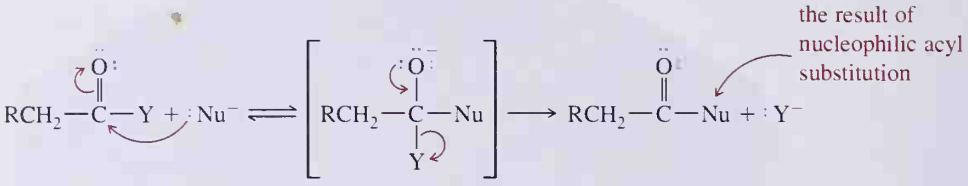
20

FUNCTIONAL DERIVATIVES OF CARBOXYLIC ACIDS

In previous chapters, we studied the structure, nomenclature, physical properties, and characteristic reactions of functional groups one at a time. In this chapter we study four functional groups derived from the carboxyl group: acid halides, acid anhydrides, esters, and amides. We also study nitriles.

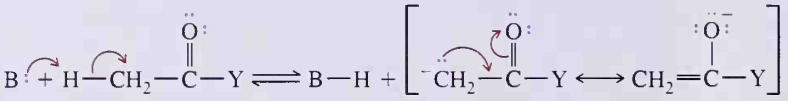
$RCCl$	$RCOCR'$	$RCOR'$	$RCNH_2$	$RC{\equiv}N$
An acid chloride	An acid anhydride	An ester	An amide	A nitrile

The relationships among these five functional groups are close. We concentrate on two of them. The first is addition to the carbonyl group to form a tetrahedral carbonyl addition intermediate, which then collapses to regenerate the carbonyl group. The result of this sequence is nucleophilic substitution at the carbonyl carbon, alternatively called **nucleophilic acyl substitution.**



Tetrahedral carbonyl
addition intermediate

The second characteristic reaction is loss of a hydrogen from the α-carbon to form an **enolate anion** that is both a nucleophile and a base. We concentrate on the properties of this anion as a nucleophile in nucleophilic acyl substitution.

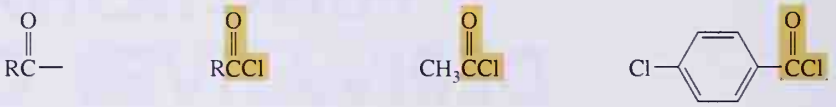


A resonance-stabilized enolate anion

20.1 Structure and Nomenclature

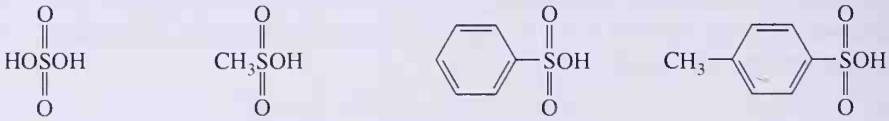
A. Acid Halides

The characteristic structural feature of an **acid halide (acyl halide)** is an **acyl group (RCO—)** bonded to a halogen atom. Acid chlorides are the most common acid halides. Acid halides are named by changing the suffix -ic acid in the name of the parent carboxylic acid to **-yl halide,** as illustrated in the following examples:

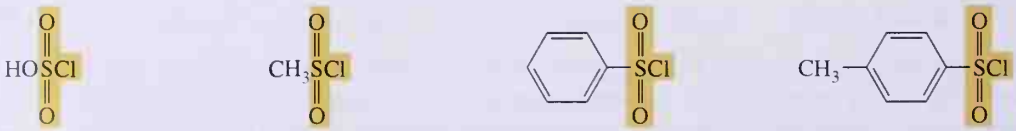


An acyl group | An acyl chloride (An acid chloride) | Ethanoyl chloride (Acetyl chloride) | 4-Chlorobenzoyl chloride (*p*-Chlorobenzoyl chloride)

Replacement of —OH on a sulfonic acid by chlorine gives a derivative called a **sulfonyl chloride.** Following are structural formulas for four sulfonic acids and the acid chloride derived from each:



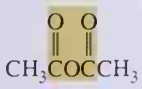
Sulfuric acid | Methanesulfonic acid | Benzenesulfonic acid | *p*-Toluenesulfonic acid



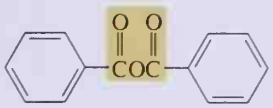
Chlorosulfonic acid | Methanesulfonyl chloride | Benzenesulfonyl chloride | *p*-Toluenesulfonyl chloride (Tosyl chloride, TsCl)

B. Acid Anhydrides

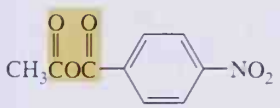
The characteristic structural feature of an **acid anhydride** is two acyl groups bonded to an oxygen atom. The acyl groups may be derived from either aliphatic or aromatic carboxylic acids. Furthermore, the anhydride may be symmetrical (two identical acyl groups), or it may be mixed (two different acyl groups).



Acetic anhydride

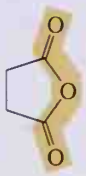


Benzoic anhydride

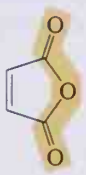


Acetic *p*-nitrobenzoic anhydride
(a mixed anhydride)

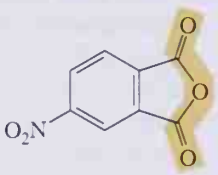
Cyclic anhydrides are named from the dicarboxylic acids from which they are derived. Following are the cyclic anhydrides derived from succinic acid, maleic acid, and 4-nitrophthalic acid.



Succinic anhydride



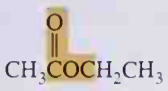
Maleic anhydride



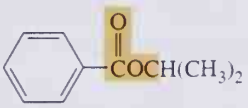
4-Nitrophthalic anhydride

C. Esters

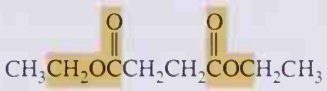
The characteristic structural feature of an **ester** is an acyl group bonded to —OR or to —OAr. Both IUPAC and common names are derived from the name of the parent carboxylic acid. The alkyl or aryl group bonded to oxygen is named first. This is followed by the name of the acid in which the suffix -ic acid is replaced by the suffix **-ate.**



Ethyl ethanoate
(Ethyl acetate)

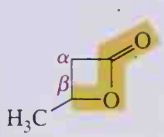


Isopropyl benzoate



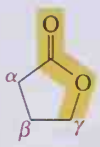
Diethyl butanedioate
(Diethyl succinate)

Cyclic esters are called **lactones.** The IUPAC system has developed a set of rules for naming these compounds. Nonetheless, the simplest lactones are still referred to by their common names derived by dropping the suffix -ic or -oic acid from the name of the parent carboxylic acid and adding the suffix **-olactone.** The location of the oxygen atom in the ring is indicated by a Greek letter α, β, γ, δ, ε, and so forth.

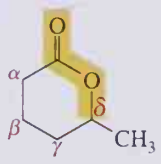


β-Butyrolactone

(IUPAC name of acid: butanoic acid;
common name of acid: butyric acid)

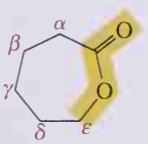


γ-Butyrolactone



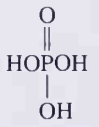
δ-Caprolactone

(IUPAC name of acid: hexanoic acid;
common name of acid: caproic acid)

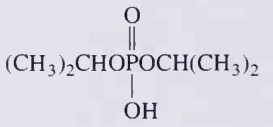


ε-Caprolactone

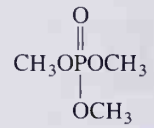
Phosphoric acid has three —OH groups and forms mono-, di-, and triesters, which are named by giving the name(s) of the alkyl or aryl group(s) attached to oxygen followed by the word "phosphate." To avoid ambiguity, the prefixes mono-, di-, and tri- are used to indicate the number of alkyl or aryl groups and the number of hydrogens attached to oxygen.



Phosphoric acid

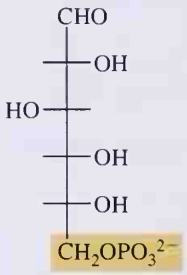


Diisopropyl hydrogen phosphate

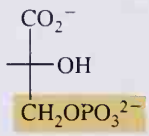


Trimethyl phosphate

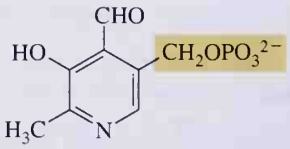
In more complex phosphate esters, it is common to name the organic molecule and then indicate the presence of the phosphate ester using either the prefix phospho- or the word "phosphate." Following are three phosphate esters, each of special importance in the biological world. Each ester is shown as it is ionized at the pH of blood plasma; the two hydrogens of each phosphate group are ionized giving the phosphate group a charge of −2.



D-Glucose-6-phosphate

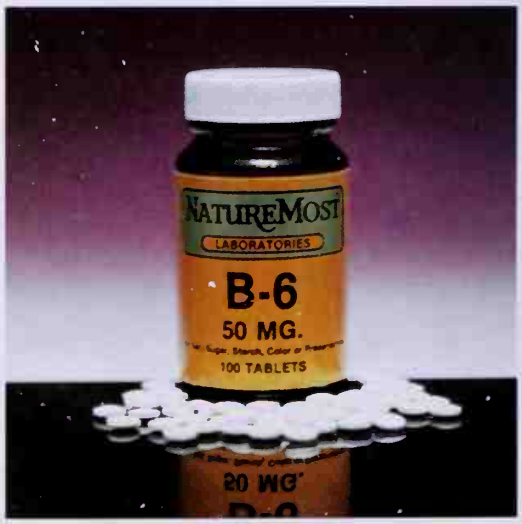


3-Phosphoglycerate



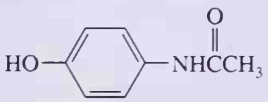
Pyridoxal phosphate

Once inside cells, one of the first reactions in the metabolism of glucose is phosphorylation to form D-glucose-6-phosphate. In the metabolic pathway known as anaerobic glycolysis, D-glucose-6-phosphate is converted to 3-phosphoglycerate and then to pyruvic acid. Pyridoxal is one of the metabolically active forms of vitamin B_6.



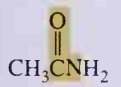
Vitamin B_6, pyridoxal. *(Charles D. Winters)*

Crystals of 4-acetamidophenol (acetaminophen, Tylenol) viewed under polarized light. *(© Phillip A. Harrington/Fran Heyl Associates)*

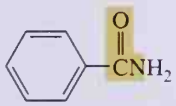


D. Amides and Imides

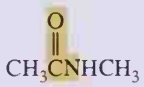
The characteristic structural feature of an **amide** is an acyl group bonded to a trivalent nitrogen atom. Amides are named by dropping the suffix -oic acid from the IUPAC name of the parent acid, or -ic acid from its common name, and adding **-amide.** If the nitrogen atom of an amide is bonded to an alkyl or aryl group, the group is named, and its location on nitrogen is indicated by *N*-. Two alkyl or aryl groups on nitrogen are indicated by *N,N*-di. *N,N*-Dimethylformamide (DMF) is a widely used polar aprotic solvent (Section 10.7F).



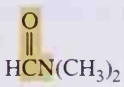
Acetamide
(a 1° amide)



Benzamide
(a 1° amide)

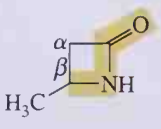


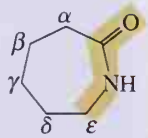
N-Methylacetamide
(a 2° amide)



N,N-Dimethylformamide (DMF)
(a 3° amide)

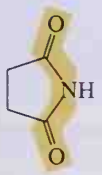
Cyclic amides are given the special name **lactam.** Their common names are derived in a manner similar to those of lactones, with the difference that the suffix -lactone is replaced by -lactam.





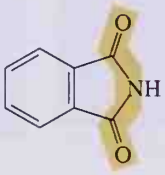
β-Butyrolactam ε-Caprolactam

The characteristic structural feature of an **imide** is two acyl groups bonded to nitrogen. Both succinimide and phthalimide are cyclic imides. *N*-Bromosuccinimide (NBS) is very effective for bringing about selective allylic halogenation of alkenes (Section 5.6).



Succinimide

N-Bromosuccinimide
(NBS)

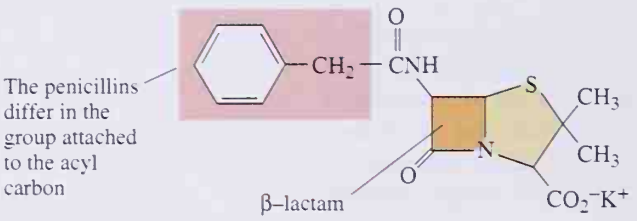


Phthalimide

E. The Penicillins and Cephalosporins: β-Lactam Antibiotics

The **penicillins** were discovered in 1928 by the Scottish bacteriologist, Sir Alexander Fleming. As a result of the brilliant experimental work of Sir Howard Florey, an Australian pathologist, and Ernst Chain, a Jewish chemist who fled Nazi Germany, penicillin G was introduced into the practice of medicine in 1943. For their pioneering work in developing a chance laboratory observation into one of the most effective antibiotics of all time, Fleming, Florey, and Chain were awarded the Nobel Prize in medicine and physiology in 1945.

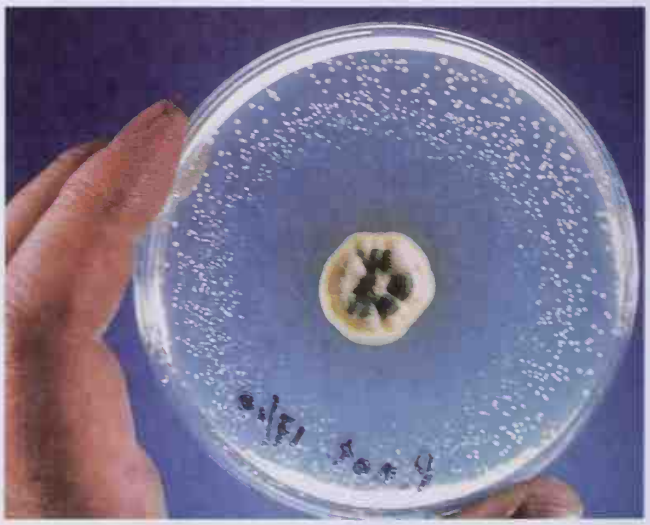
The mold from which Fleming discovered penicillin was *Penicillium notatum*, a strain that gives a relatively low yield of penicillin. It was replaced in commercial production of the antibiotic by *P. chrysogenum*, a strain cultured from a mold found growing on a grapefruit in a market in Peoria, Illinois! The structural feature common to all penicillins is a **β-lactam** ring fused to a five-member thiazole ring.



Penicillin G
(a β–lactam antibiotic)

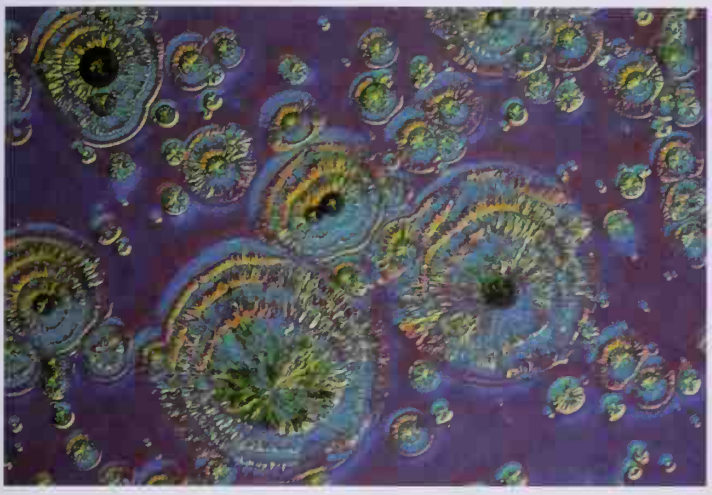
The blue-green mold *Penicillium* on the rind of an orange.
(© Herb Charles Ohlmeyer/Fran Heyl Associates)

(a)

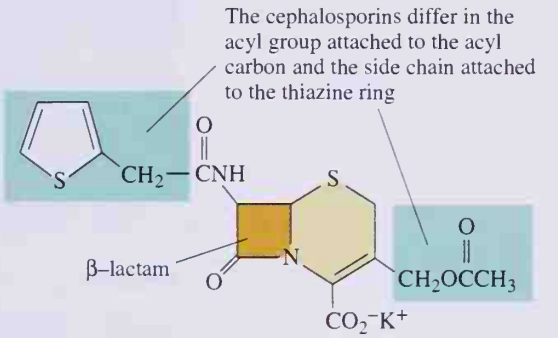


(b)

(a) Fermentation tanks used in modern penicillin production. *(Courtesy of Pfizer Inc.)* (b) A penicillin colony inhibiting growth of bacteria on a plate. *(© James Webb/Phototake NYC)*



A cephalosporin antibiotic. *(© Phillip A. Harrington/Fran Heyl Associates)*



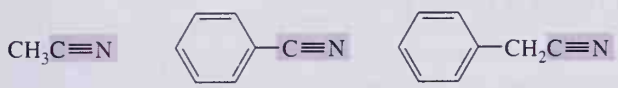
A cephalosporin, a newer generation β–lactam antibiotic

The penicillins owe their antibacterial activity to a common mechanism that inhibits the biosynthesis of a vital part of bacterial cell walls. Within certain types of bacterial cells, osmotic pressure is as high as 10 to 20 atm and without the support of a strong cell wall, these cells rupture. One type of bacterial cell wall is constructed of long chains of polysaccharides to which short polypeptide chains are attached. The final reaction in construction of this type of bacterial cell wall is enzyme-catalyzed formation of amide bonds between adjacent polypeptide chains, thus cross-linking polysaccharide chains to form an enormous bag-shaped macromolecule. The penicillins inhibit this final step. They become covalently bonded to the cross-linking enzyme, and in so doing, inactivate it. Hence, at the molecular level, the antibiotic activity of penicillins is an example of selective enzyme inhibition.

Soon after the penicillins were introduced into medical practice, penicillin-resistant strains of bacteria began to appear and have since proliferated. One approach to combating resistant strains is to synthesize newer, more effective penicillins. Among those developed are ampicillin, methicillin, and amoxicillin. Another approach is to search for newer, more effective β-lactam antibiotics. So far, the most effective of these are the **cephalosporins.** The first cephalosporin was isolated from the fungus *Cephalosporium acremonium.* This class of β-lactam antibiotics has an even broader spectrum of antibacterial activity than the penicillins and is effective against many penicillin-resistant bacterial strains.

F. Nitriles

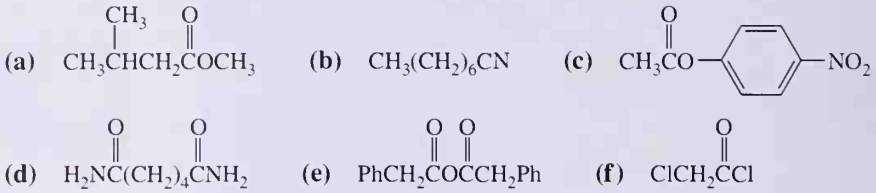
The characteristic structural feature of a **nitrile** is a cyano (C≡N) group. IUPAC names follow the pattern alkanenitrile: for example, ethanenitrile. Common names are derived by dropping the suffix -ic or -oic acid from the name of the parent carboxylic acid and adding the suffix **-onitrile.**



Ethanenitrile (Acetonitrile) | Benzonitrile | Phenylethanenitrile (Phenylacetonitrile)

EXAMPLE 20.1

Write IUPAC and common names for the following compounds:



Solution

(a) Methyl 3-methylbutanoate (methyl isovalerate, from isovaleric acid)
(b) Octanenitrile
(c) 4-Nitrophenyl ethanoate (*p*-nitrophenyl acetate, from acetic acid)
(d) Hexanediamide (adipamide, from adipic acid)
(e) Phenylacetic anhydride (from phenylacetic acid)
(f) Chloroethanoyl chloride (chloroacetyl chloride, from chloroacetic acid)

PROBLEM 20.1

Draw structural formulas for the following compounds:

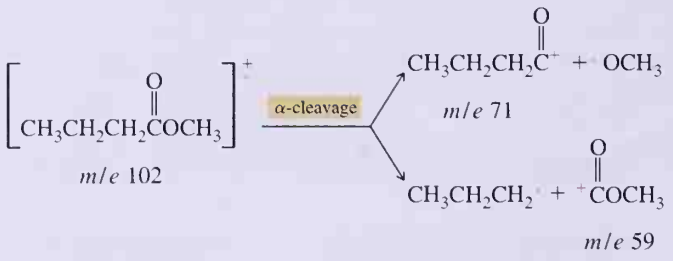
(a) *N*-Cyclohexylacetamide
(b) *sec*-Butyl methanoate
(c) Cyclobutyl butanoate
(d) *N*-(2-Octyl)succinimide
(e) Diethyl adipate
(f) *p*-Nitrobenzenesulfonyl chloride

20.2 Spectroscopic Properties

Esters and amides are the most common functional derivatives of carboxylic acids and also the most commonly analyzed. Therefore, we concentrate on the spectroscopic properties of these two functional derivatives.

A. Mass Spectrometry

Esters generally show a discernible molecular ion peak. Their most characteristic fragmentation patterns are α-cleavage and McLafferty rearrangement. Peaks in the mass spectrum of methyl butanoate (Figure 20.1) at *m/e* 71 and 59 are the result of α-cleavage.



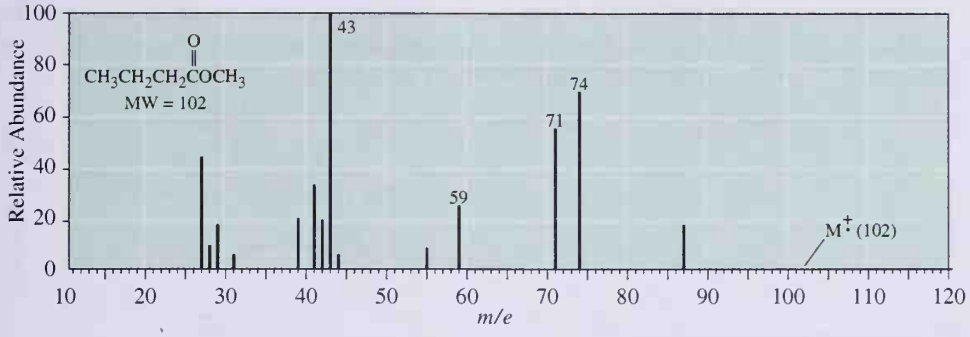
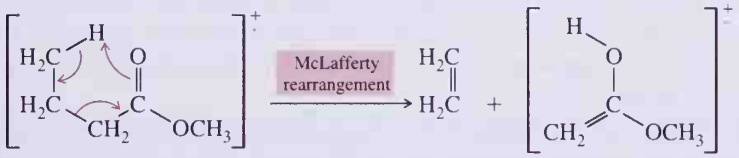


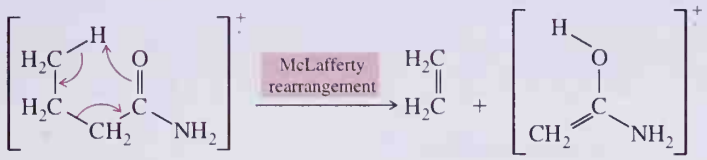
Figure 20.1
Mass spectrum of methyl butanoate. Characteristic fragmentation patterns of esters are α-cleavage and McLafferty rearrangement.

The peak at *m/e* 74 is the result of McLafferty rearrangement.

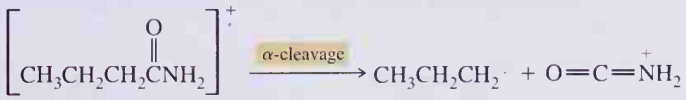


m/e 74

Amides generally show a molecular ion peak. The most common fragmentation patterns of aliphatic amides are McLafferty rearrangement and cleavage of the C—C bond α to the carbonyl group as illustrated by the peaks at *m/e* 44 and 59 in the mass spectrum of butanamide.



m/e 59

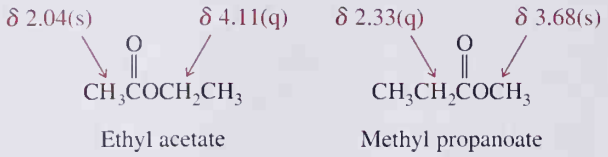


m/e 87 *m/e* 44

B. Nuclear Magnetic Resonance Spectroscopy

Hydrogens on the α-carbon to a carbonyl group are slightly deshielded and come into resonance at δ 2.0 to 2.6. It is generally not possible to distinguish the nature of the carbonyl derivative from the chemical shift of α-hydrogens. Chemical shifts are useful, however, in assigning structures to esters. Hydrogens on the carbon attached to the ester oxygen are more strongly deshielded and come into resonance at δ 3.6 to 4.1. It is possible

to distinguish between ethyl acetate and its constitutional isomer, methyl propanoate, by the chemical shifts of either the singlet $-CH_3$ absorption (compare δ 2.04 and δ 3.68), or the quartet $-CH_2-$ absorption (compare δ 4.11 and δ 2.33).



Ethyl acetate Methyl propanoate

C. Infrared Spectroscopy

The most important infrared absorption of carboxylic acids and their functional derivatives is due to the C=O stretching vibration, which is summarized in Table 20.1.

The carbonyl stretching of amides occurs at a lower wavenumber than other carbonyl compounds. Primary and secondary amides show N—H stretching in the region 3200 to 3400 cm^{-1}; primary amides ($RCONH_2$) show two N—H absorptions (Figure 20.2), whereas secondary amides (RCONHR) show only a single N—H absorption.

Esters show strong C=O stretching absorption between 1735 and 1750 cm^{-1}. In addition, they also show strong C—O stretching absorption in the region 1000 to 1300 cm^{-1} (Figure 20.3).

Anhydrides have two carbonyl stretching absorptions, in addition to which they display strong C—O stretching absorption in the region 1000 to 1300 cm^{-1}. Nitriles can be distinguished by strong C≡N stretching absorption at 2200 to 2250 cm^{-1}.

Table 20.1 Infrared absorption patterns for carboxylic acids and their functional derivatives

Compound	Stretching Absorption (cm^{-1})	Additional Absorptions (cm^{-1})
RCCl	1790–1800	
RCOCR	1740–1760 and 1800–1850	C—O stretching at 900–1300
RCOR	1735–1750	C—O stretching at 1000–1300
RCOH	1700–1725	O—H stretching at 2500–3000 C—O stretching at 1210–1320
$RCNH_2$	1630–1680	N—H stretching at 3200 and 3400 (1° amides have two N—H peaks) (2° amides have one N—H peak)
RC≡N	—	C≡N stretching at 2200–2250

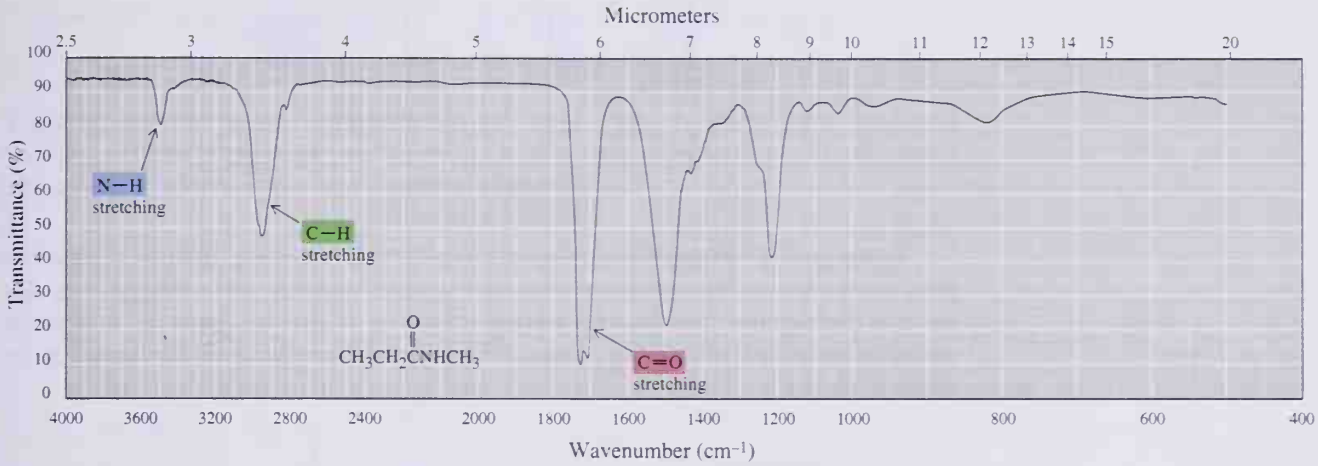


Figure 20.2
Infrared spectrum of *N*-methylpropanamide (a secondary amide).

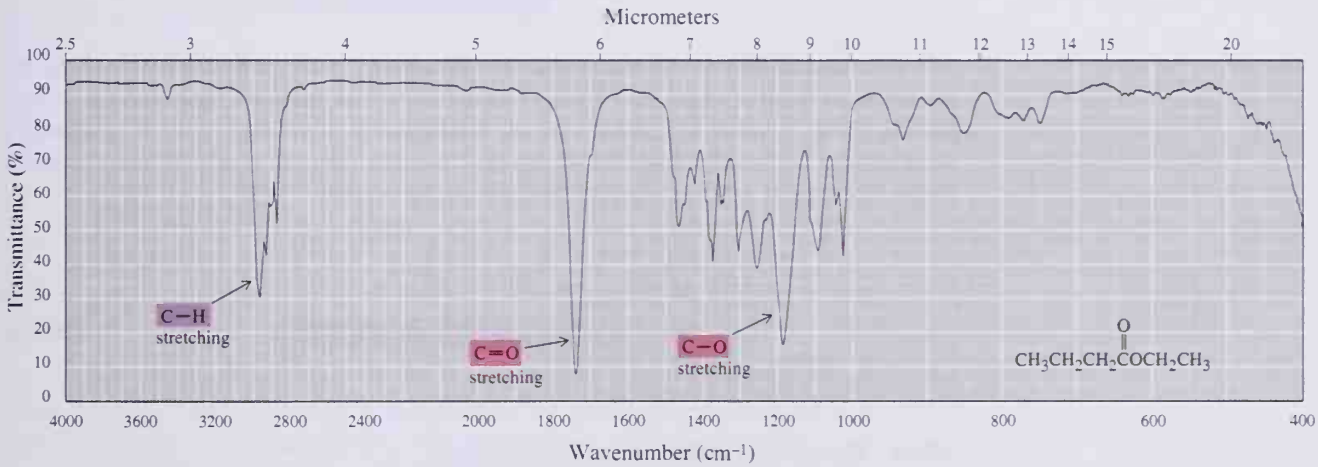
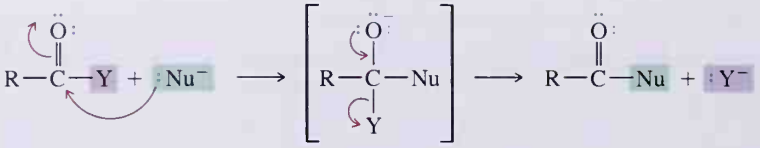


Figure 20.3
Infrared spectrum of ethyl butanoate.

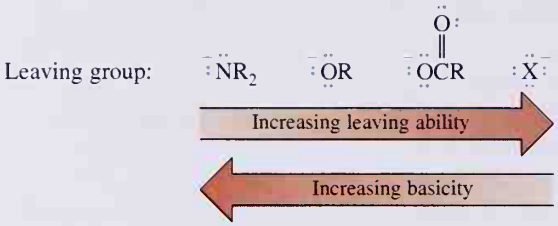
20.3 Characteristic Reactions

The most common reaction theme of acid halides, anhydrides, esters, and amides is nucleophilic addition to the carbonyl carbon to form a tetrahedral carbonyl addition intermediate, and in this sense, the reaction of these functional groups is similar to nucleophilic addition to the carbonyl groups in aldehydes and ketones (Section 17.6). For functional derivatives of carboxylic acids, however, the fate of the tetrahedral carbonyl addition intermediate is quite different. Because a reasonably good leaving group is bonded to the carbonyl carbon, the intermediate collapses to regenerate the carbonyl group. The result of this addition-elimination sequence is **nucleophilic acyl substitution.**

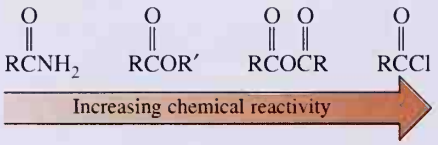


Tetrahedral carbonyl addition intermediate

In this general reaction, we show the nucleophile and the leaving group as anions. This need not be the case. Neutral molecules, such as water, alcohols, and ammonia, may also serve as nucleophiles. We show the leaving group here as an anion, however, to illustrate an important point about leaving groups: the weaker the base, the better the leaving group (Section 10.7E).



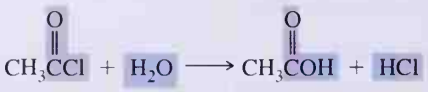
The weakest base in the series, and the best leaving group, is halide ion; acid halides are the most reactive of the four types of compounds. The strongest base, and the poorest leaving group, is amide ion; amides are the least reactive of the four types of compounds. Acid halides and acid anhydrides are so reactive that they are rarely, if ever, found in nature. Esters and amides, however, are universally present.



20.4 Reaction with Water: Hydrolysis

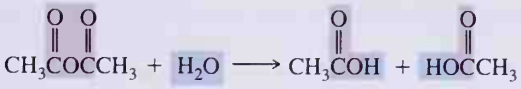
A. Acid Chlorides

Low-molecular-weight acid chlorides are moderately soluble in water and react very rapidly with it to form carboxylic acids and HX. Higher molecular-weight acid halides are less soluble and consequently react less rapidly with water.



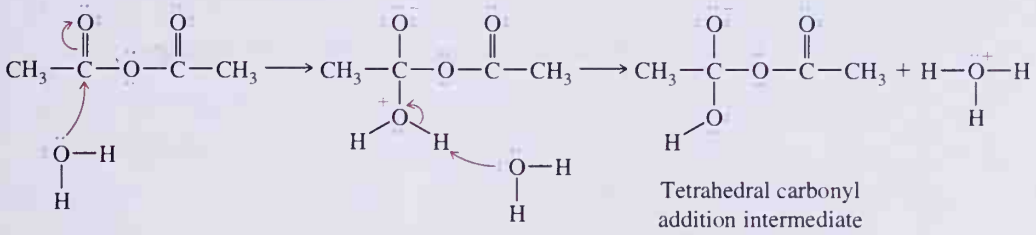
B. Acid Anhydrides

Anhydrides are generally less reactive than acid chlorides. However the lower molecular-weight anhydrides also react readily with water to form two molecules of carboxylic acid.

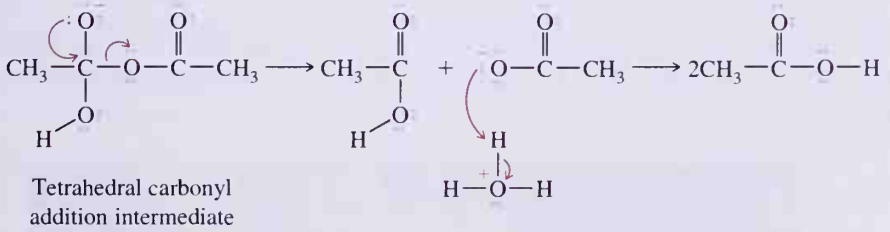


The following mechanism is divided into two stages: first, formation of a tetrahedral carbonyl addition intermediate, and second, collapse of this intermediate by elimination of acetate ion, a moderate base, and a good leaving group.

Step 1: Formation of a tetrahedral carbonyl addition intermediate



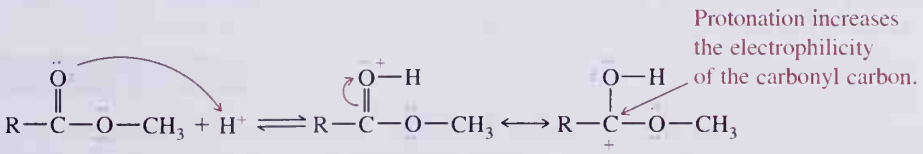
Step 2: Collapse of the tetrahedral carbonyl addition intermediate



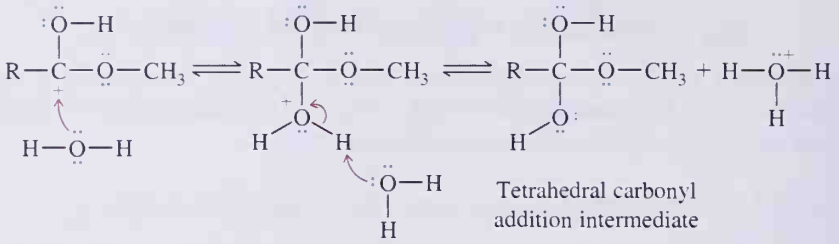
C. Esters

Esters are hydrolyzed only very slowly, even in boiling water. Hydrolysis becomes considerably more rapid, however, in the presence of refluxing aqueous acid or base. We already discussed acid-catalyzed (Fischer) esterification in Section 19.9A and pointed out that it is an equilibrium reaction. Acid-catalyzed hydrolysis of esters is also an equilibrium reaction and proceeds by the same mechanism as esterification, except in reverse. The role of the acid catalyst is to protonate the carbonyl oxygen and thereby increase the electrophilic character of the carbonyl carbon toward attack by water to form a **tetrahedral carbonyl addition intermediate.** Collapse of this intermediate gives the carboxylic acid and an alcohol. In this reaction, acid is a catalyst; it is consumed in hydrogen transfer to the carbonyl group but is regenerated later in the reaction.

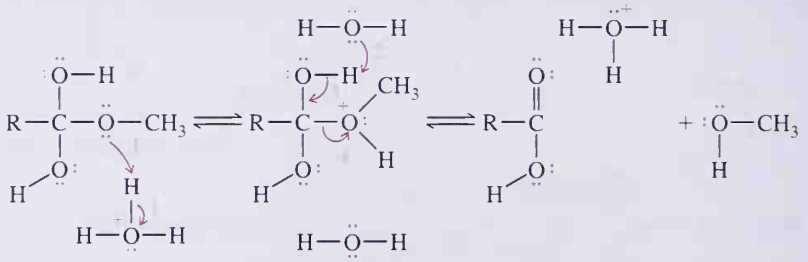
Step 1: Protonation of the carbonyl oxygen



Step 2: Formation of a tetrahedral carbonyl addition intermediate

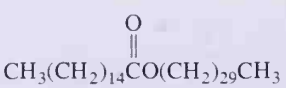


Step 3: Collapse of the tetrahedral carbonyl addition intermediate



Collapse of the tetrahedral carbonyl addition intermediate is initiated by (1) proton transfer from H_3O^+ to the intermediate followed by simultaneous (2) proton transfer from O—H to

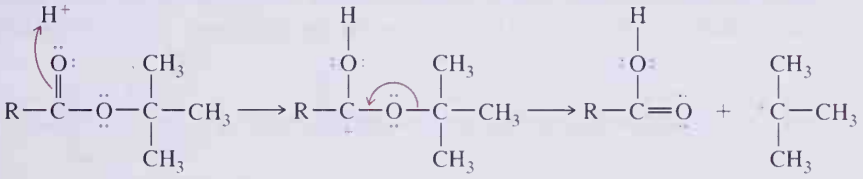
Plant and animal waxes are high-molecular-weight esters. Beeswax, for example, is largely 1-triacontanyl palmitate. The leaves of most plants are coated with wax, which helps to prevent microorganisms from attacking them and also allows them to conserve water. The feathers of birds are also coated with wax. This is what allows ducks to swim. Some commercially important waxes are carnauba wax from a Brazilian palm tree and lanolin from lamb's wool. *(Charles D. Winters)*



1-triacontanyl palmitate

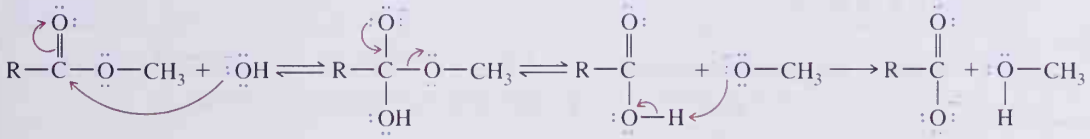
water, (3) shift of the electron pair from O—H to regenerate the C=O group and (4) finally breaking of the C—O bond to give methanol.

Although formation of a tetrahedral carbonyl addition intermediate is the most common mechanism for acid-catalyzed hydrolysis of esters, alternative mechanistic pathways are followed in special cases. Such a case occurs when the alkyl group attached to oxygen can form an especially stable carbocation. Then protonation of the carbonyl oxygen is followed by cleavage of the O—C bond to give a carboxylic acid and a carbocation. Benzyl and *tert*-butyl esters readily undergo this type of acid-catalyzed ester hydrolysis.

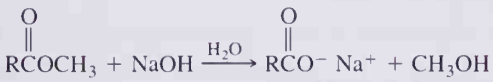


tert-Butyl cation

Hydrolysis of esters may also be carried out using hot aqueous base, as, for example, aqueous NaOH. Hydrolysis of esters in aqueous base is often called **saponification**, a reference to the use of this reaction in the manufacture of soaps (Section 23.1B). Although the carbonyl carbon of an ester is not strongly electrophilic, hydroxide ion is a good nucleophile and adds to the carbonyl carbon to form a tetrahedral carbonyl addition intermediate, which in turn collapses to give a carboxylic acid and an alkoxide ion. The carboxylic acid reacts with the alkoxide ion or other base present to form a carboxylic acid anion.



Thus, each mole of ester hydrolyzed requires one mole of base as shown in the following balanced equation:

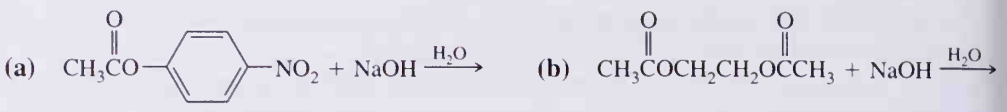


There are two major differences between hydrolysis of esters in aqueous acid and aqueous base.

1. In acid-catalyzed hydrolysis, acid is required in only catalytic amounts. In base-catalyzed hydrolysis, base is required in equimolar amounts because it is a reactant, not just a catalyst.
2. Acid-catalyzed ester hydrolysis is reversible. Because a carboxylic acid anion (very weakly electrophilic, if at all) is not attacked by ROH (a weak nucleophile), base-catalyzed hydrolysis is irreversible.

EXAMPLE 20.2

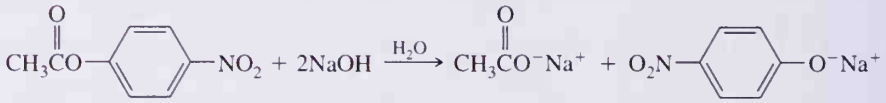
Complete and balance equations for the hydrolysis of each ester in aqueous sodium hydroxide. Show all products as they are ionized under the indicated experimental conditions.



p-Nitrophenyl acetate

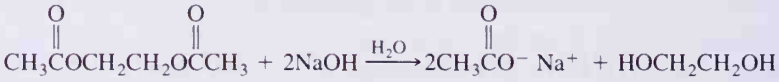
Solution

(a) The products of hydrolysis of *p*-nitrophenyl acetate are acetic acid and *p*-nitrophenol. Each is an acid, and in aqueous NaOH each is converted to its sodium salt. Therefore, 2 mol of NaOH are required for hydrolysis 1 mol of this ester.



p-Nitrophenyl acetate — Sodium acetate — Sodium *p*-nitrophenoxide

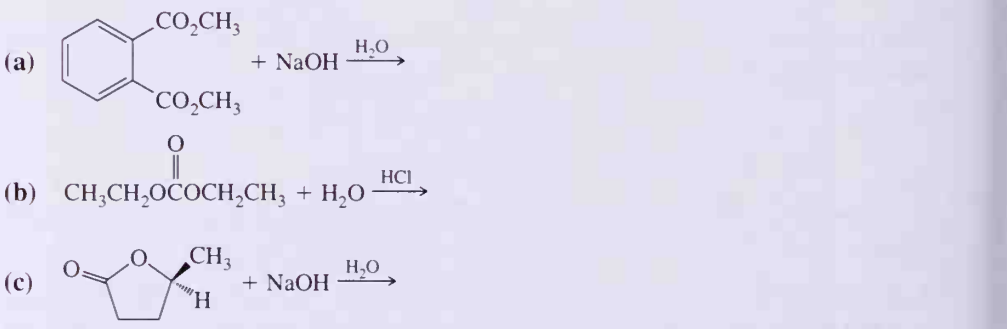
(b) This molecule is a diester of ethylene glycol. Two moles of NaOH are required for complete hydrolysis.



Sodium acetate — Ethylene glycol

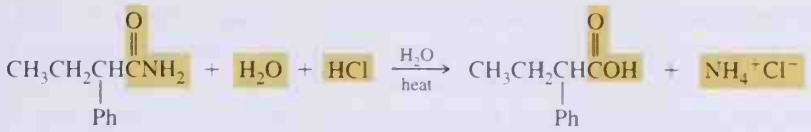
PROBLEM 20.2

Complete and balance equations for hydrolysis of each ester in aqueous solution. Show each product as it is ionized under the indicated experimental conditions.



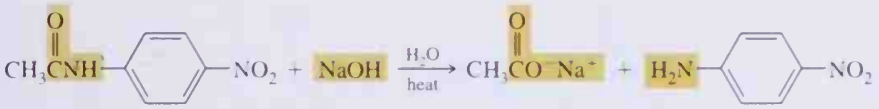
D. Amides

Amides undergo hydrolysis in aqueous acid to a give a carboxylic acid, and ammonia or an amine. Hydrolysis is driven to completion by the acid-base reaction between ammonia or the amine and acid to form an ammonium ion. One mole of acid is required per mole of amide.



2-Phenylbutanamide 2-Phenylbutanoic acid

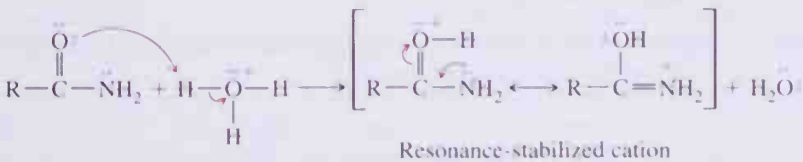
In aqueous base, the products of amide hydrolysis are a carboxylic acid salt, and ammonia or an amine. Base-catalyzed hydrolysis is driven to completion by the acid-base reaction between the carboxylic acid and base to form a salt. One mole of base is required per mole of amide.



N-4-Nitrophenylethanamide (*N*-*p*-Nitrophenylacetamide) Sodium acetate 4-Nitroaniline (*p*-Nitroaniline)

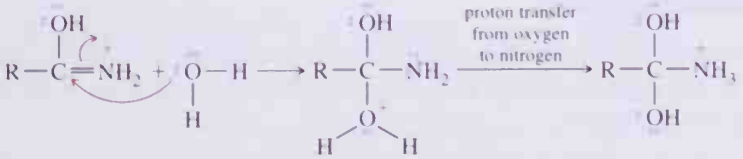
The steps in the mechanism for acid-catalyzed hydrolysis of amides are similar to those we proposed for acid-catalyzed hydrolysis of esters. The role of hydrogen ion is to protonate the carbonyl oxygen to give a resonance-stabilized cation. Following protonation, the polarized carbonyl group reacts with a molecule of water followed by proton transfer to give a tetrahedral carbonyl addition intermediate. Finally, protonation of nitrogen, collapse of the tetrahedral carbonyl addition intermediate, and loss of nitrogen as an amine or ammonia, followed by proton transfer to form an ammonium ion, complete the reaction. Thus, the leaving group in this case is a neutral amine (a weaker base), a far better leaving group than amide ion (a much stronger base).

Step 1: Protonation of the carbonyl oxygen



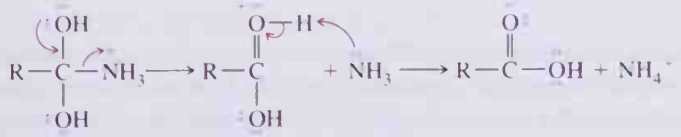
Resonance-stabilized cation

Step 2: Addition of water to the carbonyl carbon followed by proton transfer gives a tetrahedral carbonyl addition intermediate.



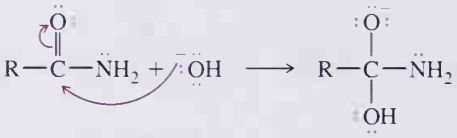
Tetrahedral carbonyl addition intermediate

Step 3: Collapse of the tetrahedral carbonyl addition intermediate coupled with proton transfer gives a carboxylic acid and ammonium ion.



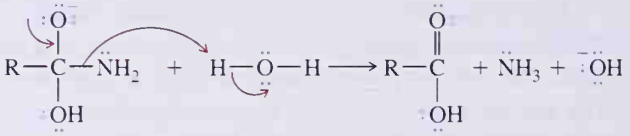
The mechanism for base-catalyzed hydrolysis of amides is similar to what we proposed for base-catalyzed hydrolysis of esters. Addition of hydroxide ion to the carbonyl carbon forms a tetrahedral carbonyl addition intermediate, which subsequently collapses to regenerate the carbonyl group and eject the nitrogen-containing group. In the following mechanism, loss of nitrogen and proton transfer from water to nitrogen are concerted so that the leaving group is not actually amide ion (a stronger base and poorer leaving group) but rather ammonia (a weaker base and better leaving group).

Step 1: Addition of hydroxide ion to the carbonyl carbon to give a tetrahedral carbonyl addition intermediate



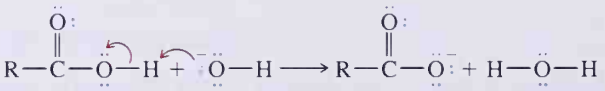
Tetrahedral carbonyl addition intermediate

Step 2: Collapse of the tetrahedral carbonyl addition intermediate to form a carboxylic acid and ammonia



Tetrahedral carbonyl addition intermediate

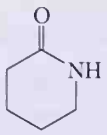
Step 3: Proton transfer to form the carboxylate anion and water. Hydrolysis is driven to completion by this acid-base reaction.



EXAMPLE 20.3

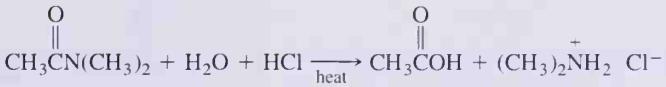
Complete equations for hydrolysis of these amides in concentrated aqueous HCl. Show all products as they exist in aqueous HCl, and show the number of moles of HCl required for hydrolysis of each amide.

(a) $CH_3CN(CH_3)_2$ **(b)**

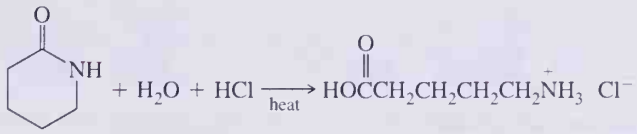


Solution

(a) Hydrolysis of *N,N*-dimethylacetamide gives acetic acid and dimethylamine. Dimethylamine, a base, is protonated by HCl to form dimethylammonium ion and is shown in the balanced equation as dimethylammonium chloride.



(b) Hydrolysis of this δ-lactam gives the protonated form of 5-aminopentanoic acid.

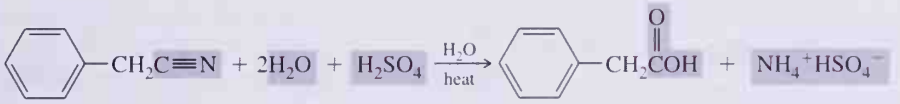


PROBLEM 20.3

Complete equations for the hydrolysis of the amides in Example 20.3 in concentrated aqueous NaOH. Show all products as they exist in aqueous NaOH, and show the number of moles of NaOH required for hydrolysis of each amide.

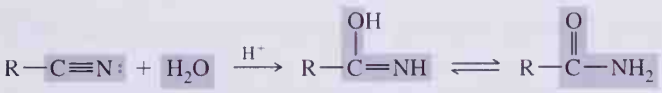
E. Nitriles

A nitrile is hydrolyzed in aqueous acid to a carboxylic acid and ammonium ion as shown in the following equation:



Phenylacetonitrile — Phenylacetic acid — Ammonium hydrogen sulfate

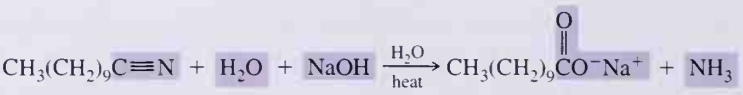
In acid-catalyzed hydrolysis of a nitrile, protonation of the nitrogen atom gives a cation that reacts with water to give an imidic acid (an enol of an amide). Keto-enol tautomerism of the imidic acid gives an amide. The amide is then hydrolyzed, as already described, to a carboxylic acid and ammonium ion.



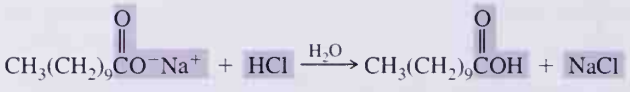
An imidic acid (enol of an amide) — An amide

The reaction conditions required for acid-catalyzed hydrolysis of a nitrile are typically more vigorous than those required for hydrolysis of an amide, and in the presence of excess water, a nitrile is hydrolyzed first to an amide and then to a carboxylic acid. It is possible, however, to stop at the amide by using sulfuric acid as a catalyst and 1 mol of water per mole of nitrile.

Hydrolysis of a nitrile in aqueous base gives a carboxylic acid anion and ammonia as illustrated in the following equation. Reaction is driven to completion by the acid-base reaction between the carboxylic acid and base to form a carboxylic acid anion. Acidification of the reaction mixture during work-up converts the anion to the carboxylic acid.

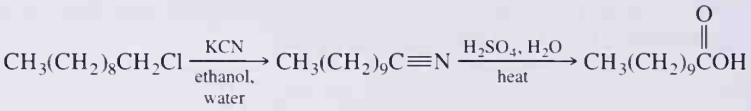


Undecanenitrile — Sodium undecanoate



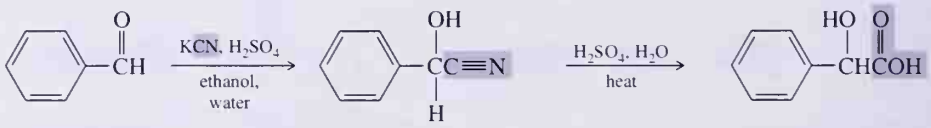
Sodium undecanoate — Undecanoic acid

Hydrolysis of a nitrile is a valuable route to the synthesis of carboxylic acids from primary or secondary alkyl halides. In this route, one carbon in the form of a cyano group (Table 10.7) is added to a carbon chain and then converted to a carboxyl group.



1-Chlorodecane — Undecanenitrile — Undecanoic acid

Nitriles also provide a valuable synthetic route to α-hydroxycarboxylic acids by addition of HCN to an aldehyde or ketone to form a cyanohydrin (Section 17.7E) followed by hydrolysis of the cyano group to a carboxyl group.



Benzaldehyde — Benzaldehyde cyanohydrin (Mandelonitrile) — 2-Hydroxyphenylacetic acid (Mandelic acid)

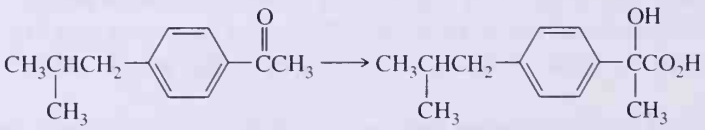
EXAMPLE 20.4

Show how to bring about the following conversions using as one step the hydrolysis of a cyano group:

(a) $(CH_3CH_2CH_2)_2CHCl \longrightarrow (CH_3CH_2CH_2)_2CHCO_2H$

4-Chloroheptane — 2-Propylpentanoic acid (Valproic acid)

(b)



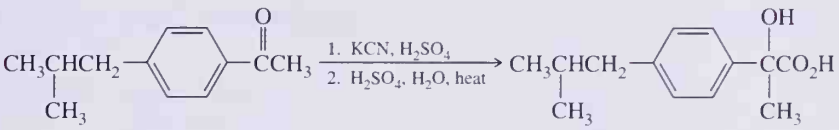
4-Isobutylacetophenone — 2-Hydroxy-2-(4-isobutylphenyl)-propanoic acid

Solution

(a) Treatment of 4-chloroheptane with potassium cyanide in aqueous ethanol by an S_N2 pathway gives a nitrile. Hydrolysis of the cyano group in concentrated sulfuric acid gives the product.

$$(CH_3CH_2CH_2)_2CHCl \xrightarrow[\text{ethanol, water}]{KCN} (CH_3CH_2CH_2)_2CHCN \xrightarrow[\text{heat}]{H_2SO_4,\ H_2O} (CH_3CH_2CH_2)_2CHCO_2H$$

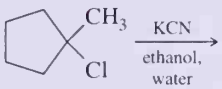
(b) Treatment of 4-isobutylacetophenone with potassium cyanide in aqueous ethanol gives a cyanohydrin. Hydrolysis of the cyano group in concentrated sulfuric acid gives the carboxyl group of the product.



This sequence was attempted as part of a synthesis of ibuprophen but failed because the cyanohydrin intermediate formed in only very poor yield (Section 17.7E).

PROBLEM 20.4

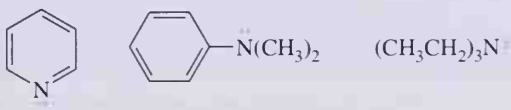
Synthesis of nitriles by nucleophilic displacement of halide from an alkyl halide is practical only with primary and secondary alkyl halides. It fails with tertiary alkyl halides. Why? What is the major product of the following reaction?



20.5 Reaction with Alcohols

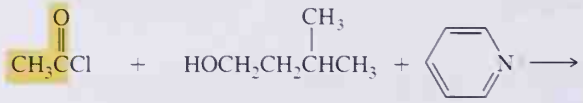
A. Acid Halides

An acid halide reacts with an alcohol to give an ester. Because acid halides are so reactive toward even weak nucleophiles, such as alcohols, no catalyst is necessary for these reactions. In cases in which the alcohol or resulting ester is sensitive to acid, reaction is carried out in the presence of a tertiary amine or heterocyclic aromatic amine to neutralize the HCl as it is formed. The amines most commonly used for this purpose are pyridine, *N*,*N*-dimethylaniline, and triethylamine. In addition to neutralizing the HCl, these tertiary amines also have a catalytic effect on the reaction.

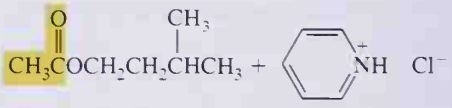


Pyridine *N*,*N*-Dimethylaniline Triethylamine

When used for this purpose, each amine is converted to its hydrochloride salt. Pyridine, for example, is converted to pyridinium chloride, as illustrated by its use in the synthesis of isoamyl acetate.

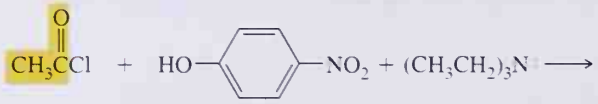


Acetyl chloride — 3-Methyl-1-butanol (Isoamyl alcohol) — Pyridine

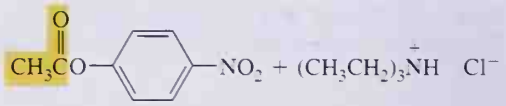


3-Methylbutyl ethanoate (Isoamyl acetate) — Pyridinium chloride

Phenol and substituted phenols also react with acid chlorides to give esters.

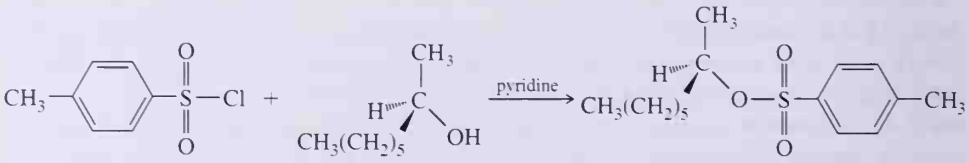


Acetyl chloride — 4-Nitrophenol — Triethylamine



4-Nitrophenyl acetate — Triethylammonium chloride

Sulfonic acid esters can be formed by reaction of an alkyl or aryl sulfonyl chloride with an alcohol or phenol. Two of the most common sulfonyl chlorides are *p*-toluenesulfonyl chloride, abbreviated TsCl, and methanesulfonyl chloride, abbreviated MsCl (Section 20.1A).

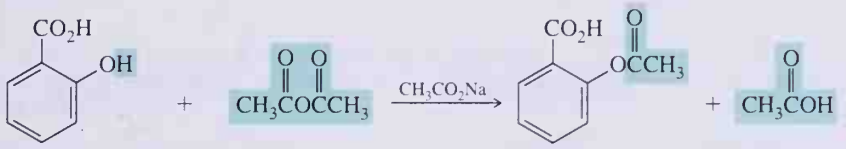


p-Toluenesulfonyl chloride (Tosyl chloride; TsCl) — (R)-2-Octanol — (R)-2-Octyl *p*-toluenesulfonate

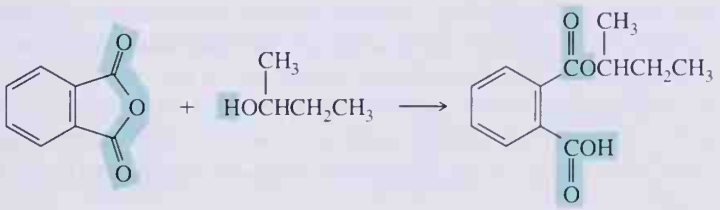
As discussed in Section 10.8, a special value of tosylate and other sulfonic esters is that in forming them, an —OH is converted from a poor leaving group (hydroxide ion) in nucleophilic displacement to an excellent leaving group (*p*-toluenesulfonate ion).

B. Acid Anhydrides

Acid anhydrides react with alcohols to give one molecule of ester and one molecule of a carboxylic acid. Thus, reaction of an alcohol with an anhydride is a useful method for the synthesis of esters. Aspirin is synthesized on an industrial scale by reaction of acetic anhydride and salicylic acid.



2-Hydroxybenzoic acid (Salicylic acid) | Acetic anhydride | Acetylsalicylic acid (Aspirin) | Acetic acid

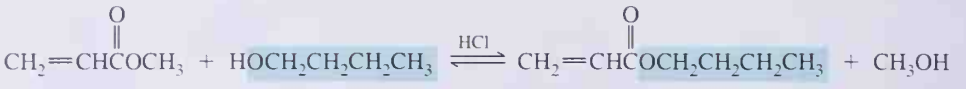


Phthalic anhydride | 2-Butanol (*sec*-Butyl alcohol) | *sec*-Butyl hydrogen phthalate

Aspirin crystals viewed under polarized light. *(© Phillip A. Harrington/Fran Heyl Associates)*

C. Esters

Esters react with alcohols in an acid-catalyzed reaction called **transesterification.** For example, it is possible to convert methyl acrylate to butyl acrylate by heating the methyl ester with 1-butanol in the presence of an acid catalyst. The acids most commonly used are HCl as a gas bubbled into the reaction medium (thereby using anhydrous HCl) and *p*-toluenesulfonic acid.

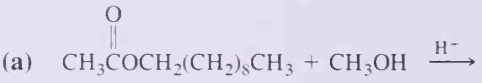


Methyl propenoate (Methyl acrylate) (bp 81°C)	1-Butanol (bp 117°C)	Butyl propenoate (Butyl acrylate) (bp 147°C)	Methanol (bp 65°C)

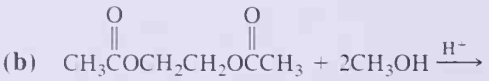
Transesterification is an equilibrium reaction and can be driven in either direction by control of experimental conditions. For example, in the reaction of methyl acrylate, transesterification is carried out at a temperature slightly above the boiling point of methanol (the lowest boiling component in the mixture). Methanol distills from the reaction mixture, thus shifting the position of equilibrium in favor of butyl acrylate. Alternatively, reaction of butyl acrylate with a large excess of methanol shifts the equilibrium to favor formation of methyl acrylate.

EXAMPLE 20.5

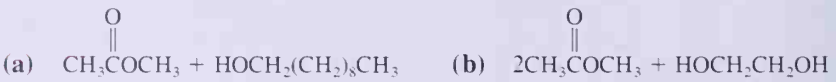
Complete the following transesterification reactions. The stoichiometry of each is given in the problem.



Decyl acetate Methanol

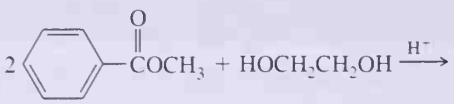


Solution



PROBLEM 20.5

Complete the following transesterification reaction. The stoichiometry is given in the equation.



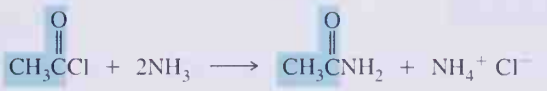
D. Amides

Amides, the least reactive of the functional derivatives of carboxylic acids, do not react with alcohols. Thus, reaction of an amide with an alcohol cannot be used to prepare an ester.

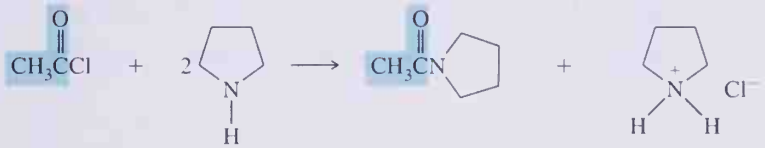
20.6 Reactions with Ammonia and Amines

A. Acid Halides

Acid halides react very readily with ammonia and amines to form amides. For complete conversion of an acid halide to an amide, two equivalents of ammonia or amine are used: one to form the amide and one to neutralize the hydrogen halide formed. The following examples illustrate reaction of an acid chloride with ammonia to form a primary amide, and reaction of an acid chloride with a secondary heterocyclic aliphatic amine to form a tertiary amide.



Acetyl chloride — Ammonia — Ethanamide (Acetamide) — Ammonium chloride



Acetyl chloride — Pyrrolidine (a secondary amine) — *N*-Acetylpyrrolidine — Pyrrolidinium chloride (Pyrrolidine hydrochloride)

B. Acid Anhydrides

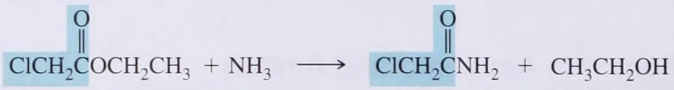
Acid anhydrides react with ammonia, as well as with primary and secondary amines, to form amides. As with acid halides, 2 mol of amine are required: 1 to form the amide and 1 to neutralize the carboxylic acid byproduct.

Acetic anhydride — Ammonia — Ethanamide (Acetamide) — Ammonium acetate

Alternatively, if the amine used to make the amide is expensive, a heterocyclic amine (e.g., pyridine) or tertiary amine (e.g., triethylamine or *N*,*N*-dimethylaniline) may be used to neutralize the carboxylic acid.

C. Esters

Esters react with ammonia and primary or secondary amines to form amides. Because an alkoxide anion is a poorer leaving group than either a halide ion or a carboxylate ion, esters are less reactive toward ammonia, primary amines, and secondary amines than are acid halides or acid anhydrides.



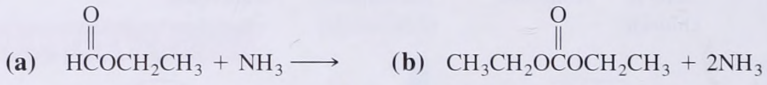
Ethyl chloroacetate Chloroacetamide

D. Amides

Amides do not react with ammonia, or primary or secondary amines.

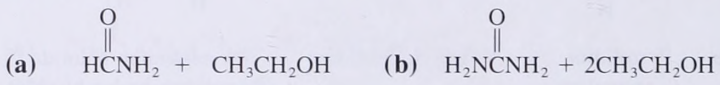
EXAMPLE 20.6

Complete the following reactions. The stoichiometry of each reaction is given in the equation.



Ethyl formate Diethyl carbonate

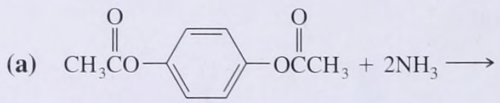
Solution

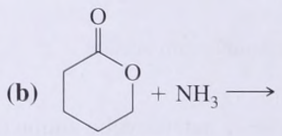


Formamide Urea

PROBLEM 20.6

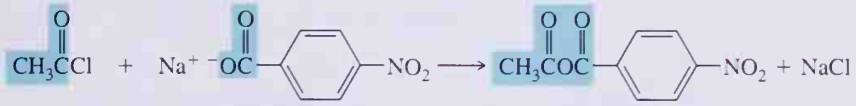
Complete and balance equations for the following reactions. The stoichiometry of each reaction is given in the equation.





20.7 Reaction of Acid Chlorides with Salts of Carboxylic Acids

Acid chlorides react with salts of carboxylic acids to give anhydrides. Most commonly used are the sodium or potassium salts.



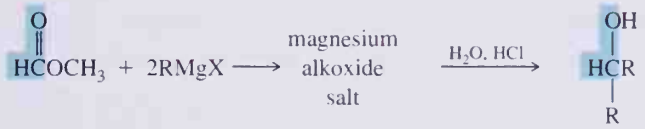
Acetyl chloride | Sodium 4-nitrobenzoate | Acetic 4-nitrobenzoic anhydride

Reaction of an acid halide with the anion of a carboxylic acid is a particularly useful method for synthesis of mixed anhydrides.

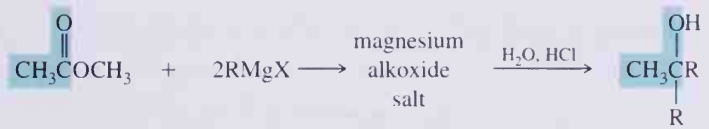
20.8 Reactions with Organometallic Compounds

A. Grignard Reagents

Treatment of a formic ester with 2 mol of a Grignard reagent followed by hydrolysis of the magnesium alkoxide salt in aqueous acid gives a secondary alcohol. Treatment of an ester other than a formate with a Grignard reagent gives a tertiary alcohol.

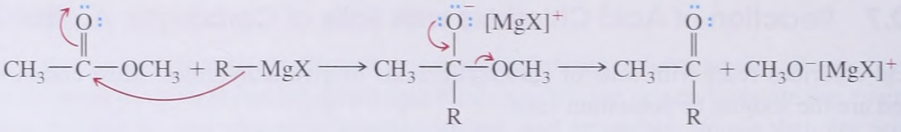


An ester of formic acid | A secondary alcohol

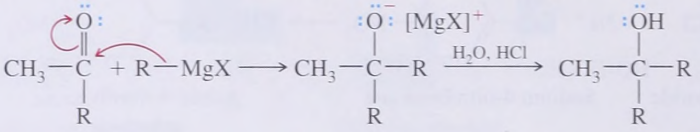


An ester of any acid other than formic acid | A tertiary alcohol

The reaction of an ester and a Grignard reagent begins with addition of 1 mol of Grignard reagent to the carbonyl carbon to form a tetrahedral carbonyl addition intermediate. Because alkoxide ion is a moderately good leaving group, this magnesium alkoxide collapses to give a new carbonyl-containing compound and a magnesium alkoxide salt. This new carbonyl-containing compound then reacts with a second mole of Grignard reagent to form a tertiary alcohol (or a secondary alcohol if the starting ester was a formate). It is important to realize that it is not possible to use RMgX and an ester to prepare a ketone; the intermediate ketone reacts immediately with Grignard reagent to give a tertiary alcohol.



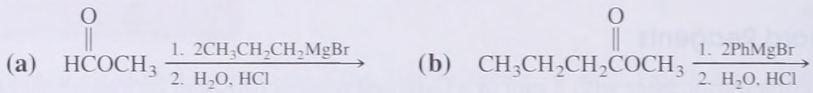
Magnesium salt A ketone



A ketone Magnesium salt A tertiary alcohol

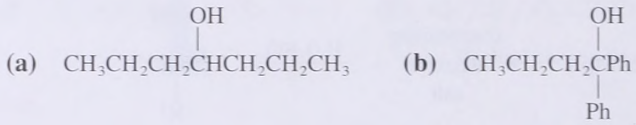
EXAMPLE 20.7

Complete the following Grignard reactions:



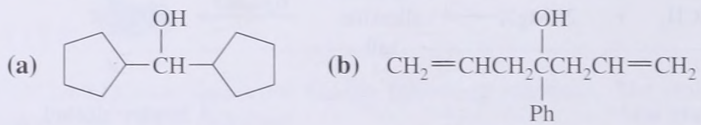
Solution

Sequence (a) gives a secondary alcohol, and sequence (b) gives a tertiary alcohol.

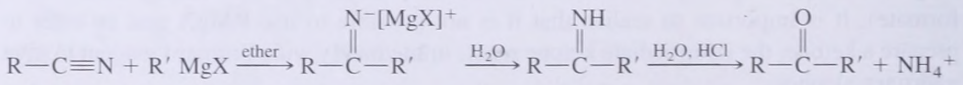


PROBLEM 20.7

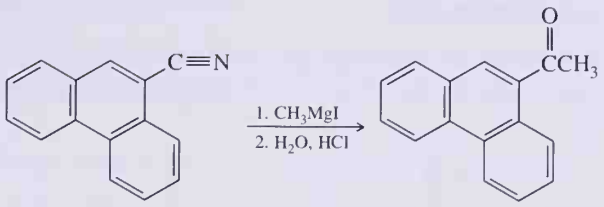
Prepare these alcohols by treatment of an ester with a Grignard reagent.



Addition of a Grignard reagent to a cyano group gives an anionic intermediate that remains in ether solution and does not react further. On addition of aqueous acid, the anionic intermediate is protonated to give an imine (Section 17.11), which then undergoes hydrolysis to a give a ketone. Thus, treatment of a cyano group with a Grignard reagent is a valuable synthetic route to ketones.



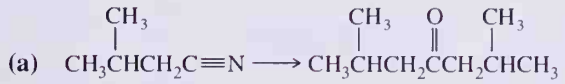
An anionic intermediate An imine

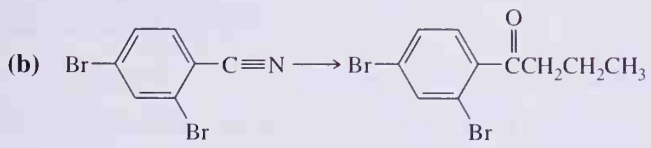


9-Phenanthrenecarbonitrile 9-Acetylphenanthrene

EXAMPLE 20.8

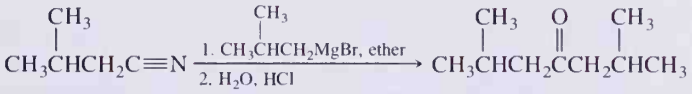
Show how to bring about the following conversions in good yield:





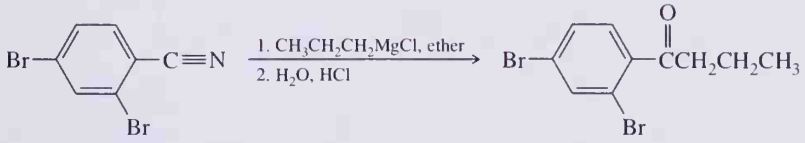
Solution

(a) Treatment of this nitrile with isobutylmagnesium bromide followed by hydrolysis in aqueous HCl gives the desired ketone.



3-Methylbutanenitrile 2,6-Dimethyl-4-heptanone

(b) Treatment of the nitrile with propylmagnesium chloride followed by hydrolysis in aqueous HCl gives the desired ketone.



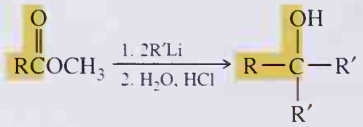
2,4-Dibromobenzonitrile 1-(2,4-Dibromophenyl)-1-butanone

PROBLEM 20.8

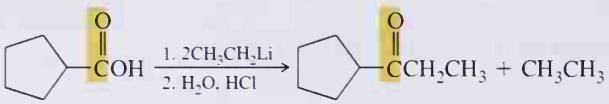
Propose a mechanism for hydrolysis of the imine intermediate in aqueous acid to give a ketone. What is the molecular formula of the nitrogen-containing ion present in solution following hydrolysis?

B. Organolithium Compounds

Organolithium compounds are even more powerful nucleophiles than Grignard reagents and react with esters to give the same types of secondary and tertiary alcohols as shown for Grignard reagents.

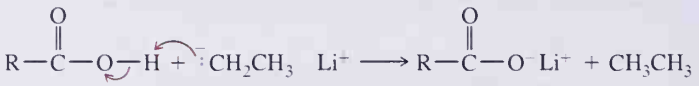


Organolithium compounds also react with carboxylic acids to give ketones. The stoichiometry of this reaction requires 2 mol of organolithium compound per mole of carboxylic acid. Treatment of cyclopentanecarboxylic acid, for example, with 2 mol of ethyllithium gives 1-cyclopentyl-1-propanone and ethane.

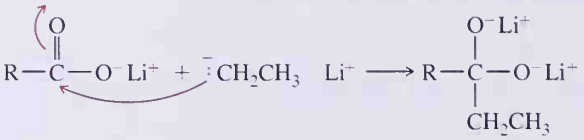


Cyclopentane-carboxylic acid | 1-Cyclopentyl-1-propanone | Ethane

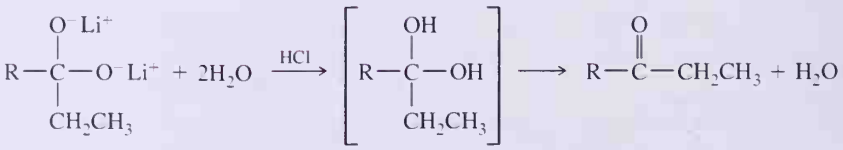
The first step in this transformation is an acid-base reaction between the alkyl group of R—Li (a strong nucleophile and a strong base) and the carboxylic acid to form a lithium salt and an alkane (ethane in the case of ethyllithium). To emphasize the acid-base nature of this reaction, the ethyllithium is shown in the following equation as ionic compound.



Magnesium carboxylates are insoluble in ether, precipitate, and do not react further. Lithium carboxylates, on the other hand, are more soluble in ether and react with a second mole of ethyllithium to give a dianion. Hydrolysis of this dianion during work-up in aqueous acid gives a 1,1-diol (a ketone hydrate, Section 17.9A), which loses water to yield a ketone.



A dianion



A dianion | A 1,1-diol (hydrate of a ketone)

Organolithium compounds, in common with organomagnesium compounds, also react with nitriles followed by hydrolysis in aqueous acid to give ketones.

C. Organocadmium Compounds

Organocadmium compounds are most often prepared from organomagnesium compounds, as illustrated by the synthesis of diethylcadmium from ethylmagnesium bromide and cadmium chloride.

$$CH_3CH_2MgBr + CdCl_2 \longrightarrow CH_3CH_2CdCH_2CH_3 + MgCl_2$$

Because of the smaller difference in electronegativity between cadmium and carbon (2.5 − 1.7 = 0.8) compared with carbon and magnesium (2.5 − 1.2 = 1.3) or carbon and lithium (2.5 − 1.0 = 1.5), organocadmium compounds are weaker nucleophiles and react only with highly polarized carbonyl groups such as those of acid halides. They do not react with aldehydes, ketones, or esters. Consequently, organocadmium compounds can be used to convert acid halides to ketones.

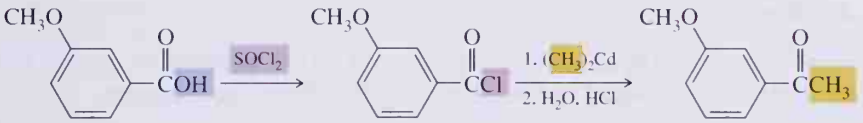
$$2RC(=O)Cl + CH_3CH_2CdCH_2CH_3 \longrightarrow 2RC(=O)CH_2CH_3 + CdCl_2$$

EXAMPLE 20.9

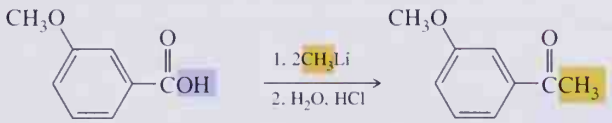
Show how to convert 3-methoxybenzoic acid to 3-methoxyacetophenone using (a) an organocadmium compound and (b) an organolithium compound.

Solution

(a) Treat 3-methoxybenzoic acid with thionyl chloride to convert the carboxylic acid to an acid chloride. Treatment of the acid chloride with dimethylcadmium followed by hydrolysis in aqueous acid gives the methyl ketone.

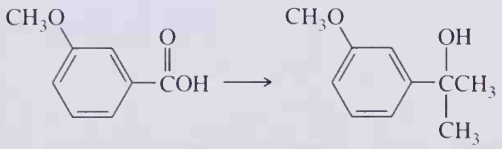


(b) Treatment of 3-methoxybenzoic acid with 2 mol of methyllithium followed by hydrolysis in aqueous acid gives the desired methyl ketone.



PROBLEM 20.9

Show how to convert 3-methoxybenzoic acid to 2-(3-methoxyphenyl)-2-propanol.



3-Methoxybenzoic acid — 2-(3-Methoxyphenyl)-2-propanol

20.9 Interconversion of Functional Derivatives

We have seen throughout these past several sections that acid chlorides are the most susceptible to nucleophilic acyl substitution and that amides are the least susceptible to this kind of reaction.

amide < ester < acid anhydride < acid chloride

Increasing reactivity toward nucleophilic acyl substitution

Another useful way to think about the relative reactivities of these four functional derivatives of carboxylic acids is summarized in Figure 20.4. Any functional group lower in this figure can be prepared from any functional group above it by treatment with an appropriate oxygen or nitrogen nucleophile. An acid chloride, for example, can be converted to an acid anhydride, an ester, an amide, or a carboxylic acid. An acid anhydride, ester, or amide, however, does not react with chloride ion to given an acid chloride.

20.10 Reduction

Most reductions of carbonyl compounds, including aldehydes and ketones, are now accomplished by transfer of hydride ions from boron or aluminum. We have already seen the use of sodium borohydride to reduce the carbonyl groups of aldehydes and ketones to hydroxyl groups (Section 17.16B) and the use of lithium aluminum hydride to reduce not only aldehydes and ketones but also carboxyl groups to alcohol groups (Section 19.8A).

A. Esters

An ester is reduced by lithium aluminum hydride to two alcohols; the alcohol derived from the acyl group is primary and is usually the objective of the reduction.

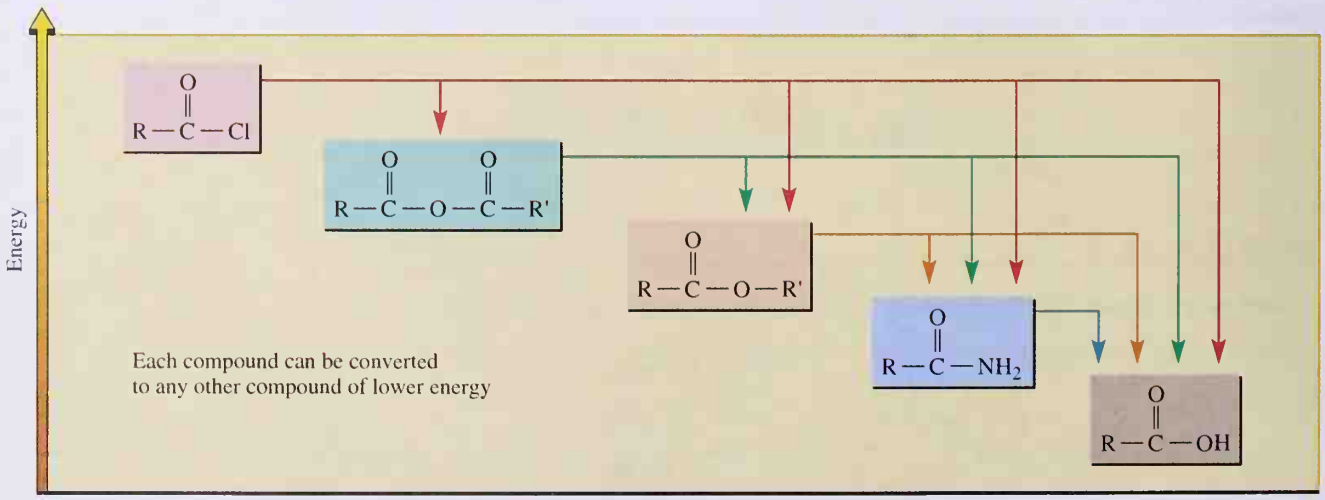
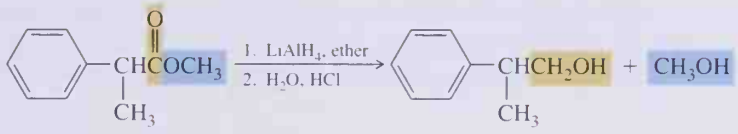
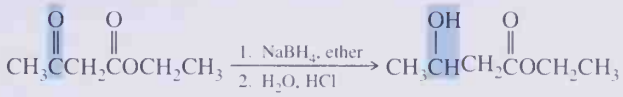


Figure 20.4
Relative reactivities of carboxylic acid derivatives toward nucleophilic acyl substitution.

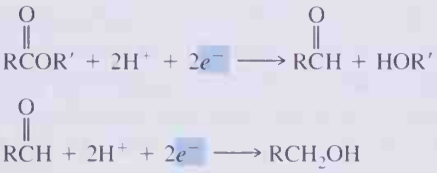


Methyl 2-phenylpropanoate — 2-Phenyl-1-propanol — Methanol

Sodium borohydride also reduces esters to primary alcohols but far more slowly than lithium aluminum hydride. Because of the selectivity of sodium borohydride, it is possible to reduce the carbonyl group of an aldehyde or ketone to a alcohol group with this reagent without reducing an ester or carboxyl group in the same molecule.



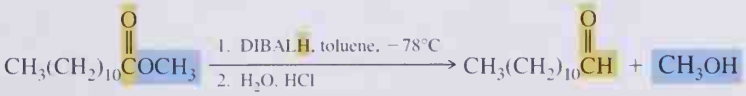
Reduction of an ester to a primary alcohol can be viewed as two successive two-electron reductions, as shown by the following balanced half-reactions:



Chemists wondered if it were possible to modify the structure of the reducing agent so as to reduce an ester to an aldehyde and no further. The most useful of the chemically modified hydride reducing agents yet discovered for this purpose is diisobutylaluminum hydride (DIBALH).

Diisobutylaluminum hydride (DIBALH)

Reductions are typically carried out in toluene or another inert solvent at $-78^{\circ}C$ followed by warming to room temperature and addition of aqueous acid to hydrolyze the aluminum salts and liberate the aldehyde. Reduction of esters using DIBALH, thus, has become a valuable method for the synthesis of aldehydes, as illustrated by the synthesis of dodecanal.

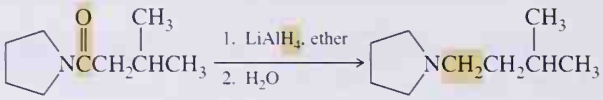


Methyl dodecanoate — Dodecanal

If reduction of an ester using DIBALH is carried out at room temperature, the ester is reduced to a primary alcohol. Thus, temperature control is critical in selective reduction of an ester to an aldehyde.

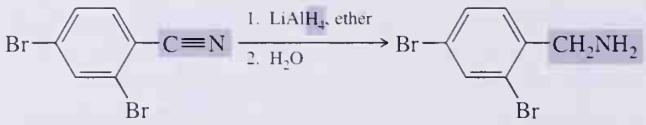
B. Amides

Lithium aluminum hydride reduction of amides can be used to prepare primary, secondary, or tertiary amines, depending on the degree of substitution of the amide.



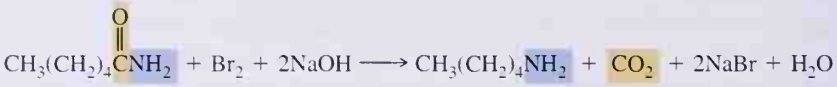
C. Nitriles

A cyano group is reduced by lithium aluminum hydride to a primary amine. Reduction of cyano groups is useful for the preparation of primary amines only.



20.11 The Hofmann Rearrangement

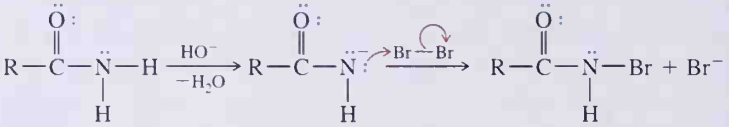
When a primary amide is treated with bromine or chlorine in aqueous sodium or potassium hydroxide, the amide is converted to a primary amine with one fewer carbon atoms, and the carbonyl group is converted to carbon dioxide. The conversion of a primary amide to a primary amine of one fewer carbons is named the **Hofmann rearrangement** after Augustus Hofmann, the German chemist who discovered it more than 100 years ago.



Hexanamide — Pentanamine

A mechanism for this rearrangement can be divided into four stages, each having some analogy to reactions we have already studied. Stage 1 begins with an acid-base reaction between hydroxide ion and the amide to form an amide anion. This anion is both a base and a nucleophile. Reaction with bromine by nucleophilic substitution gives an *N*-bromoamide.

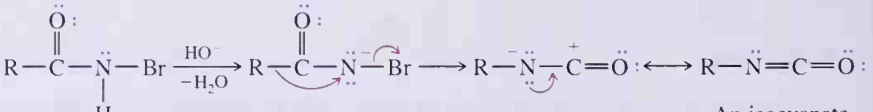
Stage 1:



An amide anion — An *N*-bromoamide

In Stage 2, the second amide proton is abstracted by base followed by migration of the R group from the carbonyl carbon to nitrogen and displacement of bromide ion. The resulting molecule belongs to the class of organic compounds called **isocyanates,** the characteristic structural feature of which is —N=C=O. Isocyanates can be prepared by other reactions, and their chemical and physical properties are well understood.

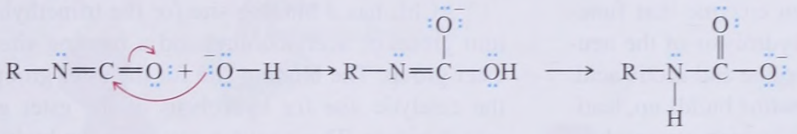
Stage 2:



An isocyanate

Reaction of the isocyanate with hydroxide ion in Stage 3 followed by keto-enol tautomerism (Section 17.12B) gives the anion of a **carbamic acid,** the characteristic structural feature of which is a carboxyl group bonded to nitrogen.

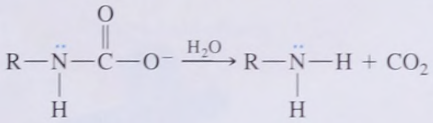
Stage 3:



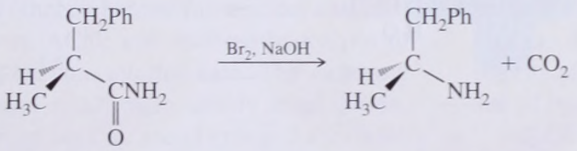
Anion of a carbamic acid

In Stage 4, the carbamic acid anion undergoes spontaneous decarboxylation to give a primary amine and carbon dioxide.

Stage 4:



A significant aspect of the Hofmann rearrangement is that the absolute configuration of the migrating group is maintained throughout, that is, the reaction proceeds with retention of configuration of the group migrating from the carbonyl carbon to nitrogen.

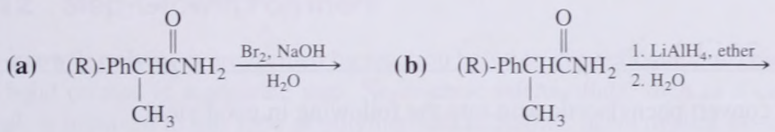


(S)-2-Methyl-3-phenylpropanamide

(S)-1-Phenyl-2-propanamine

EXAMPLE 20.10

Complete the following equations:

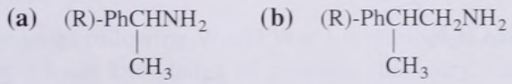


(R)-2-Phenylpropanamide

(R)-2-Phenylpropanamide

Solution

Each reaction proceeds with complete retention of configuration at the stereocenter.



(R)-1-Phenylethanamine

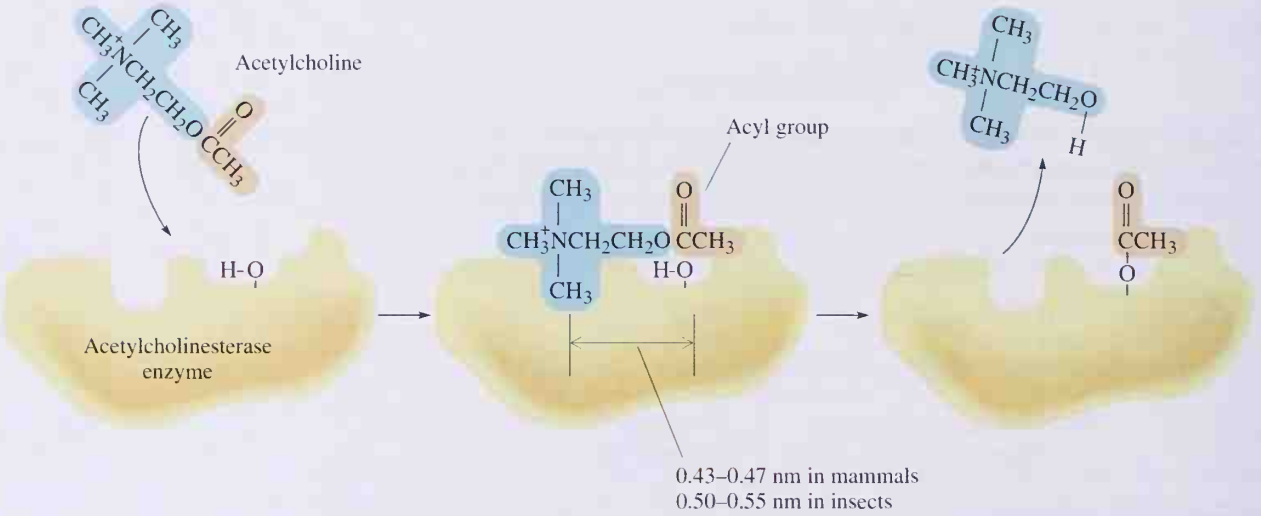
(R)-2-Phenyl-1-propanamine

CHEMISTRY IN ACTION

Carbamate Insecticides

Acetylcholinesterase (AChE) is an enzyme that functions in synapses to catalyze the hydrolysis of the neurotransmitter acetylcholine into choline and acetic acid. If this enzyme is blocked, acetylcholine builds up, leading to continuing nerve stimulation, which can produce convulsions, paralysis, and eventually death. Carbamates are effective blockers of acetylcholinesterase, especially the variety found in insects. This makes carbamates one of the most useful families of pesticides.

AChE has a binding site for the trimethylammonium group of acetylcholine and a binding site for the ester group. The binding site for the ester group is also the catalytic site for hydrolysis of the ester group of acetylcholine. This enzyme catalyzes the hydrolysis of the ester group by first transferring the acetyl group from the oxygen of choline to an oxygen in the binding–catalytic site of the enzyme. This transfer leads to the transient formation of an "acyl enzyme"

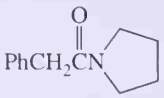
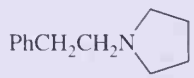


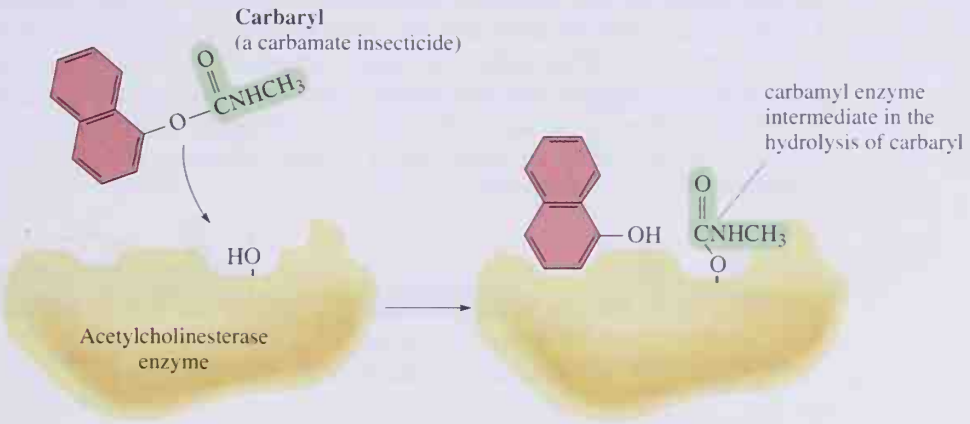
PROBLEM 20.10

Show how to convert phenylacetic acid into the following in good yield:

(a) $PhCH_2COCH_3$ (b) $PhCH_2CNH_2$

(c) $PhCH_2CH_2NH_2$ (d) $PhCH_2NH_2$

(e)  (f) 



intermediate. The acetyl group is then hydrolyzed from the enzyme's —OH, and the enzyme is regenerated for further catalysis.

Carbaryl and other carbamate insecticides also bind to the active site of AChE and undergo hydrolysis to form a carbamyl-enzyme intermediate. The carbamyl group is hydrolyzed much more slowly from the enzyme's —OH group than an acetyl group. As a result, the catalytic activity of the enzyme is decreased, the concentration of acetylcholine in synapses increases, and nerve stimulation increases, leading to paralysis and death. Carbaryl and other carbamate insecticides are much more toxic to insects than to humans because humans and insects have slightly different shapes to their AChE binding sites. The distance between the two pockets in the enzyme is greater for insects than for humans, so that compounds that fit snugly in the binding site of insect AChE do not fit as well in the binding site of human AChE.

Carbamate insecticides are considered environmentally safe. Once they are released into the environment, they are broken down rapidly by microorganisms in the soil and thus exit the food chain quickly. In water, their hydrolysis is catalyzed by sunlight.

20.12 Step-Growth Polymers

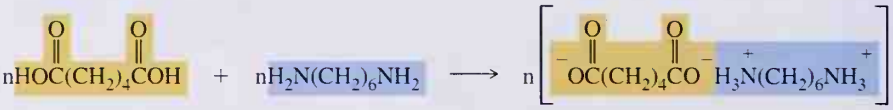
Step-growth polymers are formed by reaction between difunctional molecules, with each new bond created in a separate step. No reactive intermediate, such as a carbocation or radical, is involved in this type of polymerization. Rather, new covalent bonds are generally formed by polar reactions, as for example, nucleophilic acyl substitution. In this section, we discuss four types of step-growth polymers: polyesters, polyamides, polycarbonates, and polyurethanes.

A. Polyamides

In the years following World War I, a number of chemists recognized the need for developing a basic knowledge of polymer chemistry. One of the most creative of these was Wallace M. Carothers. In the early 1930s, Carothers and his associates at E. I. DuPont de

Nemours & Company began fundamental research into the reactions of aliphatic dicarboxylic acids and diols. From adipic acid and ethylene glycol, they obtained a polyester of high molecular weight that could be drawn into fibers. However, these first polyester fibers had melting points too low for use as textile fibers, and they were not investigated further. Carothers then turned his attention to the reactions of dicarboxylic acids and diamines, and in 1934 synthesized nylon 66, the first purely synthetic fiber. Nylon 66 is so named because it is synthesized from two different organic compounds, each containing six carbon atoms.

In the synthesis of nylon 66, hexanedioic acid (adipic acid) and 1,6-hexanediamine (hexamethylenediamine) are dissolved in aqueous ethanol where they react to form a one-to-one salt called nylon salt.



Hexanedioic acid (Adipic acid) | 1,6-Hexanediamine (Hexamethylenediamine) | Nylon salt

Nylon salt is then heated in an autoclave to 250°C where the internal pressure rises to about 15 atm. Under these conditions, $—CO_2^-$ groups from adipic acid and $—NH_3^+$ groups from hexamethylenediamine react to form amide groups. As polymerization proceeds, steam and alcohol vapors are bled from the autoclave to maintain a constant internal pressure. When reaction is complete and all water vapor removed, pressure within the reaction vessel falls to 1 atm. Nylon 66 formed under these conditions melts at 250° to 260°C and has a molecular weight range of 10,000 to 20,000.

In the first stage of fiber production, crude nylon 66 is melted, spun into fibers, and cooled. Next, the melt-spun fibers are drawn at room temperature (cold-drawn) to about four times their original length. As the fibers are drawn, individual polymer molecules become oriented in the direction of the fiber axis, and hydrogen bonds form between carbonyl oxygens of one chain and amide hydrogens of another chain (Figure 20.5). The effects of orientation of polyamide molecules on the physical properties of the fiber are dramatic; both tensile strength and stiffness are increased markedly. Cold drawing is an important step in the production of all synthetic fibers.

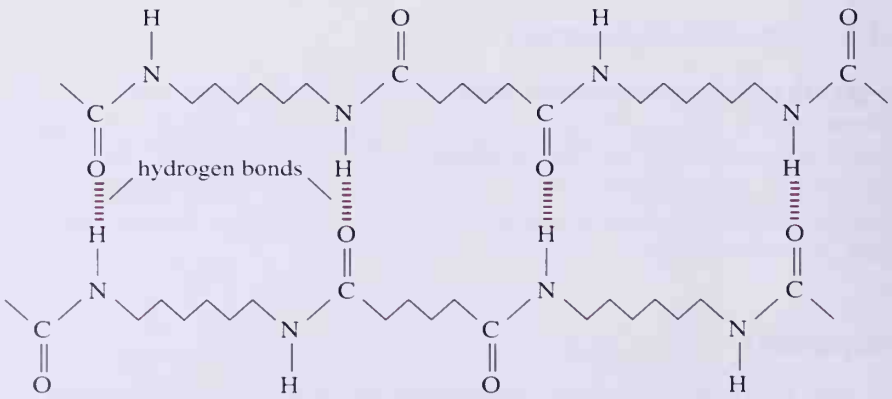
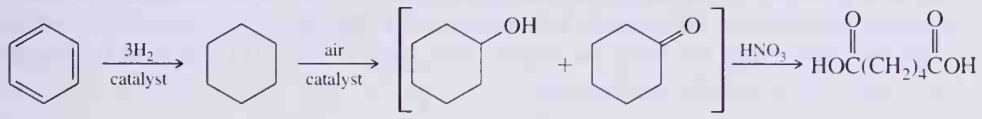


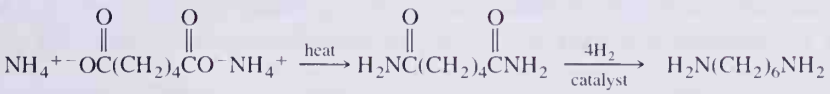
Figure 20.5
The structure of cold-drawn nylon 66. Hydrogen bonds between adjacent polymer chains provide tensile strength and stiffness to the fibers.

The raw material base for the production of nylon 66 is benzene, which is derived almost entirely from catalytic cracking and reforming of petroleum. Catalytic reduction of benzene to cyclohexane followed by catalyzed air oxidation gives a mixture of cyclohexanol and cyclohexanone. Oxidation of this mixture by nitric acid gives adipic acid.



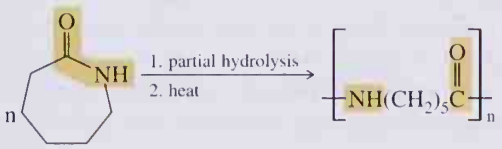
Benzene — Cyclohexane — Cyclohexanol — Cyclohexanone — Hexanedioic acid (Adipic acid)

Adipic acid in turn is a starting material for the synthesis of hexamethylenediamine. Treatment of adipic acid with ammonia gives an ammonium salt, which, when heated, gives adipamide. Catalytic reduction of adipamide gives hexamethylenediamine. Thus, carbon sources for the production of nylon 66 are derived entirely from petroleum, a non-renewable resource.



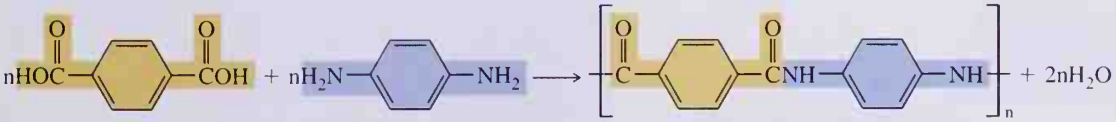
Ammonium hexanedioate (Ammonium adipate) — Hexanediamide (Adipamide) — 1,6-Hexanediamine (Hexamethylenediamine)

The nylons are a family of polymers, the two most widely used of which are nylon 66 and nylon 6. Nylon 6 is so named because it is synthesized from one six-carbon starting material, namely caprolactam, a seven-member cyclic amide. In the synthesis of nylon 6, caprolactam is partially hydrolyzed and then heated to 250°C to drive off water and bring about polymerization.



Caprolactam — Nylon 6

Based on extensive research into relationships between molecular structure and bulk physical properties, scientists at DuPont reasoned that a polyamide containing aromatic rings would be stiffer and stronger than nylon 66 or nylon 6, and in early 1960, DuPont introduced Kevlar, a polyaromatic amide (aramid) fiber synthesized from terephthalic acid and *p*-phenylenediamine.



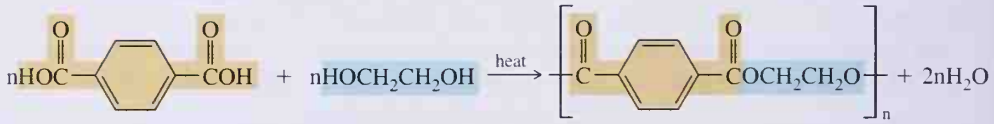
1,4-Benzenedicarboxylic acid (Terephthalic acid) — 1,4-Benzenediamine (*p*-Phenylenediamine) — Kevlar

Bulletproof vests have a thick layer of Kevlar. *(Charles D. Winters)*

One of the remarkable features of Kevlar is its light weight compared with other materials of similar strength. For example, a 3-inch cable woven of Kevlar has a strength equal to that of a similarly woven 3-inch steel cable. Whereas the steel cable weighs about 20 pounds per foot, the Kevlar cable weighs only 4 pounds per foot. Kevlar now finds use in such articles as anchor cables for offshore drilling rigs and reinforcement fibers for automobile tires. Kevlar is also woven into a fabric that stretches, like a trampoline, when struck by a bullet, thus absorbing the impact. This property has led to the use of Kevlar for bullet-proof vests, jackets, and raincoats.

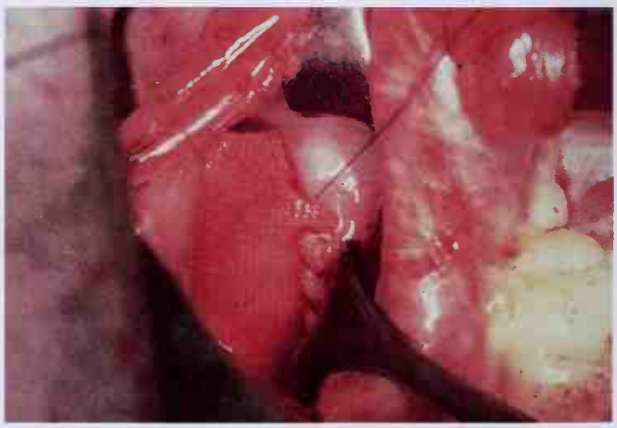
B. Polyesters

Recall that in the early 1930s, Carothers and his associates had concluded that polyester fibers from aliphatic dicarboxylic acids and ethylene glycol were not suitable for textile use because their melting points were too low. Winfield and Dickson at the Calico Printers Association in England further investigated polyesters in the 1940s and reasoned that a greater resistance to rotation in the polymer backbone would stiffen the polymer, raise its melting point, and thereby lead to a more acceptable polyester fiber. To create stiffness in the polymer chain, they used terephthalic acid. Polymerization of this aromatic dicarboxylic acid with ethylene glycol gives poly(ethylene terephthalate), abbreviated PET.



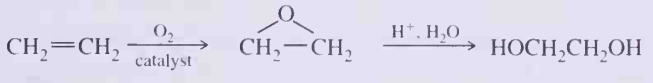
1,4-Benzenedicarboxylic acid (Terephthalic acid) | 1,2-Ethanediol (Ethylene glycol) | Poly(ethylene terephthalate) (Dacron, Terylene, Mylar)

The crude polyester can be melt-spun and then cold-drawn to form the textile fiber Dacron polyester, outstanding features of which are its stiffness (about four times that of nylon 66), very high strength, and remarkable resistance to creasing and wrinkling. Because the first Dacron polyester fibers were harsh to the touch (because of their stiffness), they were usually blended to cotton or wool to make acceptable textile fibers. Newly developed fabrication techniques now produce less harsh Dacron polyester textile fibers. Crude poly(ethylene terephthalate) is also fabricated into Mylar films.

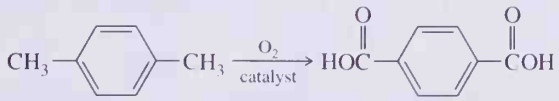


A Dacron patch used in heart surgery. *(Courtesy of Drs. James L. Monro and Gerald Shore and Wolfe Medical Publications, London, England)*

Ethylene glycol for the synthesis of poly(ethylene terephthalate) fibers and films is obtained by air oxidation of ethylene to ethylene oxide (Section 11.7B) followed by hydrolysis to the glycol (Section 11.8A). Ethylene is in turn derived entirely from cracking either petroleum or ethane derived from natural gas (Section 5.10A). Terephthalic acid is obtained by oxidation of *p*-xylene, an aromatic hydrocarbon obtained along with benzene and toluene from catalytic cracking and reforming of naphtha and other petroleum fractions (Section 2.10).



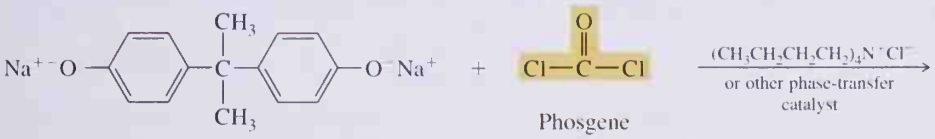
Ethylene — Oxirane (Ethylene oxide) — 1,2-Ethanediol (Ethylene glycol)



p-Xylene — Terephthalic acid

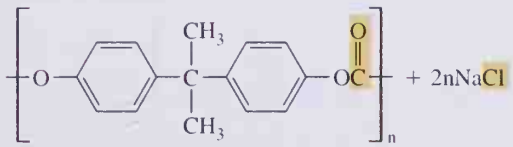
C. Polycarbonates

Polycarbonates, the most familiar of which is Lexan, are a class of commercially important engineering polyesters. In the production of Lexan, an aqueous solution of the disodium salt of bisphenol A (Problem 16.21) is brought into contact with a solution of phosgene dissolved in methylene chloride. The two solutions are immiscible and no reaction occurs until tetrabutylammonium chloride or another phase-transfer catalyst (Section 10.9) is added. The tetrabutylammonium cation carries the bisphenol A anion into the methylene chloride phase where it reacts smoothly with phosgene to form the polymer. The tetrabutylammonium ion then carries chloride ion back to the aqueous phase.



Disodium salt of bisphenol A (dissolved in H_2O)

Phosgene (dissolved in CH_2Cl_2)



A polycarbonate

Lexan is transparent, resistant to burning, has an unusually high resistance to impact, and retains its properties over a wide temperature range. It has found significant use in sporting equipment, such as bicycle, football, motorcycle, and snowmobile helmets as well as hockey and baseball catchers' face masks. In addition it is used to make light, impact resistant housings for household appliances and automotive and aircraft equipment.

Polycarbonate polymers have replaced glass in many applications. *(Charles D. Winters)*

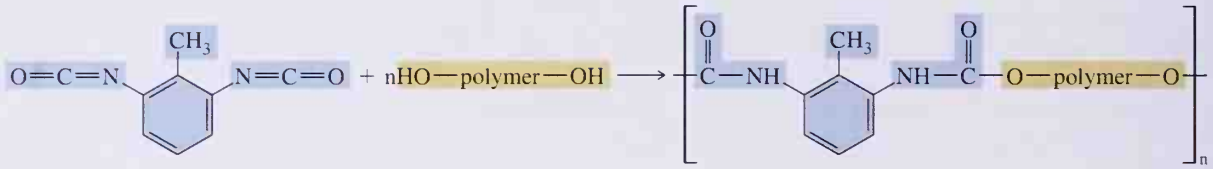
D. Polyurethanes

A urethane, or carbamate, is an ester of carbamic acid, H_2NCO_2H. Carbamates are most commonly prepared by treatment of an isocyanate with an alcohol.

$$RN{=}C{=}O + R'OH \longrightarrow RNHC(=O)OR'$$

An isocyanate — A carbamate

Polyurethanes are diblock copolymers consisting of flexible polyester or polyether units (blocks) alternating with rigid urethane units (blocks). The rigid urethane blocks are derived from a diisocyanate, commonly a mixture of 2,4- and 2,6-toluene diisocyanate. The more flexible blocks are derived from low-molecular-weight (MW 1000 to 4000) polyesters or polyethers with —OH groups at each end of the polymer chain.



Toluene 2,6-diisocyanate — Low-molecular-weight polyester or polyether — A polyurethane

Polyurethane fibers are fairly soft and elastic and have found use as spandex and Lycra, the "stretch" fabrics used in bathing suits, leotards, and undergarments.

Polyurethane foams for upholstery and insulating materials are made by adding small amounts of water during polymerization. Water reacts with isocyanate groups to produce gaseous carbon dioxide which then acts as the foaming agent.

$$RN{=}C{=}O + H_2O \longrightarrow \left[RNHC(=O)OH\right] \longrightarrow RNH_2 + CO_2$$

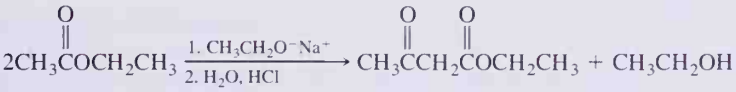
An isocyanate — A carbamic acid (not stable)

Polyurethane varnish is hard, quick-drying, and scratch-resistant. *(Charles D. Winters)*

20.13 The Claisen Condensation

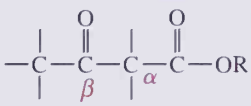
A. Claisen Condensation

In the previous sections, we described reactions of functional derivatives of carboxylic acids, all of which take place at the carbonyl carbon and involve nucleophilic acyl substitution. In this section, we examine a second type of reaction characteristic of esters, namely one that involves both formation of a nucleophilic anion at the α-carbon and nucleophilic acyl substitution. One of the first discovered of these reactions, the **Claisen condensation,** named after the German chemist Ludwig Claisen, is illustrated by the condensation of two molecules of ethyl acetate in the presence of a base followed by acidification to give ethyl acetoacetate.



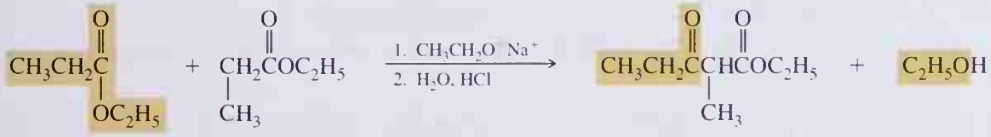
Ethyl ethanoate (Ethyl acetate) — Ethyl 3-oxobutanoate (Ethyl acetoacetate) — Ethanol

The characteristic structural feature of the product of a Claisen condensation is a **β-ketoester.**



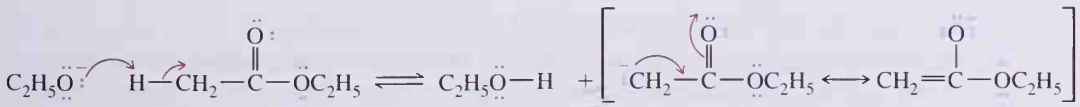
A β-ketoester

Claisen condensation of two molecules of ethyl propanoate gives the following β-ketoester.



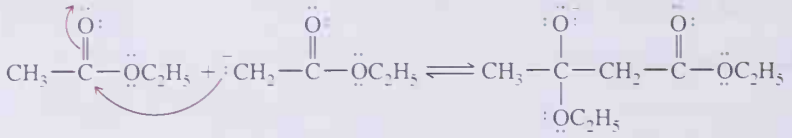
Ethyl propanoate — Ethyl propanoate — Ethyl 2-methyl-3-oxopentanoate

The first steps in the mechanism of a Claisen condensation bear a close resemblance to the first steps of the aldol reaction (Section 17.14). In each, base removes a proton from the α-carbon to form a **resonance-stabilized enolate anion.**

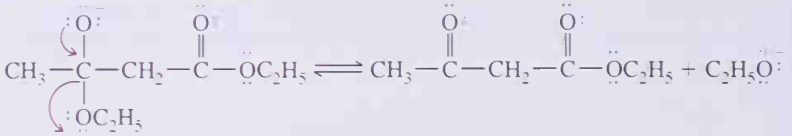


pK_a 22 (Weaker acid) — pK_a 15.9 (Stronger acid) — Resonance-stabilized enolate anion

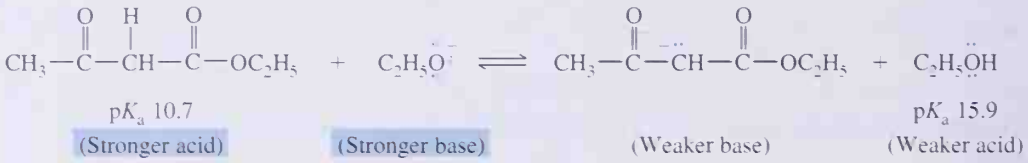
Because the α-hydrogen of the ester is the weaker acid and ethoxide ion is the weaker base, the position of this equilibrium lies very much toward the left, and the concentration of enolate anion is very low compared with that of ethoxide ion and ester. The enolate anion then attacks the carbonyl carbon of another ester molecule to form a tetrahedral carbonyl addition intermediate, which then collapses to give a β-ketoester.



A tetrahedral carbonyl addition intermediate



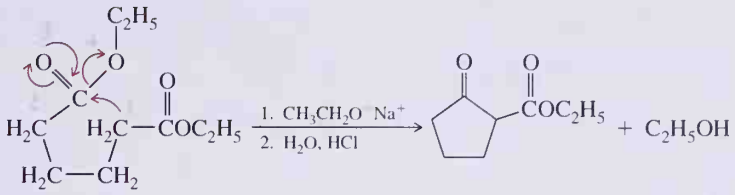
The position of equilibrium for this reaction also lies far toward the left. The overall reaction is driven to completion, however, because the β-ketoester formed is a stronger acid than ethanol. The β-ketoester (a stronger acid) reacts with ethoxide ion (a stronger base) to give ethanol (a weaker acid) and the anion of the β-ketoester (a weaker base). Thus, the structural feature required for a successful Claisen condensation is an ester with two α-hydrogens: one to form the initial enolate anion, the second to form the enolate anion of the resulting β-ketoester.



The β-ketoester is formed and isolated on acidification with aqueous acid during work-up.

B. The Dieckmann Condensation

An intramolecular Claisen condensation of an ester of a dicarboxylic acid to give a five- or six-member ring is given the special name of **Dieckmann condensation.** In the presence of one equivalent of sodium ethoxide, for example, diethyl hexanedioate (diethyl adipate) undergoes an intramolecular condensation to form a five-member ring. The bond-making and bond-breaking steps are shown by four curved arrows. (1) An anion formed on the α-carbon of one ester group (2) adds to the carbonyl of the other ester group to form a tetrahedral carbonyl addition intermediate, which (3) collapses to regenerate the carbonyl group and (4) ejects ethoxide ion. Cyclization is followed by formation of the conjugate base of the β-ketoester, just as in the Claisen condensation. The β-ketoester is formed and isolated after acidification with aqueous acid.

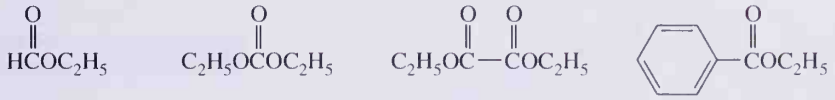


Diethyl hexanedioate (Diethyl adipate)

Ethyl 2-oxocyclopentanecarboxylate

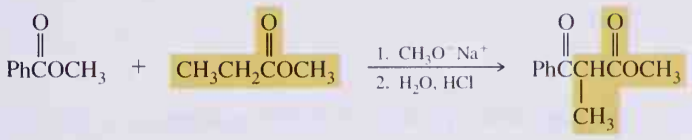
C. Crossed Claisen Condensations

In a **crossed Claisen condensation** between two different esters, each with two α-hydrogens, a mixture of four β-ketoesters is possible, and, therefore, crossed Claisen condensations of this type are generally not synthetically useful. Such condensations are useful, however, if appreciable differences in reactivity exist between the two esters, as for example, when one of the esters has no α-hydrogens and can function only as an enolate anion acceptor. Following are four examples of esters without α-hydrogens:

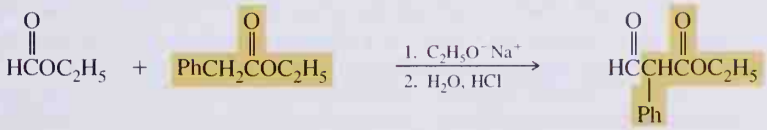


Ethyl formate | Diethyl carbonate | Diethyl ethanedioate (Diethyl oxalate) | Ethyl benzoate

In these illustrations, the ester with no α-hydrogens is used in excess.



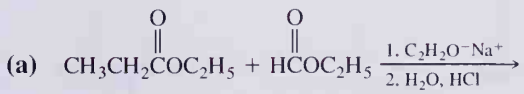
Methyl benzoate | Methyl propanoate | Methyl 2-methyl-3-oxo-3-phenylpropanoate

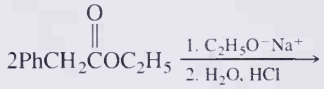


Ethyl formate | Ethyl phenylacetate | Ethyl 3-oxo-2-phenylpropanoate

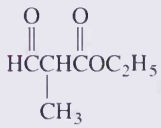
EXAMPLE 20.11

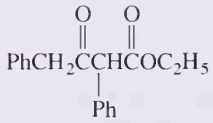
Complete the equations for the following ester condensations:



(b) 

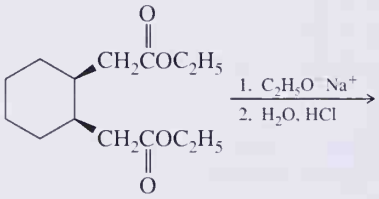
Solution

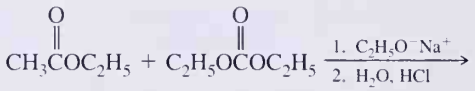
(a) 

(b) 

PROBLEM 20.11

Complete the equations for the following ester condensations:

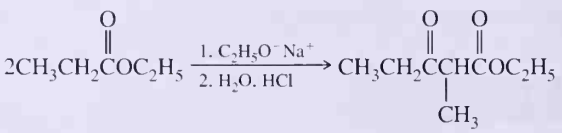
(a) 

(b) 

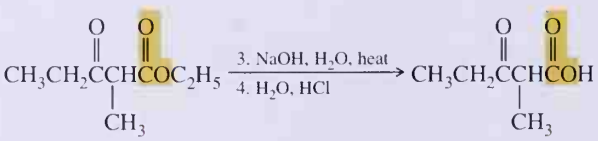
D. Hydrolysis and Decarboxylation of β-Ketoesters

Recall from Section 20.4C that hydrolysis of an ester in aqueous sodium hydroxide (saponification) followed by acidification of the reaction mixture with HCl or another mineral acid converts an ester to a carboxylic acid. Recall also from Section 19.11 that β-ketoacids and β-dicarboxylic acids readily undergo decarboxylation (lose CO_2) when heated. The following equations illustrate the results of a Claisen condensation followed by saponification, acidification, and finally decarboxylation.

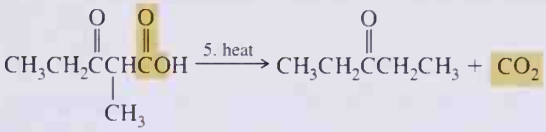
Claisen condensation:



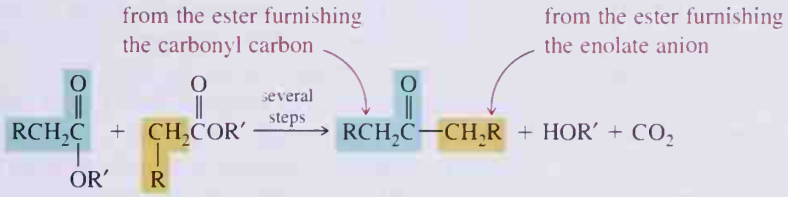
Saponification followed by acidification:



Decarboxylation:

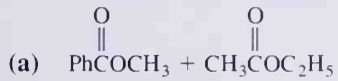


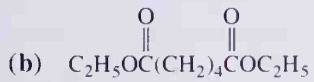
The result of these five steps is reaction between two molecules of ester (one furnishing a carbonyl group and the other furnishing an enolate anion) to give a ketone and carbon dioxide. In the general reaction, both ester molecules are the same, and, hence, the product is a symmetrical ketone.

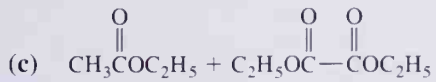


EXAMPLE 20.12

The compound(s) in each part of this example undergo (1, 2) Claisen condensation, (3) saponification followed by (4) acidification, and finally (5) thermal decarboxylation. Draw the structural formula of the product after completion of this reaction sequence.

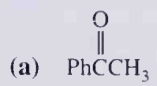


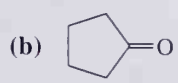


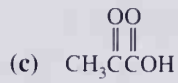


Solution

Steps 1 and 2 bring about Claisen condensation to form a β-ketoester. Steps 3 and 4 bring about saponification of the β-ketoester to give a β-ketoacid, and Step 5 brings about decarboxylation to give a ketone.







CHEMISTRY IN ACTION

Industrial Synthesis of Ibuprofen

A major difference between laboratory scale syntheses and industrial scale syntheses is the effect of byproducts on cost. A reaction that proceeds in a laboratory with a 90% yield of the desired product is often viewed as a success. However, if the same reaction on an industrial scale of 5000 kg proceeds with a 90% yield of the desired compound, 10%, or 500 kg is waste or byproduct that must be disposed of in an environmentally responsible manner. A second consideration is the atom efficiency of a process. It is most efficient to use only reagents whose atoms appear in the final product. Chromium compounds, for example, are useful reagents in the laboratory for oxidation of organic molecules, but chromium atoms do not appear in the products. This may not be a problem in a laboratory synthesis but on an industrial scale, recycling or disposing of chromium byproducts can be a major factor in determining the cost effectiveness of a synthesis.

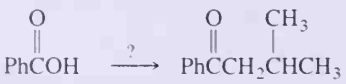
Chemists work continually to devise new routes to commercial products, to improve the efficiency of existing routes, to lower production costs, and to decrease chemical wastes. An example of the evolution of synthetic routes to a product is the syntheses of ibuprofen. The first route shown here was developed by the Boots Pure Drugs Company, the second was developed by Hoechst.

The Boots synthesis involves six steps. By use of two catalytic processes, the Hoechst route condenses the synthesis from six steps to three. Furthermore, the Hoechst process realizes a greater atom efficiency. In the Boots synthesis, the reagent $ClCH_2CO_2Et$ delivers 14 atoms to an intermediate, but only a single carbon atom of this reagent is present in the final product. Similarly, NH_2OH is incorporated into a second intermediate, but none of its atoms are present in the final product. The Hoechst process illustrates well the fact that chemists are constantly developing new reagents and new reactions using elements from different parts of the periodic table.

Chem. Eng. News, Feb. 8, 59 (1993).

PROBLEM 20.12

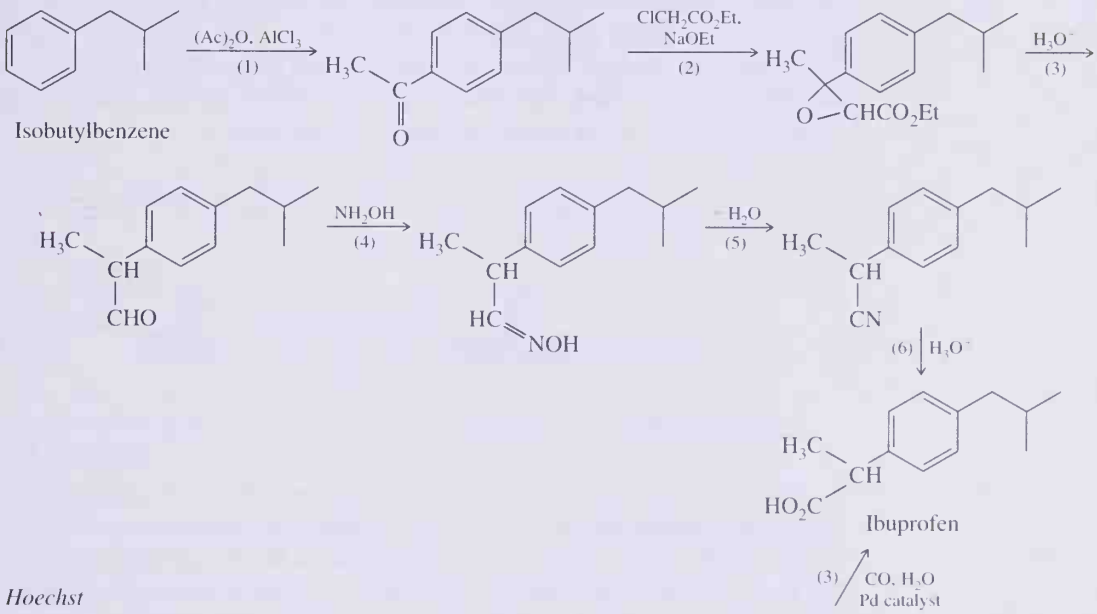
Show how to convert benzoic acid to 3-methyl-1-phenyl-1-butanone by following synthetic strategies, each of which uses a different type of reaction to form the new carbon-carbon bond to the carbonyl group of benzoic acid.



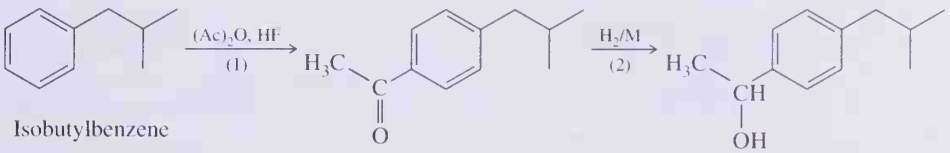
Benzoic acid — 3-Methyl-1-phenyl-1-butanone

(a) An organocadmium compound
(b) An organolithium compound
(c) A Claisen condensation

Boots Pure Drug Co.

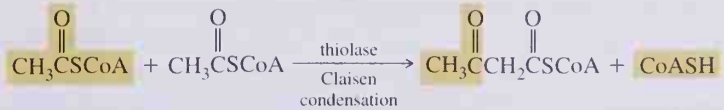


Hoechst



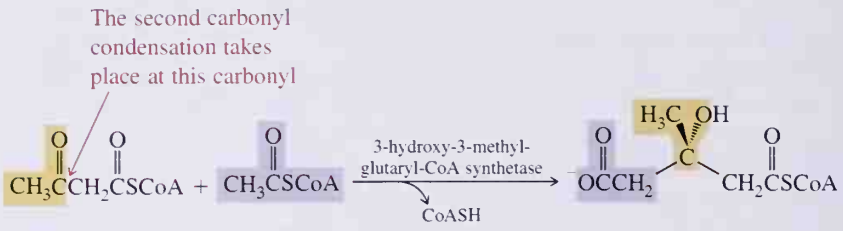
20.14 Claisen Condensations in the Biological World

Carbonyl condensations are among the most widely used reactions in the biological world for the assembly of new carbon-carbon bonds in such important biomolecules as fatty acids, cholesterol, steroid hormones, and terpenes. The common source of carbon atoms for the synthesis of these relatively more complex biomolecules is **acetyl-CoA,** a thioester of acetic acid and the thiol group of coenzyme A (Problem 20.33). The pK_a of the α-hydrogens of acetyl-CoA is approximately 8.5. In a reaction catalyzed by the enzyme, thiolase, acetyl-CoA is converted to its enolate anion, which then attacks the carbonyl group of a second molecule of acetyl-CoA to form a tetrahedral carbonyl addition intermediate. Collapse of this intermediate by loss of CoA-SH gives acetoacetyl-CoA.



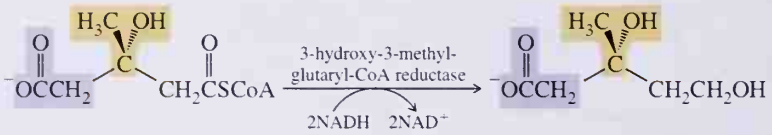
Acetyl-CoA Acetyl-CoA Acetoacetyl-CoA

Enzyme-catalyzed aldol reaction with a third molecule of acetyl-CoA on the ketone carbonyl of acetoacetyl-CoA gives (S)-3-hydroxy-3-methylglutaryl CoA. Note three features of this reaction. First, creation of the new tetrahedral stereocenter is stereospecific; only the S enantiomer is formed. Although each reactant is achiral, their condensation takes place in a chiral environment created by the enzyme, 3-hydroxy-3-methylglutaryl-CoA synthetase. Second, hydrolysis of the thioester group of acetyl-CoA is coupled with the aldol reaction. Third, the carboxyl group is shown as it is ionized at pH 7.4, the approximate pH of blood plasma and many cellular fluids.



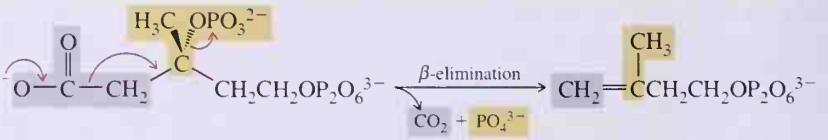
Acetoacetyl-CoA Acetyl-CoA (S)-3-Hydroxy-3-methyl-glutaryl-CoA

Enzyme-catalyzed reduction by NADH (Section 9.5G) of the thioester group of 3-hydroxy-3-methylglutaryl-CoA to a primary alcohol gives mevalonic acid, here shown as its anion. Note that in this reduction, a change occurs in the designation of configuration from S to R, not because of any change in configuration at the tetrahedral stereocenter, but rather because there is a change in priority among the four groups bonded to the stereocenter.



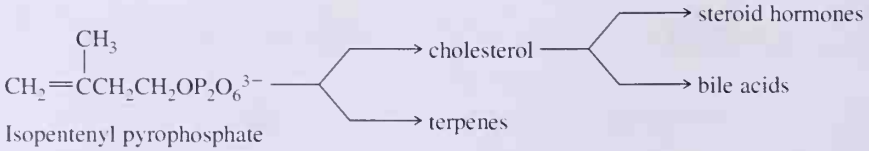
(S)-3-Hydroxy-3-methyl-glutaryl-CoA (R)-Mevalonate

On enzyme-catalyzed interaction with adenosine triphosphate (ATP), the 3-hydroxyl group of mevalonate is converted to a phosphate ester and the 5-hydroxyl group is converted to a pyrophosphate. Enzyme-catalyzed β-elimination from this molecule results in loss of CO_2 and PO_4^{3-}, both good leaving groups.



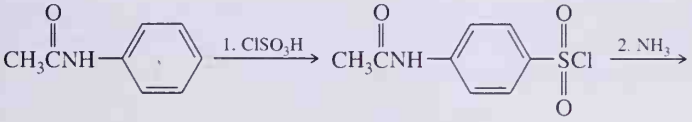
(R)-Mevalonate Isopentenyl pyrophosphate

Isopentenyl pyrophosphate has the carbon skeleton of isoprene, the unit into which terpenes can be divided (Section 4.6). This molecule is in fact a key intermediate in the synthesis of terpenes, as well as of cholesterol and steroid hormones. We have more to say about the synthesis of these biomolecules in Chapter 23.

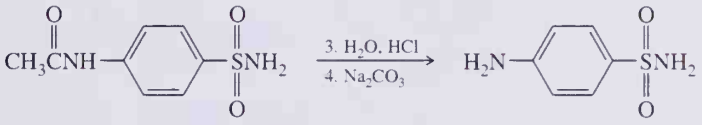


20.15 Sulfonamides

Alkyl and arylsulfonyl chlorides react with ammonia and amines to form sulfonamides as illustrated by the synthesis of 4-aminobenzenesulfonamide. Treatment of acetanilide with chlorosulfonic acid gives a sulfonyl chloride, which is then treated with ammonia to give a sulfonamide. Selective hydrolysis of the amide in aqueous acid followed by neutralization with sodium carbonate gives 4-aminobenzenesulfonamide, more commonly known as sulfanilamide.

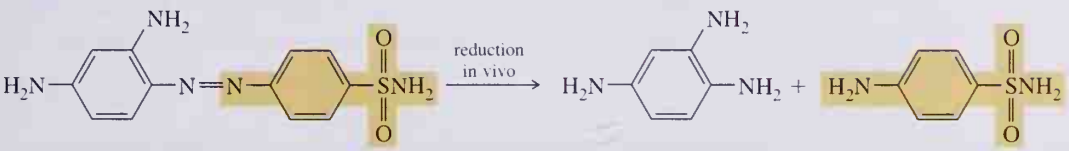


Acetanilide — 4-Acetamidobenzenesulfonyl chloride



4-Acetamidobenzenesulfonamide — 4-Aminobenzenesulfonamide (Sulfanilamide)

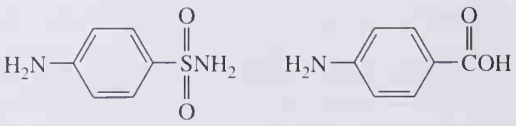
The discovery and medicinal use of sulfanilamide and its derivatives is a milestone in the history of chemotherapy because it represents one of the first rational investigations of synthetic organic compounds as potential drugs to fight infection. Sulfanilamide was first prepared in 1908 in Germany, but it was not until 1932 that its possible therapeutic value was realized. In that year, a new azo (nitrogen-containing) dye was synthesized and marketed under the trade name Prontosil (sulfamidochrysoidine). In research during the following two years, the German chemist, Gerhard Domagk, observed that mice with streptococcal septicemia (an infection of the blood) could be treated with Prontosil. He also observed the remarkable effectiveness of Prontosil in curing experimental streptococcal and staphylococcal infections in other experimental animals. Domagk further discovered that Prontosil is rapidly reduced in cells to sulfanilamide and that it is sulfanilamide, not Prontosil, that is the actual antibiotic. His discoveries were honored in 1939 by the Nobel Prize in medicine, which he was forced to decline because of a Nazi decree. In 1947, he received the medal but not the money.



Prontosil — 1,2,4-Triaminobenzene — Sulfanilamide

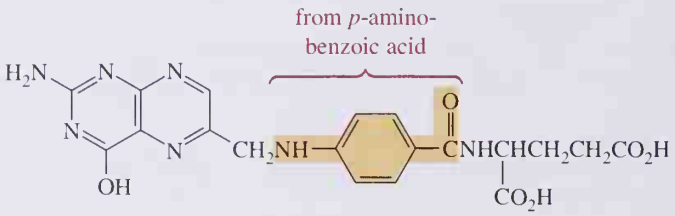
The key to understanding the action of sulfanilamide came in 1940 with the observation that inhibition of bacterial growth caused by sulfanilamide can be reversed by supplying large amounts of *p*-aminobenzoic acid (PABA). Soon thereafter it was discovered that *p*-aminobenzoic acid is a growth factor for certain bacteria and that in a way not then understood, sulfanilamide interferes with the ability of bacteria to use PABA.

There are obvious structural similarities between sulfanilamide and *p*-aminobenzoic acid. The major difference is in the presence of a sulfonamide group in place of a carboxyl group.



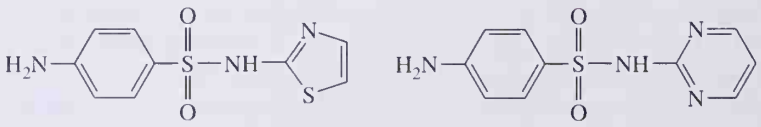
Sulfanilamide 4-Aminobenzoic acid

It is believed that sulfanilamide and other so-called "sulfa" drugs inhibit one or more enzyme-catalyzed steps in the synthesis by bacteria of folic acid from *p*-aminobenzoic acid. The ability of sulfanilamide to combat infections in humans depends on the fact that although humans also require folic acid, we are unable to synthesize folic acid, and for us this compound is a vitamin that must be supplied in the diet.



Folic acid

In search for even more effective antibiotics, literally thousands of derivatives of sulfanilamide have been synthesized in the laboratory. Two of the more effective sulfa drugs are sulfathiazole and sulfadiazine.



Sulfathiazole Sulfadiazine

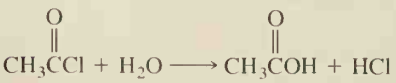
Sulfa drugs were the first of the new "wonder drugs." They were found to be effective in the treatment of tuberculosis (sulfathiazole), pneumonia (sulfadiazine), and diphtheria and helped usher in a new era in public health in the United States and throughout the world in the 1930s. During World War II, they were routinely sprinkled on wounds to prevent infection.

As a footnote in history, the use of sulfa drugs to combat infections was very soon supplanted in the mid 1940s by a newer and more effective class of antibiotics, the penicillins. These in turn have been supplanted to a degree by the even newer cephalosporins and other antibiotics.

SUMMARY OF KEY REACTIONS

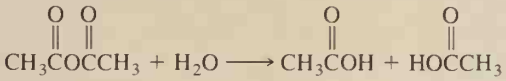
1. Hydrolysis of Acid Chlorides (Section 20.4A)

Low-molecular-weight, water-soluble acid chlorides react vigorously with water. Higher molecular-weight, less water-soluble acid chlorides react less rapidly.



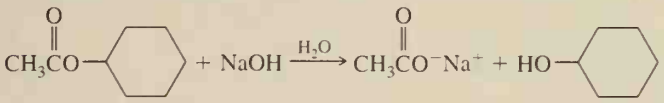
2. Hydrolysis of Acid Anhydrides (Section 20.4B)

Low-molecular-weight acid anhydrides react readily with water. Higher molecular-weight, less water-soluble acid anhydrides react less rapidly.



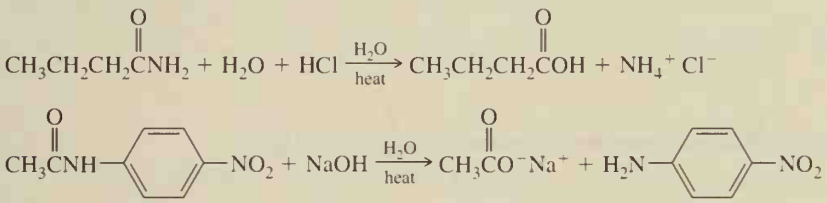
3. Hydrolysis of Esters (Section 20.4C)

Esters are hydrolyzed only in the presence of acid or base. Acid is a catalyst. Base is required in an equimolar amount.



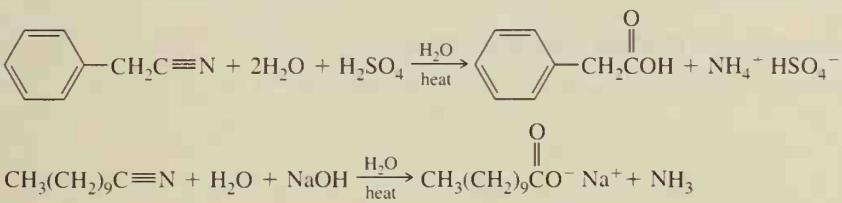
4. Hydrolysis of Amides (Section 20.4D)

Either acid or base is required in an amount equivalent to that of the amide.



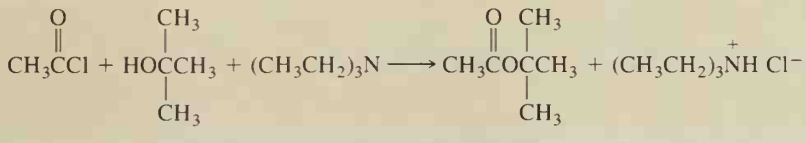
5. Hydrolysis of Nitriles (Section 20.4E)

Either acid or base is required in an amount equivalent to that of the nitrile.



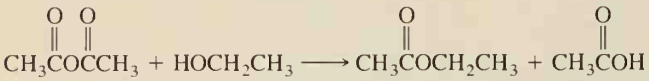
6. Reaction of Acid Chlorides with Alcohols (Section 20.5A)

Acid chlorides react with alcohols to form esters and HCl. Peparation of an acid-sensitive ester is carried out using an equimolar amount of a tertiary amine or a heterocyclic aromatic amine to neutralize the HCl.



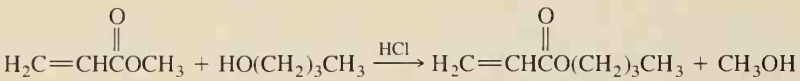
7. Reaction of Acid Anhydrides with Alcohols (Section 20.5B)

Treatment of an acid anhydride with an alcohol gives one molecule of ester and one molecule of carboxylic acid.



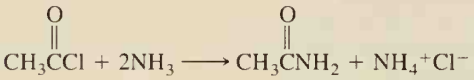
8. Reaction of Esters with Alcohols: Transesterification (Section 20.5C)

Transesterification requires an acid catalyst and an excess of alcohol to drive the reaction to completion.



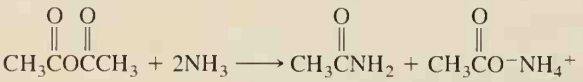
9. Reaction of Acid Chlorides with Ammonia and Amines (Section 20.6A)

Reaction requires two molar equivalents of ammonia or amine: 1 mol to form the amide and 1 mol to neutralize the HCl byproduct.



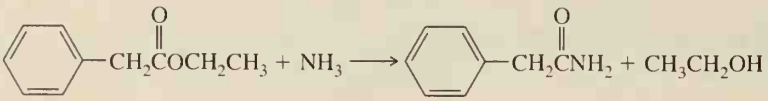
10. Reaction of Acid Anhydrides with Ammonia and Amines (Section 20.6B)

Reaction requires two molar equivalents of ammonia or amine: 1 mol to form the amide and 1 mol to neutralize the carboxylic acid byproduct.



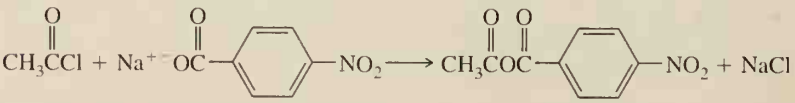
11. Reaction of Esters with Ammonia and Amines (Section 20.6C)

Treatment of an ester with ammonia, or a primary amine or secondary amine gives an amide.



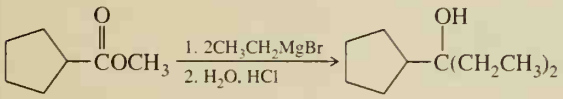
12. Reaction of Acid Chlorides with Carboxylic Acid Salts (Section 20.7)

Treatment of an acid chloride with the salt of a carboxylic acid is a valuable method for synthesizing mixed anhydrides.



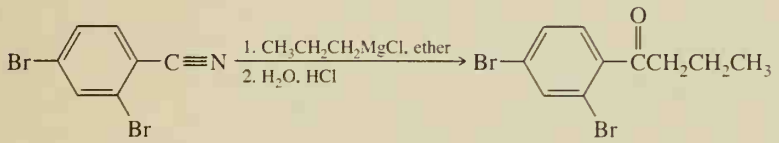
13. Reaction of Esters with Grignard Reagents (Section 20.8A)

Treatment of a formic ester with a Grignard reagent followed by hydrolysis gives a secondary alcohol. Treatment of any other ester with a Grignard reagent gives a tertiary alcohol.



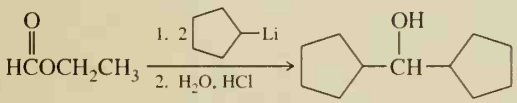
14. Reaction of Nitriles with Grignard Reagents (Section 20.8A)

Treatment of a nitrile with a Grignard reagent followed by hydrolysis gives a ketone.



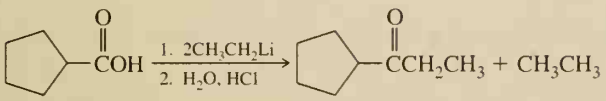
15. Reactions of Esters with Organolithium Compounds (Section 20.8B)

Treatment of a formic ester with an organolithium compound followed by hydrolysis gives a secondary alcohol. Similar treatment of any other ester gives a tertiary alcohol.



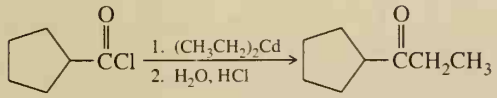
16. Reaction of Carboxylic Acids with Organolithium Compounds (Section 20.8B)

Treatment of a carboxylic acid with 2 mol of an organolithium compound followed by hydrolysis gives a ketone.



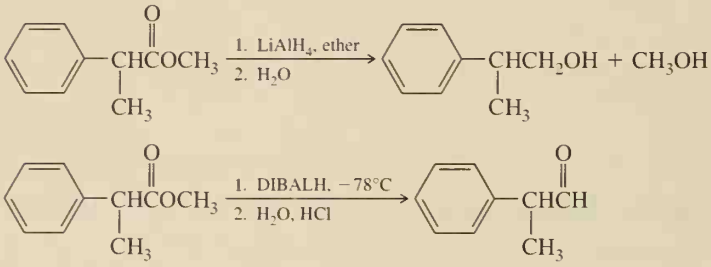
17. Reaction of Acid Chlorides with Organocadmium Compounds (Section 20.8C)

Organocadmium compounds are far weaker nucleophiles than organomagnesium or organolithium compounds and react only with the highly polarized carbonyl group of acid chlorides.



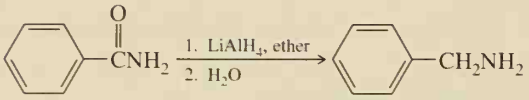
18. Reduction of Esters (Section 20.10A)

Reduction by lithium aluminum hydride gives to two alcohols. Reduction by diisobutylaluminum hydride (DIBALH) gives an aldehyde and an alcohol.



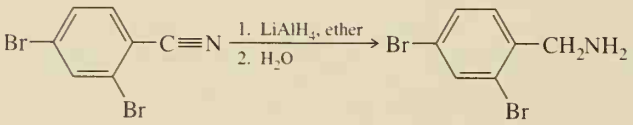
19. Reduction of Amides (Section 20.10B)

Reduction by lithium aluminum hydride gives an amine.



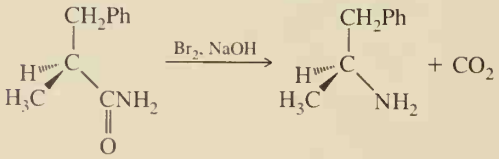
20. Reduction of Nitriles (Section 20.10C)

Reduction by lithium aluminum hydride gives a primary amine.



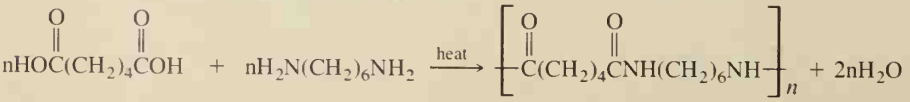
21. The Hofmann Rearrangement of Primary Amides (Section 20.11)

When treated with bromine and aqueous sodium hydroxide, a primary amide is converted to an amine with one fewer carbon. The carbon atom of the carbonyl group is lost as carbon dioxide.



22. Step-Growth Polymerization (Section 20.12)

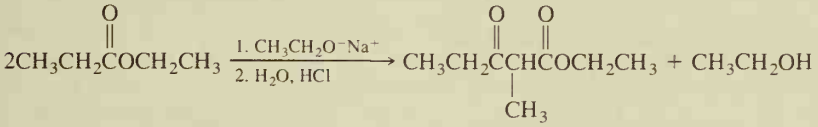
In step-growth polymerization, new covalent bonds are most commonly formed by polar reactions, such as nucleophilic acyl substitution. Important types of step-growth polymers are the polyamides, polyesters, polycarbonates, and polyurethanes.



Adipic acid Hexamethylenediamine Nylon 66

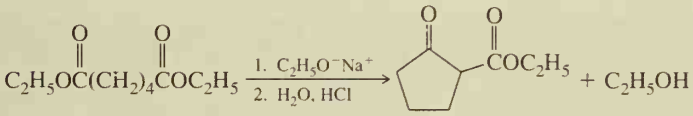
23. The Claisen Condensation (Section 20.13A)

The product of a Claisen condensation is a β-ketoester. Condensation occurs by nucleophilic acyl substitution in which the attacking nucleophile is the enolate anion of an ester.



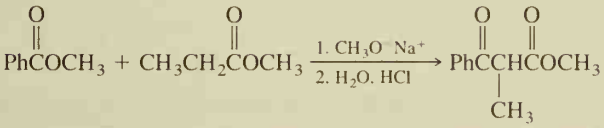
24. The Dieckmann Condensation (Section 20.13B)

An intramolecular Claisen condensation is called a Dieckmann condensation.



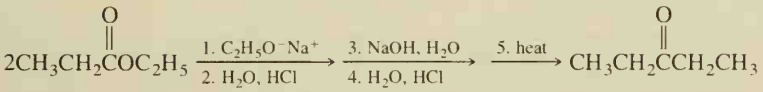
25. Crossed Claisen Condensations (Section 20.13C)

Useful only where an appreciable difference exists in the reactivity between the two esters. One such case is an ester with no α-hydrogens that can function only as an enolate anion acceptor.

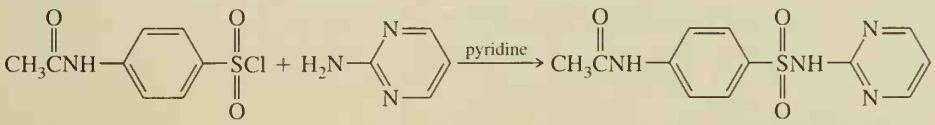


26. Hydrolysis and Decarboxylation of β-Ketoesters (Section 20.13D)

Hydrolysis of the ester followed by decarboxylation of the resulting β-ketoacid gives a ketone and carbon dioxide.



27. Reaction of Sulfonyl Chlorides with Amines (Section 20.14)



ADDITIONAL PROBLEMS

Structure and Nomenclature

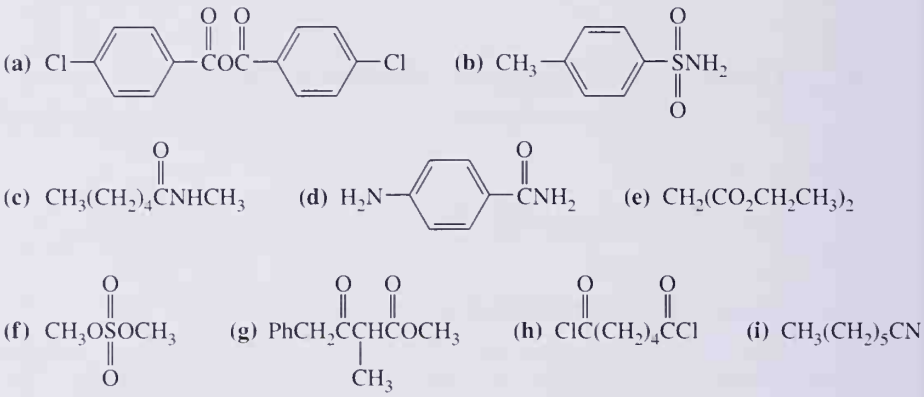
20.13 Draw structural formulas for the following compounds:

(a) Dimethyl carbonate **(b)** *p*-Nitrobenzamide

(c) Isopropyl 3-methylhexanoate **(d)** Diethyl oxalate

(e) Ethyl *cis*-2-pentenoate
(f) Butanoic anhydride
(g) Dodecanamide
(h) Ethyl 3-hydroxybutanoate
(i) Octanoyl chloride
(j) *p*-Aminobenzenesulfonamide
(k) Methanesulfonyl chloride
(l) p-toluenesulfonyl chloride
(m) Benzonitrile
(n) Diethyl *cis*-1,2-cyclohexanedicarboxylate

20.14 Give each compound an IUPAC name.



Physical Properties

20.15 Acetic acid and methyl formate are constitutional isomers. Both are liquids at room temperature: one with a boiling point of 32°C, the other with a boiling point of 118°C. Which of the two has the higher boiling point? Explain your reasoning.

20.16 Both the melting point and boiling point for acetamide are higher than those of its *N,N*-dimethyl derivative.

Acetamide
mp 82.3°C, bp 221.2°C

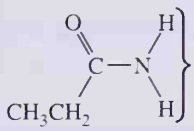
N,N-dimethylacetamide
mp −20°C, bp 165°C

How do you account for these differences?

Spectroscopy

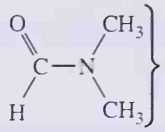
20.17 All methyl esters of long-chain aliphatic acids (for example, methyl tetradecanoate, $C_{13}H_{27}CO_2CH_3$), show significant fragment ions at *m/e* 74, 59, and 31. What are the structures of these ions and how do they form?

20.18 The two hydrogens of primary amides typically have separate ^{1}H-NMR resonances, as illustrated by the separate signals for the two amide hydrogens of propanamide. Furthermore, each methyl group of the *N,N*-dimethylformamide has a separate resonance. How do you account for these observations?



δ 6.22 and 6.58

Propanamide

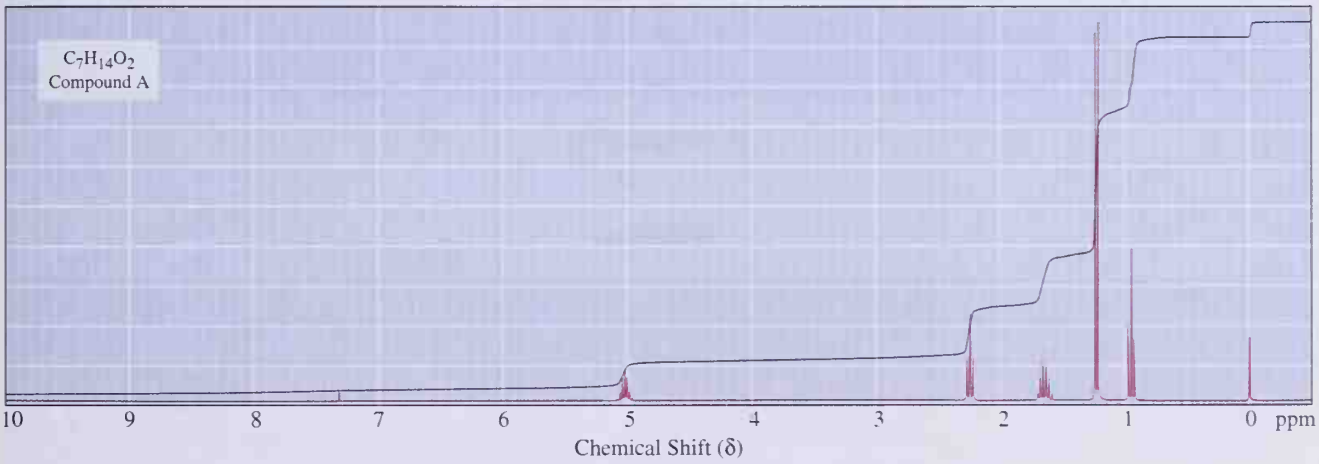


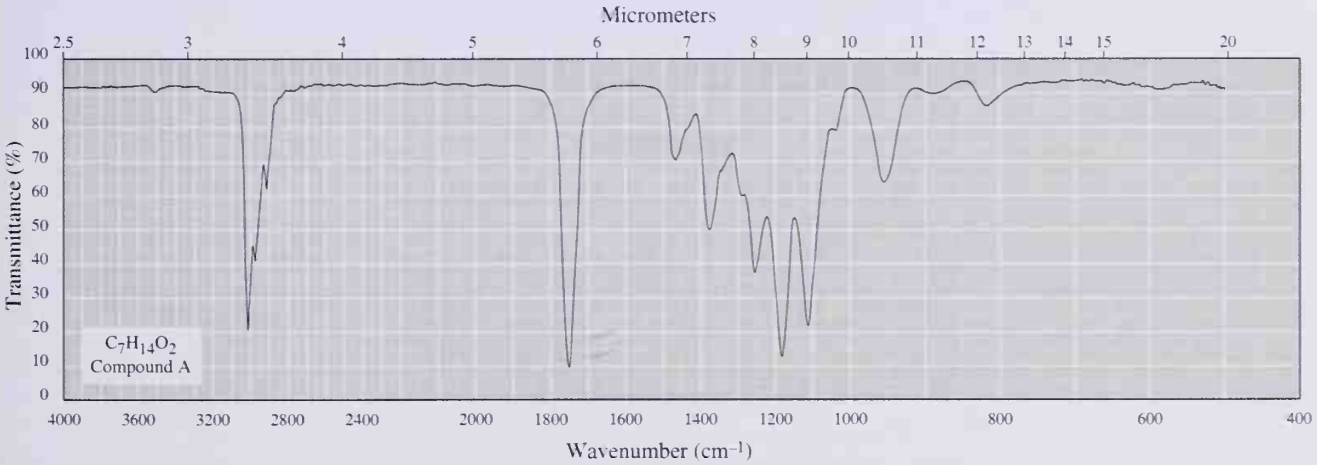
δ 3.88 and 3.98

N,N-Dimethylformamide

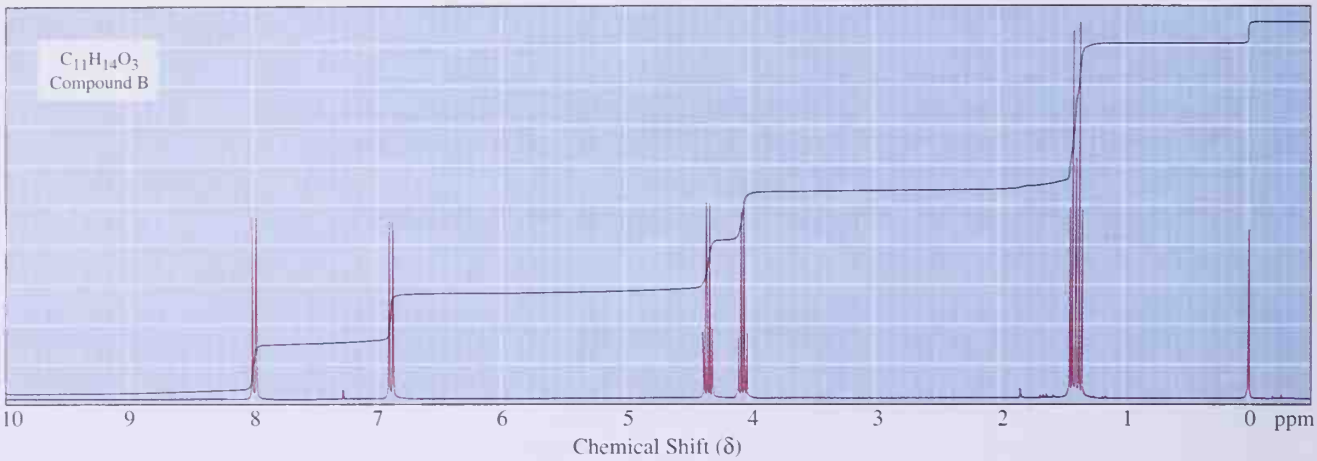
Hint: Consider the covalent bonding in an amide, hybridization of atoms required for participation in resonance stabilization by the contributing structure shown, the orientations in space of the six atoms of the amide group, and the effects *N,N*-dimethyl substitution might have on this spatial orientation and resonance stabilization.

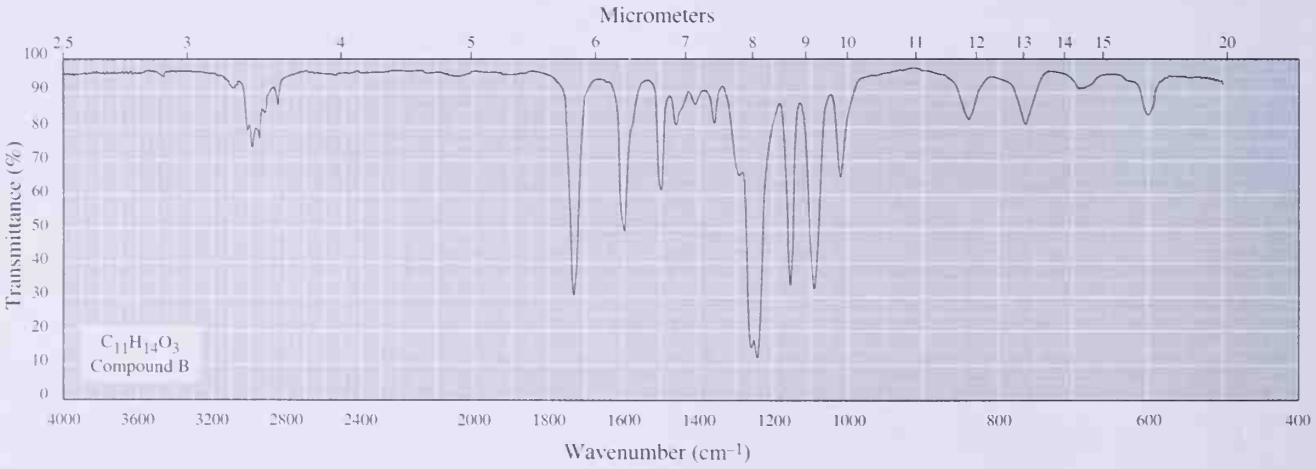
20.19 Propose a structural formula for compound A, $C_7H_{14}O_2$, consistent with its ^{1}H-NMR and infrared spectra.



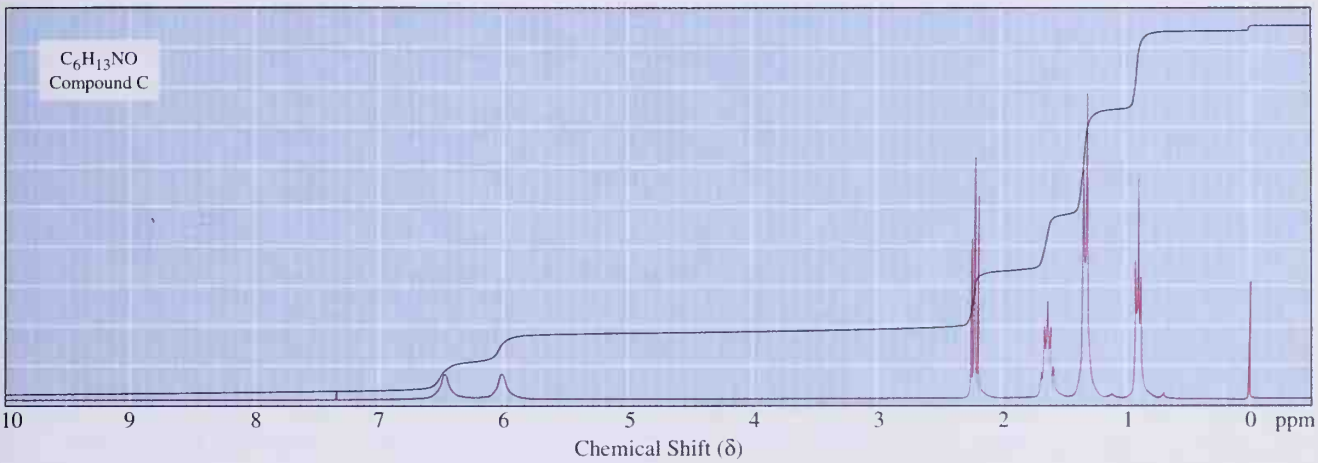


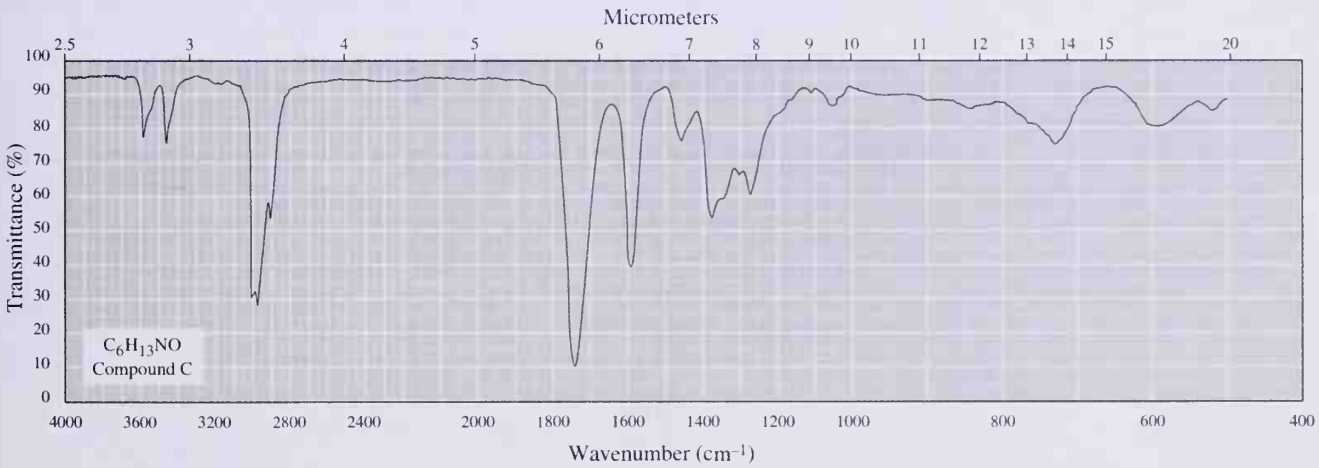
20.20 Propose a structural formula for compound B, $C_{11}H_{14}O_3$, consistent with its ^{1}H-NMR and infrared spectra.





20.21 Propose a structural formula for compound C, $C_6H_{13}NO$, consistent with its ^1H-NMR and infrared spectra.





20.22 Propose a structural formula for each compound consistent with its ^{1}H-NMR and ^{13}C-NMR spectra.

(a) $C_5H_{10}O_2$

^{1}H-NMR	^{13}C-NMR
0.96 (d, 6H)	161.11
1.96 (m, 1H)	70.01
3.95 (d, 2H)	27.71
8.08 (s, 1H)	19.00

(b) $C_7H_{14}O_2$

^{1}H-NMR	^{13}C-NMR
0.92 (d, 6H)	171.15
1.52 (m, 2H)	63.12
1.70 (m, 1H)	37.31
2.09 (s, 3H)	25.05
4.10 (t, 2H)	22.45
	21.06

(c) $C_6H_{12}O_2$

^{1}H-NMR	^{13}C-NMR
1.18 (d, 6H)	177.16
1.26 (t, 3H)	60.17
2.51 (m, 1H)	34.04
4.13 (q, 2H)	19.01
	14.25

(d) $C_7H_{12}O_4$

^{1}H-NMR	^{13}C-NMR
1.28 (t, 6H)	166.52
3.36 (s, 2H)	61.43
4.21 (q, 4H)	41.69
	14.07

(e) $C_4H_7ClO_2$

^{1}H-NMR	^{13}C-NMR
1.68 (d, 3H)	170.51
3.80 (s, 3H)	52.92
4.42 (q, 1H)	52.32
	21.52

(f) $C_4H_6O_2$

^{1}H-NMR	^{13}C-NMR
2.29 (m, 2H)	177.81
2.50 (t, 2H)	68.58
4.36 (t, 2H)	27.79
	22.17

(g) $C_9H_9BrO_2$

^{1}H-NMR	^{13}C-NMR
1.39 (t, 3H)	165.73
4.38 (q, 2H)	131.56
7.57 (d, 2H)	131.01
7.90 (d, 2H)	129.84
	127.81
	61.18
	24.28
	21.13

(h) C_8H_9NO

^{1}H-NMR	^{13}C-NMR
2.06 (s, 3H)	168.14
7.01 (t, 1H)	139.24
7.30 (m, 2H)	128.51
7.59 (d, 2H)	122.83
9.90 (s, 1H)	118.90
	23.93

(i) $C_9H_9NO_3$

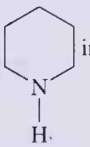
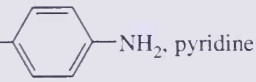
^{1}H-NMR	^{13}C-NMR
2.10 (s, 3H)	168.74
7.72 (d, 2H)	166.85
7.91 (d, 2H)	143.23
10.3 (s, 1H)	130.28
12.7 (s, 1H)	124.80
	118.09
	24.09

Reactions

20.23 Write the structural formula of the principal product formed when benzoyl chloride is treated with the following reagents:

(a) C_6H_6, $AlCl_3$ **(b)** $CH_3CH_2CH_2CH_2OH$, pyridine **(c)** $CH_3CH_2CH_2CH_2SH$, pyridine

(d) $CH_3CH_2CH_2CH_2NH_2$ (two equivalents) **(e)** $CH_3CH_2CH_2CO_2^-Na^+$ **(f)** H_2O

(g)  in the presence of pyridine **(h)**  pyridine

(i) C_6H_5MgBr (two equivalents)

(j) $[(CH_3)_2CHCH_2]_2Cd$, then HCl, H_2O

20.24 Write the structural formula of the principal product formed when ethyl benzoate is treated with the following reagents:

(a) H_2O, NaOH, heat **(b)** $CH_3CH_2CH_2CH_2OH$, HCl **(c)** H_2O, H_2SO_4, heat

(d) $CH_3CH_2CH_2CH_2NH_2$ **(e)** $LiAlH_4$, then H_2O

(f) C_6H_5MgBr (two equivalents), then H_2O **(g)** DIBALH, then H_2O

20.25 Write the structural formula of the principal product formed when benzamide is treated with the following reagents:

(a) H_2O, HCl, heat **(b)** NaOH, H_2O, heat **(c)** $LiAlH_4$, then H_2O

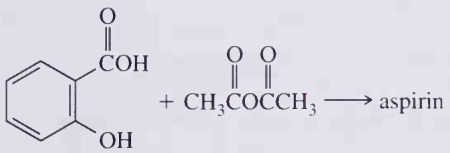
(d) Br_2, NaOH, heat

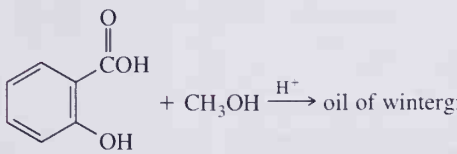
20.26 Write the structural formula of the principal product formed when benzonitrile is treated with the following reagents:

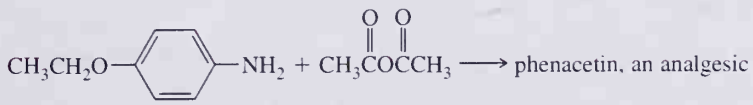
(a) H_2O (one equivalent), H_2SO_4, heat **(b)** H_2O (excess), H_2SO_4, heat

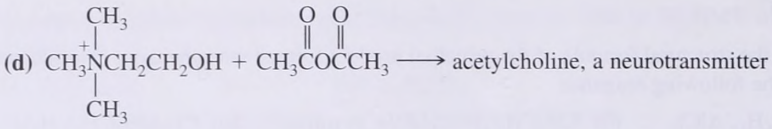
(c) NaOH, H_2O, heat **(d)** $LiAlH_4$, then H_2O

20.27 Complete the following equations:

(a)  aspirin

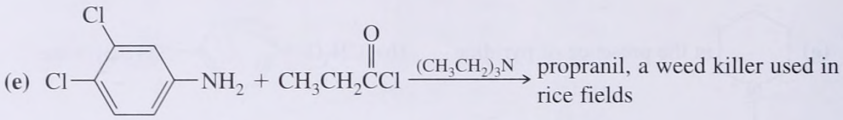
(b)  oil of wintergreen

(c)  phenacetin, an analgesic

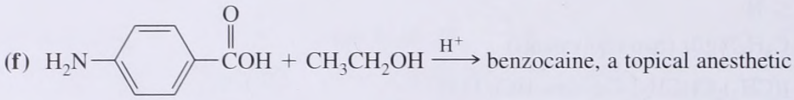


(d) acetylcholine, a neurotransmitter

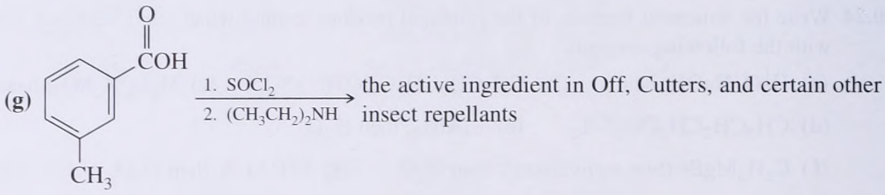
Choline



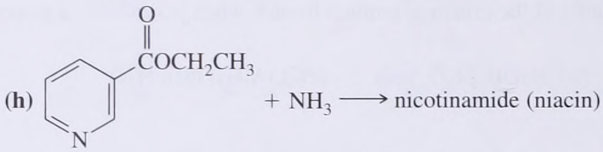
(e) propranil, a weed killer used in rice fields



(f) benzocaine, a topical anesthetic

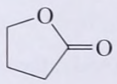


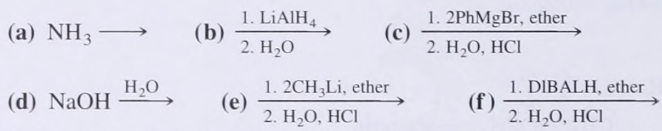
(g) the active ingredient in Off, Cutters, and certain other insect repellants



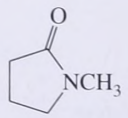
(h) nicotinamide (niacin)

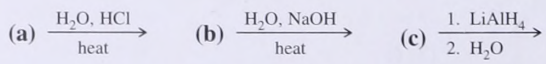
20.28 Show the product of treatment of the following γ-lactone with each reagent.



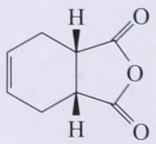


20.29 Show the product of treatment of the following γ-lactam with each reagent.





20.30 Show how the following anhydride can be prepared by a Diels-Alder reaction:



20.31 Show the product of treatment of the anhydride from the previous problem with each reagent.

(a) $\xrightarrow{H_2O,\ HCl}$

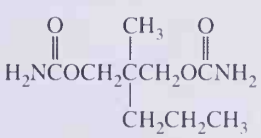
(b) $\xrightarrow{H_2O,\ NaOH}$

(c) $\xrightarrow[2.\ H_2O]{1.\ LiAlH_4}$

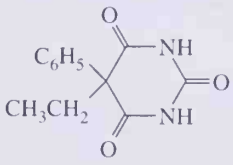
(d) $\xrightarrow{CH_3OH}$

(e) $\xrightarrow{NH_3\ (2\ mol)}$

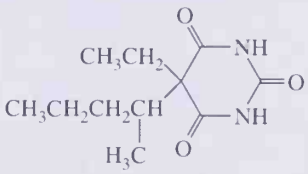
20.32 Draw structural formulas for the products of complete hydrolysis of meprobamate, phenobarbital, and pentobarbital in hot aqueous acid. Meprobamate is a tranquilizer prescribed under one or more of 58 different trade names. Phenobarbital is a long-acting sedative, hypnotic, and anticonvulsant. Luminal is one of over a dozen names under which it is prescribed. Pentobarbital is a short-acting sedative, hypnotic, and anticonvulsant. Nembutal is one of several tradenames under which it is prescribed. (*Hint:* Remember that when heated, β-dicarboxylic acids and β-ketoacids undergo decarboxylation.)



Meprobamate

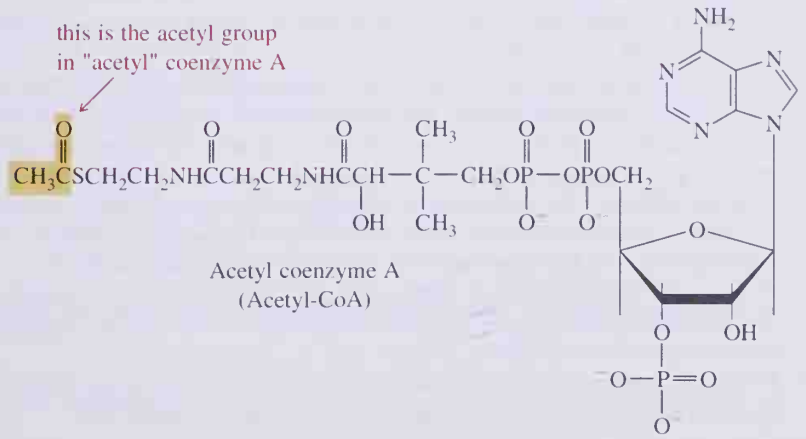


Phenobarbital



Pentobarbital

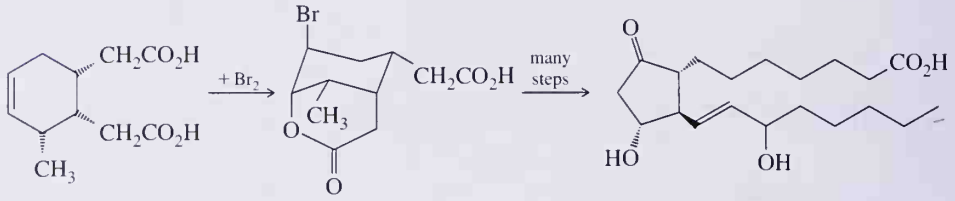
20.33 Draw structural formulas for the products formed by hydrolysis at pH 7.4, the pH of blood plasma, of all ester, thioester, amide, anhydride, and glycoside bonds in acetyl coenzyme A. Name as many of these compounds as you can.



Acetyl coenzyme A
(Acetyl-CoA)

20.34 The reagent diisobutylaluminum hydride (DIBALH) reduces esters to aldehydes. When nitriles are treated with DIBALH, followed by mild acid hydrolysis, the product is also an aldehyde. Give a mechanism for this reduction.

20.35 A step in a synthesis of PGE_1, (prostaglandin E_1, alprostadil) is reaction of a trisubstituted cyclohexene with bromine to form a bromolactone. Alprostadil is used as a temporary therapy for infants born with congenital heart defects that restrict pulmonary blood flow. It brings about dilation of the ductus arteriosus, which in turn increases blood flow in the lungs and blood oxygenation.

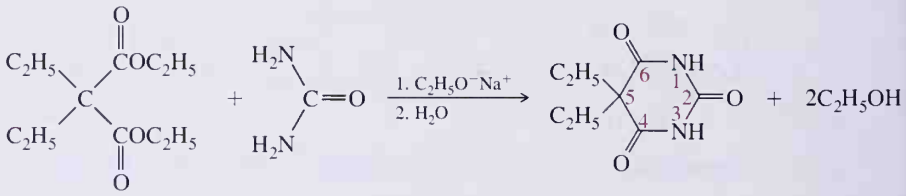


A bromolactone

PGE_1 (Alprostadil)

Propose a mechanism for formation of this bromolactone, and account for the observed stereochemistry of each substituent on the cyclohexane ring.

20.36 Barbiturates are prepared by treatment of diethyl malonate or a derivative of diethyl malonate with urea in the presence of sodium ethoxide as a catalyst. Following is an equation for the preparation of barbital, a long-duration hypnotic and sedative, from diethyl diethylmalonate and urea. Barbital is prescribed under one of a dozen or more trade names.



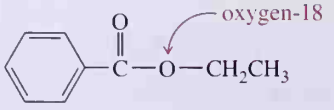
Diethyl diethylmalonate Urea 5,5-Diethylbarbituric acid (Barbital)

(a) Propose a mechanism for this reaction.

(b) The pK_a of barbital is 7.4. Which is the most acidic hydrogen in this molecule and how do you account for its acidity?

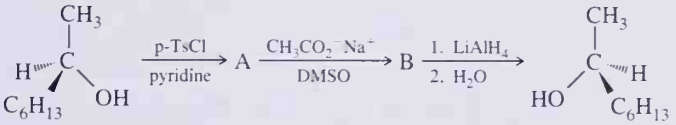
20.37 The mechanism described in Section 20.6C for acid-catalyzed hydrolysis of an ester involves formation of a tetrahedral carbonyl addition intermediate. Evidence in support of this mechanism comes from an experiment designed by Myron Bender. He first prepared ethyl benzoate enriched with oxygen-18 in the carbonyl oxygen and then carried out acid-catalyzed hydrolysis of the ester in water containing no enrichment in oxygen-18. He discovered that if he stopped the experiment after only partial hydrolysis and isolated ethyl benzoate, the recovered ethyl benzoate had lost a portion of its enrichment in oxygen-18. In other words, some exchange had occurred between oxygen-18 of the ester and oxygen-16 of water. Show how this observation bears on the formation of a tetrahedral carbonyl addition intermediate during acid-catalyzed ester hydrolysis.

20.38 Predict the distribution of oxygen-18 in the products obtained from hydrolysis of ethyl benzoate labeled in the ethoxyl oxygen under the following conditions:



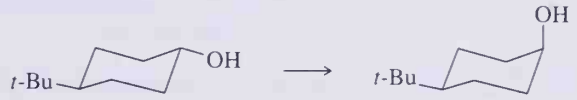
(a) In aqueous NaOH **(b)** In aqueous HCl

20.39 The following sequence of steps converts (R)-2-octanol to (S)-2-octanol. Propose structural formulas for intermediates A and B, specify the absolute configuration of each, and account for the inversion of configuration in this sequence.



(R)-2-Octanol (S)-2-Octanol

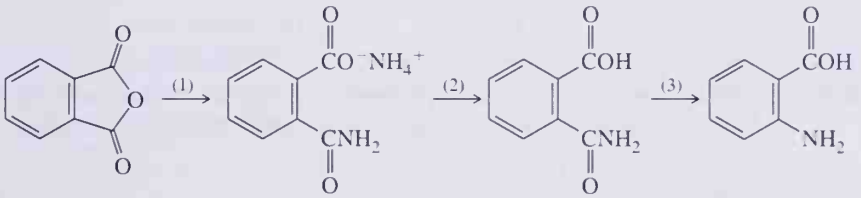
20.40 Show how to use the sequence of reactions in the previous problem to convert *trans*-4-*tert*-butylcyclohexanol to *cis*-4-*tert*-butylcyclohexanol.



trans-4-*tert*-butylcyclohexanol *cis*-4-*tert*-butylcyclohexanol

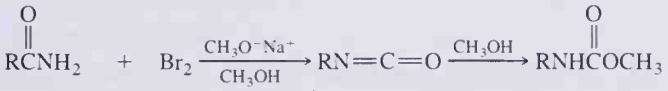
The Hofmann Rearrangement

20.41 Following are steps in a synthesis of anthranilic acid from phthalic anhydride. Describe how to bring about each step.



Phthalic anhydride Anthranilic acid

20.42 Hofmann rearrangements of lower molecular-weight primary amides can be brought about using bromine in aqueous NaOH. Primary amides larger than about seven or eight carbon atoms are not sufficiently soluble in aqueous solution to react. They are instead dissolved in methanol or ethanol, and the corresponding sodium alkoxide is used as the base. Under these conditions, the isocyanate intermediate reacts with the alcohol to form a carbamate.

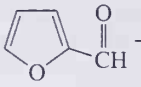


A primary amide An isocyanate A carbamate

Propose a mechanism for the reaction of an isocyanate with methanol to form a methyl carbamate.

Step-Growth Polymers

20.43 At one time, a raw material for the production of hexamethylenediamine was the pentose-based polysaccharides of agricultural wastes, such as oat hulls. Treatment of these wastes with sulfuric acid or hydrochloric acid gives furfural. Decarbonylation of furfural over a zinc–chromium–molybdenum catalyst gives furan. Propose reagents and experimental conditions for the conversion of furan to hexamethylenediamine.

oat hulls, corn cobs, sugar cane stalks, etc. $\xrightarrow[H_2O]{H_2SO_4}$  $\xrightarrow[\text{catalyst}]{\text{Zn–Cr–Mo}}$  $\xrightarrow{(1)}$  $\xrightarrow{(2)}$

Furfural — Furan — Tetrahydrofuran (THF)

$$Cl(CH_2)_4Cl \xrightarrow{(3)} N{\equiv}C(CH_2)_4C{\equiv}N \xrightarrow{(4)} H_2N(CH_2)_6NH_2$$

1,4-Dichlorobutane — Hexanedinitrile (Adiponitrile) — 1,6-Hexanediamine (Hexamethylenediamine)

20.44 Another raw material for the production of hexamethylenediamine is butadiene derived from thermal and catalytic cracking of petroleum. Propose reagents and experimental conditions for the conversion of butadiene to hexamethylenediamine.

$$CH_2{=}CHCH{=}CH_2 \xrightarrow{(5)} ClCH_2CH{=}CHCH_2Cl \xrightarrow{(6)} N{\equiv}CCH_2CH{=}CHCH_2C{\equiv}N \xrightarrow{(7)} H_2N(CH_2)_6NH_2$$

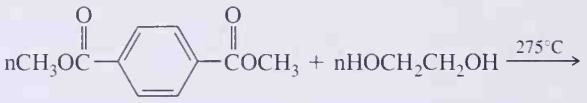
Butadiene — 1,4-Dichloro-2-butene — 1,4-Dicyano-2-butene — 1,6-Hexanediamine (Hexamethylenediamine)

20.45 Propose reagents and experimental conditions for the conversion of butadiene to adipic acid. (*Hint:* review the chemistry of the previous problem.)

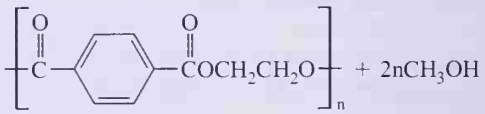
$$CH_2{=}CHCH{=}CH_2 \longrightarrow HO_2C(CH_2)_4CO_2H$$

Butadiene — Hexanedioic acid (Adipic acid)

20.46 Poly(ethylene terephthalate) can be prepared by a transesterification reaction. Propose a mechanism for the step-growth transesterification reaction in this polymerization.

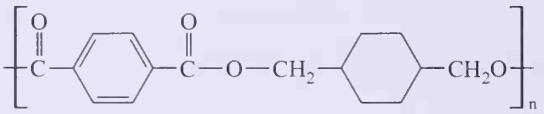


Dimethyl terephthalate — Ethylene glycol

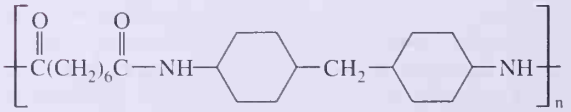


Poly(ethylene terephthalate) — Methanol

20.47 Identify the monomers required for the synthesis of these step-growth polymers.

(a) 

Kodel
(a polyester)

(b) 

Quiana
(a polyamide)

The Claisen Condensation

20.48 Draw structural formulas for the β-ketoesters formed in Claisen condensation of ethyl propanoate with each of the following esters.

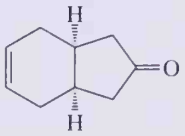
(a) $C_2H_5OC(=O)-C(=O)OC_2H_5$ (b) $PhC(=O)OC_2H_5$ (c) $HC(=O)OC_2H_5$

20.49 Draw a structural formula for the product of saponification, acidification, and decarboxylation of each β-ketoester formed in the previous problem.

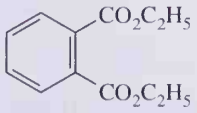
20.50 The Claisen condensation can be used as one step in the synthesis of ketones, as illustrated by the following reaction sequence. Propose structural formulas for compounds A, B, and the ketone formed in this sequence.

$$2CH_3CH_2CH_2CH_2C(=O)OC_2H_5 \xrightarrow[C_2H_5OH]{C_2H_5O^-Na^+} A \xrightarrow[\text{heat}]{NaOH,\ H_2O} B \xrightarrow[\text{heat}]{HCl,\ H_2O} C_9H_{18}O$$

20.51 Propose a synthesis of the following ketones, using as one step in the sequence a Claisen condensation and the reaction sequence illustrated in the previous problem.

(a) $PhCH_2CH_2C(=O)CH_2CH_2Ph$ (b) $PhCH_2C(=O)CH_2Ph$ (c) 

20.52 Claisen condensation between diethyl phthalate and ethyl acetate followed by saponification, acidification, and decarboxylation forms a diketone, $C_9H_6O_2$. Propose structural formulas for compounds A, B, and the diketone.



$$+ CH_3CO_2C_2H_5 \xrightarrow[C_2H_5OH]{C_2H_5O^-Na^+} A \xrightarrow[\text{heat}]{NaOH,\ H_2O} B \xrightarrow[\text{heat}]{HCl,\ H_2O} C_9H_6O_2$$

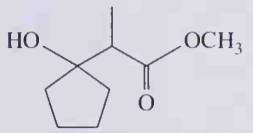
Diethyl phthalate Ethyl acetate

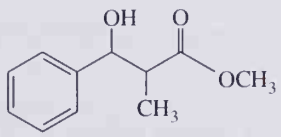
20.53 In 1887, the Russian chemist, Sergei Reformatsky, a professor at the University of Kiev, discovered that treatment of an α-haloester with zinc metal in the presence of an aldehyde or ketone results in formation of a β-hydroxyester. This reaction is similar to a Grignard reaction in that a key intermediate is an organometallic compound, in this case a zinc salt of an ester enolate anion.

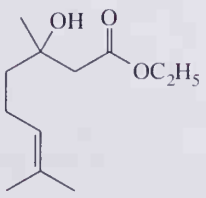
$$BrCH_2C(=O)OC_2H_5 \xrightarrow[\text{benzene}]{Zn} H_2C{=}C(O^-[ZnBr]^+)OC_2H_5 \xrightarrow[2.\ H_2O,\ HCl]{1.\ PhCHO} PhCH(OH)CH_2C(=O)OC_2H_5$$

(Zinc salt of an enolate anion) (A β-hydroxyester)

Show how a Reformatsky reaction can be used to synthesize the following compounds from an aldehyde or ketone and an α-haloester:

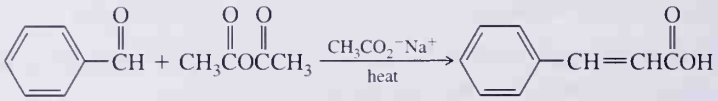
(a) 

(b) 

(c) 

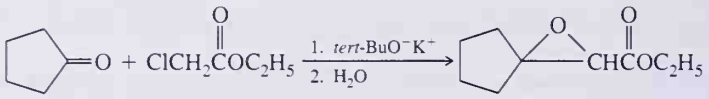
20.54 Many types of carbonyl condensation reactions have acquired specialized names, after the 19th century organic chemists who first studied them. Propose mechanisms for the following named condensations:

(a) Perkin condensation: Condensation of an aromatic aldehyde with a carboxylic acid anhydride.

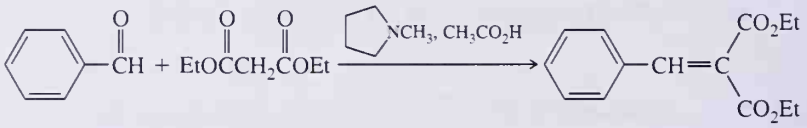


Cinnamic acid

(b) Darzens condensation: Condensation of an α-haloester with a ketone or an aromatic aldehyde. For an example, see CHEMISTRY IN ACTION: Industrial Synthesis of Ibuprofen.

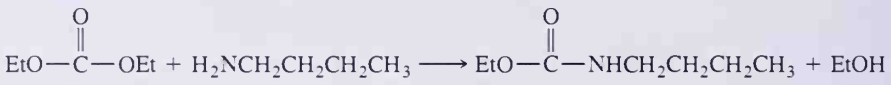


(c) Knoevenagel condensation: Condensation of an aldehyde or ketone with a malonic ester in the presence of an amine–carboxylic acid catalyst.



Synthesis

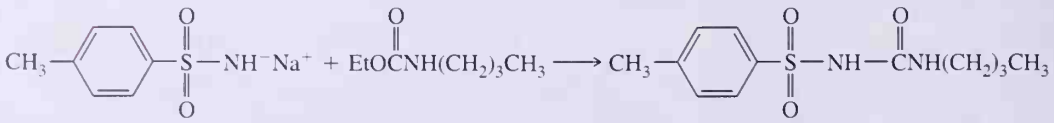
20.55 Reaction of a primary or secondary amine with diethyl carbonate under controlled conditions gives a carbamic ester. Propose a mechanism for this reaction.



Diethyl carbonate — Butylamine — A carbamic ester

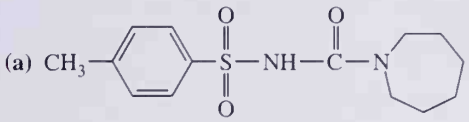
20.56 Several sulfonylureas, a class of compounds containing $RSO_2NHCONHR$, are useful drugs as orally active replacements for injected insulin in patients with adult-onset diabetes. It was discovered in 1942 that certain members of this class cause hypoglycemia in laboratory animals. Clinical trials of tolbutamide were begun in the early 1950s, and since that time more than 20 sulfonylureas have been introduced into clinical medical practice. The sulfonylureas decrease blood glucose concentrations by stimulating β cells of the pancreas to release insulin and by increasing the sensitivity of insulin receptors on peripheral tissues to insulin stimulation.

Tolbutamide is synthesized by reaction of the sodium salt of *p*-toluenesulfonamide and the carbamic ester of butylamine (see the previous problem for the synthesis of this carbamic ester). Propose a mechanism for the following step in the synthesis of tolbutamide:

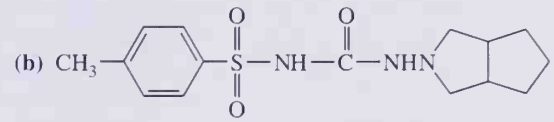


Sodium salt of *p*-toluenesulfonamide — A carbamic ester — Tolbutamide (Oramide, Orinase)

20.57 Following are structural formulas for two more widely used sulfonylurea hypoglycemic agents. Show how each might be synthesized by converting an appropriate amine to a carbamic ester and then treating the carbamate with the sodium salt of a substituted benzenesulfonamide.

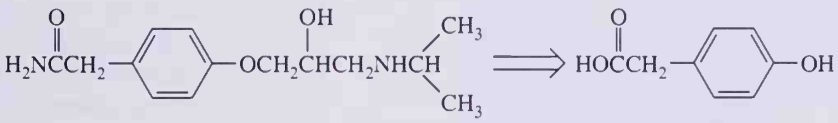


Tolazamide
(Tolamide, Tolinase)



Gliclazide
(Diamicron)

20.58 Side effects of propranolol (Problem 15.25) are disturbances of the central nervous system (CNS), such as fatigue, sleep disturbances (including insomnia and nightmares), and depression. Pharmaceutical companies wondered if this drug could be redesigned to eliminate or at least reduce these side effects. Propranolol itself is highly lipophilic (hydrophobic) and readily passes through the blood-brain barrier, a lipidlike protective membrane that surrounds the capillary system in the brain and prevents hydrophilic compounds from entering the brain by passive diffusion. Propranolol, it was reasoned, enters the CNS by passive diffusion because of the lipidlike character of its naphthalene ring. The challenge, then, was to design a more hydrophilic drug that does not cross the blood-brain barrier but still retains a β-adrenergic antagonist property. A product of this research is atenolol, a potent β-adrenergic blocker that is hydrophilic enough that it crosses the blood-brain barrier to only a very limited extent.

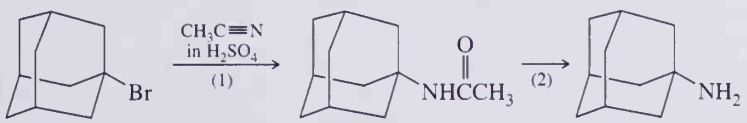


Atenolol
(a β-adrenergic antagonist)

4-Hydroxyphenylacetic acid

Propose a synthesis for atenolol starting with 4-hydroxyphenylacetic acid, epichlorohydrin (Problem 15.25), and isopropylamine.

20.59 Amantadine is effective in preventing infections caused by the influenza A virus and in treating established illnesses. It is thought to block a late stage in the assembly of the virus. Amantadine is synthesized as follows. Treatment of 1-bromoadamantane with acetonitrile in sulfuric acid gives *N*-adamantylacetamide, which is then converted to amantadine.



1-Bromoadamantane

Amantadine

(a) Propose a mechanism for the transformation in Step 1. Consider the possibility of forming an adamantyl cation under these experimental conditions and then the manner in which this carbocation might undergo reaction with acetonitrile.

(b) Describe experimental conditions to bring about Step 2.

SIEGFRIED REICH

Siegfried Reich says that since childhood he has enjoyed working with his hands, taking things apart and putting them together. As a college student, he found a fit for that interest, solving problems in the laboratory. Today, as senior scientist and project leader for Agouron Pharmaceuticals, Inc., he is still working with his hands, but now with a computer keyboard and mouse. And these days, what he is taking apart and putting together are intricate molecular configurations on a computer screen.

Reich received his B.S. in chemistry from San Diego State University in 1982, and earned a Ph.D. in chemistry at the University of California at Irvine in 1986.

After two years of postdoctoral work at the University of California at Berkeley, he joined Agouron, based in La Jolla, CA. Agouron is one of a number of youthful companies started up in the 1980s to pursue alternative approaches to drug development. Agouron's specialty is protein structure–based drug design, which combines the disciplines of chemistry, physics, and biology. Siegfried Reich helps design molecules to inhibit enzymes necessary for the replication of disease-causing microorganisms. If these discoveries make it through the demanding drug approval process, they could in the future play a role in treating even such maladies as cancer and AIDS.

A Background in Synthetic Organic Chemistry

"In graduate school, I got into a specific area of synthetic organic chemistry called asymmetric synthesis. Many compounds can take similar, but different forms—much like a right and a left hand. With asymmetric synthesis, the goal is to synthesize compounds so that you can get one form or the other—selectively. For example, compounds that make up drugs will often exist in different forms. One form may be the desired active component; the other may be inactive, or even worse, toxic. So it is crucial that you understand asymmetric synthesis and are able to synthesize the correct form."

Playing with Tinker-Toy Models

"The aspect of my graduate work I really liked was that it took chemistry from a two-dimensional to a three-dimensional perspective. And it helped me appreciate the relevance to the pharmaceutical setting—to how the three-dimensionality of molecules relates to molecular recognition. In graduate school, we often used Tinker-Toy-like scale models of small molecular structures. And in group meetings, we would have a set of these models on the table and discuss why certain reactions were working the way they

were and why they gave us certain products. You could look at these models and plan out a synthesis. My thesis project was the synthesis of a natural product—erythronolide A seco acid, which is a precursor to the antibiotic erythromycin."

From Berkeley to Agouron Pharmaceuticals

"I spent two years in postdoctoral research at the University of California at Berkeley, working with Dr. Paul Bartlett, who is very well known for his involvement in the area of bioorganic chemistry. His group tries to ask biochemical questions by synthesizing certain molecules.

"Let me tell you about the specific project I worked on. We were looking at enzymes called proteases, which have the job of clipping or cutting other proteins. We were interested in seeing if we could design a protease inhibitor based on an analysis of the three-dimensional structure of the enzyme. That is how I got my feet wet in this whole concept of using x-ray crystallography—the technology that Agouron is based on. As synthetic chemists we do not solve the crystal structures ourselves; that is done by specialists called crystallographers. But with x-ray crystallography, we can look at a protein in its three-dimensional state and ask how to design a small molecule to interact with that protein, which is how most drugs work."

Beyond Scale Models

"The basis is the same. The difference is that now we have moved from a model on your desktop to a computer graphics machine, where you are wearing special stereoptic glasses that allow you to see in three dimensions. So you are doing the same thing—asking questions about molecular recognition, which is what drives drug action. But you are doing it with more technology—and a lot greater accuracy."

Working for a Small Pharmaceutical Company

"I was excited by the concept of working for a smaller company that was doing very interesting science. I interviewed at a number of large pharmaceutical companies. They were very intriguing places, but most of the larger companies are still based on the old school, which involves screening lots of compounds until you get a hit. Agouron represents a new arm of the pharmaceutical industry—looking at the receptor at the molecular level, and asking whether we can design drugs to combine with that receptor. To me that just made a lot more scientific sense, although much is yet to be proven.

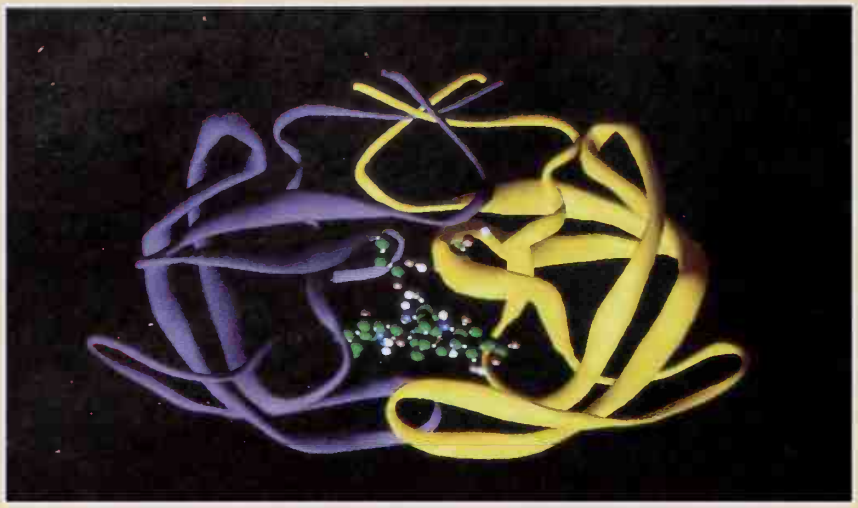
"At Agouron, I am part of the Medicinal Chemistry Group, which is made up of synthetic organic chemists. Each of us knows how to go into the laboratory and devise and execute a synthesis of a small molecule. What I do is use that background in combination with information I get from crystallographers. I have a graphics machine on my desk, and that allows me to view this enzyme in its three-dimensional state. When I look at the screen, I am looking at the active site of the enzyme, which is like a pocket where its substrate will normally bind. This is where it all happens pretty much. If you can design a small molecule to complement that active site well enough, then you can shut that enzyme down. That really is the nuts and bolts of what I try to do."

The Pluses and Minuses of Designing New Drugs

"The downside to molecular design is that it requires a significant investment in technology. Crystallography is not something you just set up in a month's time. X-ray diffractometers, the machines that collect the data, are generally custom made. And you need to employ a number of crystallographers. The other factor is that crystallography is nothing without crystals. If your particular receptor is not amenable to crystallization, then you have serious problems.

"The plus to the drug design approach is that you have an open palette of atoms to use in designing these molecules. You are really just limited by your imagination. With the new technology and with enough manpower behind it, what used to take literally years to solve can now be done in a matter of months. You have an opportunity to come up with things that have never been seen before. That makes the work very

> "As a scientist, it is nice to know that after all those years of schooling, I am doing something that I like to do and that has such a practical application."



An inhibitor of HIV protease, AG-1284, bound in the enzyme's active site. *(Courtesy of Agouron Pharmaceuticals)*

interesting. And it gives you a very strong patent position when a novel active compound is discovered this way."

Choosing a Protein to Research

"Generally we pick a protein because there is a clear connection to some disease state. A lot hinges upon previous scientific work, in the molecular biology and biochemistry arena. Usually, target proteins will have been implicated as crucial to some disease. The other thing that we will certainly take into consideration is the feasibility of getting a crystal.

"We start with a theory that there is a connection, that a particular compound will keep cells from proliferating—for example, in cancer. But generally such evidence is obtained in the test tube—*in vitro* evidence that if you shut this enzyme down, cancer cells will cease to proliferate. But that isn't the whole story. The final story is when you can actually shut that enzyme down in the body. And until you have that clinical type feedback, it's an open question.

"A good example is the [target] protein that we and other companies are working on right now. That's HIV protease, related to the AIDS virus. For a long time it was clear that the HIV virus needed this enzyme to replicate and thrive, and that was supported by clear evidence in the test tube and cell culture. But only relatively recently has there been evidence from clinical inputs that administering the compound [an HIV protease inhibitor] does have an effect. But even then, you could say we really do not have the final proof. The real proof will be if patients actually have longer lives after the compound is administered."

The HIV Protease Project at Agouron

"As group leader, it's my job to organize the project and make sure it is moving at a certain pace. We are at the stage of gearing up to put some of our compounds in patients. But even so, we probably won't have information about clinical efficacy for a year to two years from now."

Considering the Patient

"There is a problem with currently available products that inhibit HIV protease. Although they are very potent, they are not significantly orally available. A drug like this is a treatment, not a cure, for AIDS. And AIDS patients will probably take such drugs for the rest of their lives, every day. If people have to take this drug intravenously, with a needle, they are going to be a lot more hesitant to take the drug. You want it to be oral. Our compound has significantly enhanced oral availability. That means you generally do not need to administer as much of the compound orally to achieve a desired effect. If currently available compounds are given orally, maybe five to ten percent will actually be absorbed. So a higher overall level of the drug must be maintained just to get that five or ten percent into the bloodstream. Based on tests on oral delivery in three non-human species, our compound can be absorbed more readily."

More than One Solution

"There is more than just one method to finding a drug to inhibit HIV protease. And that gets back to the question about the pros and cons of drug design versus screening. When you sit in front of the screen and view this empty pocket, you ask what three-dimensional small molecule could fit in there. There are

going to be a number of answers to that question. And that is one of the powers of this design approach—in that you are not necessarily biased by any preexisting solution. You really have a full library of atoms that you can use to build into the pocket.

"I look at the active site on the protein—this pocket—and I try to decide what kind of small molecule will complement that surface, both in its three-dimensional structure and its electronic structure. Then I go ahead and build that small molecule on the screen. I build it in three dimensions and dock it, and see how well it fits. Where it does not fit as well, I refine and refine. And drawing on my organic chemistry background, I am always thinking in the back of my head about whether what I am working with is something that can actually be made, and that will be stable. There is always this practical component. You do not want to have someone sitting in front of a computer screen designing the perfect molecule that will complement everything—but that can never be made."

The Next Step After the Design

"Okay, now if I've got a molecule that looks like it fits well, and if that conclusion is supported with computational analysis, I will look into how to synthesize it. If it looks like I can devise a reasonable synthesis, I order the necessary chemicals and either I or a coworker will go ahead and start synthesizing it."

Testing the Synthesized Compound

"Once we have established that what we have synthesized is the compound we wanted, then we take it to the biochemist, who will conduct an *in vitro* assay. The biochemist begins with the enzyme; then mixes in the inhibitor, the new compound under study; then adds the substrate. The process is watched over a period of time, and is measured with a spectrophotometer. If it works, the compound will start to bind to the enzyme and inhibit its activity. Depending on how good your inhibitor is, you will see more or less inhibition.

"Most often the inhibitor does not turn out to be highly active. It's generally a slow process. For example, in the series that we recently developed and described—the HIV protease inhibitor called AG1284—we started off with a compound in which you could barely see any inhibiting activity. Over the course of a year and a half, we increased its potency over ten thousand fold.

"In a nutshell, we use protein crystallography as a tool. If we have a compound with borderline activity, the protein will be crystallized again. But this time, it is crystallized with your inhibitor bound to it. So you can get feedback. Where you previously just had this theoretical idea about how this molecule might bind to the active site, now you get to find out how it did bind."

The Outlook for HIV Treatment

"I think everyone understands that the HIV problem is one of the biggest challenges the pharmaceutical industry has ever had. One reason is that this virus mutates, and it's deadly. I think the bottom line to the HIV treatment question will be to administer a number of agents, and that will reduce the chance of mutations cropping up and being a problem."

Personal Rewards

"I have a friend who has AIDS. He is one person. But still, knowing that you can potentially do something that may give a friend some more years in this world is just . . . , you can't put it into words. Also, as a scientist, it is nice to know that after all those years of schooling, I am doing something that I like to do and that has such a practical application. Being in industry and working on a practical application for your science is very gratifying."

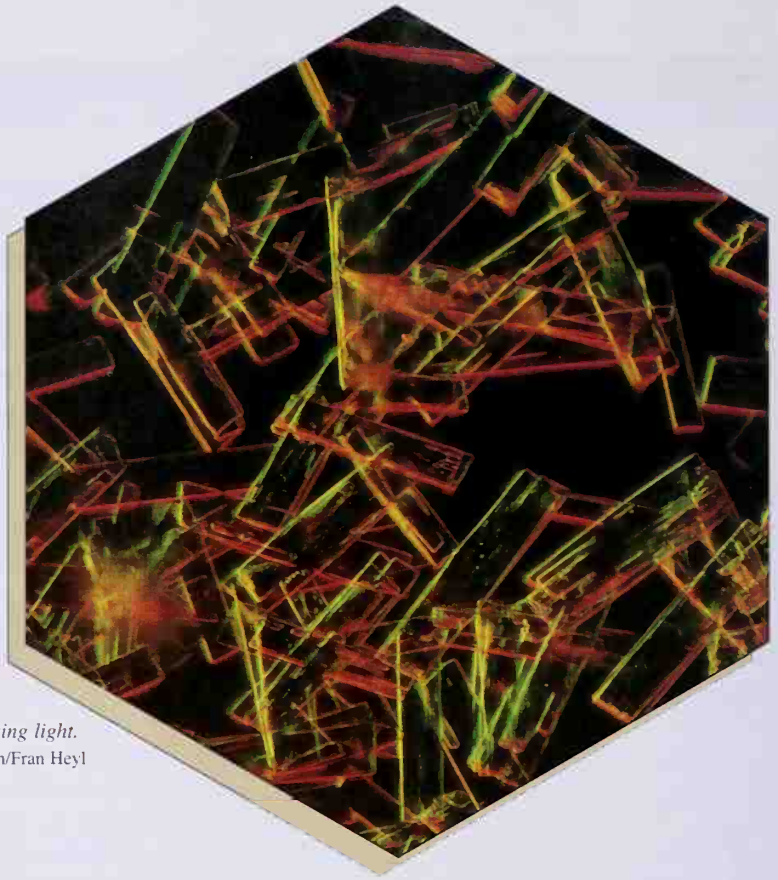
A Multidisciplinary Mindset

"None of this would be possible unless we had people from all disciplines—biochemistry, crystallography, organic chemistry, pharmacology. We have regular meetings and all these people will come together and brainstorm about how we might be able to progress."

A Career in the Pharmaceutical Industry

"The pharmaceutical industry is a very good place for organic chemists, due in large part to the explosion of the biotechnology area. It is a natural marriage—having this very powerful field of biotechnology recognizing a need for small molecules that can be designed by organic chemists. There is one other thing—the issue of creativity in this job. That is why I do what I do. There is so much room for being creative—in a small company, pushing the edge of technology."

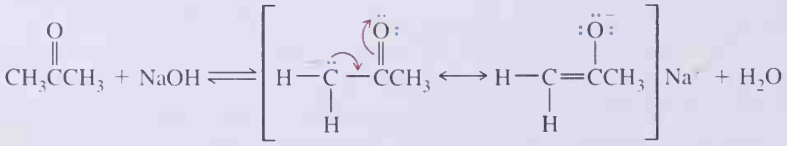
21



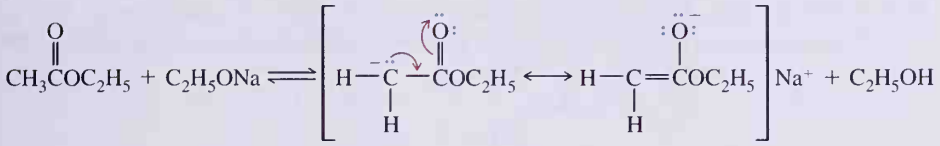
Tamoxiphen crystals viewed under polarizing light. (© Phillip A. Harrington/Fran Heyl Associates)

ENOLATE ANIONS AND ENAMINES

A major theme of this chapter is a continuation of one we already encountered in Chapters 17 and 20—removal of an α-hydrogen to form an enolate anion. Following are examples of resonance-stabilized enolate anions formed from a ketone and from an ester.



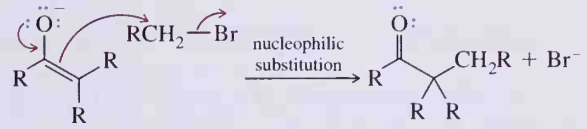
An enolate anion



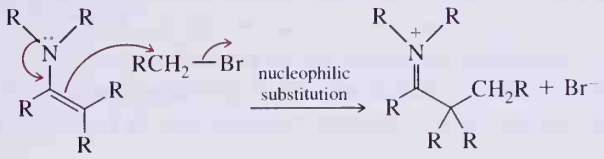
An enolate anion

Enolate anions of these types are intermediates in aldol reactions (Section 17.14) as well as in Claisen and related condensations (Section 20.13). In these carbonyl condensation reactions, they are nucleophiles and participate in nucleophilic addition to a carbonyl carbon. As we see in this chapter, enolate anions also participate as nucleophiles in S_N2 reactions.

In this chapter, we also study the preparation and reactions of enamines. Like enolate anions, they also function as nucleophiles in S_N2 reactions and in carbonyl addition reactions. The following equations show the parallel between the behavior of enolate anions and enamines in S_N2 reaction.



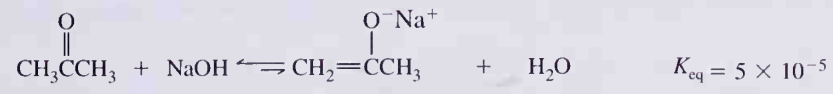
An enolate anion



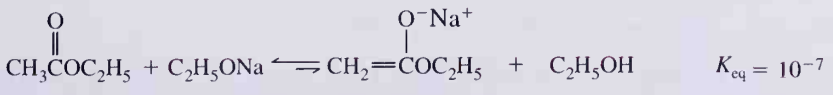
An enamine

21.1 Formation of Enolate Anions: Kinetic versus Thermodynamic Control

As noted previously, enolate anions are formed when a carbonyl compound containing an α-hydrogen is treated with base. The reactions presented in Chapters 17 and 20 leading to the formation of enolate anions are reversible, and when alkali metal hydroxides or alkoxides are used as bases, the position of equilibrium favors reactants rather than products.

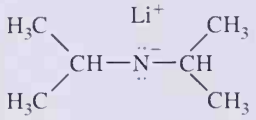


pK_a 20 (weaker acid) pK_a 15.7 (stronger acid)



pK_a 23 (weaker acid) pK_a 16 (stronger acid)

With a stronger base, however, formation of an enolate anion can be driven to the right. One of the most widely used bases for this purpose is **lithium diisopropylamide (LDA).**



Lithium diisopropylamide
(LDA)

Lithium diisopropylamide is prepared by dissolving diisopropylamine in tetrahydrofuran and treating this solution with an alkyllithium, as for example, butyllithium.

$$[(CH_3)_2CH]_2NH + CH_3(CH_2)_3Li \longrightarrow [(CH_3)_2CH]_2NLi + CH_3(CH_2)_2CH_3 \qquad K_{eq} = 10^{12}$$

Diisopropylamine	Butyllithium	LDA	Butane
pK_a 38 (stronger acid)	(stronger base)	(weaker base)	pK_a 50 (weaker acid)

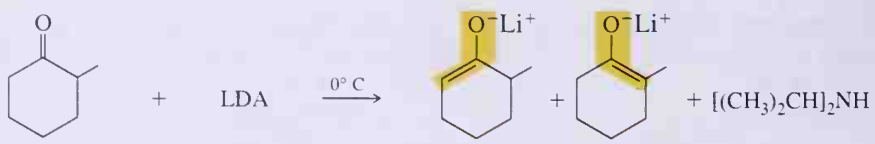
Alternatively, LDA is available commercially as a pyrophoric, moisture-sensitive solid (it bursts into flame on contact with moist air) or in solution dissolved in a mixed solvent of tetrahydrofuran and hexane.

LDA is a very strong base, but because of steric crowding around the amide nitrogen, it is a very poor nucleophile and does not add at all readily to carbonyl groups. It is, therefore, ideal for generation of enolate anions from carbonyl-containing compounds, as illustrated by treatment of ethyl acetate with LDA. By using a molar equivalent of LDA, an aldehyde, ketone, or ester can be converted completely to its lithium enolate.

$$CH_3COC_2H_5 + [(CH_3)_2CH]_2NLi \longrightarrow H_2C{=}COC_2H_5 + [(CH_3)_2CH]_2NH \qquad K_{eq} = 10^{15}$$

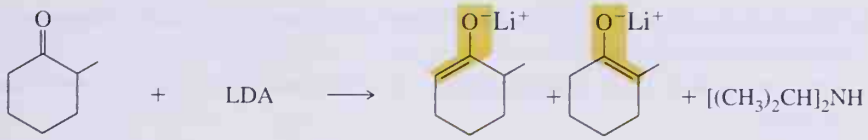
pK_a 23 (stronger acid)	LDA	A lithium enolate	pK_a 38 (weaker acid)

For a ketone with two sets of nonequivalent α-hydrogens, the following question arises: Is formation of an enolate anion regioselective, and if so, what are the factors that determine the degree of regioselectivity? It has been determined experimentally that a very high degree of regioselectivity often exists, and that the degree of regioselectivity depends on experimental conditions. When 2-methylcyclohexanone, for example, is treated with a slight excess of LDA, the ketone is converted entirely to its lithium enolate, which is composed almost entirely of the salt of the less substituted enolate anion.



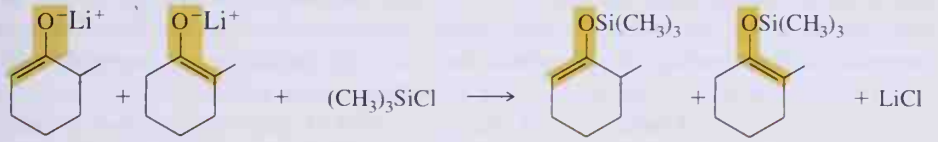
(Slight excess of LDA) 99% 1%

When 2-methylcyclohexanone is treated with LDA but under conditions in which the ketone is in a slight molar excess, then the composition of the product is quite different: it is richer in the more substituted enolate anion.



(Slight excess of the ketone) 26% 74%

A word here about how the composition of an enolate anion mixture is determined. Once the enolate anion mixture is formed, it is treated with chlorotrimethylsilane, whereby each enolate is "trapped" as the corresponding **enol trimethylsilyl ether.**



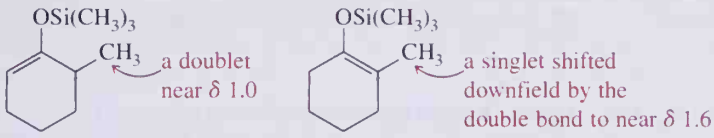
Chlorotrimethylsilane Enol trimethylsilyl ethers

The isomeric enol trimethylsilyl ethers may be separated quantitatively by gas chromatography and identified by nuclear magnetic resonance spectroscopy.

EXAMPLE 21.1

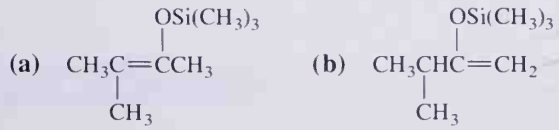
Suppose the previous mixture of enol trimethysilyl ethers is separated by gas chromatography and each collected in pure form. Show how ^{1}H-NMR spectroscopy can be used to distinguish between them by (a) the chemical shift and (b) the splitting pattern of the ring $-CH_3$ hydrogens.

Solution



PROBLEM 21.1

How might you use ^{1}H-NMR spectroscopy to distinguish between the following enol trimethylsilyl ethers?



It has been determined that the most important factor determining the composition of an enolate anion mixture is whether the reaction forming them is under kinetic (rate) control or thermodynamic (equilibrium) control (Section 7.4B). In a reaction under **thermodynamic control,**

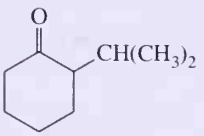
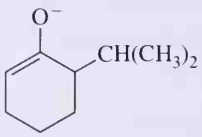
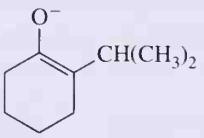
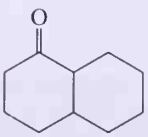
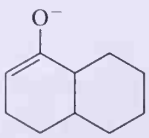
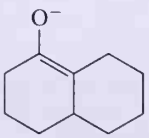
1. The products are formed under conditions which permit the establishment of equilibrium between them and
2. The composition of the product mixture is determined by the relative stabilities of the products.

Equilibrium among enolate anions is established when the ketone is in slight excess, which makes it possible for proton-transfer reactions to occur. An enolate anion, once formed, can undergo reaction with the remaining ketone by proton transfer to regenerate the ketone and form a new enolate anion. Under these conditions, it is the more stable enolate anion that predominates. The factors that determine the relative stabilities of enolate anions are the same as those that determine the relative stabilities of alkenes (Section 5.8B), namely, the more substituted the double bond of the enolate anion, the greater its stability. Thus, the composition of the enolate anion mixture formed under conditions of thermodynamic control reflects the relative stabilities of the individual enolate anions.

In a reaction under **kinetic control,** the composition of the product mixture is determined by the relative rates of formation of each product. In the case of formation of enolate anions, kinetic control refers to the relative rates of removal of the alternative α-hydrogens. The less hindered α-hydrogen is removed more rapidly, and thus the major product is the less substituted enolate anion. The less stable enolate anion cannot equilibrate with the more stable enolate anion because there is no ketone to serve as a proton source.

Listed in Table 21.1 are several examples of enolate anions formed under conditions of kinetic control and thermodynamic control. The result common to these examples is that under thermodynamic (equilibrium) control, the more substituted enolate anion predomi-

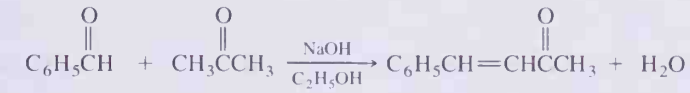
Table 21.1 Composition of enolate anion mixtures formed under conditions of kinetic control and thermodynamic control

Ketone	Composition of Enolate Anion Mixture		Control
$CH_3\overset{O}{\overset{\|}{C}}CH_2(CH_2)_2CH_3$	$H_2C{=}\overset{O^-}{\overset{\|}{C}}CH_2(CH_2)_2CH_3$	$CH_3\overset{O^-}{\overset{\|}{C}}{=}CH(CH_2)_2CH_3$	
	100%	0%	kinetic
	42%	58%	thermodynamic
			
	100%	0%	kinetic
	42%	58%	thermodynamic
			
	98%	2%	kinetic
	50%	50%	thermodynamic

nates, although often not by a large margin. Under kinetic (rate) control, the less substituted enolate anion predominates, often to the virtual exclusion of the alternative enolate anion.

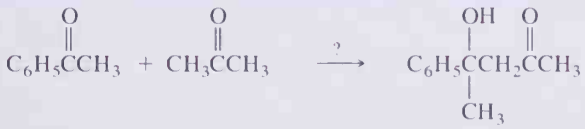
21.2 Directed Aldol Reactions

In Section 17.14 we discussed aldol reactions and pointed out a problem inherent in carrying out **mixed aldol reactions.** Mixed aldol reactions between an aldehyde with no α-hydrogens and a ketone generally give good yields of a single product because (1) only the ketone can form an enolate anion and (2) the carbonyl group of an aldehyde is a better enolate anion acceptor than the more crowded carbonyl group of a ketone. Aldol reaction of benzaldehyde and acetone followed by dehydration of the aldol intermediate, for example, gives a single product in good yield.



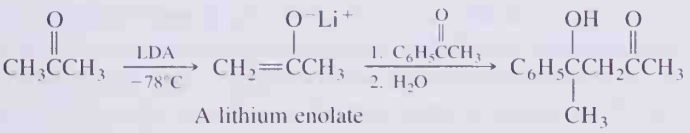
Benzaldehyde Acetone 4-Phenyl-3-buten-2-one

A problem arises in a mixed aldol reaction between two different ketones, each with α-hydrogens. Consider, for example, the problem of how to prepare the following aldol product from acetophenone and acetone.



Acetophenone Acetone 4-Hydroxy-4-phenyl-2-pentanone

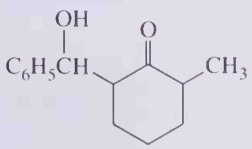
Four aldol reaction products are possible, and a mixture of the four is formed if these two ketones are mixed in the presence of NaOH or C_2H_5ONa. Aldol reaction may be carried out in another way, however, namely, reaction of one of the ketones with lithium diisopropylamide to convert it completely and irreversibly to its enolate anion. The preformed enolate anion is then treated with the other ketone or aldehyde followed by work-up in water to give the mixed aldol reaction product.

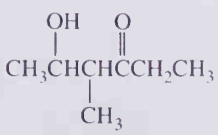


A lithium enolate

EXAMPLE 21.2

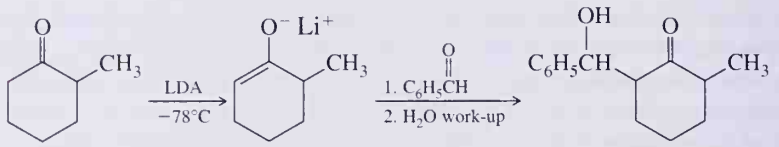
Show how to prepare the following compounds by a directed aldol reaction:

(a) 

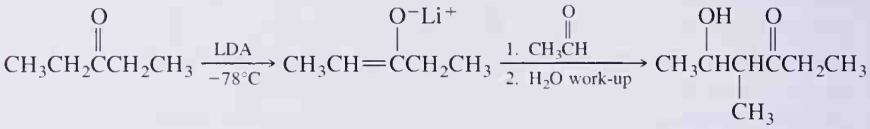
(b) 

Solution

(a) First recognize that the two carbonyl-containing compounds to be joined in the aldol reaction are 2-methylcyclohexanone and benzaldehyde. Treat the ketone with slightly more than 1.0 molar equivalent of LDA to form the lithium enolate anion. Treatment of this enolate anion with benzaldehyde followed by aqueous work-up gives the desired aldol product.



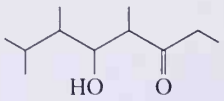
(b) The starting compounds are 3-pentanone and acetaldehyde. They are combined in the following way:



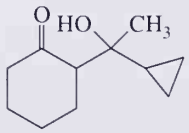
PROBLEM 21.2

Show how to prepare the following compounds by a directed aldol reaction:

(a)



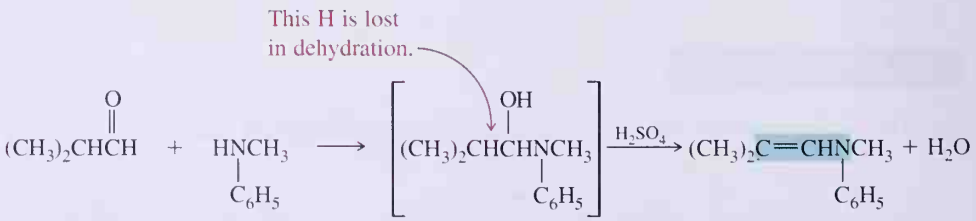
(b)



21.3 Enamines

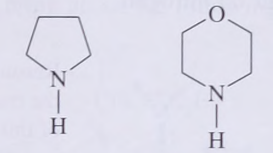
Enamines are compounds in which a trivalent nitrogen atom is attached to a carbon-carbon double bond. In this regard they are nitrogen analogs of enols.

Enamines are formed by reaction of a secondary amine with an aldehyde or ketone (Section 17.11A) as illustrated by reaction of 2-methylpropanal with *N*-methylaniline. The intermediate **aminoalcohol** undergoes acid-catalyzed dehydration. Because there is no hydrogen on the nitrogen of the aminoalcohol, hydrogen is lost from the adjacent carbon to give the enamine. It is removal of water that drives enamine reactions to completion.



2-Methylpropanal | *N*-Methylaniline (a 2° amine) | An aminoalcohol | An enamine

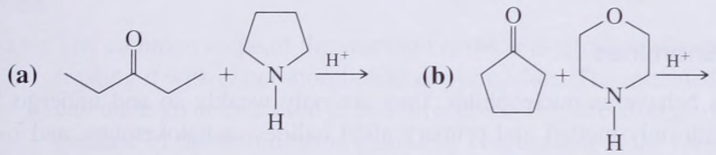
The secondary amines most commonly used to prepare enamines as synthetic intermediates are pyrrolidine and morpholine.



Pyrrolidine Morpholine

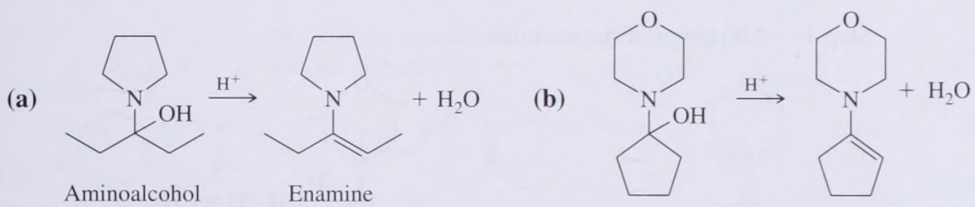
EXAMPLE 21.3

Draw structural formulas for the aminoalcohol and enamine formed in the following reactions:



Solution

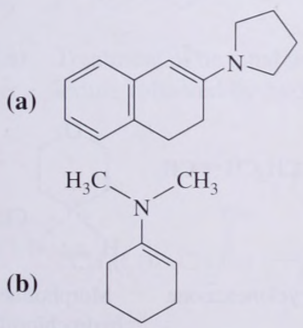
Following is the structural formula of each aminoalcohol and enamine:



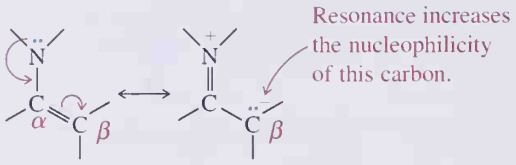
Aminoalcohol Enamine Aminoalcohol Enamine

PROBLEM 21.3

Following are structural formulas for two enamines. Draw structural formulas for the secondary amine and carbonyl compound from which each is derived.



The particular value of enamines in synthetic organic chemistry is the fact that the β-carbon of the enamine is a nucleophile by virtue of the conjugation of the carbon-carbon double bond with the electron pair on nitrogen.



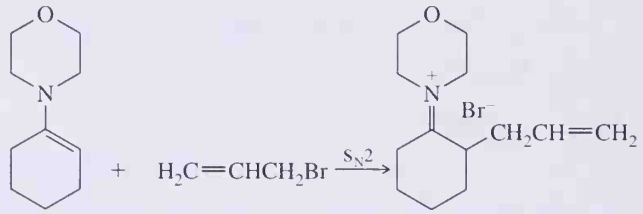
An enamine as a resonance hybrid
of two important contributing structures

Enamines can be used as nucleophiles in both alkylation and acylation reactions.

A. Alkylation of Enamines

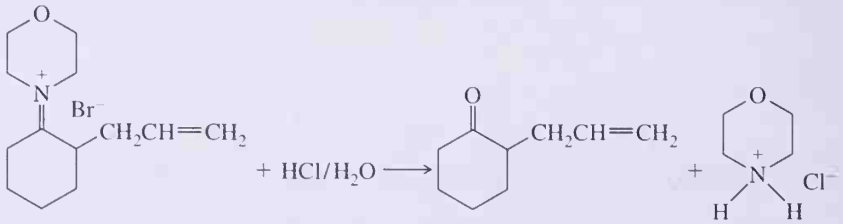
Although enamines behave as nucleophiles, they are only weakly so and undergo S_N2 reactions readily with only methyl and primary alkyl halides, α-haloketones, and α-haloesters. Alkylation is carried out in two steps. In Step 1, the enamine is treated with one equivalent of the alkylating agent to give an iminium halide. Hydrolysis of the iminium halide in Step 2 gives the alkylated aldehyde or ketone.

Step 1: Alkylation of the enamine



The morpholine enamine of cyclohexanone | Allyl bromide | An iminium bromide

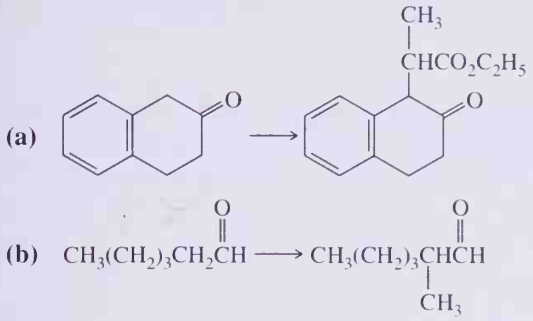
Step 2: Hydrolysis of the iminium halide



2-Allylcyclohexanone | Morpholine hydrochloride

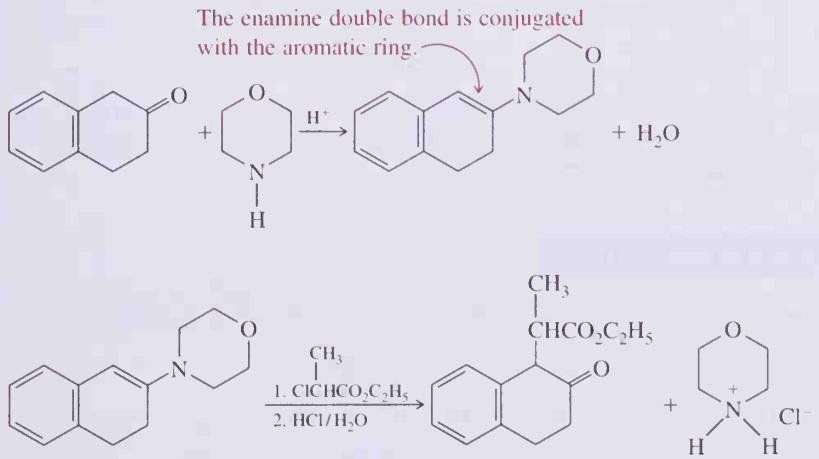
EXAMPLE 21.4

Show how to use an enamine to bring about the following syntheses:

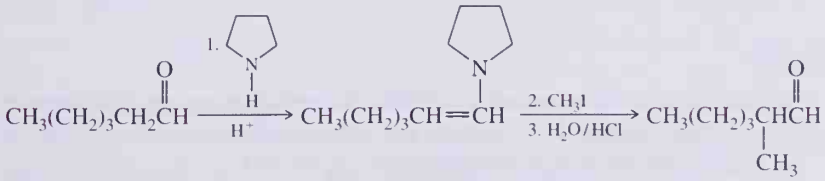


Solution

(a) The common name of the starting ketone is β-tetralone. Prepare an enamine by treating it with either morpholine or pyrrolidine. The intermediate aminoalcohol can undergo dehydration in two directions. The direction shown here is favored because of the stabilization gained by conjugation of the carbon-carbon double bond of the enamine with the aromatic ring. Treatment of the enamine with ethyl 2-chloropropanoate followed by hydrolysis of the iminium chloride in aqueous hydrochloric acid gives the product.

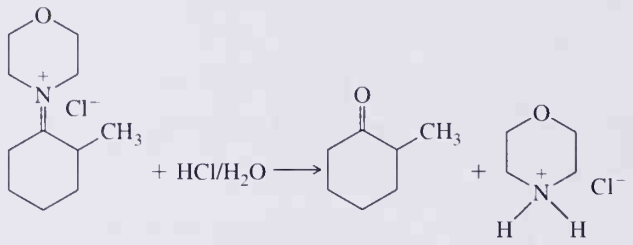


(b) Treatment of hexanal with pyrrolidine gives an enamine. Alkylation with methyl iodide followed by hydrolysis in aqueous HCl gives 2-methylhexanal.



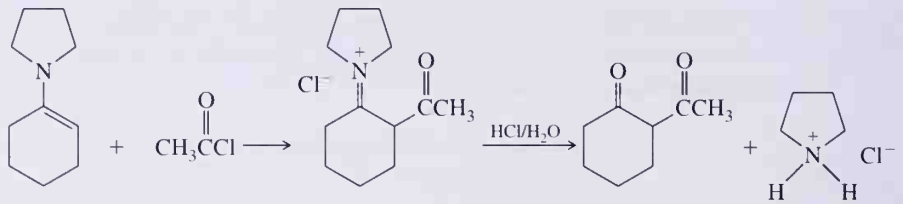
PROBLEM 21.4

Write a mechanism for the hydrolysis of the following iminium chloride in aqueous HCl:



B. Acylation of Enamines

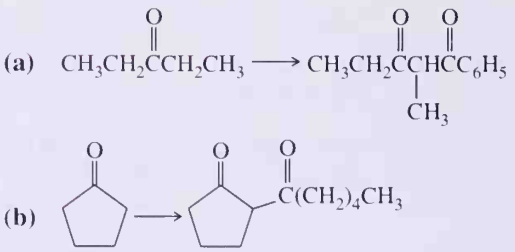
Enamines undergo acylation when treated with acid chlorides and acid anhydrides. The reaction is one of nucleophilic acyl substitution as illustrated by the conversion of cyclohexanone, via its pyrrolidine enamine, to 2-acetylcyclohexanone. Thus we can attach an acyl group to the α-carbon of an aldehyde or ketone using its enamine as an intermediate product.



The pyrrolidine enamine of cyclohexanone | Acetyl chloride | An iminium chloride | 2-Acetyl-cyclohexanone

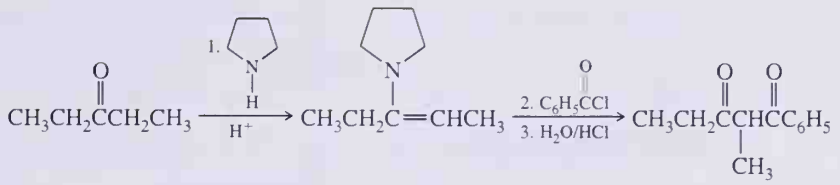
EXAMPLE 21.5

Show how to use an enamine to bring about the following syntheses:

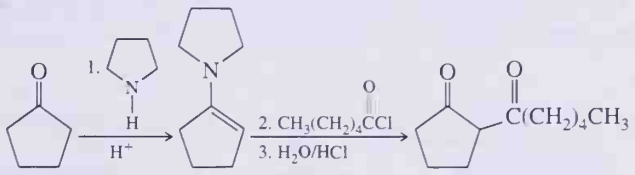


Solution

(a) Treat 3-pentanone with pyrrolidine to form an enamine. Treatment of the pyrrolidine enamine with benzoyl chloride followed by hydrolysis in aqueous HCl gives the desired β-diketone.

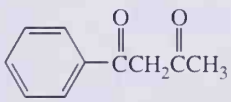


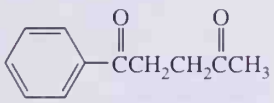
(b) Treatment of cyclopentanone with pyrrolidine gives an enamine. Treatment of the enamine with hexanoyl chloride followed by hydrolysis in aqueous HCl gives the desired β-diketone.

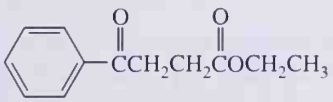


PROBLEM 21.5

Show how to use alkylation or acylation of an enamine to convert acetophenone to the following compounds:

(a) 

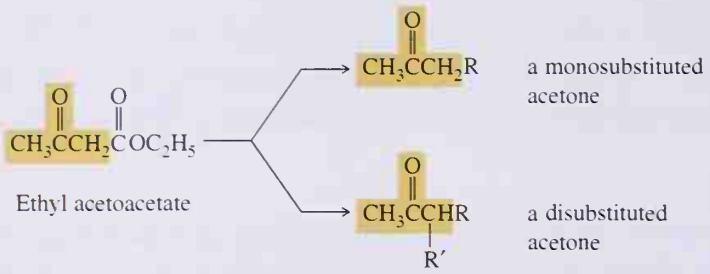
(b) 

(c) 

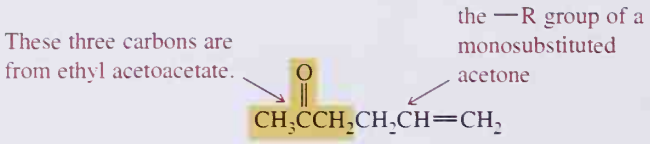
21.4 The Acetoacetic Ester Synthesis

What makes acetoacetic ester and other β-ketoesters such versatile starting materials for formation of new carbon-carbon bonds is (1) the acidity of α-hydrogens between the two carbonyl groups, (2) the nucleophilicity of the enolate anion resulting from loss of an α-hydrogen, and (3) the ease of ester hydrolysis and decarboxylation of the resulting β-ketoacid.

The **acetoacetic ester synthesis** is useful for the preparation of monosubstituted and disubstituted acetones of the following types. We have already seen the chemistry of the individual steps in this synthesis but not put together in this particular sequence.

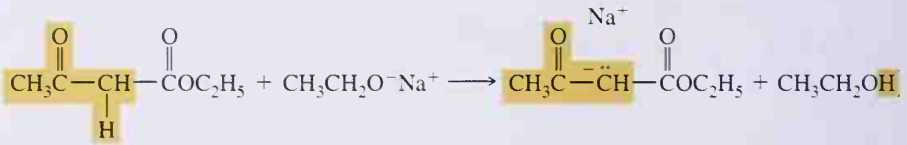


Let us illustrate the acetoacetic ester synthesis by choosing 5-hexen-2-one as a target molecule. The three carbons shown in color are provided by ethyl acetoacetate. The remaining three carbons represent an —R group of a substituted acetone.



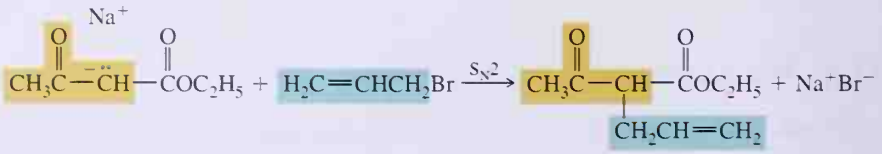
5-Hexen-2-one

1. The methylene hydrogens of ethyl acetoacetate are more acidic (pK_a 10.7) than ethanol (pK_a 15.9), and, therefore, ethyl acetoacetate is converted completely to its anion by sodium ethoxide or other alkali metal alkoxide.

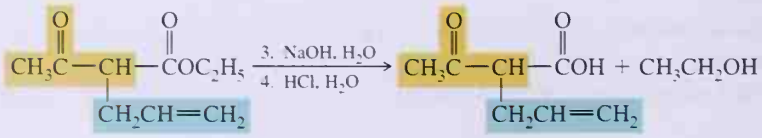


Ethyl acetoacetate	Sodium ethoxide	Sodium salt of ethyl acetoacetate	Ethanol
pK_a 10.7	(stronger base)	(weaker base)	pK_a 15.9
(stronger acid)			(weaker acid)

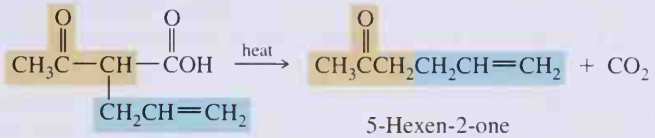
2. The enolate anion of ethyl acetoacetate is a nucleophile and reacts by an S_N2 pathway with methyl and primary alkyl halides, α-haloketones, and α-haloesters. Secondary halides give lower yields, and tertiary halides undergo elimination. In the following example, the anion of ethyl acetoacetate is alkylated with allyl bromide:



3,4. Hydrolysis of the alkylated acetoacetic ester in aqueous NaOH followed by acidification with aqueous HCl (Section 20.4C) gives a β-ketoacid.

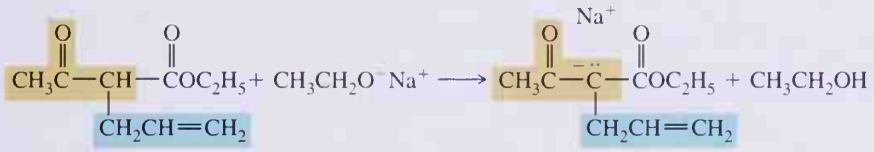


5. Heating the β-ketoacid brings about thermal decarboxylation (Section 19.11A) to give 5-hexen-2-one.

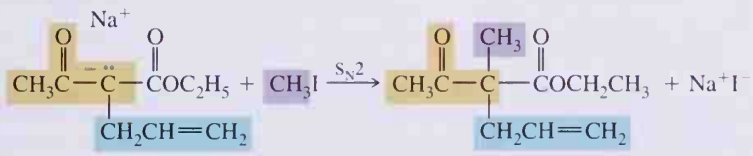


5-Hexen-2-one
(a monosubstituted acetone)

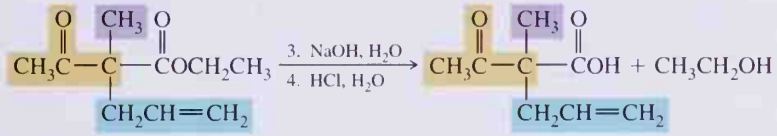
A disubstituted acetone can be prepared by interrupting the previous sequence after Step 2, treating the monosubstituted acetoacetic ester with a second equivalent of base, carrying out a second alkylation, and then proceeding with Steps 3 through 5.



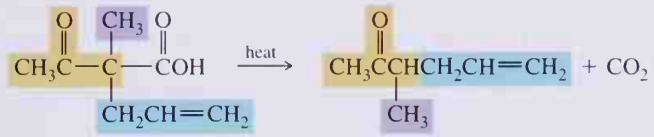
2. The second alkylation:



3,4. Hydrolysis of the ester and conversion to a β-ketoacid:



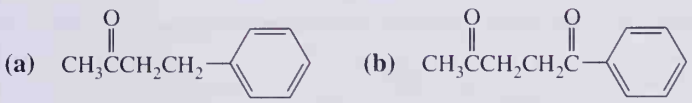
5. Thermal decarboxylation of the β-ketoacid:



3-Methyl-5-hexen-2-one
(a disubstituted acetone)

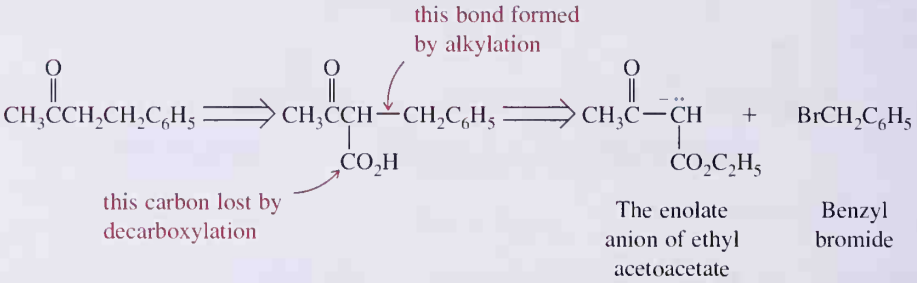
EXAMPLE 21.6

Show how the acetoacetic ester synthesis can be used to prepare the following monosubstituted acetones:

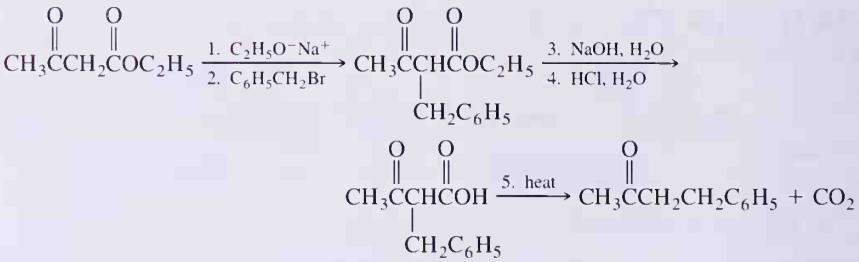


Solution

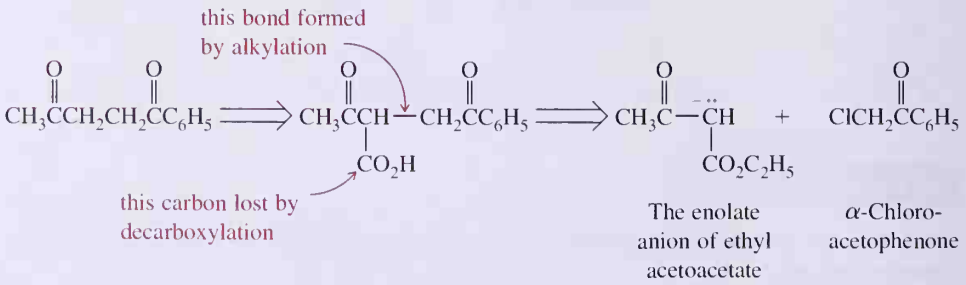
(a) Determine the starting materials by working backwards, that is, by disconnecting bonds or interconverting functional groups so as to arrive at a simple set of starting materials. In the following scheme, the open arrow ⟹ indicates a disconnection or a reverse functional group interconversion. To understand how the target molecule can be synthesized from acetoacetic ester, determine first which three carbons of the product originated from ethyl acetoacetate, then the location on the carbon chain of the $-CO_2H$ lost in decarboxylation, and finally the bond formed in the alkylation step. By this analysis, determine that the starting materials are ethyl acetoacetate and a benzyl halide.



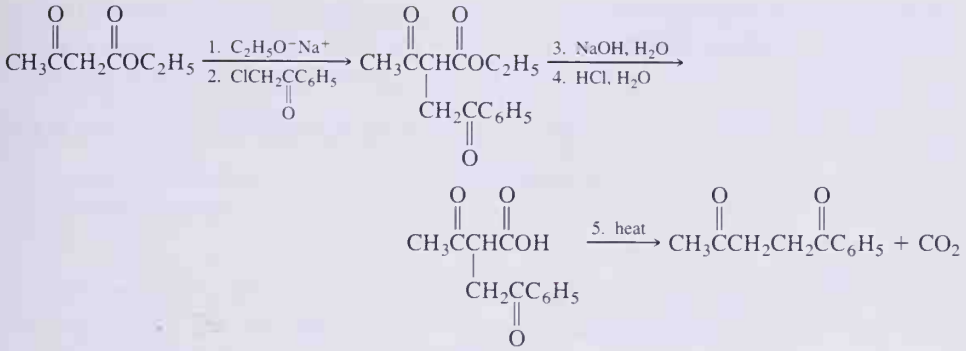
Now combine these reagents in the following way to get the desired product:



(b) Carry out the same type of analysis for this target molecule as you did in the previous example.

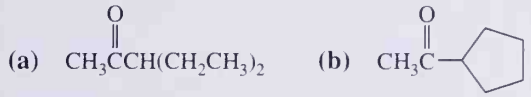


The starting materials are ethyl acetoacetate and α-chloroacetophenone. Combine them in the following sequence:

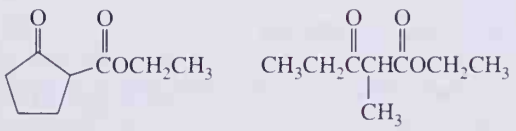


PROBLEM 21.6

Show how the acetoacetic ester synthesis can be used to prepare the following disubstituted methyl ketones:



We have described what is commonly known as the acetoacetic ester synthesis and have illustrated the use of ethyl acetoacetate as the starting reagent. This same synthetic strategy is applicable to any β-ketoester, as for example, those that are available by Claisen condensation (Section 20.12A) and the Dieckmann condensation (Section 20.12B). Following are structural formulas for two β-ketoesters that can be made to undergo (1) formation of an enolate anion, (2) alkylation or acylation, (3) hydrolysis followed by (4) acidification, and finally (5) decarboxylation just as we have shown for ethyl acetoacetate.



Ethyl 2-oxocyclopentanecarboxylate

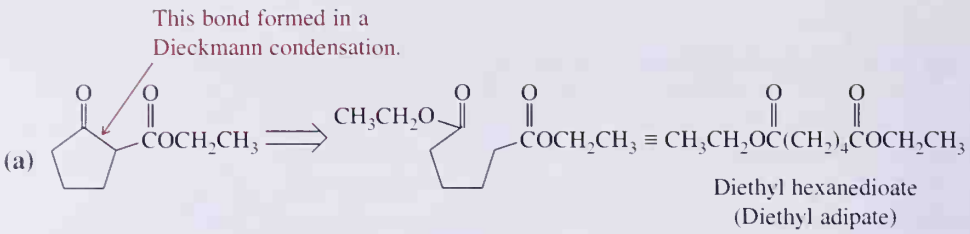
Ethyl 2-methyl-3-oxopentanoate

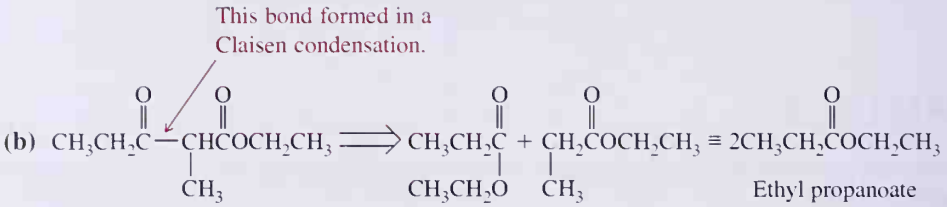
EXAMPLE 21.7

From what ester or diester might each of the previous β-ketoesters be synthesized using a Claisen or Dieckmann condensation?

Solution

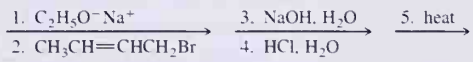
In Claisen and Dieckmann condensations, a new carbon-carbon bond is formed by reaction of the α-carbon of one ester group, as an enolate anion, with the carbonyl carbon of a second ester group. Through nucleophilic acyl substitution, the carbonyl carbon of the second ester becomes a ketone carbonyl. Following are structural formulas for the appropriate esters or diesters.





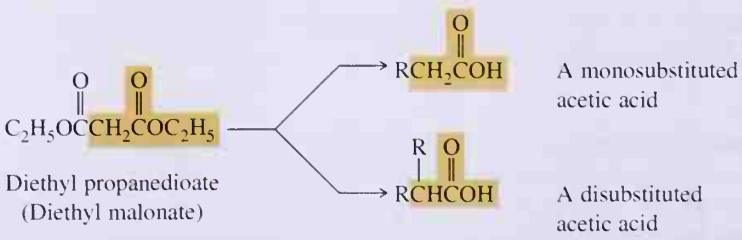
PROBLEM 21.7

Draw the structural formula of the ketone formed on treatment of the β-ketoesters shown in Example 21.7 with the following series of reagents:



21.5 The Malonic Ester Synthesis

The factors that make malonic esters and other β-diesters such versatile starting materials for formation of new carbon-carbon bonds are the same as those we have already seen for the acetoacetic ester synthesis, namely, (1) the acidity of α-hydrogens between the two carbonyl groups, (2) the nucleophilicity of the enolate anion resulting from loss of such an α-hydrogen, and (3) the ease of ester hydrolysis and decarboxylation of the resulting β-dicarboxylic acid. The **malonic ester synthesis** is useful for the preparation of monosubstituted and disubstituted acetic acids of the following types.

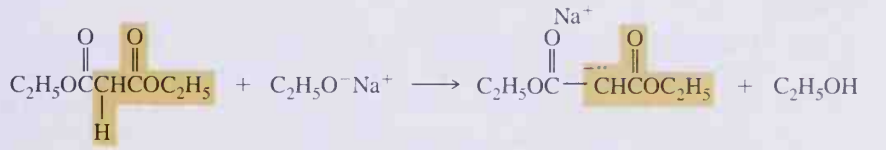


As with the acetoacetic ester synthesis of mono- and disubstituted acetones, we have already encountered all of the important chemistry of the malonic ester synthesis, although

not in this particular pattern. Let us illustrate this synthesis by choosing 4-pentenoic acid as a target molecule. The two carbons shown in color are provided by diethyl malonate. The remaining three carbons represent an —R group of a monosubstituted acetic acid.

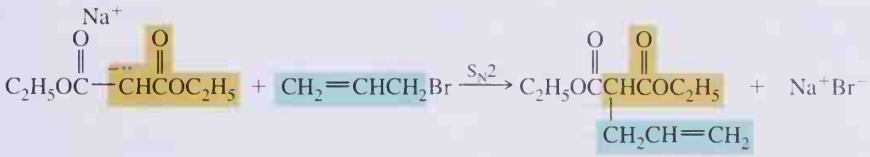
4-Pentenoic acid

1. The methylene protons of diethyl malonate (pK_a 13.3) are more acidic than ethanol (pK_a 15.9), and, therefore, diethyl malonate is converted completely to its anion by sodium ethoxide or other alkali metal alkoxide.

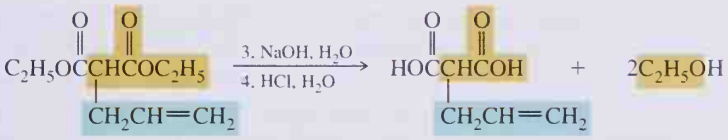


Diethyl malonate pK_a 13.3 (stronger acid)	Sodium ethoxide (stronger base)	Sodium salt of diethyl malonate (weaker base)	Ethanol pK_a 15.9 (weaker acid)

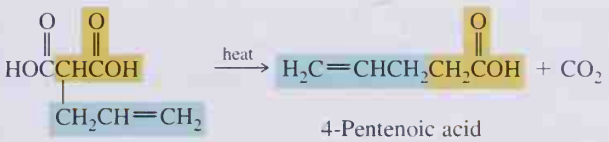
2. The enolate anion of diethyl malonate is a nucleophile and reacts by an S_N2 pathway with methyl and primary alkyl halides, α-haloketones, and α-haloesters. In the following example, the anion of diethyl malonate is alkylated with allyl bromide.



3,4. Hydrolysis of the alkylated diethyl malonate in aqueous NaOH followed by acidification with aqueous HCl (Section 20.4C) gives a β-dicarboxylic acid.



5. Heating the β-dicarboxylic acid slightly above its melting point brings about thermal decarboxylation (Section 19.11B) to give 4-pentenoic acid.



4-Pentenoic acid

A disubstituted acetic acid can be prepared by interrupting the previous sequence after Step 2, treating the monosubstituted diethyl malonate with a second equivalent of base, carrying out a second alkylation, and then proceeding with Steps 3 through 5.

EXAMPLE 21.8

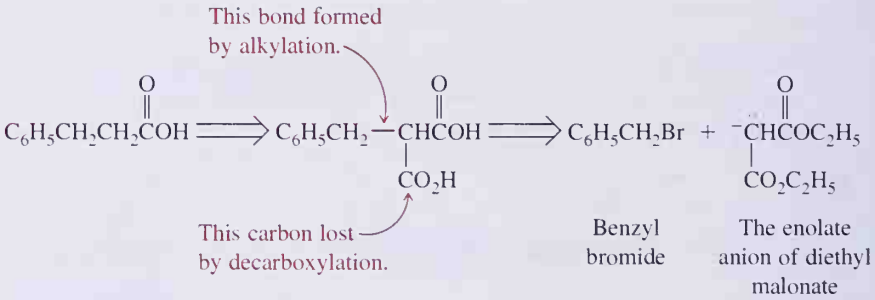
Show how the malonic ester synthesis can be used to prepare the following monosubstituted acetic acids:

(a) $C_6H_5CH_2CH_2\overset{\overset{O}{\|}}{C}OH$

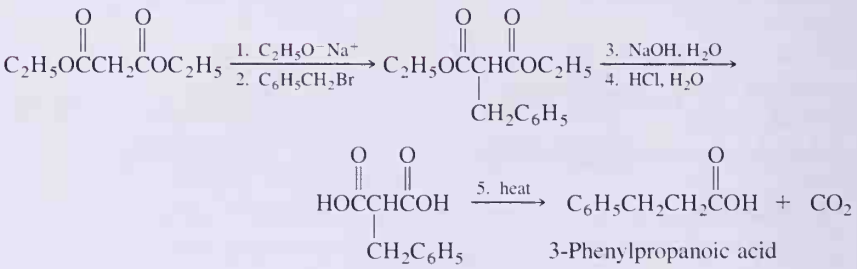
(b) $C_6H_5\overset{\overset{O}{\|}}{C}CH_2CH_2\overset{\overset{O}{\|}}{C}OH$

Solution

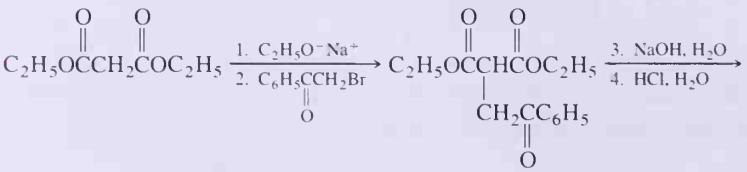
(a) Determine the starting materials by working backwards in a retrosynthetic manner. Determine first which two carbons of the product originate from diethyl malonate, then the location on the carbon chain of the $-CO_2H$ lost in decarboxylation, and finally the bond formed in the alkylation step. By this analysis, determine that the starting materials are diethyl malonate and a benzyl halide.

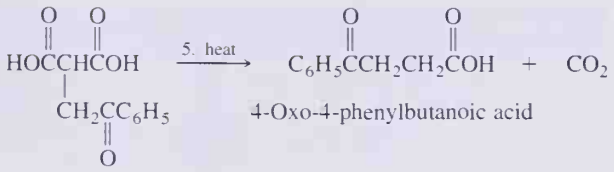


Now combine these reagents in the following way to get the desired product:



(b) Carry out the same type of analysis for this target molecule as you did for the previous one. Discover that the starting molecules are an α-haloacetophenone and diethyl malonate. Combine them in the following sequence:

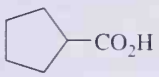




PROBLEM 21.8

Show how the malonic ester synthesis can be used to prepare the following disubstituted acetic acids:

(a) $(CH_3CH_2)_2CHCO_2H$

(b) 

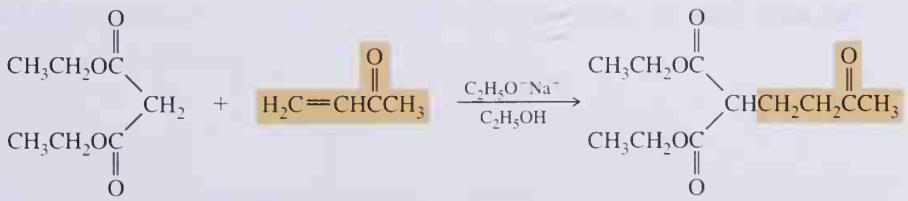
21.6 The Michael Reaction

Thus far we have used a variety of carbon nucleophiles to form new carbon-carbon bonds. Among the carbon nucleophiles we have used are

- Organometallics, including organomagnesium compounds (Grignard reagents), organolithium compounds, and organocadmium compounds
- Anions of terminal acetylenes
- Enolate anions derived from aldehydes and ketones (aldol reactions), esters (Claisen, Dieckmann, and related condensations), β-diesters (malonic ester syntheses), and β-ketoesters (acetoacetic ester syntheses)
- Anions derived from 1,3-dithianes
- Enamines (which are synthetically equivalent to enolate anions)

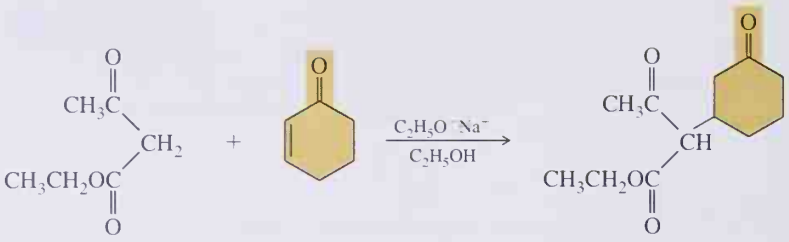
These species have been used to form new carbon-carbon bonds by only two synthetic strategies: (1) substitution by the carbon nucleophile in an S_N2 reaction or (2) addition of the carbon nucleophile to a carbonyl carbon. The **Michael reaction,** or conjugate addition as it is also known, presents a different synthetic strategy, namely, addition of a carbon nucleophile to an electrophilic carbon-carbon double or triple bond. This type of reaction was first reported in 1887 by the American chemist, Arthur Michael.

Following are two examples of Michael reactions. In the first example, the nucleophile that adds to the carbon-carbon multiple bond is the enolate anion of diethyl malonate. In the second example, the nucleophile is the enolate anion of ethyl acetoacetate.



Diethyl propanedioate (Diethyl malonate)

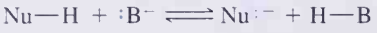
3-Buten-2-one (Methyl vinyl ketone)



Ethyl 3-oxobutanoate (Ethyl acetoacetate) 2-Cyclohexenone

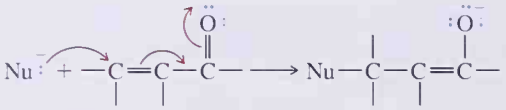
We can write the following general mechanism for a Michael reaction.

1. Treatment of H—Nu with base to form Nu^-, a weaker base and nucleophile. The most commonly used types of nucleophiles in Michael reactions are summarized in Table 21.1. The most commonly used bases are metal alkoxides, pyridine, and piperidine dissolved in alcohol or other polar, protic solvent.

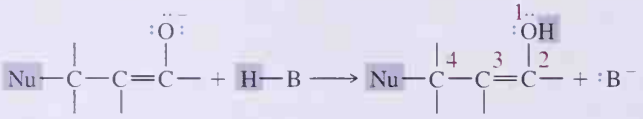


Base

2. Nucleophilic addition of Nu^- to the β-carbon of the conjugated system to form a resonance-stabilized enolate anion.



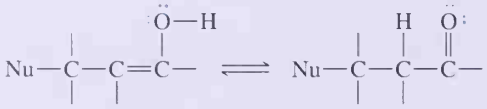
3. Proton transfer from H—B to the enolate anion to form an enol. The enol corresponds to 1,4-addition to the α,β-unsaturated carbonyl compound, and it is because of formation of this intermediate that the Michael reaction is classified as a 1,4-, or conjugate, addition.



A product of 1,4-addition

It is in this step that the base, B^-, is regenerated, in accord with the experimental observation that a Michael reaction requires only a catalytic amount of base rather than a molar equivalent.

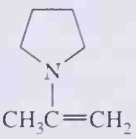
4. Isomerization of the less stable enol form to the more stable keto form (Section 17.12B).



Less stable enol form More stable keto form

The Michael reaction takes place with a wide variety of α,β-unsaturated carbonyl compounds as well as with α,β-unsaturated nitriles and nitro compounds (Table 21.2). The

Table 21.2 Combinations of reagents for effective Michael reactions

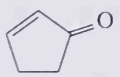
These Types of α,β-Unsaturated Compounds Are Nucleophile Acceptors in Michael Reactions		These Types of Compounds Provide Effective Nucleophiles for Michael Reactions	
$H_2C{=}CHCH$ (O)	aldehyde	$CH_3CCH_2CCH_3$ (O, O)	β-diketone
$H_2C{=}CHCCH_3$ (O)	ketone	$CH_3CCH_2COCH_2CH_3$ (O, O)	β-ketoester
$H_2C{=}CHCOCH_2CH_3$ (O)	ester	CH_3CCH_2CN (O)	β-ketonitrile
$H_2C{=}CHCNH_2$ (O)	amide	$CH_3CH_2OCCH_2COCH_2CH_3$ (O, O)	β-diester
$H_2C{=}CHC{\equiv}N$	nitrile		enamine
$H_2C{=}CHNO_2$	nitro compound		

most effective nucleophiles for Michael reactions are relatively weak bases. With stronger bases, such as organolithium compounds, Grignard compounds, and acetylide ions, addition to the carbonyl group predominates over conjugate addition.

EXAMPLE 21.9

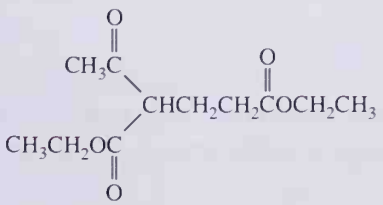
Draw structural formulas for the product of the following Michael reactions:

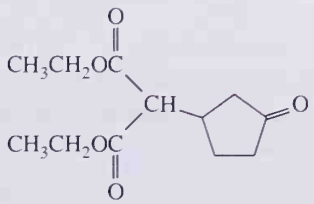
(a) $CH_3CCH_2COCH_2CH_3$ (O, O) + $H_2C{=}CHCOCH_2CH_3$ (O) $\xrightarrow[C_2H_5OH]{C_2H_5O^-Na^+}$

(b) $CH_3CH_2OCCH_2COCH_2CH_3$ (O, O) +  $\xrightarrow[C_2H_5OH]{C_2H_5O^-Na^+}$

Solution

Following are the Michael products:

(a) 

(b) 

PROBLEM 21.9

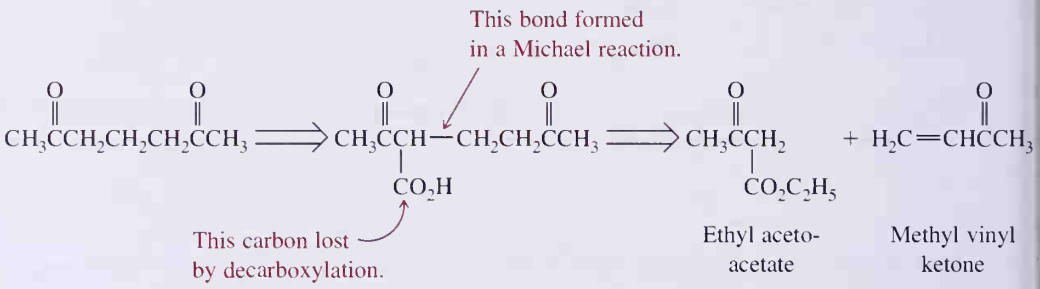
Show the product formed from each Michael product in the Solution to Example 21.9 after (1) hydrolysis in aqueous NaOH, (2) acidification, and (3) thermal decarboxylation of each β-ketoacid or β-dicarboxylic acid.

EXAMPLE 21.10

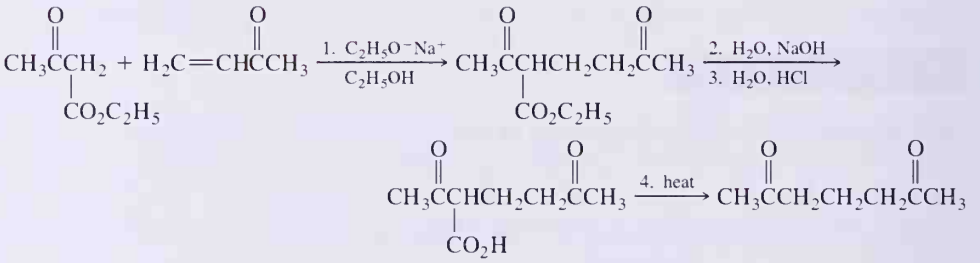
Show how the series of reactions in the previous example and problem (Michael reaction, hydrolysis, acidification, and thermal decarboxylation) can be used to prepare 2,6-heptanedione.

Solution

As shown in the following retrosynthetic analysis, this molecule can be constructed from the carbon skeletons of ethyl acetoacetate and methyl vinyl ketone.



Following are the steps in their conversion to 2,6-heptanedione.

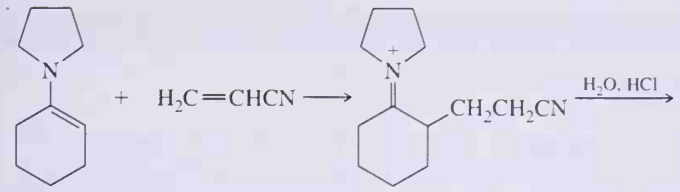


PROBLEM 21.10

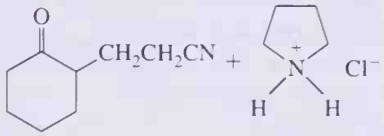
Show how the sequence of Michael reaction, hydrolysis, acidification, and thermal decarboxylation can be used to prepare pentanedioic acid (glutaric acid).

■

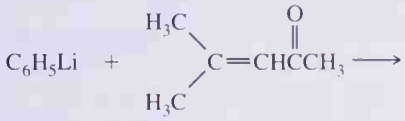
As noted in Table 21.1, enamines behave as carbon nucleophiles, and just as they undergo alkylation and acylation, they also participate in Michael reactions as illustrated by the addition of the enamine of cyclohexanone to acrylonitrile.



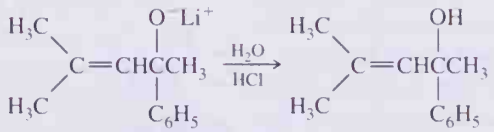
Pyrrolidine enamine of cyclohexanone — Acrylonitrile



A final word about addition of nucleophiles to α,β-unsaturated carbonyl compounds. The Michael reaction is an example of 1,4-addition (conjugate addition) to an α,β-unsaturated carbonyl compound. In general, resonance-stabilized enolate anions and enamines are weak bases, react slowly, and give 1,4-addition products. Organolithium and organomagnesium compounds, on the other hand, are stronger bases, react more rapidly, and give primarily 1,2-addition to the carbonyl carbon.

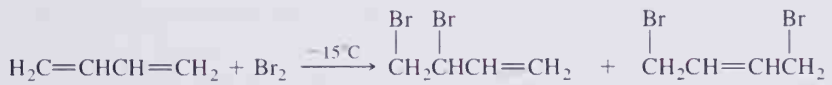


Phenyllithium — 4-Methyl-3-penten-2-one



4-Methyl-2-phenyl-3-penten-2-ol

Recall that our first encounter with conjugate addition was electrophilic addition to conjugated dienes (Section 7.4A). Treatment of 1,3-butadiene with one equivalent of bromine, for example, at −15°C gives a mixture of 1,2-addition and 1,4-addition products.



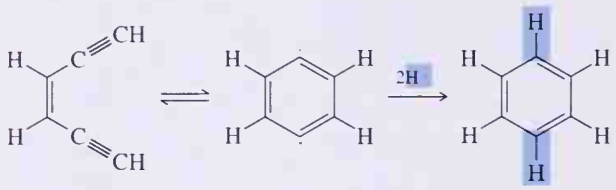
1,3-Butadiene — 3,4-Dibromo-1-butene (54%) (1,2-addition) — 1,4-Dibromo-2-butene (46%) (1,4-addition)

We accounted for product distribution in this addition in terms of kinetic versus thermodynamic control.

CHEMISTRY IN ACTION

The Bergman Reaction and Anticancer Drugs

In the early 1970s, Professor Robert Bergman, then at the California Institute of Technology, discovered an unusual cyclization reaction of "enediynes," compounds with two acetylene units linked by a double bond. When heated to 200 to 300°C, enediynes cyclize to a compound containing a benzene ring in which two of the carbon atoms have no hydrogens. This benzene diradical is extremely reactive and can abstract hydrogen atoms from many different molecules.



A (Z)-enediyne Benzene diradical Benzene

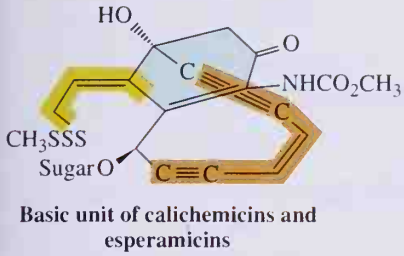
Almost 20 years later, chemists from Bristol-Myers and from American Cyanamid corporations discovered two naturally occurring and incredibly potent families of antitumor compounds, which they named esperamicins and calichemicins. Both have very similar structural formulas and show activity at doses of 1 μg/kg of body weight, which is over 1000 times more active than many currently available antitumor drugs. Common to each compound is an enediyne unit, a most unusual functional group to find in a naturally occurring substance. An obvious question arises: Is the enediyne unit involved in the drug's antitumor activity? Research on the mechanism by which these drugs kill cancer cells has established that the enediyne unit is vital to their function.

In the body, enzyme-catalyzed reduction of the trisulfide $CH_3—S—S—S—R$ unit generates a thiol anion, RS^-. This nucleophile then participates in a Michael reaction with the double bond of the nearby α,β-unsaturated ketone to form a new five-member, sulfur-containing ring. As a result of this addition, a marked change occurs in molecular geometry. The two carbon atoms that were sp^2-hybridized with trigonal planar geometry now are sp^3-hybridized with bond angles of 109.5°. This rehybridization and change of bond angles brings the ends of the enediyne unit closer together, something like a molecular nutcracker. The two end acetylenic carbons, initially 0.335 nm apart, are now squeezed together to 0.316 nm, a distance close enough for the pi clouds of the two triple bonds to interact and undergo a Bergman cyclization. Instead of taking place at 200 to 300°C, this cyclization occurs at body temperature. The resulting benzene diradical then abstracts hydrogen atoms from whatever molecule is nearby. It is believed that the sugar group in each drug helps to steer it toward DNA, so that oftentimes it is DNA that is attacked by the very reactive benzene diradical. The resulting DNA damage is difficult for the cell to repair, and so the cell dies. Cancer cells may be less able to recover from DNA damage, which accounts for the relative selectivity towards killing tumor cells.

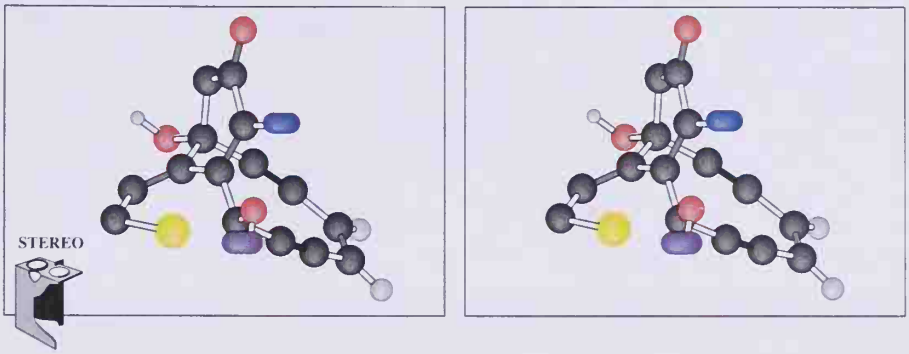
The enediyne story illustrates the remarkable way in which different areas of science can become connected by new discoveries. Professor Bergman certainly never imagined that his studies on the high-temperature rearrangements of enediynes would someday help explain the chemistry behind potent, naturally occuring antitumor drugs. Chemists can now use these ideas to synthesize completely new anticancer drugs.

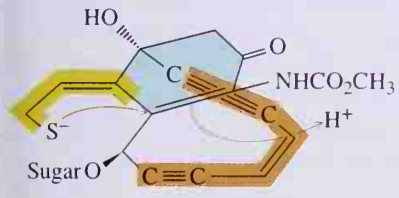
See K. C. Nicolaou, W.-M. Dai, S.-C. Tsay, et al., *Science*, **256:**1172 (1992).

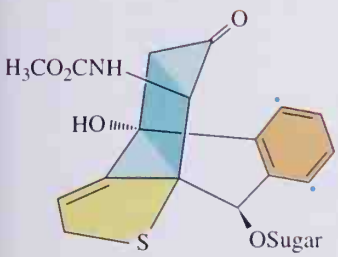
Addition of the nucleophiles listed in Table 21.2 to conjugated carbonyl compounds can also be explained in terms of **kinetic control** versus **thermodynamic control** of product formation. It has been shown that 1,2-addition of nucleophiles to the carbonyl carbon of α,β-unsaturated carbonyl compounds is faster than conjugate addition. If formation of the 1,2-addition product is irreversible, then that is the product observed. If, however, formation of the 1,2-addition product is reversible, then an equilibrium is estab-

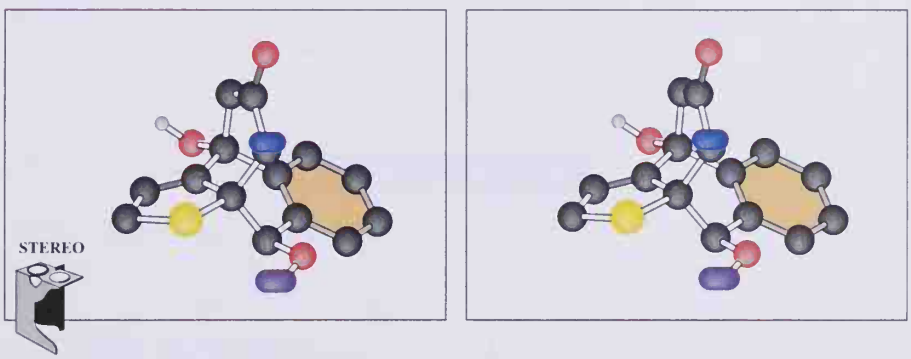


Basic unit of calichemicins and esperamicins

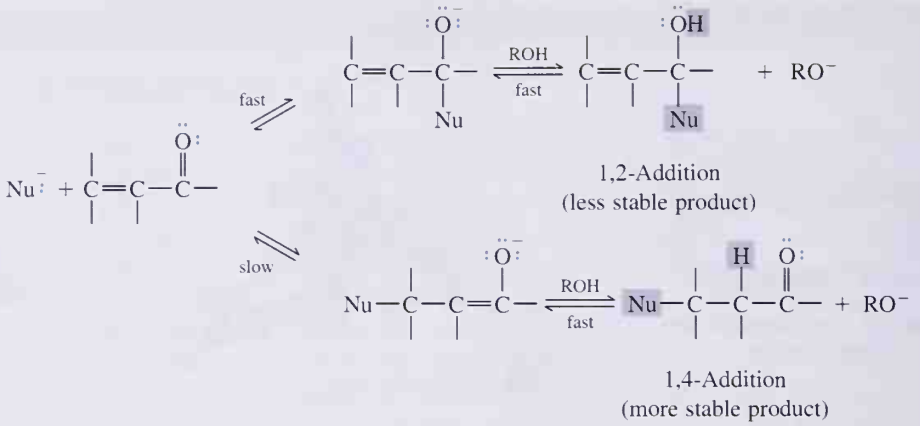




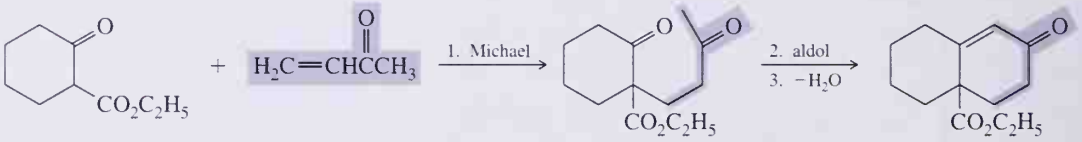




lished between the more rapidly formed 1,2-addition product and the more slowly formed 1,4-addition product. It has also been established that a molecule containing a carbon-oxygen double bond is more stable than one containing a carbon-carbon double bond. Compare, for example, the relative percentages of keto and enol forms present at equilibrium for simple aldehydes and ketones (Section 17.12B). Thus, under conditions of thermodynamic (equilibrium) control, the more stable 1,4-Michael addition product is formed.



Michael reaction with an α,β-unsaturated ketone followed by an aldol reaction has proven to be a valuable method for the synthesis of 2-cyclohexenones. An especially important example of a Michael-aldol sequence is the **Robinson annulation** in which treatment of a cyclic ketone, β-ketoester, or β-diketone with an α,β-unsaturated ketone in the presence of a base catalyst forms a new cyclohexenone ring. When the following β-ketoester, for example, is treated with methyl vinyl ketone in the presence of sodium ethoxide in ethanol, the Michael adduct is first formed and then, in the presence of sodium ethoxide, undergoes base-catalyzed aldol reaction followed by dehydration to give a cyclohexenone ring.

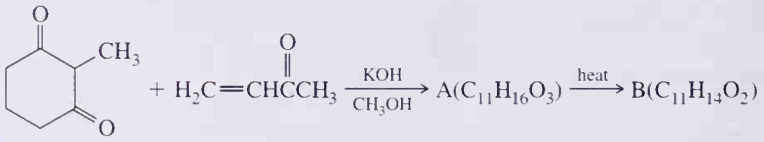


Ethyl 2-oxocyclohexanecarboxylate

3-Buten-2-one (Methyl vinyl ketone)

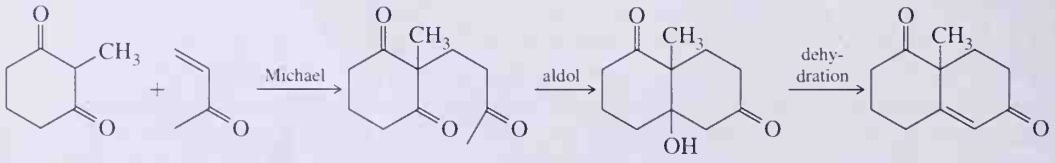
EXAMPLE 21.11

Draw structural formulas for the lettered compounds in the following synthetic sequence:



Solution

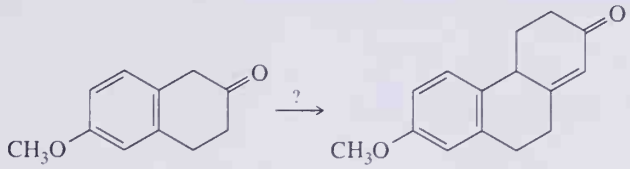
The product is the result of Michael addition to an α,β-unsaturated ketone followed by base-catalyzed aldol reaction and dehydration.



A B

PROBLEM 21.11

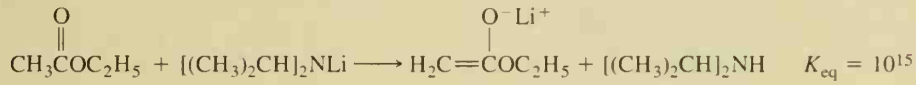
Show how to bring about the following conversion.



SUMMARY OF KEY REACTIONS

1. Formation of Enolate Anions (Section 21.1)

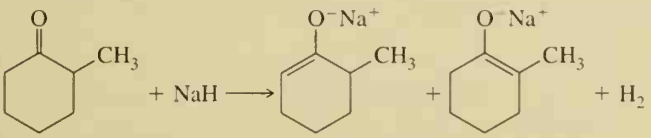
Aldehydes, ketones, esters, and other compounds with acidic α-hydrogens are converted completely to their enolate anions by strong bases, such as lithium diisopropylamide (LDA) and sodium hydride (NaH).



pK_a 23 (stronger acid)	LDA	A lithium enolate	pK_a 38 (weaker acid)	$K_{eq} = 10^{15}$

2. Formation of Enolate Anions Under Thermodynamic (Equilibrium) Control (Section 21.1)

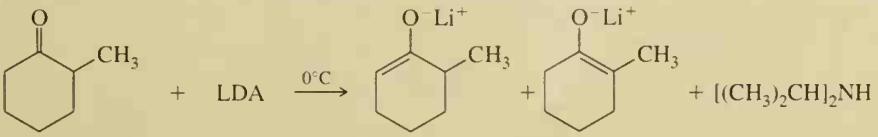
The composition of an enolate anion mixture is determined by the relative stabilities of the individual enolate anions; generally the more substituted enolate anion predominates.



(Slight excess of the ketone)	26%	74%

3. Formation of Enolate Anions Under Kinetic (Rate) Control (Section 21.1)

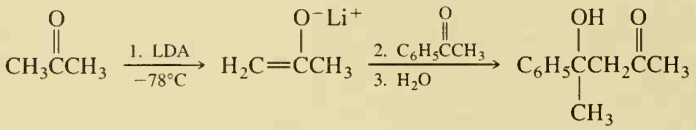
The composition of the enolate anion mixture is determined by the relative rates of removal of alternative α-hydrogens; the less substituted enolate anion predominates, often to the exclusion of alternative enolate anions.



(Slight excess of LDA)	99%	1%

4. Directed Aldol Reactions (Section 21.2)

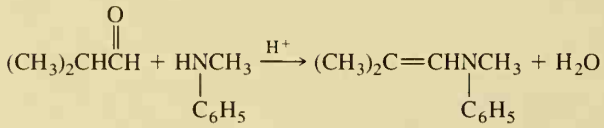
An enolate anion is preformed and then treated with a carbonyl compound acting as an enolate anion acceptor.



A lithium enolate

5. Enamines from a Secondary Amine and an Aldehyde or Ketone (Section 21.3)

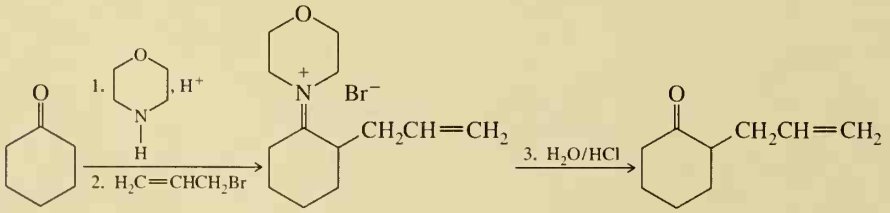
Formation of an enamine is acid-catalyzed and is driven to completion by removal of water.



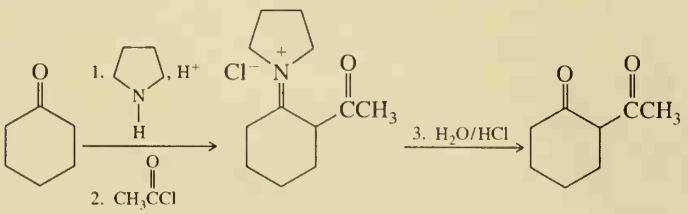
An enamine

6. Alkylation of an Enamine Followed by Hydrolysis (Section 21.3)

Enamines are reactive nucleophiles with methyl and primary alkyl halides as well as α-haloketones and α-haloesters.

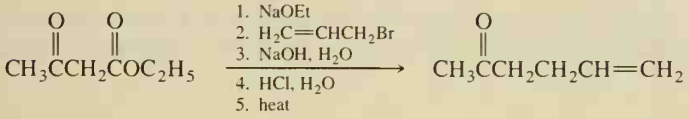


7. Acylation of an Enamine Followed by Hydrolysis (Section 21.3)



8. Acetoacetic Ester Synthesis (Section 21.4)

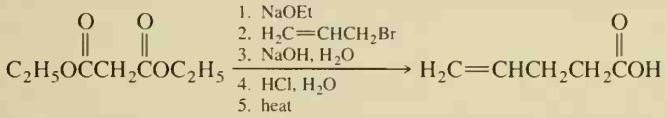
This process is useful for the synthesis of monosubstituted and disubstituted acetones.



Ethyl acetoacetate (A monosubstituted acetone)

9. Malonic Ester Synthesis (Section 21.5)

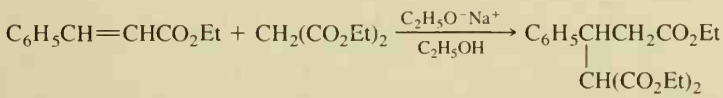
This process is useful for the synthesis of monosubstituted and disubstituted acetic acids.



Diethyl malonate (A monosubstituted acetic acid)

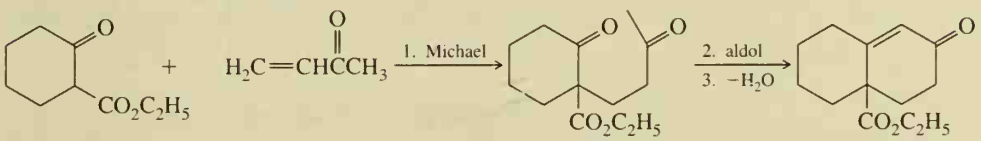
10. Michael Reaction (Section 21.6)

Addition of a relatively weak nucleophile to a carbon-carbon double bond made electrophilic by conjugation with a nitro group, a cyano group, or the carbonyl group of an aldehyde, ketone, or ester.



11. Robinson Annulation (Section 21.6)

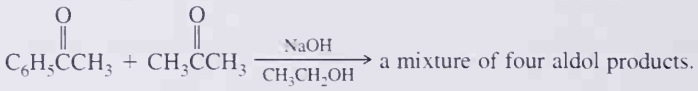
A Michael reaction followed by aldol reaction and dehydration to form a substituted 2-cyclohexenone.



ADDITIONAL PROBLEMS

Directed Aldol Reactions

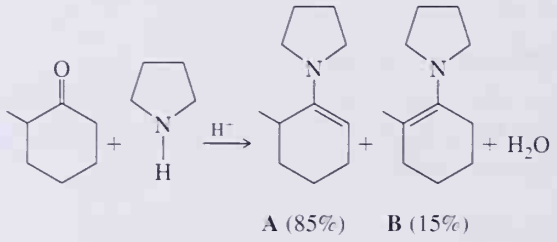
21.12 In Section 21.1, it was stated that four possible aldol products are formed when acetophenone and acetone are mixed in the presence of base. Draw structural formulas for each of these aldol products.



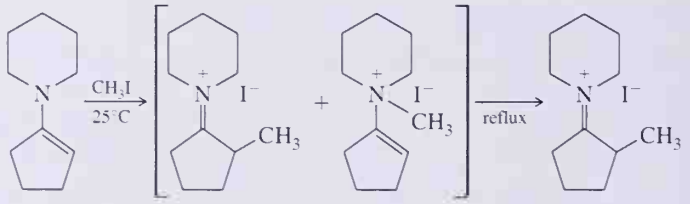
21.13 In the synthesis of a lithium enolate from a ketone and LDA, is it preferable to (a) add a solution of LDA to a solution of the ketone or (b) add a solution of the ketone to a solution of LDA or (c) the order in which the solutions are mixed makes no difference? Explain your answer.

Enamines

21.14 In forming an enamine from 2-methylcyclohexanone and piperidine, two isomeric enamines result, A (85%) and B (15%). Why is the enamine with the less substituted double bond the thermodynamically favored product? You will find it helpful to build models.



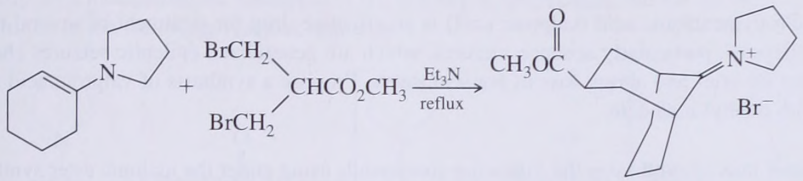
21.15 Enamines normally react with methyl iodide to give two products: one arising from alkylation at nitrogen, the second arising from alkylation at carbon. For example,

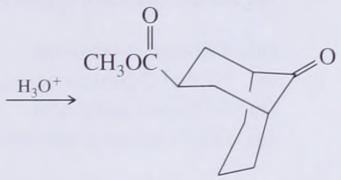


Product of C-alkylation | Product of N-alkylation

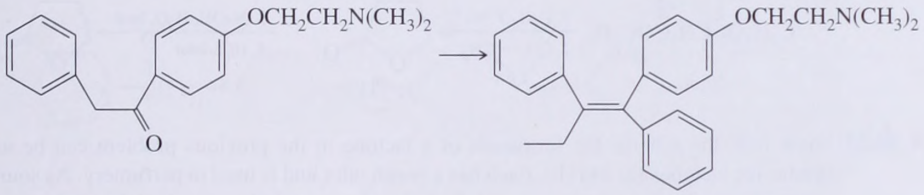
Heating the mixture of C-alkylation and N-alkylation products gives only the product from C-alkylation. Propose a mechanism for this isomerization.

21.16 Show a mechanism for the formation of the intermediate bicyclic compound in the following enamine reaction:



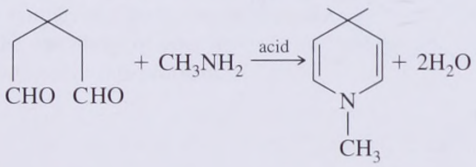


21.17 Many tumors of the breast are estrogen-dependent. Drugs that interfere with estrogen binding have antitumor activity and may even help prevent tumor occurrence. A widely used antiestrogen drug is tamoxifen. How is tamoxifen synthesized from the given aryl ketone using an enamine and a Grignard synthesis?



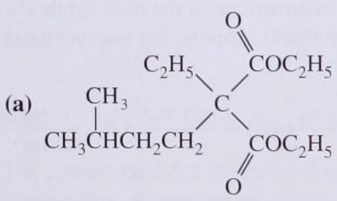
Tamoxifen

21.18 Propose a mechanism for the following reaction:

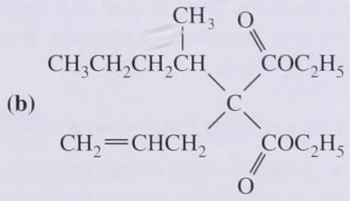


Acetoacetic Ester and Malonic Ester Syntheses

21.19 Propose syntheses of the following derivatives of diethyl malonate, each a starting material for synthesis of a barbiturate currently available in the United States.



Needed for the synthesis of amobarbital



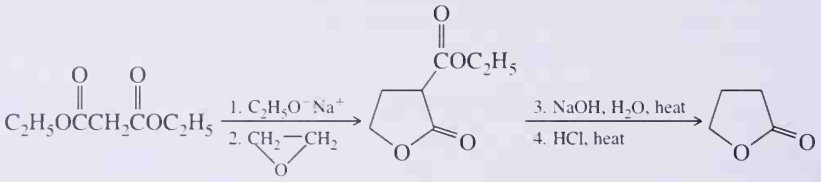
Needed for the synthesis of secobarbital

21.20 2-Propylpentanoic acid (valproic acid) is an effective drug for treatment of several types of epilepsies, particularly absence seizures, which are generalized epileptic seizures characterized by brief and abrupt loss of consciousness. Propose a synthesis of valproic acid starting with diethyl malonate.

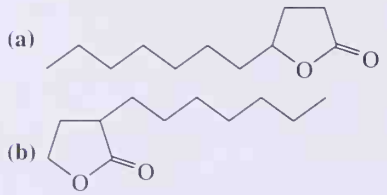
21.21 Show how to synthesize the following compounds using either the malonic ester synthesis or the acetoacetic ester synthesis.

(a) 4-Phenyl-2-butanone
(b) 2-Methylhexanoic acid
(c) 3-Ethyl-2-pentanone
(d) 2-Propyl-1,3-propanediol
(e) 4-Oxopentanoic acid
(f) 3-Benzyl-5-hexen-2-one
(g) Ethyl cyclopropanecarboxylate
(h) Cyclobutyl methyl ketone

21.22 Propose a mechanism for formation of the given lactone when diethyl malonate is treated first with sodium ethoxide followed by ethylene oxide.

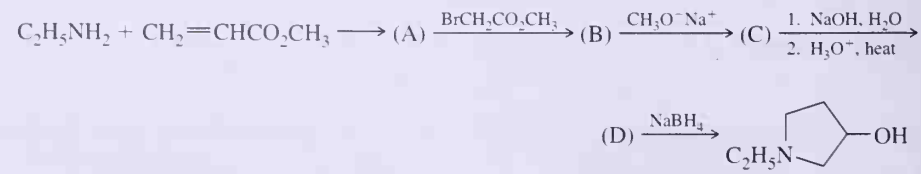


21.23 Show how the scheme for formation of a lactone in the previous problem can be used to synthesize lactones (a) and (b). Each has a peach odor and is used in perfumery. As sources of carbon atoms for these syntheses, use diethyl malonate, ethylene oxide, 1-bromoheptane, and 1-nonene.

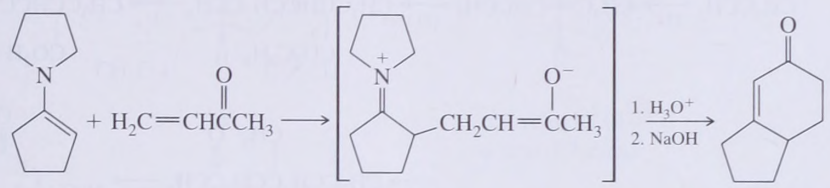


Michael Reactions

21.24 The following synthetic route is used to prepare an intermediate in the total synthesis of the anticholinergic drug, benzilonium bromide. Write structural formulas for intermediates A, B, C, and D in this synthesis.



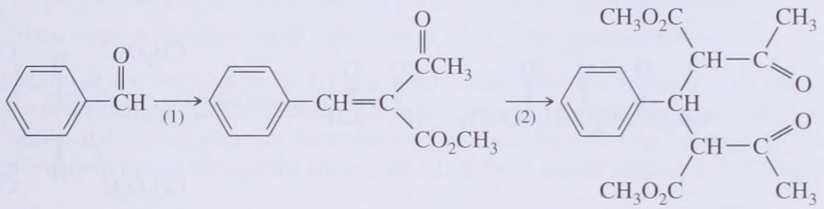
21.25 Propose a mechanism for formation of the bracketed intermediate and for the bicyclic ketone formed in the following reaction sequence:



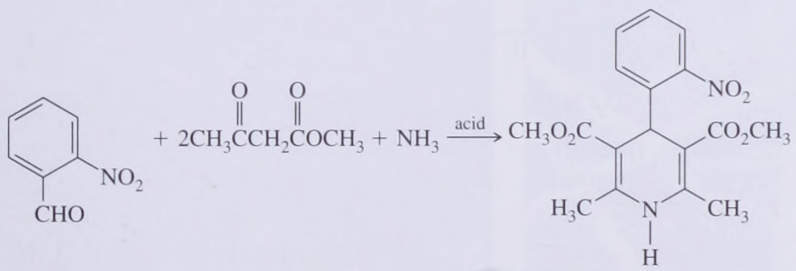
(An intermediate; not isolated)

Synthesis

21.26 Show experimental conditions by which to carry out the following synthesis starting with benzaldehyde and methyl acetoacetate.

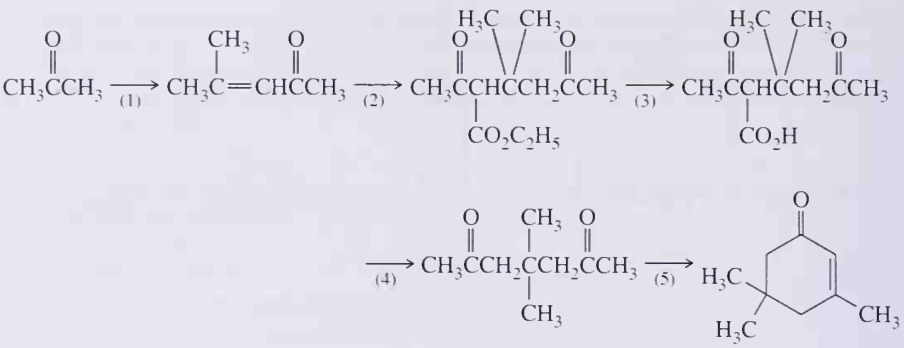


21.27 Nifedipine (Procardia, Adalat) belongs to a class of drugs called Ca^{2+}-channel blockers and is effective in treatment of various types of angina, including that induced by exercise. Show how nifedipine can be synthesized from 2-nitrobenzaldehyde, methyl acetoacetate, and ammonia. *Hint:* Review the chemistry of your answers to Problems 21.18 and 21.26, and then combine that chemistry to solve this problem.



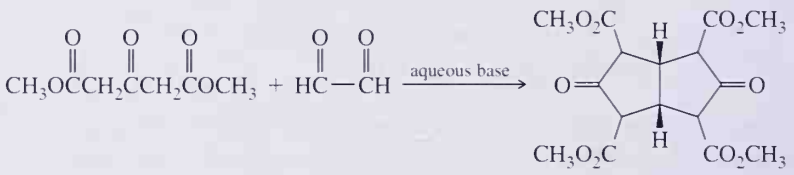
Nifedipine
(Procardia)

21.28 The compound 3,5,5-trimethyl-2-cyclohexenone can be synthesized using acetone and ethyl acetoacetate as sources of carbon atoms. New carbon-carbon bonds in this synthesis are formed by a combination of aldol reactions and Michael reactions. Show reagents and conditions by which this synthesis might be accomplished.



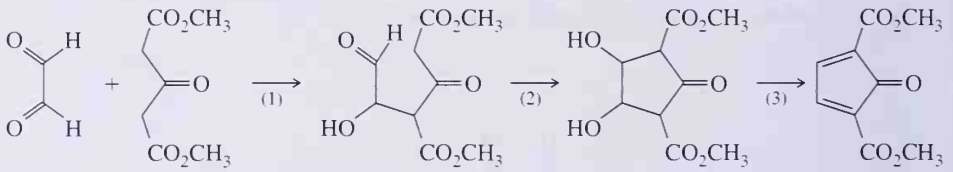
3,5,5-Trimethyl-
2-cyclohexenone

21.29 An important route to fused five-member rings is the Weiss reaction, discovered in 1968 by Dr. Ulrich Weiss at the National Institutes of Health. An example of a Weiss reaction is treating dimethyl 3-oxoglutarate with glyoxal in aqueous base under carefully controlled conditions. The bicyclo[3.3.0]octane derivative (A) is formed in 90% yield.

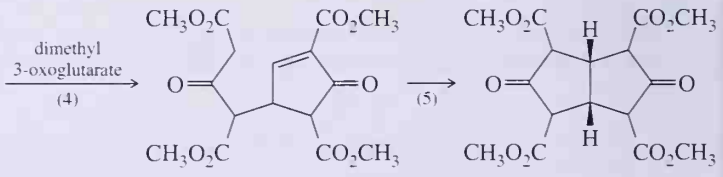


Dimethyl 3-oxoglutarate Glyoxal (A)

The mechanism of the Weiss reaction has been investigated, and the overall steps, as presently understood, involve the following series of reactions. Name the type of reaction involved in each step.

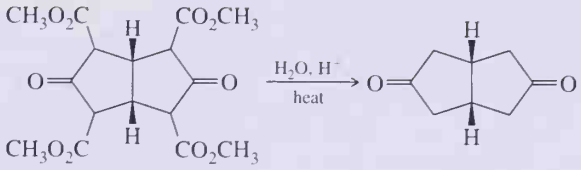


Glyoxal Dimethyl
3-oxoglutarate



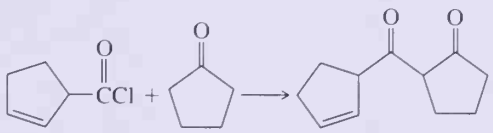
(A)

21.30 When the bicyclic diketone (A) from the previous problem is heated in aqueous acid, bicyclo[3.3.0]octane-3,7-dione is formed. Account for the formation of this product.



(A) Bicyclo[3.3.0]-octane-3,7-dione

21.31 The following β-diketone (A) can be synthesized from cyclopentanone and an acid chloride using an enamine reaction.

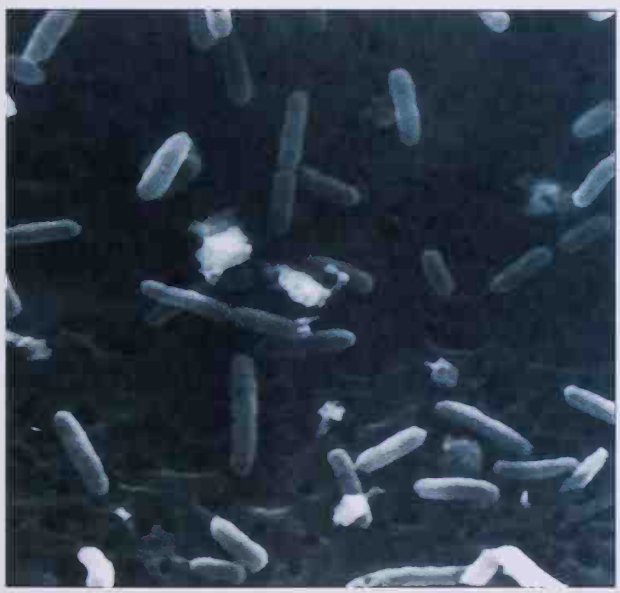


(A)

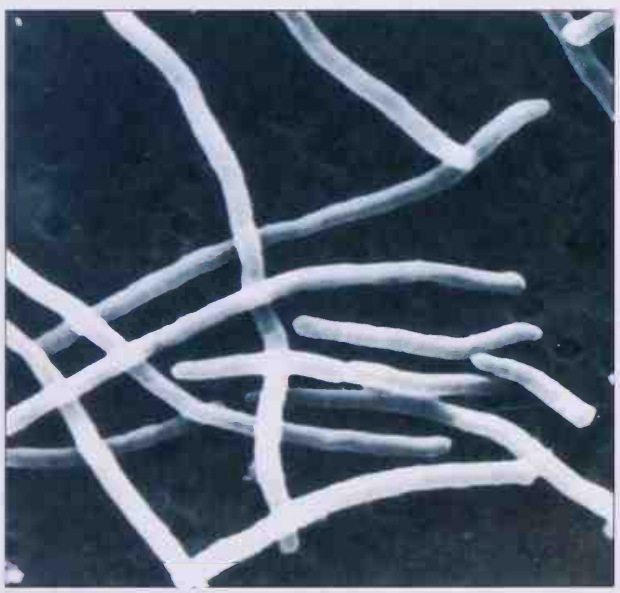
(a) Propose a synthesis of the starting acid chloride from 3-chlorocyclopentene.

(b) Show steps in the synthesis of compound A using a morpholine enamine.

21.32 Cisplatin was first prepared in 1844, but it was not until 1964 that its value as an anticancer drug was realized. In that year, Barnett Rosenberg and coworkers at Michigan State University observed that when platinum electrodes were inserted into a growing bacterial culture and electric current passed through the culture, all cell division ceased within 1 to 2 h. The result



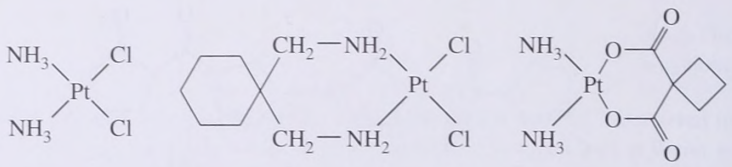
(a)



(b)

Scanning electromicrographs of (a) normal *E. coli* and (b) *E. coli* grown in a medium containing a few ppm of cisplatin. The drug inhibits cell division, but not growth, leading to long filaments.
(© Doris J. Beck, Biological Sciences, Bowling Green State University)

was surprising. Equally surprising was their finding that cell division was inhibited by *cis*-diamminedichloroplatinum(II), more commonly named cisplatin, a platinum complex formed in the presence of ammonium and chloride ions. Cisplatin has a broad spectrum of anticancer activity and is particularly useful for treatment of epithelial malignancies. Evidence suggests that platinum(II) in the complex bonds to DNA and forms intrachain and interchain cross linkages. More than 1000 platinum complexes have since been prepared and tested in attempts to discover even more active cytotoxic drugs. In spiroplatin, the two NH_3 groups are replaced by primary amino groups. This drug showed excellent antileukemic activity in animal models but was disappointing in human trials. In carboplatin, the two chloride ions are replaced by carboxylate groups. In 1989, carboplatin was approved by the FDA for treatment of ovarian cancers.



Cisplatin Spiroplatin Carboplatin

(a) Devise a synthesis for the diamine required in the synthesis of spiroplatin starting with compounds of six carbons or less.

(b) Devise a synthesis for the dicarboxylic acid required in the synthesis of carboplatin starting with diethyl malonate and 1,3-dibromopropane as sources of carbon atoms.

Opium poppy. (© Andrew Henderson: PHOTO/NATS)

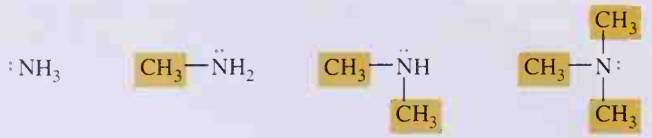
22

AMINES

Carbon, hydrogen, and oxygen are the three most common elements in organic compounds. Because of the wide distribution of amines in the biological world, nitrogen is the fourth most common component of organic compounds. The most important chemical property of amines is their basicity.

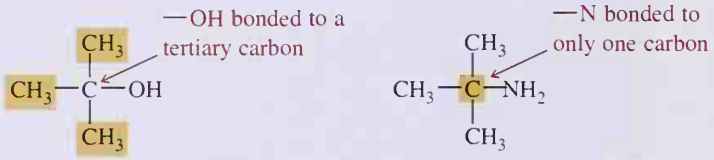
22.1 Structure and Classification

Amines are derivatives of ammonia in which one or more hydrogens are replaced by alkyl or aryl groups. Amines are classified as primary, secondary, or tertiary, depending on the number of carbon atoms bonded directly to nitrogen. In a **primary amine,** one hydrogen of ammonia is replaced by carbon. In a **secondary amine,** two hydrogens are replaced by carbons, and in a **tertiary amine** three hydrogens are replaced by carbons.



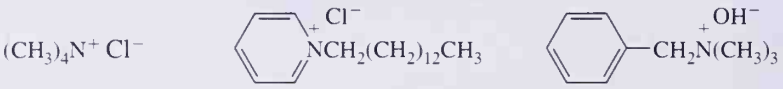
Ammonia | Methylamine (a 1° amine) | Dimethylamine (a 2° amine) | Trimethylamine (a 3° amine)

Alcohols (Section 9.2A) and alkyl halides (Section 10.2A) are also classified as primary, secondary, or tertiary, but the basis for their classification is different from that for amines. For alcohols and alkyl halides, classification depends on the number of carbon atoms attached to the carbon bearing the —OH or —X group.



A 3° alcohol | A 1° amine

An ion containing a nitrogen atom bonded to any combination of four alkyl or aryl groups is classified as a **quaternary ammonium ion.** Compounds containing such ions are fully ionic and have properties characteristic of salts.



Tetramethylammonium chloride | Tetradecylpyridinium chloride | Benzyltrimethylammonium hydroxide

Amines are further divided into aliphatic amines and aromatic amines. In an **aliphatic amine,** all of the carbons bonded directly to nitrogen are derived from alkyl groups; in an **aromatic amine,** one or more of the groups bonded to nitrogen are aromatic rings.

Several over-the-counter mouthwashes contain a pyridinium chloride salt as an antibacterial agent. *(Charles D. Winters)*

CHEMISTRY IN ACTION

Polyamines

A vigorous subdiscipline of bioorganic chemistry and biochemistry involves the study of polyamines, including putrescine, cadaverine, spermine, and spermidine.

$H_2N(CH_2)_4NH_2$ — Putrescine

$H_2N(CH_2)_4NH(CH_2)_3NH_2$ — Spermidine

$H_2N(CH_2)_5NH_2$ — Cadaverine

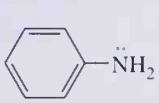
$H_2N(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2$ — Spermine

Putrescine and cadaverine were first isolated from the cholera bacterium *Vibro cholerae* and were named for the foul odors that arise from decaying flesh. It was later discovered that putrescine has only a slight odor; it is other amines coexisting with it that are the source of the unpleasant odors. Spermine and spermidine were first isolated from human seminal fluid, where they are highly concentrated, hence their names. Only a relatively small number of scientists have worked with these compounds, especially with putrescine and cadaverine. Some have suggested that the compounds' names have discouraged more workers from entering this field.

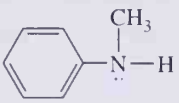
At the body's pH, these polyamines are protonated and associated with negatively charged biological molecules, especially with RNA and DNA. This association is apparently necessary for life because there is a strong correlation between high polyamine concentrations and cells that engage in high rates of protein, RNA, and DNA synthesis.

The study of polyamines exploded in 1971 when it was discovered that human cancer patients have elevated concentrations of polyamines in their urine. Might it be that measuring polyamine levels could lead to a simple blood test for the presence of cancer? Unfortunately, the answer is no. It has been found that any condition that leads to cell loss or pathological cell growth (such as inflammation) produces elevated levels of polyamines. This understanding, however, has produced hundreds of studies on polyamine levels as markers of cell regeneration, tumor regression, and even pregnancy. One wonders if even more studies might have been done if putrescine and cadaverine had been given more pleasant names.

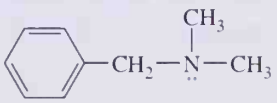
See D. H. Russell, *Nature*, **233**:144 (1981).



Aniline
(a 1° aromatic amine)

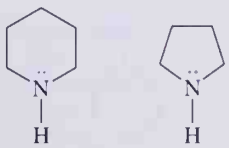


N-Methylaniline
(a 2° aromatic amine)



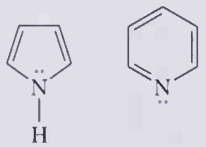
Benzyldimethylamine
(a 3° aliphatic amine)

An amine in which the nitrogen atom is part of a ring is classified as a **heterocyclic amine.** When the nitrogen is part of an aromatic ring (Section 15.2D), the amine is classified as a **heterocyclic aromatic amine.** Following are structural formulas for four heterocyclic amines: two classified as heterocyclic aliphatic amines, and two classified as heterocyclic aromatic amines.



Piperidine Pyrrolidine

(Heterocyclic aliphatic amines)



Pyrrole Pyridine

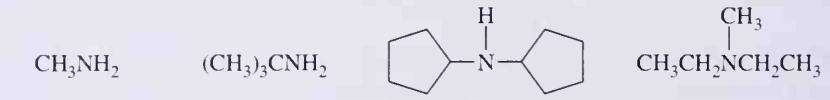
(Heterocyclic aromatic amines)

22.2 Nomenclature

The variation in conventions for naming amines is greater than for any other common functional group. Although the International Union of Pure and Applied Chemistry (IUPAC) has developed a comprehensive set of rules for naming amines, many amines are still routinely referred to by their common names. Moreover, *Chemical Abstracts* has developed an alternative set of rules for naming amines. In this text, we use common names for simple amines and *Chemical Abstracts* names for more complex amines.

A. Common Names

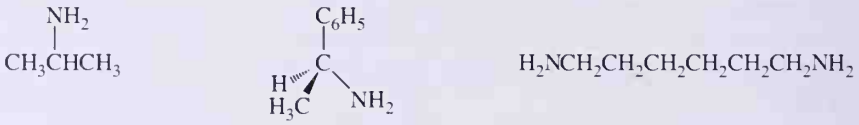
Common names for aliphatic amines are derived by listing the alkyl groups attached to nitrogen in alphabetical order in one word ending in the suffix **-amine.**



Methylamine | *tert*-Butylamine | Dicyclopentylamine | Diethylmethylamine

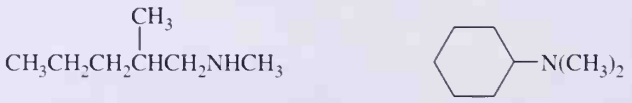
B. IUPAC Names

In the IUPAC system, the longest chain of carbon atoms that contains the amino group is taken as the parent, and —NH_2 is considered a substituent like chloro-, nitro-, and so forth. Its presence is indicated by the prefix **amino-,** and a number is used to show its location.



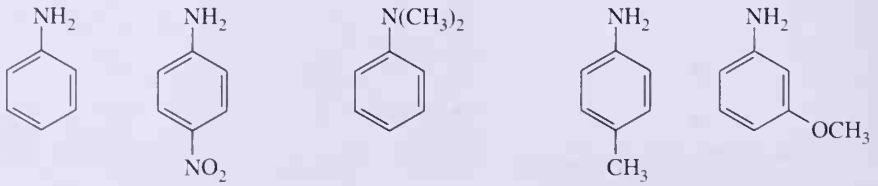
2-Aminopropane | (S)-1-Amino-1-phenylethane | 1,6-Diaminohexane

For secondary and tertiary amines, the largest alkyl group is taken as the parent; smaller groups on nitrogen are collected as a compound prefix to amino-.



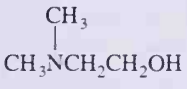
2-Methyl-1-(*N*-methylamino)pentane | *N*,*N*-Dimethylaminocyclohexane

The IUPAC system retains the common name **aniline** for $C_6H_5NH_2$, the simplest aromatic amine. Its simple derivatives are named using the prefixes *o*-, *m*-, *p*- or numbers to locate substituents. Several derivatives of aniline have common names that have also been retained by the IUPAC system. Among these are **toluidine** for a methyl-substituted aniline and **anisidine** for a methoxyl-substituted aniline.

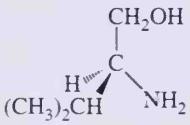


Aniline | 4-Nitroaniline | *N*,*N*-Dimethylaniline | *p*-Toluidine | *m*-Anisidine

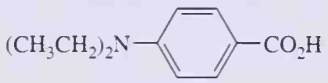
Among the various functional groups presented in this text, the $-NH_2$ group is one of the lowest in precedence (Table 17.1). The following examples each contain a functional group of higher precedence than the amine, and accordingly, the amine in each is indicated by the prefix **amino-.**



2-(*N*,*N*-Dimethylamino)ethanol



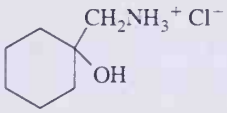
(S)-2-Amino-3-methyl-1-butanol



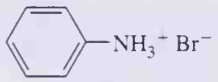
4-(*N*,*N*-Diethylamino)benzoic acid

When one or more of the four atoms bonded to a nitrogen atom is a hydrogen, the compound is named as a salt of the corresponding amine.

Triethylamine hydrochloride

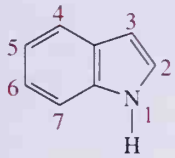


1-Aminomethylcyclohexanol hydrochloride

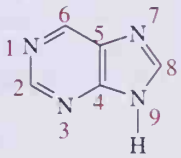


Aniline hydrobromide

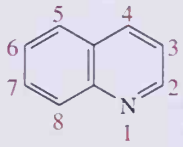
Following are structural formulas, names, and numbering systems for four heterocyclic aromatic amines, the common names of which have also been retained by the IUPAC.



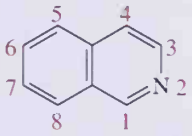
Indole



Purine



Quinoline



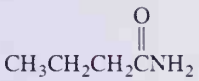
Isoquinoline

C. *Chemical Abstracts* Names

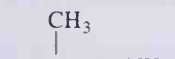
In the nomenclature introduced by *Chemical Abstracts*, amines are named as alkanamines just as alcohols are named alkanols. To name an amine, the suffix -e of the parent name is dropped and replaced by the suffix -amine, as shown in the following examples. Note the parallel between the names 1-butan**amine,** 1-butan**ol**, and butan**amide.**

1-Butanamine

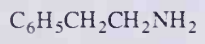
1-Butanol



Butanamide



2-Methyl-1-propanamine



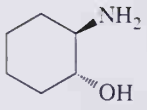
2-Phenylethanamine

1,6-Hexanediamine

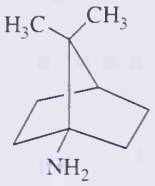
EXAMPLE 22.1

Give each compound an acceptable name.

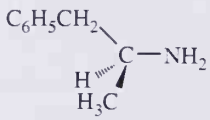
(a) $CH_3CH_2NHCH_3$ (b) $(C_6H_5)_3N$ (c)



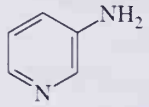
(d)



(e)



(f)



Solution

(a) Named as an alkanamine, it is *N*-methylethanamine. Named as an alkylamine, it is ethylmethylamine. Named as an aminoalkane, it is (methylamino)ethane.

(b) Triphenylamine

(c) The —OH group has higher precedence, and, therefore, the parent molecule is a cyclohexanol. Its name is *trans*-2-aminocyclohexanol.

(d) Named as an alkanamine, it is 7,7-dimethylbicyclo[2.2.1]-1-heptanamine. Named as an aminoalkane, it is 1-amino-7,7-dimethylbicyclo[2.2.1]heptane.

(e) Named as an alkanamine, it is (S)-1-phenyl-2-propanamine. Named as an aminoalkane, it is (S)-2-amino-1-phenylpropane. It has no good alkylamine name. Its common name is amphetamine. The dextrorotatory isomer of amphetamine is a central nervous system stimulant and is manufactured and sold under several trade names. The salt with sulfuric acid is marketed as Dexedrine (dextroamphetamine sulfate).

(f) 3-Aminopyridine

PROBLEM 22.1

Give IUPAC and, where possible, common names for the following.

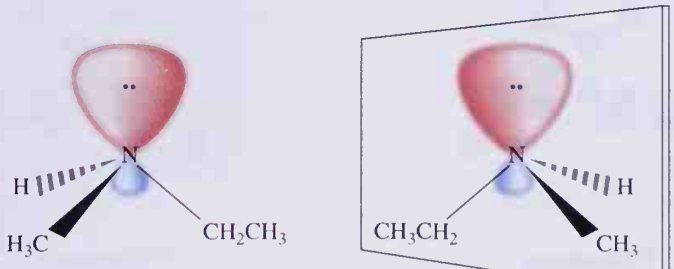
(a) $H_2N-C_6H_4-CO_2CH_2CH_3$ (b) $H_2NCH_2CH_2CH_2CO_2H$

(c) $CH_3\overset{\overset{O}{\|}}{C}CH_2CH_2N(CH_2CH_3)_2$

22.3 Chirality of Amines and Quaternary Ammonium Ions

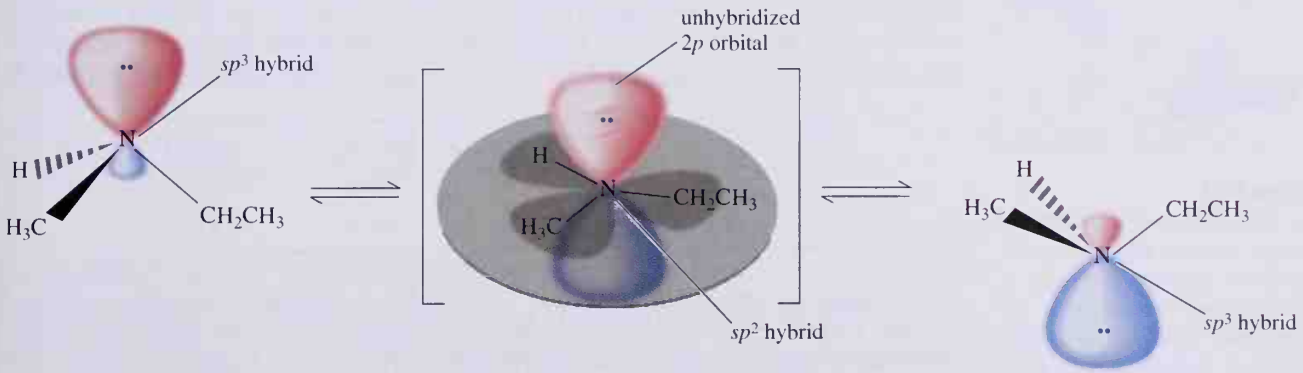
The geometry of a nitrogen atom bonded to three other atoms or groups of atoms is trigonal pyramidal (Section 1.3). The nitrogen atom is at the apex of the pyramid, and the three groups bonded to it extend downward to form the triangular base of the pyramid. If we consider the unshared pair of electrons on nitrogen as a fourth group, then the arrangement

of "groups" around nitrogen is approximately tetrahedral. Because of this geometry, an amine with three different groups bonded to nitrogen is chiral and can exist as a pair of enantiomers, as illustrated by the nonsuperposable mirror images of ethylmethylamine. In assigning absolute configuration to these enantiomers, the group of lowest priority on nitrogen is the unshared pair of electrons. In principle, a chiral amine can be resolved; that is, it can be separated into a pair of enantiomers. In practice, chiral amines cannot be resolved because they undergo rapid interconversion by a process known as pyramidal inversion. **Pyramidal inversion** is the rapid oscillation of a nitrogen atom from one side of the plane of the three atoms bonded to it to the other side of that plane.



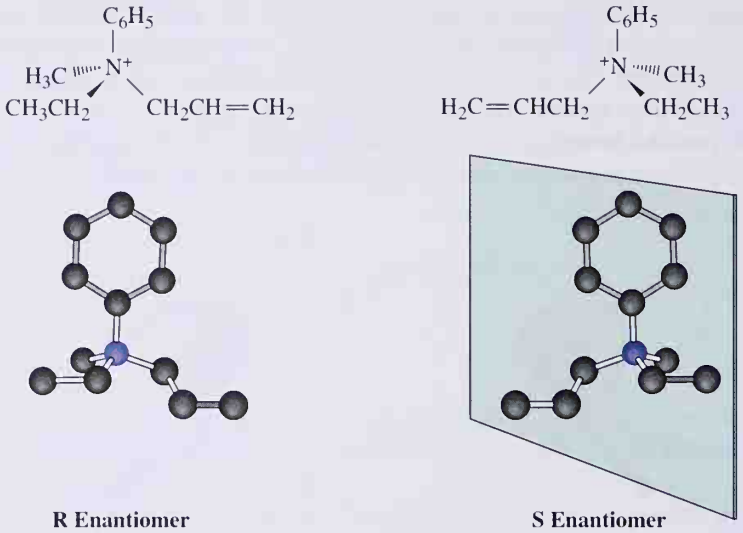
(S)-Ethylmethylamine **(R)-Ethylmethylamine**

To visualize this process, imagine the sp^3-hybridized nitrogen atom lying above the plane of the three atoms to which it is bonded. In the transition state for pyramidal inversion, the nitrogen atom and the three groups to which it is bonded become planar and achiral. In this planar transition state, nitrogen is sp^2-hybridized, and its lone pair of electrons lies in an unhybridized $2p$ orbital. Nitrogen then completes the inversion, becomes sp^3-hybridized and now lies below the plane of the three atoms to which it is bonded. As a result of pyramidal inversion, a chiral amine quite literally turns itself inside out and in the process becomes a racemic mixture. The energy of activation for pyramidal inversion is about 6 kcal/mol, and for ammonia at room temperature, the rate of nitrogen inversion is approximately 2×10^{11}/s. For simple amines and amides, the rate of inversion is less rapid but nonetheless sufficient, so it is not possible to resolve them.



S Enantiomer **Planar transition state** **R Enantiomer**

Pyramidal inversion is not possible for quaternary ammonium ions, and their salts can be resolved.



R Enantiomer S Enantiomer

Phosphorus, in the same family as nitrogen, also forms trivalent compounds with trigonal pyramidal geometry. The energy of activation for pyramidal inversion of trivalent phosphorus compounds is considerably greater than it is for trivalent compounds of nitrogen, with the result that a number of chiral phosphines have been prepared and resolved.

22.4 Physical Properties

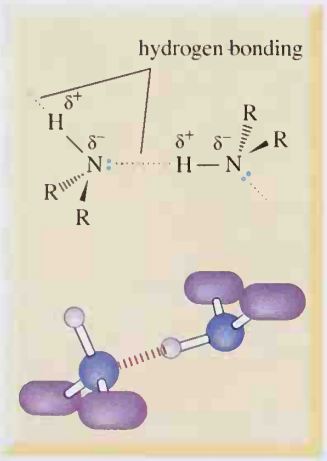


Figure 22.1
Intermolecular association by hydrogen bonding in primary and secondary amines. Nitrogen is approximately tetrahedral in shape with the axis of the hydrogen bond along the fourth position of the tetrahedron.

Amines are polar compounds, and both primary and secondary amines form intermolecular hydrogen bonds (Figure 22.1). An N—H···N hydrogen bond is not as strong as an O—H···O hydrogen bond because the difference in electronegativity between nitrogen and hydrogen (3.0 − 2.1 = 0.9) is not as great as that between oxygen and hydrogen (3.5 − 2.1 = 1.4). The effect of intermolecular hydrogen bonding can be illustrated by comparing the boiling points of ethane, methylamine, and methanol—all compounds of comparable molecular weight. Ethane is a nonpolar hydrocarbon, and the only interaction between its molecules in the pure liquid are very weak dispersion forces. Therefore, it has the lowest boiling point of the three. Both methanol and methylamine are polar molecules and interact in the pure liquid by hydrogen bonding. Hydrogen bonding is stronger in methanol than in methylamine, and, therefore, methanol has the highest boiling point.

	CH_3CH_3	CH_3NH_2	CH_3OH
MW (g/mol)	30.1	31.1	32.0
bp (°C)	−88.6	−6.3	65.0

All classes of amines form hydrogen bonds with water and are more soluble in water than are hydrocarbons of comparable molecular weight. Most low-molecular-weight amines are completely soluble in water (Table 22.1). Higher molecular-weight amines are only moderately soluble or insoluble.

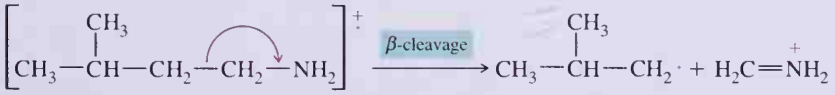
Table 22.1 Physical properties of selected amines

Name	Structural Formula	mp (°C)	bp (°C)	Solubility (g/100 g H_2O)
Ammonia	NH_3	−78	−33	very soluble
Primary Amines				
methylamine	CH_3NH_2	−95	−6	very soluble
ethylamine	$CH_3CH_2NH_2$	−81	17	very soluble
propylamine	$CH_3CH_2CH_2NH_2$	−83	48	very soluble
isopropylamine	$(CH_3)_2CHNH_2$	−95	32	very soluble
butylamine	$CH_3(CH_2)_3NH_2$	−49	78	very soluble
benzylamine	$C_6H_5CH_2NH_2$	—	185	very soluble
cyclohexylamine	$C_6H_{11}NH_2$	−17	135	slightly soluble
Secondary Amines				
dimethylamine	$(CH_3)_2NH$	−93	7	very soluble
diethylamine	$(CH_3CH_2)_2NH$	−48	56	very soluble
Tertiary Amines				
trimethylamine	$(CH_3)_3N$	−117	3	very soluble
triethylamine	$(CH_3CH_2)_3N$	−114	89	slightly soluble
Aromatic Amines				
aniline	$C_6H_5NH_2$	−6	184	slightly soluble
Heterocyclic Aromatic Amines				
pyridine	C_5H_5N	−42	116	very soluble

22.5 Spectroscopic Properties

A. Mass Spectrometry

Of the compounds containing C, H, N, O, and the halogens, only those containing an odd number of nitrogen atoms have an odd mass number. Thus, mass spectrometry can be a particularly valuable tool for identifying amines. The molecular ion for aliphatic amines is often very weak. The most characteristic fragmentation of amines and the one often giving rise to the base peak is β-cleavage. Where alternative possibilities exist for β-cleavage, it is generally the largest R group that is lost. The most prominent peak by far in the mass spectrum of 1-amino-3-methylbutane (Figure 22.2) is $[H_2C{=}NH_2]^+$, *m/e* 30, resulting from β-cleavage. β-Cleavage is also characteristic of secondary and tertiary amines.



(*m/e* 30)

B. Nuclear Magnetic Resonance Spectroscopy

The chemical shifts of amine hydrogens, like those of alcohol hydrogens (Section 13.14B), are variable and may be found in the region δ 0.6 to δ 3.0, depending on the solvent, the concentration, and the temperature. Furthermore, the rate of intermolecular exchange of

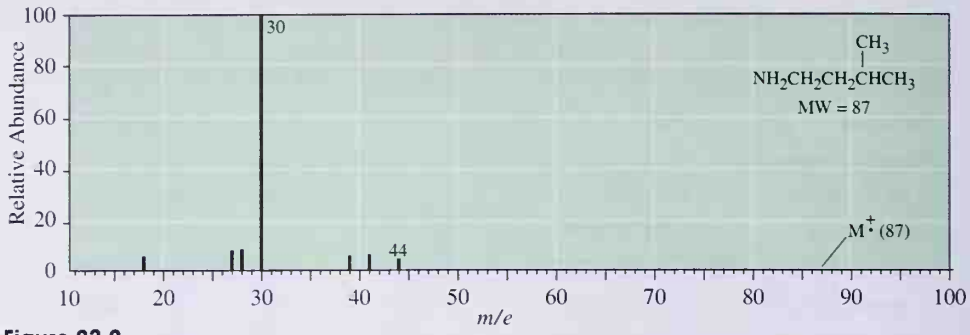


Figure 22.2
Mass spectrum of 1-amino-3-methylbutane (isopentylamine). The most characteristic fragmentation pattern of aliphatic amines is β-cleavage.

amine hydrogens is sufficiently rapid compared with the time scale of an NMR measurement that spin-spin splitting between amine hydrogens and hydrogens on an adjacent α-carbon is prevented. Thus, amine hydrogens generally appear as singlets, as can be seen in the ^{1}H-NMR spectrum of 1-phenylethylamine (Figure 22.3) and of butylamine (Figure 22.4). The NH_2 hydrogens in butylamine and 1-phenylethylamine appear as broad singlets at δ 1.11 and δ 1.44, respectively. Hydrogens on an α-carbon to a nitrogen atom are deshielded by the electronegative nitrogen atom and absorb in the region δ 2.2 to 2.8. Hydrogens on the α-carbon in butylamine, for example, appear at δ 2.70.

Carbons bonded to nitrogen are deshielded by approximately 20 ppm in the ^{13}C-NMR spectrum relative to where they would be in resonance in an alkane of comparable structure. Compare, for example, the chemical shift of carbon 1 in butylamine (42.0 ppm) with that of carbon 2 in butane (25.0 ppm). The chemical shift of carbons adjacent to oxygen is in turn approximately 20 ppm greater than for carbons adjacent to nitrogen. Compare, for example, the chemical shift of carbon 1 in butylamine (42.0 ppm) with that of carbon 1 in 1-butanol (62.4 ppm).

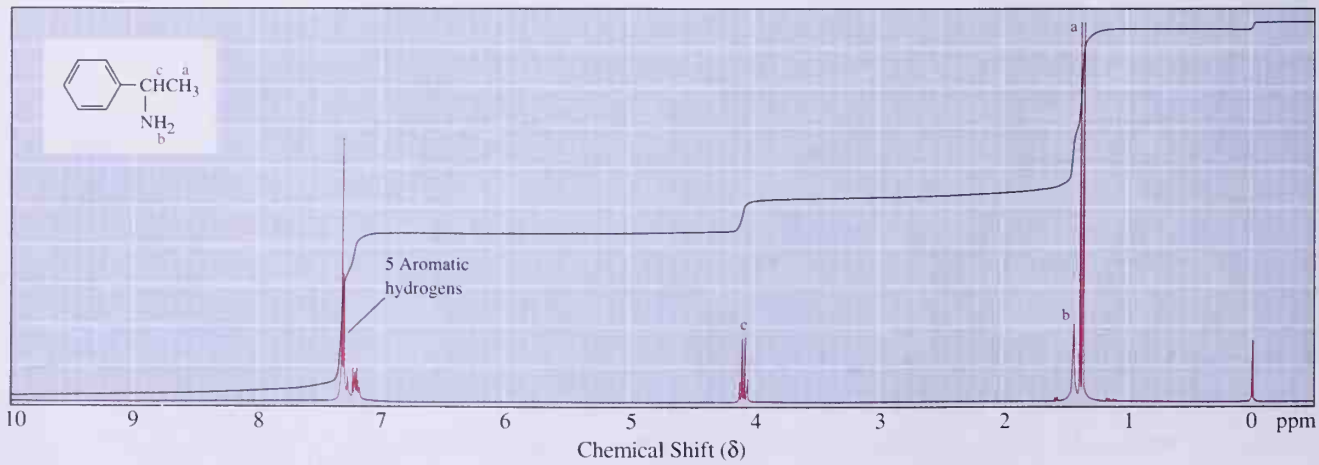


Figure 22.3
^{1}H-NMR spectrum of 1-phenylethylamine.

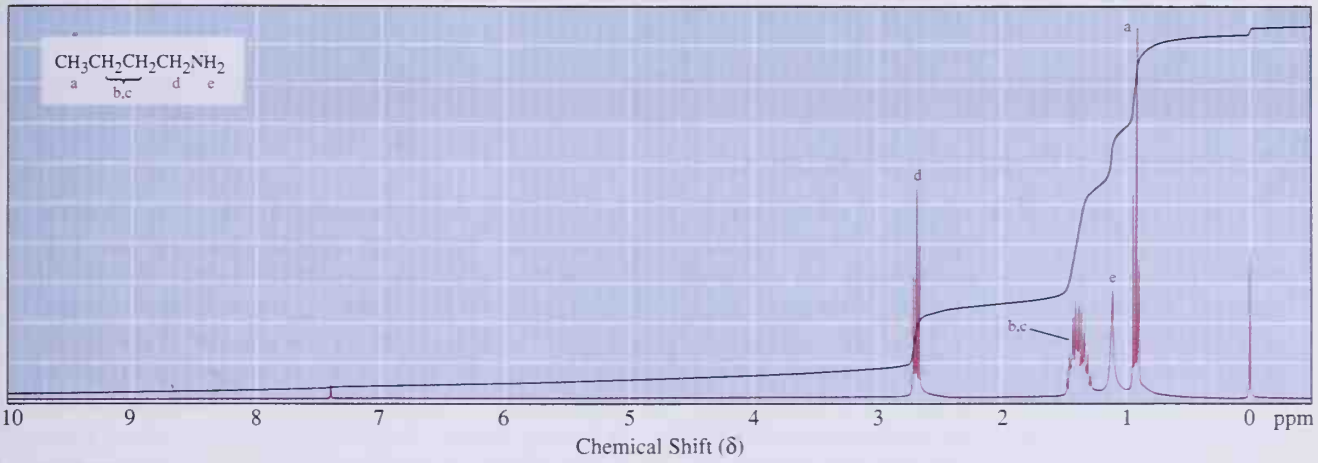


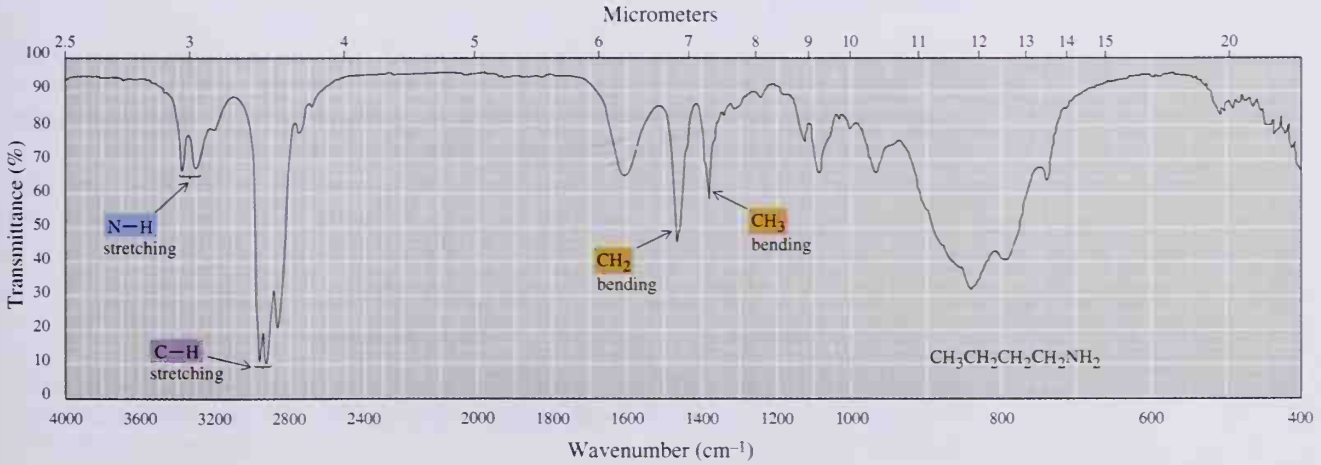
Figure 22.4
^{1}H-NMR spectrum of butylamine.

Formula	Carbon atom 1	2	3	4
$CH_3CH_2CH_2CH_2OH$	62.4	34.9	19.0	13.9
$CH_3CH_2CH_2CH_2NH_2$	42.0	36.1	20.2	13.9
$CH_3CH_2CH_2CH_3$	13.2	25.0	25.0	13.2

C. Infrared Spectroscopy

The most important and readily observed infrared absorptions of primary and secondary amines are due to N—H stretching vibrations, and appear in the region of 3100 to 3500 cm^{-1}. Primary amines have two bands in this region: one due to a symmetric stretching, the other due to an asymmetric stretching. The two N—H stretching absorptions characteristic of a primary amine can be seen in the IR spectrum of butylamine (Figure 22.5). Secondary amines give only one absorption in this region. Tertiary amines have no N—H and, therefore, are transparent in this region of the infrared spectrum.

Figure 22.5
Infrared spectrum of butylamine, a primary amine.



CHEMISTRY IN ACTION

The Poison Dart Frogs of South America

The Noanamá and Embrá peoples of the jungles of western Colombia have used poison blow darts for centuries, perhaps millennia. The poisons are obtained from the skin secretions of several highly colored frogs of the genus *Phyllobates* (*neará* and *kokoi* in the language of the natives). A single frog contains enough poison for up to 20 darts. For the most poisonous species *(Phyllobates terribilis)* just rubbing a dart over the frog's back suffices to charge the dart with poison.

Poison dart frog, *Phyllobates terribilis.* *(Animals, Animals © Juan M. Renjifo)*

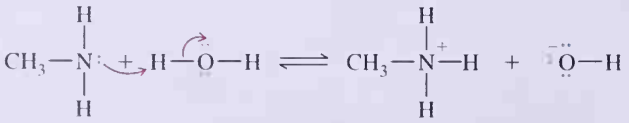
Scientists at the National Institutes of Health in the United States became interested in studying these poisons when it was discovered that they act on cellular ion channels, which would make them useful tools in basic research on mechanisms of ion transport. Establishing the structure of these frog poisons proved to be extremely difficult because a single frog makes only a tiny amount of poison. The problem was exacerbated when it was discovered that frogs raised in captivity produce almost none of the poison, compared with frogs caught in the wild.

A field station was, therefore, established in western Colombia to collect the relatively common poison dart frogs. From 5000 frogs, 11 mg of two toxins, given the names batrachotoxin and batrachotoxinin A, was isolated. These names are derived from *batrachos*, the Greek word for frog. A combination of NMR spectroscopy, mass spectrometry, and single-crystal x-ray diffraction was used to determine the structures of these compounds.

Batrachotoxin and batrachotoxinin A are among the most lethal poisons ever discovered. It is estimated that as little as 200 μg of batrachotoxin is sufficient to induce irreversible cardiac arrest in a human being. It has been determined that they act by causing voltage-gated Na^+ channels in nerve and muscle cells to be blocked in the open position, which leads to a huge influx of Na^+ ions into the affected cell. It is not sur-

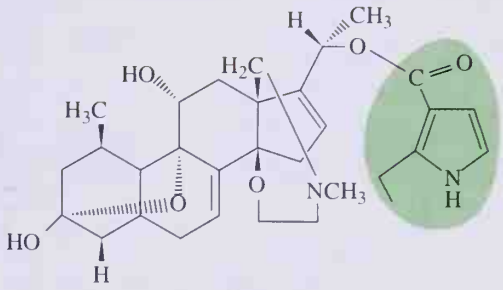
22.6 Basicity

Like ammonia, all amines are weak bases, and aqueous solutions of amines are basic. The following acid-base reaction between an amine and water is written using curved arrows to emphasize that in these proton transfer reactions, the unshared pair of electrons on nitrogen forms a new covalent bond with hydrogen and displaces hydroxide ion.

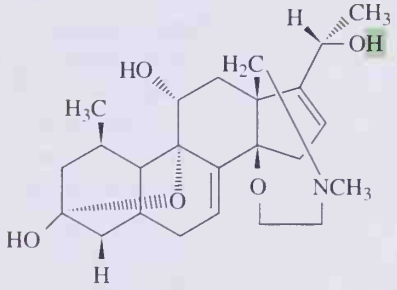


Methylamine Methylammonium Hydroxide

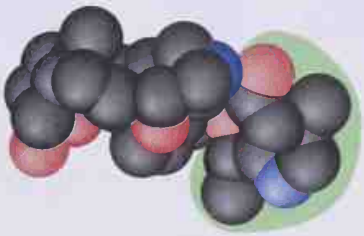
The equilibrium constant for the reaction of an amine with water has the following form, illustrated for the reaction of methylamine with water to give methylammonium hydroxide:



Batrachotoxin



Batrachotoxinin A



prising that many amines act on Na^+ or K^+ channels because amines are protonated at physiological pH, giving them the same charge (but a vastly different size) as Na^+ or K^+.

The batrachotoxin story illustrates several common themes in drug discovery. First, information about the kinds of biologically active compounds and their sources is available from the native peoples of a region. Second, tropical rain forests are a rich source of structurally complex, biologically active substances. Third, the entire ecosystem, not only the plants, are potential sources of fascinating organic molecules.

See J. W. Daly, *Progress in the Chemistry of Organic Natural Products*, volume 41, W. Herz, H. Grisebach, and G. W. Kirby, eds. (Springer Verlag, Wien 1982), p. 205.

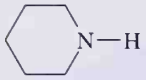
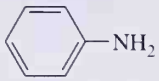
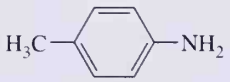
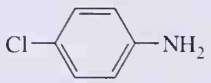
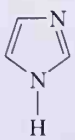
$$K_{eq} = \frac{[CH_3NH_3^+][OH^-]}{[CH_3NH_2][H_2O]}$$

Because the concentration of water in pure water and in a dilute solution of methylamine in water is essentially a constant ($[H_2O] = 55.5$ mol/L), it is collected along with K_{eq} in a new constant called a base ionization constant, given the symbol K_b. The value of K_b for methylamine is 4.4×10^{-4} ($pK_b = 3.36$).

$$K_b = K_{eq}[H_2O] = \frac{[CH_3NH_3^+][OH^-]}{[CH_3NH_2]} = 4.4 \times 10^{-4}$$

It is also common to discuss the basicity of amines by reference to the acid ionization constant of the corresponding conjugate acid, as illustrated for the ionization of methylammonium ion.

Table 22.2 Base strengths of selected amines and acid strengths of their conjugate acids. For each amine, $pK_a + pK_b = 14.00$

Amine	Structure	pK_b	pK_a
Ammonia	NH_3	4.74	9.26
Primary Amines			
methylamine	CH_3NH_2	3.36	10.64
ethylamine	$CH_3CH_2NH_2$	3.19	10.81
isopropylamine	$(CH_3)_2CHNH_2$	3.18	10.82
tert-butylamine	$(CH_3)_3CNH_2$	3.17	10.83
cyclohexylamine	$C_6H_{11}NH_2$	3.34	10.66
Secondary Amines			
dimethylamine	$(CH_3)_2NH$	3.27	10.73
diethylamine	$(CH_3CH_2)_2NH$	3.02	10.98
piperidine		3.25	10.75
Tertiary Amines			
trimethylamine	$(CH_3)_3N$	4.19	9.81
triethylamine	$(CH_3CH_2)_3N$	3.25	10.75
Aromatic Amines			
aniline		9.37	4.63
4-methylaniline		8.92	5.08
4-chloroaniline		9.85	4.15
4-nitroaniline		13.0	1.0
Heterocyclic Aromatic Amines			
pyridine		8.75	5.25
imidazole		7.05	6.95

$$CH_3NH_3^+ \rightleftharpoons CH_3NH_2 + H^+$$

$$K_a = \frac{[CH_3NH_2][H^+]}{[CH_3NH_3^+]} = 2.3 \times 10^{-11}$$

$$pK_a = 10.64$$

Values for pK_a and pK_b for any conjugate acid-base pair are related by the following equation:

$$pK_a + pK_b = 14.00$$

By using values of pK_a, we can compare acidities of conjugate acids of amines with other acids. It is this approach we developed in Chapter 3 to predict the position of equilibrium in acid-base reactions. Equilibrium favors formation of the weaker acid and weaker base, as illustrated by reactions of methylamine with water and with acetic acid.

$$CH_3NH_2 + H_2O \rightleftharpoons CH_3NH_3^+ + OH^- \qquad K_{eq} = 8.7 \times 10^{-6}$$

(pK_a 15.7) (pK_a 10.64)

Weaker base | Weaker acid | Stronger acid | Stronger base

$$CH_3NH_2 + CH_3CO_2H \rightleftharpoons CH_3NH_3^+ + CH_3CO_2^- \qquad K_{eq} = 7.6 \times 10^5$$

(pK_a 4.76) (pK_a 10.64)

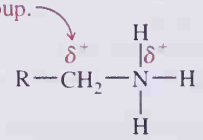
Stronger base | Stronger acid | Weaker acid | Weaker base

Values of pK_a and pK_b for selected aliphatic amines, aromatic amines, heterocyclic aliphatic amines, and heterocyclic aromatic amines are given in Table 22.2. Given information such as that in Table 22.2, we can make the following generalizations about the acid-base properties of the various classes of amines.

Aliphatic amines are slightly stronger bases than ammonia.

This increase in basicity compared to ammonia can be attributed to the electron-releasing effect of alkyl groups and the resulting partial dispersion of the positive charge from nitrogen onto carbon in an alkylammonium ion.

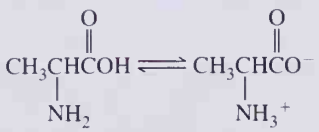
Positive charge is partially delocalized onto the alkyl group.



Recall that we invoked a similar argument in Section 5.3D to account for the effect of alkyl groups in stabilizing carbocations.

EXAMPLE 22.2

Following are two structural formulas for alanine (2-aminopropanoic acid), one of the building blocks of proteins (Chapter 24). Is alanine better represented by structural formula (A) or structural formula (B)? Explain.



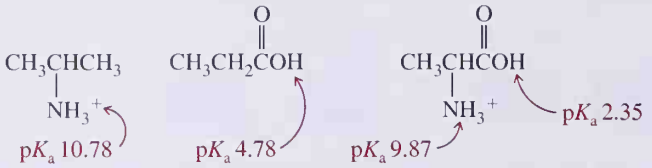
(A) (B)

Solution

Structural formula (A) contains both an amine (a base) and a carboxylic acid (an acid). Proton transfer from the stronger acid ($—CO_2H$) to the stronger base ($—NH_2$) gives an internal salt, and, therefore, (B) is the better representation for alanine. Within the field of amino acid and protein chemistry, the internal salt represented by (B) is called a **zwitterion.**

PROBLEM 22.2

Following are structural formulas for propanoic acid, and the conjugate acids of isopropylamine and alanine, along with pK_a for each functional group:

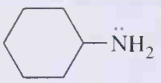
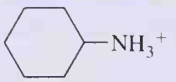
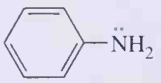
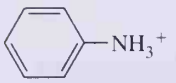


(a) How do you account for the fact that the $—NH_3^+$ group of alanine is a stronger acid than the $—NH_3^+$ group of the conjugate acid of isopropylamine, a typical primary aliphatic amine?

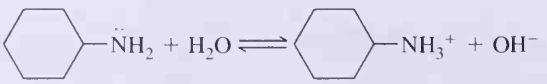
(b) How do you account for the fact that the $—CO_2H$ group of the conjugate acid of alanine is a stronger acid than the $—CO_2H$ group of propanoic acid, a typical aliphatic carboxylic acid?

Aromatic amines are considerably weaker bases than aliphatic amines.

Compare, for example, values of pK_b for aniline and cyclohexylamine. The base ionization constant for aniline is smaller (the larger the value of pK_b, the weaker the base) than that for cyclohexylamine by a factor of 10^6. Alternatively, the conjugate acids of aromatic amines are considerably stronger acids than the conjugate acids of aliphatic amines. Compare, for example values of pK_a for the anilinium ion and the cyclohexylammonium ion.

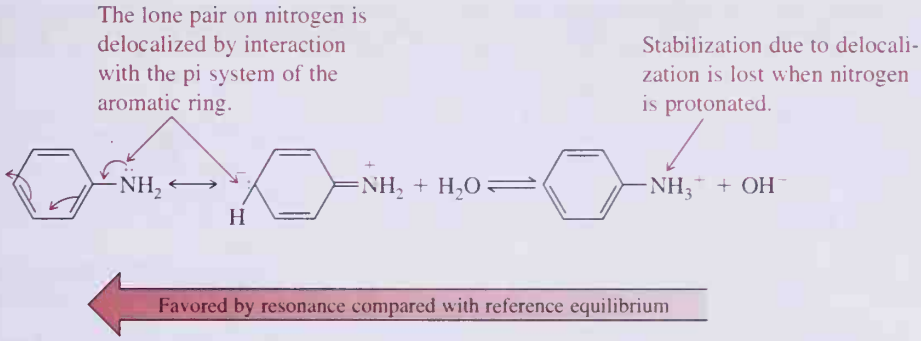
Name	Base	pK_b	Conjugate Acid	pK_a
Cyclohexylamine		3.34		10.66
Aniline		9.37		4.63

To account for the reduced basicity of aromatic amines compared with aliphatic amines, we use the guideline: The more stable the products are compared with the reactants, the farther the position of the equilibrium is shifted toward the right. Take a primary aliphatic amine as a reference standard. There is no resonance stabilization in either the amine or the ammonium ion.



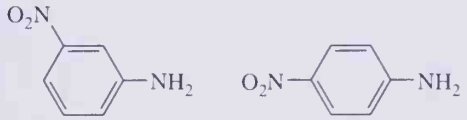
(Reference equilibrium)

For aniline or other aromatic amines, the aromatic ring is equally resonance-stabilized in both the free base and the protonated form. Additional stabilization occurs in the free base due to delocalization of the lone pair on nitrogen by interaction with the pi system of the aromatic ring. This lone-pair stabilization is lost by proton transfer to nitrogen. The resonance energy of benzene is approximately 36 kcal/mol. For aniline, it is 39 kcal/mol.



Thus, the unprotonated aromatic amine has a greater degree of resonance stabilization (electron delocalization), and the position of this equilibrium is shifted to the left compared with the reference equilibrium, thereby accounting for the fact that an aromatic amine is a weaker base than a similarly substituted aliphatic amine.

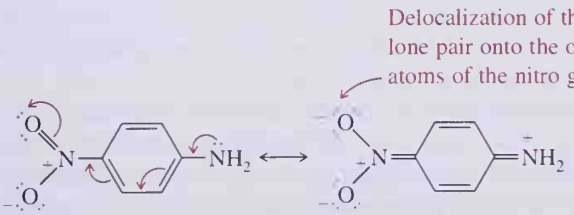
Electron-releasing groups (e.g., methyl, ethyl, and other alkyl groups) increase the basicity of aromatic amines, whereas electron-withdrawing groups (halogen, nitro, carbonyl) decrease their basicity. Decrease in basicity by halogen substitution is due to the electron-withdrawing inductive effect of the electronegative halogen. Decrease in basicity due to the presence of $-NO_2$ on the aromatic ring is due to a combination of inductive and resonance effects as can be seen by comparing the base ionization constants of 3-nitroaniline and 4-nitroaniline.



3-Nitroaniline (pK_b 11.5)

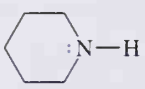
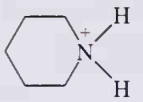
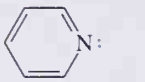
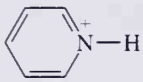
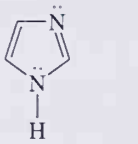
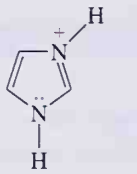
4-Nitroaniline (pK_b 13.0)

The base-decreasing effect of nitro substitution in the 3 position is due almost entirely to its inductive effect, whereas nitro substitution in the 4 position is due to both inductive and resonance effects. In the case of para substitution (and ortho substitution as well), delocalization of the lone pair on the amino nitrogen involves not only the carbons of the aromatic ring but also oxygen atoms of the nitro group.

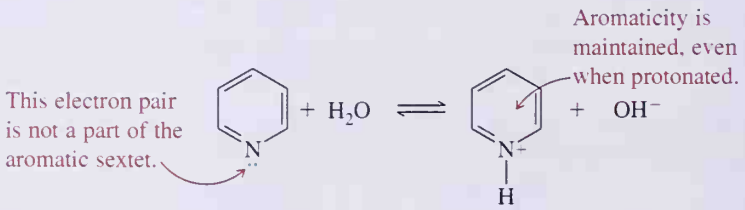


Heterocyclic aromatic amines are considerably weaker bases than heterocyclic aliphatic amines.

Compare, for example, pK_b values for piperidine, pyridine, and imidazole. Or, alternatively, compare pK_a values for the conjugate acid of each.

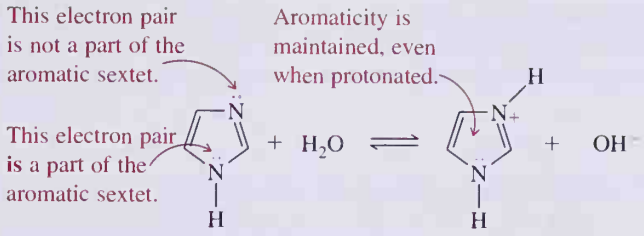
Name	Base	pK_b	Conjugate Acid	pK_a
Piperidine		3.25		10.75
Pyridine		8.75		5.25
Imidazole		7.05		6.95

In accounting for the relative basicities of these and other heterocyclic aromatic amines, it is important to determine first if the unshared pair of electrons on nitrogen is or is not a part of the $(4n + 2)$ pi electrons giving rise to aromaticity. In the case of pyridine, the unshared pair of electrons is not a part of the aromatic sextet. Rather it lies in an sp^2 hybrid orbital in the plane of the ring and perpendicular to the six $2p$ orbitals giving rise to the aromatic character of the ring (Section 15.2D).



Proton transfer from water or other acid to pyridine does not involve any change in the number of electrons giving rise to the aromaticity of the ring. Why, then, is pyridine a considerably weaker base than aliphatic amines? The answer is that the unshared pair of electrons on the pyridine nitrogen lies in an sp^2 hybrid orbital, whereas in aliphatic amines, the unshared pair lies in an sp^3 hybrid orbital. Because of the greater percent s character of an sp^2 hybrid orbital, electrons in it are held more tightly to the nucleus, thus decreasing their availability for sharing. It is this effect that decreases markedly the basicity of the electron pair bonded to an sp^2-hybridized nitrogen.

There are two nitrogen atoms in imidazole, each with an unshared pair of electrons. One unshared pair lies in a $2p$ orbital and is an integral part of the $(4n + 2)$ pi electrons of the aromatic system. The other unshared pair lies in an sp^2 hybrid orbital and is not a part of the aromatic sextet. It is the pair of electrons not a part of the pi system that functions as the proton acceptor.

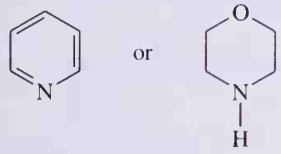


Imidazole Imidazolium ion

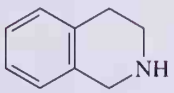
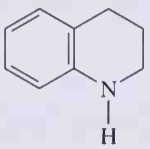
As with pyridine, the unshared pair of electrons functioning as the proton acceptor in imidazole also lies in an sp^2 hybrid orbital and has markedly decreased basicity compared with an unshared pair of electrons in an sp^3 hybrid orbital.

EXAMPLE 22.3

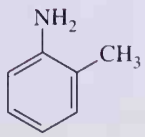
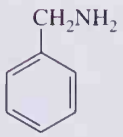
Select the stronger base in each pair of amines.

(a)  or

(A) (B)

(b)  or 

(C) (D)

(c)  or 

(E) (F)

Solution

(a) Morpholine (B) is the stronger base (pK_b 5.79, pK_a 8.21). It has a basicity comparable to that of secondary aliphatic amines. Pyridine (A), a heterocyclic aromatic amine (pK_b 8.75, pK_a 5.25), is considerably less basic than aliphatic amines.

(b) Tetrahydroisoquinoline (C) has a basicity comparable to that of secondary aliphatic amines ($pK_b \approx 3.3$, $pK_a \approx 10.7$) and is the stronger base. Tetrahydroquinoline (D) has a basicity comparable to an *N*-substituted aniline $pK_b \approx 9.4$, $pK_a \approx 4.6$) and is the weaker base.

(c) Benzylamine (F) is the stronger base (pK_b 4.37, pK_a 9.73). Its basicity is comparable to that of other aliphatic amines. The basicity of *o*-toluidine (E), an aromatic amine, is comparable to that of aniline (pK_b 9.37, pK_a 4.63).

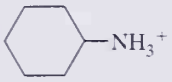
Guano deposits on Galapagos Islands. Guanidine is the compound by which migratory birds excrete waste metabolic nitrogen. *(Animals, Animals © B. G. Murray, Jr.)*

PROBLEM 22.3

Select the stronger acid from each pair of compounds.

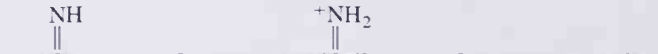
(a) O_2N–C$_6$H$_4$–NH_3^+ or H_3C–C$_6$H$_4$–NH_3^+

(A) (B)

(b)  or 

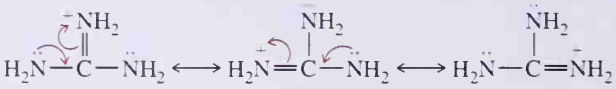
(C) (D)

Guanidine, pK_b 0.4, is the strongest base of any neutral compound. Alternatively, its conjugate acid is a weaker acid (pK_a 13.6) than almost any other protonated amine.



Guanidine Guanidinium ion

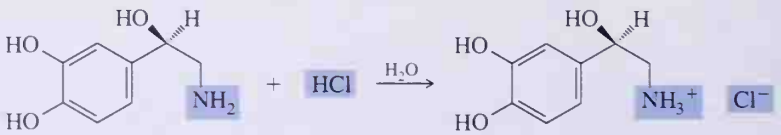
The remarkable basicity of guanidine is attributed to the very large resonance stabilization of the protonated base for which three equivalent contributing structures can be drawn.



Three equivalent contributing structures

Two drugs that are amine salts. *(Charles D. Winters)*

All amines, whether soluble or insoluble in water, react quantitatively with strong acids to form water-soluble salts as illustrated by the reaction of norepinephrine (noradrenaline) with aqueous HCl to form a hydrochloride salt.



(R)-(−)-Norepinephrine (only slightly soluble in water)

(R)-(−)-Norepinephrine hydrochloride (a water-soluble salt)

Norepinephrine, secreted by the medulla of the adrenal gland, is a neurotransmitter. It has been suggested that it is a neurotransmitter in those areas of the brain that mediate emotional behavior.

The basicity of amines and the solubility of amine salts in water can be used to separate amines from water-insoluble, nonbasic compounds. Shown in Figure 22.6 is a flowchart for the separation of aniline from its acetylation product, acetanilide.

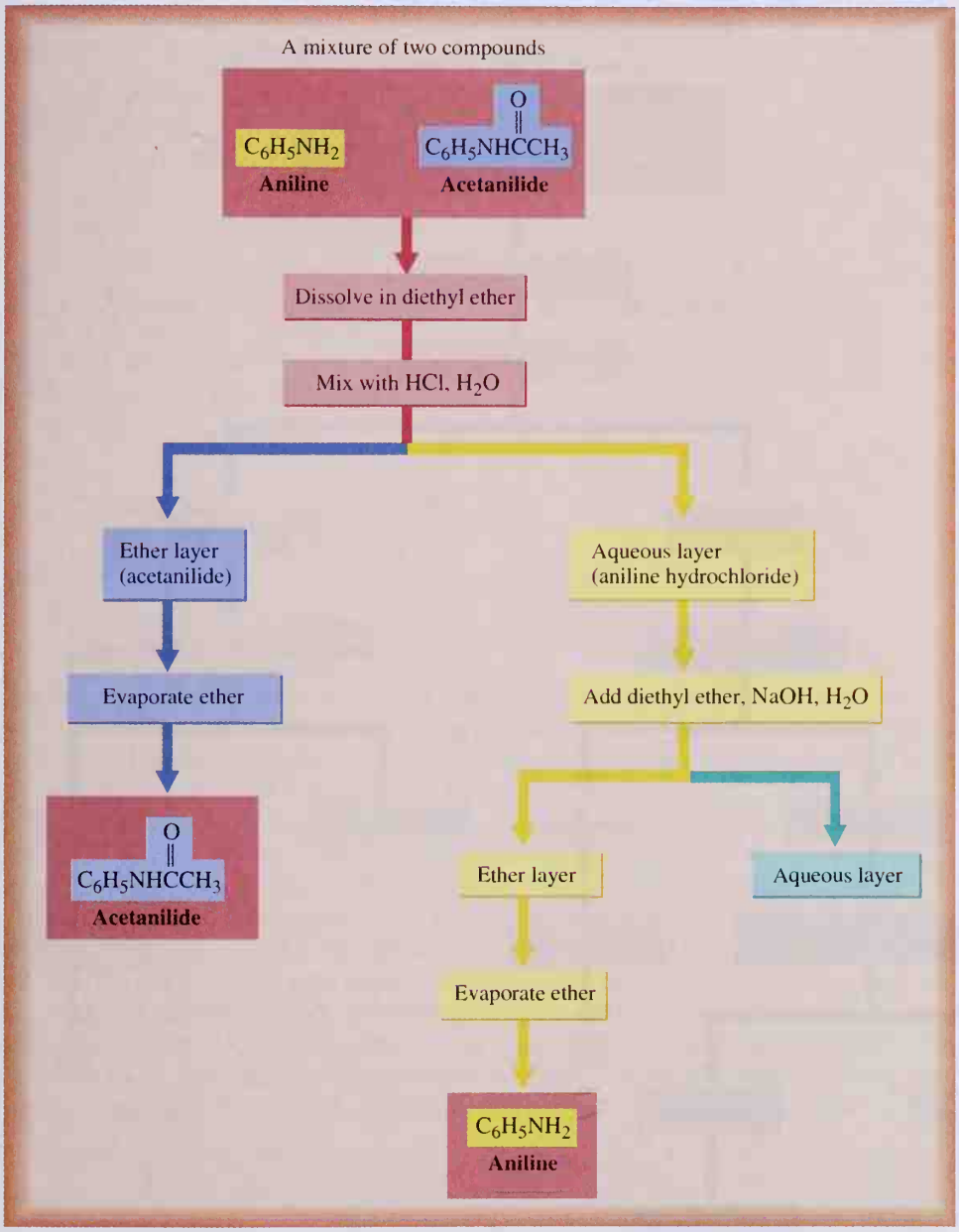
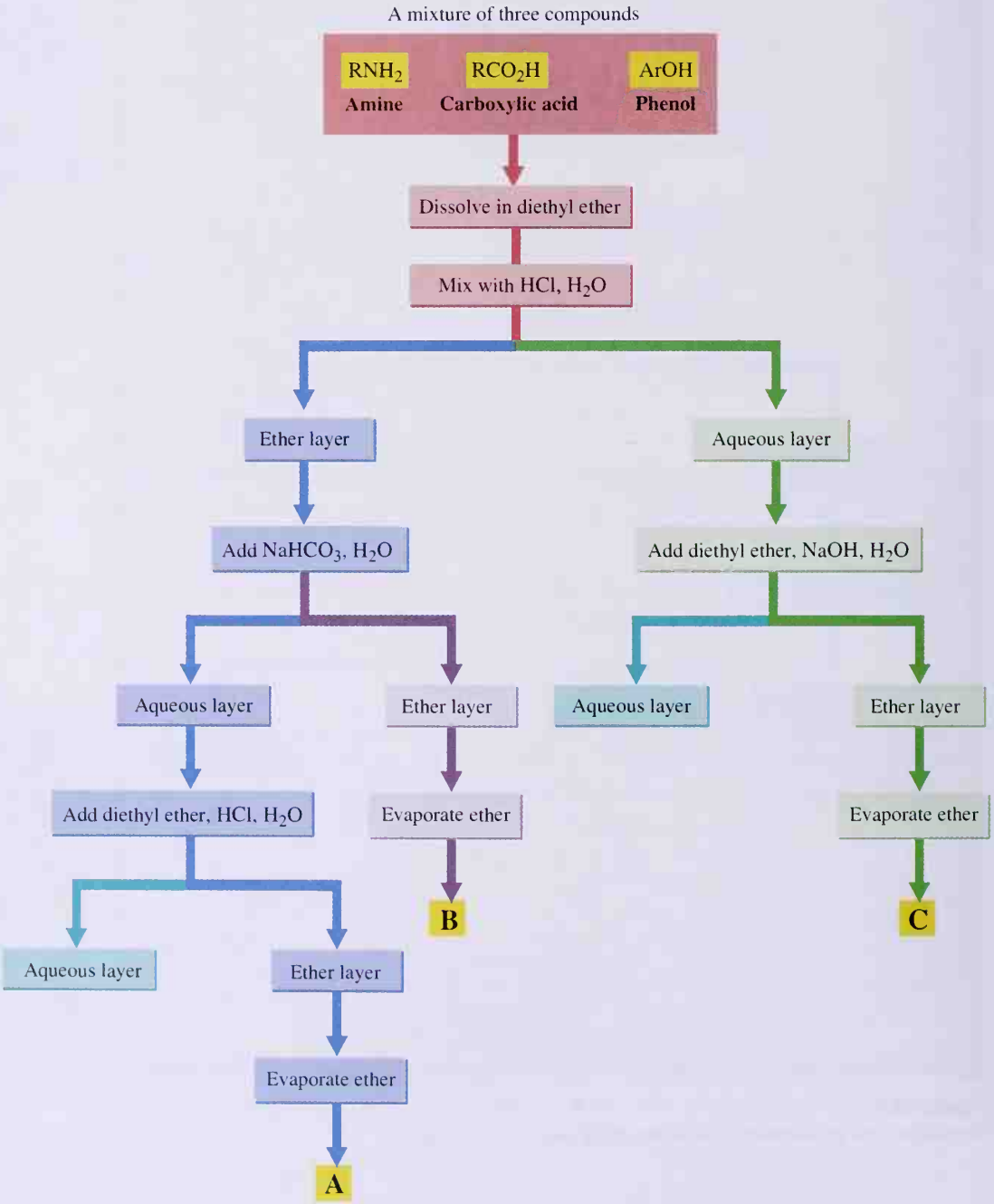


Figure 22.6
Separation and purification of an amine and a neutral compound.

EXAMPLE 22.4

Following is a flowchart for the separation of a water-insoluble mixture of a primary aliphatic amine (RNH_2, pK_a 10.8), a carboxylic acid (RCO_2H, pK_a 5), and a phenol (ArOH, pK_a 10). The mixture is separated into fractions A, B, and C. Which fraction contains the amine, which the carboxylic acid, and which the phenol?



Solution

Fraction C is RNH_2, fraction B is ArOH, and fraction A is RCO_2H.

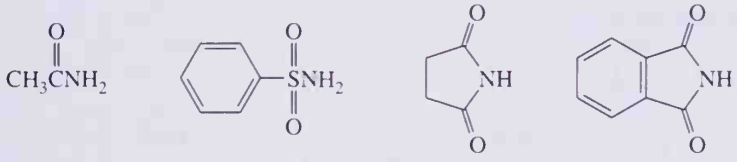
PROBLEM 22.4

In what way(s) might the results of the separation and purification procedure outlined in Example 22.4 be different if

(a) Aqueous Na_2CO_3 is used in place of aqueous $NaHCO_3$?
(b) The starting mixture contains an aromatic amine, $ArNH_2$, rather than an aliphatic amine, RNH_2?

22.7 Acidity of Amides, Imides, and Sulfonamides

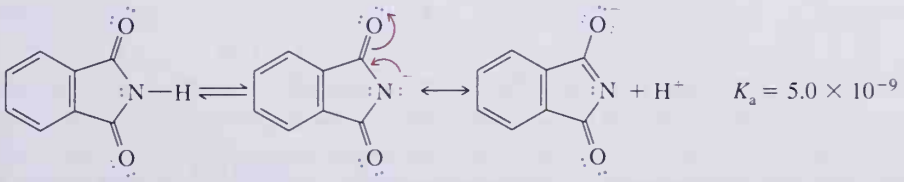
Following are structural formulas for a primary amide, a sulfonamide, and two cyclic imides, along with pK_a values for each.



Acetamide (pK_a 15–17) | Benzenesulfonamide (pK_a 10) | Succinimide (pK_a 9.7) | Phthalimide (pK_a 8.3)

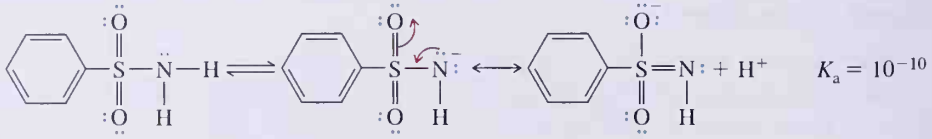
Amides of carboxylic acids show no evidence of acidity in aqueous solution, that is, water-insoluble amides do not react with aqueous solutions of NaOH or other alkali metal hydroxides to form water-soluble salts. Values of pK_a for amides are in the range of 15 to 17, which means they are comparable in acidity to alcohols.

Imides are considerably more acidic than amides and readily dissolve in 5% aqueous NaOH by forming water-soluble salts. Phthalimide, a cyclic amide used in the Gabriel synthesis of amines and amino acids (Section 22.9D), has a pK_a of 8.3. The pK_a of succinimide is 9.7. Both of these cyclic imides are slightly stronger acids than phenol (pK_a 9.98, Section 15.5B) but considerably weaker acids than carboxylic acids (pK_a 4–5, Section 19.7A). We can account for the acidity of imides in the same manner as we accounted for the acidity of carboxylic acids in Section 19.7A, namely: (1) the electron-withdrawing inductive effect of the adjacent carbonyl groups and (2) the resonance stabilization of the resulting anion. The more important contributing structures for the anion formed by ionization of an imide delocalize the negative charge on the two carbonyl oxygens.



Phthalimide (A resonance-stabilized anion)

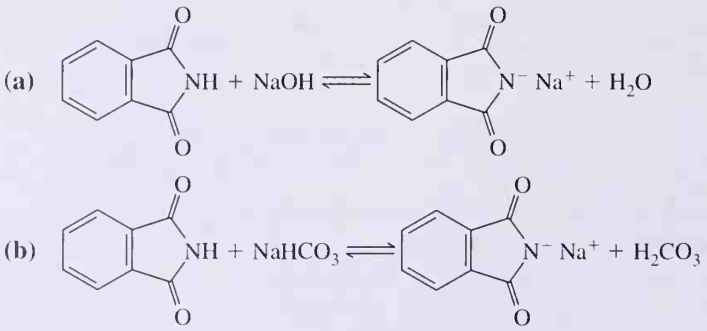
Sulfonamides derived from ammonia and from primary amines are also sufficiently acidic to dissolve in aqueous solutions of NaOH or other alkali metal hydroxides by forming water-soluble salts. The pK_a of benzenesulfonamide is approximately 10; it is comparable in acidity to phenol. We can account for the acidity of sulfonamides in the same manner as we did for imides, namely: (1) the electron-withdrawing inductive effect of the two adjacent S=O bonds and (2) the resonance stabilization of the resulting anion.



Benzenesulfonamide (A resonance-stabilized anion)

EXAMPLE 22.5

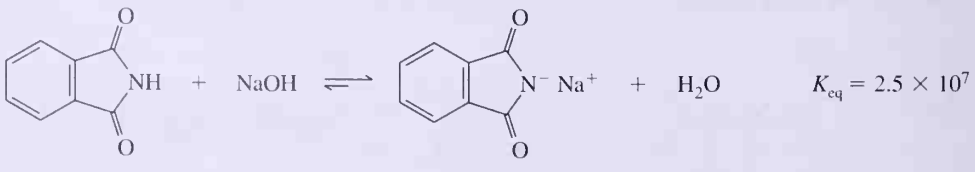
Following are equations for the reaction of phthalimide with aqueous sodium hydroxide and with aqueous sodium bicarbonate. Does phthalimide react with each of these bases to form a water-soluble salt? Stated alternatively, does phthalimide dissolve in aqueous NaOH? in aqueous $NaHCO_3$?



Solution

The pK_a of phthalimide is 8.3. From Table 3.2 (Section 3.3), find that for water, $pK_a = 15.7$ and for carbonic acid, $pK_a = 6.36$. Using these values, determine which species in each equilibrium is the stronger acid and stronger base, and calculate the equilibrium constant for each reaction.

(a) Phthalimide is the stronger acid, and NaOH is the stronger base. The position of equilibrium, therefore, lies to the right. $K_{eq} = 2.5 \times 10^7$. Phthalimide dissolves in aqueous NaOH by forming a water-soluble sodium salt.

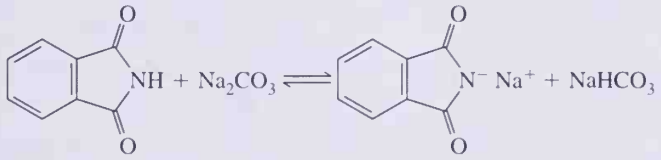


(pK_a 8.3) Stronger acid — Stronger base — Weaker base — (pK_a 15.7) Weaker acid

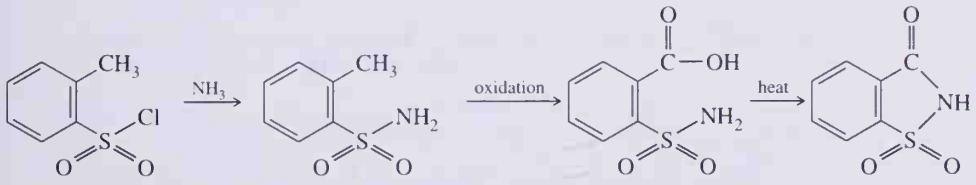
(b) Carbonic acid is the stronger acid, and the phthalimide anion is the stronger base. Equilibrium lies to the left. Phthalimide does not dissolve in aqueous sodium bicarbonate by forming a water-soluble salt.

PROBLEM 22.5

Does phthalimide dissolve in aqueous sodium carbonate by reacting according to the following equation to form a water-soluble salt? Explain.



The noncaloric artificial sweetener, saccharin, is an imide. The starting material for its synthesis is toluene. Treatment of toluene with chlorosulfonic acid (Section 20.14) gives a mixture of ortho- and para-substitution products. Separation of the ortho isomer followed by treatment with ammonia gives *o*-toluenesulfonamide. Next, the methyl group is oxidized by alkaline permanganate to give a carboxylic acid, which undergoes intramolecular dehydration on heating to give saccharin. The amide proton of saccharin is sufficiently acidic that it reacts with sodium hydroxide and aqueous ammonia to form water-soluble salts. The ammonium salt is used to make liquid sweeteners. Saccharin is used in solid form as the Ca^{2+} salt.



o-Toluenesulfonyl chloride — *o*-Toluenesulfonamide — Saccharin

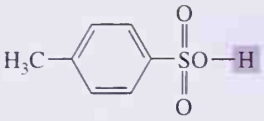
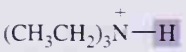
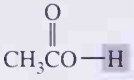
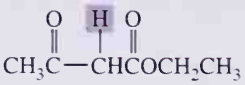
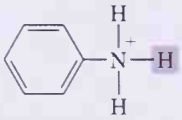
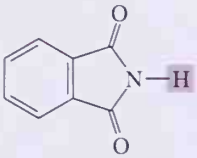
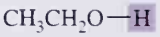
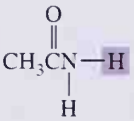
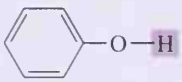
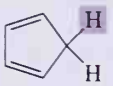
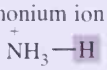
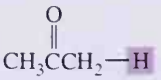
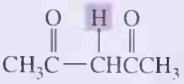
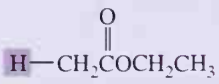
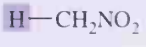
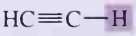
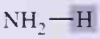
Saccharin is approximately 500 times sweeter than sugar, and at one time was the most important noncaloric sweetener used in foods. However, it has been found to cause cancer in laboratory test animals and for a time was banned by the Food and Drug Administration (FDA) for human consumption. At the present time, the most widely used noncaloric artificial sweetener is Nutrasweet (aspartame) (Chapter 24).

22.8 Summary of Acidity and Basicity of Organic Compounds

With the study of the basicity of amines and the acidity of amides, imides, and sulfonamides, we now have examples of all of the major classes of organic acids and bases with which we are concerned in this course. Values of pK_a for these classes of organic acids are collected in Table 22.3. You will find it helpful to review the discussion of the acidity of each entry in this table and to review the relationships between structure and acidity.

Table 22.3 Acid ionization constants for the major classes of organic acids

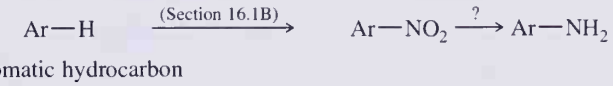
Increasing acid strength

Name and Example	Typical pK_a	Name and Example	Typical pK_a
sulfonic acid 	0–2	aliphatic ammonium ion 	10–12
carboxylic acid 	3–5	β-ketoester 	11
aromatic ammonium ion 	4–5	water 	15.7
imide 	8–9	alcohol 	15–19
thiol 	8–12	amide 	15–19
phenol 	9–10	cyclopentadiene 	16
ammonium ion 	9.24	aldehyde, ketone 	18–20
β-diketone 	10	ester 	23–25
nitroalkane 	10	alkyne 	25
		ammonia 	35
		amine 	40

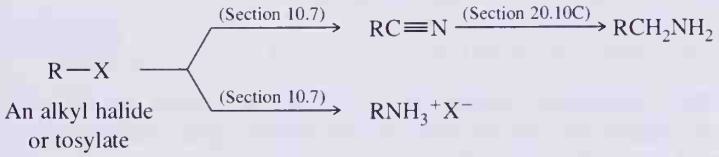
22.9 Preparation of Amines

The synthesis of amines is primarily a problem of how to form a carbon-nitrogen bond and, if the newly formed nitrogen-containing compound is not already an amine, how to convert it into an amine. In previous chapters we studied how to form a variety of nitrogen-containing functional groups, and in many cases we also studied how to convert these functional groups to amino groups. Following is a summary of these reaction sequences. Over each arrow is the section or sections in which the chemistry of the particular reaction was presented. A question mark over an arrow indicates that we have not yet seen how to bring about the indicated transformation. That chemistry is presented in this chapter.

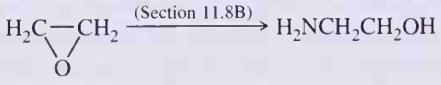
From aromatic hydrocarbons by nitration:



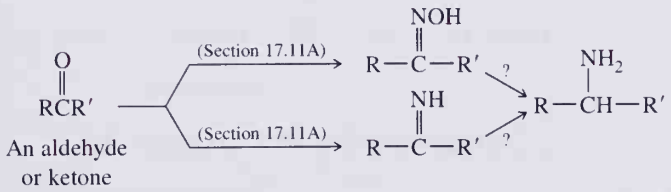
From alkyl halides or tosylates by nucleophilic substitution:



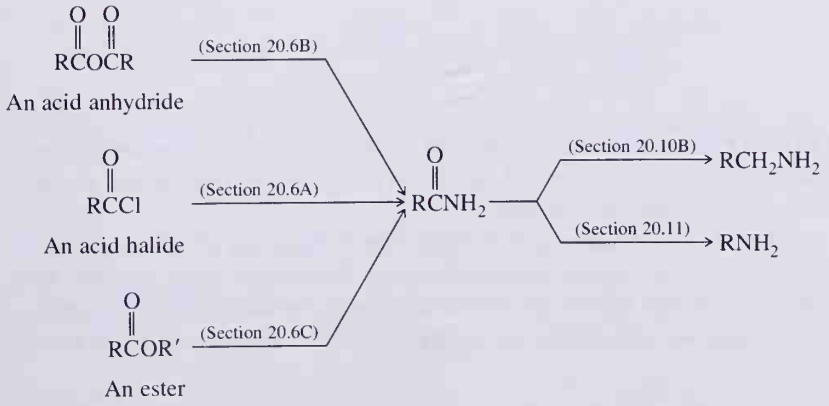
From epoxides by nucleophilic substitution and ring opening:



From aldehydes and ketones by nucleophilic addition to the carbonyl carbon followed by reduction:



From functional derivatives of carboxylic acids by nucleophilic acyl substitution followed by reduction:



In this section, we look at each of these reaction schemes in more detail. Realize as we do so, however, that you have already encountered the most important chemistry of each of these methods for the preparation of amines. The new reagents and experimental conditions that you encounter in this section are variations and extensions of familiar chemistry.

A. Alkylation of Ammonia and Amines

Surely one of the most direct synthetic routes to an amine seems to be treatment of an alkyl halide with ammonia or an amine. Reaction between these two compounds by a second-order nucleophilic substitution (S_N2) reaction gives an amine, as illustrated by treatment of bromomethane with ammonia to give methylammonium bromide.

$$CH_3Br + NH_3 \xrightarrow{S_N2} \overset{+}{C}H_3NH_3\ Br^-$$

Methylammonium bromide

Unfortunately, reaction does not stop at this stage but continues to give a complex mixture of products as shown in the following equation:

$$CH_3Br + NH_3 \longrightarrow \overset{+}{C}H_3NH_3\ Br^- + (CH_3)_2\overset{+}{N}H_2\ Br^- + (CH_3)_3\overset{+}{N}H\ Br^- + (CH_3)_4\overset{+}{N}\ Br^-$$

The relative proportions of the various alkylation products depend on the ratio of alkyl halide to ammonia in the reaction mixture. Whatever the starting mixture, however, the product is almost invariably a mixture of alkylated forms.

This complex mixture is formed in the following way. Proton transfer between ammonia and methylammonium ion gives ammonium ion and methylamine, also a good nucleophile, which then undergoes reaction with bromomethane to give dimethylammonium bromide. A second proton transfer reaction converts dimethylammonium bromide to dimethylamine, yet another good nucleophile, which also participates in nucleophilic substitution and so on.

$$\overset{+}{C}H_3NH_3\ Br^- + NH_3 \overset{\text{proton transfer}}{\rightleftharpoons} CH_3NH_2 + NH_4^+\ Br^-$$

Methylamine

$$CH_3Br + CH_3NH_2 \xrightarrow{S_N2} (CH_3)_2\overset{+}{N}H_2\ Br^-$$

Dimethylammonium bromide

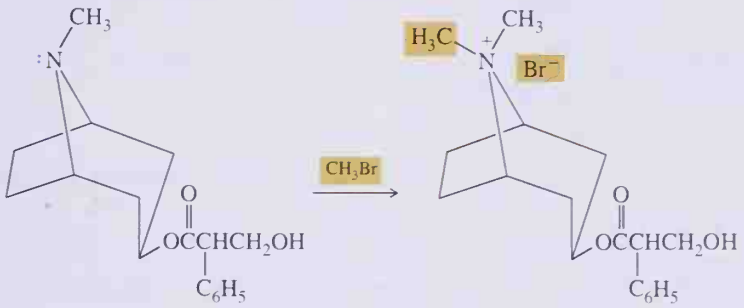
$$(CH_3)_2\overset{+}{N}H_2\ Br^- + NH_3 \overset{\text{proton transfer}}{\rightleftharpoons} (CH_3)_2NH + NH_4^+\ Br^-$$

Dimethylamine

The final product from such a series of nucleophilic substitution and proton transfer reactions is a tetraalkylammonium halide. In the example just shown, the final product is tetramethylammonium bromide.

There is one instance in which the direct alkylation of amines is useful, namely, in preparation of quaternary ammonium salts. Because of their freedom from steric hindrance, the methyl halides are particularly useful for this purpose. The process of converting any primary, secondary, or tertiary amine to a quarternary ammonium ion is called

exhaustive methylation. Following is an equation for the exhaustive methylation of atropine, an amine isolated from *Atropa belladonna* L. and other plants of the Solanaceae family.



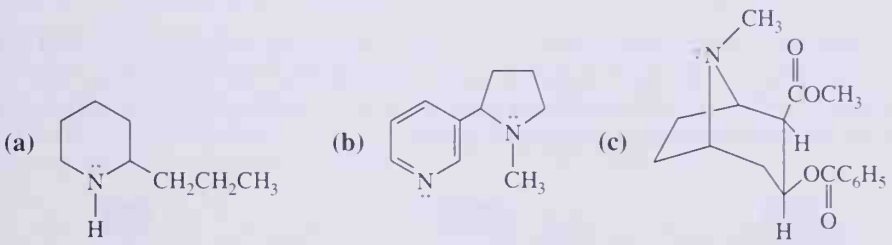
Atropine
(pK_a 4.35)

A quaternary ammonium bromide

Jimsonweed, *Datura stramonium*, from which atropine is isolated. *(E. R. Degginger, © Color-Pic, Inc.)*

EXAMPLE 22.6

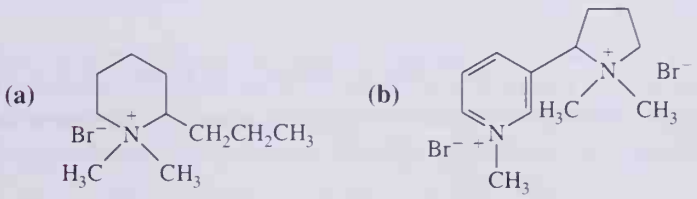
Following are structural formulas for three nitrogen-containing compounds isolated from natural sources. Coniine, isolated from water hemlock, is highly toxic. Ingestion can cause weakness, labored respiration, paralysis, and eventually death. The levorotatory isomer of coniine is the toxic substance in "poison hemlock" used in the death of Socrates. Nicotine is one of the principal heterocyclic amines of the tobacco plant. In small doses, it is a stimulant. In larger doses, it causes depression, nausea, and vomiting. In still larger doses, it is a deadly poison. Solutions of nicotine in water are used as insecticides. Cocaine is a central nervous system stimulant obtained from the leaves of the coca plant. Draw structural formulas for the products of exhaustive methylation of each with excess bromomethane.



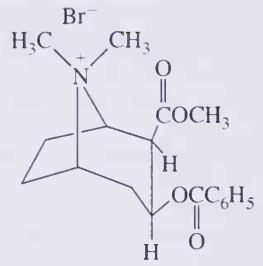
Coniine Nicotine Cocaine

Solution

Each nitrogen in these molecules is a nucleophile and reacts to form an ammonium salt.



(c)

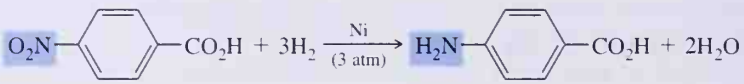


PROBLEM 22.6

Identify all stereocenters in atropine, coniine, nicotine, and cocaine.

B. Reduction of Nitro Groups to Primary Amino Groups

A nitro group is reduced to a primary amino group by hydrogenation in the presence of a transition metal catalyst such as nickel, palladium, or platinum. This method has the potential disadvantage that other susceptible groups such as carbon-carbon double and triple bonds, and aldehyde and ketone carbonyl groups are also reduced under these conditions. Note that neither the $-CO_2H$ nor the aromatic ring is reduced under these conditions.

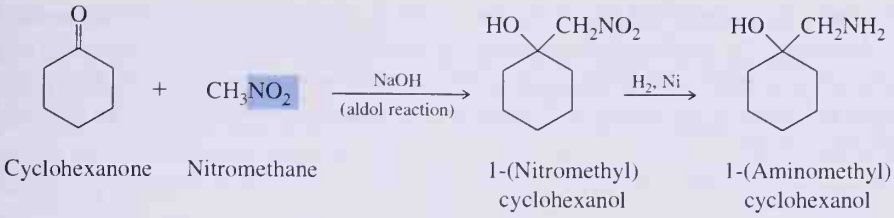


4-Nitrobenzoic acid 4-Aminobenzoic acid

Alternatively, a nitro group can be reduced to a primary amino group by a metal in acid. Most commonly used metal reducing agents are iron, zinc, and tin in dilute HCl. When reduced with a metal and hydrochloric acid, the amine is obtained as a salt which then must be treated with strong base to liberate the free amine.

2,4-Dinitrotoluene 2,4-Diaminotoluene

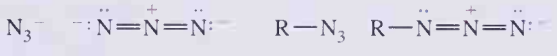
Nitro groups can be introduced into aliphatic compounds by way of an aldol reaction between nitromethane and an aldehyde or a ketone. Reaction with nitromethane in the presence of a strong base followed by reduction of the nitro group is a convenient way to form β-aminoalcohols.



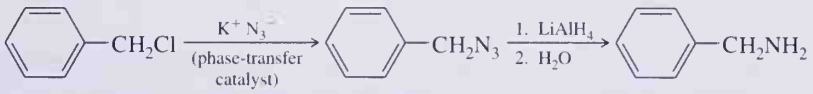
Cyclohexanone Nitromethane 1-(Nitromethyl) cyclohexanol 1-(Aminomethyl) cyclohexanol

C. Alkylation of Azide Ion to Prepare Primary Amines

As we have just seen in the previous subsection, alkylation of ammonia or amines is generally not a useful method for preparation of amines. One strategy for eliminating the problem of overalkylation is to use a form of nitrogen that can function as nucleophile, but once it has formed a new carbon-nitrogen bond, it is no longer an effective nucleophile. One such nucleophilic form of nitrogen is the azide ion, N_3^-. Another is the anion of phthalimide (Section 22.7). Alkyl azides are easily prepared by the reaction of sodium or potassium azide with a primary or secondary alkyl halide by an S_N2 reaction. Azides are in turn reduced to primary amines by a variety of reducing agents, including lithium aluminum hydride.

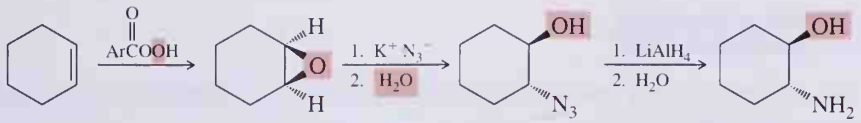


Azide ion (a good nucleophile) An alkyl azide



Benzyl chloride Benzyl azide Benzylamine

The azide ion can also be used for stereoselective ring opening of epoxides. Reduction of the resulting β-azidoalcohol gives a β-aminoalcohol as illustrated by the conversion of cyclohexene to *trans*-2-aminocyclohexanol. Oxidation of cyclohexene by a peroxyacid (Section 11.7B) gives an epoxide. Stereoselective nucleophilic attack by azide ion anti to the leaving oxygen of the epoxide ring (Section 11.8B) followed by reduction of the azide with lithium aluminum hydride gives *trans*-2-aminocyclohexanol.

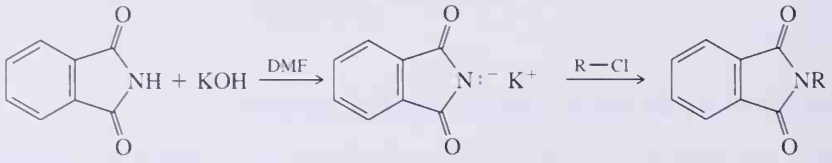


Cyclohexene 1,2-Epoxy-cyclohexane *trans*-2-Azido-cyclohexanol *trans*-2-Amino-cyclohexanol

D. Gabriel Synthesis of Primary Alkylamines

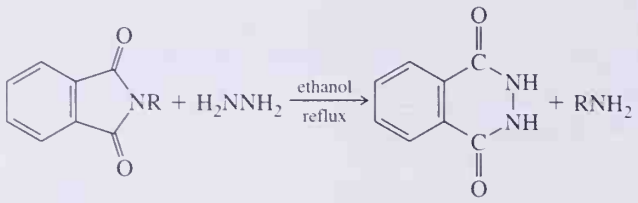
An amide normally has no nucleophilic character but becomes a good nucleophile if it is first converted to its conjugate base. The Gabriel synthesis is a synthetic sequence that uses

phthalimide as a source of nitrogen for the synthesis of primary amines. Phthalimide, pK_a 8.3 (Section 22.7), is converted completely to its conjugate base by treatment with potassium hydroxide in dimethylformamide (DMF) or other polar aprotic solvent. This anion is a good nucleophile and reacts with primary and secondary alkyl halides to give an *N*-alkylphthalimide.



Phthalimide (pK_a 8.3) | Potassium phthalimide | An *N*-alkylphthalimide

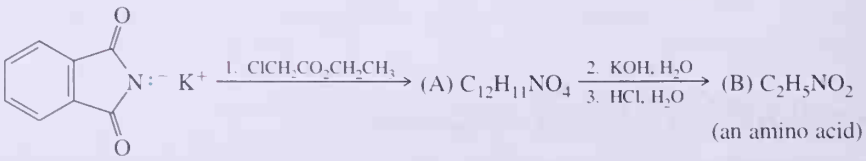
Hydrolysis of the *N*-alkylated imide in either aqueous acid or aqueous base gives phthalic acid and a primary amine. Hydrolysis under these conditions, however, is often very slow. A more effective way to liberate the amine is an exchange reaction in which the *N*-alkylphthalimide is heated with hydrazine.



There are two limitations on the Gabriel synthesis of amines. First, it is limited to the synthesis of primary amines; it cannot be used for the synthesis of secondary or tertiary amines. This is the case because only one hydrogen is replaceable on the starting phthalimide. Second, it is limited to the use of primary and secondary alkyl halides. This is the case because formation of the new carbon-nitrogen bond involves nucleophilic substitution, and although the phthalimide anion is a good nucleophile, it is also a moderately strong base. With a good nucleophile and moderately strong base, tertiary alkyl halides react almost exclusively by an E2 pathway to give an alkene (Section 10.10B).

EXAMPLE 22.7

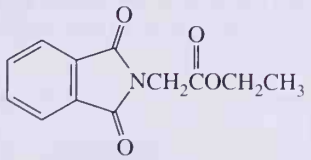
The Gabriel synthesis can be used to prepare α-aminoacids according to the following sequence of reactions:



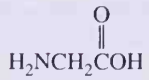
Draw structural formulas for compounds (A) and (B), and account for their formation.

Solution

Reaction of the phthalimide anion by nucleophilic substitution gives compound (A), an *N*-alkylphthalimide. Refluxing compound (A) in aqueous sodium hydroxide results in hydrolysis of the two amide groups (Section 20.4D) and one ester group (Section 20.4C) to give the potassium salt of phthalic acid and the potassium salt of the aminoacid glycine (2-aminoacetic acid). Acidification of the solution gives phthalic acid and glycine (B).



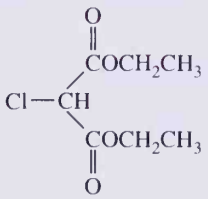
(A)



2-Aminoacetic acid
(Glycine)
(B)

PROBLEM 22.7

Glycine was prepared in Example 22.7 using ethyl 2-chloroacetate as the source of the two-carbon chain of glycine. The same amino acid can be prepared using diethyl 2-chloropropanedioate, more commonly named diethyl 2-chloromalonate, as the source of the two-carbon chain of glycine.

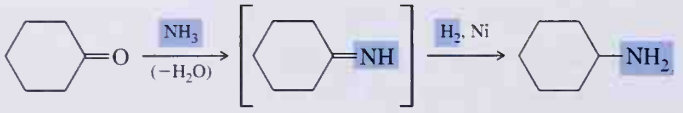


Diethyl 2-chloropropanedioate
(Diethyl 2-chloromalonate)

Using structural formulas, show how a part of the carbon skeleton of this derivative of malonic acid becomes incorporated into the two-carbon skeleton of glycine. (*Hint:* You will want to review Section 19.11B on decarboxylation of substituted malonic acids.)

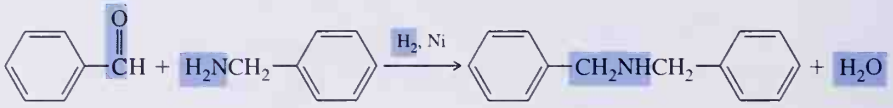
E. Reductive Amination of Aldehydes and Ketones

Aldehydes and ketones react with ammonia and a variety of its derivatives (Section 17.11) to give imines. Imines can, in turn, be reduced by hydrogen in the presence of a transition metal catalyst to amines. Formation of an imine followed by its reduction to an amine is called **reductive amination.** This two-step conversion of an aldehyde or ketone to an amine can be carried out in one laboratory operation by mixing together the carbonyl-containing compound, the amine, hydrogen, and the transition metal catalyst, as illustrated by conversion of cyclohexanone to cyclohexylamine, a primary amine. The imine intermediate is not isolated.



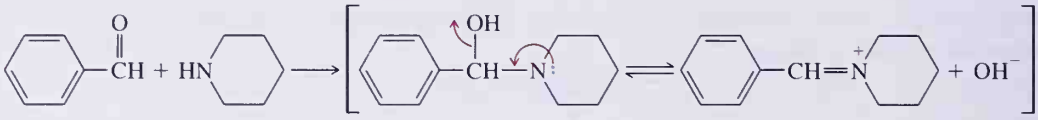
Cyclohexanone (An imine; not isolated) Cyclohexylamine

Reductive amination can be used for the synthesis of secondary and tertiary amines as well. Secondary amines are prepared using an aldehyde or ketone and a primary amine in the presence of hydrogen and a hydrogenation catalyst.

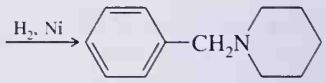


Benzaldehyde Benzylamine Dibenzylamine

Tertiary amines are prepared in a similar manner using a secondary amine and an aldehyde or ketone. In this instance, it is not possible to form an imine intermediate. The intermediate that undergoes reduction is most probably either an aminoalcohol or an iminium ion derived from it by loss of hydroxide ion.

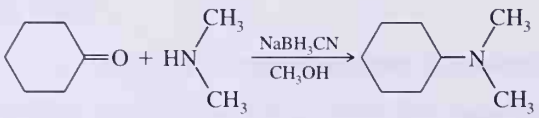


Benzaldehyde Piperidine An aminoalcohol An iminium ion



N-Benzylpiperidine

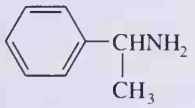
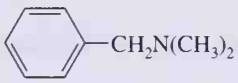
Reduction of the intermediate imine can also be accomplished using a metal hydride reducing agent. What is needed is a hydride reducing agent that reduces an imine faster than it reduces an aldehyde or ketone. The hydride reducing agent most commonly used for this purpose is **sodium cyanoborohydride, $NaBH_3CN$,** a white, crystalline solid that is stable in alcohol and other protic solvents. In practice, the carbonyl compound, amine, and sodium cyanoborohydride are dissolved in methanol or ethanol and allowed to react.



A limitation on the use of reductive amination is the formation of secondary and tertiary amines as byproducts. When an aldehyde or ketone is treated with ammonia, for example, under conditions of reductive amination, the newly formed primary amine can then react with the aldehyde or ketone to form a secondary amine, and this product in turn can undergo reaction to form a tertiary amine. To minimize this unwanted side reaction, the aldehyde or ketone is treated with a considerable excess of ammonia, or primary or secondary amine to maximize the yield of the desired amine.

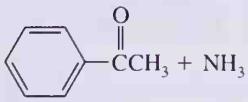
EXAMPLE 22.8

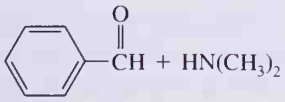
Show how to synthesize the following amines by reductive amination:

(a)  (b) $[(CH_3)_2CH]_2NH$ (c) 

Solution

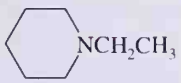
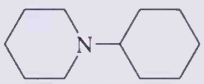
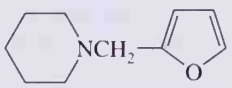
The carbonyl compound is treated with ammonia or an amine in the presence of H_2/Ni.

(a)  (b) $CH_3CCH_3 + CH_3CHCH_3$ (NH$_2$ on the second)

(c) 

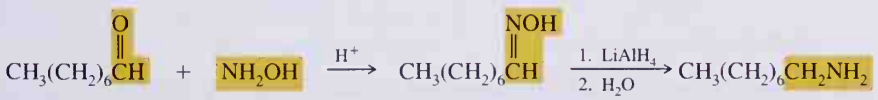
PROBLEM 22.8

Show how to convert piperidine to the following compounds:

(a)  (b)  (c) 

F. Reduction of Oximes to Primary Amines

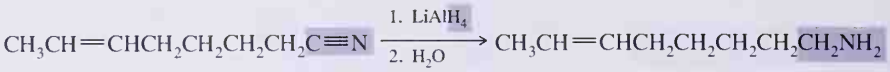
Oximes are prepared by treating an aldehyde or ketone with hydroxylamine (Section 17.11A). They are generally obtained as crystalline solids and easily purified. Reduction of an oxime to a primary amine is most conveniently carried out using lithium aluminum hydride.



Octanal Hydroxylamine (An oxime) 1-Octanamine

G. Reduction of Nitriles to Primary Amines

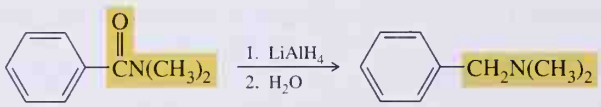
Nitriles are reduced to primary amines by several reducing agents, the most commonly used of which are hydrogen in the presence of Ni or other transition metal catalyst, and lithium aluminum hydride (Section 20.10C). Sodium borohydride also reduces nitriles to amines but only slowly and under special conditions.



6-Octenenitrile 6-Octen-1-amine

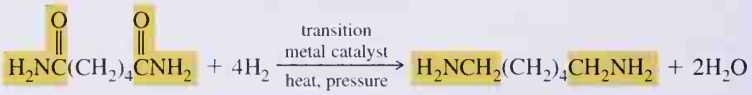
H. Reduction of Amides

An especially valuable method for the preparation of pure primary, secondary, or tertiary amines is reduction of amides by lithium aluminum hydride (Section 20.10B).



N,*N*-Dimethylbenzamide *N*,*N*-Dimethylbenzylamine

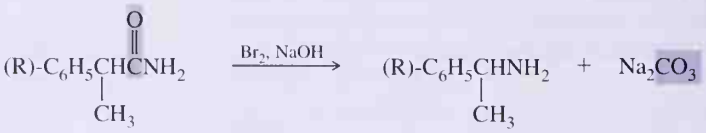
They are also reduced by hydrogen in the presence of a transition metal catalyst. At one time the major commercial preparation of 1,6-hexanediamine, one of the two monomers needed for the synthesis of nylon 66, was by catalytic reduction of hexanediamide.



Hexanediamide (adipamide) 1,6-Hexanediamine (Hexamethylenediamine)

I. Hofmann Rearrangement of Primary Amides

When a primary amide is treated with bromine or chlorine in aqueous sodium or potassium hydroxide, it is converted to a primary amine with one fewer carbon atom than the starting amide (Section 20.11). Further, when the migrating group is chiral, it does so with complete retention of configuration.

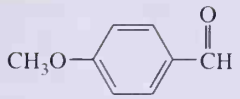


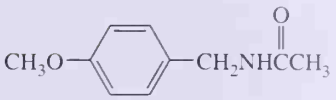
(R)-2-Phenylpropanamide (R)-1-Phenylethanamine

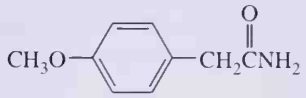
The disadvantage of the Hofmann rearrangement is that it cannot be used for amides that contain other functional groups that also react with either bromine or chlorine or with aqueous base. Examples of other functional groups that might also react with bromine or chlorine under these conditions are carbon-carbon double bonds (Section 5.3F), carbon-carbon triple bonds (Section 6.5C), and aldehyde or ketone carbonyls with α-hydrogens (Section 17.13C).

EXAMPLE 22.9

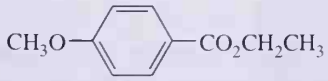
Show how to convert each starting material into 4-methoxybenzylamine in good yield.

(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

Solution

(a) Either reductive amination of the aldehyde group using NH_3, H_2, and Ni (Section 22.9E) or treatment of the aldehyde with NH_2OH to form an oxime followed by its reduction to the amine (Section 22.9F)

(b) Hydrolysis of the amide in aqueous NaOH (Section 20.4D)

(c) Hofmann rearrangement of the amide using Br_2 in NaOH (Section 20.13)

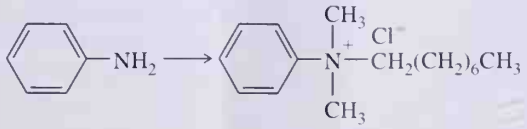
(d) Several methods might be used. One method is alkylation of NH_3 (Section 22.9A) using a large molar excess of NH_3 to reduce the extent of overalkylation. A second method is nucleophilic displacement of chloride using azide ion (from NaN_3) followed by $LiAlH_4$ reduction of the azide (Section 22.9C). A third method is nucleophilic displacement of chloride ion by phthalimide anion (the Gabriel synthesis, Section 22.9D) followed by hydrolysis of the imide. Of these methods, nucleophilic displacement by azide is the most convenient on a laboratory scale.

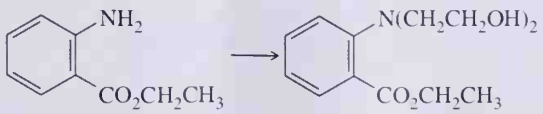
(e) Treatment of the ester with NH_3 (Section 20.6C) to give an amide followed by reduction of the amide using $LiAlH_4$ (Section 20.10B)

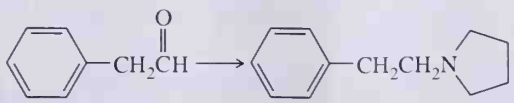
(f) The key is to convert the carboxylic acid to an amide and then reduce the amide with $LiAlH_4$. The amide can be prepared by treatment of the carboxylic acid with $SOCl_2$ to form the acid chloride (Section 19.10) and then treatment of the acid chloride with NH_3 (Section 20.6A). Reduction of the amide using $LiAlH_4$ (Section 20.10B) gives the amine.

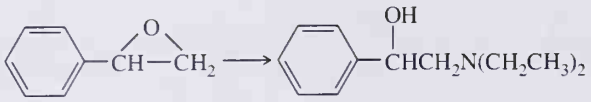
PROBLEM 22.9

Show how to bring about each conversion in good yield. In addition to the given starting material, use any other reagents as necessary.

(a) 

(b) 

(c) 

(d) 

22.10 Reactions of Amines

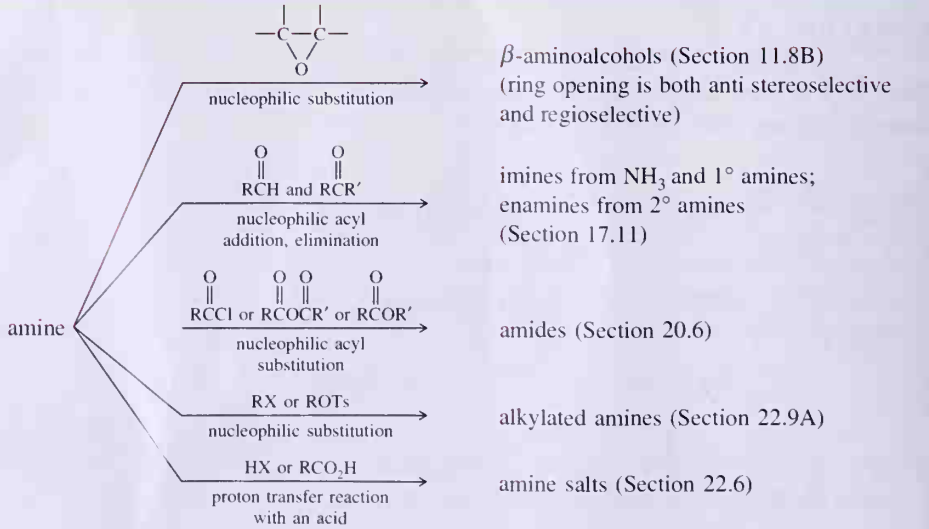
The most important reactions of amines derive from the presence of the lone pair of electrons on nitrogen. Because of the presence of this electron pair, amines act as bases and as nucleophiles in both S_N2 reactions and nucleophilic acyl substitution reactions. The reactions of amines we have studied thus far are summarized in Table 22.4. We have already covered a great deal of the chemistry of amines and you should review that chemistry so that you can correlate it with the chemistry of amines presented in the following sections. As you shall see, the few additional reactions of amines that follow are extensions of the chemistry we have already encountered.

22.11 Reaction with Nitrous Acid

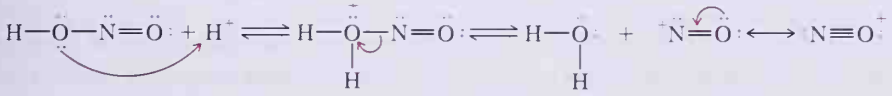
Nitrous acid, HNO_2, is an unstable compound which is prepared when it is to be used by adding a cold aqueous solution of sodium nitrite, $NaNO_2$, to aqueous sulfuric acid or aqueous hydrochloric acid. Nitrous acid is a weak oxygen acid and ionizes according to the following equation:

$$HNO_2 \rightleftharpoons H^+ + NO_2^- \qquad K_a = 4.26 \times 10^{-4} \qquad pK_a = 3.37$$

Table 22.4 Review of important reactions of amines covered to this point



Nitrous acid undergoes reaction with amines in different ways depending on whether the amine is primary, secondary, or tertiary and whether it is aliphatic or aromatic. These reactions are all related by the facts that nitrous acid (1) participates in proton transfer reactions and (2) is a source of the **nitrosyl cation,** a weak electrophile. The nitrosyl cation is generated by protonation of the —OH of nitrous acid followed by loss of H_2O. It is here represented as a resonance hybrid of two important contributing structures.



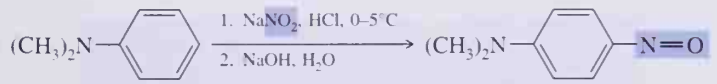
Nitrosyl cation as a hybrid of two contributing structures

A. Reaction of Tertiary Aliphatic Amines

When treated with nitrous acid, tertiary aliphatic amines, whether water-soluble or water-insoluble, form water-soluble salts. No further reaction occurs beyond salt formation. This reaction is of little practical use.

B. Reaction of Tertiary Aromatic Amines

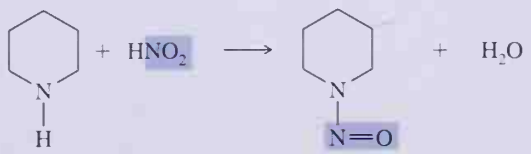
Tertiary aromatic amines are bases and can also form salts with nitrous acid. An alternative pathway, however, is open to tertiary aromatic amines, namely, electrophilic aromatic substitution involving the nitrosyl cation. The nitrosyl cation is a very weak electrophile and reacts only with aromatic rings containing strongly activating, ortho-para directing groups such as hydroxyl and dialkylamino groups. When treated with nitrous acid, these compounds undergo **nitrosation,** predominantly in the para position.



N,*N*-Dimethylaniline *N*,*N*-Dimethyl-4-nitrosoaniline

C. Reaction of Secondary Aliphatic and Aromatic Amines

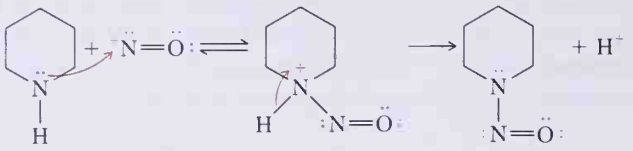
Secondary amines, whether aliphatic or aromatic, undergo reaction with nitrous acid to give ***N*-nitrosoamines,** more commonly called *N*-nitrosamines, as illustrated by the reaction of piperidine with nitrous acid.



Piperidine *N*-Nitrosopiperidine

Formation of an *N*-nitrosamine involves interaction of the unshared pair of electrons of the amine (a Lewis base and nucleophile) with the positively charged nitrosyl cation (a Lewis

acid and electrophile) to form a new carbon-nitrogen bond. Loss of a proton from the ammonium ion gives the *N*-nitrosamine.



N-Nitrosamines are of little synthetic or commercial value. They have received considerable attention in recent years, however, because many of them are potent carcinogens. Following are structural formulas for two *N*-nitrosamines, each of which is a known carcinogen.

N-Nitrosodimethylamine (found in cigarette smoke and when bacon "cured" with sodium nitrite is fried)

N-Nitrosopyrrolidine (formed when bacon "cured" with sodium nitrite is fried)

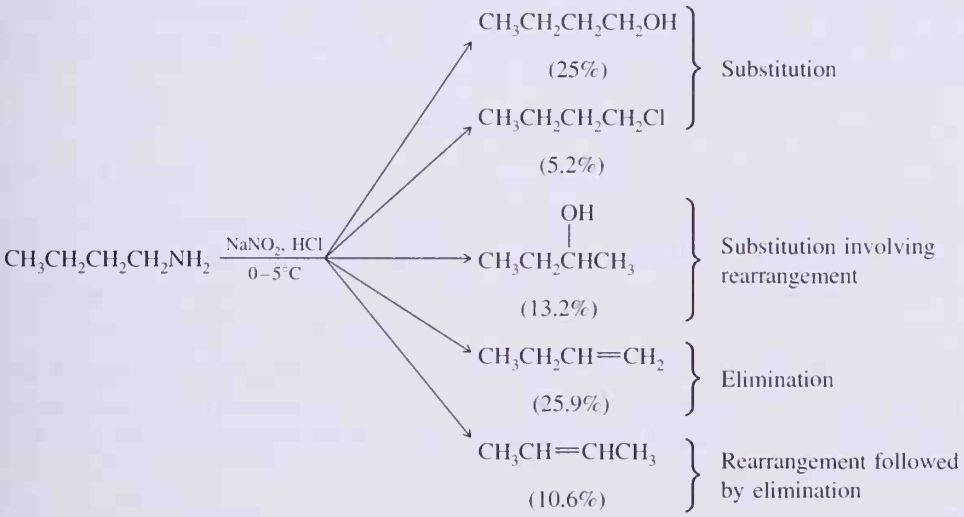
It has been common practice within the food industry to add sodium nitrite to processed meats to "retard spoilage," that is, to inhibit the growth of *Clostridium botulinum*, the bacterium responsible for botulism poisoning. Although this practice was well grounded before the days of adequate refrigeration, it is of questionable value today. Sodium nitrite is also added to prevent red meats from turning brown. Controversy over the use of sodium nitrite has been generated by the demonstration that nitrite ion in the presence of acid converts secondary amines to *N*-nitrosamines and that many *N*-nitrosamines are powerful

Sodium nitrite is added to processed meats to "retard spoilage." *(Charles D. Winters)*

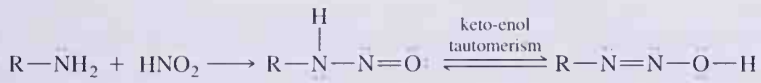
carcinogens. This demonstration led in turn to pressure by consumer groups to force the Food and Drug Administration to ban the use of nitrite additives in foods. The strength of the argument to ban nitrites was weakened with the finding that enzymes in our mouths and intestinal tracts have the ability to catalyze reduction of nitrate to nitrite. Nitrate ion is normally found in a wide variety of foods and in drinking water. To date, there is no evidence that nitrite as a food additive poses any risk not already present through our existing dietary habits. The FDA has established the current permissible level of sodium nitrite in processed meats as 50 to 125 ppm (that is, 50–125 μg nitrite per gram of cured meat).

D. Reaction of Primary Aliphatic Amines

Treatment of a primary aliphatic amine with nitrous acid results in loss of nitrogen, N_2, and formation of substitution, elimination, and rearrangement products as illustrated by the treatment of butylamine with nitrous acid.

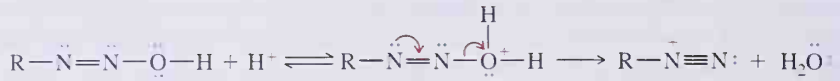


We can account for formation of this mixture of products in the following way. As a first step, treatment of a primary aliphatic amine with nitrous acid gives an *N*-nitrosamine, which can then undergo keto-enol tautomerism (Section 17.12B) to give a diazotic acid, so named because it has two (di-) nitrogen (-azot-) atoms within its structure.

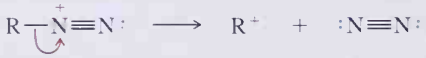


A primary aliphatic amine — An *N*-nitrosamine — A diazotic acid

Protonation of the —OH group of the diazotic acid followed by loss of water gives a diazonium ion. This conversion of a primary amine to a diazonium ion is called **diazotization.** Aliphatic diazonium ions are unstable, even at 0°C, and immediately lose nitrogen to give carbocations and nitrogen gas. The driving force for this reaction is the fact that N_2 is one of the best of all possible leaving groups because it is an unusually stable molecule and is removed from the reaction mixture as a gas as it is formed.



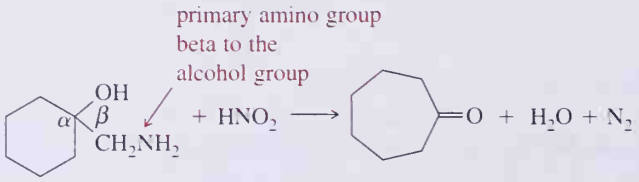
A diazotic acid A diazonium ion



A carbocation

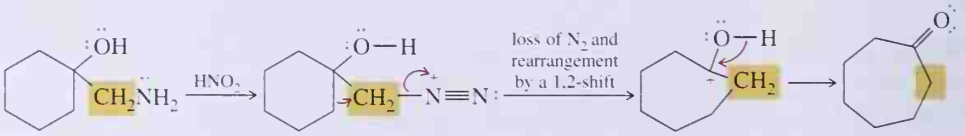
The carbocation now has open to it the three reactions in the repertoire of aliphatic carbocations: (1) loss of a proton to form an alkene, (2) reaction with a nucleophile to give a substitution product, and (3) rearrangement to a more stable carbocation and then reaction further by (1) or (2).

Because treatment of a primary aliphatic amine with HNO_2 gives a mixture of products, it is generally not a useful reaction. An exception is treatment of cyclic ***β*-aminoalcohols**, which undergo reaction with nitrous acid to form ring-expanded ketones as illustrated by treatment of 1-aminomethylcyclohexanol with nitrous acid. In this reaction, nitrogen is evolved, the ring is expanded, and a ketone is formed.



A β-aminoalcohol Cycloheptanone

We can account for this molecular rearrangement in the following way. Treatment of the primary amine with nitrous acid generates a diazonium ion. Concerted loss of nitrogen and rearrangement by a 1,2-shift gives a ring-expanded cation. Loss of a proton from this cation gives cycloheptanone.

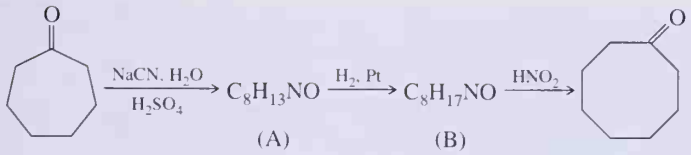


(A diazonium ion)

The driving force for this molecular rearrangement is precisely that which we already saw for other cation rearrangements: transformation of a less stable cation into a more stable cation. Note also the manner in which this transformation is in accord with our understanding of the repertoire of carbocation reactions: The less stable primary carbocation rearranges to a more stable carbocation and then loses a proton from an adjacent atom to give a double bond, in this case a carbon-oxygen double bond.

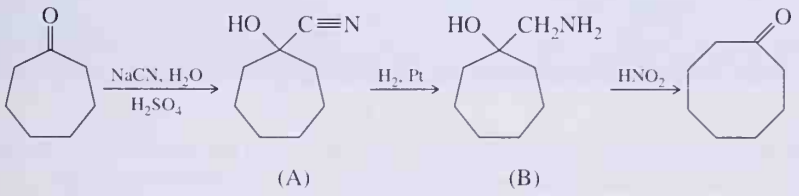
EXAMPLE 22.10

Following is a sequence of reactions that converts cycloheptanone to cyclooctanone. Propose structural formulas for compounds (A) and (B), and account for their formation.



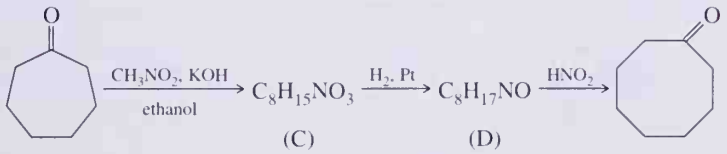
Solution

Reaction of an aldehyde or ketone with sodium cyanide, NaCN, gives a cyanohydrin (Section 17.7E). Catalytic hydrogenation using hydrogen over a platinum catalyst reduces the carbon-nitrogen triple bond to a single bond (Section 20.10C) and gives a β-aminoalcohol. Treatment of the β-aminoalcohol with nitrous acid results in loss of N_2 and expansion of the seven-member ring to an eight-member cyclic ketone.



PROBLEM 22.10

The following sequence of reactions can also be used to convert cycloheptanone to cyclooctanone. Propose structural formulas for compounds (C) and (D), and account for their formation. (*Hint:* For the formation of compound (C), you will want to review the aldol reaction in Section 17.14).



Reaction with nitrous acid has been used as both a qualitative and a quantitative test for primary aliphatic amines. In each case, the amine is treated with nitrous acid. Only from a primary amine is nitrogen evolved. A secondary amine reacts to form a water-insoluble *N*-nitrosamine, and a tertiary amine reacts to form a water-soluble salt. Thus, although all three classes of amines react with nitrous acid, only primary amines generate N_2. For a quantitative analysis, nitrogen gas is collected, and its volume, temperature, and pressure are determined. From these measurements, the number of moles of N_2 is determined. Each mole of $-NH_2$ gives one mole of N_2.

E. Reaction of Primary Aromatic Amines

Primary aromatic amines, like primary aliphatic amines, undergo reaction with nitrous acid to form diazonium ions. Aryl diazonium ions, unlike their aliphatic counterparts, however, are stable at 0°C and can be kept in solution for short periods without decomposition. When an aryl diazonium salt is treated with an appropriate reagent, nitrogen is lost and

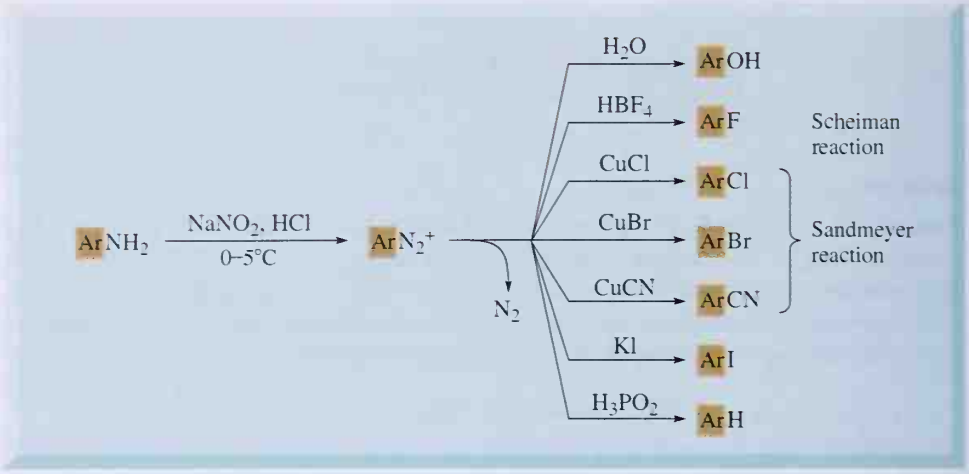
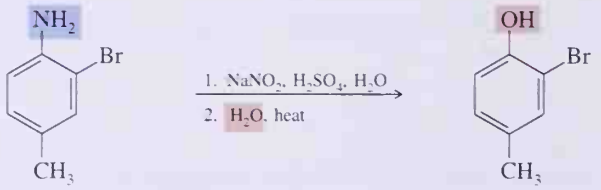


Figure 22.7
A primary aromatic amine can be converted to an aromatic diazonium ion which allows replacement of the original amino group in a regioselective manner by several other functional groups.

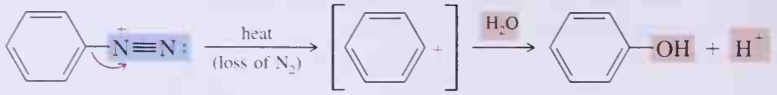
replaced by another atom or functional group. What makes reactions of primary aromatic amines with nitrous acid so valuable is the fact that the amino group can be replaced in a totally regioselective manner by the groups shown in Figure 22.7.

Aromatic amines can be converted to phenols by first forming the diazonium salt and then heating the solution in which it is formed. In this manner, 2-bromo-4-methylaniline is converted to 2-bromo-4-methylphenol.



2-Bromo-4-methylaniline 2-Bromo-4-methylphenol

The intermediate in the decomposition of an aryl diazonium ion in water is an aryl cation, which then undergoes reaction with water to form the phenol.

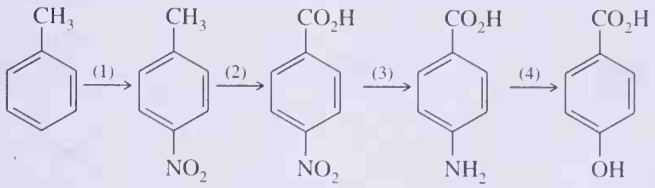


Benzenediazonium ion (An aryl cation) Phenol

This reaction of aryl diazonium salts represents the main laboratory preparation of phenols.

EXAMPLE 22.11

Toluene can be converted to 4-hydroxybenzoic acid by the following series of reactions. What reagents and experimental conditions bring about each step?



Solution

Step 1: Nitration of the aromatic ring using HNO_3 in H_2SO_4 followed by separation of the *ortho*-isomer gives 4-nitrotoluene. This reaction is an electrophilic aromatic substitution (Section 16.1B).

Step 2: Oxidation at a benzylic carbon (Section 15.6A) can be brought about using $KMnO_4$ in H_2SO_4 to give 4-nitrobenzoic acid.

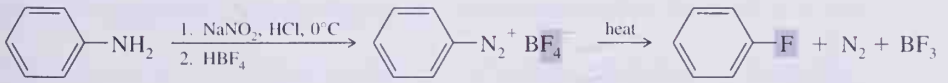
Step 3: Reduction of the nitro group to 4-aminobenzoic acid can be brought about using H_2 in the presence of Ni or other transition metal catalyst. Alternatively, it can be brought about using Zn, Sn, or Fe metal in aqueous HCl.

Step 4: Reaction of the aromatic amine with HNO_2 followed by heating gives 4-hydroxybenzoic acid.

PROBLEM 22.11

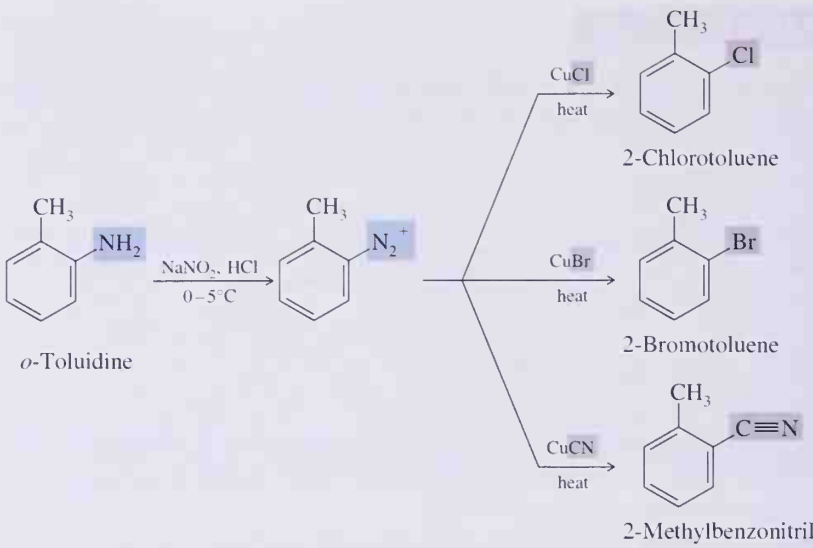
Show how to convert toluene to 3-hydroxybenzoic acid using the same set of reactions as in Example 22.11 but changing the order in which the steps are carried out.

The **Schiemann reaction** is the most common method for introduction of fluorine onto an aromatic ring. It is carried out by treatment of a primary aromatic amine with sodium nitrite in aqueous HCl followed by addition of HBF_4 or $NaBF_4$. The diazonium fluoroborate salt precipitates and is collected and dried. Heating the dry salt brings about its decomposition to an aryl fluoride, nitrogen, and boron trifluoride. The Schiemann reaction is also thought to involve an aryl cation as an intermediate.

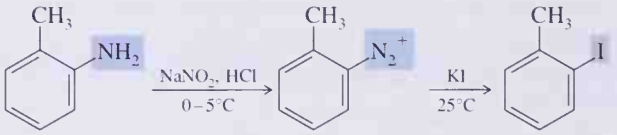


A diazonium fluoroborate Fluorobenzene

Treatment of a primary aromatic amine with nitrous acid followed by heating in the presence of CuCl, CuBr, or CuCN results in replacement of the diazonium group by —Cl, —Br, or —CN, respectively, and is known as the **Sandmeyer reaction.** The Sandmeyer reaction fails, however, when attempted with CuI or CuF.

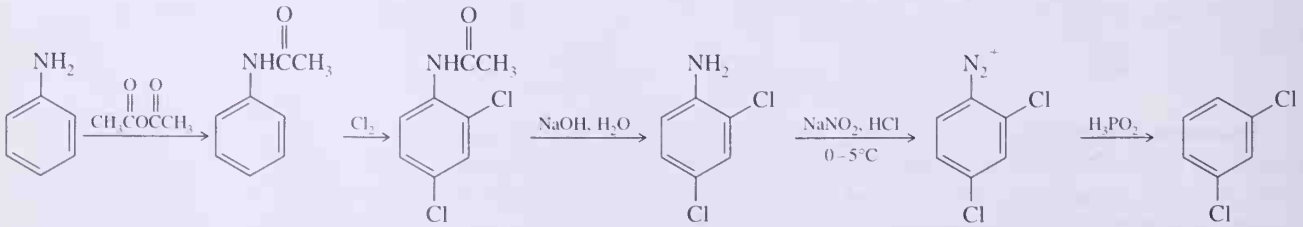


Treatment of an aryl diazonium ion with iodide ion, generally from potassium iodide, is the best and most convenient method for introduction of iodine onto an aromatic ring.



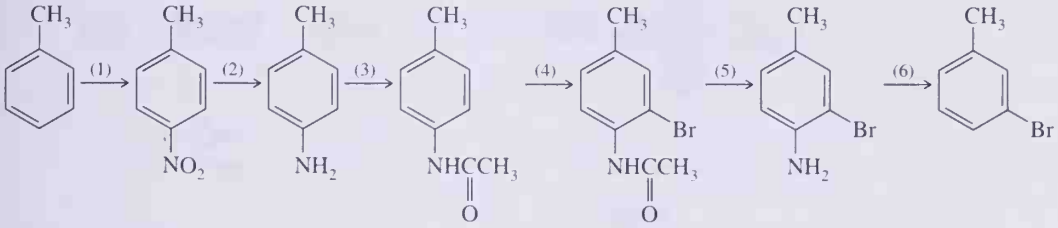
Treatment of an aryl diazonium ion with **hypophosphorous acid, H_3PO_2,** results in reduction of the diazonium group and its replacement by —H as illustrated by the following conversion of aniline to 1,3-dichlorobenzene. Note that in this conversion, the $-NH_2$ group is used to control orientation of further substitution and is then removed once it has served its purpose.

Aniline is first treated with acetic anhydride (Section 20.6B) to form acetanilide, which is then treated with 2 mol of chlorine to give 2,4-dichloroacetanilide. Why first form acetanilide? Recall that $-NH_2$ is a powerful activating group (Section 16.2A). Treatment of aniline with chlorine requires no catalyst and gives 2,4,6-trichloroaniline. It is necessary, therefore, to reduce the activating effect of $-NH_2$ by first converting it to an amide. To complete the conversion, the amide group of 2,4-dichloroacetanilide is hydrolyzed in aqueous NaOH (Section 20.4D), and the resulting $-NH_2$ group is removed by treatment with nitrous acid followed by hypophosphorous acid to give 1,3-dichlorobenzene.



EXAMPLE 22.12

Show reagents and conditions that bring about the conversion of toluene to 3-bromotoluene. Note that $-CH_3$ is an ortho-para director (Section 16.2A), and, therefore, bromination of toluene gives largely 2-bromotoluene and 4-bromotoluene.



Solution

Step 1: HNO_3 in H_2SO_4. Nitration by electrophilic aromatic substitution (Section 16.2A). Methyl is ortho-para directing and slightly activating.

Step 2: Either catalytic reduction of the nitro group using H_2/Ni or chemical reduction using Sn, Zn, or Fe in aqueous HCl.

Step 3: Acetylation of the amine using acetic anhydride to form the amide (Section 20.6B).

Step 4: Bromination using Br_2 in acetic acid. Methyl is weakly activating. Nitrogen of the amide group is moderately activating and, therefore, controls the orientation of bromination (Section 16.2A).

Step 5: Hydrolysis of the amide in aqueous NaOH (Section 20.4D).

Step 6: Diazotization of the amine with HNO_2 followed by treatment of the diazonium ion with H_3PO_2 to replace $-N_2^+$ by $-H$.

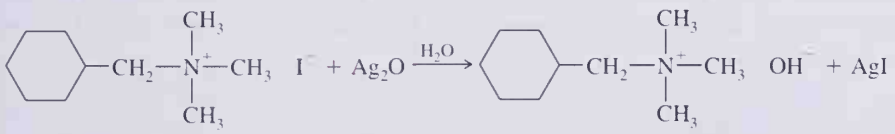
PROBLEM 22.12

Starting with 3-nitroaniline, show how to prepare the following compounds:

(a) 3-Nitrophenol
(b) 3-Bromoaniline
(c) 1,3-Dihydroxybenzene (resorcinol)
(d) 3-Fluoroaniline
(e) 3-Fluorophenol
(f) 3-Hydroxybenzonitrile

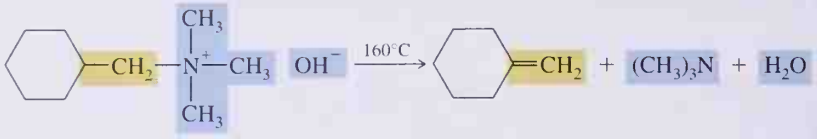
22.12 Hofmann Elimination

When a quaternary ammonium halide is treated with moist silver oxide (a slurry of Ag_2O in H_2O), silver halide precipitates, leaving a solution of quaternary ammonium hydroxide.

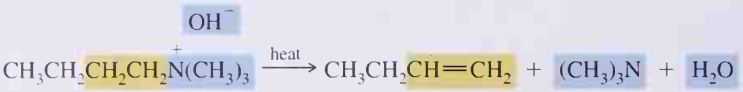


(Cyclohexylmethyl)trimethylammonium iodide — Silver oxide — (Cyclohexylmethyl)trimethylammonium hydroxide

In the mid-19th century, Augustus Hofmann (for whom the Hofmann rearrangement is named) discovered that when a quaternary ammonium hydroxide is heated, it decomposes to an alkene, a tertiary amine, and water. Thermal decomposition of a quaternary ammonium hydroxide to an alkene is known as the **Hofmann elimination.**

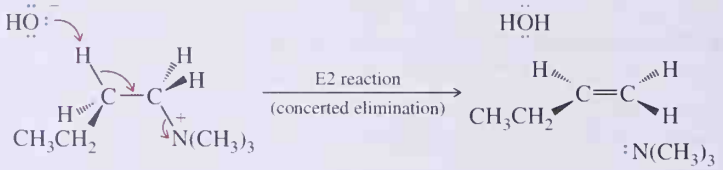


(Cyclohexylmethyl)trimethylammonium hydroxide — Methylenecyclohexane — Trimethylamine

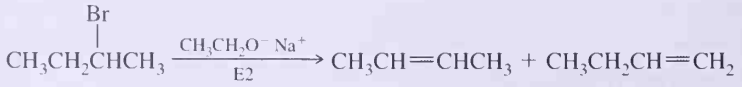


Butyltrimethylammonium hydroxide — 1-Butene — Trimethylamine

The Hofmann elimination has most of the characteristics of an E2 elimination reaction (Section 10.10B). First, Hofmann eliminations are concerted, meaning that bond-breaking and bond-making steps occur simultaneously or nearly so. Second, Hofmann eliminations are anti stereoselective, meaning that —H and the leaving group must be anti and coplanar to each other. The following mechanism illustrates the concerted nature of bond making and bond breaking, and the anti and coplanar arrangement of —H and the trialkylamino group.

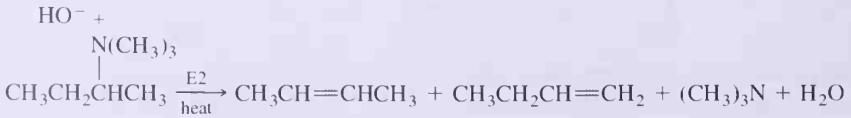


When we first studied E2 reactions in Sections 4.5 and 10.10, we saw that a β-hydrogen must be anti and coplanar to the leaving group. If only one β-hydrogen meets this requirement, then the double bond is formed in that direction. If two β-hydrogens meet this requirement, then elimination follows Zaitsev's rule: elimination occurs preferentially to form the most substituted double bond.



(75%) (25%)

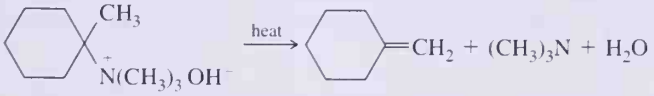
Thermal decomposition of quaternary ammonium hydroxides is different because elimination occurs preferentially to form the least substituted double bond. Thermal decomposition of *sec*-butyltrimethylammonium hydroxide, for example, gives 1-butene as the major product.

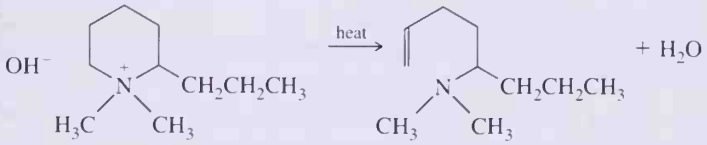


(5%) (95%)

All elimination reactions that give the less substituted alkene as the major product are said to follow Hofmann's rule. According to **Hofmann's rule,** elimination occurs preferentially to give the least substituted double bond. Thus, we say that thermal decomposition of quaternary ammonium hydroxides follows Hofmann's rule.

The following examples illustrate Hofmann elimination.





From exhaustive methylation of coniine

EXAMPLE 22.13

Draw the structural formula of the major alkene formed in each β-elimination.

(a) $CH_3(CH_2)_5CHCH_3$ (NH$_2$) $\xrightarrow[3.\ \text{heat}]{1\ CH_3I\ (\text{excess}),\ 2.\ Ag_2O,\ H_2O}$

(b) $CH_3(CH_2)_5CHCH_3$ (I) $\xrightarrow{CH_3O^-\ Na^+}$

Solution

(a) Thermal decomposition of a quaternary ammonium hydroxide in (a) follows Hofmann's rule and gives 1-octene as the major product. E2 elimination from an alkyl iodide in (b) by sodium methoxide follows Zaitsev's rule and gives 2-octene as the major product.

(a) $CH_3(CH_2)_5CH{=}CH_2 + (CH_3)_3N + H_2O$
1-Octene

(b) $CH_3(CH_2)_4CH{=}CHCH_3 + CH_3OH$
2-Octene

PROBLEM 22.13

The procedure for exhaustive methylation and thermal decomposition of quaternary ammonium hydroxides was first reported by Hofmann in 1851, but its value as a means of structure determination was not appreciated until 1881 when he published a report of its use in determining the structure of piperidine. Following are the results obtained by Hofmann:

$$C_5H_{11}N \xrightarrow[3.\ \text{heat}]{1.\ CH_3I\ (\text{excess}),\ 2.\ Ag_2O,\ H_2O} C_7H_{15}N \xrightarrow[6.\ \text{heat}]{4.\ CH_3I\ (\text{excess}),\ 5.\ Ag_2O,\ H_2O} CH_2{=}CHCH_2CH{=}CH_2$$

Piperidine (A) 1,4-Pentadiene

(a) Show that these results are consistent with the structure of piperidine (Section 22.1).

(b) Propose two additional structural formulas (excluding stereoisomers) for $C_5H_{11}N$ that are also consistent with the results obtained by Hofmann.

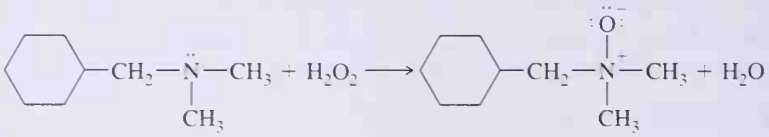
In summary, both Hofmann and Zaitsev eliminations are always anti. If only one β-hydrogen is anti and coplanar to the leaving group, then that is the one removed. If more than one β-hydrogen is anti and coplanar, then there is competition between Hofmann and Zaitsev elimination.

1. Eliminations involving a neutral leaving group, for example —Cl, —Br, —I, and —Ts almost always follow Zaitsev's rule.
2. Eliminations involving a positively charged leaving group, for example $-N(CH_3)_3^+$ and $-S(CH_3)_2^+$, almost always follow Hofmann's rule.
3. The bulkier the base, as for example $(CH_3)_3CO^-K^+$ compared with $CH_3O^-Na^+$, the greater the percentage of Hofmann product.

One of the likeliest explanations for orientation of the double bond in the Hofmann elimination is that it is governed largely by steric factors, namely the bulk of the $-N(CH_3)_3^+$ group. The hydroxide ion preferentially approaches and removes the least hindered β-hydrogen and gives the least substituted alkene as product.

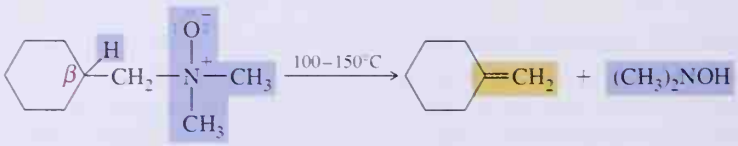
22.13 Cope Elimination

Treatment of a tertiary amine with hydrogen peroxide results in a two-electron oxidation of the amine to an **amine oxide.**



An amine oxide

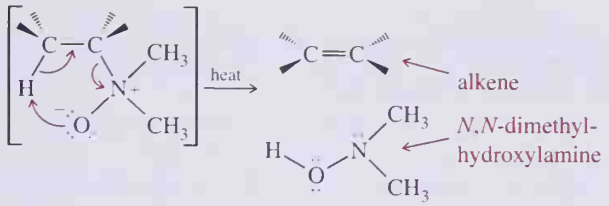
When an amine oxide with at least one β-hydrogen is heated, it undergoes thermal decomposition and an alkene and an *N,N*-dialkylhydroxylamine are formed. Thermal decomposition of an amine oxide to an alkene is known as a **Cope elimination** after its discoverer, Arthur C. Cope, then of the Massachusetts Institute of Technology.



Methylene-cyclohexane

N,N-Dimethylhydroxylamine

All experimental evidence indicates that the Cope elimination is syn stereoselective and concerted. As shown in the following mechanism, the transition state involves a planar or nearly planar arrangement of the five participating atoms and a cyclic flow of three pairs of electrons.



Transition state
(cyclic flow of three
pairs of electrons)

When two or more β-hydrogens might be removed in a Cope elimination, there is little preference for one over the other, and, hence, as a method of preparation of alkenes, Cope eliminations are best used where only one alkene is possible.

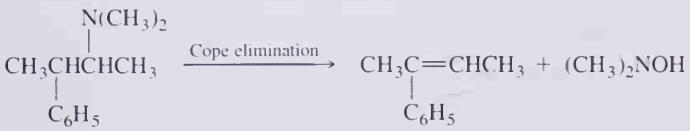
One more point needs to be made about the Cope elimination: it is another example of a concerted reaction that involves flow of six electrons in a cyclic, planar transition state. In this regard, the Cope elimination is similar to the Diels-Alder reaction (Section 7.5), the Claisen rearrangement of allyl phenyl ethers (Section 15.5E), and thermal decarboxylation of β-keto acids and malonic acids (Section 19.11).

These last three reactions involve a cyclic flow of six electrons in a six-member transition state. In the Cope elimination, a cyclic flow of six electrons occurs in a five-member transition state. The central point is that there are six electrons and the transition state is cyclic.

We can place the transition states of these four reactions in a larger context called **transition state aromaticity.** Recall the Hückel criteria for aromaticity (Section 15.2A): the presence of $(4n + 2)$ pi electrons in a ring that is planar and fully conjugated. Just as aromaticity imparts a special stability to molecules, in a similar manner $(4n + 2)$ electrons in a cyclic and planar arrangement impart a special stability to transition states. Reactions that can proceed by a planar transition state involving a cyclic flow of $(4n + 2)$ electrons have especially low energies of activation and take place readily. Thus, the Hückel theory of aromaticity gives us a clearer understanding not only of the stability of certain types of molecules, but also of certain types of transition states.

EXAMPLE 22.14

Following is a formula for 2-dimethylamino-3-phenylbutane. When it is treated with hydrogen peroxide and then made to undergo a Cope elimination, the major alkene formed is 2-phenyl-2-butene.



2-Dimethylamino-3-phenylbutane

2-Phenyl-2-butene

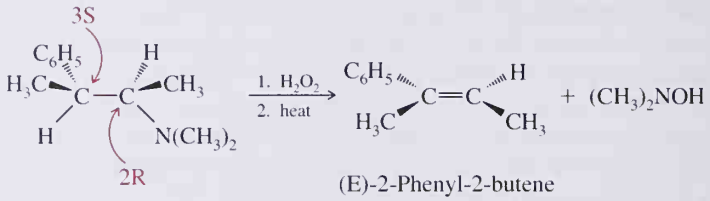
(a) How many stereoisomers are possible for 2-dimethylamino-3-phenylbutane?
(b) How many stereoisomers are possible for 2-phenyl-2-butene?
(c) Suppose the starting amine is the (2R, 3S) isomer. What is the configuration of the product?

Solution

(a) Two tetrahedral stereocenters occur in the starting amine. Four stereoisomers are possible: two pair of enantiomers.

(b) There is one carbon-carbon double bond about which stereoisomerism is possible. Two stereoisomers are possible: one E-Z pair.

(c) Following is a stereodrawing of the (2R, 3S) stereoisomer showing a syn conformation of the dimethylamino group and the β-hydrogen. Cope elimination of this stereoisomer gives (E)-2-phenyl-2-butene.



(E)-2-Phenyl-2-butene

PROBLEM 22.14

In Example 22.14, you considered the product of Cope elimination from the (2R, 3S) stereoisomer of 2-dimethylamino-3-phenylbutane. What is the product of Cope elimination from the

(a) (2S, 3R) Stereoisomer? **(b)** (2S, 3S) Stereoisomer?

SUMMARY OF KEY REACTIONS

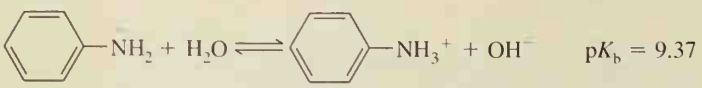
1. Basicity of Aliphatic Amines (Section 22.6)

Aliphatic amines are slightly stronger bases than ammonia due to the electron-releasing effect of alkyl groups and partial dispersion of positive charge in the alkylammonium ion. pK_a for $CH_3NH_3^+$ is 10.64.

$$CH_3NH_2 + H_2O \rightleftharpoons CH_3NH_3^+ + OH^- \qquad pK_b = 3.36$$

2. Basicity of Aromatic Amines (Section 22.6)

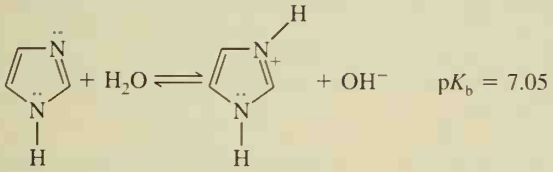
Aromatic amines are considerably weaker bases than aliphatic amines. Resonance stabilization from interaction of the unshared electron pair on nitrogen with the pi system of the aromatic ring is lost on protonation. pK_a for $C_6H_5NH_3^+$ is 4.63.



$pK_b = 9.37$

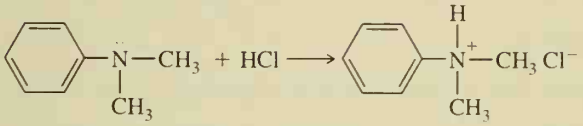
3. Basicity of Heterocyclic Aromatic Amines (Section 22.6)

Heterocyclic aromatic amines are considerably weaker bases than aliphatic amines.



4. Reaction of Amines with Strong Acids (Section 22.6)

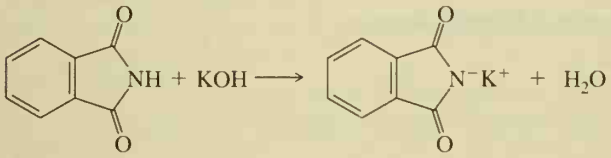
All amines react quantitatively with strong acids to form water-soluble salts.



Insoluble in water — A water-soluble salt

5. Acidity of Imides (Section 22.7)

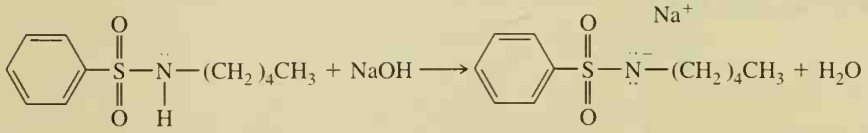
Imides (pK_a 8.0–9.5) dissolve in aqueous NaOH by forming water-soluble salts. Increased acidity of an imide hydrogen is due to (1) the electron-withdrawing inductive effect of the two adjacent carbonyl groups and (2) resonance stabilization of the resulting anion.



Phthalimide (pK_a 8.3) — Potassium phthalimide

6. Acidity of Sulfonamides (Section 22.7)

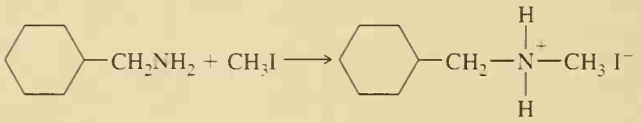
Sulfonamides (pK_a 9–10), like imides, also dissolve in aqueous NaOH by forming water-soluble salts. Increased acidity of the amide hydrogen is due to (1) the electron-withdrawing inductive effect of the two adjacent S=O groups and (2) resonance stabilization of the resulting anion.



Insoluble in water — A water-soluble salt

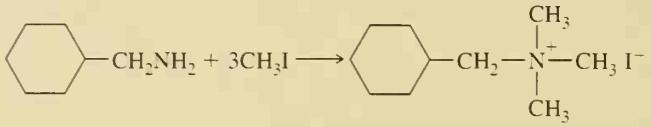
7. Alkylation of Ammonia and Amines (Section 22.8A)

This method is seldom used for preparation of pure amines because of overalkylation and the difficulty of separating products.



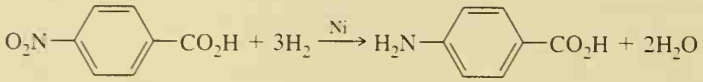
8. Exhaustive Methylation (Section 22.8A)

The methyl halide most commonly used for this purpose is CH_3I.



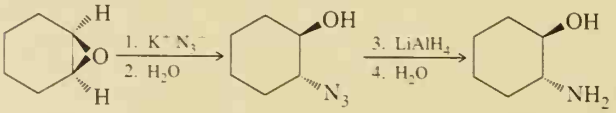
9. Reduction of a Nitro Group to a Primary Amine (Section 22.8B)

Reduction can be accomplished using (1) H_2/Ni or other transition metal catalysts or (2) Fe, Sn, or Zn in aqueous HCl.



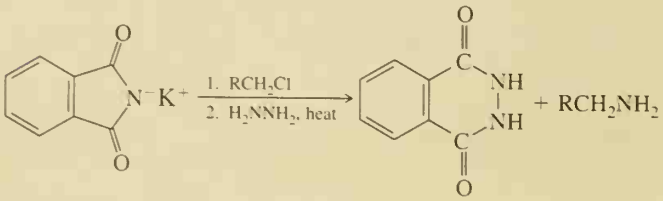
10. Alkylation of Azide Ion Followed by Reduction to a Primary Amine (Section 22.8C)

Azides are prepared by treatment of a primary or secondary alkyl halide or an epoxide with NaN_3 and are reduced to primary amines by a variety of reducing agents, including lithium aluminum hydride.



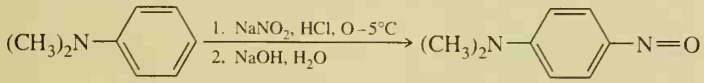
11. Gabriel Synthesis of Primary Amines and Amino Acids (Section 22.8D)

The primary amine or amino acid is liberated by hydrolysis in aqueous NaOH. Alternatively, it can be liberated by an exchange reaction in which the *N*-alkylated phthalimide is converted to a phthalylhydrazide.



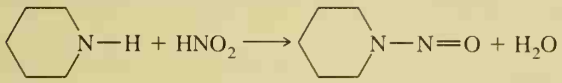
12. Nitrosation of Tertiary Aromatic Amines (Section 22.10B)

The nitrosyl cation is a very weak electrophile and participates in electrophilic aromatic substitution only with highly activated rings.



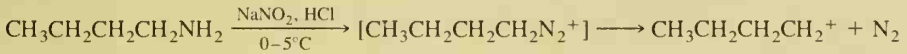
13. Formation of *N*-Nitrosoamines from Secondary Amines (Section 22.10C)

Several low-molecular-weight *N*-nitrosoamines have been identified as carcinogens in laboratory test animals.



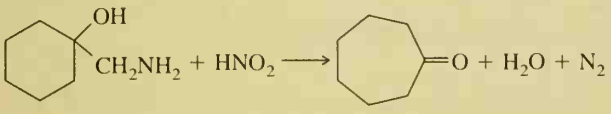
14. Treatment of Primary Aliphatic Amines with Nitrous Acid (Section 22.10D)

Treatment of a primary aliphatic amine with nitrous acid gives an unstable diazonium ion that loses N_2 to give a carbocation. The carbocation may (1) lose a proton to give an alkene, (2) react with a nucleophile, or (3) rearrange, followed by (1) or (2).



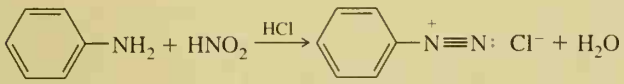
15. β-Aminoalcohols Treated with Nitrous Acid Undergo Rearrangement (Section 22.10D)

Conversion of a cyclic ketone to a β-aminoalcohol followed by treatment with nitrous acid leads to rearrangement and a ring-expanded ketone.



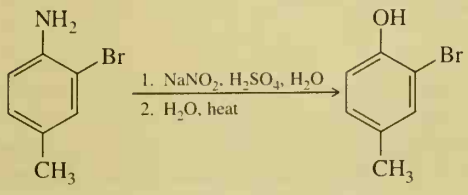
16. Formation of Aryl Diazonium Ions (Section 22.10E)

Aryl diazonium ions are stable in aqueous solution at 0°C for short periods.



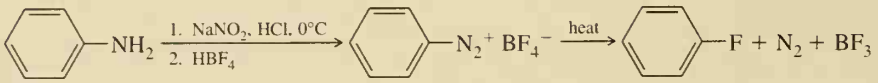
17. Conversion of a Primary Aryl Amine to a Phenol (Section 22.10E)

Formation of an aryl diazonium ion followed by loss of nitrogen gives an aryl cation intermediate, which then reacts with water to give a phenol.



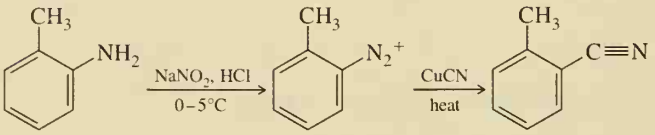
18. Schiemann Reaction (Section 22.10E)

Heating a diazonium fluoroborate is the most common synthetic method for introducing fluorine onto an aromatic ring.



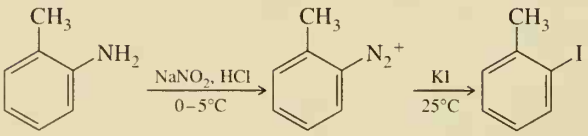
19. Sandmeyer Reaction (Section 22.10E)

Treatment of an aryl diazonium salt with CuCl, CuBr, or CuCN results in displacement of the diazonium group by —Cl, —Br, or —CN, respectively.



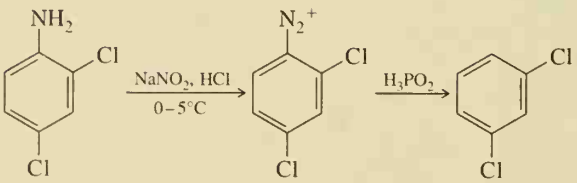
20. Treatment of an Aryl Diazonium Ion with KI (Section 22.10E)

Reaction of an aryl diazonium ion with KI is the most convenient method for introducing iodine onto an aromatic ring.



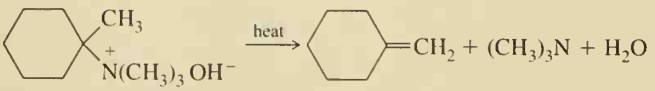
21. Reduction of an Aryl Diazonium Ion with Hypophosphorous Acid (Section 22.10E)

An —NO_2 or —NH_2 group can be used to control orientation of further substitution and then removed once it has served its purpose.



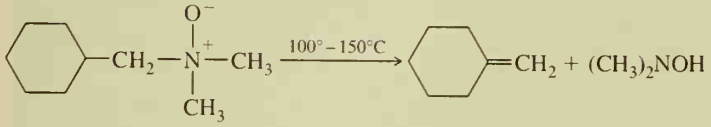
22. Hofmann Exhaustive Methylation/Elimination (Section 22.11)

Elimination occurs preferentially to form the least substituted double bond (Hofmann's rule).



23. Cope Elimination: Pyrolysis of a Tertiary Amine Oxide (Section 22.12)

Elimination is syn stereoselective and involves a cyclic flow of six electrons in a planar transition state, that is, it involves transition state aromaticity.



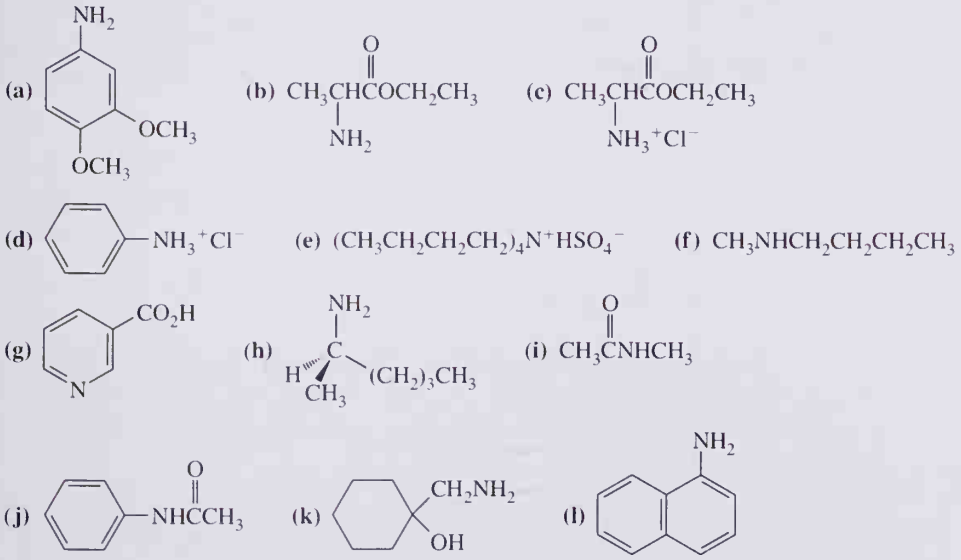
ADDITIONAL PROBLEMS

Structure and Nomenclature

22.15 Draw structural formulas for the following amines and amine derivatives:

(a) *N,N*-Dimethylaniline
(b) Triethylamine
(c) *tert*-Butylamine
(d) 1,4-Diaminobenzene
(e) 4-Aminobutanoic acid
(f) 2-Aminoethanol (ethanolamine)
(g) Ethyl *p*-aminobenzoate
(h) *trans*-2-Aminocyclohexanol
(i) (R)-2-Aminobutane
(j) Lithium diisopropylamide (LDA)
(k) 2-Amino-1-phenylpropane (amphetamine)
(l) Benzylamine
(m) Benzyltrimethylammonium hydroxide (Triton B)

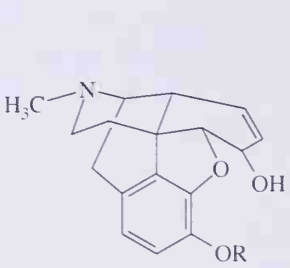
22.16 Give an acceptable name for the following compounds:



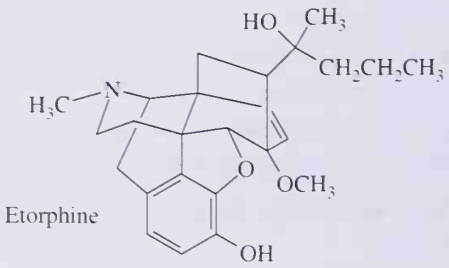
22.17 Morphine and its *O*-methylated derivative codeine are among the most effective pain killers known. However, they possess two serious drawbacks: They are addictive, and repeated use induces a tolerance to the drug. Increasingly larger doses become necessary which can lead to respiratory arrest. Many morphine analogs have been prepared in an effort to find drugs that

The opium poppy, *Papaver somniferum*. (© Andrew Henderson, PHOTO/NATS)

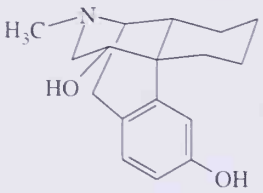
are equally effective as pain killers but which have less risk of physical dependence and potential for abuse. Following are structural formulas for etorphine (1000 times more potent than morphine), levorphanol (similar to morphine), pentazocine (one-third the potency of codeine), meperidine (one-half the potency of morphine), and dextropropoxyphene (one-half the potency of codeine). Methadone with a potency equal to that of morphine is used to treat opiate withdrawal symptoms in heroin abusers.



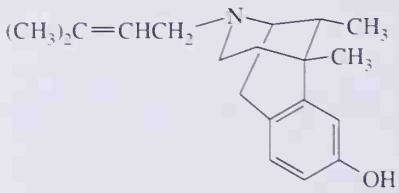
R═H; morphine
R═CH_3; codeine



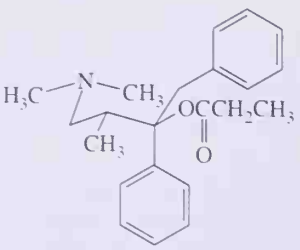
Etorphine



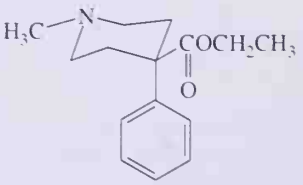
Levorphanol
(Levo-dromoran)



Pentazocine
(Talwin)



Dextropropoxyphene
(Darvon)



Meperidine
(Demerol)

Methadone

(a) List the structural features common to each of these molecules.

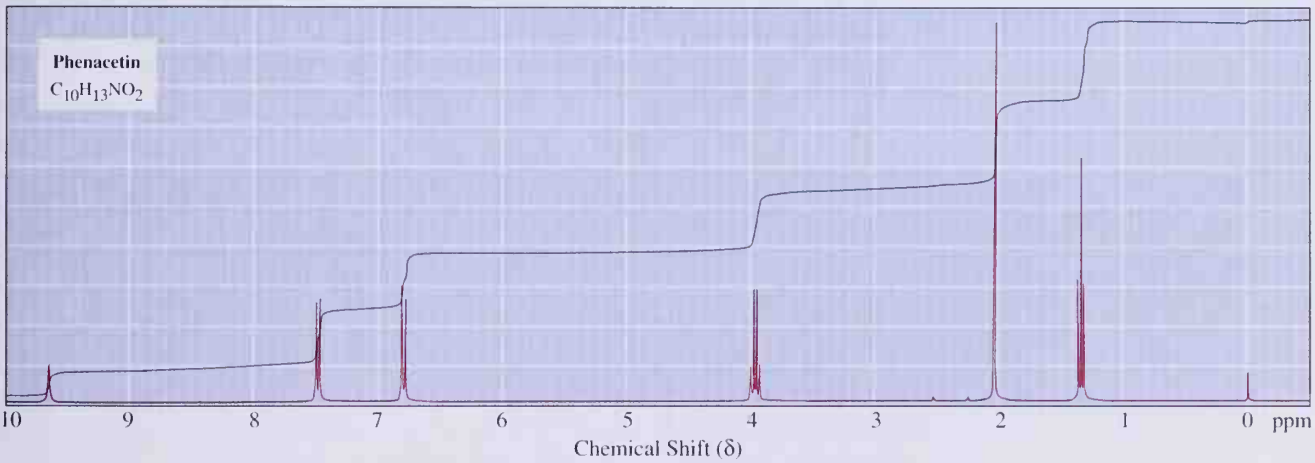
(b) The Beckett-Casy rules are a set of empirical rules that predict the structures of molecules that bind to morphine receptors and act as analgesics. According to these rules, to provide effective morphine-like analgesia, a molecule must have (1) an aromatic ring attached to (2) a quaternary carbon and (3) a nitrogen at a distance equal to two carbon-carbon single bond lengths from the quaternary center. Are each of these structural requirements present in the molecules given in this problem?

Spectroscopy

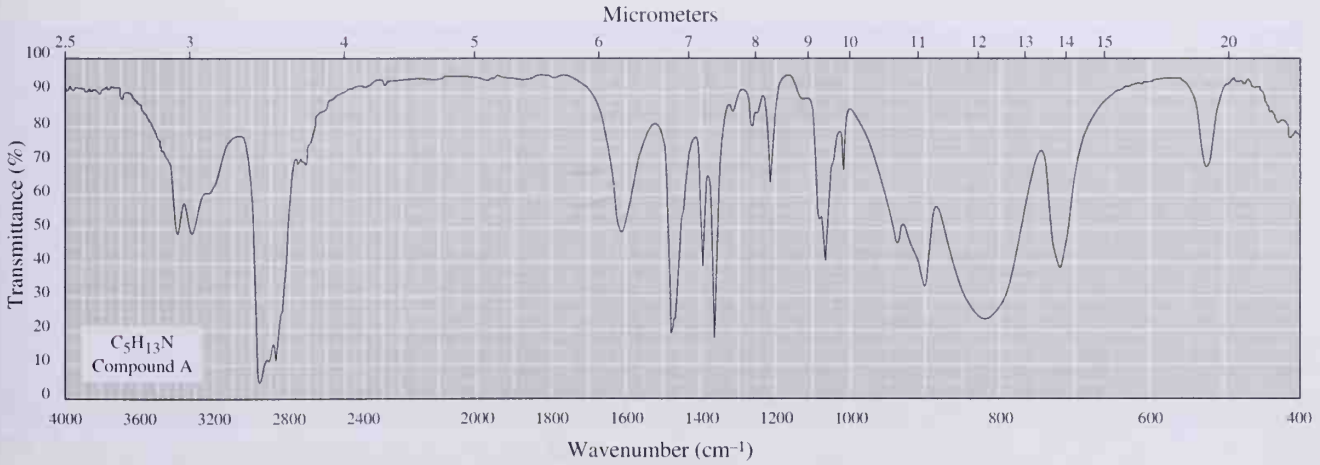
22.18 Account for the formation of the base peaks in these mass spectra.

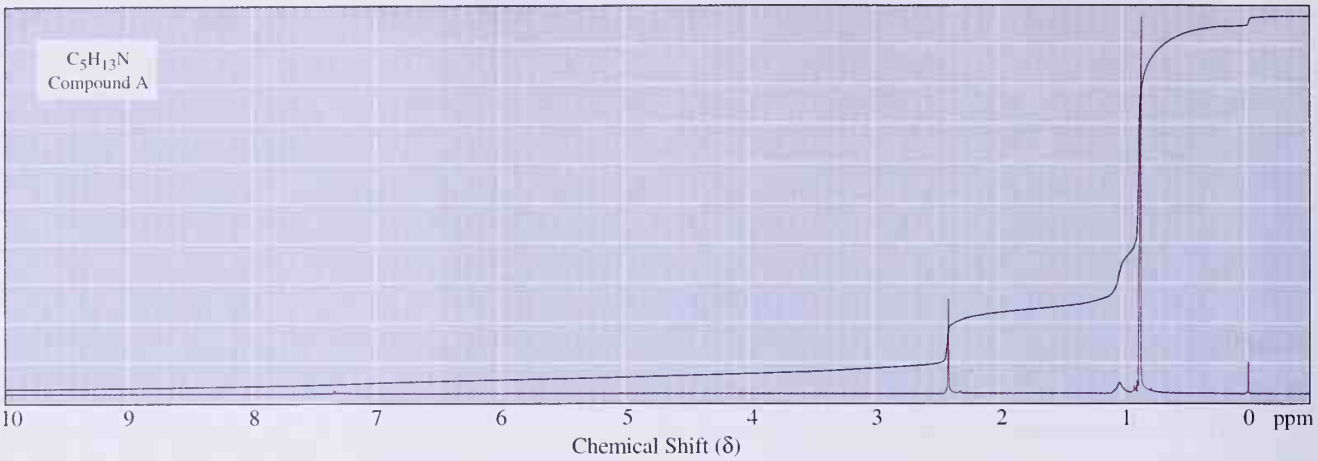
(a) Methylisobutylamine, *m/e* 44 **(b)** Diethylamine, *m/e* 58

22.19 Propose a structural formula for the analgesic phenacetin, molecular formula $C_{10}H_{13}NO_2$, based on its ^{1}H-NMR spectrum.

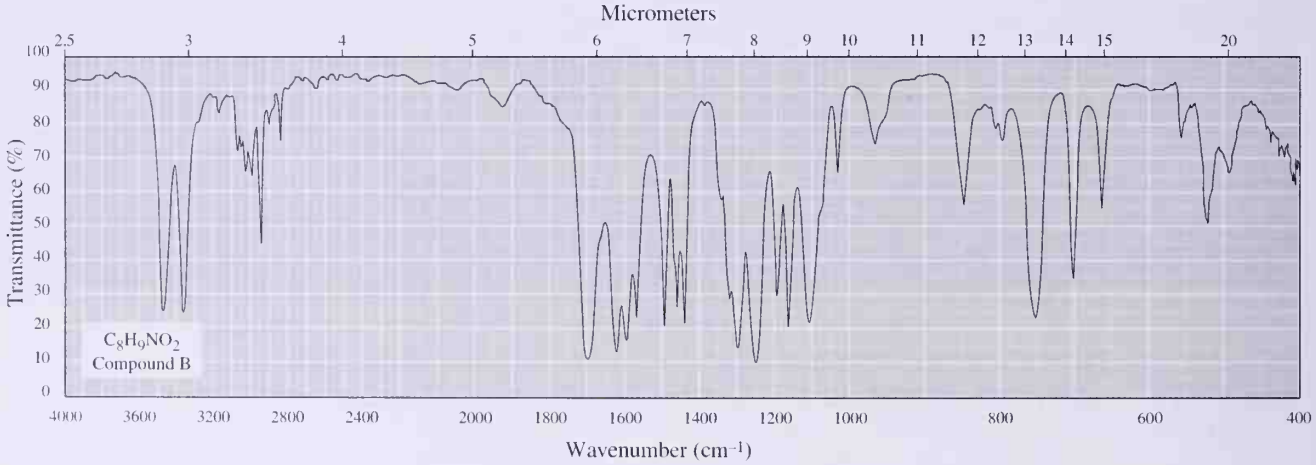


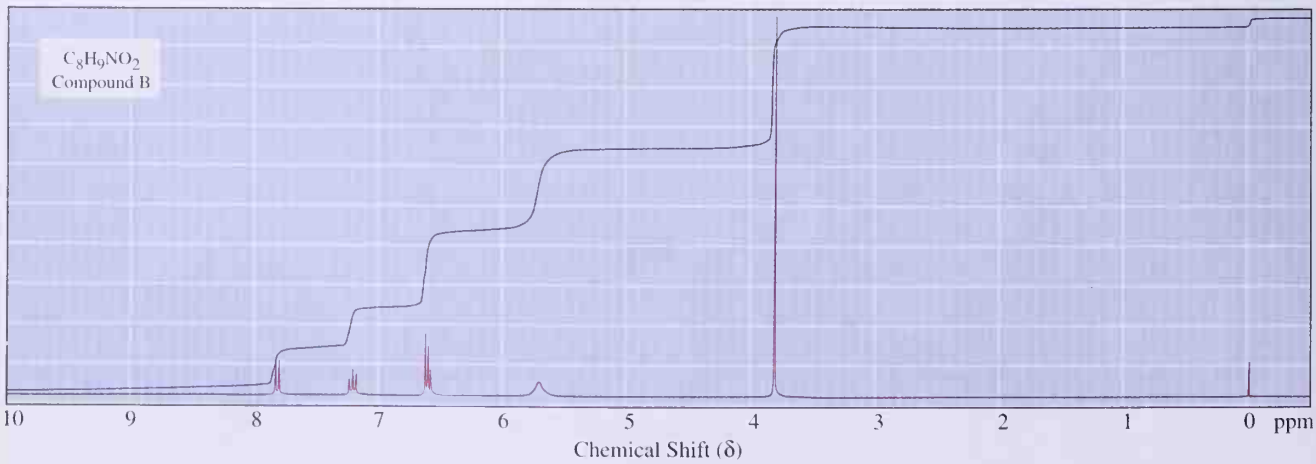
22.20 Propose a structural formula for compound A, molecular formula $C_5H_{13}N$, given its IR and ^{1}H-NMR spectra.



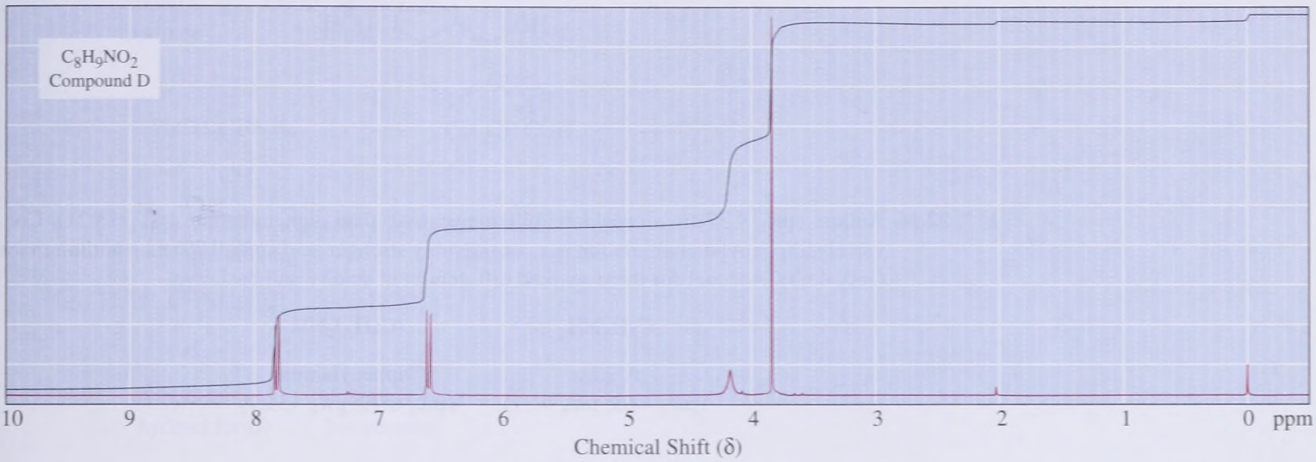


22.21 Propose a structural formula for compound B, molecular formula $C_8H_9NO_2$, given the following information. Compound B is insoluble in water and in 5% NaOH but dissolves readily in 5% HCl. It dissolves slowly in refluxing 5% NaOH, and upon careful neutralization of the resulting solution to pH 7.0, compound C, molecular formula $C_7H_7NO_2$, precipitates. Compound C is insoluble in water but dissolves readily in both dilute NaOH and dilute HCl. Following are IR and ^{1}H-NMR spectra of compound B.



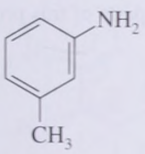
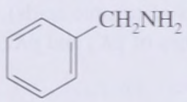


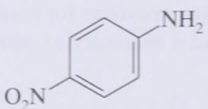
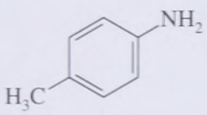
22.22 Following is the ^{1}H-NMR spectrum of compound D, molecular formula $C_8H_9NO_2$. Propose a structural formula for compound D consistent with this spectrum.

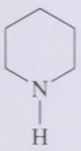
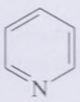


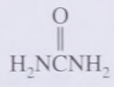
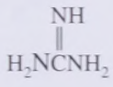
Basicity of Amines

22.23 Select the stronger base in each pair of compounds.

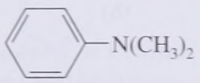
(a)  or 

(b)  or 

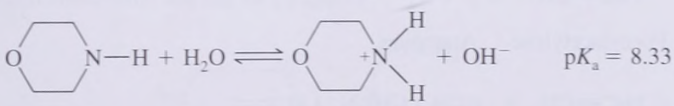
(c)  or 

(d)  or 

(e)  or 

(f) $(CH_3CH_2CH_2)_3N$ or 

22.24 The pK_a of morpholine is 8.33.

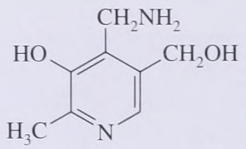


Morpholine — Morpholinium ion

(a) Calculate the ratio of morpholine to morpholinium ion in aqueous solution at pH 7.0.

(b) At what pH are the concentrations of morpholine and morpholinium ion equal?

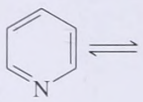
22.25 Which of the two nitrogens in pyridoxamine (a form of vitamin B_6) is the stronger base? Explain your reasoning.



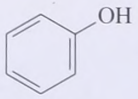
22.26 Aniline (pK_b 9.37) is a considerably stronger base than diphenylamine (pK_b 13.21). Conversely, diphenylammonium ion is a considerably stronger acid (pK_a 0.79) than anilinium ion (pK_b 4.63). Account for these marked differences in acidity and basicity.

$C_6H_5NH_2$	$(C_6H_5)_2NH$
Aniline	Diphenylamine
(pK_a 4.63; pK_b 9.37)	(pK_a 0.79; pK_b 13.21)

22.27 Complete the following acid-base reactions and predict the direction of equilibrium (to the right or to the left) for each. Justify your prediction by citing values of pK_a for the stronger and weaker acid in each equilibrium. For values of acid ionization constants, consult Table 3.2 (Strengths of some inorganic and organic acids), Table 6.2 (Acidity of alkanes, alkenes, and alkynes), Table 9.3 (Acidity of alcohols), Section 15.5 (Acidity of phenols), Section 19.4 (Acidity of carboxylic acids), Table 22.2 (Base strengths of amines), and Table 22.3 (Acid ionization constants for major classes of organic acids). For some parts of this problem, you will find it necessary to estimate values of pK_a and pK_b.

(a) CH_3COH +  $\rightleftharpoons$

Acetic acid — Pyridine

(b)  + $(CH_3CH_2)_3N$ $\rightleftharpoons$

Phenol — Triethylamine

(c) $PhC{\equiv}CH$ + NH_3 $\rightleftharpoons$

Phenylacetylene — Ammonia

(d) $PhC{\equiv}CH$ + $[(CH_3)_2CH]_2N^-\ Li^+$ $\rightleftharpoons$

Phenylacetylene — Lithium diisopropylamide (LDA)

(e) $PhCO^- Na^+ + (CH_3CH_2)_3NH^+ Cl^- \rightleftharpoons$

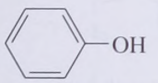
Sodium benzoate — Triethylammonium chloride

(f) $PhCH_2CH(CH_3)NH_2 + CH_3CH(OH)COH \rightleftharpoons$

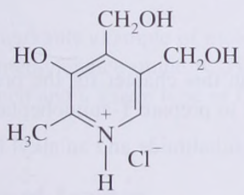
2-Amino-1-phenylpropane (Amphetamine) — 2-Hydroxypropanoic acid (Lactic acid)

(g) $PhCH_2CH(CH_3)NH_3^+ Cl^- + NaHCO_3 \rightleftharpoons$

Amphetamine hydrochloride — Sodium bicarbonate

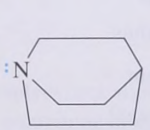
(h)  $+ (CH_3)_4N^+OH^- \rightleftharpoons$

Phenol — Tetramethylammonium hydroxide

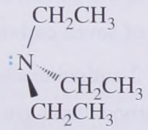
(i)  $+ NaHCO_3 \rightleftharpoons$

Pyridoxine hydrochloride (Vitamin B_6 hydrochloride) — Sodium bicarbonate

22.28 Quinuclidine and triethylamine are both tertiary amines. Quinuclidine, however, is a considerably stronger base than triethylamine. Stated alternatively, the conjugate acid of quinuclidine is a considerably weaker acid than the conjugate acid of triethylamine. Propose an explanation for these differences in acidity and basicity. (*Hint:* The answer lies in the ease with which each ammonium ion can be solvated.)

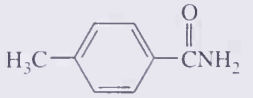


Quinuclidine (pK_a 10.6)



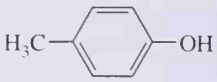
Triethylamine (pK_a 8.6)

22.29 Suppose you have a mixture of the following three compounds. Devise a chemical procedure based on their relative acidity or basicity to separate and isolate each in pure form.



4-Methylbenzamide
(*p*-Toluamide)

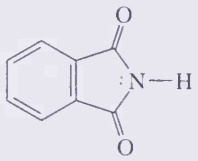
4-Methylaniline
(*p*-Toluidine)



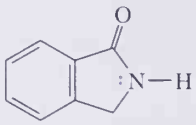
4-Methylphenol
(*p*-Cresol)

Basicity of Amides and Imides

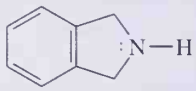
22.30 The following imide is a weak acid, the amide is neutral, and the secondary amine is a weak base. Provide an explanation for the marked differences in acidity/basicity of the nitrogen atom in each compound.



A weak acid
(pK_a 8.3)



Neutral



A weak base

Preparation of Amines

22.31 Following are the seven synthetic methods presented in this chapter for the preparation of primary aliphatic amines. Show how each may be used to prepare 1-aminoheptane.

(a) The Gabriel synthesis using the potassium salt of phthalimide and an alkyl halide

(b) Amination of an alkyl halide

(c) Reduction of an amide using $LiAlH_4$

(d) Reduction of an azide using H_2 in the presence of a transition metal catalyst

(e) Reductive amination of an aldehyde

(f) Reduction of a nitrile by $LiAlH_4$ or H_2 in the presence of a transition metal catalyst

(g) Hoffman rearrangement of a primary amide using Br_2 in aqueous NaOH

22.32 Propose a synthesis of 1-aminohexane from

(a) An aldehyde of six carbon atoms

(b) A bromoalkane of six carbon atoms (three ways)

(c) A bromoalkane of five carbon atoms

(d) A carboxylic acid of six carbon atoms

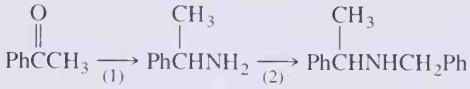
(e) A carboxylic acid of seven carbon atoms

22.33 Propose a synthesis of 2-aminohexane from

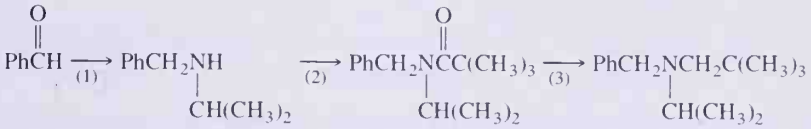
(a) A ketone of six carbon atoms (two ways)

(b) A bromoalkane of six carbon atoms (three ways)

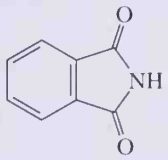
22.34 Show how the following secondary amine can be prepared by two successive reductive aminations:



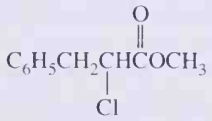
22.35 Show reagents for the synthesis of the following tertiary amine:



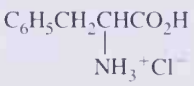
22.36 One of the most important uses of the Gabriel synthesis has been the preparation of amino acids (Chapter 24), including amino acids labeled with nitrogen-15. Show how to prepare ^{15}N-labeled phenylalanine hydrochloride starting from ^{15}N-labeled phthalimide and the following α-chloroester.



Phthalimide



Methyl 2-chloro-3-phenylpropanoate



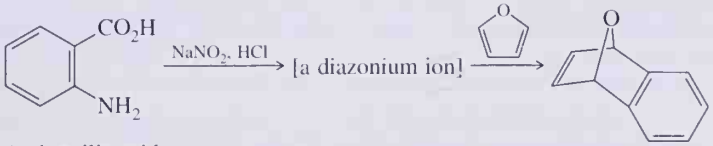
Phenylalanine hydrochloride

22.37 A remarkable example of molecular self-assembly is the reaction of NH_3 and CH_2O to give hexamethylenetetramine, $C_6H_{12}N_4$. This highly symmetrical molecule has a single type of nitrogen and a single type of CH_2 group. What is its structure?

Reactions of Amines

22.38 Treatment of benzylamine with cyclohexanecarbaldehyde generates an imine. Treatment of this imine with strong base followed by mild acid hydrolysis produces benzaldehyde and (cyclohexylmethyl)amine. Propose a mechanism for this transformation.

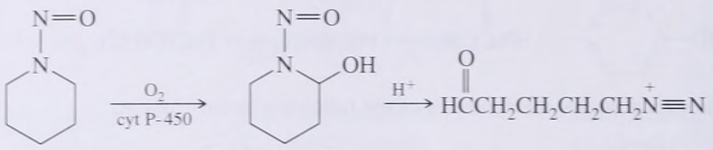
22.39 Treatment of anthranilic acid with nitrous acid gives a diazonium ion. When heated in the presence of furan, a bicyclic compound is formed. Propose a mechanism for formation of the bicyclic product.



Anthranilic acid

22.40 *N*-Nitrosamines are, by themselves, not significant carcinogens. However, they are activated in the liver by a class of iron-containing enzymes (members of the cytochrome P-450 family). Activation involves the oxidation of a C—H bond next to the amine nitrogen to a C—OH

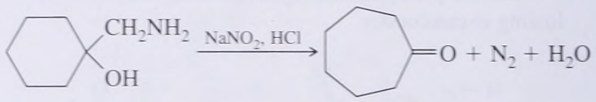
group. Show how this hydroxylation product can be transformed into an alkyl diazonium ion, an active carcinogen, in the presence of an acid catalyst.



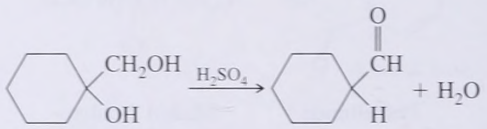
N-Nitroso-piperidine | 2-Hydroxy-*N*-nitrosopiperidine | An alkyl diazonium ion (a carcinogen)

22.41 Marked similarities exist between the mechanism of nitrous acid deamination of β-aminoalcohols and the pinacol rearrangement. Following are examples of each. Analyze the mechanism of each rearrangement and list their similarities.

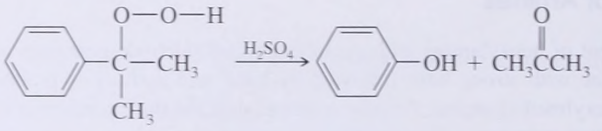
Nitrous acid deamination of a β-aminoalcohol:



Pinacol rearrangement:



22.42 Each rearrangement in the previous problem involves generation of an electron-deficient atom (in each case a positively charged carbon atom) followed by a 1,2-shift of an atom or group of atoms from an adjacent carbon to the electron-deficient atom. A mechanism that can be written for the following reaction also involves generation of an electron-deficient atom (in this case an oxygen) followed by a 1,2-shift from an adjacent carbon to the electron-deficient atom.

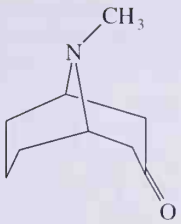


Cumene hydroperoxide | Phenol | Acetone

Propose a mechanism for the rearrangement of cumene hydroperoxide to phenol and acetone based on the previous rationale. In completing a mechanism, you will want to review the characteristic structural feature of a hemiacetal (Section 17.9B) and its equilibration by loss of water with a ketone.

Hofmann and Cope Eliminations

22.43 The following sequence of Clemmensen reduction, exhaustive methylation, and Hofmann elimination was used in the determination of the structure of pseudopelletierine, a compound isolated from the root bark of *Punica granatum* L., Punicaceae.



Pseudopelletierine
($C_9H_{15}NO$)

$$\xrightarrow{\text{1. Zn/HCl}} C_9H_{17}N \xrightarrow[\text{4. heat}]{\text{2. } CH_3I,\ \text{3. } Ag_2O,\ H_2O} C_{10}H_{19}N \xrightarrow[\text{7. heat}]{\text{5. } CH_3I,\ \text{6. } Ag_2O,\ H_2O} C_8H_{12}$$

(A) (B) (C)

(a) Propose structural formulas for compounds (A), (B), and (C).

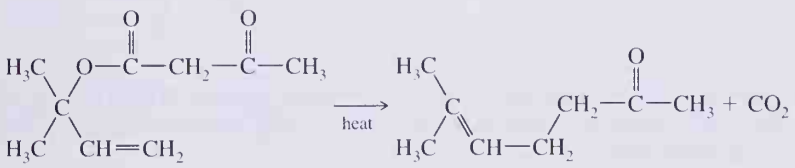
(b) Suppose you were given the structural formula of compound (C) but only molecular formulas for compounds (B), (A), and pseudopelletierine. Given this information, is it possible, working backward, to arrive at an unambiguous structural formula for compound (B)? for compound (A)? for pseudopelletierine?

22.44 We have seen examples of three reactions that involve a planar transition state and cyclic redistribution of $(4n + 2)$ electrons; the Diels-Alder reaction (Section 7.5D), the Claisen rearrangement of allyl phenyl ethers (Section 15.5E), and Cope elimination of tertiary amine *N*-oxides (Section 22.13). The pyrolysis of acetate esters to give an alkene and acetic acid is also thought to involve a planar transition state and cyclic redistribution of $(4n + 2)$ electrons. Write a transition state for the pyrolysis of the following ester. Use curved arrows to show the redistribution of valence electrons in the transition state.

$$CH_3CH_2CH_2CH_2O\overset{\overset{O}{\|}}{C}CH_3 \xrightarrow{500\ ^\circ C} CH_3CH_2CH{=}CH_2 + CH_3\overset{\overset{O}{\|}}{C}OH$$

Butyl acetate 1-Butene Acetic acid

22.45 The following transformation is an example of the Carroll reaction, named after the English chemist, M. F. Carroll, who first reported it. Propose a mechanism for this reaction.



6-Methyl-5-hepten-2-one

Synthesis

22.46 Show how to bring about the following conversions using a reaction of a diazonium salt in at least one step of each synthesis.

(a) Aniline to 2,4,6-tribromobenzoic acid **(b)** Nitrobenzene to 3-bromophenol

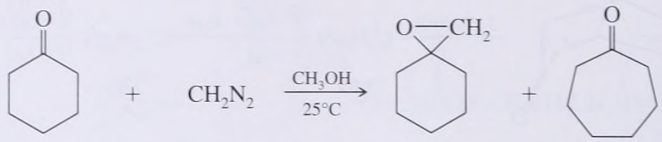
(c) Toluene to *p*-bromobenzoic acid **(d)** Phenol to *p*-iodoanisole

(e) Acetanilide to *p*-aminobenzylamine **(f)** Toluene to 4-fluorobenzoic acid

(g) 3-Methylaniline (*m*-toluidine) to 2,4,6-tribromobenzoic acid

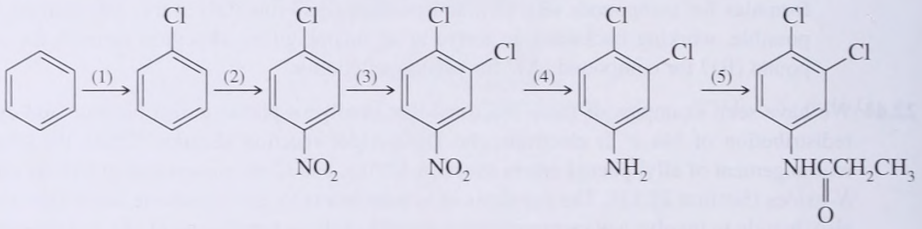
22.47 Example 22.10 and Problem 22.10 that followed it presented two reaction sequences for conversion of cyclohexanone to cycloheptanone. Still a third way to bring about this transfor-

mation is to treat cyclohexanone with diazomethane. In addition to cycloheptanone, small amounts of an epoxide are also formed. Propose a mechanism for the formation of these products.



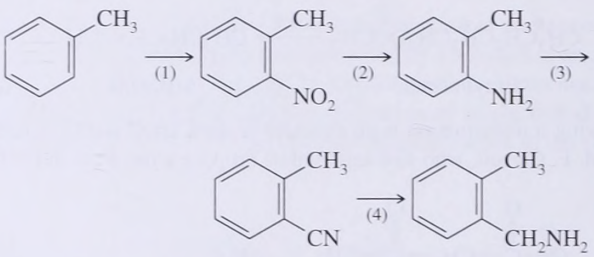
Cyclohexanone Diazomethane An epoxide Cycloheptanone (major product)

22.48 Starting materials for the synthesis of the herbicide Propranil are benzene and propanoic acid. Show how to bring about the following series of steps in this synthesis:

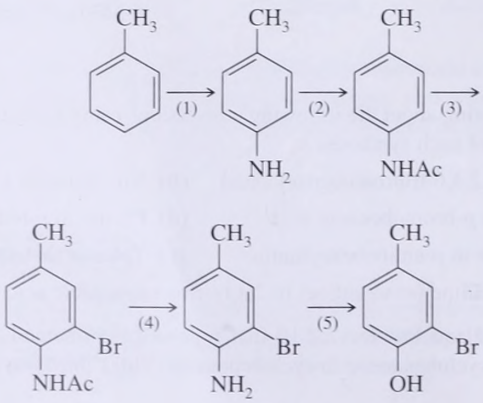


Propranil

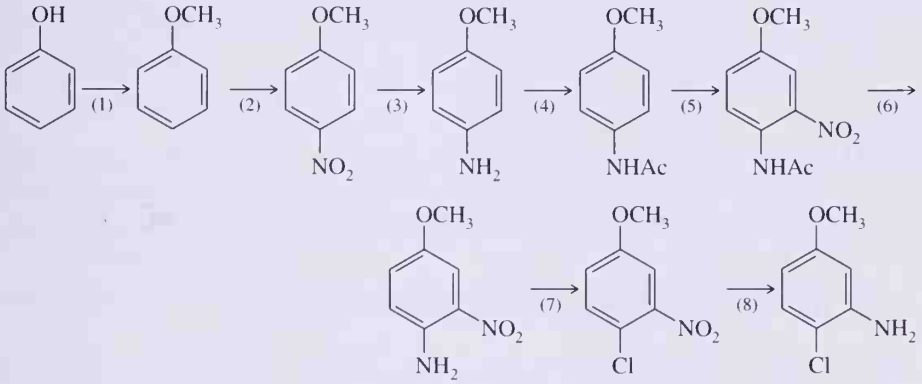
22.49 Show how to bring about each step in the following synthesis:



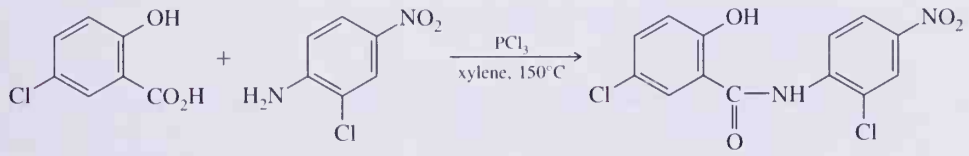
22.50 Show how to bring about each step in the following synthesis. Why is it necessary to convert the $—NH_2$ group to $—NHCOCH_3$ (an amide) in Step 2 before carrying out bromination of the aromatic ring?



22.51 Following are steps in a conversion of phenol to 2-chloro-5-methoxyaniline. Show how to bring about each step in good yield. Why is it necessary to convert the $-NH_2$ group to an amide before nitration of the aromatic ring in Step 5?



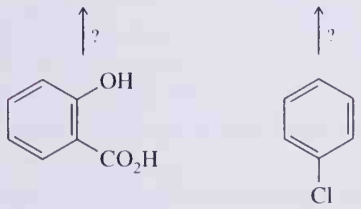
△ **22.52** The World Health Organization estimates that the tropical disease schistosomiasis (bilharziasis) affects between 180 and 200 million persons and, next to malaria, is the world's most serious parasitic infection in humans. The disease is caused by blood flukes, small flatworms of the family Schistosomatidae, which live in the blood vessels of humans and other mammals. Female blood flukes release from 300 to 3000 eggs daily into the bloodstream. Those evacuated in the feces or urine into fresh water hatch to larvae, which find their way to host water snails, and develop further. The disease is most often contracted by humans from contaminated water populated by snails that carry the worms. Symptoms of the disease range from cough and fever to liver, lung, and brain damage. As one attack on this disease, the compound Bayluscid (niclosamide) has been developed to kill infected water snails.



5-Chloro-2-hydroxybenzoic acid

2-Chloro-4-nitroaniline

Bayluscid (Niclosamide)



Salicylic acid

Chlorobenzene

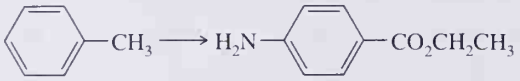
(a) Propose a synthesis of 5-chloro-2-hydroxybenzoic acid from salicylic acid.

(b) Propose a synthesis of 2-chloro-4-nitroaniline from chlorobenzene.

(c) What is the function of PCl_3 in the final stage of this synthesis?

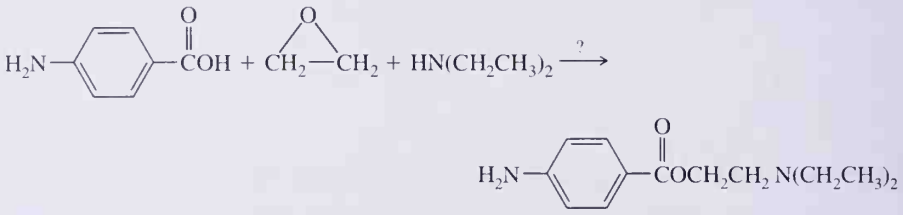
△ **22.53** Following is the structural formula of Benzocaine (ethyl *p*-aminobenzoate), a local anesthetic. Show how this molecule can be synthesized from toluene. Keep in mind as you plan your

synthesis that oxidation of aniline or a substituted aniline leads to substantial oxidation of the aromatic ring itself.



Toluene — Benzocaine (Ethyl 4-aminobenzoate)

22.54 Procaine (hydrochloride marketed as Novocaine) was one of the first local anesthetics for infiltration and regional anesthesia. Show how to synthesize this molecule using *p*-aminobenzoic acid, ethylene oxide, and diethylamine as sources of carbon atoms.



Procaine (Novocaine)

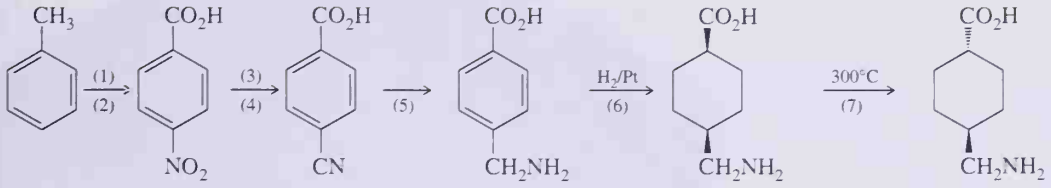
22.55 Following are structural formulas for three local anesthetics. Lidocaine was introduced in 1948 and is now the most widely used local anesthetic for infiltration and regional anesthesia. Its hydrochloride is marketed under the name Xylocaine. Etidocaine (hydrochloride marketed as Duranest) is comparable to lidocaine in onset, but its analgesic action lasts two to three times longer. Anesthetic action from mepivacaine (hydrochloride marketed as Carbocaine) is faster and somewhat longer in duration than lidocaine.

Xylocaine (Lidocaine) — Duranest (Etidocaine) — Carbocaine (Mepivacaine)

(a) Propose a synthesis of lidocaine from 2,6-dimethylaniline and α-chloroacetyl chloride.

(b) Propose a synthesis of etidocaine from 2,6-dimethylaniline and 2-chlorobutanoyl chloride.

22.56 Blood clotting is a mechanism by which the body prevents excessive loss of blood after an injury. After the injury is healed, the clot is dissolved by enzyme-catalyzed hydrolysis of peptide (amide) bonds of clot polypeptides. Among the enzymes activated for this purpose are fibrinolysin and plasmin. Plasmin is in turn generated as needed by enzyme-catalyzed hydrolysis of the polypeptide, plasminogen. Excessive generation of plasmin can lead to pathological conditions, in which cases a way must be found to decrease plasmin production. The generation of plasmin is inhibited by *p*-aminomethylbenzoic acid and its reduction product *trans*-4-aminomethylcyclohexanecarboxylic acid. Each of these compounds is synthesized from toluene by the following sequence of reactions. Catalytic reduction of the aromatic ring in Step 6 gives largely the *cis* isomer. When heated at 315 to 325°C in an atmosphere of nitrogen, the *cis* isomer is converted to the *trans* isomer.



p-Aminomethylbenzoic acid

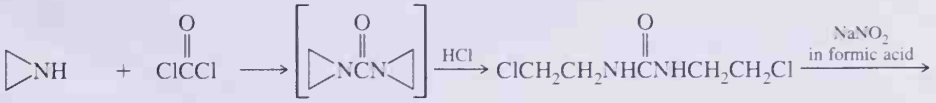
trans-4-Aminomethylcyclohexanecarboxylic acid

(a) Describe experimental conditions by which to bring about Steps 1 through 5.

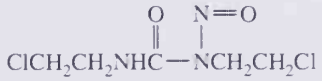
(b) Which is more stable, the *cis* isomer formed in Step 6 or the *trans* isomer formed in Step 7? Explain your reasoning.

(c) Propose a mechanism to account for the thermal isomerization of the *cis* isomer to the *trans* isomer.

22.57 Carmustine (Bicnu) belongs to the class of compounds called *N*-nitrosoureas. Carmustine and several of its analogs are potent antitumor drugs against a wide variety of human malignancies. This drug is synthesized from phosgene and ethyleneimine by the following steps:



Ethyleneimine Phosgene

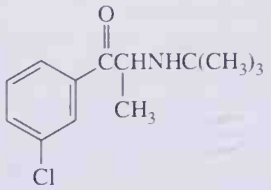


N,*N*′-bis(2-Chloroethyl)-*N*-nitrosourea
(Carmustine, Bicnu)

(a) Propose a mechanism for reaction of phosgene with 2 mol of ethyleneimine to give the bracketed intermediate, and for reaction of the bracketed intermediate with HCl to give the *N*,*N*′-disubstituted urea.

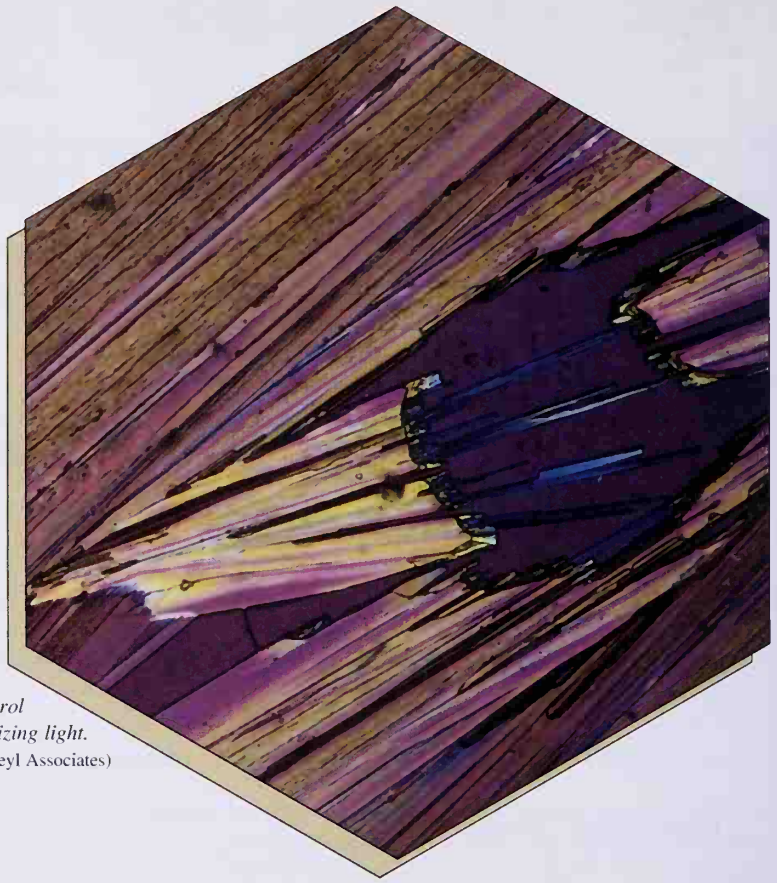
(b) Propose a mechanism for reaction of this *N*,*N*′-disubstituted urea with sodium nitrite in formic acid to give carmustine.

22.58 The drug, bupropion, is a recently introduced antidepressant. Propose a synthesis of this drug starting from benzene and any other necessary reagents.



Bupropion

23



Crystals of cholesterol viewed under polarizing light. (Mel Pollinger/Fran Heyl Associates)

LIPIDS

Lipids are a heterogeneous class of naturally occurring organic compounds classified together on the basis of common solubility properties. They are insoluble in water but soluble in aprotic organic solvents, including diethyl ether, methylene chloride, and acetone. Carbohydrates and nucleic acids, as well as amino acids and proteins, are largely insoluble in these organic solvents.

Lipids are divided into two main groups. First are those lipids that contain both a relatively large nonpolar hydrophobic region, most commonly aliphatic in nature, and a polar hydrophilic region. Found among this group are triacylglycerols, phospholipids, prostaglandins, and the fat-soluble vitamins. Second are those lipids that contain the tetracyclic ring system called the steroid nucleus. Found among this group are cholesterol, steroid hormones, and bile acids.

In this chapter we describe the structures and biological functions of each group of lipids. In addition, we describe the biosynthesis of terpenes and steroids, and show how the carbon skeletons of these biomolecules are derived entirely from the two-carbon acetyl group of acetyl-CoA.

23.1 Fatty Acids, Soaps, and Detergents

Fatty acids are monocarboxylic acids obtained from the hydrolysis of fats and oils (Section 23.2) and phospholipids of biological membranes (Section 23.5). While more than 500 different fatty acids have been isolated from various cells and tissues, only about 5 are common (Table 23.2).

A. Structure of Fatty Acids

Given in Table 23.1 are common names, structural formulas, and chain length–unsaturation notations for several of the most abundant fatty acids. The number of carbons in a fatty acid and the number of carbon-carbon double bonds in its hydrocarbon chain are shown by two numbers separated by a colon. In this notation, for example, linoleic acid is designated as an 18 : 2 fatty acid; its 18-carbon chain contains two double bonds. Following are several characteristics of the most abundant fatty acids found in higher plants and animals.

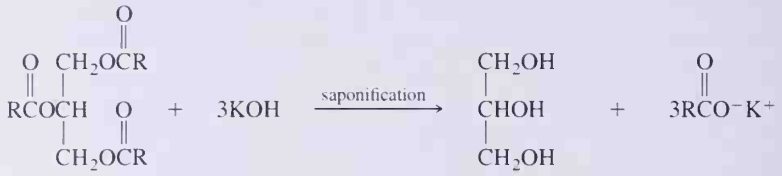
1. Nearly all fatty acids have an even number of carbon atoms, most between 10 and 20, in an unbranched chain.
2. The three most abundant fatty acids in nature are palmitic acid (C_{16}), stearic acid (C_{18}), and oleic acid (C_{18}).
3. In most unsaturated fatty acids of fats, oils, and biological membranes, the Z isomer *(cis)* predominates; the E isomer *(trans)* is rare.
4. Unsaturated fatty acids have lower melting points than their saturated counterparts. The greater the degree of unsaturation, the lower the melting point.

Table 23.1 The most abundant fatty acids in fats, oils, and biological membranes

Carbon Atoms/ Double Bonds	Structure	Common Name	Melting Point (°C)
Saturated Fatty Acids			
12:0	$CH_3(CH_2)_{10}CO_2H$	lauric acid	44
14:0	$CH_3(CH_2)_{12}CO_2H$	myristic acid	58
16:0	$CH_3(CH_2)_{14}CO_2H$	palmitic acid	63
18:0	$CH_3(CH_2)_{16}CO_2H$	stearic acid	70
20:0	$CH_3(CH_2)_{18}CO_2H$	arachidic acid	77
Unsaturated Fatty Acids			
16:1	$CH_3(CH_2)_5CH{=}CH(CH_2)_7CO_2H$	palmitoleic acid	−1
18:1	$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H$	oleic acid	16
18:2	$CH_3(CH_2)_4(CH{=}CHCH_2)_2(CH_2)_6CO_2H$	linoleic acid	−5
18:3	$CH_3CH_2(CH{=}CHCH_2)_3(CH_2)_6CO_2H$	linolenic acid	−11
20:4	$CH_3(CH_2)_4(CH{=}CHCH_2)_4(CH_2)_2CO_2H$	arachidonic acid	−49

B. Structure and Preparation of Natural Soaps

Natural soaps are potassium or sodium salts of fatty acids. Their preparation by boiling lard or other animal fat with potash is one of the most ancient organic reactions known. Potash (pot + ash), so named because it is the solid residue obtained by extracting wood ashes with water and then evaporating the water in iron pots, is a mixture of potassium carbonate and potassium hydroxide. The reaction that takes place when a fat or oil is boiled with potash is called saponification (Latin: *saponem*, soap). At the molecular level, saponification corresponds to base-promoted hydrolysis of ester groups in triglycerides (Section 23.2).



A triglyceride (a triester of glycerol) | 1,2,3-Propanetriol (Glycerol; Glycerin) | Potassium soaps

In Europe, soap manufacture started in Marseilles in the Middle Ages, but by no means was soap a commonly available product. By the late 1700s, however, manufacture of soap was widespread throughout Europe and North America and had become a big industry. As the soap as well as the glass and paper industries prospered, more and more wood had to be burned to provide the potash needed in their manufacture, and it seemed for a time that the forests of Europe might be threatened. Fortunately, through a new technology called the LeBlanc process, sodium carbonate (soda) became commercially available on a large scale and could in turn be used to produce sodium hydroxide. The change from potassium hydroxide to sodium hydroxide meant a change from potassium soaps to sodium soaps.

The common triglycerides used today are from beef tallow (from the meat-packing industry) and from coconut and palm oils. After hydrolysis is complete, sodium chloride is added to precipitate the soap as thick curds. The water layer is then drawn off and glycerol is recovered by vacuum distillation. The crude soap contains sodium chloride, sodium hydroxide, and other impurities. These are removed by boiling the curd in water and reprecipitating with more sodium chloride. After several purifications the soap can be used without further processing as an inexpensive industrial soap. Other treatments transform the crude soap into pH-controlled cosmetic soaps, medicated soaps, and the like.

C. How Soaps Clean

Soap owes its remarkable cleansing properties to its ability to act as an emulsifying agent. Because the long hydrocarbon chains of natural soaps are insoluble in water, they tend to cluster in such a way as to minimize their contact with surrounding water molecules. The polar carboxylate groups, on the other hand, tend to remain in contact with the surrounding water molecules. Thus, in water, soap molecules spontaneously cluster into micelles. In a soap micelle, the carboxylate groups form a negatively charged surface and the nonpolar hydrocarbon chains lie buried within the micelle (Figure 23.1). Most of the things we commonly think of as dirt, such as grease, oil, and fat stains, are nonpolar and insoluble in water. When soap and this type of dirt are mixed together, as in a washing machine, the

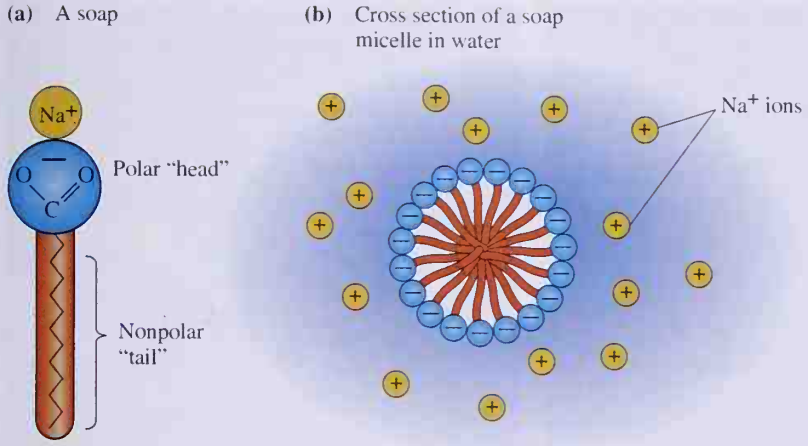


Figure 23.1
Soap micelles. (a) A sodium soap molecule. (b) Nonpolar (hydrophobic) hydrocarbon chains are clustered in the interior of the micelle, and polar (hydrophilic) carboxylate groups are on the surface of the micelle. Soap micelles repel each other because of their negative surface charges.

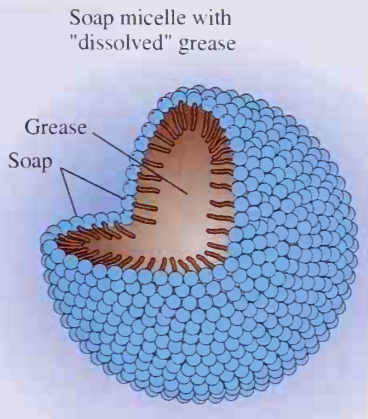


Figure 23.2
Soap micelles with a "dissolved" oil or grease droplet.

nonpolar hydrocarbon ends of the soap micelles "dissolve" the nonpolar dirt molecules. In effect, new soap micelles are formed, this time with nonpolar dirt molecules in the center (Figure 23.2). In this way, nonpolar organic grease, oil, and fat are "dissolved" and washed away in the polar wash water. Soaps are not without their disadvantages. First, they are salts of weak acids, and in the presence of mineral acids, they are converted to free fatty acids. Whereas soaps are soluble in water as micelles, free fatty acids are insoluble and form a scum. For this reason, soaps cannot be used in acidic solutions.

$$\underset{\text{A sodium soap (soluble in water as micelles)}}{CH_3(CH_2)_{14}CO_2^-Na^+} + HCl \longrightarrow \underset{\text{A fatty acid (insoluble in water)}}{CH_3(CH_2)_{14}CO_2H} + NaCl$$

Second, soaps form insoluble salts when used in water containing Ca(II), Mg(II), or Fe(III) ions (hard water).

$$\underset{\text{A sodium soap (soluble in water as micelles)}}{2CH_3(CH_2)_{14}CO_2^-\ Na^+} + Ca^{2+} \longrightarrow \underset{\text{Calcium salt of a fatty acid (insoluble in water)}}{[CH_3(CH_2)_{14}CO_2^-]_2Ca^{2+}} + 2Na^+$$

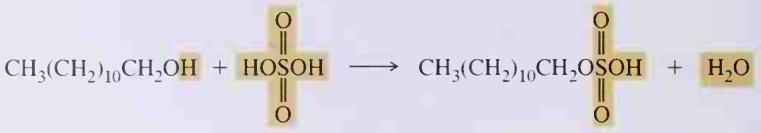
These calcium, magnesium, and iron salts of fatty acids create problems, including rings around the bathtub, films that spoil the luster of hair, grayness and roughness that build up on textiles after repeated washings, and wasting of soap to "soften" hard water.

D. Synthetic Detergents

Once the cleansing action of soaps was understood, a synthetic detergent could be designed; a molecule with a long hydrocarbon chain, preferably 12 to 20 carbon atoms, and a polar group at one end of the molecule that does not form insoluble salts with Ca(II),

Mg(II), or Fe(III) ions present in hard water. Chemists recognized that these essential characteristics of a soap could be produced in a molecule containing a sulfate or sulfonate group instead of a carboxylate group. Calcium, magnesium, and iron salts of monoalkylsulfuric and sulfonic acids are much more soluble in water than comparable salts of fatty acids.

The first synthetic detergent was made from 1-dodecanol (lauryl alcohol) by treating it with sulfuric acid to form a sulfate ester, followed by neutralization with sodium hydroxide to form the detergent commonly known as sodium dodecyl sulfate (SDS).

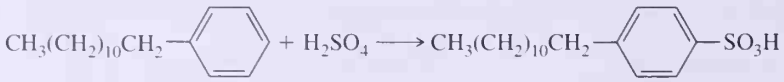


1-Dodecanol (Lauryl alcohol) — Dodecyl hydrogen sulfate (Lauryl hydrogen sulfate)

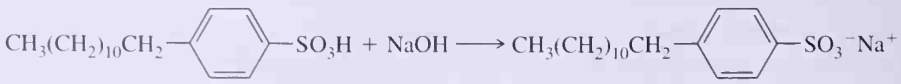
Dodecyl hydrogen sulfate (Lauryl hydrogen sulfate) — Sodium dodecyl sulfate (SDS) (Sodium lauryl sulfate)

The physical resemblance between SDS and a natural soap is obvious; both have a long nonpolar (hydrophobic) hydrocarbon chain and a highly polar (hydrophilic) end group. Large-scale commercial production of SDS was not possible because bulk quantities of 1-dodecanol were not available. However, because of its high foaming properties, SDS is used in numerous specialized applications, including shampoos and cosmetics. It is also used in biochemistry to denature proteins and to disrupt biological membranes.

Currently the most important synthetic detergents are the linear alkylbenzenesulfonates (LAS). One of the most common of these is sodium dodecylbenzenesulfonate. To prepare this type of detergent, a linear alkylbenzene is treated with sulfuric acid to form an alkylbenzenesulfonic acid. The sulfonic acid is then neutralized with NaOH, the product is mixed with builders, and spray-dried to give a smooth flowing powder. The most common builder is sodium silicate.



Dodecylbenzene — 4-Dodecylbenzenesulfonic acid

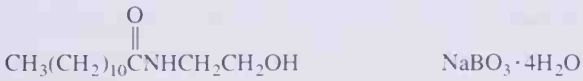


4-Dodecylbenzenesulfonic acid — Sodium 4-dodecylbenzenesulfonate (an anionic detergent)

Alkylbenzenesulfonate detergents were introduced in the late 1950s, and today they command close to 90% of the market once held by natural soaps.

Effects of optical bleaches: (*left*) ordinary light; (*right*) black light. *(Charles D. Winters)*

Among the most common additives to detergent preparations are foam stabilizers, bleaches, and optical brighteners. A common foam stabilizer added to liquid soaps but not laundry detergents (for obvious reasons: think of a top-loading washing machine with foam spewing out the lid!) is the amide prepared from dodecanoic acid (lauric acid) and 2-aminoethanol (ethanolamine). The most common bleach is sodium perborate tetrahydrate, which decomposes at temperatures above 50°C to give hydrogen peroxide, the actual bleaching agent.



N-(2-Hydroxyethyl)dodecanamide (a foam stabilizer)

Sodium perborate tetrahydrate (a bleach)

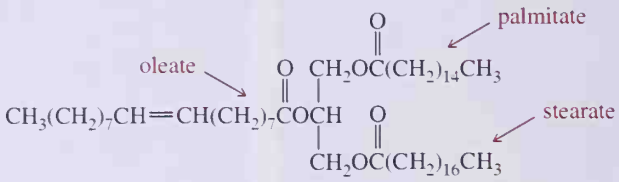
Also added to laundry detergents are optical brighteners, also called optical bleaches, that are absorbed into fabrics, and fluoresce with a blue color, offsetting the yellow color due to fabric aging. Quite literally, these optical brighteners produce a "whiter-than-white" appearance. You most certainly have observed the effects of optical brighteners if you have ever been in the presence of black light (ultraviolet radiation) and seen the glow of "white" T-shirts or blouses.

23.2 Triacylglycerols

A. Structure

Triacylglycerols, the most abundant naturally occurring lipids, are triesters of glycerol and fatty acids (Section 23.1A). A more common name for these compounds is triglycerides. Following is a structural formula for a triacylglycerol formed from glycerol and one

molecule each of stearic acid, palmitic acid, and oleic acid, three of the most abundant fatty acids in the biological world.



A triacylglycerol
(a triglyceride)

B. Physical Properties

The physical properties of a triacylglycerol depend on its fatty acid components. In general, the melting point of a triacylglycerol increases as the number of carbons in its hydrocarbon chains increases, and as the degree of saturation increases. Triacylglycerols rich in oleic acid, linoleic acid, and other unsaturated fatty acids are generally liquid at room temperature and are called **oils.** Triacylglycerols rich in palmitic, stearic, and other saturated fatty acids are generally semisolids or solids at room temperature and are called **fats.** Fats of land animals typically contain approximately 40% to 50% saturated fatty acids by weight (Table 23.2). Most plant oils, on the other hand, contain 20% or less saturated fatty acids and 80% or more unsaturated fatty acids. The notable exception to this generalization about plant oils are the tropical oils (e.g., coconut and palm oils), which are considerably richer in the lower molecular-weight saturated fatty acids.

The lower melting points of triacylglycerols rich in unsaturated fatty acids are related to differences in three-dimensional shape between hydrocarbon chains of their unsaturated and saturated fatty acid components. Shown in Figure 23.3 is a space-filling model of

Table 23.2 Grams of fatty acid per 100 g of triacylglycerol of several fats and oils. Only the most abundant fatty acids are given; other fatty acids are also present in lesser amounts

	Saturated Fatty Acids			Unsaturated Fatty Acids	
Fat or Oil	Lauric (12:0)	Palmitic (16:0)	Stearic (18:0)	Oleic (18:1)	Linoleic (18:2)
human fat	—	24.0	8.4	46.9	10.2
beef fat	—	27.4	14.1	49.6	2.5
butter fat	2.5	29.0	9.2	26.7	3.6
coconut oil	45.4	10.5	2.3	7.5	trace
corn oil	—	10.2	3.0	49.6	34.3
olive oil	—	6.9	2.3	84.4	4.6
palm oil	—	40.1	5.5	42.7	10.3
peanut oil	—	8.3	3.1	56.0	26.0
soybean oil	0.2	9.8	2.4	28.9	50.7

Figure 23.3
Tripalmitin, a saturated triacylglycerol.

Figure 23.4
A polyunsaturated triacylglycerol.

tripalmitin, a saturated triacylglycerol. In this model, the hydrocarbon chains lie parallel to each other, giving the molecule an ordered, compact shape. Because of this compact three-dimensional shape and the resulting strength of the dispersion forces between hydrocarbon chains, triacylglycerols rich in saturated fatty acids have melting points above room temperature.

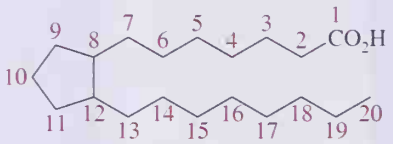
The three-dimensional shape of an unsaturated fatty acid is quite different from that of a saturated fatty acid. Recall from Section 23.1A that unsaturated fatty acids of higher organisms are predominantly of the *cis* configuration; *trans* configurations are rare. Figure 23.4 shows a space-filling model of a polyunsaturated triacylglycerol derived from one molecule each of stearic acid, oleic acid, and linoleic acid. Each double bond in this polyunsaturated triacylglycerol has the *cis* configuration. Polyunsaturated triacylglycerols have a less ordered structure and do not pack together so closely or so compactly as saturated triglycerides. Intramolecular and intermolecular dispersion forces are weaker, with the result that polyunsaturated triacylglycerols have lower melting points than their saturated counterparts.

C. Reduction of Fatty Acid Chains

For a variety of reasons, in part convenience and in part dietary preference, conversion of oils to fats has become a major industry. The process is called hardening of oils and involves treatment of a polyunsaturated plant oil with hydrogen in the presence of a transition metal catalyst, which results in reduction (hydrogenation) of some or all of the carbon-carbon double bonds. In practice, the degree of hardening is carefully controlled to produce fats of a desired consistency. The resulting fats are sold for kitchen use (Crisco, Spry, and others). Oleomargarine and other butter substitutes are prepared by hydrogenation of corn, soybean, cottonseed, and peanut oils. The resulting product is then churned with milk and artificially colored to give it a flavor, color, and consistency resembling those of butter.

23.3 Prostaglandins

The prostaglandins are a family of compounds all having the 20-carbon skeleton of prostanoic acid.



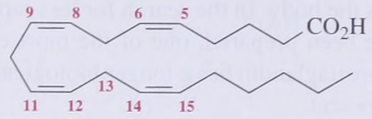
Prostanoic acid

The story of the discovery and structure determination of these remarkable compounds began in 1930 when gynecologists Raphael Kurzrok and Charles Lieb reported that human seminal fluid stimulates contraction of isolated uterine muscle. A few years later in Sweden, Ulf von Euler confirmed this report and noted that human seminal fluid also produces contraction of intestinal smooth muscle and lowers blood pressure when injected into the bloodstream. Von Euler proposed the name **prostaglandin** for the mysterious substance(s) responsible for these diverse effects because it was believed at the time that they were synthesized in the prostate gland. Although we now know that prostaglandin production is by no means limited to the prostate gland, the name nevertheless stuck. By the 1960s, several prostaglandins had been isolated and their structural formulas determined. Within the following decades chemists have devised strategies for synthesizing not only naturally occurring prostaglandins but also prostaglandin analogs, several of which are now used in clinical medicine.

Prostaglandins are not stored as such in target tissues. Rather, they are synthesized in response to specific physiological triggers. Starting materials for the biosynthesis of prostaglandins are polyunsaturated fatty acids of 20 carbon atoms, stored until needed as membrane phospholipid esters. In response to a physiological trigger, the ester is hydrolyzed, the fatty acid released, and the synthesis of prostaglandins initiated. Figure 23.5 outlines the steps in the synthesis of several prostaglandins from the tetraunsaturated fatty acid, arachidonic acid. A key step in the biosynthesis is the reaction of arachidonic acid with 2 mol of O_2 to form prostaglandin G_2 (PGG_2). There is now good evidence that the antiinflammatory effect of aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs) is due to their ability to inhibit the action of cyclooxygenase, the first enzyme in the prostaglandin cascade. This enzyme, with the systematic name prostaglandin H synthase, catalyzes both cyclooxygenation of arachidonic acid and reduction of PGG_2 to PGH_2.

A word about the nomenclature of prostaglandins. They are abbreviated PG with an additional letter and number to indicate the type and series. Those of the G type (for example PGG_2) have a cyclic peroxide and a hydroperoxide; PG**E**s have a β-hydroxyketone in the five-member ring; PG**F**s have a 1,3-diol in the five-member ring. Those of the **1** series have one double bond in the hydrocarbon side chains; those of the **2** series (for example $PGF_{2\alpha}$) have two double bonds in the side chains. The subscript α (for example in $PGF_{2\alpha}$) indicates that the —OH group at C-9 is below the plane of the five-member ring and on the same side as the —OH on C-11.

Research on the involvement of prostaglandins in reproductive physiology and the inflammatory process has produced the first clinically useful prostaglandin derivatives. The observations that $PGF_{2\alpha}$ stimulates contractions of uterine smooth muscle led to the suggestion that this substance could be used as a therapeutic abortifacient. One problem with the use of the natural prostaglandins for this purpose is that they are very rapidly



Arachidonic acid
(5Z, 8Z, 11Z, 14Z–Eicosatetraenoic acid)

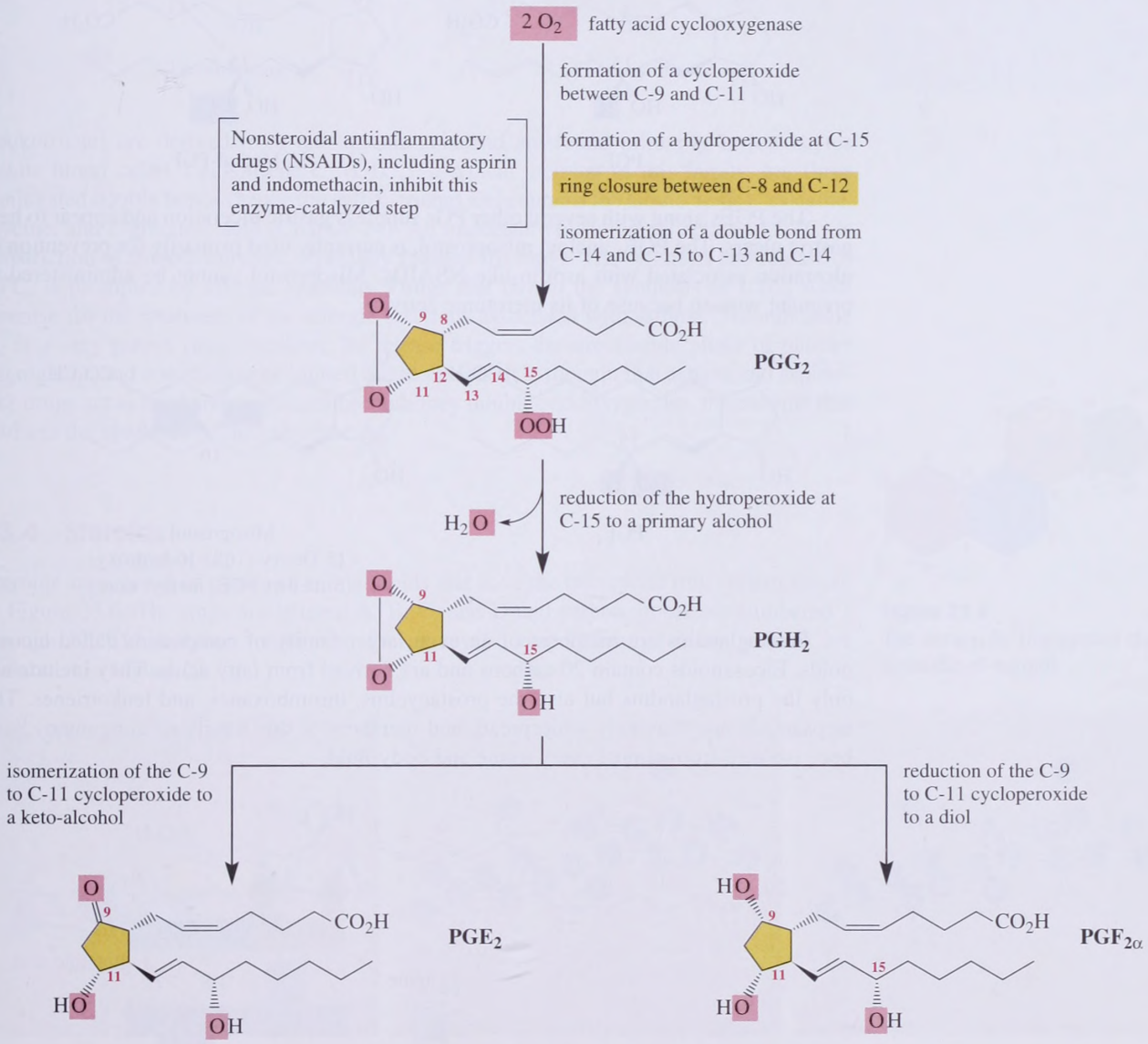
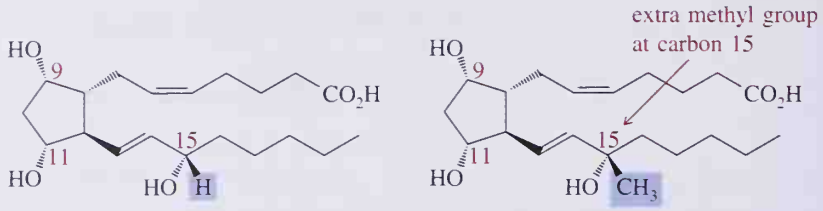


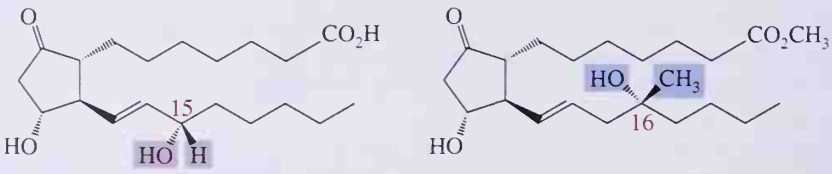
Figure 23.5
Key intermediates in the conversion of arachidonic acid to PGE_2 and $PGF_{2\alpha}$.

degraded within the body. In the search for less rapidly degraded prostaglandins, a number of analogs have been prepared, one of the most effective of which is 15-methyl $PGF_{2\alpha}$. This synthetic prostaglandin has a longer biological half-life than its parent PG and is 10 to 20 times more potent.



$PGF_{2\alpha}$ 15-Methyl-$PGF_{2\alpha}$

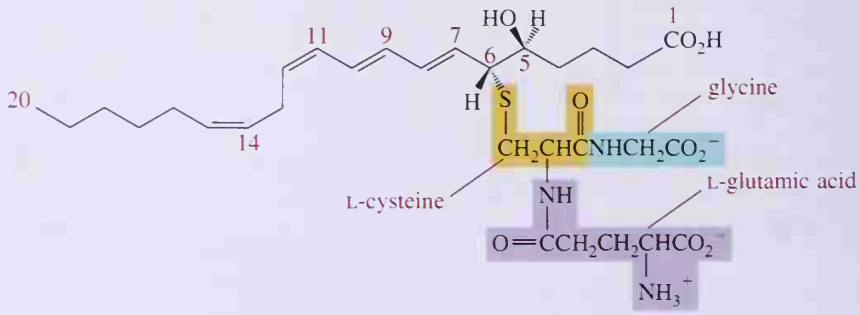
The PGEs along with several other PGs suppress gastric ulceration and appear to heal gastric ulcers. The PGE_1 analog, misoprostol, is currently used primarily for prevention of ulceration associated with aspirin-like NSAIDs. Misoprostol cannot be administered to pregnant women because of its uterotonic activity.



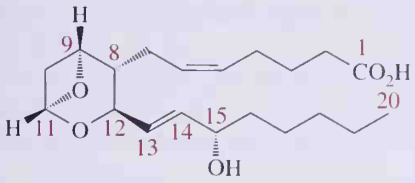
PGE_1

Misoprostol
(15-Deoxy-(16S)-16-hydroxy-
16-methyl-PGE_1 methyl ester)

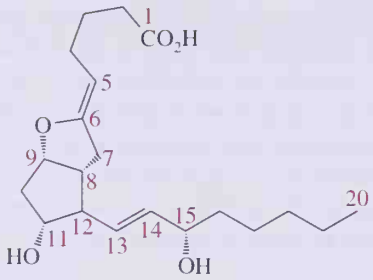
Prostaglandins are members of an even larger family of compounds called eicosanoids. Eicosanoids contain 20 carbons and are derived from fatty acids. They include not only the prostaglandins but also the prostacyclins, thromboxanes, and leukotrienes. The eicosanoids are extremely widespread, and members of this family of compounds have been isolated from almost every tissue and body fluid.



Leukotriene C_4(LTC_4)
(three conjugated double bonds)



Thromboxane A_2



Prostacyclin

Leukotrienes are derived from arachidonic acid and are found primarily in leukocytes (white blood cells). Leukotriene C_4 (LTC_4), a typical member of this family, has three conjugated double bonds (hence the suffix -triene) and contains the amino acids L-cysteine, glycine, and L-glutamic acid (Chapter 24). An important physiological action of LTC_4 is constriction of smooth muscles, especially those of the lungs. The synthesis and release of LTC_4 is prompted by allergic reactions. Drugs that inhibit the synthesis of LTC_4 show promise for the treatment of the allergic reactions associated with asthma. Thromboxane A_2 is a very potent vasoconstrictor; its release triggers the irreversible phase of platelet aggregation and constriction of injured blood vessels. It is thought that aspirin and aspirin-like drugs act as mild anticoagulants because they inhibit cyclooxygenase, the enzyme that initiates the synthesis of thromboxane A_2.

23.4 Steroids

Steroids are a group of plant and animal lipids that have the tetracyclic ring system shown in Figure 23.6. The rings are lettered A, B, C, and D and carbon atoms are numbered 1 through 17. The features common to the tetracyclic ring system of many steroids are illustrated in Figure 23.7.

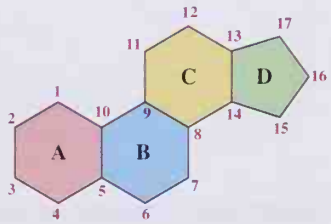


Figure 23.6
The tetracyclic ring system characteristic of steroids.

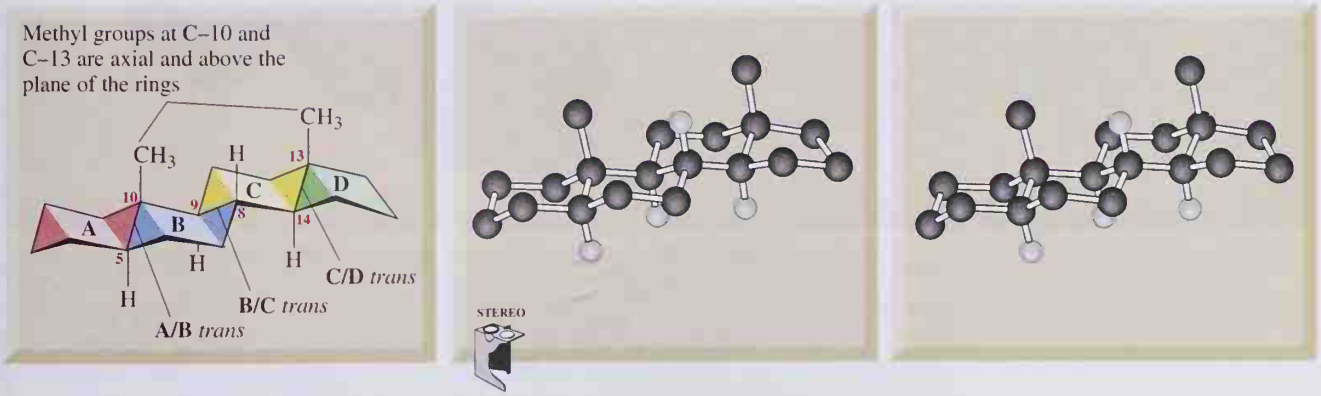
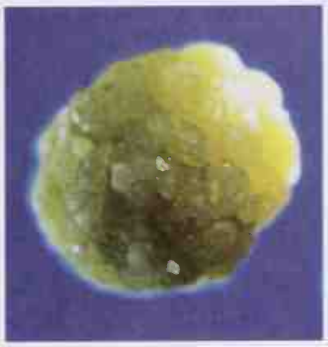


Figure 23.7
Features common to the tetracyclic ring of many steroids.



Human gallstones are almost pure cholesterol; this gallstone is about 0.5 cm in diameter. *(© Carolina Biological Supply Company, Phototake NYC)*

1. Most have a double bond between carbons 4 and 5, or between carbons 5 and 6.
2. The fusion of rings is *trans*, and each atom or group at a ring junction is axial. Compare, for example, the orientations of —H at C-5 and —CH_3 at C-10.
3. The pattern of atoms or groups along the points of ring fusion (carbons 10 to 9 to 8 to 14 to 13) is nearly always anti-*trans*-anti-*trans*.
4. Because of the anti-*trans*-anti-*trans* arrangement of atoms or groups along the points of ring fusion, the tetracyclic steroid ring system is particularly flat and rigid, a feature we return to when we consider the manner in which cholesterol is incorporated into biological membranes.
5. Many steroids have axial methyl groups at C-10 and C-13 of the tetracyclic ring system.

A. Structure of the Major Classes of Steroids

Cholesterol is a white, water-insoluble, waxy solid found in blood plasma and in all animal tissues. This substance is an integral part of human metabolism in two ways: (1) It is an essential component of biological membranes. The body of a healthy adult contains approximately 140 g of cholesterol, about 120 g of which is present in membranes. Membranes of the central and peripheral nervous systems, for example, contain about 10% cholesterol by weight. (2) It is the compound from which sex hormones, adrenocorticoid hormones, bile acids, and vitamin D are synthesized. Thus, cholesterol is, in a sense, the parent steroid.

Cholesterol has eight tetrahedral stereocenters, and a molecule with this structural feature can exist as 2^8, or 256, stereoisomers (128 pairs of enantiomers). Only one of these stereoisomers is known to exist in nature: the stereoisomer with the absolute configuration shown in Figure 23.8.

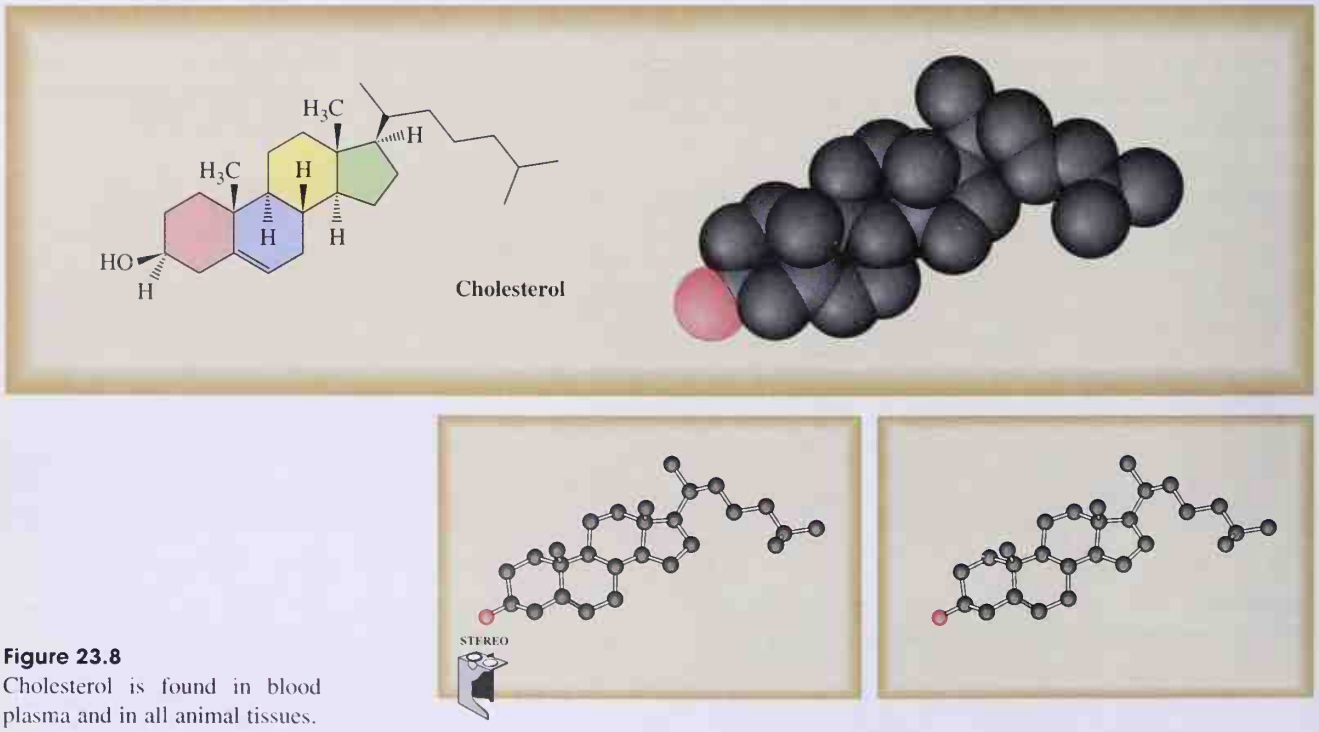
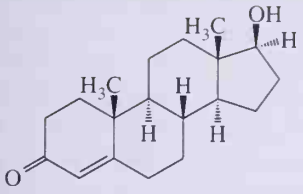
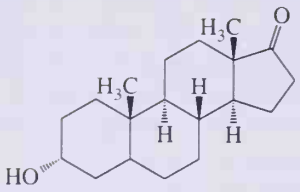
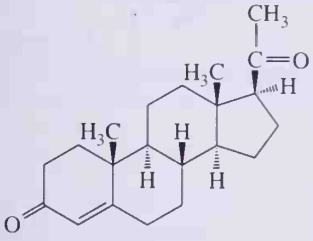
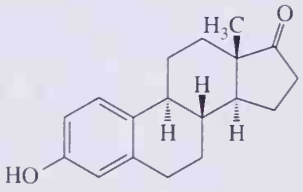
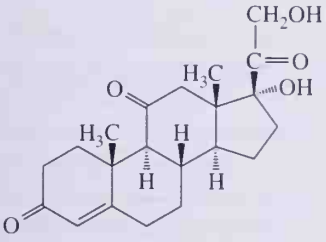
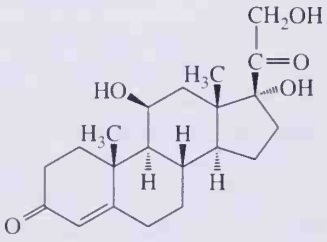
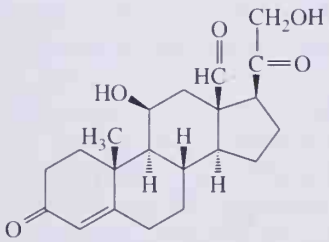


Figure 23.8
Cholesterol is found in blood plasma and in all animal tissues.

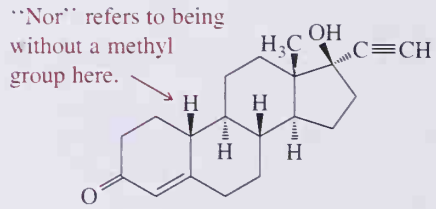
Table 23.3 Selected steroid hormones

Structure	Source and Major Effects
 Testosterone  Androsterone	Androgens (male sex hormones). Synthesized in the testes; responsible for development of male secondary sex characteristics.
 Progesterone  Estrone	Estrogens (female sex hormones). Synthesized in the ovaries; responsible for development of female secondary sex characteristics and control of the estrous cycle.
 Cortisone  Cortisol	Glucocorticoid hormones. Synthesized in the adrenal cortex; regulate metabolism of carbohydrates, decrease inflammation, and are involved in the reaction to stress.
 Aldosterone	A mineralocorticoid hormone. Synthesized in the adrenal cortex; regulates blood pressure and volume by stimulating the kidneys to absorb Na^+, Cl^-, and HCO_3^-.

Cholesterol is insoluble in blood plasma but can be transported as a complex with a class of proteins called lipoproteins. Low-density lipoproteins (LDL) transport cholesterol from the site of its synthesis in the liver to the various tissues and cells of the body where it is to be used. It is primarily cholesterol attached to LDLs that builds up in atherosclerotic deposits in blood vessels. High-density lipoproteins (HDL) transport excess and unused cholesterol from cells back to the liver for its degradation to bile acids and eventual excretion in the feces. It is thought that HDLs retard or reduce atherosclerotic deposits.

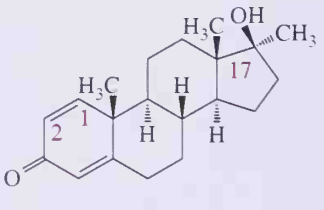
Given in Table 23.3 are representations of each major class of steroid hormones, along with the principal functions of each. Estrogens are synthesized in the ovaries and are

responsible for the development of secondary sex characteristics in females and the regulation of the estrous cycle. Once the role of progesterone in inhibiting ovulation was understood, its potential as a possible contraceptive was realized. Progesterone itself is relatively ineffective when taken orally. As a result of a massive research program in both industrial and academic laboratories, many synthetic progesterone-mimicking steroids became available in the 1960s (see "A Conversation with Carl Djerassi"). When taken regularly, these drugs prevent ovulation, yet allow women to maintain a normal menstrual cycle. Some of the most effective of these preparations contain a progesterone analog, such as norethindrone, combined with a smaller amount of an estrogen-like material to help prevent irregular menstrual flow during prolonged use of contraceptive pills.

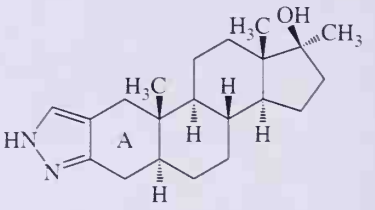


Norethindrone
(a synthetic progestin)

The chief function of testosterone and other androgens is to promote normal growth of male reproductive organs (primary sex characteristics) and development of the characteristic deep voice, pattern of body and facial hair, and musculature (secondary sex characteristics). Although testosterone produces these effects, it is not active when taken orally because it is metabolized in the liver to an inactive steroid. A number of oral anabolic steroids have been developed for use in rehabilitation medicine, particularly when muscular atrophy occurs during rehabilitation from an injury. Among the synthetic anabolic steroids most widely prescribed for this purpose are methandrostenolone and stanozolol. The structural formula of methandrostenolone differs from that of testosterone by introduction of (1) a methyl group at C-17 and (2) an additional carbon-carbon double bond between C-1 and C-2. In stanozolol, ring A is modified by attachment of a pyrazole ring.



Methandrostenolone



Stanozolol

The use of anabolic steroids among certain athletes to build muscle mass and strength, particularly for sports that require explosive action, is common knowledge. Risks associated with abuse of anabolic steroids for this purpose, however, are enormous: heightened aggressiveness, sterility, impotence, and risk of premature death from complications of diabetes, coronary artery disease, and liver cancer.

Shown in Figure 23.9 is a structural formula for cholic acid, an important constituent of human bile. The molecule is shown as an anion, as it is ionized in bile and intestinal fluids. Bile acids, or more properly, bile salts, are synthesized in the liver, stored in the gallblader, and secreted into the intestine, where their function is to emulsify dietary fats

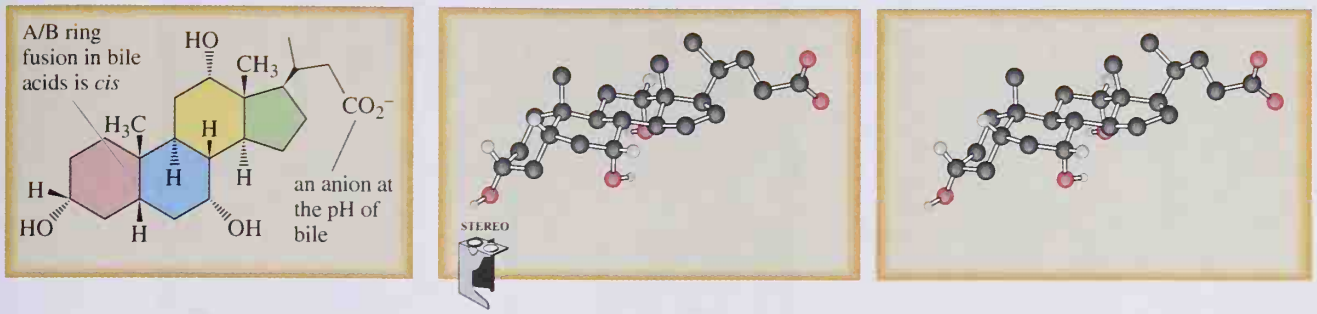


Figure 23.9
Cholic acid, an important constituent of human bile. (a) Planar representation and (b) stereorepresentation showing each six-member ring in a chair conformation.

and thereby aid in their absorption and digestion. Furthermore, bile salts are the end products of the metabolism of cholesterol and, thus, are a principal pathway for the elimination of this substance from the body. A characteristic structural feature of bile salts is a *cis* fusion of rings A and B.

B. Biosynthesis of Steroids

We present the biosynthesis of steroids in some detail because it illustrates several of the important mechanistic principles we have developed so far: the formation and reactions of carbocations including loss of H^+ to give an alkene, reaction of a carbocation with an alkene (a nucleophile) to form a new carbon-carbon bond, and rearrangement by a 1,2-shift to form a new carbocation of equal or greater stability. In addition, we illustrate a point we first made in our introduction to the structure of terpenes (Section 4.6): that in building large molecules, one of the common patterns in the biological world is to begin with one or more smaller subunits, join them together by an iterative process, and then chemically modify the completed carbon skeleton by oxidation, reduction, cross-linking, addition, elimination, or related processes to give a biomolecule with a unique identity.

The building block from which all carbon atoms of steroids are derived is the two-carbon acetyl group of acetyl-CoA. The American biochemist, Konrad Bloch (who shared the 1964 Nobel Prize in medicine and physiology with the German biochemist Feodor Lynen for their discoveries concerning the biosynthesis of cholesterol and fatty acids), showed that 15 of the 27 carbon atoms of cholesterol are derived from the methyl group of acetyl-CoA; the remaining 12 carbon atoms are derived from the carbonyl group of acetyl-CoA (Figure 23.10).

Stage 1: From Acetyl-CoA to Isopentenyl Pyrophosphate

The first stage in the biosynthesis of cholesterol is the synthesis of isopentenyl pyrophosphate (Section 20.14). To review, the synthesis of isopentenyl pyrophosphate begins with condensation of three molecules of acetyl-CoA to give the six-carbon acid, mevalonic acid, followed by a concerted decarboxylation and loss of phosphate ion to give isopentenyl pyrophosphate. The enzyme, isopententyl pyrophosphate isomerase, catalyzes the interconversion of isopentenyl pyrophosphate and its constitutional isomer, dimethylallyl pyro-

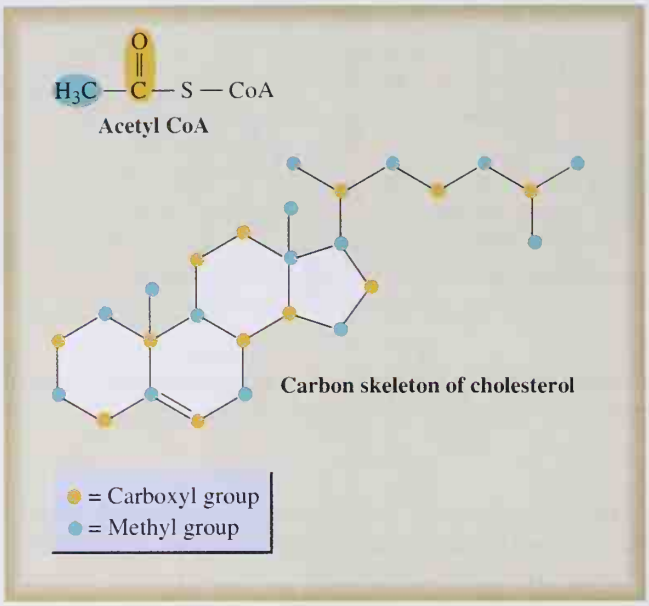
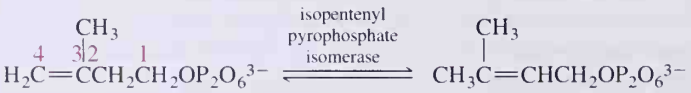


Figure 23.10
Carbon atoms of cholesterol are derived from the acetyl group of acetyl-CoA.

phosphate, possibly by protonation of carbon 4 to form a 3° carbocation followed by loss of H^+ from carbon 2 to give the isomeric alkene.



Isopentenyl pyrophosphate — Dimethylallyl pyrophosphate

These two pyrophosphate esters are key intermediates in the synthesis of all terpenes (Section 4.6), including the triterpenes, squalene, and lanosterol. Cholesterol is then synthesized from lanosterol by loss of three carbon atoms. Names of key intermediates in this biosynthetic pathway are shown in Figure 23.11, along with the change in size of the carbon skeleton with each step. Doing the carbon-atom bookkeeping, you discover that 18 acetyl groups are required for the synthesis of one molecule of cholesterol. A remarkable feature of this synthetic pathway is that the biosynthesis of cholesterol from acetyl-CoA is completely stereospecific; it is synthesized as only one of 256 possible stereoisomers. We cannot duplicate this exquisite degree of stereospecificity in the laboratory.

Stage 2: From Isopentenyl Pyrophosphate and Dimethylallyl Pyrophosphate to Squalene

Pyrophosphate is nature's good leaving group; it is a weak base (the anion of a strong acid) and, therefore, a good leaving group (Section 10.7E). In the following structural formulas, the pyrophosphate group is written out in full. Loss of this ion from dimethylallyl pyrophosphate gives a resonance-stabilized dimethylallyl cation, which then performs electro-

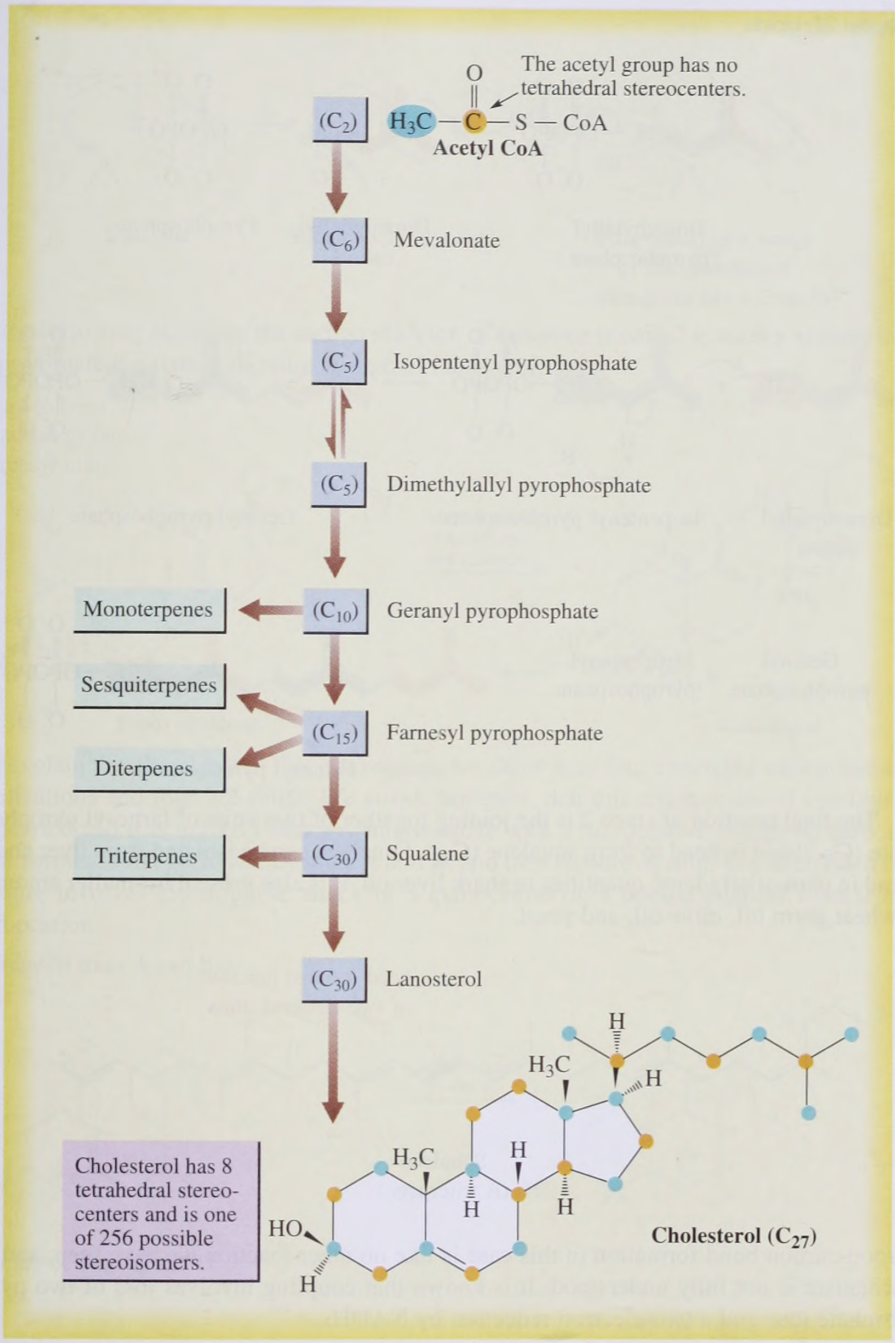
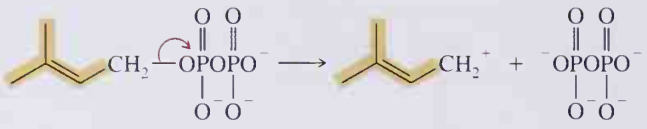
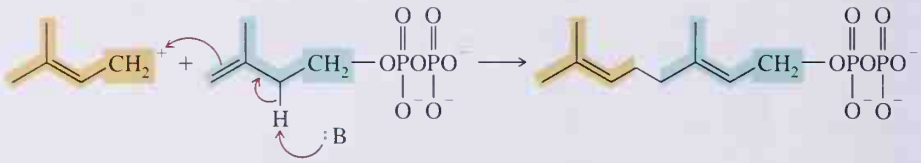


Figure 23.11
Several key intermediates in the synthesis of cholesterol from acetyl groups of acetyl-CoA. Eighteen moles of acetyl-CoA are required for the synthesis of one mole of cholesterol.

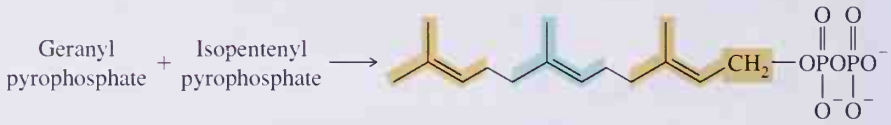
philic attack on the carbon-carbon double bond of isopentenyl pyrophosphate to give a 3° carbocation (not shown), which then loses H^+ to give geranyl pyrophosphate. Further reaction of geranyl pyrophosphate by cation-initiated electrophilic attack on isopentenyl pyrophosphate followed by loss of H^+ gives farnesyl pyrophosphate.



Dimethylallyl pyrophosphate — Dimethylallyl cation — Pyrophosphate

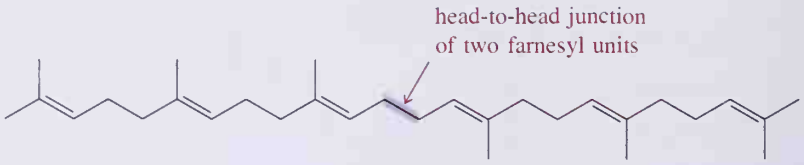


Dimethylallyl cation — Isopentenyl pyrophosphate — Geranyl pyrophosphate



Geranyl pyrophosphate + Isopentenyl pyrophosphate → Farnesyl pyrophosphate

The final reaction of stage 2 is the joining together of two units of farnesyl pyrophosphate (C_{15}) head to head to form squalene (C_{30}). Squalene can be isolated from liver and is found in particularly large quantities in shark liver oil. It is also present in smaller amounts in wheat germ oil, olive oil, and yeast.

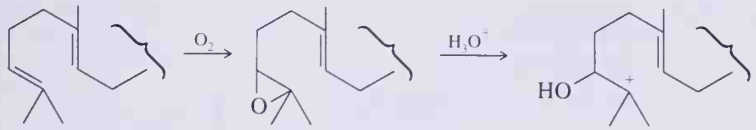


Squalene
(A triterpene)

Carbon-carbon bond formation in this case is like no other reaction we have seen, and its mechanism is not fully understood. It is known that coupling involves loss of two pyrophosphate ions and a two-electron reduction by NADH.

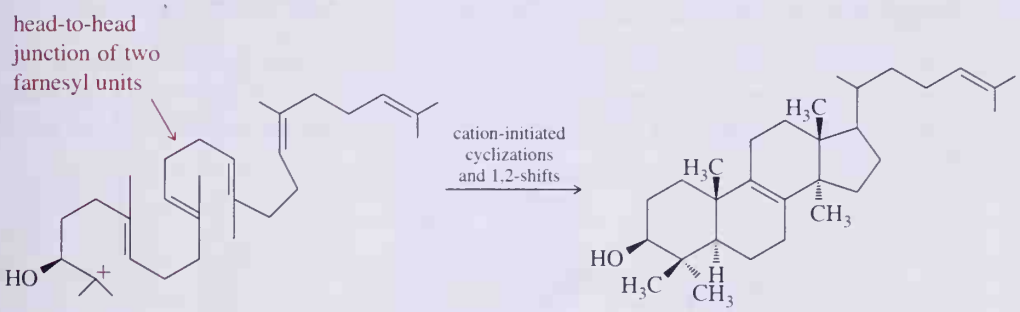
Stage 3: From Squalene to Lanosterol

Stage 3 begins with an enzyme-catalyzed oxidation of squalene by molecular oxygen to form squalene epoxide. In this transformation, molecular oxygen is reduced to H_2O by NADH. Acid-catalyzed opening of this epoxide gives a 3° carbocation, which then sets in motion a series of reactions that leads ultimately to lanosterol.



Squalene | Squalene 2,3-epoxide | First cation in a series of cation-initiated cyclizations and 1,2-shifts

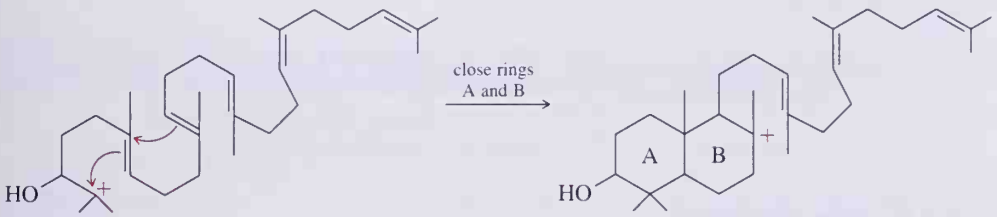
In the following equation, the carbon skeleton of squalene is coiled in such a manner as to approximate the tetracyclic ring system of lanosterol.



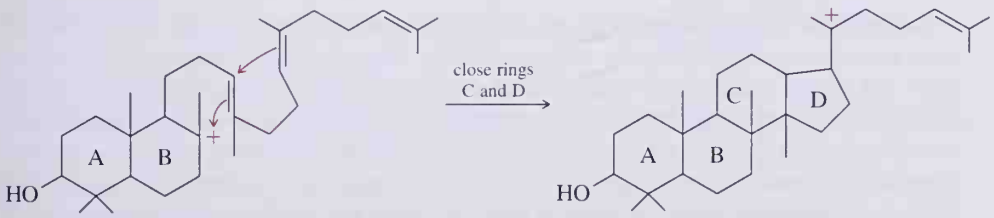
From squalene | Lanosterol

To explain the chemistry of this conversion, we show it as four concerted cation-initiated cyclizations and four 1,2-shifts. We stress, however, that this entire series of reactions is concerted and it is unlikely that any intermediate with a full positive charge on carbon is ever formed. First is closure of rings A and B, and then closure of rings C and D. Each ring closure involves electrophilic attack of a carbocation on a double bond to form a new carbocation.

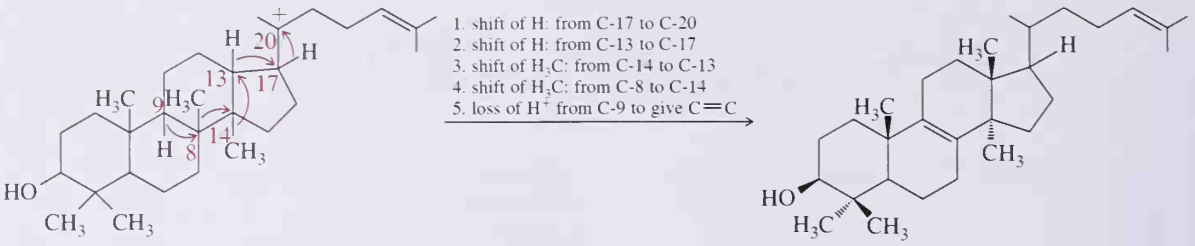
Closure of rings A and B:



Closure of rings C and D:



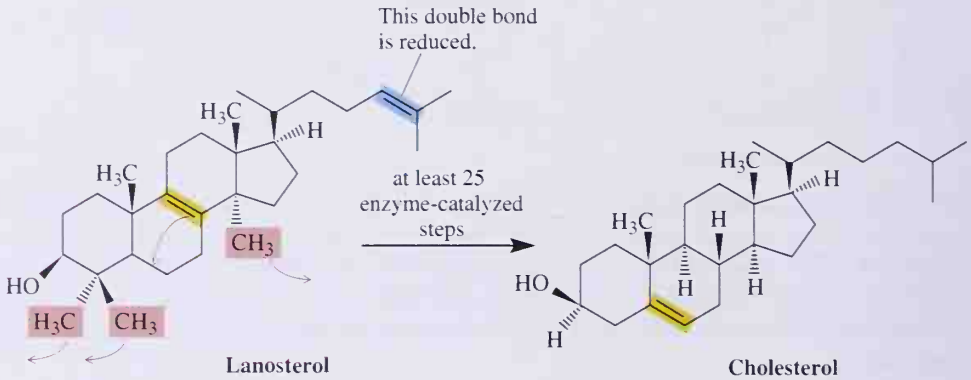
There then follows a series of four concerted 1,2-shifts culminating in loss of H^+ to give the carbon-carbon double bond at the junction of rings B and C.



Lanosterol

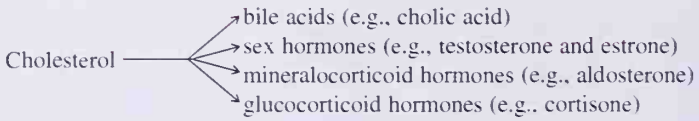
Stage 4: From Lanosterol to Cholesterol

Conversion of lanosterol to cholesterol involves at least 25 enzyme-catalyzed reactions, the details of which are only poorly understood. This transformation involves loss of three methyl groups, migration of one double bond of lanosterol, and reduction of the other double bond.



Lanosterol **Cholesterol**

Cholesterol is then the starting material for the synthesis of bile acids and the host of steroid hormones.



23.5 Phospholipids

A. Structure

Phospholipids, or phosphoacylglycerols as they are more properly named, are the second most abundant group of naturally occurring lipids. They are found almost exclusively in plant and animal membranes, which typically consist of about 40% to 50% phospholipids and 50% to 60% proteins. The most abundant phospholipids are derived from phosphatidic acid (Figure 23.12), a molecule containing glycerol esterified with two molecules of fatty acids and one molecule of phosphoric acid. The fatty acids most common in phosphatidic acids are palmitic and stearic acids (both fully saturated) and oleic acid (one double bond in the hydrocarbon chain). Further esterification of phosphatidic acid with a low-molecular-weight alcohol gives a phospholipid. Several of the most common alcohols forming phospholipids are given in Table 23.4. All functional groups in this table and in Figure 23.12 are

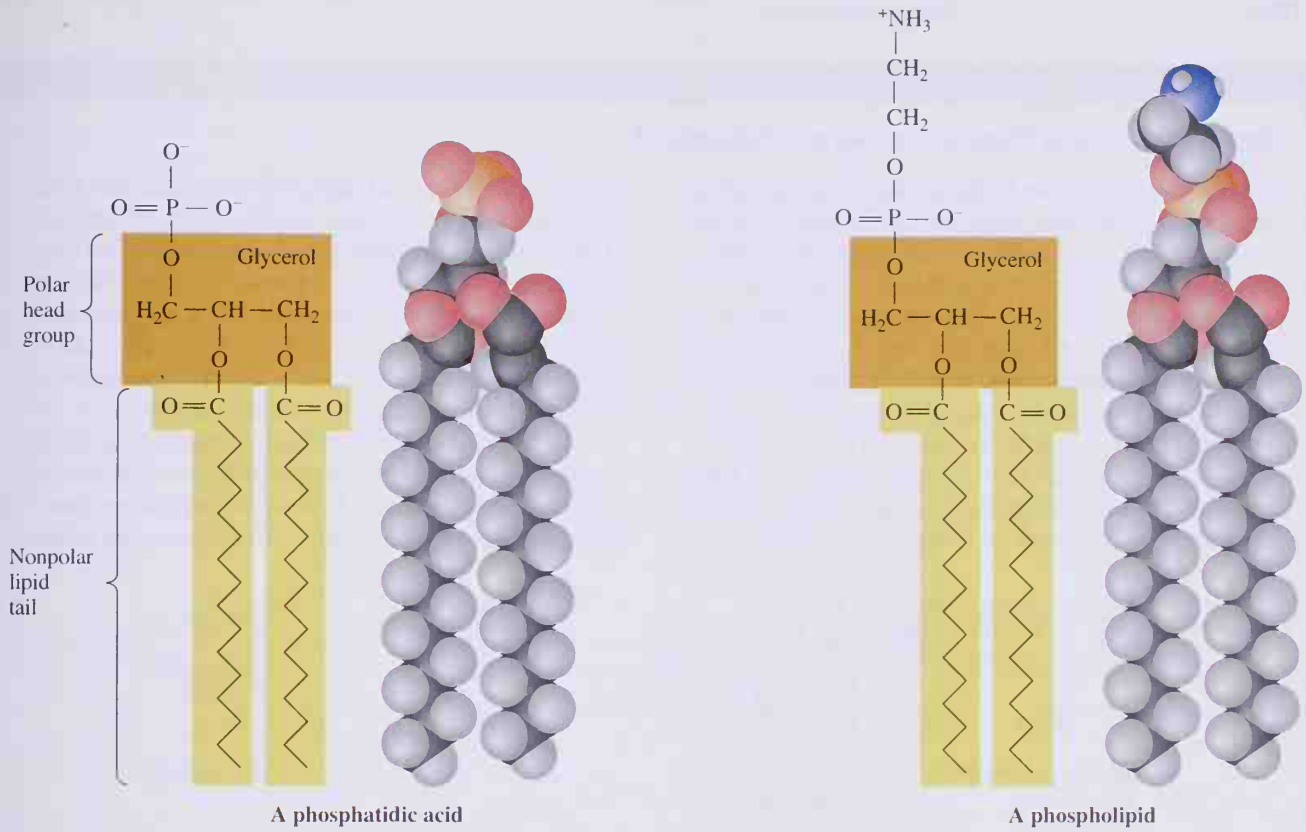
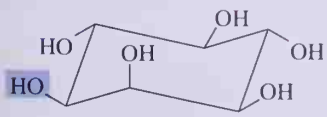


Figure 23.12
In a phosphatidic acid, glycerol is esterified with 2 mol of fatty acid and 1 mol of phosphoric acid. Further esterification of phosphoric acid with a low-molecular-weight alcohol gives a phospholipid.

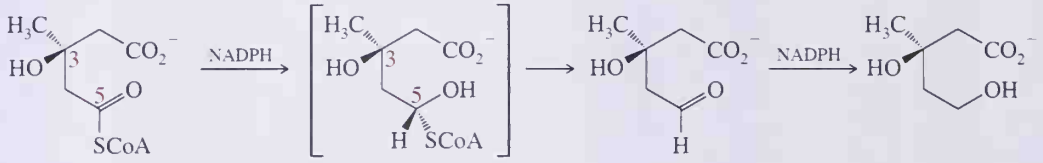
Table 23.4 Low-molecular-weight alcohols most common to phospholipids

Alcohols Found in Phospholipids		
Structural Formula	**Name**	**Name of Phospholipid**
$HOCH_2CH_2NH_3^+$	ethanolamine	phosphatidylethanolamine (cephalin)
$HOCH_2CH_2N^+(CH_3)_3$	choline	phosphatidylcholine (lecithin)
$HOCH_2CHCO_2^-$ (NH$_3^+$)	serine	phosphatidylserine
	inositol	phosphatidylinositol

CHEMISTRY IN ACTION

Drugs that Lower Plasma Levels of Cholesterol

Coronary artery disease is the leading cause of death in the United States and other Western countries, where about one-half of all deaths can be attributed to atherosclerosis. Atherosclerosis results from build-up of fatty deposits called plaque on the inner walls of arteries. A major component of plaque is cholesterol derived from low-density-lipoproteins (LDL) that circulate in blood plasma. Because more than half of total body cholesterol in humans is synthesized in the liver from acetyl-CoA, intensive efforts have been directed toward ways of inhibiting this synthesis. The rate-limiting step in cholesterol biosynthesis is reduction of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) to mevalonic acid. This four-electron reduction is catalyzed by the enzyme HMG-CoA reductase and requires 2 mol of NADPH per mol of HMG-CoA. Beginning in the early 1970s, researchers at the Sankyo Company in Tokyo screened more than 8000 strains of microorganisms and in 1976 announced the isolation of mevastatin, a potent inhibitor of HMG-CoA reductase, from culture broths of the fungus *Penicillium citrinum*. The same compound was isolated by researchers at Beecham Pharmaceuticals in England from cultures of *Penicillium brevicompactum*. Soon thereafter, a second, more active compound called



3-Hydroxy-3-Methyl-glutaryl-CoA (HMG-CoA)

A thiohemiacetal intermediate formed by the first two-electron reduction

Mevalonate

shown as they are ionized at pH 7.4, the approximate pH of blood plasma and of many biological fluids. Under these conditions, each phosphate group bears a negative charge, and each amino group bears a positive charge.

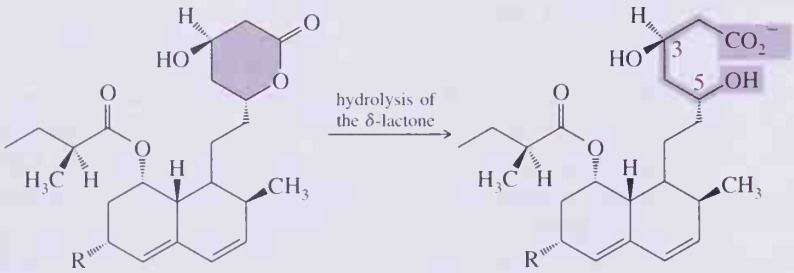
B. Lipid Bilayers

Figure 23.13 shows a space-filling model of a lecithin (a phosphatidylcholine). It and other phospholipids are elongated, almost rodlike molecules, with the nonpolar (hydrophobic) hydrocarbon chains lying roughly parallel to one another and the polar (hydrophilic) phosphate ester pointing in the opposite direction. When placed in aqueous solution, phospholipids spontaneously form lipid bilayers (Figure 23.14) in which polar head groups lie on the surface, giving the bilayer an ionic coating. Nonpolar hydrocarbon chains of fatty acids lie buried within the bilayer. This self-assembly of phospholipids into a bilayer is a spontaneous process, driven by two types of noncovalent forces: (1) hydrophobic effects, which result when nonpolar hydrocarbon chains cluster together and exclude water molecules, and (2) electrostatic interactions, which result when polar head groups develop dipole-dipole and ion-dipole interactions with water and other polar molecules in the aqueous environment.

lovastatin was isolated at the Sankyo Company from the fungus *Monascus ruber*, and by Merck Sharpe & Dohme from *Aspergillus terreus*. Both mold metabolites are extremely effective in lowering plasma concentrations of LDL. The active form of each is the 5-hydroxycarboxylic acid formed by hydrolysis of the δ-lactone.

It is thought that these drugs and several synthetic modifications now available inhibit HMG-CoA reductase by forming an enzyme-inhibitor complex that prevents further catalytic action of the enzyme. It is reasoned that the 3,5-dihydroxycarboxylic acid part of each drug binds tightly to the enzyme because it mimics the thiohemiacetal intermediate formed after the first two-electron reduction of HMG-CoA.

Systematic studies have shown the importance of each part of the drug for effectiveness. It was found, for example, that the carboxylate anion is essential, and both the 3-OH and 5-OH groups must be free (not masked as ethers). Insertion of a bridging unit other than $—CH_2—CH_2—$ between carbon 5 and the bicyclo[4.4.0] ring reduces potency as does almost any modification of the bicyclic ring system and its pattern of substitution.



R=H, mevastatin
R=CH_3, lovastatin

The active form of each drug

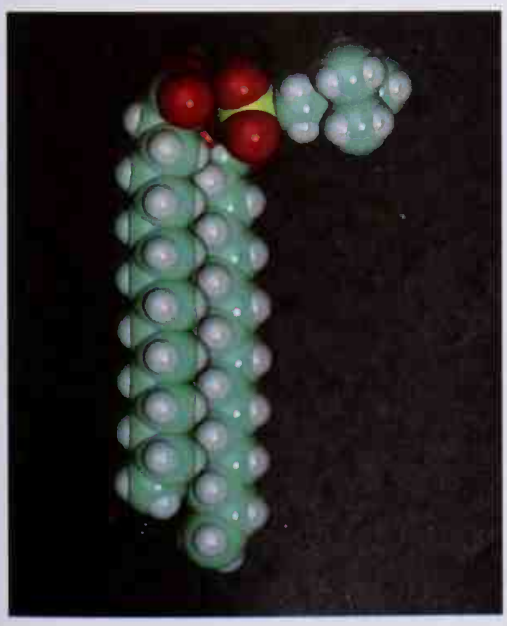


Figure 23.13
Space-filling model of a lecithin.

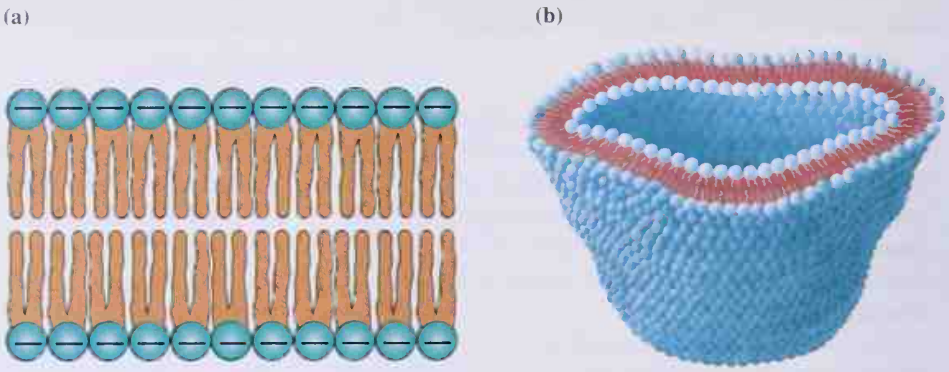


Figure 23.14
Lipid bilayers. Schematic drawing of a portion of a bilayer consisting of phospholipids. The polar surface of the bilayer contains charged groups, which interact with the aqueous environment by ion-dipole and dipole-dipole interactions. The nonpolar hydrocarbon chains lie in the interior of the bilayer, shielded from contact with the aqueous environment.

Recall from Section 23.1C that formation of soap micelles is driven by these same noncovalent forces; the polar (hydrophilic) carboxylate groups of soap molecules lie on the surface of the micelle and associate with water molecules by both ion-dipole and dipole-dipole interactions, and the nonpolar (hydrophobic) hydrocarbon chains cluster within the micelle and thus are removed from contact with water.

The arrangement of hydrocarbon chains in the interior of the phospholipid bilayer varies from rigid to fluid, depending on the degree of unsaturation of the hydrocarbon chains themselves. Saturated hydrocarbon chains tend to lie parallel and closely packed, leading to rigidity in the bilayer. Unsaturated hydrocarbon chains, on the other hand, have one or more *cis* double bonds, which cause "kinks" in the chains, and, as a result, they do not pack as closely and with as great an order as saturated chains. The disordered packing of unsaturated hydrocarbon chains leads to fluidity in the bilayer.

C. The Fluid-Mosaic Model of Membrane Structure

Biological membranes contain proteins as well as phospholipids. The percentage of protein is directly related to the metabolic activity carried out by the particular membrane. Membranes of myelin sheaths, for example, which function chiefly as an insulator for nerve fibers, contain less than 20% protein. Inner membranes of mitochondria, which are intimately involved with a host of metabolic reactions, including oxidative phosphorylation, contain more than 75% protein.

The most satisfactory current model for the arrangement of proteins and phospholipids in plant and animal membranes is the fluid-mosaic model proposed in 1972 by S. J. Singer and G. Nicolson. The term "mosaic" signifies that the various components in the membrane coexist side by side, as discrete units, rather than combining to form new molecules or ions. "Fluid" signifies that the same sort of fluidity exists in membranes that we have already seen for lipid bilayers. Furthermore, the protein components of membranes "float" in the bilayer and can move laterally along the plane of the membrane.

According to the fluid-mosaic model (Figure 23.15), membrane phospholipids form a lipid bilayer with membrane proteins associated with this bilayer as (1) peripheral proteins

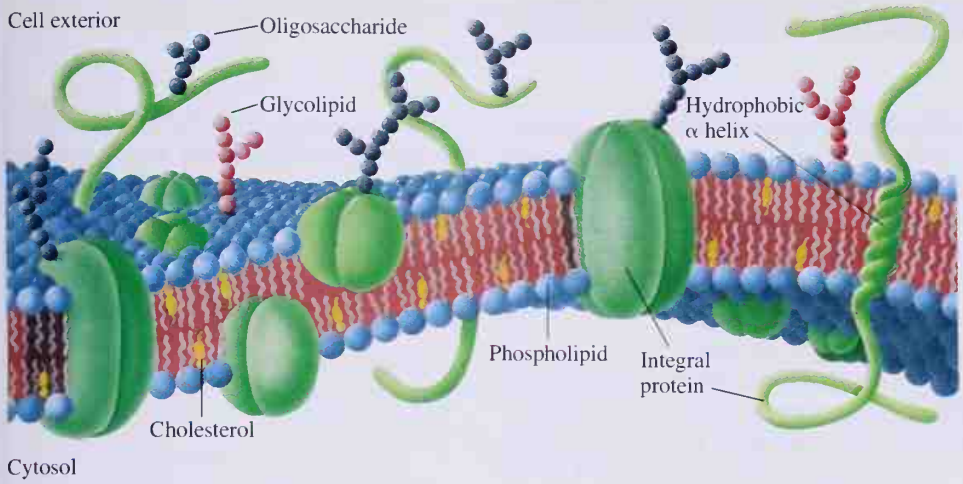


Figure 23.15
Fluid-mosaic model of a biological membrane, showing the lipid bilayer and membrane proteins oriented on the inner and outer surfaces of the membrane and penetrating the entire thickness of the membrane.

both on the inside and outside surfaces of the membrane, and as (2) integral proteins penetrating the bilayer. It is possible to freeze membranes and then to fracture them along the interface between the lipid bilayers, thus exposing the interior of the membrane. Figure 23.16 is a schematic drawing of such a freeze-fractured membrane. The presence of cholesterol adds rigidity to a membrane. The tetracyclic ring system of cholesterol itself is quite rigid, and when it is embedded in the hydrocarbon interior of a lipid bilayer, it imparts additional rigidity to the bilayer.

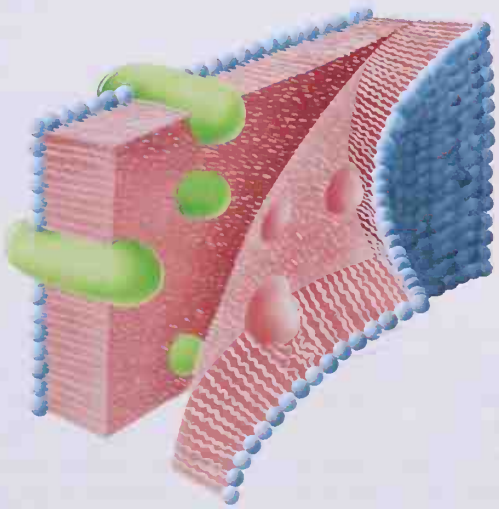


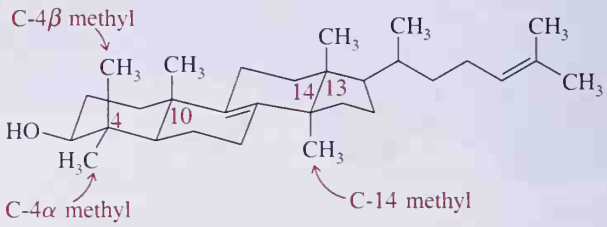
Figure 23.16
Replica of a freeze-fractured membrane. The lipid bilayer is split parallel to the surface of the membrane, and the hydrocarbon tails of the phospholipids are separated from each other.

CHEMISTRY IN ACTION

Why Cholesterol?

The conversion of lanosterol to cholesterol is a remarkably complex transformation. Removing methyl groups from hydrocarbon rings is not a reaction organic chemists can carry out with any degree of success, and even nature needs a multitude of steps and specialized enzymes to carry out this transformation. Why does nature bother? A way to think about this question is to assume that there is some evolutionary advantage for an organism to have cholesterol in its body as opposed to lanosterol or other sterol (steroid alcohol), and then to look for some function that is improved when lanosterol is replaced by cholesterol.

The American biochemist Konrad Bloch has proposed one advantage cholesterol provides over lanosterol. He found that when artificial membranes that mimic cell membranes are prepared, the fluidity of the membrane is strongly affected by the addition of different sterols. Membranes with lanosterol are the least solid. Small molecules such as glucose readily pass through lanosterol-containing membranes. The order of biological demethylation of lanosterol is the C-14 methyl group first, followed by the C-4β methyl, and finally the C-4α methyl. Bloch discovered that as each methyl group is removed from lanosterol, the resulting membrane becomes increasingly rigid and less permeable. If the methyl groups in cholesterol at ring junctions C-10 and C-13 are removed, the resulting sterol again produces less rigid, more permeable membranes.



Lanosterol

Professor Bloch concludes from these studies that cholesterol is a molecule selected by evolutionary pressures for efficient membrane function. He further concludes that to understand the function of a biomolecule, it is not enough merely to study its structure. We must also examine the molecule's interactions with its cellular environment.

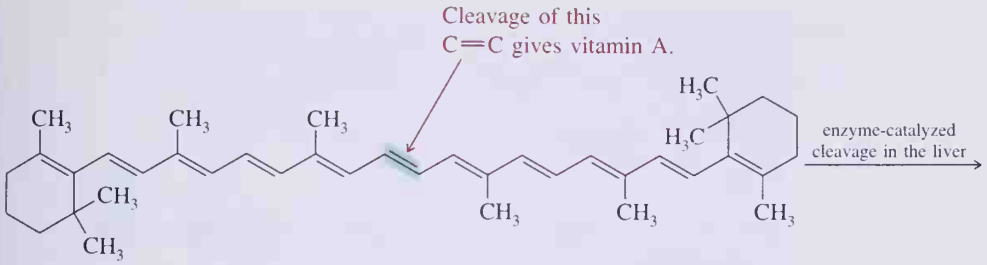
See K. Bloch, *Chimia*, **33:** 337(1979).

23.6 Fat-Soluble Vitamins

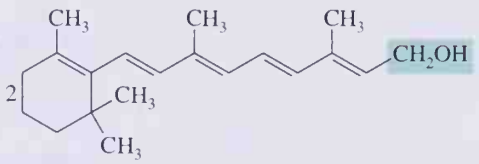
Vitamins are divided into two broad classes on the basis of solubility: those that are fat-soluble (and hence classed as lipids) and those that are water-soluble. The fat-soluble vitamins include A, D, E, and K.

A. Vitamin A

Vitamin A, or retinol, occurs only in the animal world, where the best sources are cod-liver oil and other fish-liver oils, animal liver, and dairy products. Vitamin A in the form of a precursor, or provitamin, is found in the plant world in a group of tetraterpene (C_{40}) pigments called carotenes. The most common of these is β-carotene, abundant in carrots but also found in some other vegetables, particularly yellow ones. β-Carotene has no vitamin A activity; however, after ingestion, it is cleaved at the central carbon-carbon double bond to give retinol (vitamin A).



β-Carotene



Retinol
(Vitamin A)

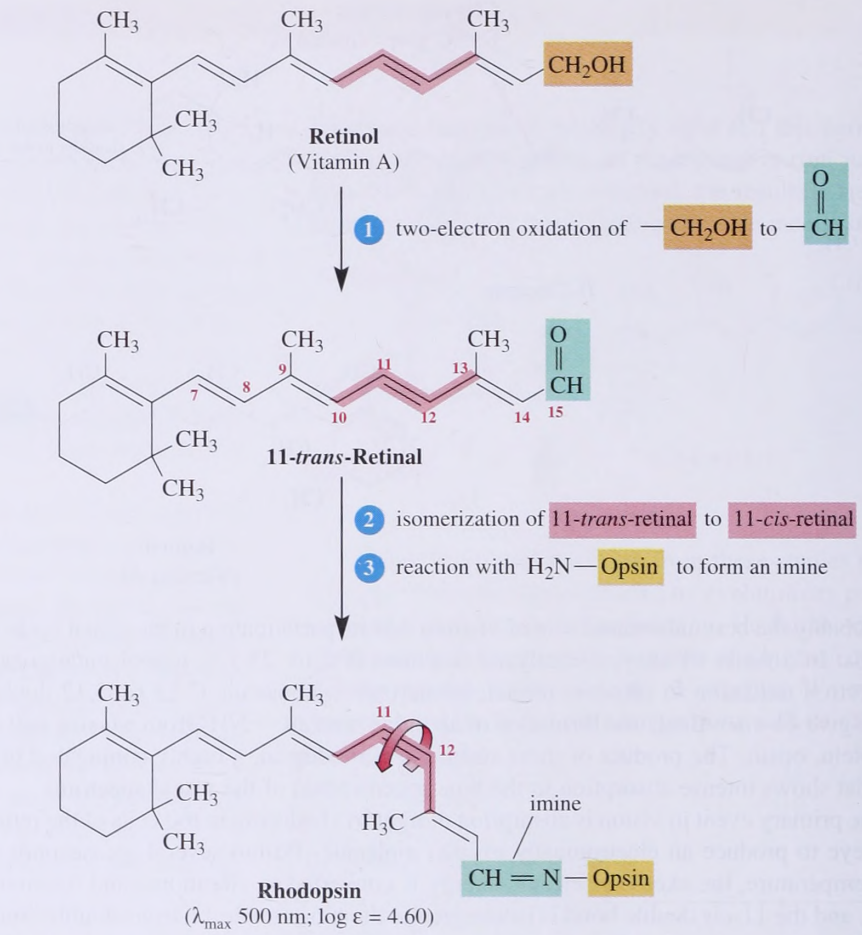
Probably the best understood role of vitamin A is its participation in the visual cycle in rod cells. In a series of enzyme-catalyzed reactions (Figure 23.17), retinol undergoes a two-electron oxidation to all-*trans*-retinal, isomerization about the C-11 to C-12 double bond to give 11-*cis*-retinal, and formation of an imine with an $—NH_2$ from a lysine unit of the protein, opsin. The product of these reactions is rhodopsin, a highly conjugated pigment that shows intense absorption in the blue-green region of the visual spectrum.

The primary event in vision is absorption of light by rhodopsin in rod cells of the retina of the eye to produce an electronically excited molecule. Within several picoseconds at room temperature, the excess electronic energy is converted to vibrational and rotational energy, and the 11-*cis* double bond is isomerized to the more stable 11-*trans* double bond. This alkene isomerization triggers a conformational change in the protein, opsin, that causes firing of neurons in the optic nerve and produces a visual image. Coupled with this light-induced change is hydrolysis of rhodopsin to give 11-*trans*-retinal and free opsin. At this point, the visual pigment is bleached and in a refractory period. Rhodopsin is regenerated by a series of enzyme-catalyzed reactions that converts 11-*trans*-retinal to 11-*cis*-retinal and then to rhodopsin. The visual cycle is shown in abbreviated form in Figure 23.18.

B. Vitamin D

Vitamin D is the name for a group of structurally related compounds that play a major role in the regulation of calcium and phosphorus metabolism. A deficiency of vitamin D in childhood is associated with rickets, a mineral-metabolism disease that leads to bowlegs, knock-knees, and enlarged joints. Vitamin D_3, the most abundant form of the vitamin in the circulatory system, is produced in the skin of mammals by the action of ultraviolet

(Text continued on p. 1025)



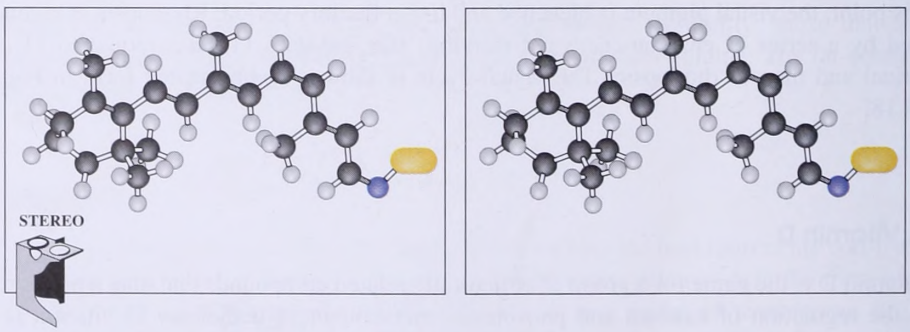
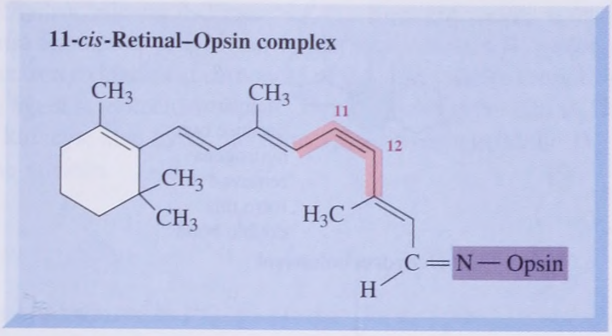


Figure 23.17
Formation of rhodopsin (visual purple).



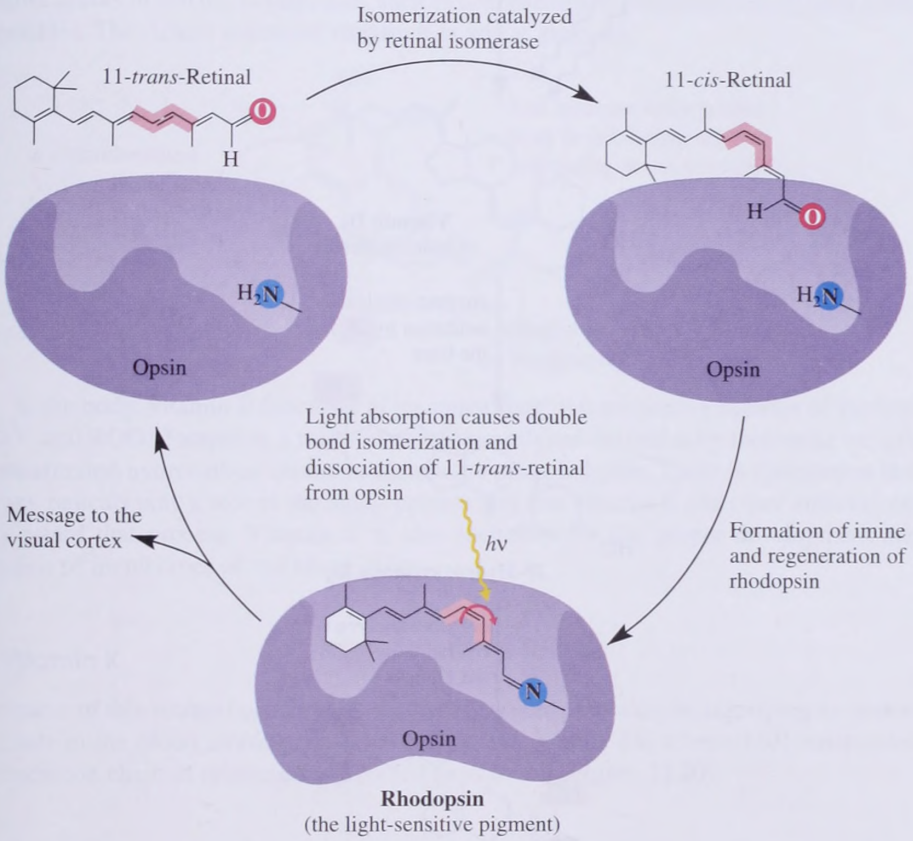


Figure 23.18
The primary chemical reaction of vision in rod cells is absorption of light by rhodopsin followed by isomerization of a carbon-carbon double bond from a *cis* configuration to a *trans* configuration.

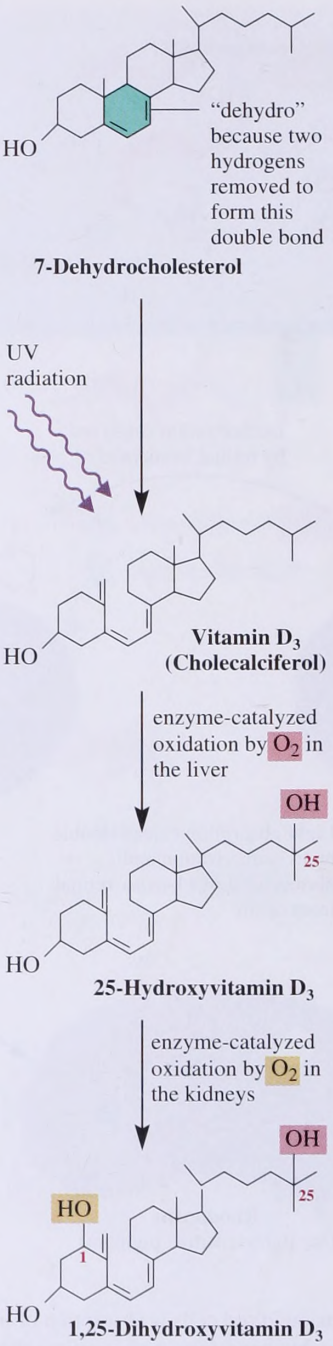
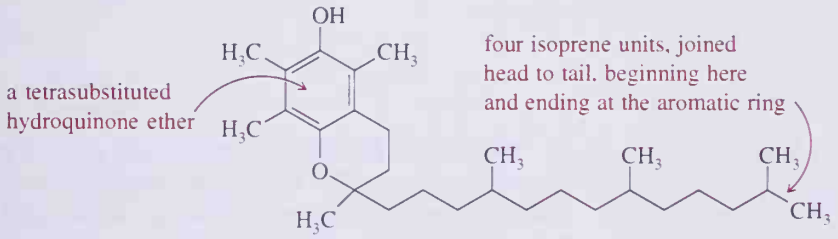


Figure 23.19
Synthesis of three members of the vitamin D family from 7-dehydrocholesterol.

radiation on 7-dehydrocholesterol (Figure 23.19). Sunlight causes opening of the cyclohexadiene ring and formation of a triene. In the liver, vitamin D_3 undergoes an enzyme-catalyzed two-electron oxidation at carbon 25 of the side chain to form 25-hydroxyvitamin D_3; the oxidizing agent is molecular oxygen, O_2. 25-Hydroxyvitamin D_3 undergoes further oxidation in the kidneys, also by O_2, to form 1,25-dihydroxyvitamin D_3, the hormonally active form of the vitamin.

C. Vitamin E

Vitamin E was first recognized in 1922 as a dietary factor essential for normal reproduction in rats, hence its name from the Greek: *tocopherol,* promoter of childbirth. Vitamin E is a group of compounds of similar structure, the most active of which is α-tocopherol. This vitamin occurs in fish oil, in other oils, such as cottonseed and peanut oil, and in leafy green vegetables. The richest source of vitamin E is wheat germ oil.

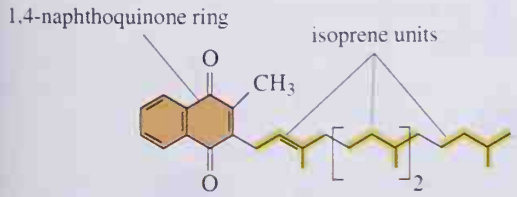


Vitamin E
(α-Tocopherol)

In the body, vitamin E functions as an antioxidant: it traps peroxy radicals of the type HOO· and ROO· formed as a result of enzyme-catalyzed oxidation by molecular oxygen of unsaturated hydrocarbon chains in membrane phospholipids. There is speculation that peroxy radicals play a role in the aging process and that vitamin E and other antioxidants may retard that process. Vitamin E is also necessary for the proper development and function of membranes of red blood cells.

D. Vitamin K

The name of this vitamin comes from the German word *koagulation,* signifying its important role in the blood clotting process. The natural vitamin has a branched, unsaturated hydrocarbon chain of isoprene units joined head to tail (Figure 23.20).



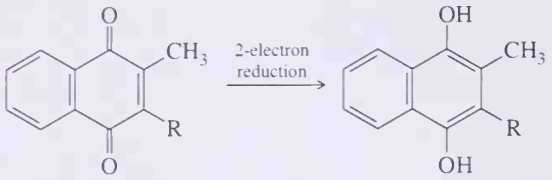
Vitamin K_1
(2-Methyl-3-phytyl-1,4-naphthoquinone)

Figure 23.20
Vitamin K. Vitamin K_1 has four isoprene units in the side chain, vitamin K_2 has five isoprene units in the side chain.

CHEMISTRY IN ACTION

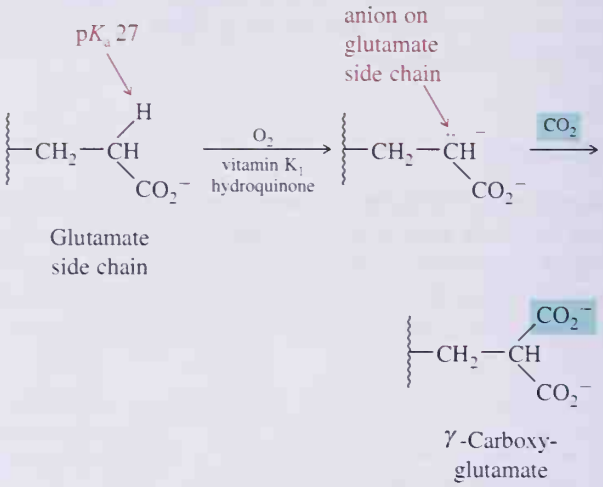
Vitamin K, Blood Clotting, and Basicity

Vitamin K (Section 23.6D) is a fat-soluble vitamin, which must be obtained from the diet. A deficiency of vitamin K results in slowed blood clotting, which can be a serious threat to a wounded animal or human. In the process of blood clotting the natural vitamin, a quinone, is converted to its active hydroquinone form by reduction.



Vitamin K_1 quinone — Vitamin K_1 hydroquinone

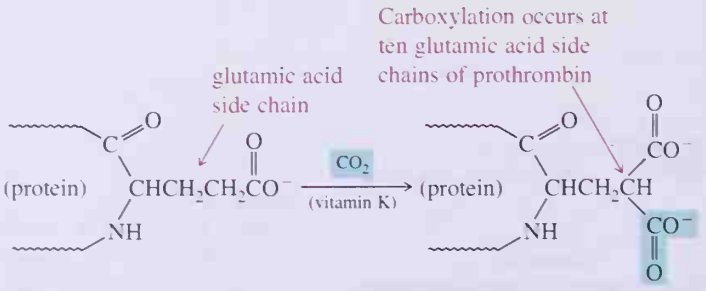
In the presence of vitamin K_1 hydroquinone, O_2, CO_2, and an enzyme called microsomal carboxylase, glutamate side chains in several proteins essential for blood-clotting are modified by addition of carboxyl groups (from CO_2) to form γ-carboxyglutamate units. The two carboxyl groups of each γ-carboxyglutamate then act as a Ca^{2+} binding site during the blood-clotting process.



These facts have been known for many years. Until quite recently, however, the role of vitamin K_1 in this process remained a mystery. The anion of vitamin K_1 hydroquinone is a weak base (pK_a of approximately 9). To remove a proton from glutamate, however, requires a very strong base derived from a conjugate acid of pK_a approximately 27. How can molecular oxygen increase the base strength of vitamin K_1 hydroquinone by 18

Natural vitamins of the K family have for the most part been replaced in vitamin supplements by synthetic preparations. Menadione, one such synthetic material with vitamin K activity, has only hydrogen in the place of the alkyl chain.

Vitamin K is required for blood clotting. Although many of the details of this very complex process are only poorly understood, it is clear that the role of vitamin K is to catalyze chemical modification of the protein, prothrombin. Specifically, vitamin K is necessary for carboxylation of the side chains of ten glutamic acid residues of each molecule of prothrombin.

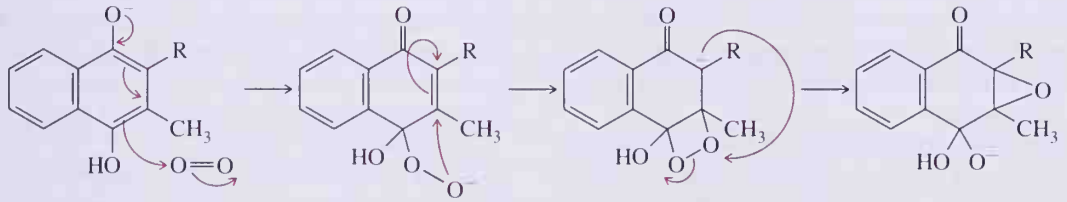


Prothrombin — Carboxylated prothrombin

orders of magnitude? The answer was discovered recently.

The vitamin K_1 hydroquinone anion reacts with oxygen to give the peroxide anion intermediate 1, which collapses to compound 2, which contains a weak O—O bond in a highly strained four-member ring. Compound 2 rearranges to vitamin K_1 base, a strong, sterically hindered alkoxide base.

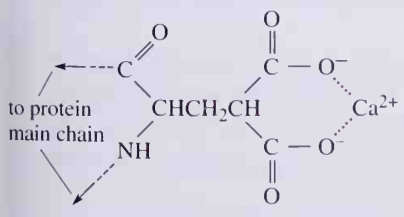
The weak O—O bond has, in this way, been converted into a stronger C—O bond in vitamin K_1 base. The extra stability provides the driving force for turning a weak phenoxide base into a strong alkoxide base, which is able to remove a proton from glutamate side chains. This makes possible the addition of CO_2 to form γ-carboxyglutamate side chains which bind calcium ions during the clotting cascade. Thus, it is now understood why O_2, CO_2, and vitamin K_1 are essential for this phase of blood clotting. Synthetic vitamin K analogs are as effective in this process as naturally occurring vitamin K_1.



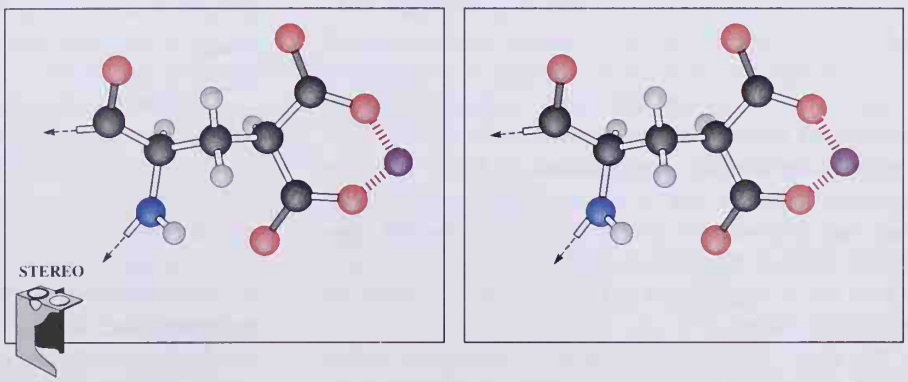
Vitamin K_1 hydroquinone anion (a weak base) (1) (2) Vitamin K_1 base (a very strong base)

Note that this reaction is the reverse of the decarboxylation of β-dicarboxylic (malonic) acids seen in Section 19.11B.

The two carboxyl groups of the chemically modified glutamic acid residue now form a tight bidentate ("two teeth") complex with calcium ion. Although more needs to be understood about blood clotting, it is at least clear that if prothrombin is not carboxylated, it does not bind calcium, and blood does not clot.



Carboxylated prothrombin complexed with Ca^{2+}



SUMMARY

Lipids are a heterogeneous class of compounds grouped together on the basis of solubility properties; they are insoluble in water and soluble in diethyl ether, acetone, and methylene chloride. Carbohydrates, amino acids, and proteins are largely insoluble in these organic solvents.

Fatty acids (Section 23.1A) are long-chain carboxylic acids derived from the hydrolysis of fats, oils, and the phospholipids of biological membranes. Names and molecular formulas for the most abundant fatty acids are given in Table 23.1. **Soaps** are sodium or potassium salts of fatty acids (Section 23.1B). In water, soaps form **micelles** (Section 23.1C), which "dissolve" nonpolar organic grease and oil. Natural soaps precipitate (form a scum) in acid solution, and form water-insoluble salts with Mg^{2+}, Ca^{2+}, and Fe^{3+} of hard water. The most common and most widely used **synthetic detergents** (Section 23.1D) are linear alkylbenzenesulfonates. Synthetic detergents may also contain one or more of the following: optical brighteners, foam stabilizers, and bleaches.

Triacylglycerols (triglycerides), the most abundant lipids, are triesters of glycerol and fatty acids (Section 23.2). The melting point of a triacylglycerol increases as (1) the length of hydrocarbon chains increases and (2) as the degree of saturation increases. Triacylglycerols rich in saturated acids are generally solids at room temperature; those rich in unsaturated fatty acids are generally oils at room temperature (Section 23.2B).

Prostaglandins are a group of eicosanoids having the 20-carbon skeleton of prostanoic acid (Section 23.3). They are synthesized in response to physiological triggers from phospholipid-bound arachidonic acid (20 : 4) and other 20-carbon fatty acids. Also included among the eicosanoids are the **leukotrienes, prostacyclins,** and **thromboxanes.**

Steroids are a group of plant and animal lipids that have a characteristic tetracyclic structure of three six-member rings and one five-member ring (Section 23.4). **Cholesterol** is an integral part of animal membranes, and it is the compound from which human sex hormones, adrenocorticoid hormones, bile acids, and vitamin D are synthesized. Cholesterol is transported in the blood by lipoproteins. **Low-density lipoproteins (LDLs)** transport cholesterol from the site of its synthesis in the liver to tissues and cells where it is to be used. **High-density lipoproteins (HDLs)** transport cholesterol from cells back to the liver for its degradation to bile acids and eventual excretion in the feces.

The structural features common to estrogens, androgens, glucocorticoid hormones, and mineralocorticoid hormones are illustrated in Table 23.3. **Oral contraceptive** pills contain a synthetic progestin, for example norethindrone, which prevents ovulation, yet allows women to maintain an otherwise normal menstrual cycle. A variety of synthetic **anabolic steroids** are available for use in rehabilitation medicine where muscle tissue has weakened or deteriorated due to injury. **Bile acids** differ from most other steroids in that they have a *cis* configuration at the junction of rings A and B.

The carbon skeleton of cholesterol and those of all biomolecules derived from it originate with the acetyl group (a C_2 unit) of **acetyl-CoA** (Section 23.4B). Key intermediates in the biosynthesis of cholesterol are mevalonic acid (a C_6 unit), isopentenyl pyrophosphate (a C_5 unit), dimethylallyl pyrophosphate (also a C_5 unit), geranyl pyrophosphate (a C_{10} unit), farnesyl pyrophosphate (a C_{15} unit), and squalene (a C_{30} unit). By epoxidation followed by a series of cation-initiated cyclizations and 1,2-shifts, squalene is converted to lanosterol and then to cholesterol.

Phospholipids (Section 23.5A), the second most abundant group of naturally occurring lipids, are derived from phosphatidic acid, a molecule containing glycerol esterified with two molecules of fatty acid and a molecule of phosphoric acid. Further esterification of the phosphoric acid part with a low-molecular-weight alcohol, most commonly ethanolamine, choline, serine, or inositol gives a phospholipid. When placed in aqueous solution, phospholipids spontaneously form a **lipid bylayer** (Section 23.5B). This self-assembly is driven by a combination of the hydrophobic effect, ion-dipole interactions, and dipole-dipole interactions.

According to the **fluid-mosaic model** (Section 23.5C), membrane phospholipids form a lipid bilayer with membrane proteins associated with the bilayer as both peripheral proteins and as integral proteins. Cholesterol is associated with animal membranes and, because of the rigidity of its tetracyclic ring system, imparts increased rigidity to membranes.

Vitamin A (Section 23.6A) occurs only in the animal world. The carotenes of the plant world are tetraterpenes (C_{40}) and are cleaved after ingestion into vitamin A. The best understood role of vitamin A is its participation in the **visual cycle.**

Vitamin D (Section 23.6B) is synthesized in the skin of mammals by the action of ultraviolet radiation on 7-dehydrocholesterol. This vitamin plays a major role in the regulation of calcium and phosphorus metabolism. **Vitamin E** (Section 23.6C) is a group of compounds of similar

structure, the most active of which is α-tocopherol. In the body, vitamin E functions as an antioxidant. **Vitamin K** (Section 23.6D) is required for the carboxylation of the glutamic acid side chains in the protein, prothrombin. Carboxylated prothrombin then forms a tight bidentate complex with Ca^{2+}.

ADDITIONAL PROBLEMS

Fatty Acids and Triacylglycerols

23.1 How many isomers, including stereoisomers, are possible for a triglyceride containing one molecule each of palmitic, stearic, and oleic acids—three of the most abundant fatty acids?

23.2 It is common now to see "contains no tropical oils" on a cooking oil label, meaning that the oil contains no palm or coconut oil. What is the difference between the composition of tropical oils and that of vegetable oils, such as corn oil, soybean oil, and peanut oil?

23.3 What is meant by the term "hardening" as applied to fats and oils?

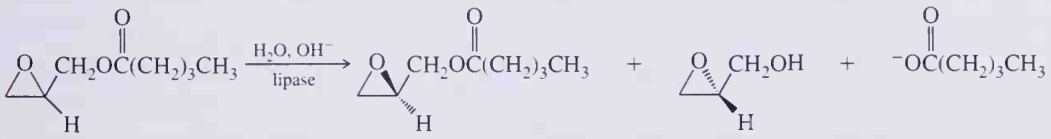
23.4 Saponification number is defined as the number of milligrams of potassium hydroxide required for saponification of 1.00 g of fat or oil.

(a) Write a balanced equation for the saponification of tristearin.

(b) The molecular weight of tristearin is 890 g/mol. Calculate the saponification number of tristearin.

23.5 The saponification number of butter fat is approximately 230; that of oleomargarine is approximately 195. Calculate the average molecular weight of butter fat and of oleomargarine.

23.6 Lipases are enzymes that catalyze the hydrolysis of esters, especially esters of glycerol. Because enzymes are chiral catalysts, they catalyze the hydrolysis of only one enantiomer of a racemic mixture. For example, porcine pancreatic lipase catalyzes the hydrolysis of only one enantiomer of the following racemic epoxyester. Calculate the number of grams of epoxyalcohol that can be obtained from 100 g of racemic epoxy ester by this method.



A racemic mixture | (This enantiomer is recovered unhydrolyzed) | (This epoxyalcohol is obtained in pure form)

23.7 Characterize the structural features necessary to make a good synthetic detergent.

23.8 Following are structural formulas for a cationic detergent and a neutral detergent. Account for the detergent properties of each.

Benzyldimethyloctylammonium chloride (a cationic detergent) | Pentaerythrityl palmitate (a neutral detergent)

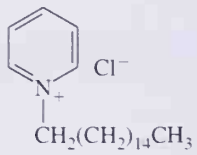
23.9 Show how to convert palmitic acid (hexadecanoic acid) into the following:

(a) Ethyl palmitate **(b)** Palmitoyl chloride

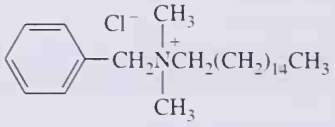
(c) 1-Hexadecanol (cetyl alcohol) **(d)** 1-Aminohexadecane

(e) *N,N*-Dimethylhexadecanamide

23.10 Palmitic acid (hexadecanoic acid) is the source of the hexadecyl (cetyl) group in the following compounds. Each is a mild surface-acting germicide and fungicide and is used as a topical antiseptic and disinfectant.



Cetylpyridinium chloride



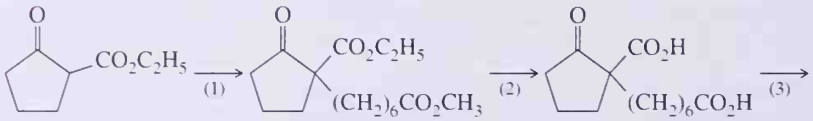
Benzylcetyldimethylammonium chloride

(a) Cetylpyridinium chloride is prepared by treating pyridine with 1-chlorohexadecane (cetyl chloride). Show how to convert palmitic acid to cetyl chloride.

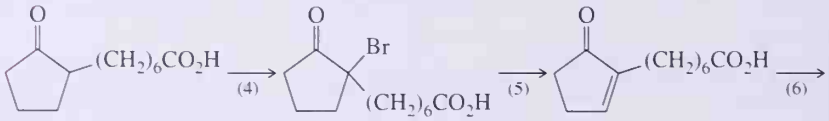
(b) Benzylcetyldimethylammonium chloride is prepared by treating benzyl chloride with 1-(*N*,*N*-dimethylamino)hexadecane. Show how this tertiary amine can be prepared from palmitic acid.

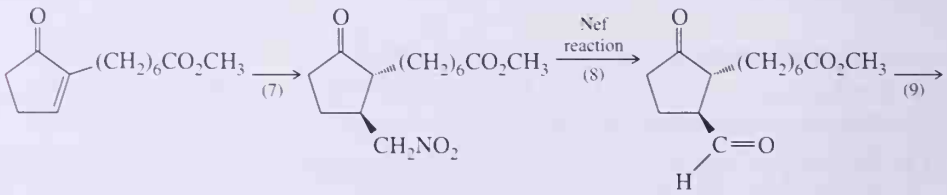
Prostaglandins

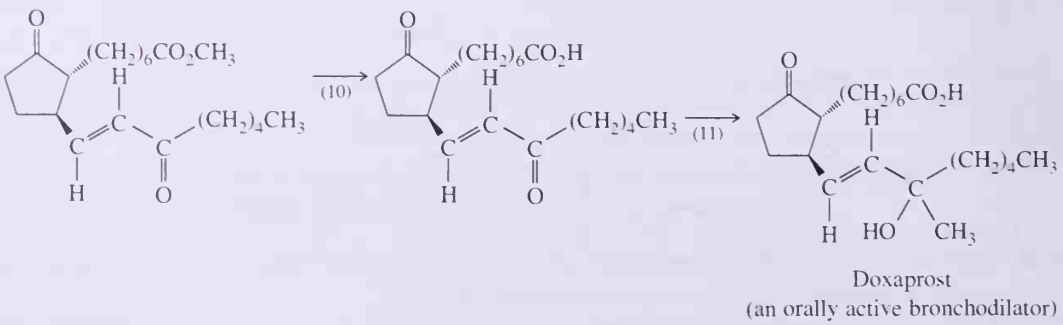
23.11 Doxaprost, an orally active bronchodilator patterned after the natural prostaglandins (Section 23.3), is synthesized in the following series of reactions starting with 2-carbethoxycyclopentanone. Except for the Nef reaction in Step 8, we have seen examples of all other types of reactions involved in this synthesis.



2-Carbethoxycyclopentanone







Doxaprost
(an orally active bronchodilator)

(a) Propose a set of experimental conditions to bring about the alkylation in Step 1. Account for the regioselectivity of the alkylation, that is, that it takes place on the carbon between the two carbonyl groups rather than on the other side of the ketone carbonyl.

(b) Propose experimental conditions to bring about Steps 2 and 3, and propose a mechanism for the loss of carbon dioxide in Step 3.

(c) Propose experimental conditions for bromination of the ring in Step 4 and dehydrobromination in Step 5.

(d) Write equations to show that Step 6 can be brought about using either methanol or diazomethane (CH_2N_2) as a source of the $—CH_3$ in the methyl ester.

(e) Describe experimental conditions to bring about the Michael reaction of Step 7.

(f) The two side chains in the product of Step 7 can be either *cis* or *trans* to each other. Which of the two do you expect to be the more stable configuration? Account for the fact that the *trans* isomer is formed in this step.

(g) Step 9 is done by a Wittig reaction. Suggest a structural formula for a Wittig reagent that gives the product shown.

(h) Name the type of reaction involved in Step 10.

(i) Step 11 can best be described as a Grignard reaction with methylmagnesium bromide under very carefully controlled conditions. In addition to the observed reaction, what other Grignard reactions might take place in Step 11?

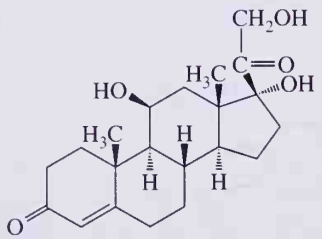
(j) Assuming that the two side chains on the cyclopentanone ring are *trans*, how many stereoisomers are produced in this synthetic sequence?

Steroids

23.12 Examine the structural formulas of testosterone (a male sex hormone) and progesterone (a female sex hormone). What are the similarities in structure between the two? What are the differences?

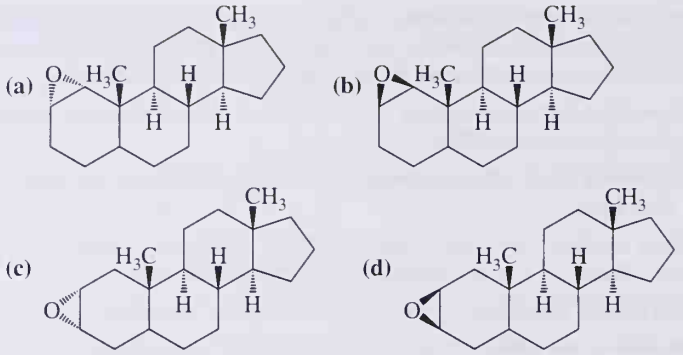
23.13 Examine the structural formula of cholic acid and account for the ability of this and other bile acids to emulsify fats and oils and thus aid in their digestion.

23.14 Following is a structural formula for cortisol (hydrocortisone). Draw a conformational representation of this molecule.

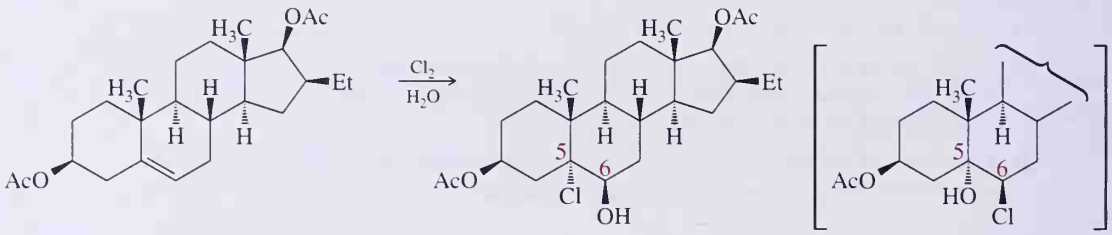


Cortisol
(Hydrocortisone)

23.15 Much of our understanding of conformational analysis has arisen from studies on the reactions of rigid steroid nuclei. For example, the concept of *trans*-diaxial ring opening of epoxides was proposed to explain the stereospecific reactions seen with steroidal epoxides. Predict the product when each of the following steroidal epoxides is treated with $LiAlH_4$:



23.16 Addition of the HOCl in the following reaction is both regioselective and stereoselective. Only one stereoisomer is formed. Alternative regioisomers, as for example the regioisomer with —OH on carbon 5 and —Cl on carbon 6, are not formed.



Not formed

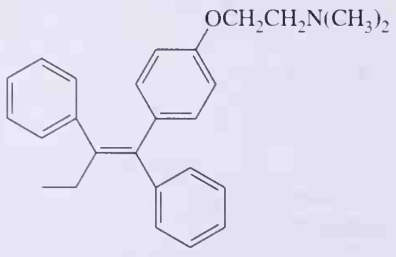
(a) Show the four stereoisomers that place —Cl and —OH *trans* to each other on carbons 5 and 6. (In two of these, —Cl is on carbon 5 and in the other two, it is on carbon 6).

(b) Draw a conformational representation for the product formed in this reaction.

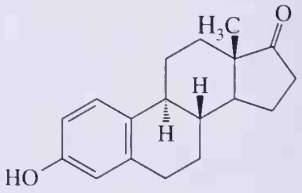
(c) According to the mechanism proposed in Section 5.3F, addition of HOCl is initiated by interaction of the alkene and chlorine to form a bridged chloronium ion intermediate. From which face of this steroid, top or bottom, is it more likely for chlorine to approach?

(d) Show that both the regioselectivity and the stereoselectivity of this addition are consistent with the mechanism proposed in Section 5.3F for addition of HOCl to an alkene.

23.17 Because some types of tumors need an estrogen, a steroid hormone, to survive, compounds that compete with the estrogen receptor on tumor cells are useful anticancer drugs. The compound tamoxifen is one such drug. To what part of the estrone molecule is the shape of tamoxifen similar?



Tamoxifen



Estrone

Phospholipids

23.18 The hydrophobic effect is one of the most important noncovalent forces directing the self-assembly of biomolecules in aqueous solution. The hydrophobic effect arises from tendencies (1) to arrange polar groups so that they interact with the aqueous environment by hydrogen bonding and (2) to arrange nonpolar groups so that they are shielded from the aqueous environment. Show how the hydrophobic effect is involved in directing

(a) Formation of micelles by soaps and detergents.

(b) Formation of lipid bilayers by phospholipids.

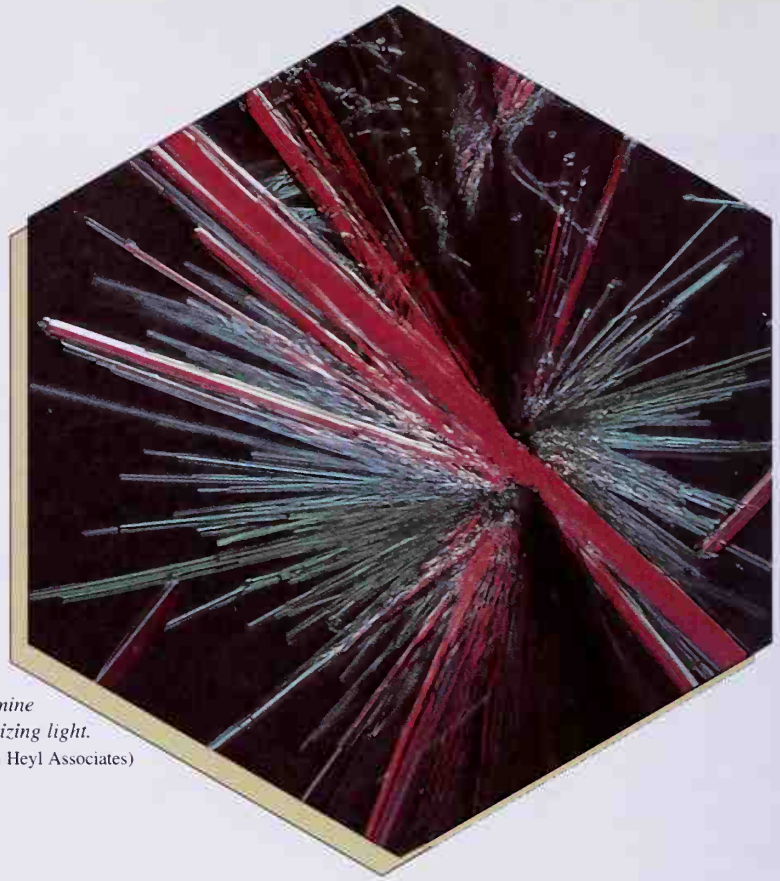
(c) Orientation of cholesterol in a phospholipid bilayer.

Fat-Soluble Vitamins

23.19 Examine the structural formula of vitamin A and state the number of *cis-trans* isomers possible for this molecule.

23.20 Examine the structural formulas of vitamins A, D_3, E, and K_1. Do you expect them to be more soluble in water or in dichloromethane? Do you expect them to be soluble in blood plasma?

24



Crystals of L-glutamine viewed under polarizing light.
(© Mel Pollinger/Fran Heyl Associates)

AMINO ACIDS AND PROTEINS

We begin this chapter with a study of amino acids—compounds whose chemistry is built on carboxylic acids (Chapter 19) and amines (Chapter 22). The fact that these molecules are difunctional presents a special challenge to chemists because in dealing with a reaction of a carboxyl group of an amino acid, we must also be aware of reactions that the amino group might undergo at the same time, and vice versa. We concentrate in particular on the acid-base properties of amino acids for it is these properties that are so important in determining many of the properties of proteins, including the catalytic functions of enzymes.

One of the triumphs of organic chemistry has been to synthesize molecules, many of them of almost bewildering complexity. Both this challenge and triumph are well illustrated in our ability to synthesize proteins from their monomer units, namely amino acids. First we examine some of the ways chemists have devised for determining the composition and order of attachment of amino acids in proteins. Then, we examine a few of the many ways for joining amino acids together by amide bonds to synthesize proteins.

Finally in this chapter we look at the three-dimensional structures of several globular proteins and at the noncovalent forces (hydrophobic effects, hydrogen bonding, and salt linkages) that direct specific folding patterns.

24.1 Amino Acids

A. Structure

An **amino acid** is a compound that contains both a carboxyl group and an amino group. Although many types of amino acids are known, the **α-amino acids** are the most significant in the biological world because they are the monomers from which proteins are constructed. A general structural formula for an α-amino acid is shown in Figure 24.1. Although Figure 24.1(a) is a common way of writing structural formulas for amino acids, it is not accurate because it shows an acid ($-CO_2H$) and a base ($-NH_2$) within the same molecule. These acidic and basic groups react with each other to form a dipolar ion or internal salt (Figure 24.1[b]). The internal salt of an amino acid is given the special name **zwitterion.** Note that a zwitterion has no net charge because it contains one positive charge and one negative charge.

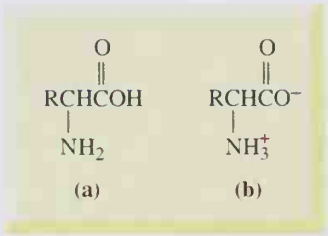


Figure 24.1
An α-amino acid. (a) Un-ionized form and (b) dipolar ion.

B. Chirality of Amino Acids

With the exception of glycine, $H_2NCH_2CO_2H$, all protein-derived amino acids have at least one tetrahedral stereocenter and, therefore, are chiral and show enantiomerism. Figure 24.2 shows stereorepresentations and Fischer projection formulas for the enantiomers of serine and glutamic acid. Shown for comparison is D-glyceraldehyde. Whereas the vast majority of carbohydrates in the biological world are of the D-series, the vast majority of α-amino acids in the biological world are of the L-series. The alternative R-S convention is also used to specify the absolute configuration of amino acids. According to this convention, L-serine is designated S-serine. Because D- and L- are used more commonly to describe the absolute configuration of amino acids, we use this convention throughout the remainder of the chapter.

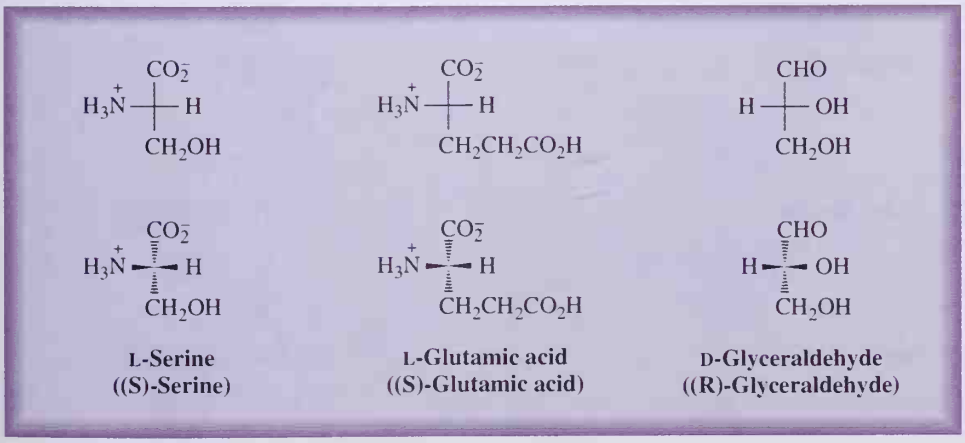


Figure 24.2
Amino acids of the L configuration, as illustrated by L-serine and L-glutamic acid, are found in proteins. The majority of carbohydrates in the biological world are related in stereochemistry to D-glyceraldehyde.

C. Protein-Derived Amino Acids

Table 24.1 gives names, structural formulas, and standard three-letter and one-letter abbreviations for the 20 common L-amino acids found in proteins. The amino acids in this table could be listed in several ways, for example, alphabetically or in order of increasing molecular weight. However, a more useful classification, and one that is of great value when we discuss the physical properties of amino acids and the three-dimensional shapes of proteins, is to group them according to the polarity of their side chains. For this reason, the amino acids in Table 24.1 are divided into the following four side-chain categories: nonpolar, polar but un-ionized, acidic, and basic. The following structural features of these amino acids should be noted:

1. All 20 of these protein-derived amino acids are α-amino acids, meaning that the amino group is located on the carbon alpha to the carboxyl group.
2. For 19 of the 20 amino acids, the α-amino group is primary. Proline is different; its α-amino group is secondary.
3. With the exception of glycine, the α-carbon of each amino acid is a tetrahedral stereocenter. Although not shown in this table, all chiral amino acids have the same relative configuration at the α-carbon. In the D-L convention, all are L-amino acids. In the R-S convention, 18 are S-amino acids. Cysteine is an R-amino acid, not because it differs in relative configuration from the other 18 but because of the manner in which priority is assigned to groups on the stereocenter.
4. Isoleucine and threonine contain a second tetrahedral stereocenter. Four stereoisomers are possible for each amino acid, but only one is found in proteins.
5. The sulfhydryl group of cysteine, the imidazole group of histidine, and the phenolic hydroxyl of tyrosine are partially ionized at pH 7.0, but the ionic form is not the major form present at this pH.

Table 24.1 The 20 common amino acids found in proteins. Each ionizable functional group is shown in the form present in highest concentration at pH 7.0

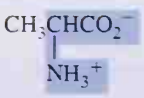
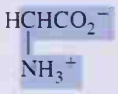
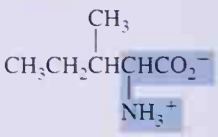
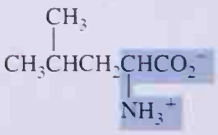
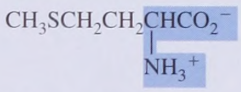
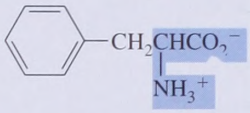
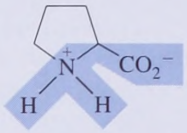
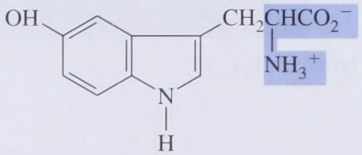
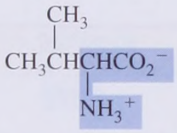
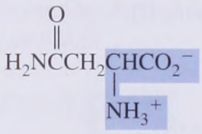
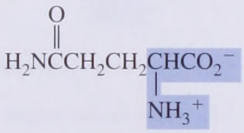
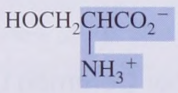
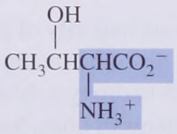
Nonpolar Side Chains	
alanine (Ala, A)	
glycine (Gly, G)	
isoleucine (Ile, I)	
leucine (Leu, L)	

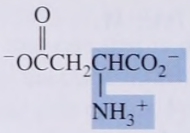
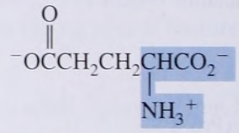
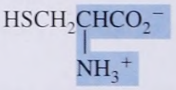
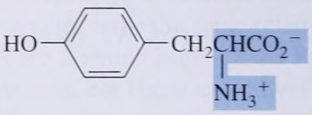
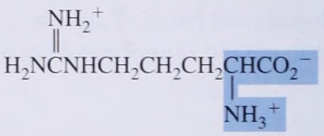
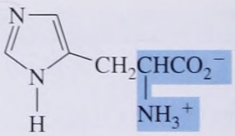
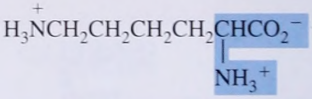
Table 24.1 *(Continued)*

Nonpolar Side Chains *(continued)*	
methionine (Met, M)	
phenylalanine (Phe, F)	
proline (Pro, P)	
tryptophan (Trp, W)	
valine (Val, V)	

Polar but Un-ionized Side Chains	
asparagine (Asn, N)	
glutamine (Gln, Q)	
serine (Ser, S)	
threonine (Thr, T)	

(Table 24.1 continued on next page)

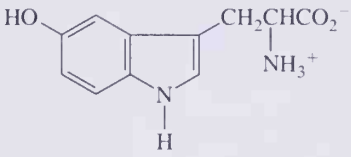
Table 24.1 *(Continued)*

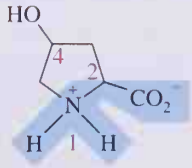
Acidic Side Chains	
aspartic acid (Asp, D)	
glutamic acid (Glu, E)	
cysteine (Cys, C)	
tyrosine (Tyr, Y)	
Basic Side Chains	
arginine (Arg, R)	
histidine (His, H)	
lysine (Lys, K)	

D. Some Other Common L-Amino Acids

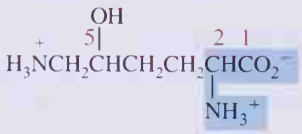
Although the vast majority of plant and animal proteins are constructed from just these 20 amino acids, a few other amino acids are also found in proteins. For example, 4-hydroxy-L-proline and 5-hydroxy-L-lysine are important components of collagens. Collagens, the protein constituents of bone, teeth, blood vessels, tendons, cartilage, and connective tissue, make up almost 30% of the total body mass in humans. These L-amino acids are synthesized by enzyme-catalyzed oxidation of L-proline and L-lysine after each is incorporated into collagen.

Crystals of 5-hydroxy-L-tryptophan viewed under polarizing light. *(© Herb Charles Ohlmeyer/Fran Heyl Associates)*



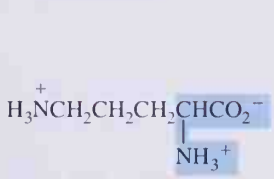


4-Hydroxy-L-proline

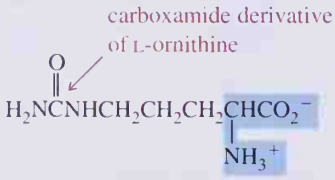


5-Hydroxy-L-lysine

L-Ornithine and L-citrulline are found predominantly in the liver and are an integral part of the urea cycle—the metabolic pathway that converts ammonia to urea.

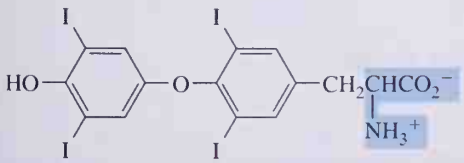


L-Ornithine

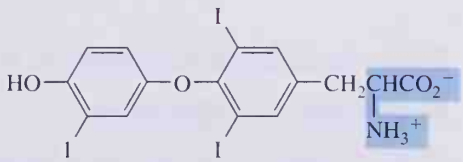


L-Citrulline

Thyroxine, one of several hormones derived from the amino acid, tyrosine, was first isolated from thyroid tissue in 1914. In 1952, triiodothyronine, a compound similar in structure to thyroxine except that it contains only three atoms of iodine, was also discovered in thyroid tissue. The principal function of these hormones is to stimulate metabolism in other cells and tissues.



L-Thyroxine, T_4

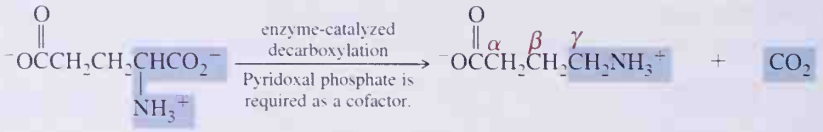


L-Triiodothyronine, T_3

Table 24.2 Some polypeptide antibiotics containing one or more D-amino acids

Antibiotic	D-Amino Acid(s)	Produced by
Actinomycin D	D-valine	*Streptomyces parralus*
Bacitracin A	D-asparagine	*Bacillus subtilis*
	D-glutamic acid	
	D-ornithine	
	D-phenylalanine	
Fungisporin	D-phenylalanine	*Penicillium* spp.
Gramicidin S	D-phenylalanine	*Bacillus brevis*

4-Aminobutanoic acid (γ-aminobutyric acid, GABA) is a neurotransmitter found in high concentration (0.8 m*M*) in the brain but in no significant amounts in any other mammalian tissue. This amino acid is synthesized in neural tissue by decarboxylation of the α-carboxyl group of glutamic acid. Glutamic acid is one of the most important excitatory neurotransmitters in the central nervous system of invertebrates and possibly in humans as well. In contrast, 4-aminobutanoic acid is an inhibitory neurotransmitter. Whereas an excitatory neurotransmitter brings about depolarization (firing) of a postsynaptic membrane, an inhibitory neurotransmitter leads to hyperpolarization and makes it more difficult to excite a postsynaptic membrane.



Glutamic acid

4-Aminobutanoic acid (γ-Aminobutyric acid, GABA)

D-Amino acids are not found in proteins and are rarely a part of the metabolism of higher organisms. However, several D-amino acids, along with their L enantiomers, are found in structural components and the metabolism of lower forms of life. As examples, both D-alanine and D-glutamic acid are structural components of cell walls of certain bacteria. A variety of D-amino acids is found in peptide antibiotics. A few of these are listed in Table 24.2.

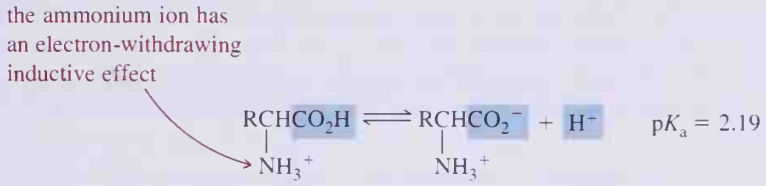
24.2 Acid-Base Properties of Amino Acids

A. Ionization of Amino Acids

Given in Table 24.3 are pK_a values for ionizable groups of amino acids. Several things should be noticed from the data in this table.

Acidity of α-Carboxyl Groups

The average value of pK_a for an α-carboxyl group of a protonated amino acid is 2.19. Thus, the α-carboxyl group of an amino acid is a considerably stronger acid than acetic acid (pK_a 4.76) and other low-molecular-weight aliphatic carboxylic acids. This greater acidity is accounted for by the electron-withdrawing inductive effect of the adjacent $-NH_3^+$ group. Recall that we used similar reasoning in Section 19.4A to account for the relative acidities of acetic acid and its mono-, di-, and trichloroderivatives.



Acidity of Side-Chain Carboxyl Groups

Due to the electron-withdrawing inductive effect of the α-NH_3^+ group, the side-chain carboxyl groups of aspartic acid and glutamic acid are stronger acids than acetic acid (pK_a

Table 24.3 pK_a values for ionizable groups of amino acids

Amino Acid	pK_a of α-CO_2H	pK_a of α-NH_3^+	pK_a of Side Chain	Isoelectric Point (pI)
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

4.76). Notice that this acid-strengthening inductive effect decreases with increasing distance of the $-CO_2H$ from the α-NH_3^+; compare the acidities of the α-CO_2H of alanine (pK_a 2.35), and β-CO_2H of aspartic acid (pK_a 3.86), and the γ-CO_2H of glutamic acid (pK_a 4.07).

Basicity of α-Amino Groups

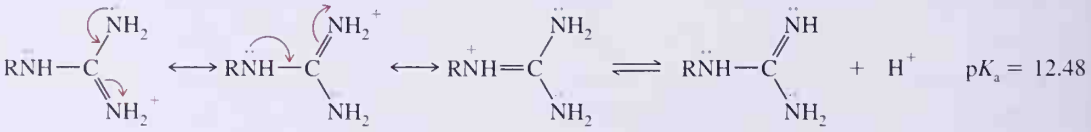
The average value of pK_a for an α-ammonium group is 9.47, compared with a value of 10.76 for primary aliphatic amines (Section 22.6). Thus, the α-ammonium group of an amino acid is a slightly stronger acid than a primary aliphatic ammonium ion. Conversely, an α-amino group is a slightly weaker base than a primary aliphatic amine.

$$RCHCO_2^- \rightleftharpoons RCHCO_2^- + H^+ \qquad pK_a = 9.47$$
$$\quad\;\; NH_3^+ \qquad\quad NH_2$$

$$CH_3CHCH_3 \rightleftharpoons CH_3CHCH_3 + H^+ \qquad pK_a = 10.60$$
$$\quad\;\; NH_3^+ \qquad\quad NH_2$$

Basicity of the Guanidine Group of Arginine

The side-chain guanidine group of arginine is a considerably stronger base than an aliphatic amine. As we saw in Section 22.6, guanidine (pK_a 0.4) is the strongest base of any neutral compound. The remarkable basicity of the guanidine group of arginine is attributed to the very large resonance stabilization of the protonated form relative to the neutral form.

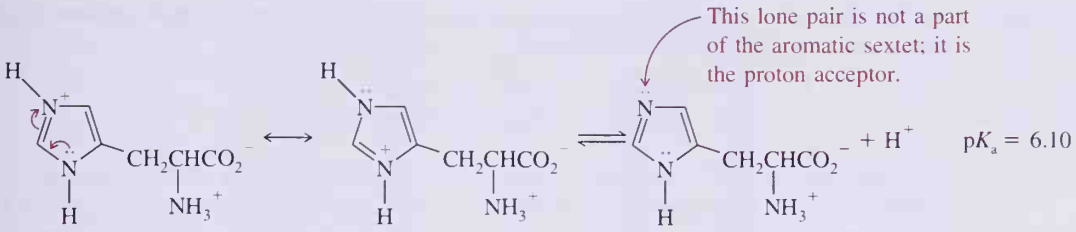


The guanidinium ion side chain of arginine is a hybrid of three contributing structures.

No resonance stabilization without charge separation

Basicity of the Imidazole Group of Histidine

Because the imidazole group on the side chain of histidine contains six pi electrons in a planar, fully conjugated ring, imidazole is classified as a heterocyclic aromatic amine (Section 15.2D). Whereas the unshared pair of electrons on one nitrogen is a part of the aromatic $4n + 2$ system, the unshared pair on the other nitrogen is not. It is the pair of electrons that is not part of the aromatic system that is responsible for the basic properties of the imidazole ring. Protonation of this nitrogen produces a resonance-stabilized cation.



Resonance-stabilized imidazolium cation

B. Ionization of Amino Acids as a Function of pH

In the previous section, we considered each ionizable group of an amino acid separately. Now let us consider how the interaction of ionizable groups within a particular amino acid affects the properties of that amino acid. Given values for the pK_a of each functional group, we can calculate the ratio of each acid to its conjugate base at any given pH. As an example, let us calculate these ratios at pH 7.0. Consider first the ionization of the weak acid, α-CO_2H, to form H^+ and its conjugate base α-CO_2^-. For the purposes of this calculation and to simplify the mathematics, we use a value of 2.00 for the pK_a of an α-carboxyl group of a protonated amino acid.

$$\alpha\text{-}CO_2H \rightleftharpoons \alpha\text{-}CO_2^- + H^+ \qquad pK_a = 2.00 \qquad K_a = 1.00 \times 10^{-2}$$

The equilibrium constant for this ionization is given by the expression

$$K_a = \frac{[H^+][\alpha\text{-}CO_2^-]}{[\alpha\text{-}CO_2H]}$$

Rearranging this expression gives

$$\frac{[\alpha\text{-}CO_2^-]}{[\alpha\text{-}CO_2H]} = \frac{K_a}{[H^+]}$$

Substituting values of K_a for an α-CO_2H group (1.00×10^{-2}) and the hydrogen ion concentration at pH 7.0 (1.0×10^{-7}) in this equation gives

$$\frac{[\alpha\text{-}CO_2^-]}{[\alpha\text{-}CO_2H]} = \frac{1.00 \times 10^{-2}}{1.00 \times 10^{-7}} = 1.00 \times 10^5$$

Thus, we see that a pH 7.0, the ratio of $[\alpha$-$CO_2^-]$ to $[\alpha$-$CO_2H]$ is 10^5 to 1. It is clear that at pH 7.0, an α-carboxyl group is virtually 100% in the ionized, or conjugate base, form and it has a charge of -1.

We can also calculate the ratio of acid to conjugate base for an α-amino group. For this calculation, let us use a value of 10.0 for the pK_a of an α-amino group.

$$\alpha\text{-}NH_3^+ \rightleftharpoons \alpha\text{-}NH_2 + H^+ \qquad pK_a = 10.00 \qquad K_a = 1.00 \times 10^{-10}$$

The acid ionization constant for the ionization of α-NH_3^+ can be rearranged to give the following expression:

$$\frac{[\alpha\text{-}NH_2]}{[\alpha\text{-}NH_3^+]} = \frac{K_a}{[H^+]}$$

Substituting values of K_a for an α-NH_3^+ group (1.0×10^{-10}) and the hydrogen ion concentration at pH 7.0 (1.0×10^{-7}) gives

$$\frac{[\alpha\text{-}NH_2]}{[\alpha\text{-}NH_3^+]} = \frac{1.00 \times 10^{-10}}{1.00 \times 10^{-7}} = 1.00 \times 10^{-3}$$

Thus, the ratio of α-NH_2 to α-NH_3^+ at pH 7.0 is approximately 1 to 1000. At this pH, an α-amino group is more than 99.9% in the acid, or protonated, form and has a charge of +1. As can be seen from these calculations, the dipolar form of an amino acid predominates at pH 7.0.

We have calculated the ratio of weak acid to conjugate base at pH 7.0 for an α-carboxyl group and an α-amino group. We can do the same type of calculation at any other pH. To do this for any weak acid and its conjugate base, it is convenient to transform the acid ionization constant in the following way:

$$\text{Weak acid} \rightleftharpoons \text{conjugate base} + H^+ \qquad K_a = \frac{[\text{conjugate base}][H^+]}{[\text{weak acid}]}$$

Taking the logarithm of this equation and rearranging gives

this term, by definition, is pH — this term, by definition, is pK_a

$$-\log[H^+] = -\log K_a + \log \frac{[\text{conjugate base}]}{[\text{weak acid}]}$$

Thus, in rearranged form, the equation for the ionization of a weak acid to its conjugate base and hydrogen ion has the following form, known as the **Henderson-Hasselbalch equation** after the two biochemists who first pointed out its particular usefulness.

Henderson-Hasselbalch equation:

$$pH = pK_a + \log \frac{[\text{conjugate base}]}{[\text{weak acid}]}$$

The Henderson-Hasselbalch equation provides a direct way to calculate the ratio of conjugate base to weak acid at any given pH. Figure 24.3 shows graphically the percentage of molecules present as undissociated weak acid at pH values 1 and 2 units greater (more basic), and 1 and 2 units smaller (more acidic) than the value of pK_a. At any pH greater (more basic) than pK_a, the conjugate base predominates. At any pH less (more acidic) than pK_a, the weak acid predominates. When pH equals pK_a, the weak acid and its conjugate base are present in equal concentrations.

EXAMPLE 24.1

Draw a structural formula for L-serine, and estimate the net charge on this amino acid at pH 3.0, 7.0, and 10.0.

Solution

Start with the Henderson-Hasselbalch equation, substitute values for pH and pK_a, and solve for the ratio of conjugate base to weak acid. The pK_a of the α-carboxyl group of serine is 2.21. At pH of 3.0, which is 0.79 unit greater than its pK_a, the α-carboxyl group is approximately 86% in the ionized (conjugate base) form.

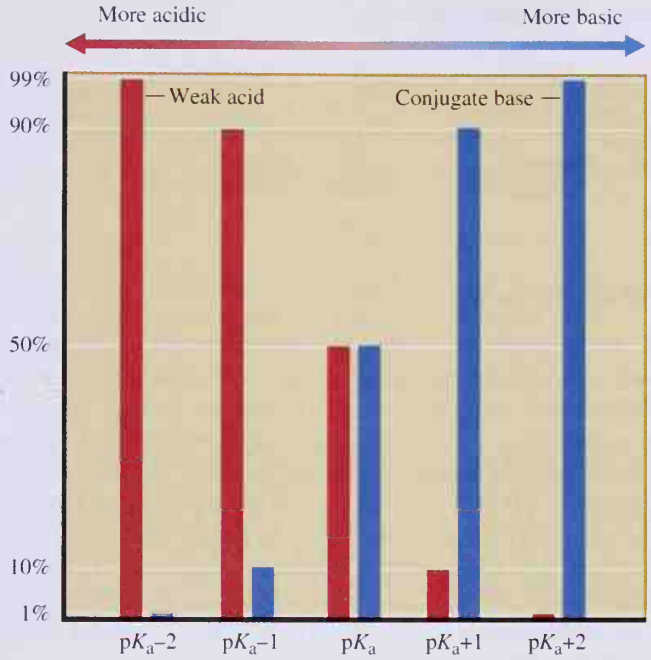


Figure 24.3
The dependence of concentration of a weak acid and its conjugate base on pH.

$$\log \frac{[\alpha\text{-}CO_2^-]}{[\alpha\text{-}CO_2H]} = 3.0 - 2.21 = 0.79$$

Taking the antilog of 0.79 gives the ratio of $[\alpha\text{-}CO_2^-]$ to $[\alpha\text{-}CO_2H]$ at this pH.

$$\frac{[\alpha\text{-}CO_2^-]}{[\alpha\text{-}CO_2H]} = \frac{6.17}{1}$$

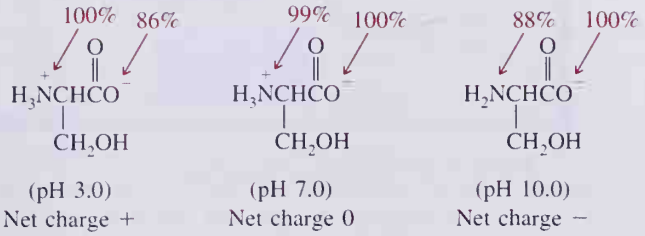
$$\alpha\text{-}CO_2^- = \frac{[\alpha\text{-}CO_2^-]}{[\alpha\text{-}CO_2H] + [\alpha\text{-}CO_2^-]} \times 100 = \frac{6.17}{1.00 + 6.17} \times 100 = 86\%$$

The pK_a of the α-amino group of serine is 9.15. Calculation for the α-amino group of serine gives the following:

$$\frac{[\alpha\text{-}NH_2]}{[\alpha\text{-}NH_3^+]} = \frac{7.1 \times 10^{-7}}{1.00}$$

Thus, at pH 3.0, which is 6.15 pH units less (more acidic) than its pK_a, the α-amino group is completely in the protonated (positively charged) form.

The same type of calculations can be repeated at pH 7.0 and 10.0. Results are shown on the following structural formulas.



PROBLEM 24.1

Draw a structural formula for lysine, and estimate the net charge on each functional group at pH 3.0, 7.0, and 10.0.

C. Titration of Amino Acids

Values of pK_a for the ionizable groups of amino acids are most commonly obtained by acid-base titration and measuring the pH of the solution as a function of added base (or added acid, depending on how the titration is done). To illustrate this experimental procedure, consider a solution containing 1.0 mol of glycine to which has been added enough strong acid so that both the amino and carboxyl groups are fully protonated. Next, this solution is titrated with 1.0 *M* NaOH; the volume of base added and the pH of the resulting solution are recorded and then plotted as shown in Figure 24.4. The most acidic group and the one to react first with added sodium hydroxide is the carboxyl group. When exactly 0.5 mol of NaOH has been added, the carboxyl group is half neutralized. At this point, the concentration of the dipolar ion equals that of the positively charged ion, and the pH (2.35) equals the pK_a of the carboxyl group.

$$\text{At pH} = pK_{a1}: \quad [\overset{+}{H_3}NCH_2CO_2H] = [\overset{+}{H_3}NCH_2CO_2^-]$$

Positive ion Dipolar ion

The end point of the first part of the titration is reached when 1.0 mol of sodium hydroxide has been added. At this point, the predominant species present is the dipolar ion, and the observed pH of the solution is 6.06. The next section of the curve represents titration of the $—NH_3^+$ group. When another 0.5 mol of sodium hydroxide has been added (bringing the total to 1.5 mol), half of the $—NH_3^+$ groups are neutralized and converted to

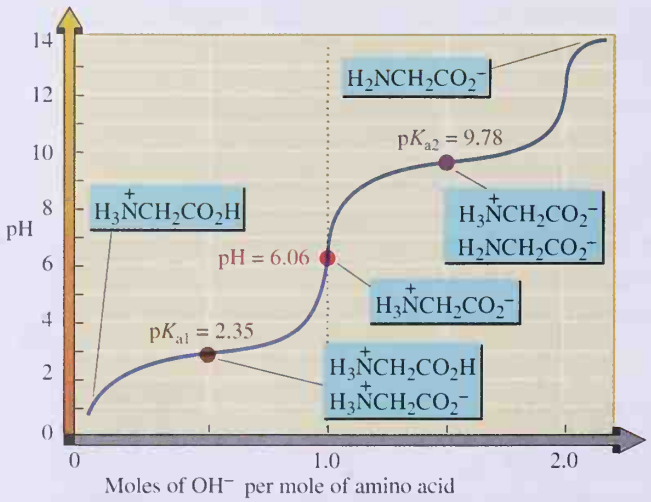


Figure 24.4
Titration of glycine with sodium hydroxide.

$—NH_2$. At this point, the concentrations of the dipolar ion and negatively charged ion are equal, and the observed pH is 9.78, the pK_a of the amino group of glycine.

$$\text{At pH} = pK_{a2}: \qquad [\overset{+}{H_3N}CH_2CO_2^-] = [H_2NCH_2CO_2^-]$$

Dipolar ion Negative ion

The second end point of the titration is reached when a total of 2.0 mol of sodium hydroxide have been added and glycine is converted entirely to an anion.

D. Isoelectric Point

Titration curves such as that for glycine permit us to determine pK_a values for the ionizable groups of an amino acid. They also permit us to determine another important property—isoelectric point. **Isoelectric point, pI,** for an amino acid is the pH at which the majority of molecules in solution have no net charge, that is, a net charge of zero. By examining the titration curve, you can see that the isoelectric point for glycine falls halfway between the pK_a values for the carboxyl and amino groups.

$$pI = \frac{1}{2}(pK_a\ \alpha\text{-}CO_2H + pK_a\ \alpha\text{-}NH_3^+)$$

$$= \frac{1}{2}(2.35 + 9.78) = 6.06$$

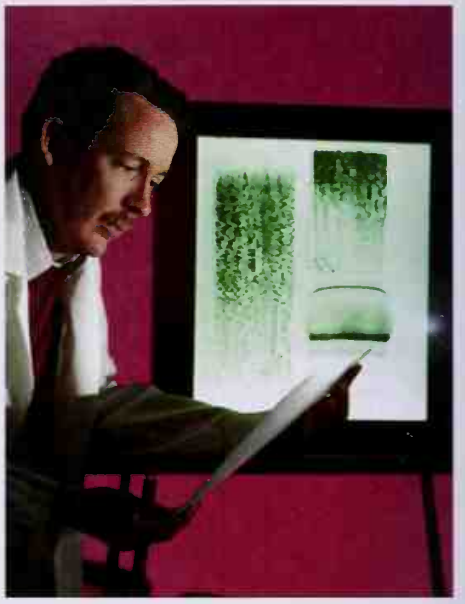
At pH 6.06, the predominant form of glycine molecules is the dipolar ion; furthermore, at this pH the number of positively charged glycine molecules equals the number of negatively charged glycine molecules.

Given a value for the isoelectric point of an amino acid, it is possible to estimate the charge on that amino acid at any pH. For example, the charge on tyrosine at pH 5.63, its isoelectric point, is zero. A small fraction of tyrosine molecules are positively charged at pH 5.00 (0.63 unit less than its pI) and virtually all are positively charged at pH 3.63 (2.00 units less than its pI). As another example, the net charge on lysine is zero at pH 9.74. At pH values smaller than 9.74 an increasing fraction of lysine molecules are positively charged.

E. Isoelectric Precipitation and Electrophoresis

An understanding of isoelectric point is important for two reasons. First, it helps us to understand the solubility of amino acids as a function of pH. Second, it enables us to understand the direction in which the components of a mixture of amino acids migrate in an electric field during electrophoresis.

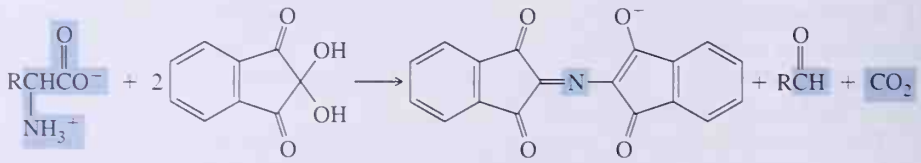
The solubility of an amino acid is at a minimum at its isoelectric point and increases as pH is increased or decreased. At the isoelectric point, molecules of an amino acid have no net charge and are most likely to cluster together and form a precipitate. At a lower or higher pH, molecules have either a net positive charge or a net negative charge and hence are more likely to repel each other and stay in solution. To crystallize an amino acid from aqueous solution, the pH of the solution is adjusted to the pI of the particular amino acid, and the compound is precipitated, filtered, and collected. This process is called **isoelectric precipitation.**



Chromosome maps from gel electrophoresis provide clues to adult onset diabetes. *(© Will & Deni McIntyre, Photo Researchers, Inc.)*

Electrophoresis is a process of separating compounds on the basis of their electric charges. Electrophoretic separations can be carried out using paper, starch, agar, certain plastics, and cellulose acetate as solid supports. This technique is extremely important in biochemical research and is also an invaluable tool in the clinical chemistry laboratory. In paper electrophoresis, a paper strip saturated with an aqueous buffer of predetermined pH serves as a bridge between two electrode vessels (Figure 24.5). Next, a sample of amino acid is applied as a spot. When an electric potential is then applied to the electrode vessels, amino acids migrate toward the electrode carrying the charge opposite to their own. Molecules having a high charge density move more rapidly than those with a lower charge density. Any molecule already at its isoelectric point remains at the origin. After separation is complete, the strip is dried and sprayed with a dye to make the separated components visible.

The dye most commonly used for amino acids is ninhydrin (1,2,3-indanetrione monohydrate). Ninhydrin reacts with α-amino acids to produce an aldehyde, carbon dioxide, and a purple-colored anion with an absorption maximum at 580 nm. This reaction is used very commonly in both qualitative and quantitative analysis of amino acids.



An α-amino acid

Ninhydrin (1,2,3-Indanetrione monohydrate)

Purple-colored anion (λ_{max}580 nm)

Nineteen of the 20 protein-derived α-amino acids have primary amino groups and give the same purple-colored ninhydrin-derived anion. Proline, a secondary amine, gives a different, orange-colored compound.

EXAMPLE 24.2

The isoelectric point of tyrosine is 5.63. Toward which electrode does tyrosine migrate on paper electrophoresis at pH 7.0?

Solution

On paper electrophoresis at pH 7.0 (more basic than the isoelectric point of tyrosine), tyrosine has a net negative charge and migrates toward the positive electrode.

PROBLEM 24.2

The isoelectric point of histidine is 7.64. Toward which electrode does histidine migrate on paper electrophoresis at pH 7.0?

EXAMPLE 24.3

Electrophoresis of a mixture of lysine, histidine, and cysteine is carried out at pH 7.64. Describe the behavior of each amino acid under these conditions.

Solution

The isoelectric point of histidine is 7.64. At this pH, histidine has a net charge of zero and does not move from the origin. The pI of cysteine is 5.02; at pH 7.64 (more basic than its isoelectric point), cysteine has a net negative charge and moves toward the positive electrode. The pI of lysine is 9.74; at pH 7.64 (more acidic than its isoelectric point), lysine has a net positive charge and moves toward the negative electrode.

PROBLEM 24.3

Describe the behavior of a mixture of glutamic acid, arginine, and valine on paper electrophoresis at pH 6.0.

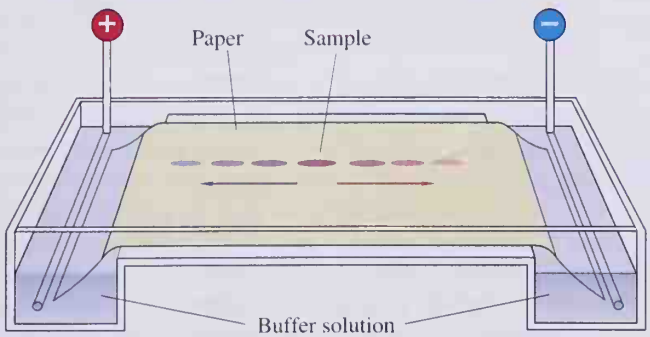


Figure 24.5
An apparatus for electrophoresis of a mixture of amino acids.

24.3 Amino Acids, Proteins, and Nutrition

Most dietary proteins contain all of the amino acids humans need for synthesizing their proteins. They are often present in different proportions, however. For protein synthesis to take place, all of the required amino acids must be present at the time of synthesis and in the correct proportions. Studies of protein synthesis have led to the concept of essential amino acids and nonessential amino acids. Nonessential amino acids are synthesized in the body at a rate equal to the needs for protein synthesis. **Essential amino acids** cannot be synthesized in the body fast enough to support normal protein synthesis.

Of the 20 amino acids required for the synthesis of proteins, 10 can be synthesized by enzyme-catalyzed reactions using carbon atoms derived from carbohydrates and fatty acids, and a source of nitrogen atoms. For the remaining amino acids, either no biochemical pathway is available for their synthesis, or the available pathways do not provide proper amounts for adequate nutrition. Therefore, these ten amino acids must be supplied in the diet, and are called essential amino acids (Table 24.4).

The **biological value of a dietary protein** is a measure of the percentage that is absorbed and used to build body tissue. Some of the first information on the biological value of dietary proteins came from studies on rats. In one series of experiments, young rats were fed diets containing protein in the form of either casein (a milk protein), gliadin (a wheat protein), or zein (a corn protein). With casein as the sole dietary source of protein, the rats remained healthy and grew normally. Those fed gliadin maintained their weight but did not grow much. Those fed zein not only failed to grow but lost weight and, if kept on this diet, eventually died. Because casein evidently supplies all required amino acids in the correct proportions needed for growth, it is called a complete protein. Analysis revealed that gliadin contains too little lysine, and that zein is low in both lysine and tryptophan. When a gliadin diet was supplemented with lysine, or a zein diet with lysine and tryptophan, test animals grew normally.

Table 24.5 gives the biological value for rats of some common dietary sources of protein. The proteins in egg are the best quality natural proteins. The proteins of milk are next, followed by those of meats and soybeans. The legumes, vegetables, and cereal grains are in the range 50% to 70%.

Table 24.4 Amino acid requirements for humans

Essential	Nonessential
arginine	alanine
histidine	asparagine
isoleucine	aspartic acid
leucine	cysteine
lysine	glutamic acid
methionine	glutamine
phenylalanine	glycine
threonine	proline
tryptophan	serine
valine	tyrosine

Table 24.5 Biological value for rats of some common sources of dietary proteins

Food	Protein as % of Dry Solid	Biological Value of Protein (%)
hen's egg, whole	48	94
cow's milk, whole	27	84
fish	72	83
beef, lean	45	74
soybean	41	73
rice, brown	9	73
potato, white	6	67
wheat, whole-grain	14	65
corn, whole-grain	11	59
beans, dry, common	25	58

Plant proteins generally vary more from the amino acid pattern required by humans than do animal proteins. Fortunately, however, not all plant proteins are deficient in the same amino acids. For example, beans are low in the sulfur-containing amino acids, cysteine and methionine, yet high in lysine. Wheat has just the opposite pattern. By eating wheat and beans together, it is possible to increase by 33% the usable protein obtained by eating either of these foods alone.

To provide a diet adequate in protein and essential amino acids is a grave problem in the world today, especially in areas of Asia, Africa, and South America. The overriding dimension of this problem is poverty and an inability to afford foods of adequate protein and caloric content. The best overall sources of calories are the cereal grains, which provide not only calories but protein as well. When these are supplemented with a proper selection of plant or animal protein, the diet is adequate for even the most vulnerable. However, the ability to provide protein in the diet decreases as income decreases, and even cereal grains are often replaced by cheaper sources of calories, such as starches or tubers, foods that have either very little or no protein. The poorest 25% of the world's population consumes diets with caloric and protein content that fall below, often dangerously below, the calculated minimum daily requirements.

Those most likely to show symptoms of too little food, too little protein, or both, are young children in the years immediately following weaning. These children fail to grow properly and show a wasting of tissue. This sickness is called marasmus, a name derived from a Greek word meaning "to waste away." Muscles become atrophied, and the face develops a wizened "old man's" look. Another disease, kwashiorkor, leads to tragically high death rates among children. As long as a child is breast-fed, it is healthy. At weaning (often forced when a second child is born), the first child's diet is switched to starch or other inadequate sources of protein. Such children develop bloated bellies and patchy, discolored skin and are often doomed to short lives.

One solution to the problem of quantity and quality of protein has been to breed new varieties of cereal grains with higher protein content, better quality protein, or both. Alternatively, cereals and their derived products can be supplemented (fortified) with amino

acids in which they are deficient; principally lysine for wheat, lysine or lysine and threonine for rice, and lysine and tryptophan for corn. New methods of synthesis and fermentation now provide cheap sources of these amino acids, thus making the economics of food fortification entirely practical. In another attack on the problem of protein malnutrition, nutritionists have developed several high-protein, low-cost infant foods. Clearly, advances in food chemistry and technology have provided the means of eradicating hunger and malnutrition. What remains is for the world's political and social systems to put this knowledge into practice.

24.4 Polypeptides and Proteins

In 1902, Emil Fischer proposed that proteins are long chains of amino acids joined together by amide bonds between the α-carboxyl group of one amino acid and the α-amino group of another. For these amide bonds, Fischer proposed the special name **peptide bond.** Figure 24.6 shows the peptide bond formed between glycine and alanine in the dipeptide glycylalanine.

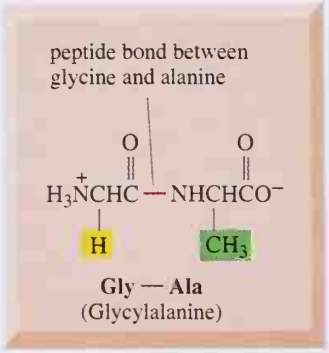
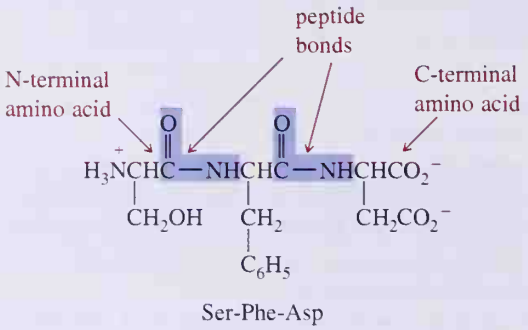


Figure 24.6
The peptide bond in glycylalanine.

A molecule containing two amino acids joined by an amide bond is called a **dipeptide.** Those containing larger numbers of amino acids are called **tripeptides, tetrapeptides, pentapeptides,** and so on. Molecules containing ten or more amino acids are generally called **polypeptides. Proteins** are biological macromolecules of molecular weight 5000 or greater, consisting of one or more polypeptide chains.

By convention, polypeptides are written from the left, beginning with the amino acid having the free $-NH_3^+$ group and proceeding to the right toward the amino acid with the free $-CO_2^-$ group. The amino acid with the free $-NH_3^+$ group is called the ***N*-terminal amino acid,** and that with the free $-CO_2^-$ group is called the ***C*-terminal amino acid.**

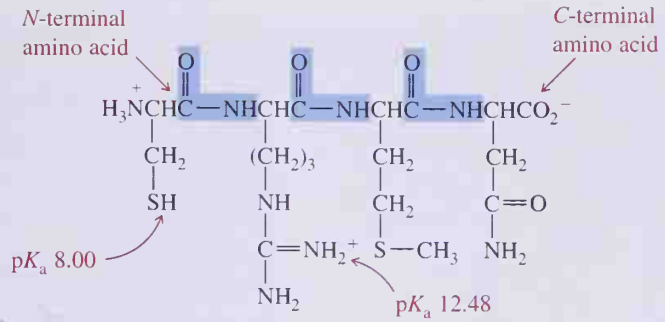


EXAMPLE 24.4

Draw a structural formula for Cys-Arg-Met-Asn. Label the *N*-terminal amino acid and the *C*-terminal amino acid. What is the net charge on this tetrapeptide at pH 6.0?

Solution

The backbone of the tetrapeptide chain is a repeating sequence of nitrogen-α-carbon-carbonyl. The net charge on this tripeptide at pH 6.0 is + 1.



PROBLEM 24.4

Name and draw a structural formula for Lys-Phe-Ala. Label the *N*-terminal amino acid and the *C*-terminal amino acid. What is the net charge on this tripeptide at pH 6.0?

24.5 Primary Structure of Polypeptides and Proteins

The **primary (1°) structure** of a polypeptide or protein refers to the sequence of amino acids in a polypeptide chain. In this sense, primary structure is a complete description of all covalent bonding in a polypeptide or protein.

To appreciate the problem of deciphering the primary structure of a polypeptide chain, imagine the incredibly large number of different chemical words (polypeptides) that can be constructed with a 20-letter alphabet in which words can range from fewer than 10 letters to more than 100. With only three amino acids, $3 \times 3 \times 3$, or 27, different tripeptides are possible if we assume that each amino acid can be repeated in any position.

For a polypeptide containing 1 each of the 20 different amino acids, and assuming that each amino acid is used only once in the polypeptide, the number of possible polypeptides is $20 \times 19 \times 18 \times \cdots \times 2 \times 1$, or more than 2×10^{18}. With larger polypeptides and proteins, the number of possible combinations becomes truly countless!

A. Amino Acid Analysis

The first step in determining the primary structure of a polypeptide is hydrolysis and quantitative analysis of its amino acid composition. Recall from Section 20.4D that amide bonds are very resistant to hydrolysis. Hydrolysis of polypeptides requires heating in 6 *M* HCl at 110°C for 24 to 70 h, or heating in 4 *M* NaOH at comparable temperatures and for comparable times. Once the polypeptide is hydrolyzed, the resulting mixture of amino acids is analyzed by ion-exchange chromatography. Amino acids are detected as they emerge from the column by reaction with ninhydrin (Section 24.2E). Current procedures for hydrolysis of polypeptides and analysis of amino acid mixtures have been refined to the point where it is possible to obtain amino acid composition from as little as 50 nmol (50×10^{-9} mol) of polypeptide. Figure 24.7 shows the analysis of a polypeptide hydrolysate by ion-exchange chromatography. Note that during hydrolysis, the side-chain amide groups of asparagine and glutamine are hydrolyzed, and these amino acids are detected as aspartic acid and glutamic acid. For each glutamine or asparagine hydrolyzed, an equivalent amount of ammonia is formed.

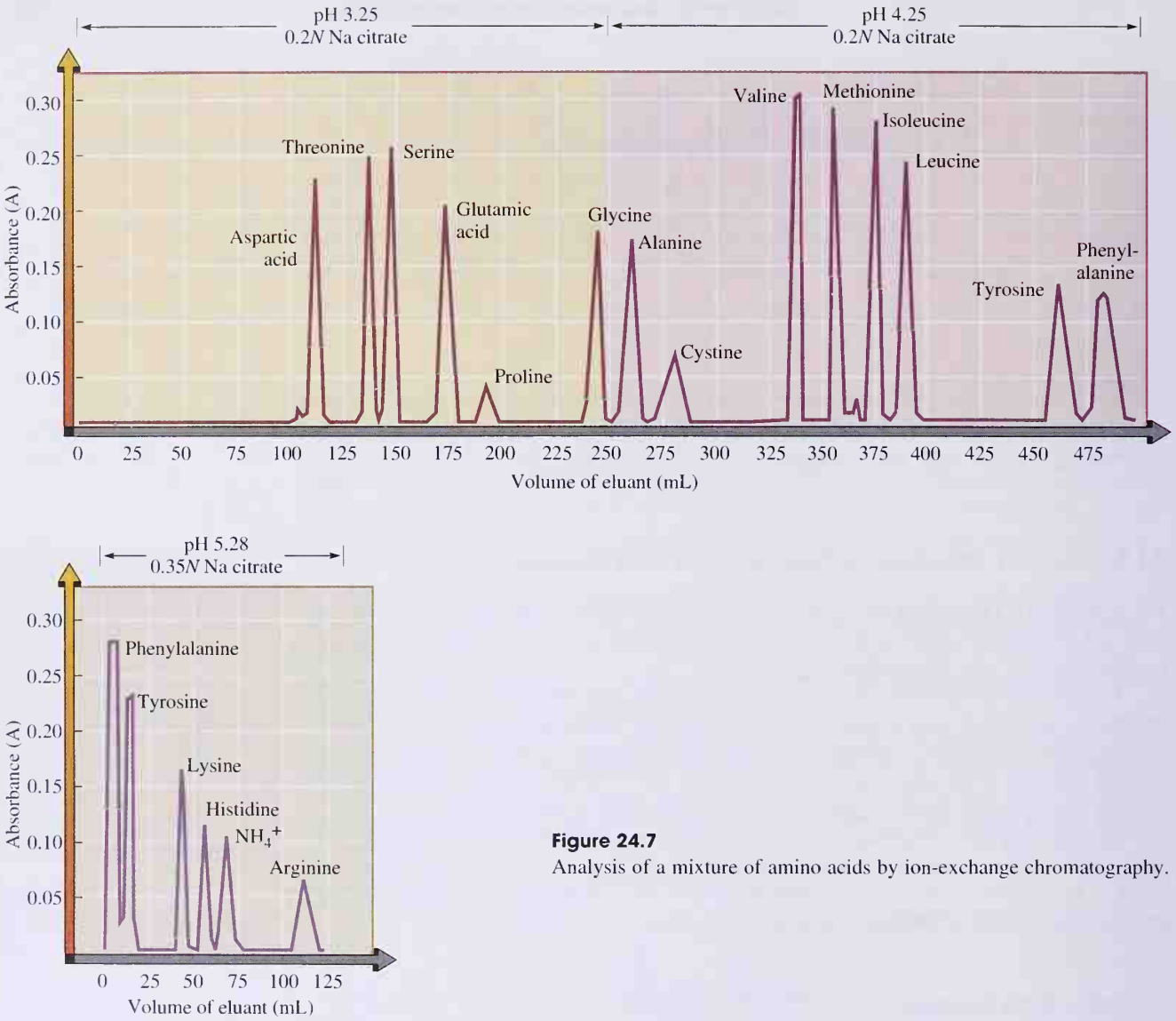


Figure 24.7
Analysis of a mixture of amino acids by ion-exchange chromatography.

B. Sequence Analysis

Once the amino acid composition of a polypeptide has been determined, the next step is to determine the order in which the amino acids are joined in the polypeptide chain. The most common sequencing strategy is to cleave the polypeptide at specific peptide bonds (using, for example, cyanogen bromide or certain proteolytic enzymes), determine the sequence of each fragment (using for example, the Edman degradation), and then match overlapping fragments to arrive at the sequence of the polypeptide.

Cyanogen Bromide

Cyanogen bromide (Br—CN) is specific for cleavage of peptide bonds formed by the carboxyl group of methionine (Figure 24.8). The product of this cleavage is a substituted γ-lactone containing the *N*-terminal end of the polypeptide, and a second fragment derived from the *C*-terminal end of the polypeptide.

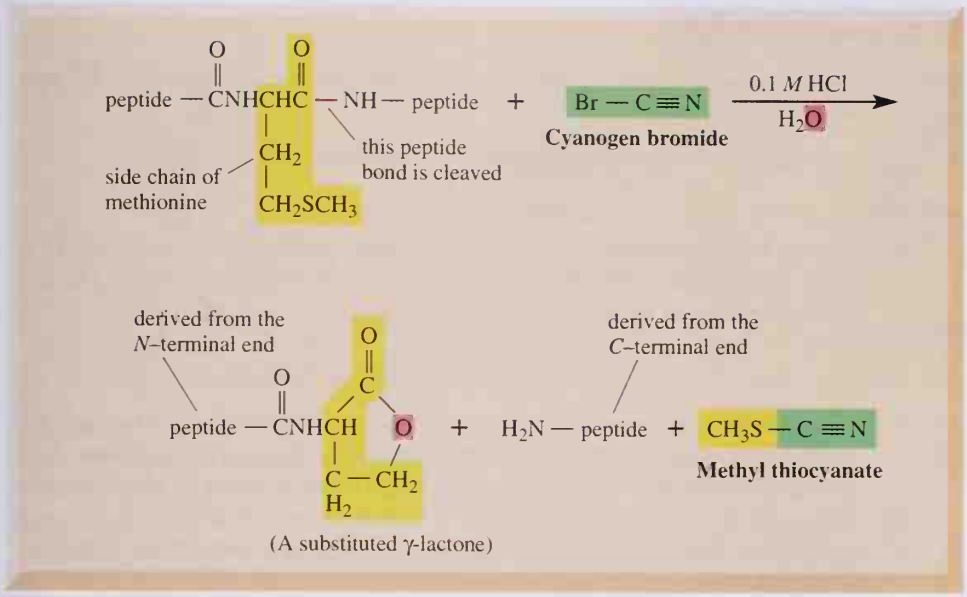


Figure 24.8
Cleavage by cyanogen bromide, Br—CN, of a peptide bond formed by the carboxyl group of methionine.

Enzyme-Catalyzed Hydrolysis of Peptide Bonds

A group of proteolytic enzymes can be used to catalyze the hydrolysis of specific peptide bonds. Among these are trypsin and chymotrypsin. Trypsin catalyzes the hydrolysis of peptide bonds formed by the carboxyl groups of arginine and lysine; chymotrypsin catalyzes the hydrolysis of peptide bonds formed by the carboxyl groups of phenylalanine, tyrosine, and tryptophan (Table 24.6).

Table 24.6 Specific cleavage of peptide bonds catalyzed by trypsin and chymotrypsin

Enzyme	Catalyzes Hydrolysis of Peptide Bond Formed by Carboxyl of	Side Chain of Amino Acid Undergoing Selective Hydrolysis
trypsin	arginine	—$(CH_2)_3NHC(=NH_2^+)NH_2$
	lysine	—$(CH_2)_4NH_3^+$
chymotrypsin	phenylalanine	—CH_2—C$_6$H$_5$
	tyrosine	—CH_2—C$_6$H$_4$—OH
	tryptophan	—CH_2—C$_8$H$_6$N (indole)

EXAMPLE 24.5

Following are amino acid sequences for three tripeptides. Which are hydrolyzed by trypsin? Which by chymotrypsin?

(a) Arg-Glu-Ser **(b)** Phe-Gly-Lys **(c)** Phe-Lys-Met

Solution

(a) Trypsin catalyzes hydrolysis of peptide bonds formed by the carboxyl groups of lysine and arginine. Therefore, the peptide bond between arginine and glutamic acid is hydrolyzed in the presence of trypsin.

$$\text{Arg-Glu-Ser} + H_2O \xrightarrow{\text{trypsin}} \text{Arg} + \text{Glu-Ser}$$

Chymotrypsin catalyzes the hydrolysis of peptide bonds formed by the carboxyl groups of phenylalanine, tyrosine, and tryptophan. Because none of these three aromatic amino acids is present, tripeptide (a) is not affected by chymotrypsin.

(b) Tripeptide (b) is not affected by trypsin. Although lysine is present, its carboxyl group is at the *C*-terminal end and not involved in peptide bond formation. Tripeptide (b) is hydrolyzed in the presence of chymotrypsin.

$$\text{Phe-Gly-Lys} + H_2O \xrightarrow{\text{chymotrypsin}} \text{Phe} + \text{Gly-Lys}$$

(c) Tripeptide (c) is hydrolyzed by both trypsin and chymotrypsin.

$$\text{Phe-Lys-Met} + H_2O \xrightarrow{\text{trypsin}} \text{Phe-Lys} + \text{Met}$$

$$\text{Phe-Lys-Met} + H_2O \xrightarrow{\text{chymotrypsin}} \text{Phe} + \text{Lys-Met}$$

PROBLEM 24.5

Following are amino acid sequences for three tripeptides. Which are hydrolyzed by trypsin? Which by chymotrypsin?

(a) Tyr-Gln-Val **(b)** Thr-Phe-Ser **(c)** Thr-Ser-Phe

Edman Degradation

Of the various chemical methods developed for determining the amino acid sequence of a polypeptide, the one most widely used today is the **Edman degradation,** introduced in 1950 by Pehr Edman of the University of Lund, Sweden. In this procedure, a polypeptide is treated with phenyl isothiocyanate, $C_6H_5\text{-}N{=}C{=}S$ and then with acid. The effect of Edman degradation is to selectively remove the *N*-terminal amino acid as a substituted phenylthiohydantoin (Figure 24.9), which is then separated and identified.

The special value of Edman degradation is that it cleaves the *N*-terminal amino acid from a polypeptide without affecting any other bonds in the chain. Furthermore, Edman degradation can be repeated on the shortened polypeptide, causing the next amino acid in the sequence to be cleaved and identified. In practice, it is now possible to sequence as many as the first 20 to 30 amino acids in a polypeptide by this method using as little as a few milligrams of material.

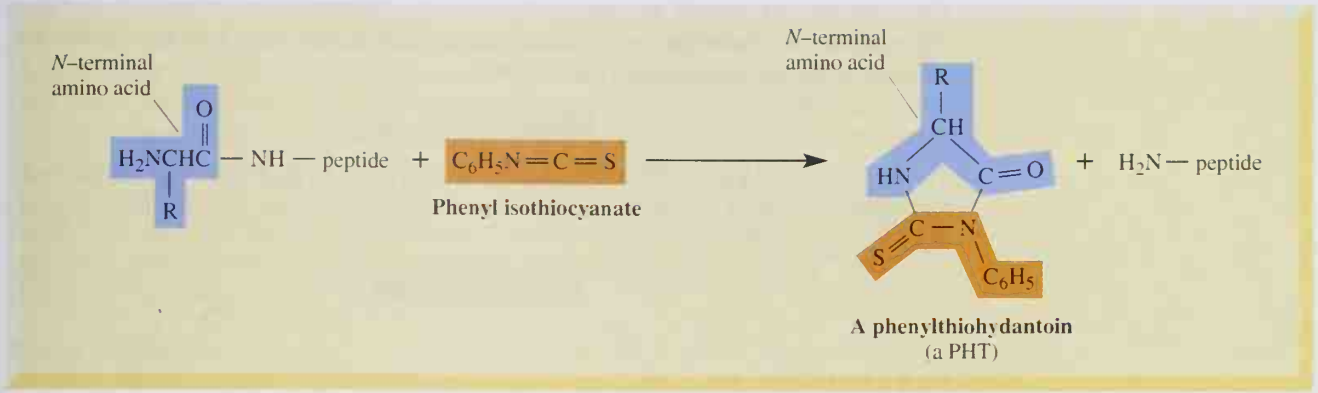


Figure 24.9
Edman degradation. Treatment of a polypeptide with phenyl isothiocyanate selectively cleaves the *N*-terminal amino acid as a substituted phenylthiohydantoin.

Most polypeptides in nature are longer than 20 to 30 amino acids, the practical limit to the number of amino acids that can be sequenced by repetitive Edman degradation. The special value of cleavage with cyanogen bromide, trypsin, and chymotrypsin is that a long polypeptide chain can be cleaved at specific peptide bonds into smaller polypeptide fragments, and each fragment can then be sequenced separately.

EXAMPLE 24.6

Deduce the amino acid sequence of a pentapeptide from the following experimental results. Note that under the column Amino Acid Composition, the amino acids are listed in alphabetical order. In no way does this listing give any information about primary structure.

Experimental Procedure	Amino Acid Composition
Pentapeptide:	Arg, Glu, His, Phe, Ser
Edman degradation:	Glu
Hydrolysis Catalyzed by Chymotrypsin	
Fragment A:	Glu, His, Phe
Fragment B:	Arg, Ser
Hydrolysis Catalyzed by Trypsin	
Fragment C:	Arg, Glu, His, Phe
Fragment D:	Ser

Solution

Edman degradation cleaves Glu from the pentapeptide; therefore, glutamic acid must be the *N*-terminal amino acid:

Glu-(Arg, His, Phe, Ser)

Fragment A from chymotrypsin-catalyzed hydrolysis contains Phe. Because of the specificity of chymotrypsin, Phe must be the *C*-terminal amino acid of fragment A. Fragment A

also contains Glu, which we already know is the *N*-terminal amino acid. From these observations, conclude that the first three amino acids in the chain must be Glu-His-Phe, and now write the following partial sequence:

Glu-His-Phe-(Arg, Ser)

The fact that trypsin cleaves the pentapeptide means that Arg must be within the pentapeptide chain; it cannot be the *C*-terminal amino acid. Therefore, the complete sequence must be

Glu-His-Phe-Arg-Ser

PROBLEM 24.6

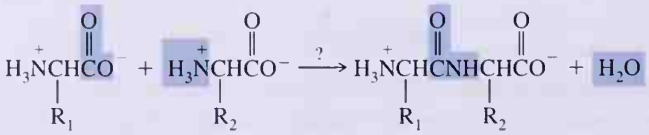
Deduce the amino acid sequence of a undecapeptide (11 amino acids) from the experimental results shown in the table.

Experimental Procedure	Amino Acid Composition
Undecapeptide:	Ala, Arg, Glu, Lys_2, Met, Phe, Ser, Thr, Trp, Val
Edman degradation:	Ala
Trypsin-Catalyzed Hydrolysis	
Fragment E:	Ala, Glu, Arg
Fragment F:	Thr, Phe, Lys
Fragment G:	Lys
Fragment H:	Met, Ser, Trp, Val
Chymotrypsin-Catalyzed Hydrolysis	
Fragment I:	Ala, Arg, Glu, Phe, Thr
Fragment J:	Lys_2, Met, Ser, Trp, Val
Reaction with Cyanogen Bromide	
Fragment K:	Ala, Arg, Glu, Lys_2, Met, Phe, Thr, Val
Fragment L:	Trp, Ser

24.6 Synthesis of Polypeptides

A. The Problems

The synthesis of polypeptides presents special problems quite different from those we have encountered so far, and for this reason has presented a particular challenge to chemists. The fundamental reaction in peptide synthesis is to join the carboxyl group of one amino acid by an amide (peptide) bond to the amino group of another.

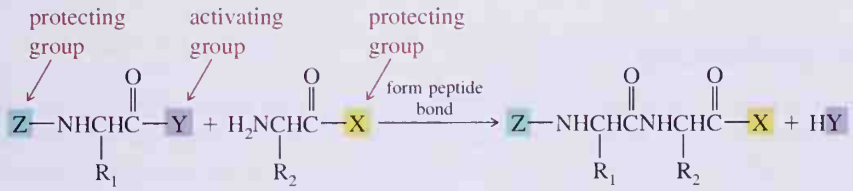


Amide bonds can be formed by heating carboxylic acids with amines. Under these conditions amino and carboxyl groups form salts, which then decompose to form amides. This strategy, however, is completely impractical for several reasons. First, it offers no control over which amino group reacts with which carboxyl group. Second, it offers no control over the number of peptide bonds formed. The final product is a mixture of di-, tri-, tetra-, and higher polypeptides, all of essentially random primary structure. Third, heating amino acids in this manner leads to extensive loss of configuration by racemization. Fourth is the problem of the side-chain carboxyl groups of glutamic and aspartic acids, as well as the side-chain amino groups of lysine and arginine, also participating in peptide bond formation.

B. The Strategies

A rational strategy for the synthesis of peptide bonds and polypeptides is to block all carboxyl and amino groups that are not to be involved in peptide bond formation with protecting groups and then form the peptide bond between the remaining free amino group and carboxyl group. Consider this strategy, for example, in the synthesis of dipeptide aa_1-aa_2 from amino acids aa_1 and aa_2. It is necessary to do three things:

1. Protect the α-amino group of amino acid aa_1 to reduce its nucleophilicity so that it does not participate in nucleophilic addition to the carbonyl group of aa_2.
2. Protect the α-carboxyl group of amino acid aa_2 so that it is not susceptible to nucleophilic attack by the α-amino group of another molecule of aa_2.
3. Activate the α-carboxyl group of amino acid aa_1 so that it is susceptible to nucleophilic attack by the α-amino group from aa_2.



Once dipeptide aa_1-aa_2 has been formed, the protecting group Z can be removed and chain growth continued from the *N*-terminal end of the dipeptide. Alternatively, the protecting group X can be removed and chain growth continued from the *C*-terminal end. The range of protecting groups and activating groups is large, and experimental conditions have been found to attach and remove them as desired.

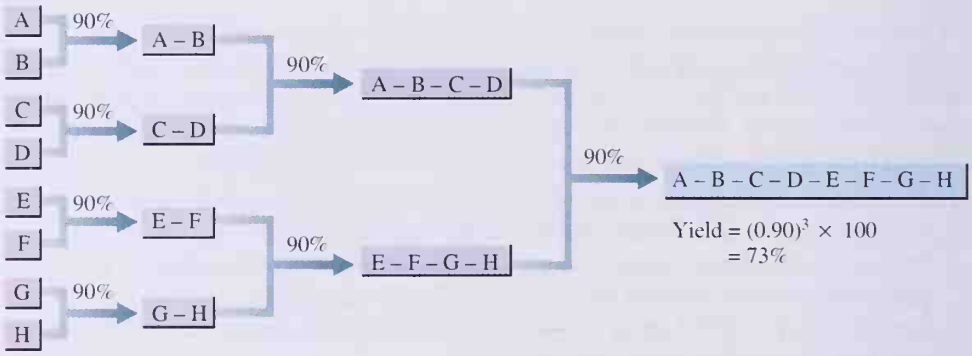
Before we go on to discuss specific protecting and activating groups and formation of peptide bonds, another experimental problem should be considered. **Linear synthesis,** one strategy of polypeptide synthesis, starts with the first amino acid of the polypeptide and adds successive amino acids one at a time. In linear synthesis, the final yield is the product of the yield in each step. We can illustrate the problem of yield by considering a linear synthesis of an octapeptide. If we assume a 90% yield for each of the seven coupling steps, the overall yield is 48%.

$$\begin{aligned}\text{Yield} &= 0.90 \times 0.90 \times 0.90 \times 0.90 \times 0.90 \times 0.90 \times 0.90 \times 100\% \\ &= (0.90)^7 \times 100 = 48\%\end{aligned}$$

If the yield in each step is only 80%, then the final yield after seven coupling steps falls to 21%.

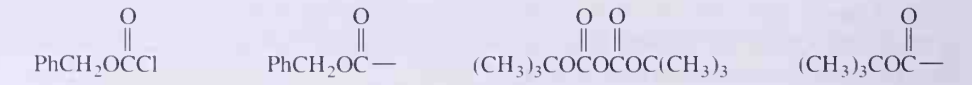
In another strategy called **convergent synthesis,** small polypeptide fragments are made separately and then joined together to form larger fragments, the larger fragments are

then joined together, and so on until the final polypeptide is completed. One clear advantage of the convergent synthesis over linear synthesis is that the overall yield is not simply the product of the yield of each step. As an illustration, suppose that amino acids A and B are coupled to form the dipeptide A-B, and that the same is done with the pairs C and D, E and F, and G and H. Pairs of dipeptides are then coupled to give tetrapeptides, and finally the two tetrapeptides are coupled to give an octapeptide. Assuming a yield of 90% in each coupling step, the overall yield for this convergent synthesis is shown in the figure. Even if the yield in each successive set of coupling steps falls to 80%, the yield of octapeptide by this convergent synthesis is still 50%. Linear synthesis is impractical for large polypeptides unless, of course, exceptionally high yields can be achieved in each step. The most practical strategy is convergent synthesis.

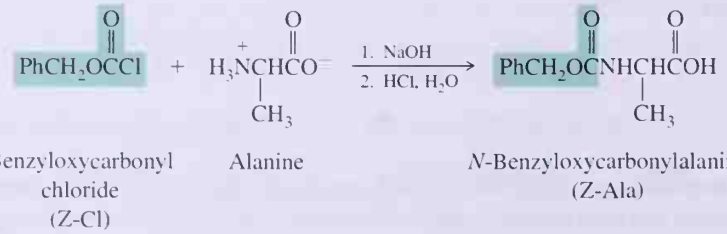


C. Amino-Protecting Groups

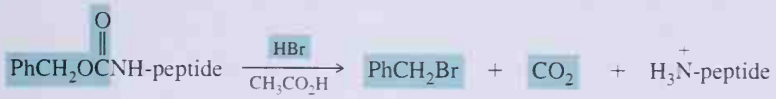
The most common strategy for protecting amino groups and reducing their nucleophilicity is to convert them to amides. The reagents most commonly used for this purpose are benzyloxycarbonyl chloride and di-*tert*-butyl dicarbonate. In the terminology adopted by the IUPAC, the benzyloxycarbonyl group is given the symbol Z-, and the *tert*-butoxycarbonyl group is given the symbol BOC-.



Treatment of an amino group with either of these reagents forms a new functional group called a carbamate. A carbamate is an ester of carbamic acid, that is, it is an ester of the monoamide of carbonic acid.

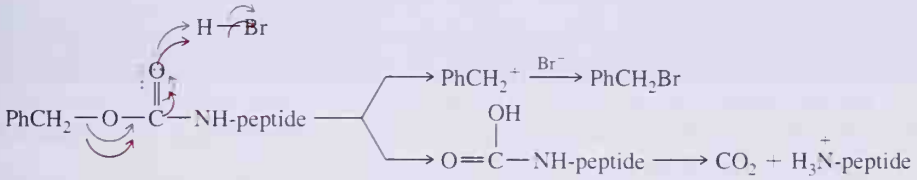


The special advantage of the carbamate group is that it is stable to dilute base but can be removed at will by treatment with HBr in acetic acid.



A Z-protected peptide Benzyl bromide Unprotected peptide

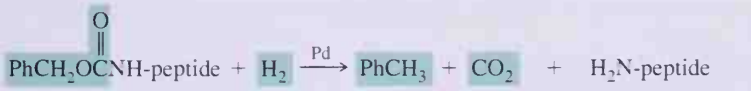
A study of the mechanism for removal of this protecting group has shown that the reaction is first order in $[H^+]$ and involves formation of a carbocation and a carbamic acid. A carbamic acid spontaneously loses carbon dioxide to form the free amine. The carbocation reacts with an available nucleophile, such as bromide ion, to form an alkyl halide.



A carbamic acid

Note that because acid-catalyzed removal of these protecting groups is carried out in nonaqueous media, there is no danger of simultaneous acid-catalyzed hydrolysis of peptide (amide) bonds within the newly synthesized polypeptide. Why? Because water is required for hydrolysis of a peptide bond.

The benzyloxycarbonyl group can also be removed by hydrogen gas in the presence of a transition metal catalyst in a reaction called hydrogenolysis. Hydrogenolysis is the cleavage of a single bond by H_2. Raney nickel desulfurization (Section 17.16C) is another example of hydrogenolysis. In hydrogenolysis of a Z-protecting group, one product is toluene. The other is a carbamic acid, which undergoes spontaneous decarboxylation to give carbon dioxide and the unprotected peptide.



A Z-protected peptide Toluene Unprotected peptide

D. Carboxyl-Protecting Groups

Carboxyl groups are most often protected by conversion to methyl, ethyl, or benzyl esters. Methyl and ethyl esters are prepared by Fischer esterification (Section 19.9A) and are removed by hydrolysis in aqueous base (Section 20.4C) under mild conditions. Benzyl esters are conveniently removed by hydrogenolysis with H_2 over a palladium or platinum catalyst. Benzyl groups can also be removed by treatment with HBr in acetic acid.

E. Peptide Bond-Forming Reactions

As we saw in Section 20.6A, amides are readily prepared by treating an amino group with an acid halide. This method is rarely used in peptide synthesis, however, because acid

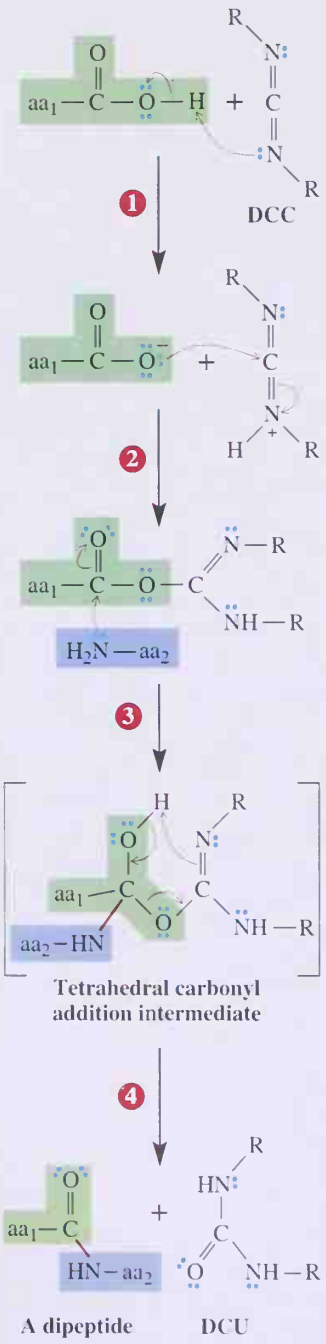
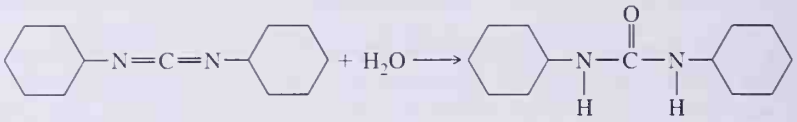


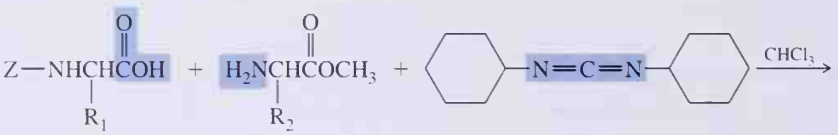
Figure 24.10
The role of 1,3-dicyclohexylcarbodiimide (DCC) in formation of a peptide bond between an amino-protected amino acid, aa_1, and a carboxyl-protected amino acid, aa_2.

halides of di- and higher polypeptides undergo extensive racemization at the stereocenter alpha to the acid halide. A great deal of research has gone into finding groups that activate α-carboxyl groups and at the same time minimize racemization. The reagent most commonly used to bring about peptide bond formation is 1,3-dicyclohexylcarbodiimide (DCC). This reagent is the anhydride of a disubstituted urea, and when treated with water, it is converted to *N,N′*-dicyclohexylurea (DCU).

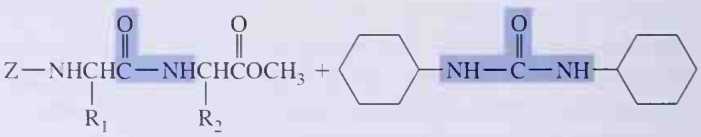


1,3-Dicyclohexylcarbodiimide (DCC) | *N,N′*-Dicyclohexylurea (DCU)

When an amino-protected amino acid aa_1 and a carboxyl-protected amino acid aa_2 are treated with DCC, this reagent acts as a molecular dehydrating agent; it removes —OH from the carboxyl group and —H from the amino group to form an amide. More specifically, DCC activates the α-carboxyl group of aa_1 toward nucleophilic acyl substitution by converting its —OH group into a better leaving group.



Amino-protected aa_1 | Carboxyl-protected aa_2 | 1,3-Dicyclohexylcarbodiimide (DCC)



Amino- and carboxyl-protected dipeptide | *N,N′*-Dicyclohexylurea (DCU)

An abbreviated mechanism for this intermolecular dehydration is shown in Figure 24.10. An acid-base reaction in Step 1 between the carboxyl group of aa_1 and a nitrogen of DCC followed in Step 2 by addition of the carboxylate anion to the C=N double bond results in electrophilic addition to a C=N double bond. The *O*-acylisourea formed is the nitrogen analog of a mixed anhydride. Nucleophilic addition of the amino group of aa_2 to the carbonyl group of the *O*-acylisourea in Step 3 generates a tetrahedral carbonyl addition intermediate that collapses in Step 4 to give a dipeptide and DCU.

F. Solid-Phase Synthesis

A major problem associated with polypeptide synthesis, whether it involves a linear or convergent strategy, is purification of intermediates after each protection, activation, coupling, and deprotection step. If unreacted starting materials are not removed after each step, the final product is contaminated by polypeptides missing one or more amino acids. The required purification steps are not only laborious and time-consuming, but they inevitably

An automated polypeptide synthesizer. *(Perkin-Elmer's Applied Biosystems Division, Foster City, CA)*

result in some loss of the desired product. These losses become especially severe in the synthesis of larger polypeptides.

A major advance in polypeptide synthesis came in 1962 when R. Bruce Merrifield of Rockefeller University described a **solid-phase synthesis** (alternatively called polymer-supported synthesis) of the tetrapeptide, Leu-Ala-Gly-Ala, by a technique that now bears his name. Merrifield was awarded the 1984 Nobel Prize in chemistry for his work in developing the solid-phase method for peptide synthesis.

The solid support used by Merrifield was a styrene polymer containing 2% divinylbenzene as a cross-linking agent (Figure 24.11). This polymer, in the form of 200 to 400 mesh beads, has an open structure into which solvents and reagents can easily penetrate. The solid support phase is then prepared by treatment of the copolymer with methyl

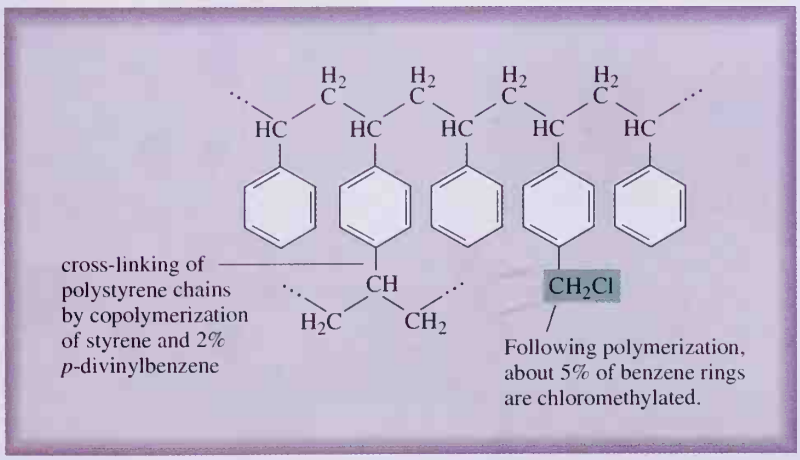
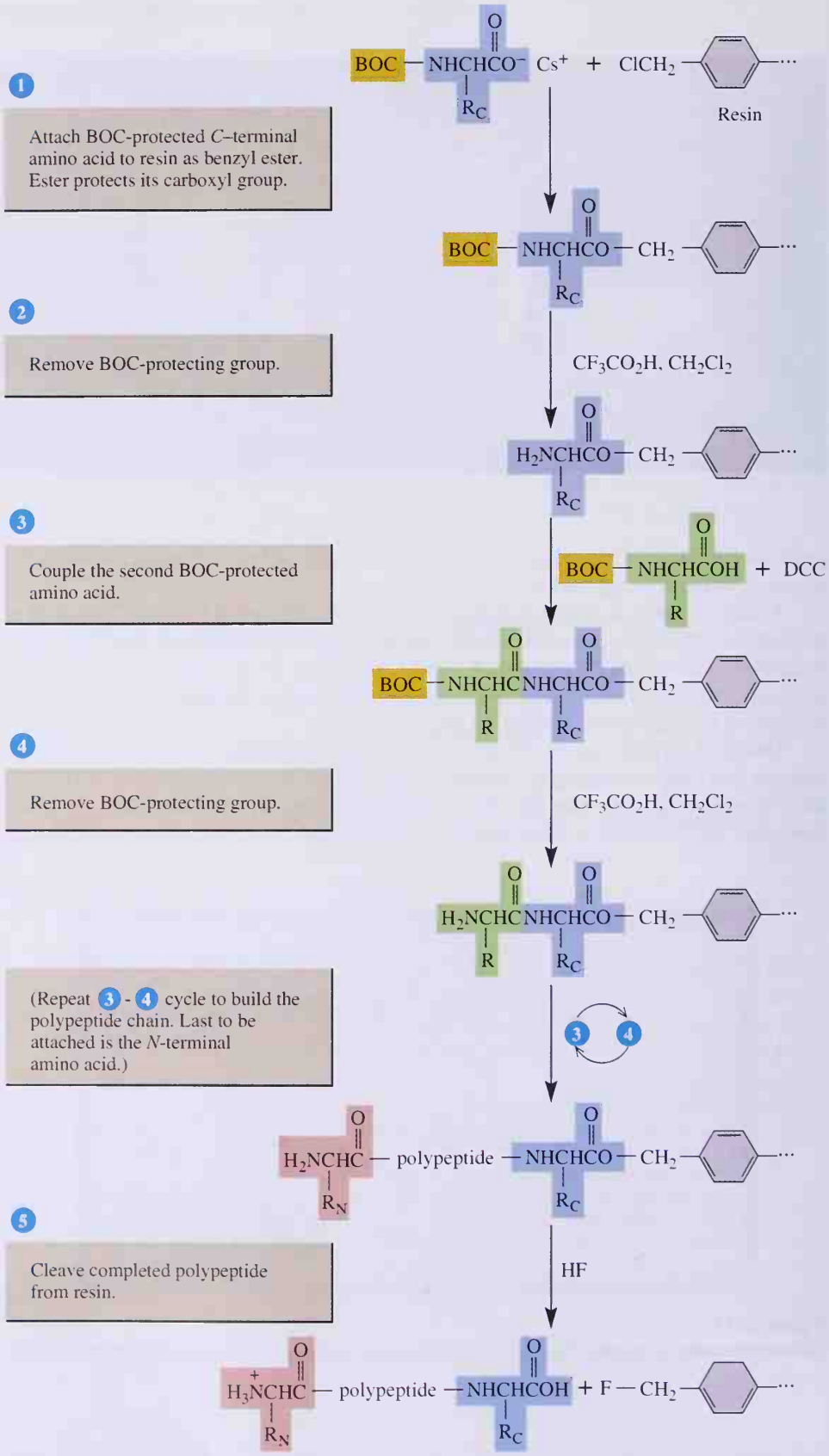


Figure 24.11
The support used for the Merrifield solid-phase synthesis is a chloromethylated polystyrene resin.

Figure 24.12
Steps in the Merrifield solid-phase polypeptide synthesis.



chloromethyl ether in the presence of a Lewis acid catalyst, usually tin(IV) chloride. Conditions of this Friedel-Crafts alkylation (Section 16.1C) are adjusted so that about 5% of the phenyl groups of the polymer are chloromethylated.

In the Merrifield method, the *C*-terminal amino acid is joined as a benzyl ester to the solid polymer support, and then the polypeptide chain is extended one amino acid at a time from the *N*-terminal end. The advantage of polypeptide synthesis on a solid support is that removal of byproducts and excess reagents after each step is simply a matter of filtration and washing and is very fast and efficient. Thus, the highly insoluble polymer beads containing the growing peptide chain are easily separated from excess reagents (for example, DCC) and byproducts (for example, DCU) by filtration and thorough washing. When synthesis is completed, the polypeptide is released from the solid support by cleavage of the benzyl ester. The steps in solid-phase synthesis of a polypeptide are summarized in Figure 24.12.

A dramatic illustration of the power of the solid-phase method was the synthesis of the enzyme ribonuclease by Merrifield in 1969. The synthesis involved 369 chemical reactions and 11,931 operations, all of which were performed by an automated machine and without any intermediate isolation stages. Each of the 124 amino acids was added as an *N-tert*-butoxycarbonyl derivative and coupled using DCC. Cleavage from the resin and removal of all protective groups gave a mixture that was purified by ion-exchange chromatography. The specific activity of the synthetic enzyme was 13% to 24% of that of the natural enzyme. The fact that the specific activity of the synthetic enzyme was lower than that of the natural enzyme was probably due to the presence of polypeptide byproducts closely related to but not identical to the natural enzyme.

24.7 Three-Dimensional Shapes of Polypeptides and Proteins

A. Geometry of a Peptide Bond

In the late 1930s, Linus Pauling began a series of studies to determine the geometry of a peptide bond. One of his first discoveries was that a peptide bond itself is planar. As shown in Figure 24.13, the four atoms of a peptide bond and the two α-carbons joined to it all lie in the same plane.

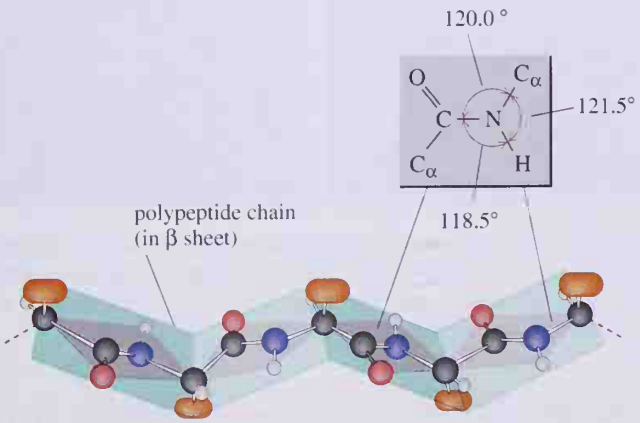
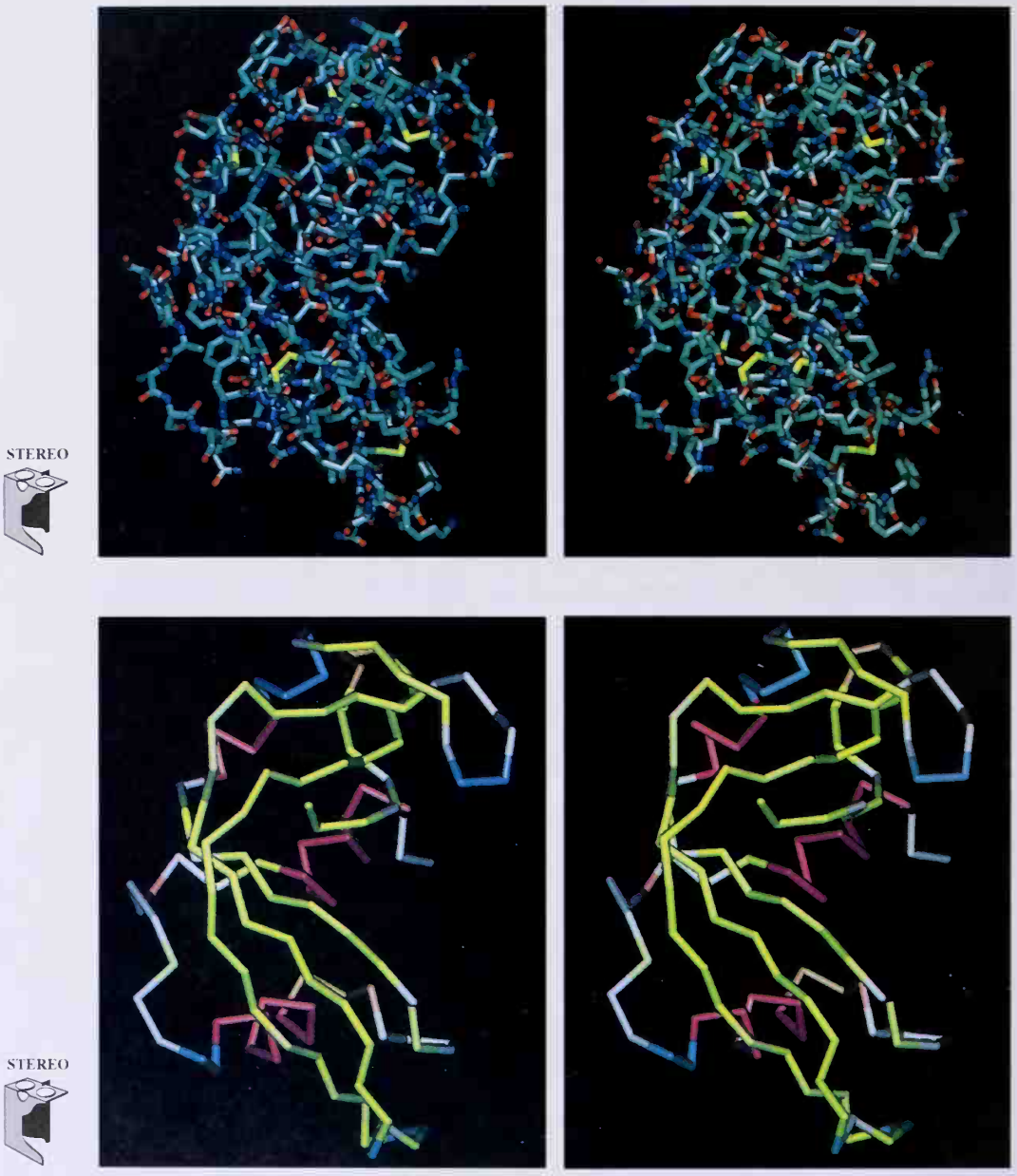
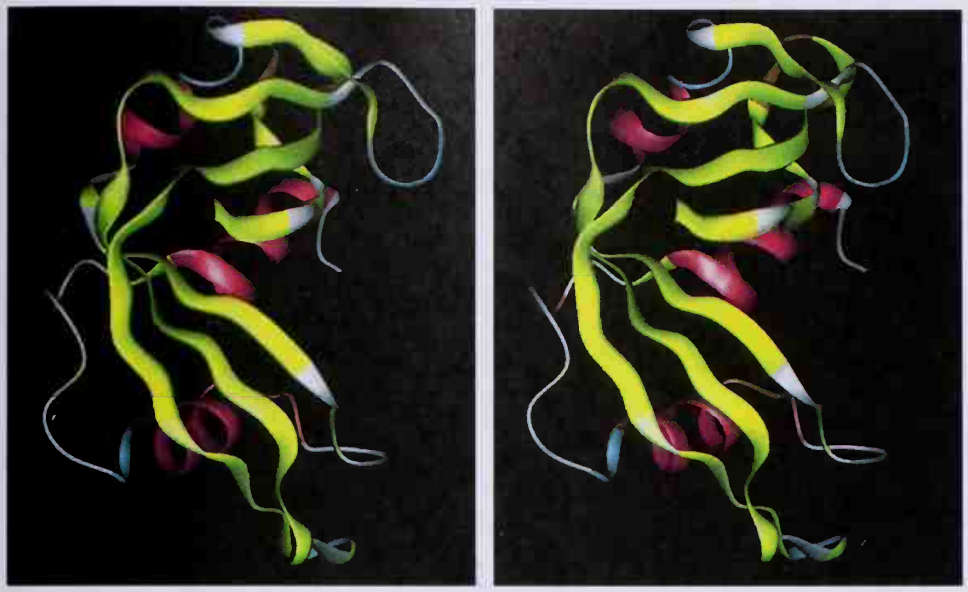


Figure 24.13
Planarity of a peptide bond. Bond angles about the carbonyl carbon and the amide nitrogen are approximately 120°.



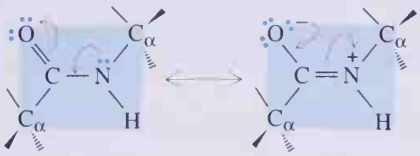
Ball-and-stick, "licorice," and "ribbon" models of the protein ribonuclease A in stereoview. In the upper structure, carbon is green, oxygen is red, nitrogen is blue and sulfur is yellow. In the bottom structure and the one on the facing page, the purple segments are the α-helix, the yellow is the β-sheet, and the rest are the loop regions.

Had you been asked in Chapter 1 to describe the geometry of a peptide bond, you probably would have predicted bond angles of 120° about the carbonyl carbon and 109.5° about the amide nitrogen. This prediction agrees with the observed bond angles of approximately 120° about the carbonyl carbon. However, a bond angle of 120° about the amide



STEREO

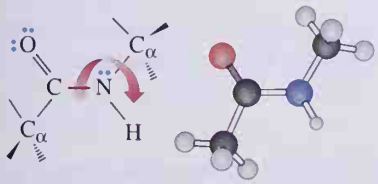
nitrogen is unexpected. To account for this observed geometry, Pauling proposed that a peptide bond is more accurately represented as a resonance hybrid of two contributing structures (shown in the figure below). Contributing structure (1) shows a carbon-oxygen double bond, and structure (2) shows a double bond between the carbonyl carbon and the



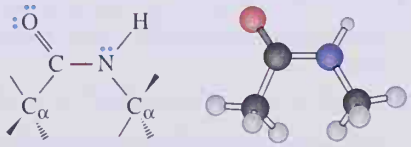
(1) (2)

nitrogen atom of the peptide bond. The hybrid, of course, is neither of these; in the real structure, the carbon-nitrogen bond has considerable double-bond character. Accordingly, in the hybrid, the six-atom group is planar.

Two configurations are possible for the atoms of a planar peptide bond. In one, the two α-carbons are *cis* to each other; in the other, they are *trans* to each other. The s-*trans* configuration is more favorable because the α-carbons with bulky groups attached to them are farther from each other than they are in the s-*cis* configuration. Virtually all peptide bonds in naturally occurring proteins studied to date have the s-*trans* configuration.

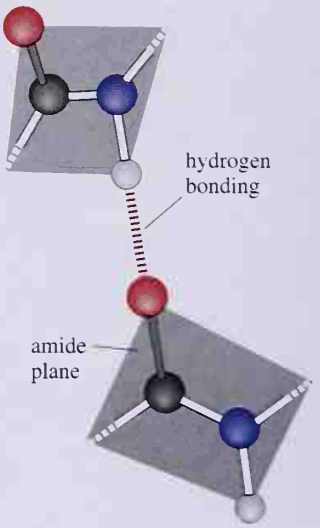


s-*trans* configuration



s-*cis* configuration

Figure 24.14
Hydrogen bonding between amide groups.



B. Secondary Structure

Secondary (2°) structure refers to ordered arrangements (conformations) of amino acids in localized regions of a polypeptide or protein molecule. The first studies of polypeptide conformations were carried out by Linus Pauling and Robert Corey, beginning in 1939. They assumed that in conformations of greatest stability, (1) all atoms in a peptide bond lie in the same plane, and (2) each amide group is hydrogen-bonded between the N—H of one peptide bond and the C=O of another as shown in Figure 24.14.

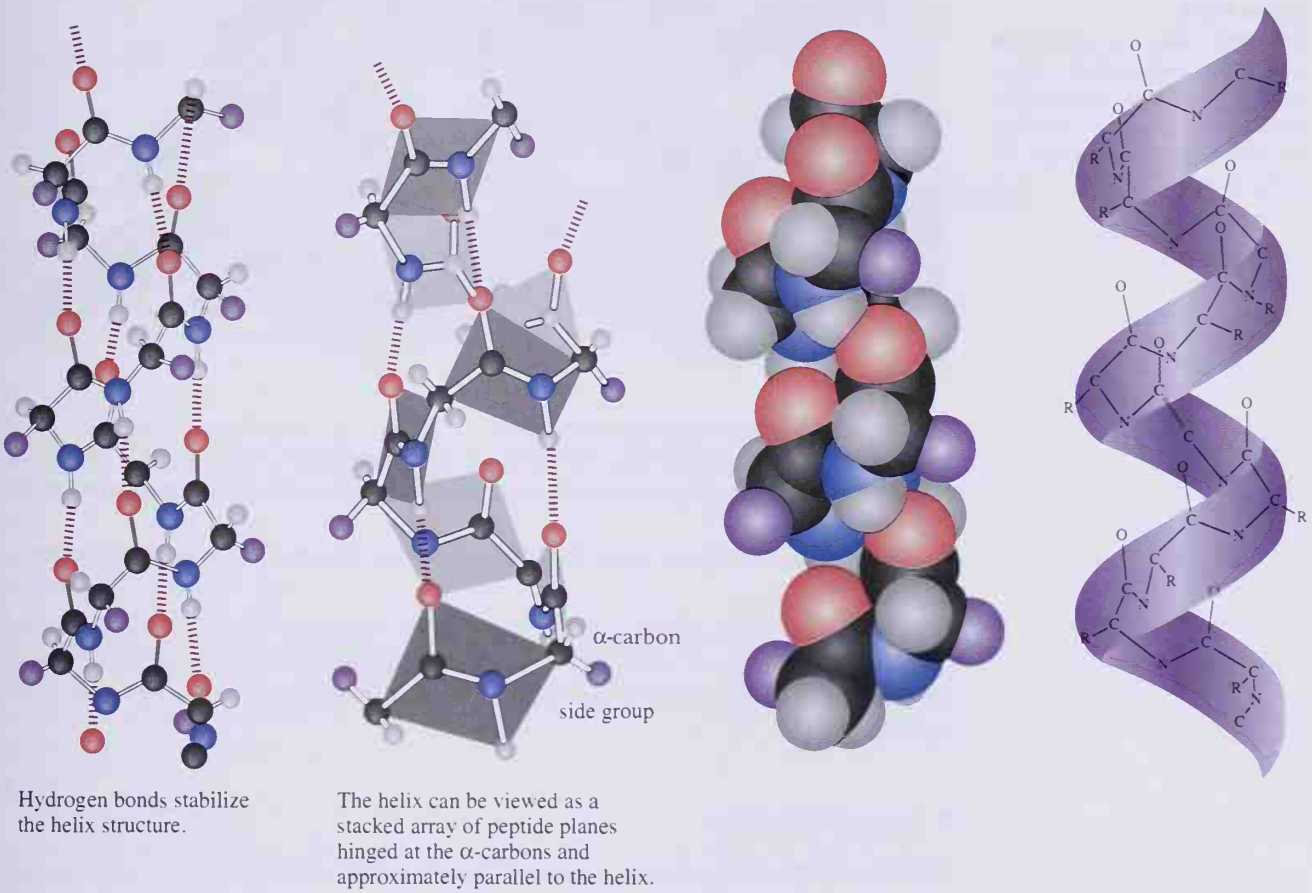
On the basis of model building, Pauling proposed that two folding patterns should be particularly stable: the α-helix and the antiparallel β-pleated sheet. The term "secondary structure" is used to describe α-helix, β-pleated sheet, and other types of periodic conformations in localized regions of polypeptide or protein molecules.

The α-Helix

In an **α-helix** pattern shown in Figure 24.15, a polypeptide chain is coiled in a spiral. As you study the α-helix in Figure 24.15, note the following:

1. The helix is coiled in a clockwise, or right-handed, manner. Right-handed means that if you turn the helix clockwise, it twists away from you. In this sense, a right-handed helix is analogous to the right-handed thread of a common wood or machine screw.
2. There are 3.6 amino acids per turn of the helix.
3. Each peptide bond is s-*trans* and planar.
4. The N—H group of each peptide bond points roughly upward, parallel to the axis of the helix, and the C=O of each peptide bond points roughly downward, also parallel to the axis of the helix.
5. The carbonyl group of each peptide bond is hydrogen-bonded to the N—H group of the peptide bond four amino acid units away from it. Hydrogen bonds are shown as dotted lines.
6. All R-groups point outward from the helix.

Almost immediately after Pauling proposed the α-helix conformation, other researchers proved the presence of α-helix conformations in keratin, the protein of hair and



Hydrogen bonds stabilize the helix structure.

The helix can be viewed as a stacked array of peptide planes hinged at the α-carbons and approximately parallel to the helix.

Figure 24.15
An α-helix. *(Left)* Ball-and-stick models showing intrachain hydrogen bonding. *(Right)* Space-filling and ribbon models.

wool. It soon became obvious that the α-helix is one of the fundamental folding patterns of polypeptide chains.

The β-Pleated Sheet

An antiparallel **β-pleated sheet** consists of an extended polypeptide chain with neighboring chains running in opposite (antiparallel) directions. In a parallel β-pleated sheet, the polypeptide chains run in the same direction and parallel to each other. Unlike the α-helix arrangement, N—H and C=O groups lie in the plane of the sheet and are roughly perpendicular to the long axis of the sheet. The C=O group of each peptide bond is hydrogen-bonded to the N—H group of a peptide bond of a neighboring chain (Figure 24.16). As you study the section of β-pleated sheet shown in Figure 24.16, note the following:

1. The two polypeptide chains lie adjacent to each other and run in opposite (antiparallel) directions.

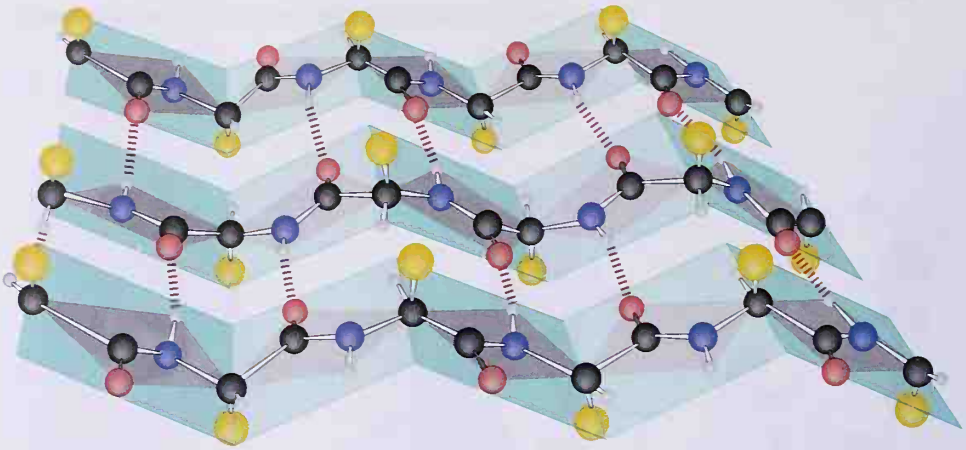


Figure 24.16
β-Pleated sheet conformation with three polypeptide chains running in opposite (antiparallel) directions. Hydrogen bonding between chains is indicated by dotted lines.

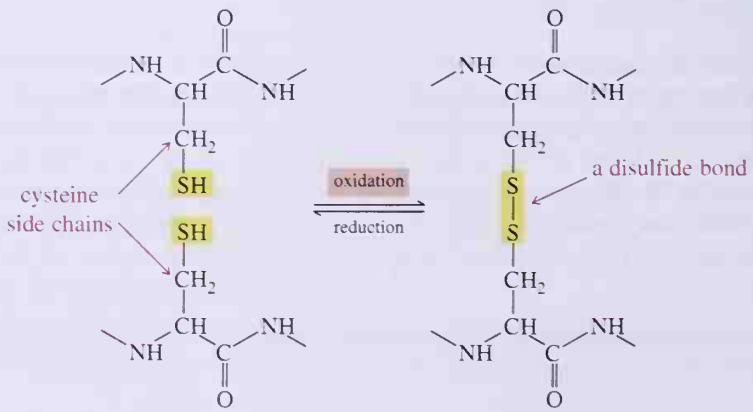
2. Each peptide bond is s-*trans* and planar.
3. The C═O and N—H groups of peptide bonds from adjacent chains point at each other and are in the same plane so that hydrogen bonding is possible between adjacent polypeptide chains.
4. The R-groups on any one chain alternate, first above, then below the plane of the sheet, and so on.

The pleated sheet conformation is stabilized by hydrogen bonding between N—H groups of one chain and C═O groups of an adjacent chain. By comparison, the α-helix is stabilized by hydrogen bonding between —NH and C═O groups within the same polypeptide chain.

C. Tertiary Structure

Tertiary (3°) structure refers to the overall folding pattern and arrangement in space of all atoms in a single polypeptide chain. No sharp dividing line exists between secondary and tertiary structures. Secondary structure refers to the spatial arrangement of amino acids close to one another on a polypeptide chain, whereas tertiary structure refers to the three-dimensional arrangement of all atoms of a polypeptide chain.

Disulfide bonds play an important role in maintaining tertiary structure. Disulfide bonds are formed between side chains of cysteine by oxidation of two thiol groups (—SH) to form a disulfide bond (—S—S—). Treatment of a disulfide bond with a reducing agent regenerates the thiol groups.



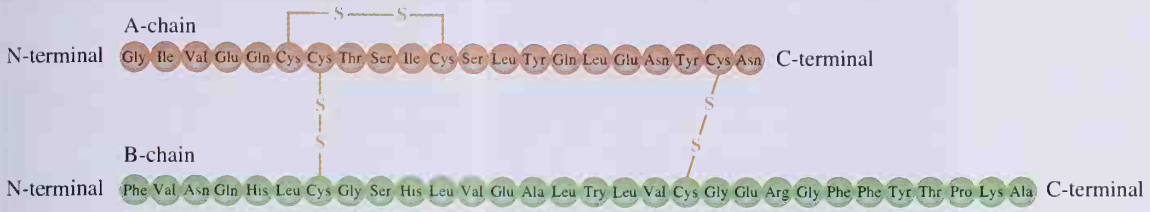


Figure 24.17
Human insulin. The A chain of 21 amino acids and B chain of 30 amino acids are connected by interchain disulfide bonds between A7 and B7 and between A20 and B19. In addition, a single intrachain disulfide bond occurs between A6 and A11.

Figure 24.17 shows the amino acid sequence of human insulin. This protein consists of two polypeptide chains: an A chain of 21 amino acids and a B chain of 30 amino acids. The A chain is bonded to the B chain by two interchain disulfide bonds. An intrachain disulfide bond also connects the cysteine units at positions 6 and 11 of the A chain.

We now know the primary structure for several hundred polypeptides and proteins and we know the secondary and tertiary structure of scores of these. As an example, let us look at the three-dimensional structure of myoglobin—a protein found in skeletal muscle and particularly abundant in diving mammals, such as seals, whales, and porpoises. Myoglobin and its structural relative, hemoglobin, are the oxygen transport and storage molecules of vertebrates. Hemoglobin binds molecular oxygen in the lungs and transports it to myoglobin in muscles. Myoglobin stores molecular oxygen until it is required for metabolic oxidation.

Myoglobin consists of a single polypeptide chain of 153 amino acids. Myoglobin also contains a single heme unit. Heme consists of one Fe^{2+} ion coordinated in a square planar array with the four nitrogen atoms of a molecule of porphyrin (Figure 24.18).

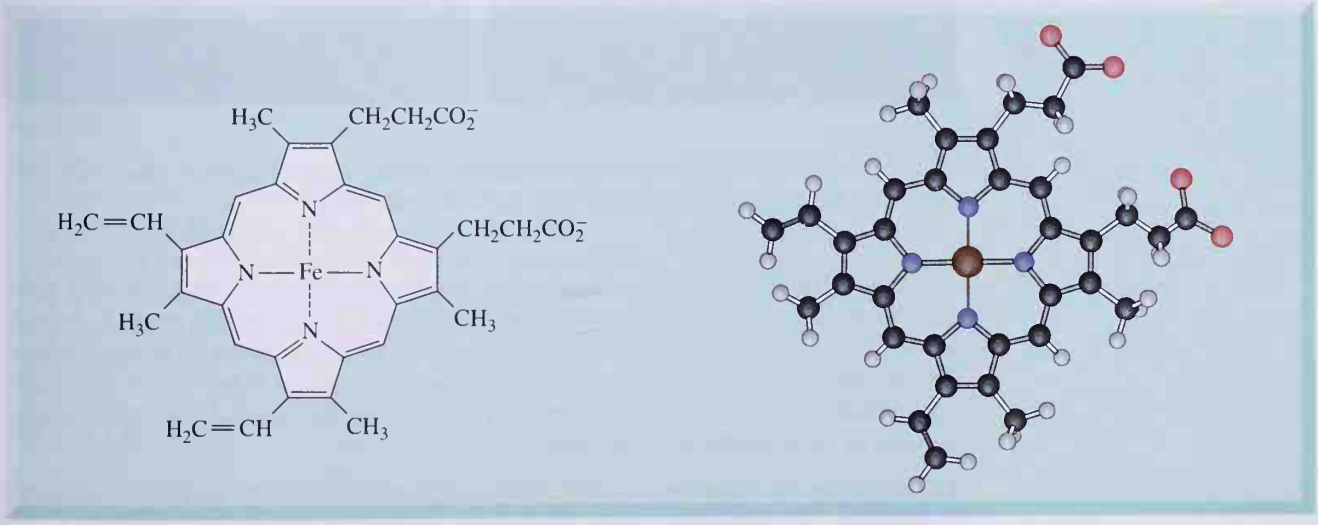


Figure 24.18
The structure of heme, found in myoglobin and hemoglobin.

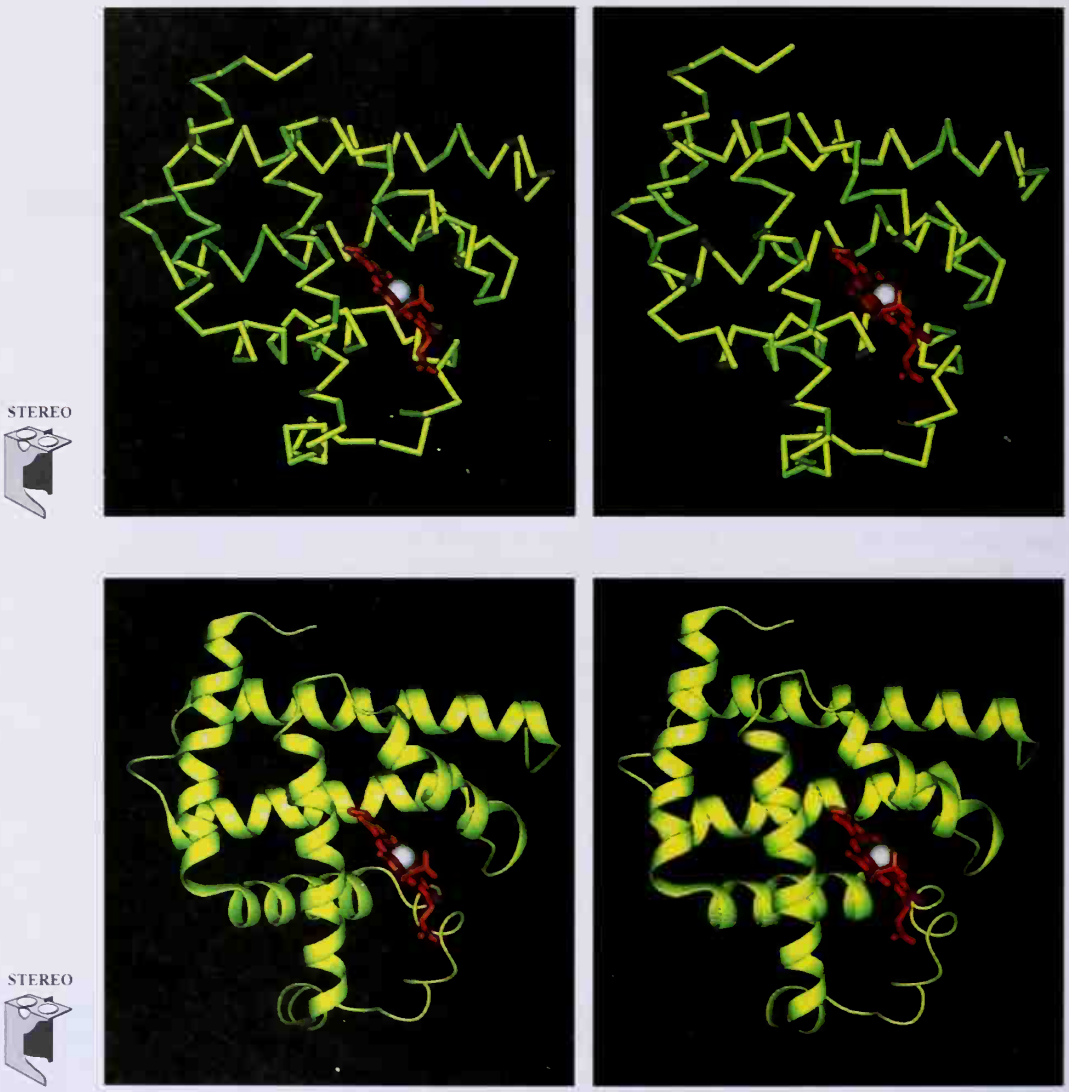


Figure 24.19
"Licorice" and "ribbon" models of sperm whale myoglobin in stereo. The protein chain is shown in yellow, the heme ligand in red, and the Fe atom is the white sphere.

Determination of the three-dimensional structure of myoglobin represented a milestone in the study of molecular architecture. For their contribution to this research, John C. Kendrew and Max F. Perutz, both of Britain, shared the 1962 Nobel Prize in chemistry. The secondary and tertiary structure of myoglobin are shown in Figure 24.19. The single polypeptide chain is folded into a complex, almost boxlike shape. Important structural features of the three-dimensional shape of myoglobin are

1. The backbone consists of eight relatively straight sections of α-helix, each separated by a bend in the polypeptide chain. The longest section of α-helix has 24 amino acids, the

shortest has 7. Some 75% of the amino acids are found in these eight regions of α-helix.

2. Hydrophobic side chains of phenylalanine, alanine, valine, leucine, isoleucine, and methionine are clustered in the interior of the molecule where they are shielded from contact with water. The hydrophobic effect is a major factor in directing the folding of the polypeptide chain of myoglobin into this compact, three-dimensional shape.
3. The outer surface of myoglobin is coated with hydrophilic side chains, such as those of lysine, arginine, serine, glutamic acid, histidine, and glutamine, which interact with the aqueous environment by hydrogen bonding. The only polar side chains that point to the interior of the myoglobin molecule are those of two histidine units. These side chains point inward toward the heme group.
4. Oppositely charged amino acid side chains close to each other in the three-dimensional structure interact by electrostatic attractions called salt linkages. An example of a salt linkage is the attraction of the side chains of lysine ($—NH_3^+$) and glutamic acid ($—CO_2^-$).

The tertiary structures of several other globular proteins have also been determined. It is clear that globular proteins contain α-helix and β-pleated sheet structures, but that wide variations exist in the relative amounts of each. Lysozyme, with 129 amino acids in a single polypeptide chain, has only 25% of its amino acids in α-helix regions. Cytochrome, with 104 amino acids in a single polypeptide chain, has no α-helix structure but does contain several regions of β-pleated sheet. Yet, whatever the proportions of α-helix, β-pleated sheet, or other periodic structure, virtually all nonpolar side chains of globular proteins are directed toward the interior of the molecule, whereas polar side chains are on the surface of the molecule and in contact with the aqueous environment. Note that this arrangement of polar and nonpolar groups in globular proteins very much resembles the arrangement of polar and nonpolar groups of soap molecules in micelles (Figure 23.2) and the arrangement of phospholipids in lipid bilayers (Figure 23.14).

EXAMPLE 24.7

With which of the following amino acid side chains can the side chain of threonine form hydrogen bonds?

(a) Valine **(b)** Asparagine **(c)** Phenylalanine
(d) Histidine **(e)** Tyrosine **(f)** Alanine

Solution

The side chain of threonine contains a hydroxyl group that can participate in hydrogen bonding in two ways: its oxygen has a partial negative charge and can function as a hydrogen bond donor; its hydrogen has a partial positive charge and can function as a hydrogen bond acceptor. Therefore, the side chain of threonine can function as a hydrogen bond acceptor for the side chains of tyrosine, asparagine, and histidine. The side chain of threonine can also function as a hydrogen bond donor for the side chains of tyrosine, asparagine, and histidine.

PROBLEM 24.7

At pH 7.4, with what amino acid side chains can the side chain of lysine form salt linkages? ■

CHEMISTRY IN ACTION

Enzymes Through the Looking Glass

Proteins are polymers of α-amino acids, and because all α-amino acids except glycine are chiral, proteins are also chiral. This chirality results in remarkable stereospecificity for those proteins that act as enzymes to catalyze organic reactions. For example, if a substrate is chiral, an enzyme normally processes only one of the two substrate enantiomers. An obvious question is: Does an enantiomeric enzyme (one made up of D-amino acids instead of the naturally occuring L-amino acids) catalyze reactions of the enantiomeric substrate? From everything we have learned about chirality during the last 100 years, the answer to this question should be yes. If, experimentally, the answer was found to be no, the change in organic chemistry would be as great as the change that took place in astronomy when the sun, not the earth, was placed at the center of the solar system.

Until recently, there was no way of obtaining an enzyme built up of D-amino acids. However, with advances in chemical peptide synthesis, it is now possible for chemists and biochemists to complete chemical syntheses of moderately sized enzymes. One such example is HIV-1-protease (a human immunodeficiency virus protease that catalyzes the hydrolysis of peptide bonds), an enzyme containing 99 amino acids in a single polypeptide chain. This enzyme is essential for the life cycle of the HIV-1 virus, which causes AIDS (acquired immune deficiency syndrome). Stephen Kent of Scripps Research Institute in La Jolla, California, has synthesized HIV-1-protease from both natural L-amino acids and unnatural D-amino acids (for technical reasons, two slight modifications were made in each protein's sequence). Under achiral conditions, the properties of the synthetic D-HIV-1 and L-HIV-1-proteases are identical. For example, their mass spectra are identical, their behavior during purification on achiral chromatographic supports is identical, and the specific rotations of the two polypeptides are equal in magnitude but opposite in sign. Furthermore, an achiral inhibitor of the natural enzyme inhibits both synthetic D- and L-enzymes.

Under chiral conditions, however, the D-HIV-1 and L-HIV-1 proteases are different. Kent observed that the synthetic L-enzyme (as well as the natural L-enzyme isolated from cells infected with the HIV-1 virus) reacts with a synthetic L-polypeptide substrate to catalyze the hydrolysis of a specific peptide bond. The D-enzyme catalyzes the same hydrolysis of a mirror image D-polypeptide substrate. Most importantly, no cross reactivity occurs between the L-enzyme and the D-substrate or between the D-enzyme and the L-substrate.

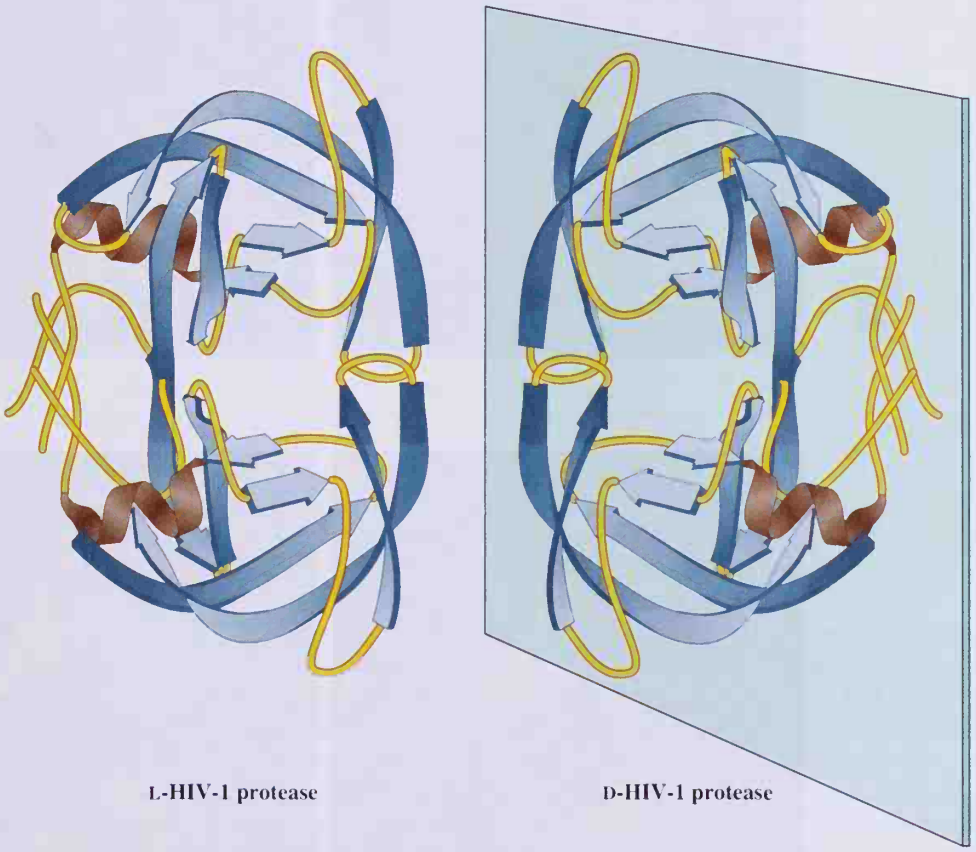
Fortunately for organic chemistry, our ideas on stereochemistry are fully confirmed. The mirror image enzyme reacts only with the mirror image substrate. This work has biochemical implications as well. For example, it proves that polypeptide chains can fold spontaneously into the complex shapes found in enzymes without any help from biochemical factors of any sort. In other words, the shape of an enzyme, at least HIV-1 protease, is encoded in its sequence.

Shown below are computer-generated representations of the polypeptide backbones of L-HIV-1-protease dimer, and its mirror image, the D-HIV-1-protease dimer. Regions of β-sheets and α-helices are shown as ribbons. Regions of less regular secondary structure are shown as thin lines.

See R. C. deL. Milton, S. C. F. Milton, S. B. H. Kent, *Science*, **256:**1445 (1992).

D. Quaternary Structure

Most proteins of molecular weight greater than 50,000 consist of two or more noncovalently linked polypeptide chains. The arrangement of protein monomers into an aggregation is known as **quaternary (4°) structure.** A good example is hemoglobin, a protein that consists of four separate protein monomers: two α-chains of 141 amino acids each and two β-chains of 146 amino acids each. The quaternary structure of hemoglobin is shown in Figure 24.20.



L-HIV-1 protease D-HIV-1 protease

The major factor stabilizing the aggregation of protein subunits is the hydrophobic effect. When separate monomers fold into compact three-dimensional shapes to expose polar side chains to the aqueous environment and shield nonpolar side chains from water, hydrophobic "patches" still appear on the surface, in contact with water. These patches can be shielded from water if two or more monomers assemble so that their hydrophobic patches are in contact. The molecular weights, numbers of subunits, and biological functions of several proteins of known quaternary structure are shown in Table 24.7.

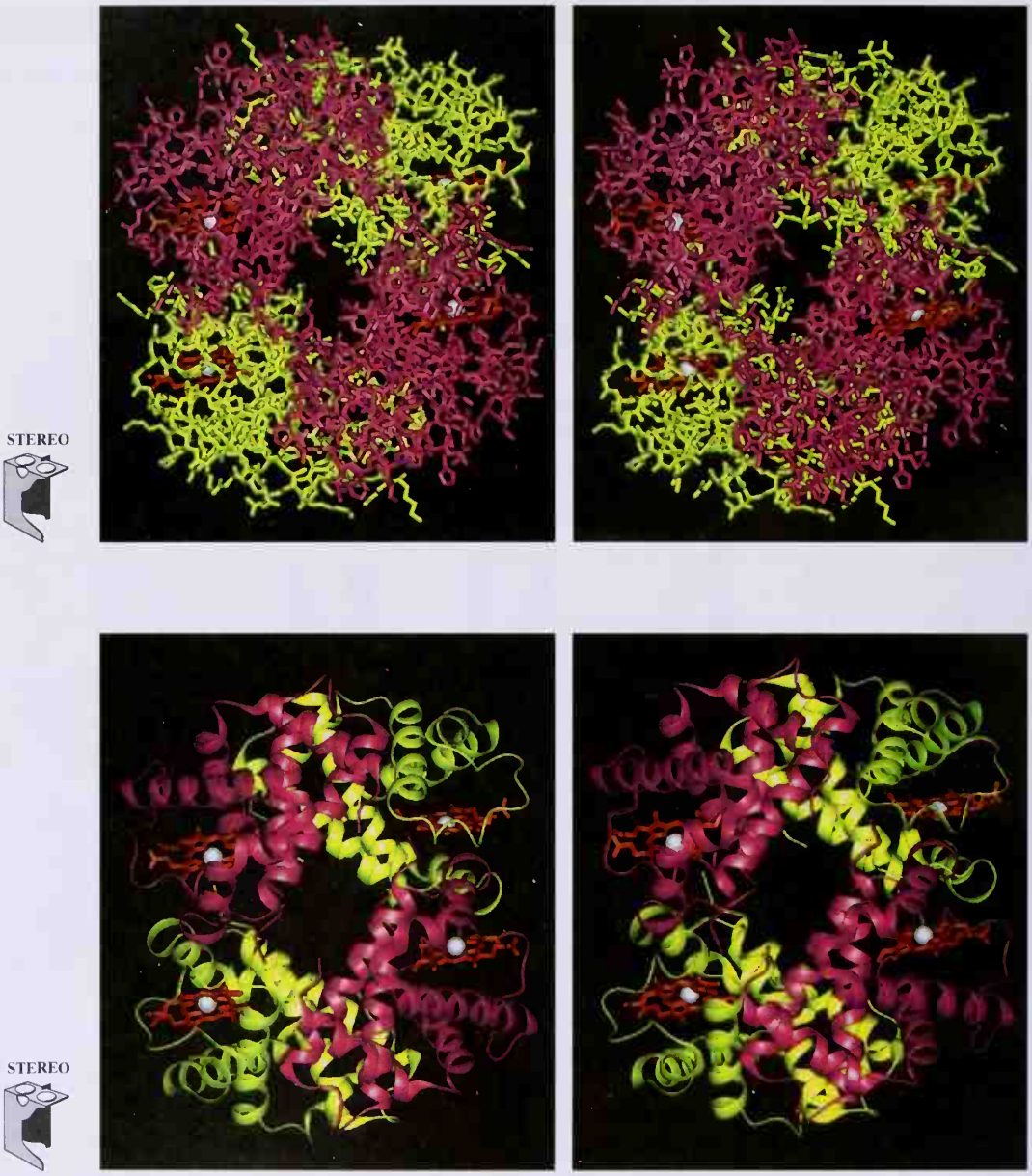


Figure 24.20
A stereoview of deoxyhemoglobin in "licorice" and "ribbon" forms. The α-chains are shown in purple, the β-chains in yellow, the heme ligands in red, and the Fe atoms as white spheres.

Table 24.7 Quaternary structure of selected proteins

Protein	Molecular Weight	Number of Subunits	Molecular Weight of Subunit	Biological Function
insulin	11,446	2	5,733	a hormone regulating glucose metabolism
hemoglobin	64,500	4	16,100	a molecule transporting oxygen in blood plasma
alcohol dehydrogenase	80,000	4	20,000	an enzyme of alcohol fermentation
lactate dehydrogenase	134,000	4	33,500	an enzyme of anaerobic glycolysis
aldolase	150,000	4	37,500	an enzyme of anaerobic glycolysis
fumarase	194,000	4	48,500	an enzyme of the tricarboxylic acid cycle
tobacco mosaic virus	40,000,000	2200	17,500	a plant virus coat

CHEMISTRY IN ACTION

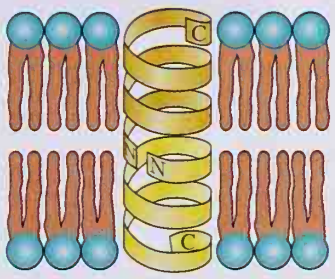
Making Channels for Ions

For life to exist, cells have to control the flow of ions (for example, Na^+, Ca^{2+}, and Cl^-) across their nonpolar cell membranes. If this flow is disturbed, disease, paralysis, or even death can result. Proteins provide the structures that act as channels for ions to pass into and out of cells. Because naturally occurring transmembrane ion channel proteins are typically large and difficult to work with, many studies have been done on simpler model systems. In particular, studies of the polypeptide antibiotic, gramicidin A, have provided much information about ion channels.

Gramicidin A is a 15-amino acid polypeptide with alternating D- and L-amino acids. The bacteria that make gramicidin A have special enzymes that convert some L-amino acids into their D forms and then string them together to make the polypeptide. The primary sequence of this peptide is

HCONH-L-Val-Gly-L-Ala-D-Leu-L-Ala-D-Val-L-Val-D-Val-L-Trp-D-Leu-L-Trp-D-Leu-L-Trp-D-Leu-L-Trp-$CONHCH_2CH_2OH$

The *N*-terminus of gramicidin A is modified by addition of a formyl group, and the *C*-terminus has added to it an ethanolamine group. In a lipid bilayer environment, which mimics a cell membrane (Section 23.5B), gramicidin A adopts a helical structure. The alternation of D- and L-amino acids leads to an unusual kind of helix, called a β-helix, in which carbonyl groups alter-



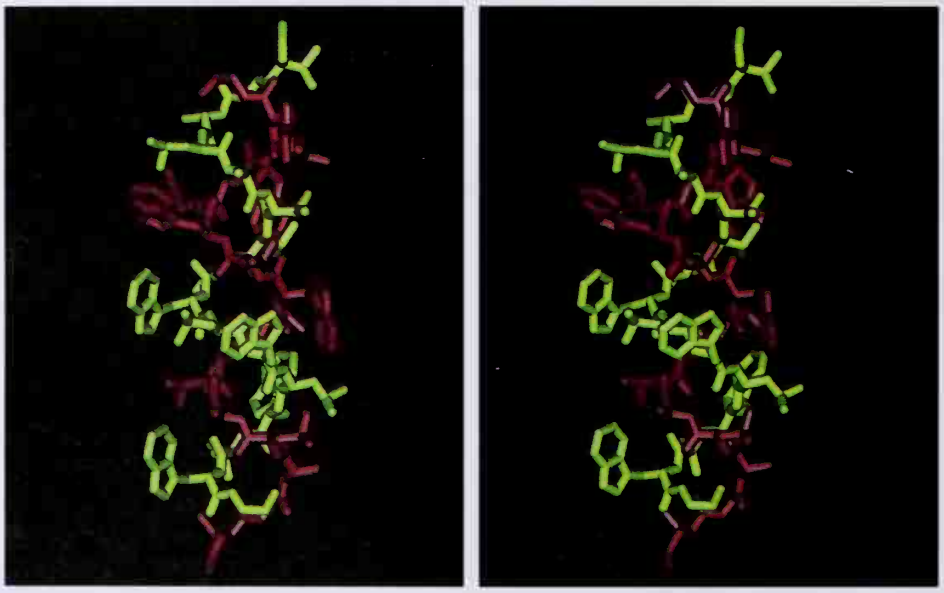
The head-to-head dimer of gramicidin A is in the form of a β-helix 2.6 nm long with a central pore approximately 0.4 nm in diameter.

Box continued on next page.

CHEMISTRY IN ACTION (Continued)

nately point up and then down relative to the axis of the helix. The side-chain groups, which are nonpolar and thus mix with the lipid surroundings of the bilayer, point outward, away from the helix.

A second interesting feature of gramicidin A is that in the environment of a lipid bilayer, two molecules dimerize head to head, producing a helix 2.6 nm long with a central pore approximately 0.4 nm in diameter (see the figure). Using a special measuring technique called the "patch clamp" technique, the ion flux through a single gramicidin A dimer can be measured. It has been discovered that larger monovalent ions, such as NH_4^+ and Cs^+, are conducted through the pore, but smaller ions, such as Na^+ as Li^+, are selected against. In time, studies of the gramicidin A and related ion channels should give organic chemists the ability to design and build structures that control the flow of virtually any ion. Applications ranging from new kidney dialysis materials to novel wastewater treatment methods are possible.



STEREO

The protein gramicidin A in stereoview. Each chain is drawn in a different color, but the chains are actually identical.

SUMMARY OF KEY REACTIONS

1. Acidity of an α-Carboxyl Group (Section 24.2A)

An α-CO_2H (pK_a approximately 2.19) is a considerably stronger acid than acetic acid (pK_a 4.76) or other low-molecular-weight aliphatic carboxylic acid due to the electron-withdrawing inductive effect of the α-NH_3^+ group.

$$\underset{\underset{NH_3^+}{|}}{RCHCO_2H} \rightleftharpoons \underset{\underset{NH_3^+}{|}}{RCHCO_2^-} + H^+ \qquad pK_a = 2.19$$

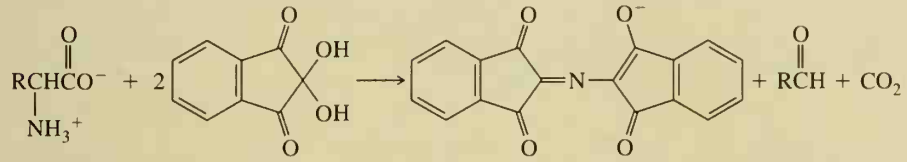
2. Acidity of an α-Amino Group (Section 24.2A)

An α-NH_3^+ group (pK_a approximately 9.47) is a slightly stronger acid than a primary aliphatic ammonium ion (pK_a 10.76).

$$\underset{\underset{NH_3^+}{|}}{RCHCO_2^-} \rightleftharpoons \underset{\underset{NH_2}{|}}{RCHCO_2^-} + H^+ \qquad pK_a = 9.47$$

3. Reaction of an α-Amino Acid with Ninhydrin (Section 24.2E)

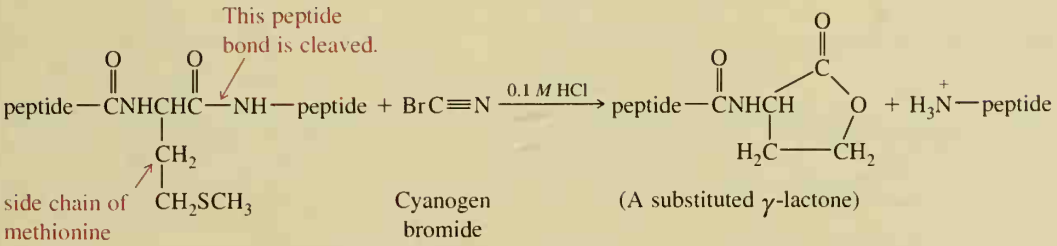
Treatment of an α-amino acid with ninhydrin gives a purple-colored anion with an absorption maximum at 580 nm. Treatment of proline with ninhydrin gives an orange-colored solution.



An α-amino acid — Ninhydrin — Purple-colored anion (λ_{max} 580 nm)

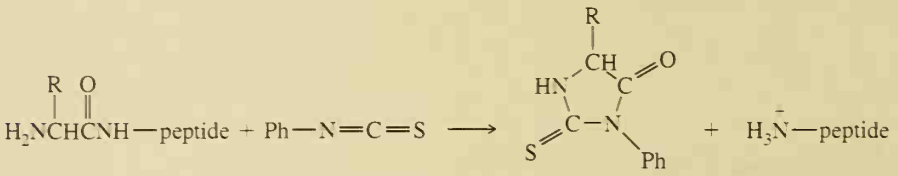
4. Cleavage of a Peptide Bond by Cyanogen Bromide (Section 24.5B)

Cleavage is regioselective for a peptide bond formed by the carboxyl group of methionine.



5. Edman Degradation (Section 24.5B)

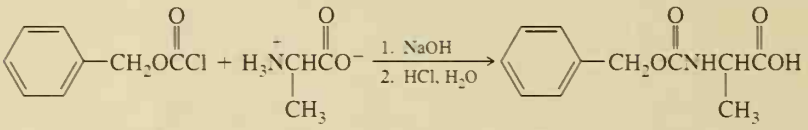
Treatment with phenyl isothiocyanate followed by acid removes the *N*-terminal amino acid as a substituted phenylthiohydantoin, which is then separated and identified. It is possible to sequence as many as 20 to 30 amino acids in a polypeptide chain by repetitive Edman degradation.



A phenylthiohydantoin

6. The *N*-Benzyloxycarbonyl (Z-) Protecting Group (Section 24.6B)

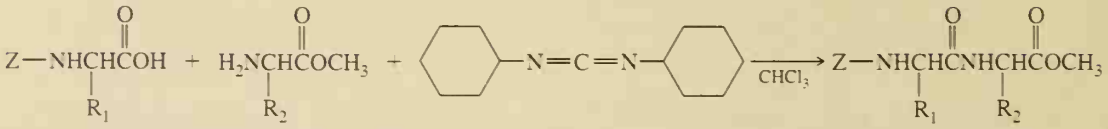
Prepared by treatment of an unprotected α-NH_2 group with benzyloxycarbonyl chloride. Removed by treatment with HBr in acetic acid or by hydrogenolysis.



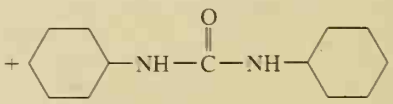
Benzyloxycarbonyl chloride (Z-Cl) | Alanine | *N*-Benzyloxycarbonylalanine (Z-ala)

7. Peptide Bond Formation Using 1,3-Dicyclohexylcarbodiimide (Section 24.6E)

The substituted carbodiimide is a molecular dehydrating agent and is converted to a disubstituted urea. Reaction is efficient, and yields are generally very high.



Amino-protected aa_1 | Carboxyl-protected aa_2 | 1,3-Dicyclohexylcarbodiimide (DCC) | Amino- and carboxyl-protected dipeptide



N,*N*′-Dicyclohexylurea (DCU)

ADDITIONAL PROBLEMS

Amino Acids

24.8 Referring to Tables 24.1 and Table 24.3, identify the

(a) One achiral amino acid

(b) Two amino acids that have diastereomers

(c) The two sulfur-containing amino acids

(d) Four amino acids with aromatic side chains

(e) Amino acid with the most basic side chain

(f) Amino acid with the most acidic side chain

24.9 How many stereoisomers are possible for 4-hydroxyproline and 5-hydroxylysine (Section 24.1D)?

24.10 As discussed in the Chemistry in Action: Vitamin K, Blood Clotting, and Basicity (Chapter 23), vitamin K participates in carboxylation of glutamate residues of the blood-clotting protein, prothrombin.

(a) Write a structural formula for γ-carboxyglutamate.

(b) Account for the fact that the presence of γ-carboxyglutamate escaped detection for many years; on routine amino acid analyses, only glutamate was detected.

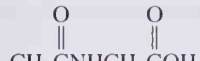
24.11 Isoleucine has two tetrahedral stereocenters, and four stereoisomers are possible. The protein-derived stereoisomer, L-isoleucine, is named (2S,3S)-(+)-2-amino-3-methylpentanoic acid.

(a) What is the meaning of the designation (+) in this name?

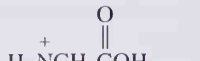
(b) Draw a stercorepresentation showing the configuration of each stercocenter in L-isoleucine.

(c) Draw a stereorepresentation of D-isoleucine, the enantiomer of L-isoleucine.

24.12 Following are values of pK_a for *N*-acetylglycine and the protonated forms of glycine and glycine methyl ester.



N-Acetylglycine
(pK_a 3.70)



Glycine
(pK_1 2.35, pK_2 9.78)

Glycine methyl ester
(pK_a 7.80)

(a) Which is the stronger acid, the carboxyl group of *N*-acetylglycine or the carboxyl group of protonated glycine? How do you account for this difference in acidity?

(b) Which is the stronger acid, the ammonium ion of protonated glycine or the ammonium ion of protonated glycine methyl ester? Account for this difference in acidity.

24.13 Account for the fact that the isoelectric point of glutamine (pI 5.65) is higher than the isoelectric point of glutamic acid (pI 3.08).

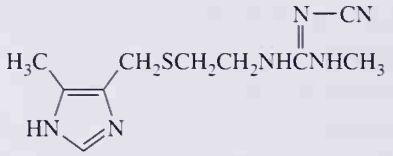
24.14 Enzyme-catalyzed decarboxylation of glutamic acid gives 4-aminobutanoic acid (Section 24.1D). Estimate the pI of 4-aminobutanoic acid.

24.15 Given pK_a values for ionizable groups from Table 24.3, sketch curves for the titration of (a) glutamic acid with NaOH, and (b) histidine with NaOH.

24.16 Guanidine and the guanidino group present in arginine are two of the strongest organic bases known. Account for this basicity.

24.17 A chemically modified guanidino group is present in cimetidine (Tagamet), a widely prescribed drug for the control of gastric acidity and peptic ulcers. Cimetidine reduces gastric

acid secretion by inhibiting the interaction of histamine with gastric H_2-receptors. In the development of this drug, a cyano group was added to the substituted guanidino group to significantly alter its basicity. Do you expect this modified guanidino group to be more basic or less basic than the guanidino group of arginine? Explain.



Cimetidine
(Tagamet)

24.18 Only three amino acids have appreciable absorption in the ultraviolet spectrum. Which three amino acids contribute to the commonly quoted λ_{max} of 280 nm for proteins?

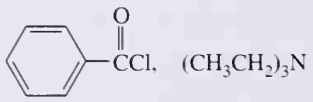
24.19 Draw a structural formula for the product formed when alanine is treated with the following reagents:

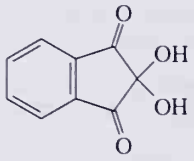
(a) Aqueous NaOH

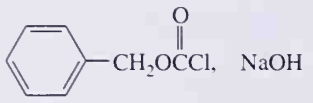
(b) Aqueous HCl

(c) CH_3CH_2OH, H_2SO_4

(d) $(CH_3CO)_2O$, CH_3CO_2Na

(e) 

(f) 

(g) 

(h) 

(i) Product (g) + product (c) + DCC

(j) Product (h) + product (c) + DCC

24.20 At pH 7.4, the pH of blood plasma, do the majority of protein-derived amino acids bear a net negative or a net positive charge?

24.21 Do the following molecules migrate to the cathode or to the anode on electrophoresis at the specified pH?

(a) Histidine at pH 6.8

(b) Lysine at pH 6.8

(c) Glutamic acid at pH 4.0

(d) Glutamine at pH 4.0

(e) Glu-Ile-Val at pH 6.0

(f) Lys-Gln-Tyr at pH 6.0

24.22 Examine the amino acid sequence of human insulin (Figure 24.17) and list each Asp, Glu, His, Lys, and Arg in this molecule. Do you expect human insulin to have an isoelectric point nearer that of the acidic amino acids (pI 2.0–3.0), the neutral amino acids (pI 5.5–6.5), or the basic amino acids (pI 9.5–11.0)?

Primary Structure of Polypeptides and Proteins

24.23 If a protein contains four different —SH groups, how many different disulfides bonds are possible if only a single disulfide bond is formed? How many different disulfides are possible if two disulfide bonds are formed?

24.24 A decapeptide has the following amino acid composition:

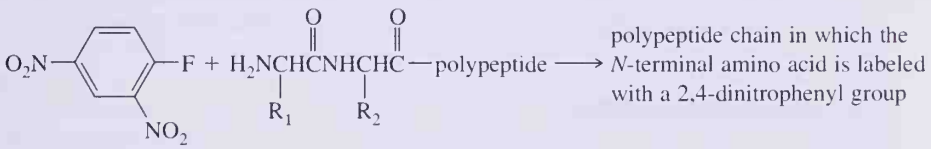
$$Ala_2, Arg, Cys, Glu, Gly, Leu, Lys, Phe, Val$$

Partial hydrolysis yields the following tripeptides:

Cys-Glu-Leu + Gly-Arg-Cys + Leu-Ala-Ala + Lys-Val-Phe + Val-Phe-Gly

One round of Edman degradation yields a lysine phenylthiohydantoin. From this information, deduce the primary structure of this decapeptide.

24.25 2,4-Dinitrofluorobenzene, very often known as Sanger's reagent after the English chemist Frederick Sanger who popularized its use, reacts selectively with the *N*-terminal amino group of a polypeptide chain. Sanger was awarded the 1958 Nobel Prize in chemistry for his work in determining the primary structure of bovine insulin. One of the few persons to be awarded two Nobel Prizes, he also shared the 1980 award in chemistry with American chemists, Paul Berg and Walter Gilbert, for development of chemical and biological analyses of DNAs.



2,4-Dinitrofluorobenzene (*N*-Terminal end of a polypeptide chain)

Following reaction with 2,4-dinitrofluorobenzene, all amide bonds of the polypeptide chain are hydrolyzed, and the amino acid labeled with a 2,4-dinitrophenyl group is separated by either paper or column chromatography and identified.

(a) Write the structural formula for the product formed by treatment of the *N*-terminal amino group with Sanger's reagent and propose a mechanism for its formation. (*Hint:* Review nucleophilic aromatic substitution, Section 16.3B).

(b) When bovine insulin is treated with Sanger's reagent followed by hydrolysis of all peptide bonds, two labeled amino acids are detected: glycine and phenylalanine. What conclusions can be drawn from this information about the primary structure of bovine insulin?

(c) Compare and contrast the structural information that can be obtained from use of Sanger's reagent with that from use of the Edman degradation.

24.26 Write structural formulas for the products formed after one cycle of Edman degradation on the tripeptide Ser-Leu-Phe.

24.27 Following is the primary structure of glucagon, a polypeptide hormone of 29 amino acids. Glucagon is produced in α-cells of the pancreas and helps maintain blood glucose levels in a normal concentration range.

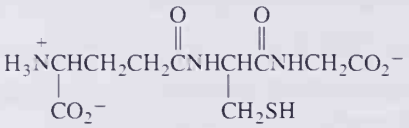
1 5 10 15
His-Ser-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-
20 25 29
Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr

Glucagon

Which peptide bonds are hydrolyzed when this polypeptide is treated with

(a) Phenyl isothiocyanate **(b)** Chymotrypsin **(c)** Trypsin **(d)** Br—CN

24.28 Glutathione (G-SH), one of the most common tripeptides in animals, plants, and bacteria, is a scavenger of oxidizing agents. In reacting with oxidizing agents, glutathione is converted to G-S-S-G.



Glutathione

(a) Name the amino acids in this tripeptide.

(b) What is unusual about the peptide bond formed by the *N*-terminal amino acid?

(c) Write a balanced half-reaction for the reaction of two molecules of glutathione to form a disulfide bond. Is glutathione a biological oxidizing agent or a biological reducing agent?

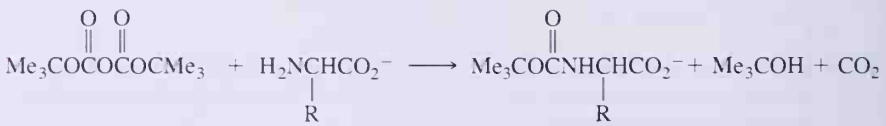
(d) Write a balanced equation for reaction of glutathione with molecular oxygen, O_2, to form G-S-S-G and H_2O. Is molecular oxygen oxidized or reduced in this process?

Synthesis of Polypeptides

24.29 In a variation of the Merrifield solid-phase peptide synthesis, the amino group is protected as by a fluorenylmethoxycarbonyl (FMOC-) group. This protecting group is removed by treatment with a weak base such as the secondary amine, piperidine. Write a balanced equation and propose a mechanism for this deprotection.

Fluorenylmethoxy-
carbonyl (FMOC) group

24.30 The BOC protecting group may be added by treatment of an amino acid with di-*tert*-butyl dicarbonate as shown in the following reaction sequence:

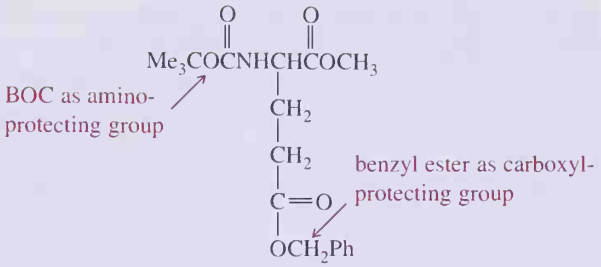


Di-*tert*-butyl dicarbonate BOC-Amino acid

Propose reaction mechanisms to account for formation of these products.

24.31 In peptide synthesis with BOC protecting groups, acid is used for deprotection. What is the initial fate of the *tert*-butyl group during acid deprotection? Why is a nucleophile such as anisole often added to the peptide deprotection mixture? (*Hint:* Review Section 16.2.)

24.32 The side-chain carboxyl groups of aspartic acid and glutamic acid are often protected as benzyl esters.



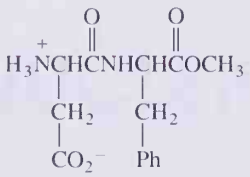
(a) Show how to convert the side-chain carboxyl group to a benzyl ester using benzyl chloride as a source of the benzyl group.

(b) How do you deprotect the side-chain carboxyl under mild conditions without removing the BOC protecting group at the same time?

24.33 In solid-phase peptide synthesis, it is important that the coupling reaction give as close to a 100% yield as possible, otherwise shorter peptides (failure sequences) accumulate. Using a large excess of the BOC-protected amino acid and long reaction times maximize the coupling yield but can also lead to wasteful, expensive, and slow peptide syntheses. Suppose you removed a small amount of the Merrifield resin from the reaction vessel after a coupling reaction. How could you tell, based on the chemistry covered in this chapter, if the coupling reaction had gone to completion?

24.34 Outline a synthesis of the tripeptide Phe-Val-Ala from its constituent amino acids using the Merrifield solid-support synthesis.

24.35 Following is a structural formula for the artificial sweetener aspartame. Each amino acid has the L configuration.



Aspartame

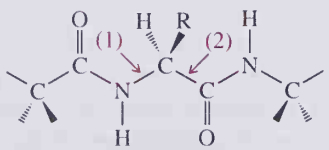
(a) Name the two amino acids in this molecule.

(b) How do you account for the observation that L-aspartyl-L-phenylalanine methyl ester has a sweet taste (it is significantly sweeter than sugar), whereas its enantiomer, D-aspartyl-D-phenylalanine methyl ester, has a bitter taste?

(c) Propose a synthesis of aspartame starting from its constituent amino acids.

Three-Dimensional Shapes of Polypeptides and Proteins

24.36 Following is a diagram of the groups that make up the backbone of a polypeptide chain:



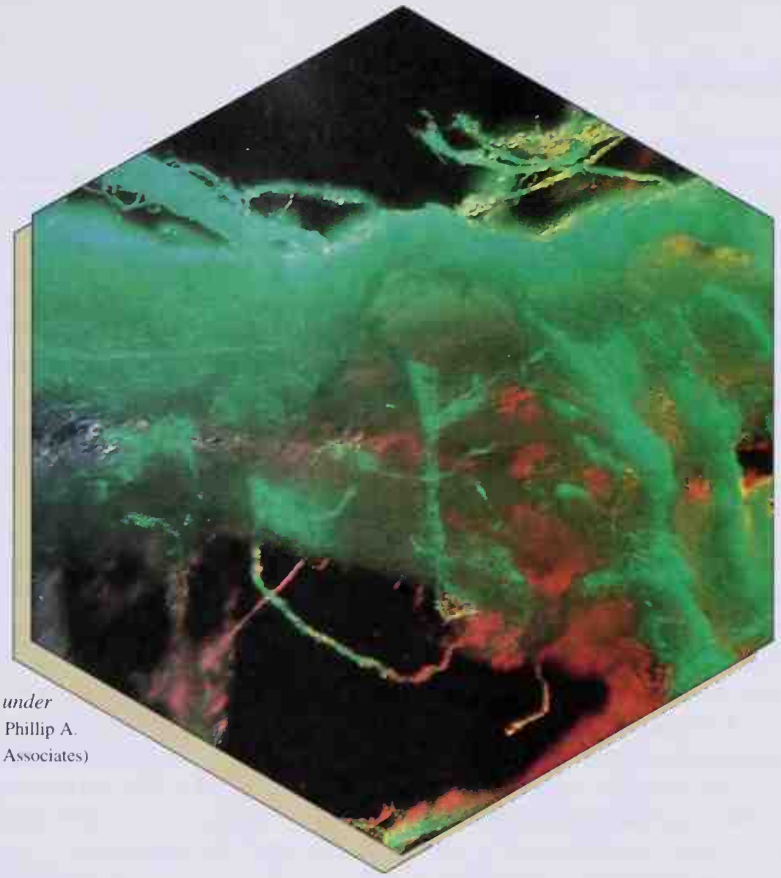
Draw a Newman projection looking down bond (1) with the nitrogen atom toward the front. Also, draw a Newman projection down bond (2) with the tetrahedral carbon in the front. What favorable conformations can you identify on the basis of these projections?

24.37 Examine the α-helix conformation. Are amino acid side chains arranged all inside the helix, all outside the helix, or is their arrangement random?

24.38 From the diagram in Figure 24.15, what do you predict to be the direction of the dipole moment of an α-helix?

24.39 The terms s-*cis* and s-*trans* are not as well defined for a peptide bond involving proline as they are for the other naturally occuring amino acids. Draw what you predict to be the more stable and less stable conformations of a peptide bond between proline and another amino acid.

24.40 Denaturation of a protein is a physical change, the most readily observable result of which is loss of biological activity. Denaturation stems from changes in secondary, tertiary, and quaternary structure through disruption of noncovalent interactions, including hydrogen bonding and hydrophobic interactions. Two common denaturing agents are sodium dodecyl sulfate (SDS) and urea. What kinds of noncovalent interactions might each reagent disrupt?



DNA fibers viewed under polarizing light. (© Phillip A. Harrington/Fran Heyl Associates)

25

NUCLEIC ACIDS

The organization, maintenance, and regulation of cellular function requires a tremendous amount of information, all of which must be processed each time a cell is replicated. With very few exceptions, this information, termed **genetic information,** is stored and transmitted from one generation to the next in the form of **deoxyribonucleic acids (DNA). Genes,** the hereditary units of chromosomes, are long stretches of double-stranded DNA. Each human chromosome is approximately 4 cm in length. The length of cellular DNA in 23 double-stranded human chromosomes is $2 \times 23 \times 4$ cm or approximately 1.8 m.

Genetic information is expressed in two stages: transcription from DNA to **ribonucleic acids (RNA)** and then translation for the synthesis of proteins.

$$\text{DNA} \longrightarrow \text{RNA} \longrightarrow \text{protein}$$

An important exception to the DNA-RNA-protein expression of genetic information are the retroviruses, simple particles that store their genetic information in the form of RNA instead of DNA. Viruses are unable to reproduce themselves and must rely, instead, on the biosynthetic machinery of host cells for reproduction. Because host cells do not recognize RNA as a storage form of genetic information, the information encoded in viral RNA must

first be transcribed to DNA by a process called reverse transcription. This viral information is then transcribed into forms of RNA recognized by the protein-synthesizing machinery of the host cell. The **human immunodeficiency virus (HIV)** is a retrovirus and produces a condition known as **acquired immune deficiency syndrome (AIDS).**

In this chapter, we examine the structure of nucleosides and nucleotides and the manner in which these monomers are covalently bonded to form nucleic acids. We restrict our discussion in this text to the structure of DNA. As we did with polypeptides, we examine their primary, secondary, and tertiary structure. Finally, we examine one of the methods devised by chemists for their synthesis.

25.1 Nucleosides and Nucleotides

Controlled hydrolysis of nucleic acids yields three components: heterocyclic aromatic amine bases, the monosaccharides D-ribose and 2-deoxy-D-ribose (Section 18.1), and phosphate. The heterocyclic aromatic amine bases most common to nucleic acids are shown in Figure 25.1. Uracil, cytosine, and thymine are referred to as pyrimidine bases after the name of the parent base; adenine and guanine are referred to as purine bases.

A **nucleoside** is a compound containing D-ribose or 2-deoxy-D-ribose bonded to a heterocyclic aromatic amine base by a β-*N*-glycoside bond. The glycoside bond is between C-1′ (the anomeric carbon) of ribose or deoxyribose and *N*-1 of a pyrimidine base or *N*-9 of a purine base. Figure 25.2 shows structural formulas for two nucleosides: the first derived from ribose and uracil, the second from 2-deoxyribose and adenine.

A **nucleotide** is a nucleoside in which a molecule of phosphoric acid is esterified with a free hydroxyl of the monosaccharide, most commonly either the 3′-hydroxyl or the 5′-hydroxyl (Figure 25.3). A nucleotide is named by giving the name of the parent nucleoside followed by the word "monophosphate." The position of the phosphate ester is specified by the number of the carbon to which it is attached. Monophosphate esters are

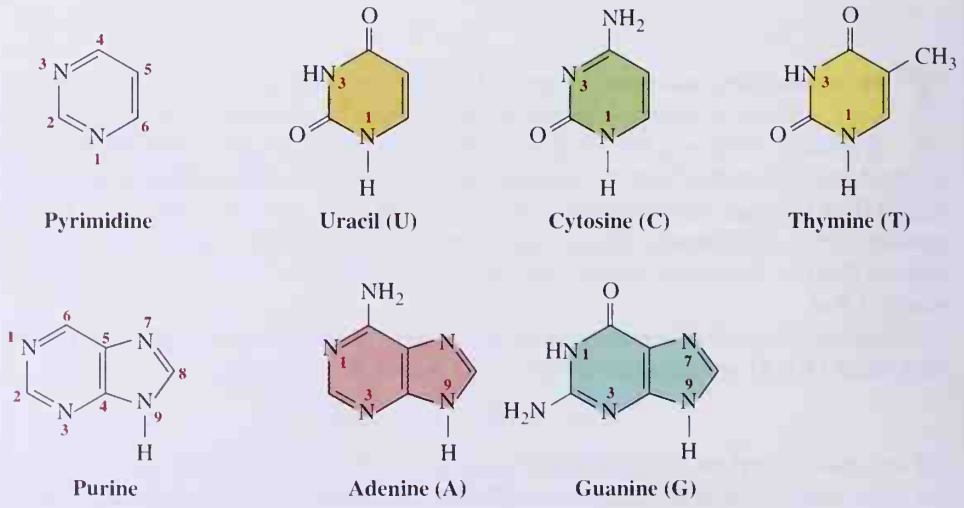


Figure 25.1
Names and one-letter abbreviations for the heterocyclic aromatic amine bases most common to DNA and RNA. Bases are numbered according to the patterns of the parent compounds, pyrimidine and purine.

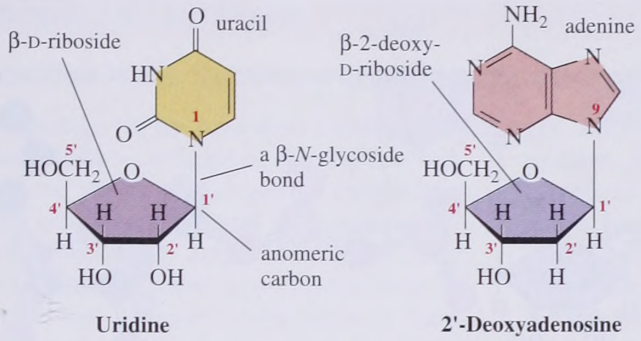


Figure 25.2
Structural formulas for two nucleosides. Atom numbers on the monosaccharide rings are primed to distinguish them from atom numbers on the heterocyclic bases.

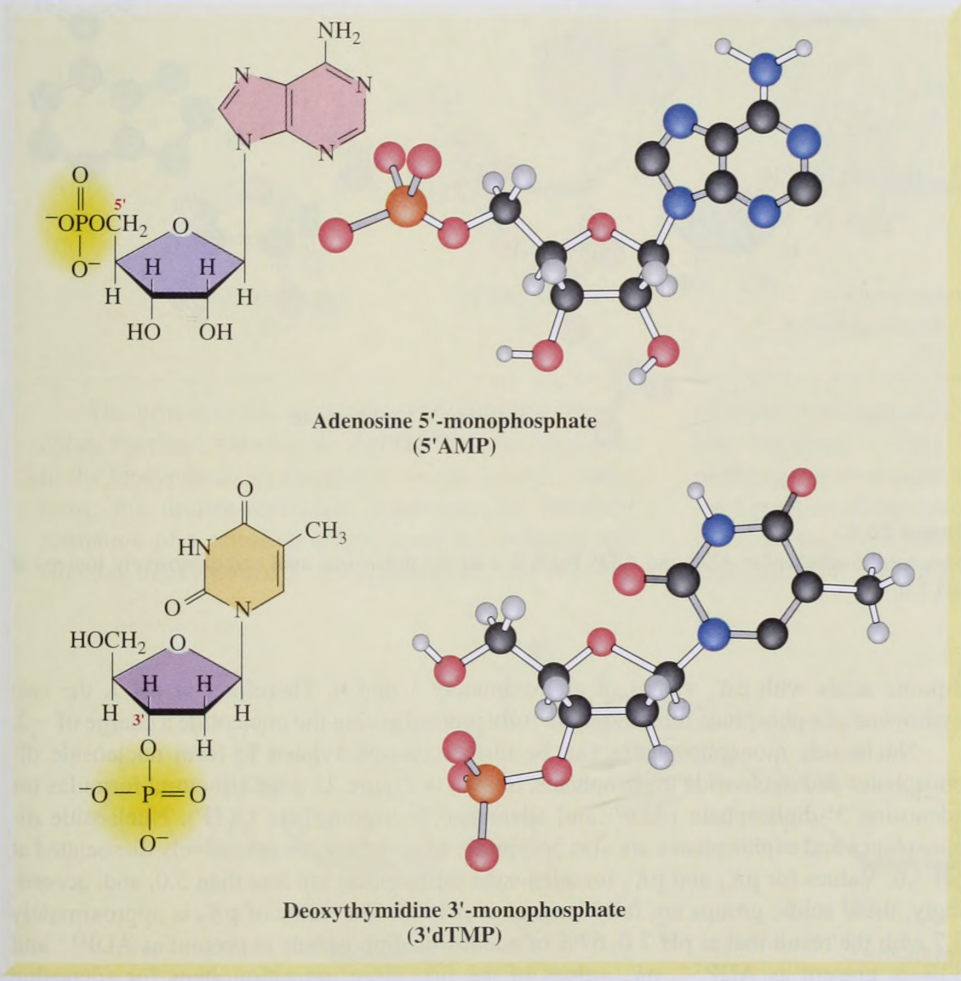


Figure 25.3
The structure of two nucleotides. Each phosphate group is fully ionized at pH 7.0, giving each nucleotide a charge of −2.

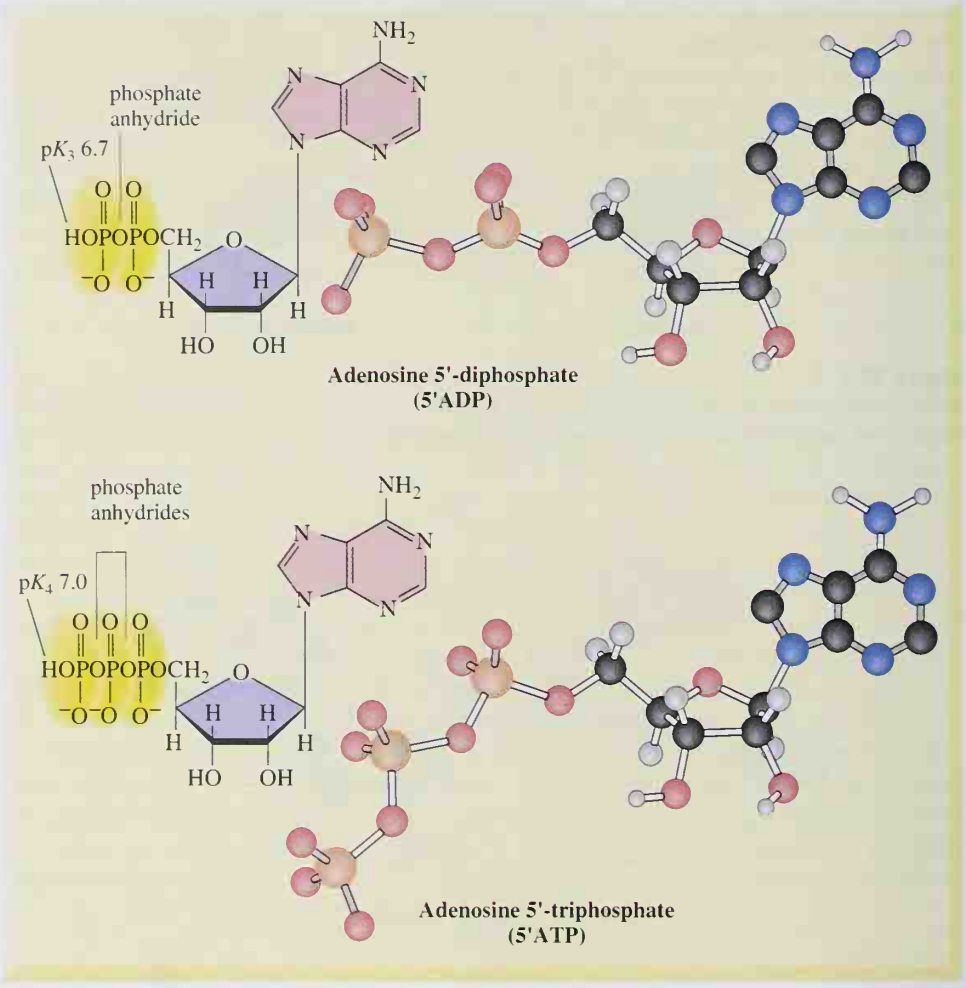


Figure 25.4
Structural formulas for ADP and ATP. Each is a strong polyprotic acid and extensively ionized at pH 7.0.

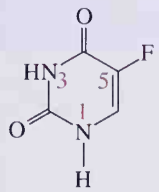
diprotic acids with pK_a values of approximately 1 and 6. Therefore, at pH 7, the two hydrogens of a phosphate monoester are fully ionized giving the nucleotide a charge of −2.

Nucleoside monophosphates can be further phosphorylated to form nucleoside diphosphates and nucleoside triphosphates. Shown in Figure 25.4 are structural formulas for adenosine 5′-diphosphate (ADP) and adenosine 5′-triphosphate (ATP). Nucleoside diphosphates and triphosphates are also polyprotic acids which are extensively dissociated at pH 7.0. Values for pK_1 and pK_2 for adenosine diphosphate are less than 5.0, and, accordingly, these acidic groups are fully ionized at pH 7.0. The value of pK_3 is approximately 6.7 with the result that at pH 7.0, 67% of adenosine diphosphate is present as ADP^{3-} and 33% is present as ADP^{2-}. pK_a values of the first three ionization steps for adenosine triphosphate are less than 5.0. The value of pK_4 is approximately 7.0. Therefore, at pH 7.0, approximately 50% of adenosine triphosphate is present as ATP^{4-}, and 50% is present as ATP^{3-}.

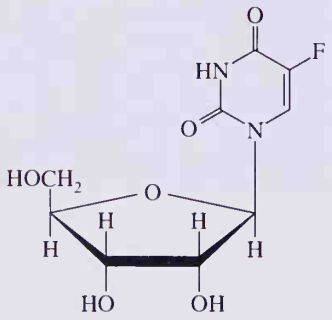
CHEMISTRY IN ACTION

Antimetabolites in the Treatment of Neoplastic Diseases

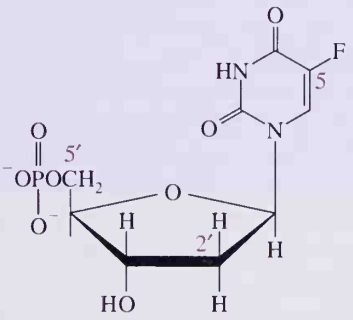
An important strategy for the treatment of disease is to design **antimetabolites,** compounds that interfere with the formation and use of normal cellular metabolites. The following compounds illustrate two strategies for the design of antimetabolite drugs: inhibition of a key enzyme in a biochemical pathway and incorporation of a false, or dead-end, substrate. Application of these strategies to the treatment of cancer has led to the development of 5-fluorouracil (1) and 5-fluorouridine (2), antimetabolites related in structure to the pyrimidines involved in the synthesis of DNA. Each compound is inactive, but is converted in vivo to its active form, 5-fluorodeoxyuridine 5′-monophosphate (5-FdUMP) (3). Note that 5-fluorouridine contains D-ribose. Conversion to its active form requires two transformations; formation of a 5′-phosphate ester and reduction of carbon 2′ from the CHOH of ribose to the CH_2 of deoxyribose.



5-Fluorouracil
(1)

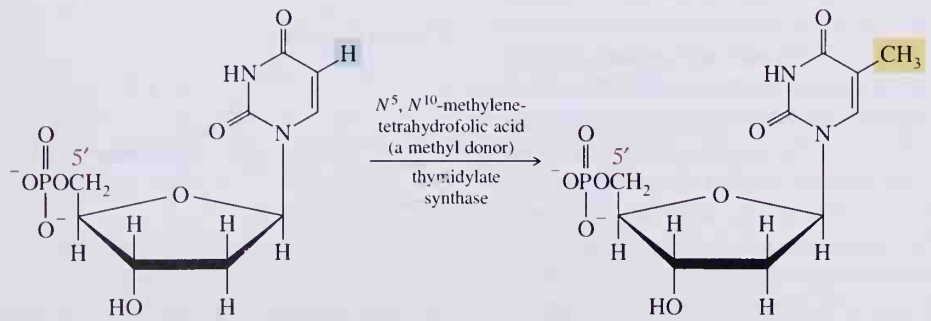


5-Fluorouridine
(2)



5-Fluorodeoxyuridine
5′-monophosphate (5-FdUMP)
(3)

The principal site of action of 5-FdUMP is thymidylate synthase, the enzyme that catalyzes the final step in the biosynthesis of thymidine. Under normal conditions, the uridine-thymidine transformation involves formation of a covalent ternary complex between the enzyme, deoxyuridine 5′-monophosphate, and N^5,N^{10}-methylenetetrahydrofolic acid (a carrier of the one-carbon fragments $—CH_3$, $—CH_2OH$, and —CHO). A methyl group is transferred from the carrier molecule to the 5 position of deoxyuridine, and the ternary complex collapses to give thymidine, the enzyme, and the carrier molecule minus its methyl group.



Deoxyuridine
5′-monophosphate

Deoxythymidine
5′-monophosphate

Box continued on next page.

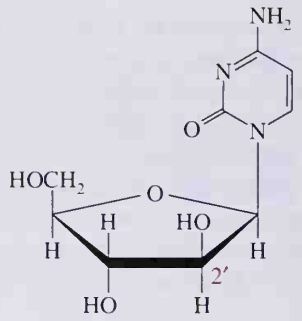
CHEMISTRY IN ACTION (Continued)

The van der Waals radius of fluorine (0.135 nm) is similar enough to that of hydrogen (0.12 nm) so that 5-FdUMP is recognized and bound by thymidylate synthase. The ternary complex forms, but methyl transfer cannot occur because the 5 position of 5-FdUMP is blocked by fluorine. The enzyme remains bound in the ternary complex (now a dead-end complex) and is unable to catalyze further reaction. Therefore, tumor cells are deprived of a source of thymidine and are said to suffer a "thymidineless death."

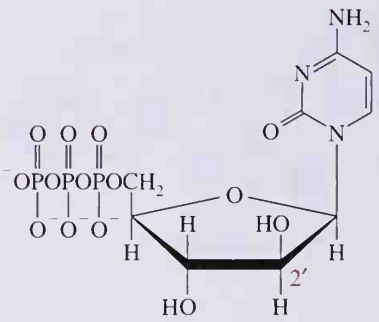
D-Arabinose is the epimer of D-ribose at carbon 2, that is, the —OH on carbon 2 is below the plane of the ring in D-ribofuranose and above the plane of the ring in D-arabinofuranose. The pyrimidine derivative arabinosylcytosine (Ara-C) is an important antimetabolite for the treatment of certain types of acute leukemia and non-Hodgkin's lymphoma. This compound is activated by conversion to its 5′-triphosphate, which is an inhibitor of DNA polymerase. Arabinosyladenine (Ara-A) is similarly converted to its active form, the 5′-triphosphate, which is also an inhibitor of DNA polymerase.

The search for antiviral drugs has been more difficult than the search for antimicrobial drugs primarily because viral replication depends on the metabolic processes of the invaded cell. Thus, antiviral drugs are also likely to cause harm to the cells that harbor the virus. The challenge in developing antiviral drugs has been to understand the biochemistry of viruses and to develop drugs that target processes specific to them.

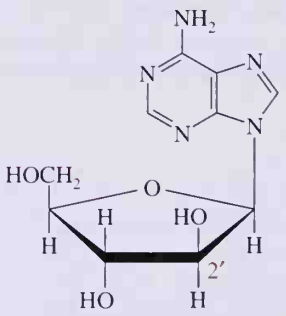
Acyclovir is one of the first of a new family of drugs for the treatment of infectious diseases caused by DNA viruses called herpesvirus. Herpes infections in humans are of two kinds: herpes simplex type 1, which gives rise to mouth and eye sores, and herpes simplex type 2, which gives rise to serious genital infections. Acyclovir is highly effective against herpesvirus-caused genital infections. The drug is activated in vivo by conversion of the primary —OH (which corresponds to the 5′-OH of a riboside or of a deoxyriboside) to a triphosphate. The selective viral toxicity of acyclovir arises because uninfected cells do not catalyze its phosphorylation. Because of its close resemblance to deoxyguanosine triphosphate, an essential precursor for DNA synthesis, acyclovir triphosphate is taken up by viral DNA polymerase where it leads to the formation of an enzyme-substrate complex, on which no 3′-OH exists for replication to continue. Thus, the enzyme-substrate complex is no longer active (it is a dead-end complex), viral replication is disrupted, and the virus is destroyed.



Arabinosylcytosine
(Ara-C)

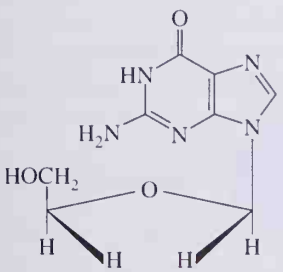


Arabinosylcytosine 5′-triphosphate
(Ara-CTP)

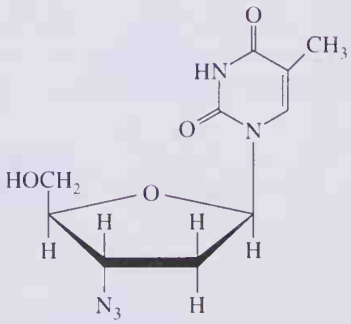


Arabinosyladenine
(Ara-A)

Crystals of acyclovir *(left)* and AZT *(right)* viewed under polarizing light. *(© Mel Pollinger/Fran Heyl Associates)*



Acyclovir
(drawn to show its structural relationship to 2-deoxyguanosine



Azidothymidine (AZT)

Perhaps the best known of the new viral antimetabolites is azidothymidine (AZT), an analog of deoxythymidine in which the 3′-OH has been replaced by an azido group. AZT is effective against HIV-1, a retrovirus that is the causative agent of AIDS. It is converted in vivo by cellular enzymes to the 5′-triphosphate, recognized as deoxythymidine 5′-triphosphate by viral RNA-dependent DNA polymerase (reverse transcriptase), and added to a growing DNA chain. There it stops chain elongation because there is no 3′-OH on which to add the next deoxynucleotide. AZT owes its effectiveness to the fact that it binds more strongly to viral reverse transcriptase than it does to human DNA polymerase.

25.2 The Structure of DNA

In Chapter 24 we saw that the four levels of structural complexity to polypeptides and proteins are primary, secondary, tertiary, and quaternary structure. There are three levels of structural complexity in nucleic acids, and although these levels of structural complexity are somewhat comparable to those in polypeptides and proteins, they also differ in significant ways.

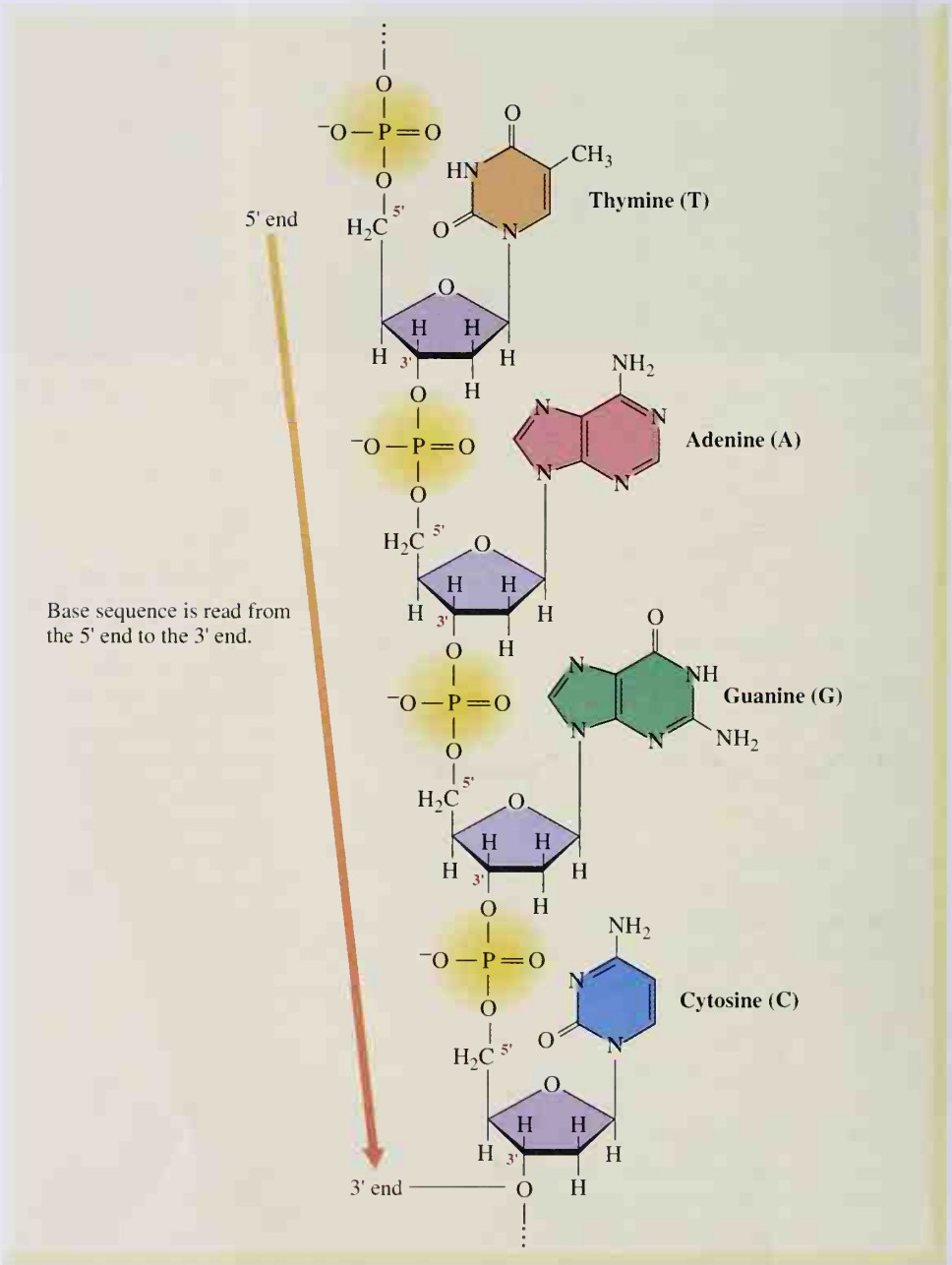


Figure 25.5
A tetranucleotide section of a single-stranded DNA.

A. Primary Structure: The Covalent Backbone

Deoxyribonucleic acids (DNA) consist of a backbone of alternating units of deoxyribose and phosphate in which the 3′-hydroxyl of one deoxyribose unit is joined by a phosphodiester bond to the 5′-hydroxyl of another deoxyribose unit (Figure 25.5). This pentose-phosphodiester backbone is constant throughout an entire DNA molecule. A heterocyclic aromatic amine base—adenine, guanine, thymine, or cytosine—is bonded to each deoxyribose unit by a β-*N*-glycoside bond. Primary structure of DNA refers to the order of heterocyclic bases along the pentose-phosphodiester backbone.

Two important differences exist between the primary structure of RNA and DNA. (1) The monosaccharide unit in RNA is D-ribose; in DNA it is 2-deoxy-D-ribose. (2) Both RNA and DNA contain the purine bases adenine (A) and guanine (G), and the pyrimidine base cytosine (C). As the fourth base, however, RNA contain uracil (U), whereas DNA contain thymine (T).

B. Secondary Structure: The Double Helix

By the early 1950s, it was clear that DNA molecules consist of chains of alternating units of deoxyribose and phosphate joined by 3′,5′-phosphodiester bonds with a base attached to each deoxyribose unit by a β-*N*-glycoside bond. In 1953, the American biologist, James D. Watson, and the British physicist, Francis H. C. Crick, proposed a **double-helix model** for the secondary structure for DNA. Their model was accepted immediately because it explained so many of the physical and chemical properties of DNA and provided a rationale for its biological properties. Further, the double-helix model made it possible to develop hypotheses for how DNA is replicated during cell division and how genetic information encoded in DNA is used to direct the biosynthesis of RNA and of proteins.

The **Watson-Crick model** was based on two lines of experimental observations: chemical analyses of DNA base compositions, and mathematical analyses of x-ray diffraction patterns of crystals of DNA.

Base Composition

At one time it was thought that the four principal bases occur in the same ratios and perhaps repeat in a regular pattern along the pentose-phosphodiester backbone of DNA for all species. However, more precise determinations of base composition by Erwin Chargaff revealed that bases do not occur in the same ratios (Table 25.1). Researchers drew the following conclusions from this and related data. To within experimental error

Table 25.1 Comparison in base composition, in mole-percent, of DNA from several organisms

	Purines		Pyrimidines				
Organism	A	G	C	T	A/T	G/C	Purines/Pyrimidines
human	30.4	19.9	19.9	30.1	1.01	1.00	1.01
sheep	29.3	21.4	21.0	28.3	1.04	1.02	1.03
yeast	31.7	18.3	17.4	32.6	0.97	1.05	1.00
E. coli	26.0	24.9	25.2	23.9	1.09	0.99	1.04

1. The mole-percent base composition in any organism is the same in all cells of the organism and is characteristic of the organism.
2. The mole-percents of adenine (a purine base) and thymine (a pyrimidine base) are equal. The mole-percents of guanine (a purine base) and cytosine (a pyrimidine base) are also equal.
3. The mole-percent of purine bases (A + G) and pyrimidine bases (C + T) are equal.

Analyses of X-Ray Diffraction Patterns

Additional information of the structure of DNA emerged when x-ray diffraction photographs taken by Rosalind Franklin and Maurice Wilkins were analyzed. These diffraction patterns revealed that, even though the base composition of DNA isolated from different organisms varies, DNA molecules themselves are remarkably uniform in thickness. They are long and fairly straight, with an outside diameter of approximately 2 nm and not more than a dozen atoms thick. Furthermore, the crystallographic pattern repeats every 3.4 nm. Herein lay one of the chief problems to be solved. How could the molecular dimensions of DNA be so regular even though the relative percentages of the various bases differ so widely?

The Watson-Crick model not only accounted for many of the physical and chemical properties of DNA but also suggested a mechanism by which genetic information could be replicated repeatedly and accurately. Watson, Crick, and Wilkins shared the 1962 Nobel Prize in physiology and medicine for "their discoveries concerning the molecular structure

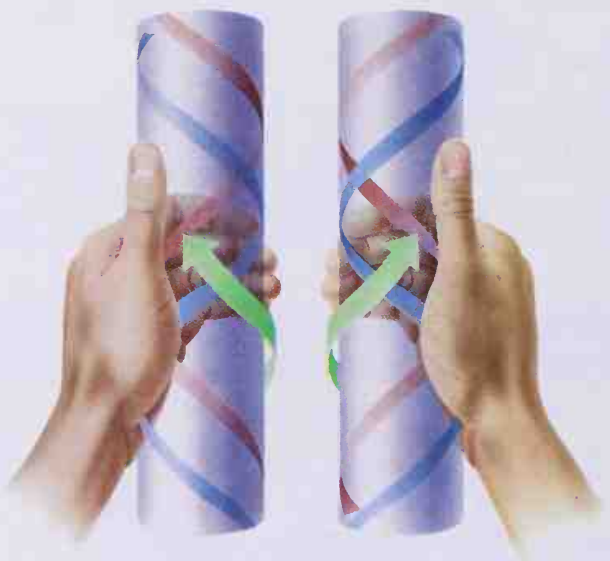


Figure 25.6
A DNA double helix has a chirality associated with the helix. Right-handed and left-handed double helices are nonsuperposable mirror images of each other.

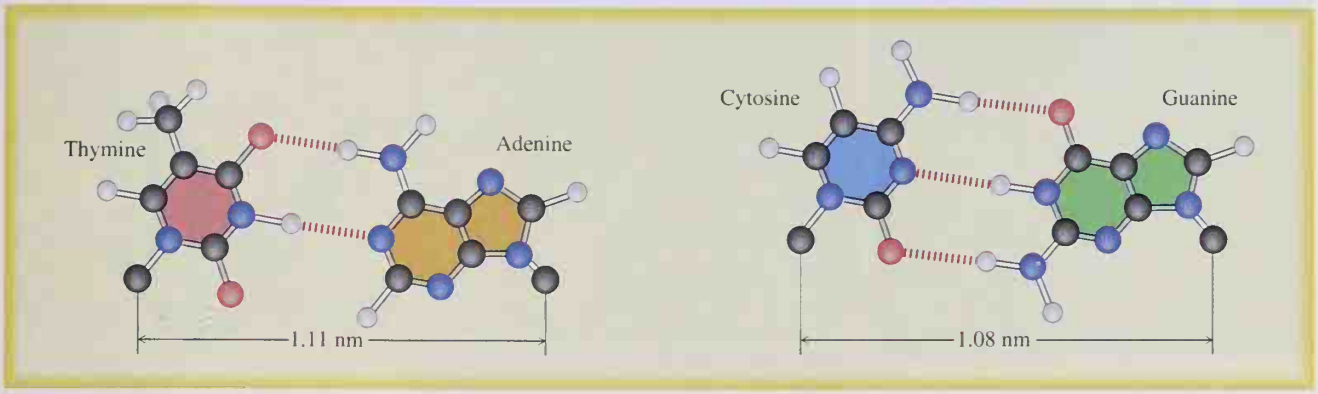


Figure 25.7
Base-pairing between adenine and thymine (A-T) and between guanine and cytosine (G-C). An A-T base pair is held by two hydrogen bonds, whereas a G-C base pair is held by three hydrogen bonds. In this representation, base pairs are planar and are viewed as they would be seen looking along the longitudinal axis of a double-stranded DNA molecule.

of nucleic acids, and its significance for information transfer in living material." It should be noted that although Rosalind Franklin took part in this research, her name was omitted from the Nobel list because of her death in 1958 at age 37. It is the policy of the Nobel foundation not to make awards posthumously.

The heart of the Watson-Crick model is the postulate that a molecule of DNA consists of two antiparallel polynucleotide strands coiled in a right-handed manner about the same axis to form a double helix. As illustrated in the ribbon models in Figure 25.6, chirality is associated with a double helix; left-handed and right-handed double helices are related by reflection just as a pair of enantiomers are related by reflection. Model building suggested to Watson and Crick that the secondary structure of DNA is a right-handed helix rather than a left-handed helix.

To account for the observed base ratios, Watson and Crick postulated that purine and pyrimidine bases project inward toward the axis of the helix and are always paired in a very specific manner. According to scale models, the dimensions of an adenine-thymine base pair are almost identical to the dimensions of a guanine-cytosine base pair, and the length of each pair is consistent with the core thickness of a DNA strand (Figure 25.7).

A significant feature of Watson and Crick's model is that no other base pairing is consistent with the observed thickness of a DNA molecule. A pair of pyrimidine bases is too small to account for the observed thickness, whereas a pair of purine bases is too large. Thus, according to the Watson-Crick model, the repeating units in a double-stranded DNA molecule are not single bases of differing dimensions, but rather base pairs of almost identical dimensions.

To account for the periodicity observed from x-ray data, Watson and Crick postulated that base pairs are stacked one on top of the other with a distance of 0.34 nm between base pairs and with 10 base pairs in one complete turn of the helix. There is one complete turn of the helix every 3.4 nm. Shown in Figure 25.8 is a ribbon model of double-stranded **B-DNA**, the predominant form of DNA in dilute aqueous solution and thought to be the most common form in nature.

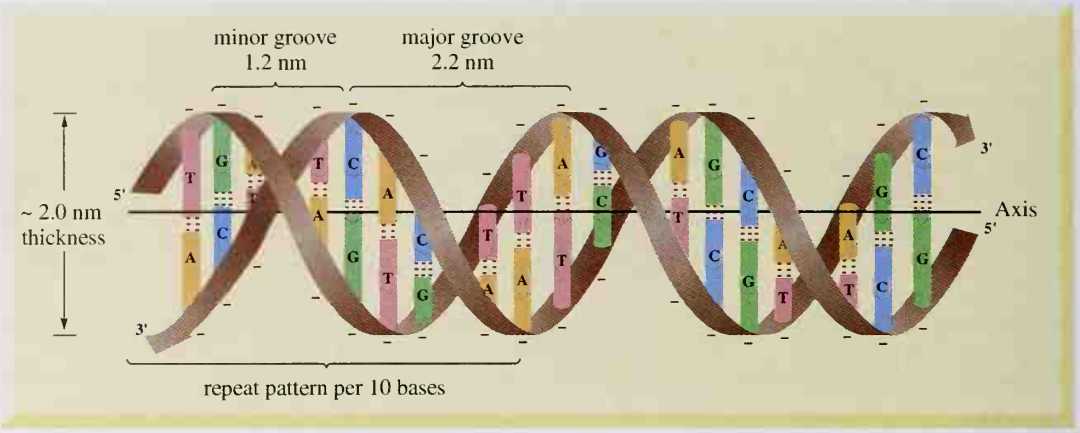
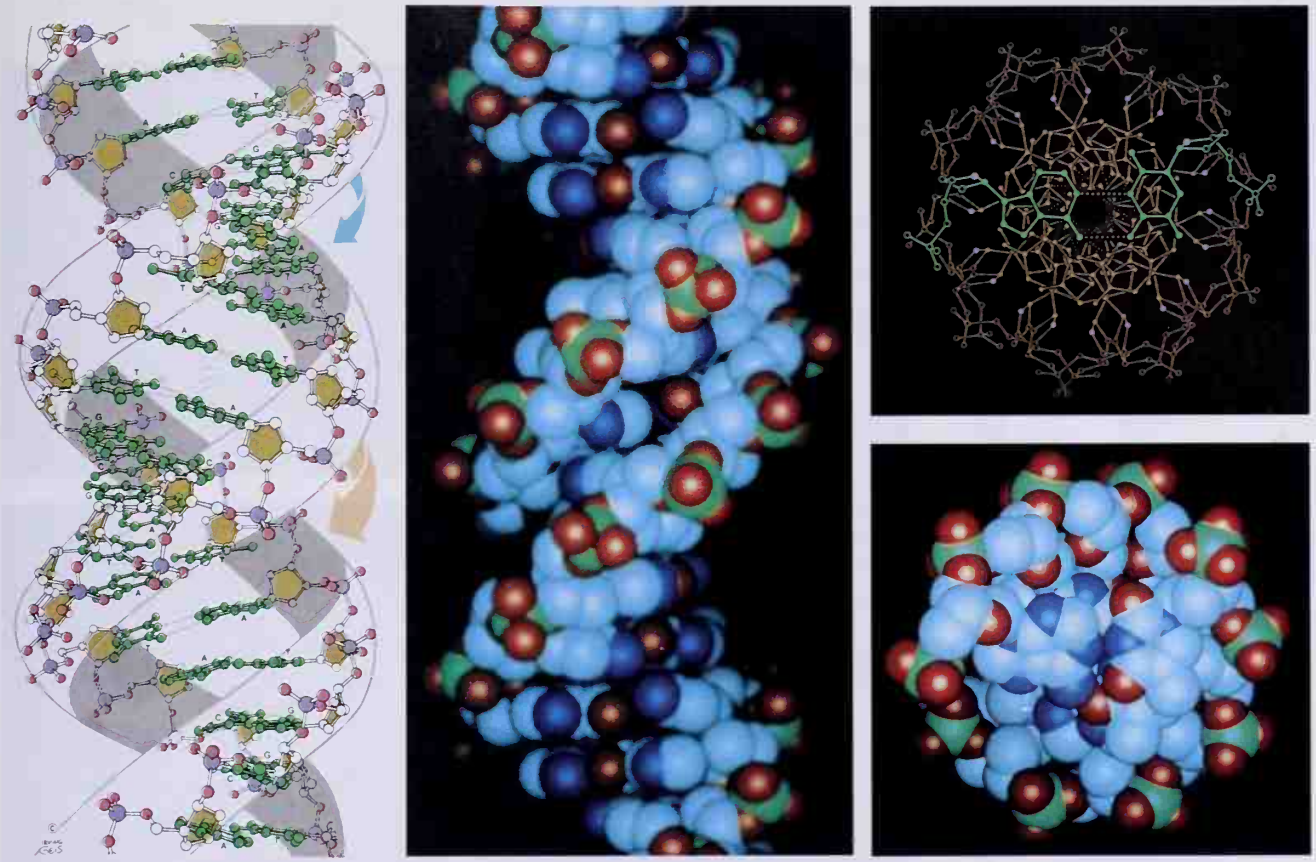


Figure 25.8
Ribbon model of double-stranded B-DNA. Each ribbon shows the pentose-phosphodiester backbone of a single-stranded DNA molecule. The strands are antiparallel; one strand runs upward from the 5′ end to the 3′ end, the other runs downward from the 5′ end to the 3′ end. Hydrogen-bonded base pairs project inward toward the center of the helix with a spacing of 0.34 nm between base pairs. The diameter of base pairs in the center of the helix is 1.1 nm, and the outside diameter of the helix is 2.0 nm.

Figure 25.9 shows two additional models, each showing more detail of a DNA double helix. The major and minor grooves are most clearly recognized in the space-filling model. The major groove is approximately 2.2 nm wide; the minor groove is approximately 1.2 nm wide. The type of secondary structure we have just described is B-DNA. Other forms of secondary structure are known that differ in the distance between stacked base pairs and in the number of base pairs per turn of the helix. All of these forms are interconvertible depending on variations in temperature, ionic strength and polarity of the solvent, and cations associated with the negatively charged phosphodiester groups. **A-DNA,** also a right-handed helix, has approximately the same thickness as B-DNA but has a repeat distance of only 2.8 nm (Figure 25.10). There are 11 base pairs per turn (per 2.8 nm) of the helix with a spacing of 0.256 nm between base pairs.

At the structural level, a fundamental difference between B-DNA and A-DNA is the conformation of the furanose form of 2-deoxy-D-ribose. Figure 25.11 shows ball-and-stick models and stereoviews of two conformations of 2′-deoxyadenosine 3′,5′-diphosphate. To appreciate the significance of these models, recall from Section 2.6B that C—C—C bond angles in a planar conformation of cyclopentane are 108°. This angle differs only slightly from the tetrahedral angle of 109.5°, and, hence, there is only negligible angle strain in a planar conformation of cyclopentane. There are, however, ten sets of fully eclipsed hydrogens. The observed C—C—C bond angles in cyclopentane are 105°, indicating that, in its most stable conformation, the ring is slightly puckered. In forming a puckered or envelope conformation (there are five of them depending on which carbon atom is puckered out of the plane of the other four), C—C—C bond angles are reduced (increasing ring strain), but at the same time eclipsed hydrogen interactions are also reduced (decreasing potential energy).

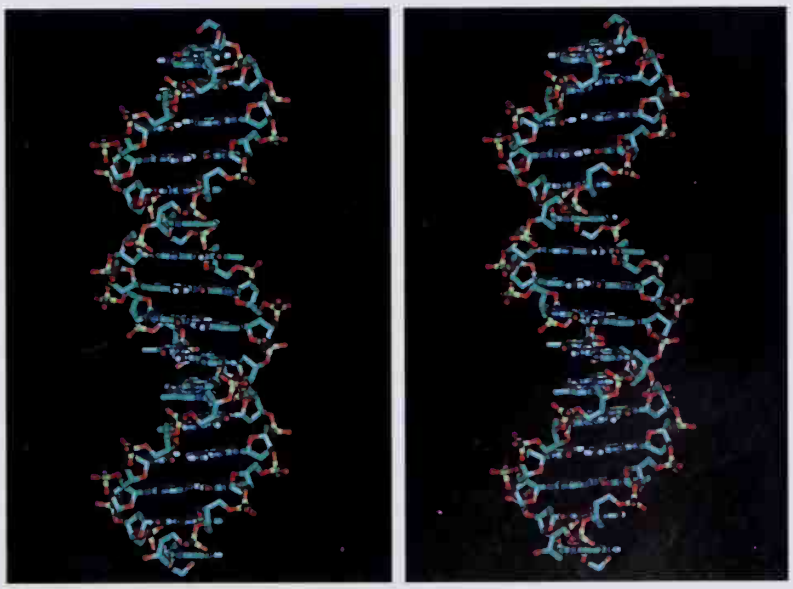
Although in principle a number of puckered conformations are possible for the furanose ring of a nucleoside, only two are common: the (C)2′-endo conformation and the



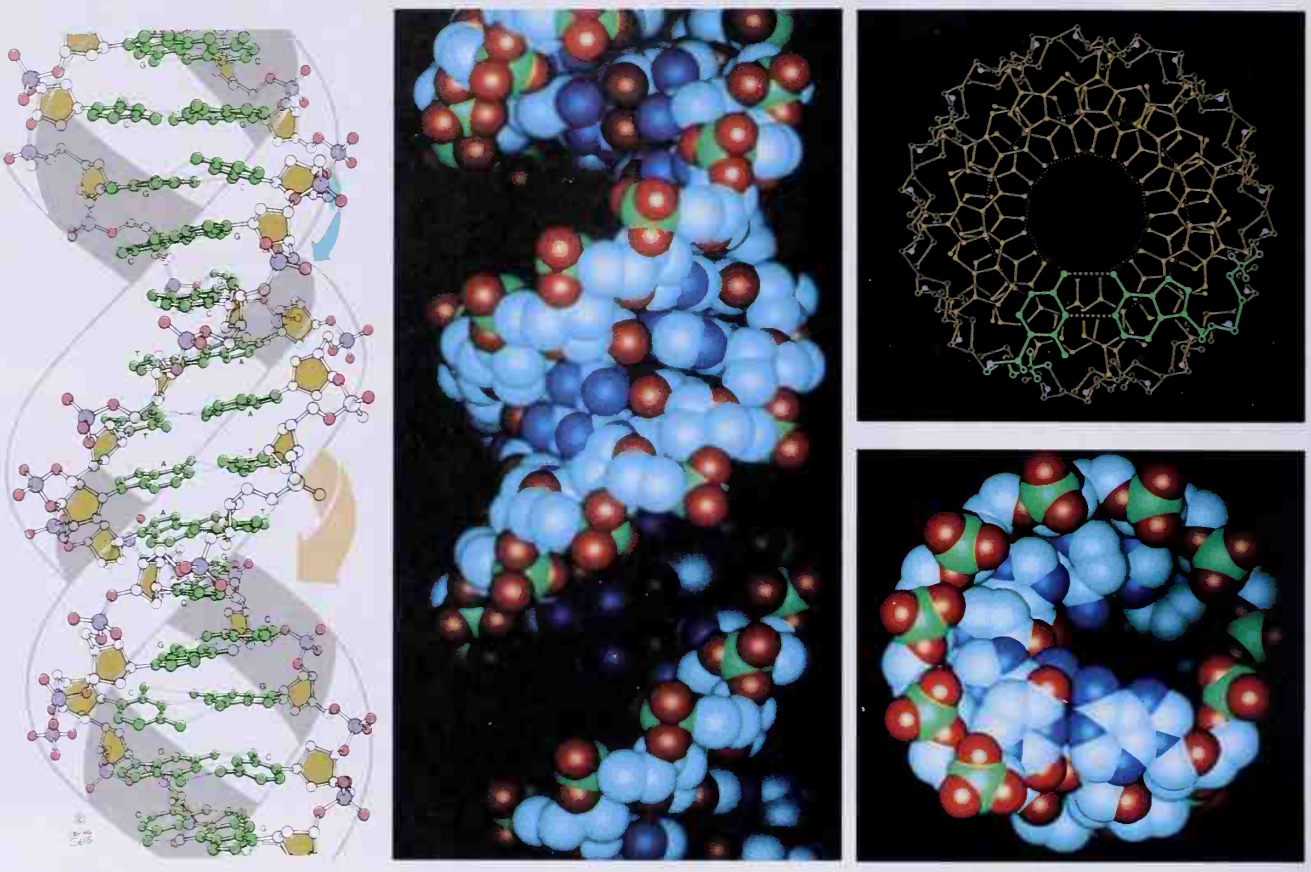
(a) Side view of B-DNA

(b) View down helix axis (top view)

Figure 25.9
(a,b) Ball-and-stick and space-filling models of B-DNA. In both models, the pentose-phosphodiester backbone is visible on the outside of the molecule. Base pairs are stacked one on top of another on the inside of the molecule, in planes roughly perpendicular to the longitudinal axis of the helix. Hydrogen bonds are shown by three dotted lines between each G-C base pair and two dotted lines between each A-T base pair. (c) An idealized model of the B-form of DNA in stereoview.



(c) Stereoview



(a) Side view of A-DNA

(b) View down helix axis (top view)

Figure 25.10
(a,b) Space-filling and ball-and-stick models of A-DNA. The spacing between stacked base pairs is 0.256 nm. The repeat distance is 2.8 nm, and there are 11 base pairs per repeat.

(C)3′-endo conformation. The designations (C)2′ and (C)3′ indicate which atom of the ring is puckered relative to the plane created by the other atoms of the ring. The designation endo indicates puckering upward, on the same side as the heterocyclic aromatic amine base. The alternative to endo is exo, meaning downward, on the side opposite the amine base.

β-DNA exists in the (C)2′-endo conformation, whereas A-DNA exists in the (C)3′-endo conformation. Although the differences in spatial orientation of ring atoms may seem small, they produce significant differences in spatial orientation of atoms attached to the ring. In particular, compare the relative orientations in space and internuclear distances between the (C)3′-phosphate ester and (C)5′-phosphate ester on the furanose ring. The phosphate esters are significantly closer in the (C)3′-endo conformation than they are in the (C)2′-endo conformation, a difference that is reflected in the shorter repeat distance and reduced stacking distance in the A-DNA helix compared with the B-DNA helix.

Both B-DNA and A-DNA are right-handed helices. Another form of DNA, named Z-DNA, has been discovered that has a left-handed double helix.

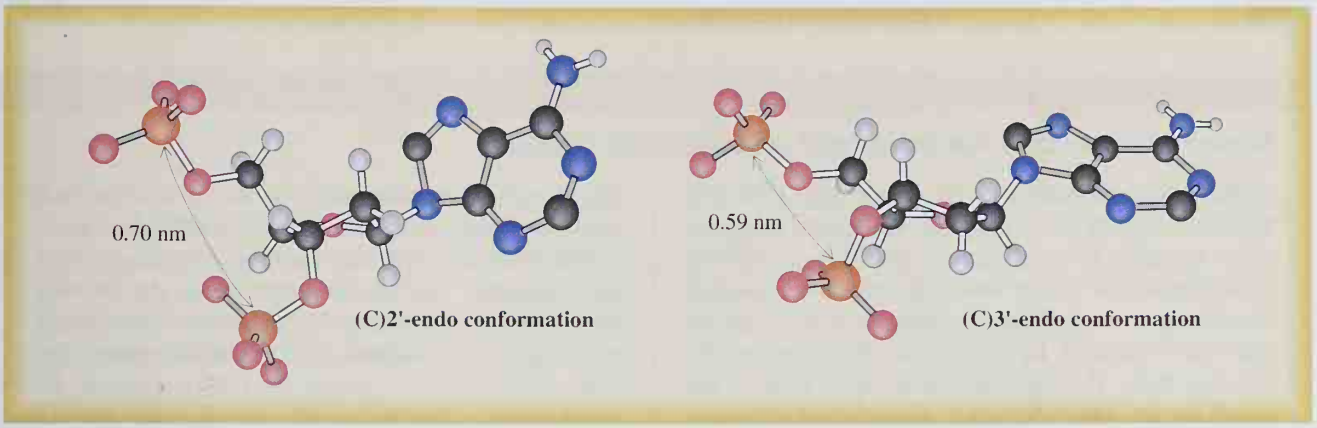


Figure 25.11
(C)2′-endo and (C)3′-endo conformations of the furanose ring of 2′-deoxyadenosine 3′,5′-diphosphate. In B-DNA, the phosphate esters are spaced at a distance of 0.7 nm, which leads to a spacing of 0.34 nm between stacked base pairs and 10 base pairs per 3.4-nm repeat. In A-DNA, the phosphate esters are spaced at a distance of 0.59 nm, which leads to a spacing of 0.256 nm between stacked base pairs and 11 base pairs per 2.8-nm repeat.

C. Tertiary Structure: Supercoiled DNA

The length of a DNA molecule is considerably greater than its diameter, and the extended molecule is quite flexible. A DNA molecule is said to be relaxed if it has no twists other than that imposed by its secondary structure. Said another way, relaxed DNA does not have a clearly defined tertiary structure. We consider two types of tertiary structure: one type induced by perturbations in circular DNA, and a second type introduced by coordination of DNAs with nuclear proteins called histones. Tertiary structure, whatever the type, is referred to as **supercoiling.**

Supercoiling of Circular DNA

Circular DNA is a type of double-stranded DNA in which the two ends of each strand are joined by phosphodiester bonds (Figure 25.12[a]). This type of DNA, the most prominent form in bacteria and viruses, is also referred to as circular duplex (because it is double-

(Text continued on p. 1104)

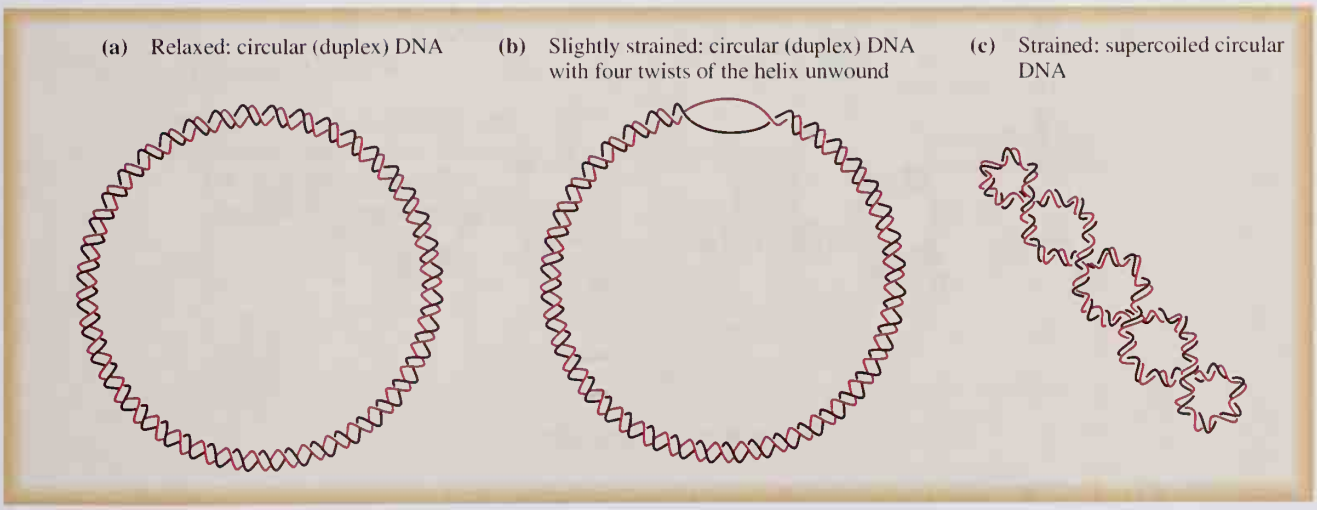
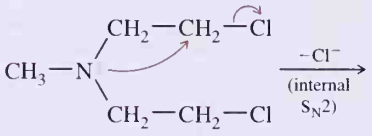


Figure 25.12
Relaxed and supercoiled (superhelical) DNA. (a) Circular DNA is relaxed. (b) One strand is broken, unwound by four turns, and the ends then rejoined. The strain of unwinding is localized in the nonhelical gap. (c) Superhelical coiling by four twists distributes the strain of unwinding uniformly over the entire molecule of circular DNA.

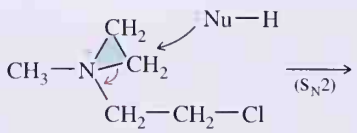
CHEMISTRY IN ACTION

Mustard Gases and the Treatment of Neoplastic Diseases

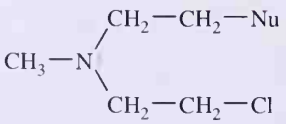
Sulfur mustard (Section 10.7H) is a highly toxic gas used in World War I. Autopsies of soldiers killed by sulfur mustards revealed, among other things, very low white blood cell counts and defects in bone marrow development. From these observations, it was realized that sulfur mustards have profound effects on rapidly dividing cells. This became a lead observation in the search for less toxic alkylating agents for use in clinical medicine. Attention turned to the less reactive nitrogen mustards. One of the first compounds tested was mechlorethamine. In reactions of this and other nitrogen mustards, assisted ionization of halogen (Section 10.7H) forms a cyclic aziridinium ion intermediate. This is followed by attack of a nucleophile on a carbon atom of the three-member ring to give an alkylated product.



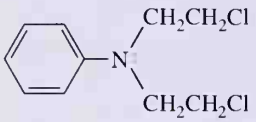
Mechlorethamine



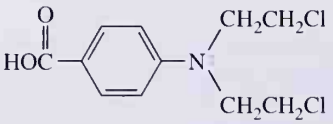
(An aziridinium ion intermediate)



Mechlorethamine undergoes very rapid reaction with water (hydrolysis) and with other nucleophiles, so much so that within minutes after injection into the body, it has completely reacted. The problem for the chemist, then, was to find a way to decrease the nucleophilicity of nitrogen while maintaining a reasonable water solubility. Substitution of phenyl for methyl reduced the nucleophilicity, but the resulting compound was not sufficiently soluble in water for intravenous injection. The solubility problem was solved by adding a carboxyl group. When the carboxyl group was added directly to the aromatic ring, however, the resulting compound was too stable and, therefore, not biologically active.

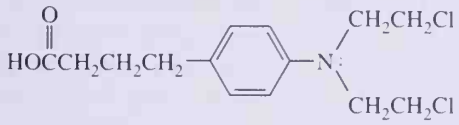


The nucleophilicity of nitrogen is acceptable, but the compound is too insoluble in water for intravenous injection.

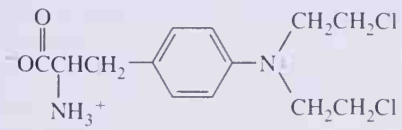


The solubility in water is acceptable, but the nucleophilicity of nitrogen is reduced so much that the compound is unreactive.

Adding a propyl bridge (chlorambucil) or an aminoethyl bridge (melphalan) between the aromatic ring and the carboxyl group solved both the solubility problem and the reactivity problem. Note that melphalan is a chiral compound. It has been demonstrated that the R and S enantiomers have approximately equal therapeutic potency.



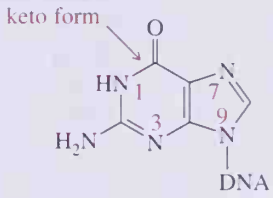
Chlorambucil



Melphalan

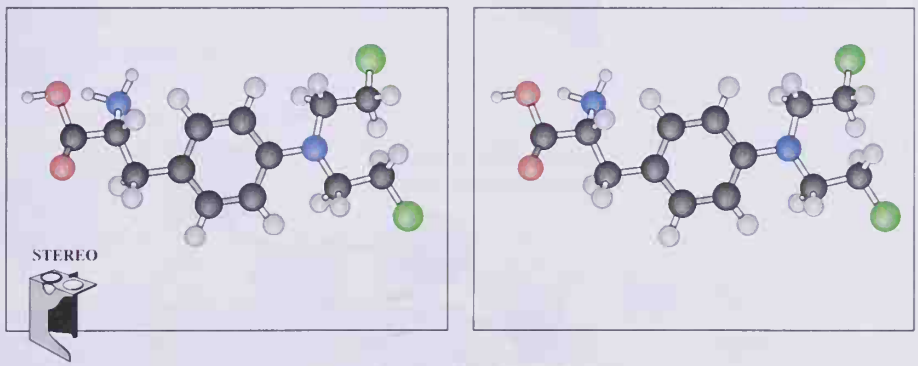
The clinical value of the nitrogen mustards lies in the fact that they undergo reaction with certain nucleophilic sites on the heterocyclic aromatic amine bases in DNA.

For DNA, the most reactive nucleophilic site is N-7 of guanine. Next in reactivity is N-3 of adenine, followed by N-3 of cytosine.



Guanine (G)

The nitrogen mustards are bifunctional alkylating agents; one molecule of nitrogen mustard undergoes reaction with two molecules of nucleophile. When guanine is the target nucleophile, N-7 of each guanine is converted to an ammonium ion. This in turn increases the acidity of guanine and shifts the keto-enol equilibrium from the keto form to the enol form. In the keto form, guanine forms a base pair with cytosine. In the enol form, however, it forms a base pair with thymine, which leads to miscoding during DNA replication. The therapeutic value of the nitrogen mustards, then, lies in their ability to form covalent cross-links on DNA strands and their ability to disrupt normal base pairing.



stereopair of melphalan

stranded) DNA. One strand of circular DNA may be opened, partially underwound so that it contains more than 10 base pairs per turn of the helix, and then rejoined. Alternatively, a strand may be opened, partially overwound so that it contains fewer than 10 base pairs per turn of the helix, and then rejoined. The overwound or underwound section introduces a strain into the molecule because the nonhelical gap is less stable than hydrogen-bonded, base-paired helical sections. The strain can be localized in the nonhelical gap. Alternatively, it may be spread uniformly over the entire circular DNA by introduction of **superhelical twists,** one twist for each turn of a helix unwound. The circular DNA shown in Figure 25.12(b) has been unwound by four complete turns of the helix. The strain introduced by this unwinding is spread uniformly over the entire molecule by introduction of four superhelical twists (Figure 25.12[c]). Interconversion of relaxed and supercoiled DNA is catalyzed by groups of enzymes called topoisomerases and gyrases.

Supercoiling of linear DNA in plants and animals takes another form and is driven by interaction between negatively charged DNA molecules and a group of positively charged proteins called **histones.** Histones are particularly rich in lysine and arginine and, therefore, have an abundance of positively charged sites along their length at the pH of most body fluids. The complex between negatively charged DNA and positively charged histones is called **chromatin.** Figure 25.13 shows a schematic diagram of the structure of chromatin. Histones associate to form core particles about which double-stranded DNA then wraps. Further coiling of DNA produces the chromatin found in cell nuclei.

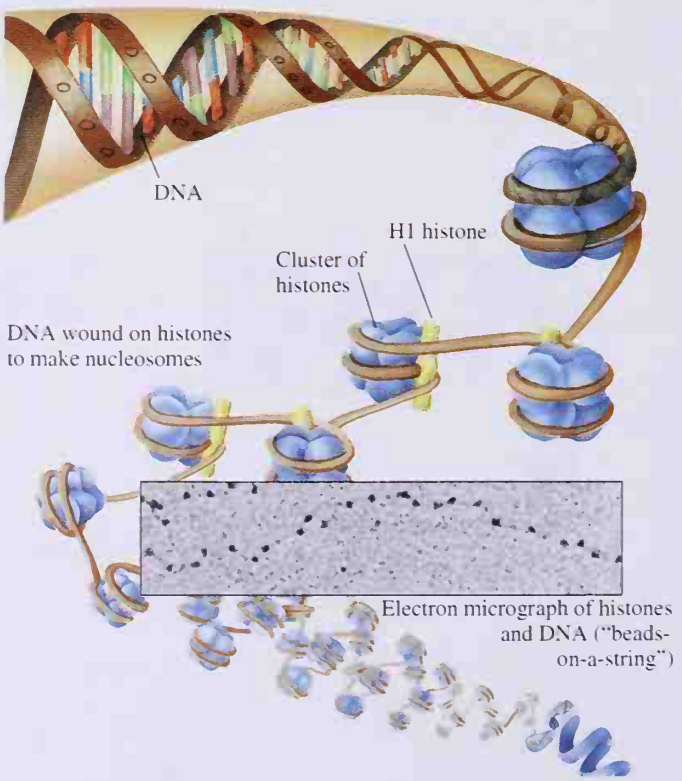


Figure 25.13
The structure of chromatin. Chromatin consists of DNA molecules wound around particles of histones in a beadlike structure. Further coiling produces the dense chromatin found in nuclei of plant and animal cells.

DNA as a Drug

Scattered through the United States and concentrated on the East and West coasts are biotechnology companies seeking to turn the explosive advances in molecular biology into commercial products. Millions of dollars from venture capitalists and, in some cases optimistic stockholders, are being bet on one good idea or another. Several of these new companies have been established to try and turn the idea of **antisense nucleic acids** into viable drugs.

The idea of antisense nucleic acids is based on how biological molecules transfer information. For most species, double-stranded DNA are the information-carrying molecules and act as recipes for the organism. Molecules called RNA polymerases read appropriate parts of DNA and synthesize singled-stranded RNA called messenger RNA. Single-stranded messenger RNA interacts with ribosomes, the cell's protein-synthesizing factory, and directs the synthesis of proteins.

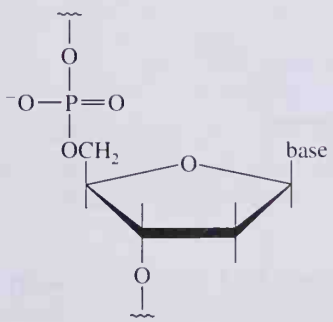
Single-stranded messenger RNA is the cell's "Achilles heel," which antisense nucleic acids seek to target. Suppose that in a messenger RNA a sequence 5′-AAAGGCCACGG-3′ reads in the 5′ → 3′ direction. If there is a second single-stranded RNA molecule with the sequence 3′-UUUCCGGUGCC-5′ (read in the antiparallel 3′ → 5′ direction), it base-pairs to this part of the messenger RNA. Two sequences that base-pair with each other are said to be complementary. Because the messenger RNA contains a sequence that makes sense to the protein-synthesizing machinery of the cell, its complementary strand is called an antisense strand. Because protein synthesis needs singled-stranded messenger RNA, trapping a messenger RNA molecule with its antisense strand turns off synthesis of that particular protein. However, other proteins can still be made.

Why should an antisense nucleic acid that can base-pair with a single-stranded messenger RNA molecule be useful as a drug? The reason is that some messenger RNA molecules in a cell may not be native to the cell. When a virus, for example, infects a cell, it causes its own messenger RNA molecules to be made, leading to the synthesis of specific viral proteins. Because the sequences of viral messenger RNA are different from those of host cell messenger RNA, it should be possible to design antisense sequences that bind to viral RNA and thus interfere with the synthesis of viral proteins without at the same time interfering with the synthesis of host cell proteins.

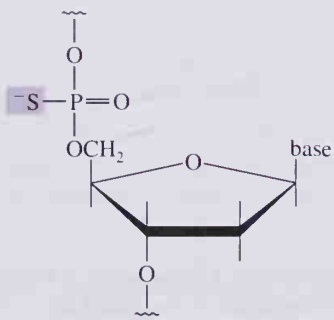
Several problems must be solved before antisense nucleic acids can be used as drugs. First, single-stranded nucleic acids are very rapidly broken down by enzymes in the body. To get around this problem, modifications in the DNA backbone have been tried, such as replacing one of the phosphate oxygen atoms with sulfur to produce phosphorothioate DNA analogs. Such molecules are considerably more resistant to enzymatic breakdown. Second, molecules with many negative charges (such as nucleic acids) do not cross cell membranes easily, which makes it difficult if not impossible to deliver them to sites within cells where they must function. As medicinal chemists are well aware, having a drug that interacts with a target is not enough. It must get to the target and last there long enough to have effect. Thus, alkylating the phosphate oxygen, which leads to neutral nucleic acid polymers, has been tried.

Whether these or other possible modifications will lead to clinically useful drugs remains to be established.

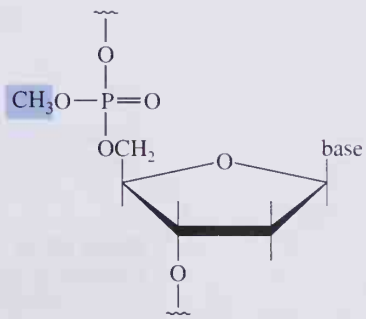
See E. Uhlman and A. Peyman, *Chem. Rev.*, **90:** 544 (1990)



DNA



Phosphorothioate derivative of DNA



Methyl phosphate derivative of DNA

25.3 Solid-Phase Synthesis of DNA

Enormous effort has been devoted by many investigators in many laboratories toward the synthesis of oligonucleotides and polynucleotides. These synthetic materials have become essential for the study of gene cloning and the effects of site-specific mutations. Just as with the synthesis of polypeptides and, for that matter, most other difunctional and polyfunctional molecules, the synthesis of polynucleotides is a problem of protecting groups, coupling agents, and removal of protecting groups. The particular problems associated with the synthesis of polynucleotides are summarized in Figure 25.14 for the dinucleotide X-Y. These problems are

1. The primary $-NH_2$ groups of the heterocyclic aromatic amines of nucleosides X and Y are both bases and nucleophiles, and must be protected.
2. To ensure the proper order of phosphodiester bond formation, the 5′-hydroxyl group of nucleoside X and the 3′-hydroxyl group of nucleoside Y must be protected.
3. Phosphodiester bonds must be formed in such a way that 3′-hydroxyl group of nucleoside X condenses with the 5′-hydroxyl group of nucleoside Y. This must be done in such a way that the alternative phosphodiester bonds giving X-X or Y-Y are not formed.

As with polypeptide syntheses, the construction of polynucleotides is done by a combination of linear and convergent syntheses and by both solution and solid-phase (solid-supported) methods. We describe here the protecting, condensing, and deprotecting strategies used most for automated **solid-phase syntheses** of polynucleotides.

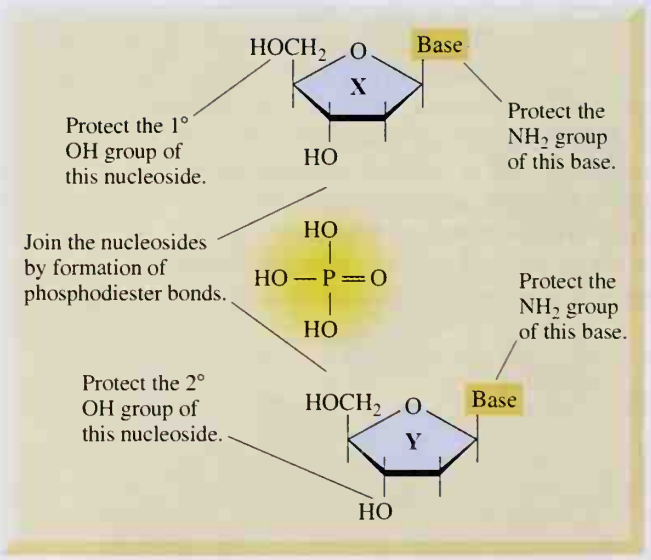
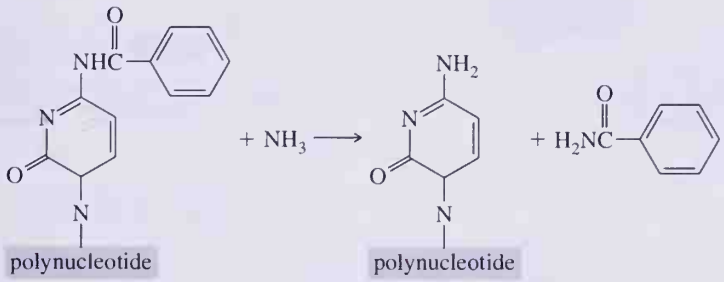
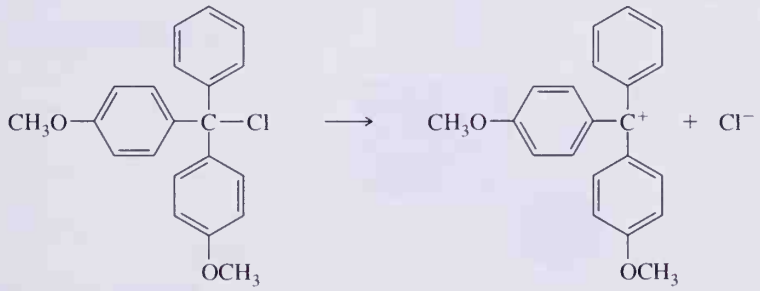


Figure 25.14
Problems in the synthesis of a dinucleotide X-Y are to protect the 5′-hydroxyl of nucleoside X and the 3′-hydroxyl of nucleoside Y, to protect the $-NH_2$ groups of the heterocyclic aromatic amine bases on X and Y, and to join the two nucleosides by formation of phosphodiester bonds between X and Y.

As shown in Figure 25.15, the basic/nucleophilic $-NH_2$ groups of the heterocyclic aromatic amine bases are most often protected as amides, such as benzamides in the case of the adenine (A^{Bz}) and cytosine (C^{Bz}), and as the isobutyramide in the case of guanine (G^{iBu}). Amide-protecting groups are removed at the final stage of synthesis by treatment with ammonia, which results in ammonolysis of the amide bonds and formation of benzamide or isobutyramide as the case may be, and the free heterocyclic aromatic amine bases.

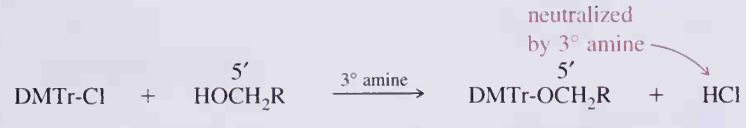


The 5′-hydroxyl is most commonly protected as a 4,4′-dimethoxytriphenylmethyl (abbreviated 4,4′-dimethoxytrityl, or DMTr) ether formed by regioselective reaction of the less hindered primary alcohol on the 5′ position of the nucleoside with 4,4′-dimethoxytrityl chloride in the presence of a tertiary amine to neutralize HCl formed in the reaction. 4,4′-Dimethoxytrityl chloride ionizes readily to form a resonance-stabilized carbocation that then undergoes reaction with the less hindered 5′-hydroxyl to form a DMTr-ether.



4,4′-Dimethoxytriphenylmethyl chloride (4,4′-Dimethoxytrityl chloride, DMTr-Cl)

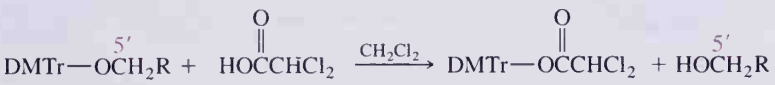
4,4′-Dimethoxytrityl cation



(An $-NH_2$ protected nucleoside)

(An $-NH_2$ and 5′ $-OH$ protected nucleoside)

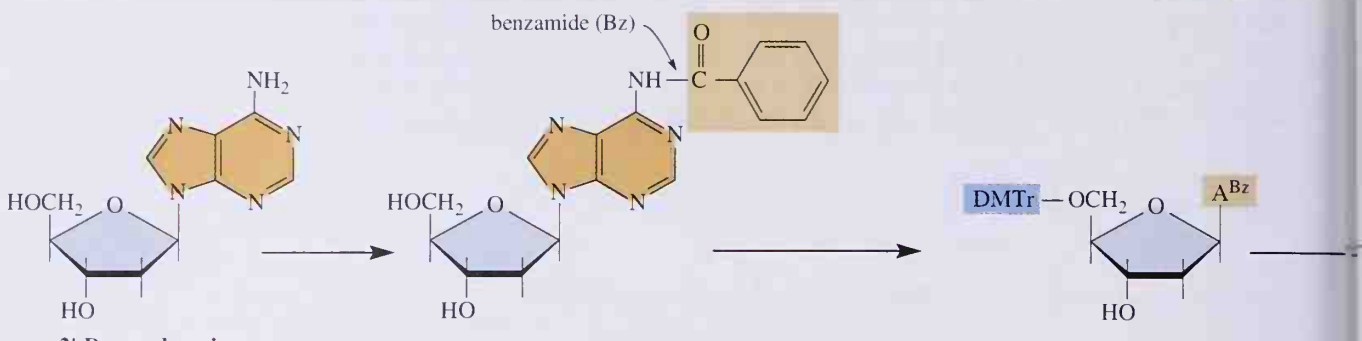
The 4,4′-dimethoxytrityl protecting group is removed, with formation of a resonance-stabilized carbocation intermediate by treatment of the dimethoxytrityl ether with dichloroacetic acid in dichloromethane.



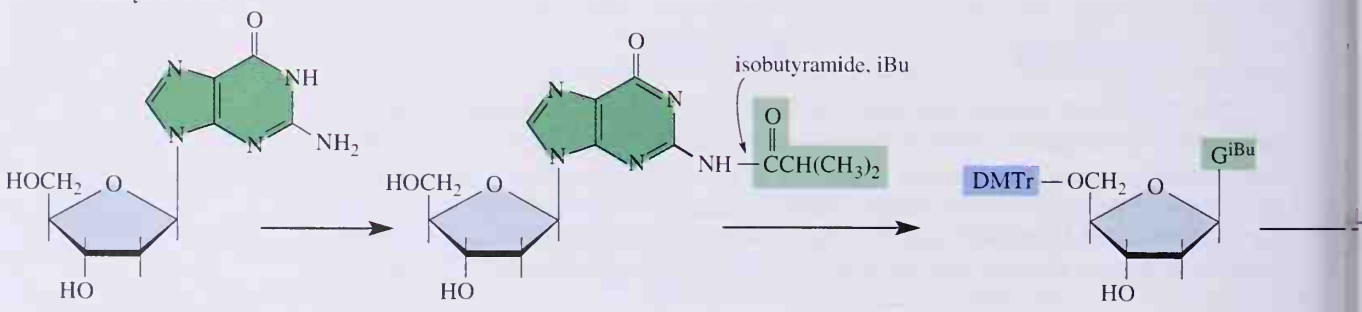
Dichloroacetic acid

4,4′-Dimethoxytrityl dichloroacetate

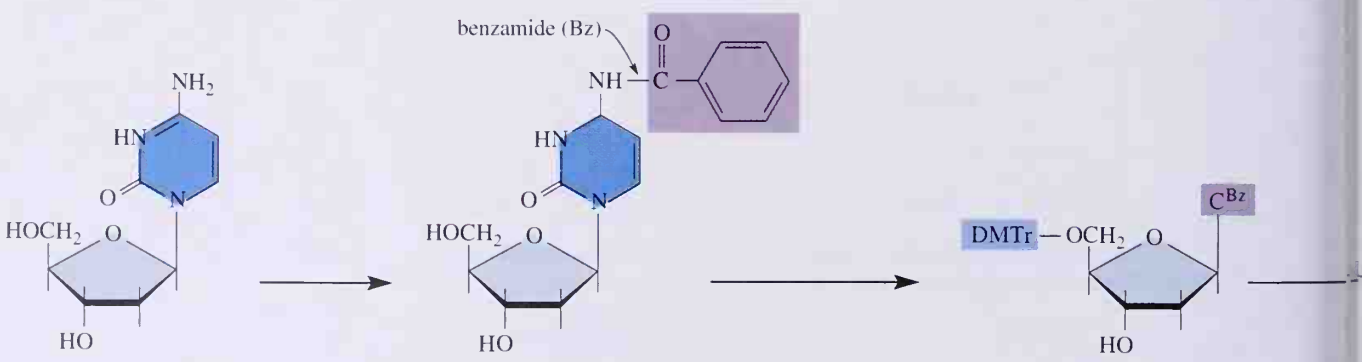
Nucleoside	Protect —NH_2 groups of adenosine, guanosine, and cytosine	Protect —CH_2OH groups; treat with DMTr-Cl



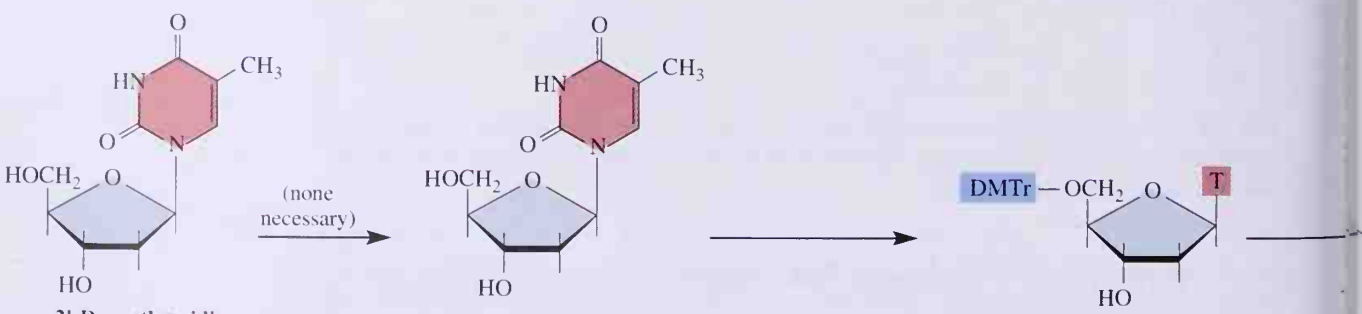
2'-Deoxyadenosine



2'-Deoxyguanosine



2'-Deoxycytosine



2'-Deoxythymidine

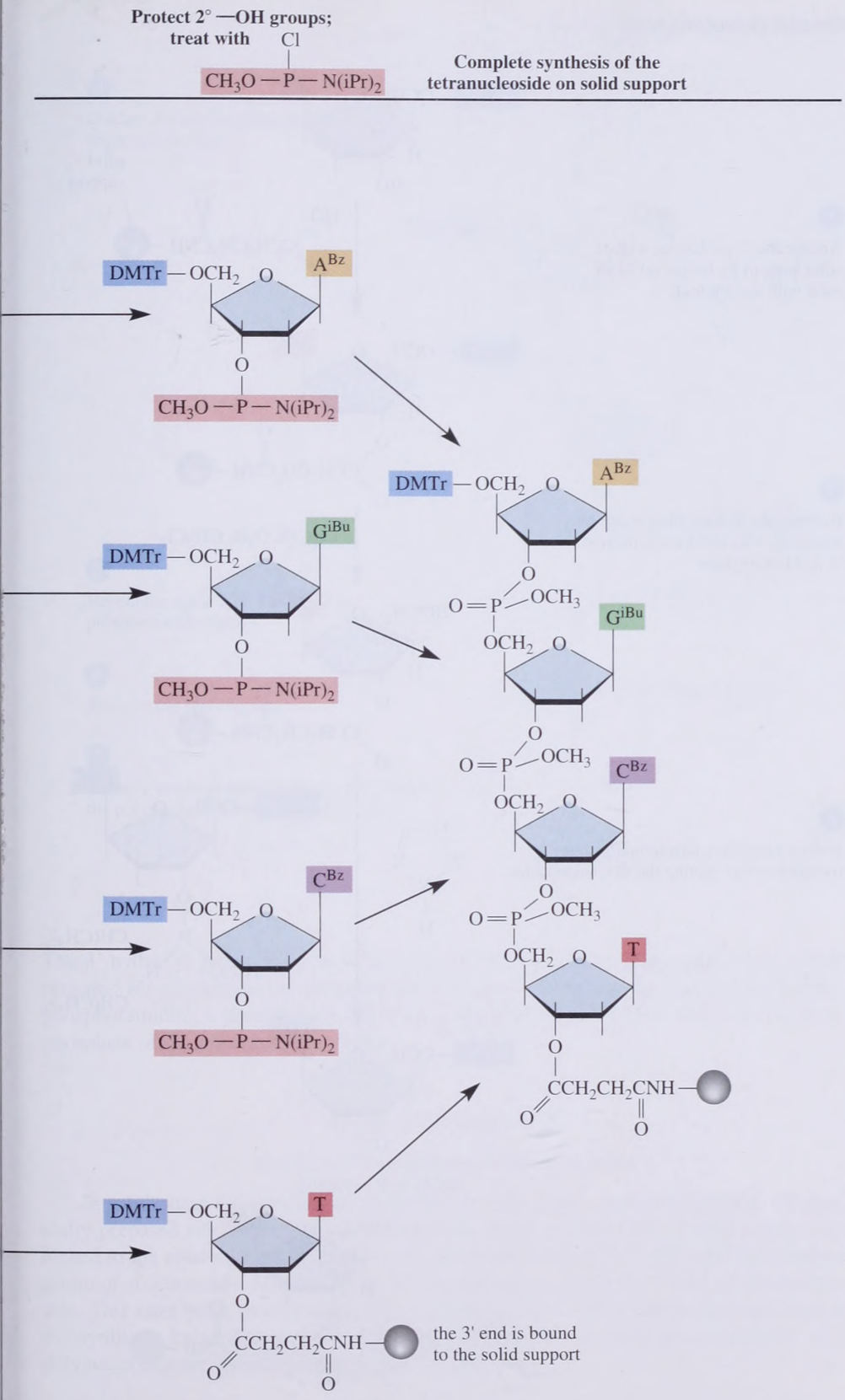
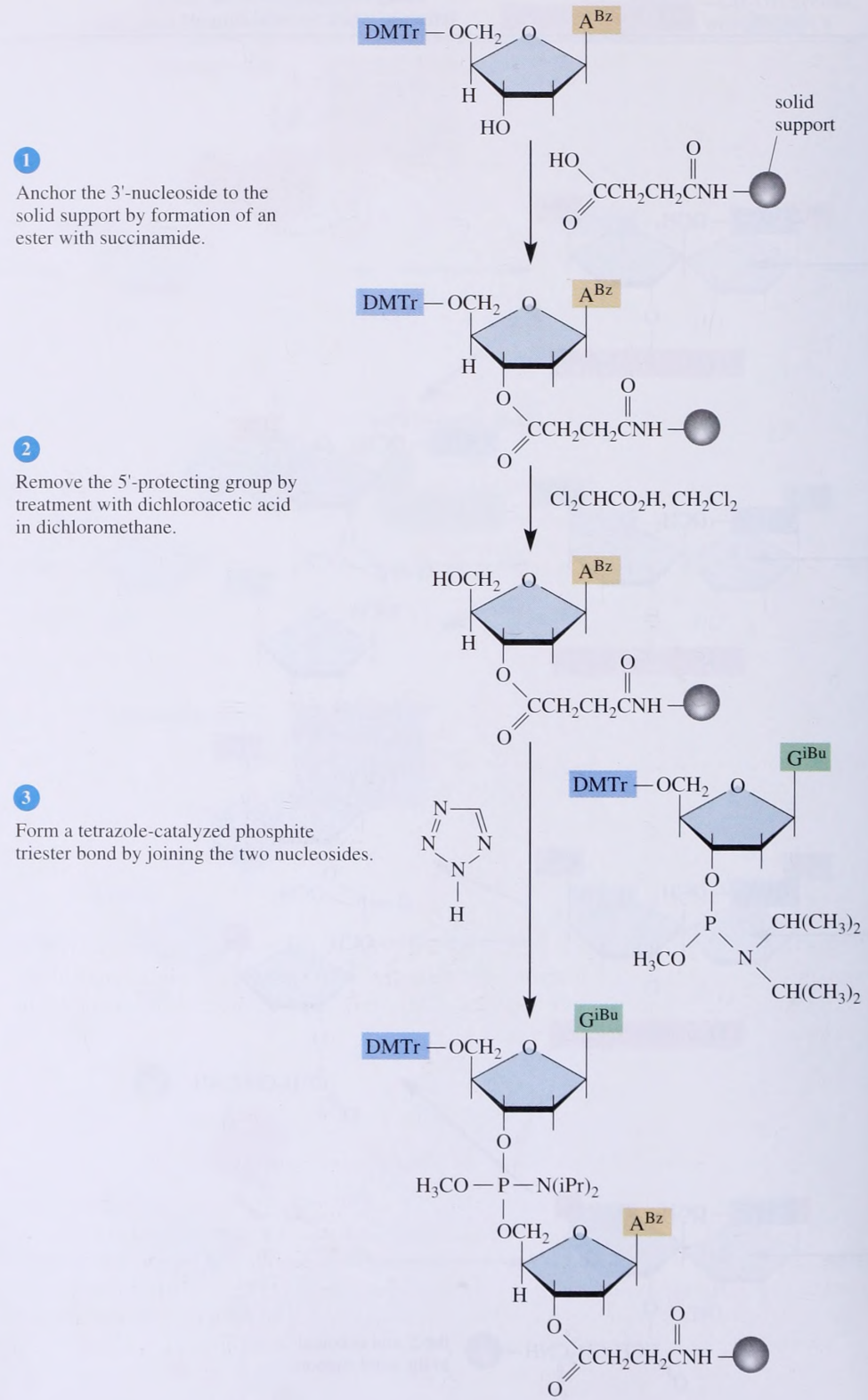
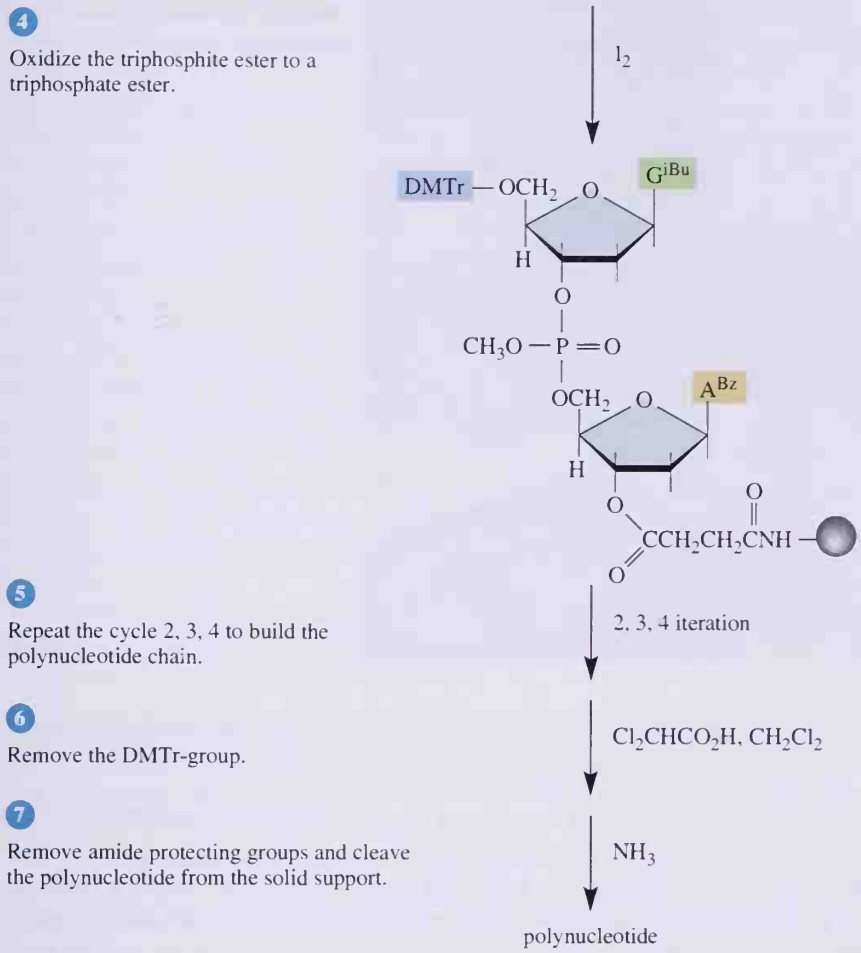


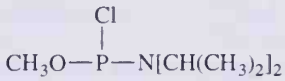
Figure 25.15
—NH_2 groups of heterocyclic aromatic amine bases are protected as amides. Amide-protecting groups are later removed by treatment with NH_3.

Figure 25.16
Steps in the solid-phase synthesis of a polynucleotide.





The 3′-hydroxyl group, the only remaining unprotected group of the nucleoside, is now prepared for phosphodiester formation by treatment with methyl *N*,*N*-diisopropylchlorophosphoramidite, a phosphorus-containing compound that, at a later stage, becomes the phosphate of the phosphodiester bond.



Methyl *N*,*N*-diisopropylchlorophosphoramidite

In solid-phase oligonucleotide synthesis, the solid phase consists of particles of especially prepared silica to which succinamide has been attached. The 3′-nucleoside is attached to the solid support (Step 1) by an ester bond between the 3′-OH and the carboxyl group of succinamide. Attachment in this manner also protects the 3′-OH of this nucleoside. This ester bond, as well as protecting amide bonds, is cleaved at the terminal stage in the synthesis by treatment with ammonia. The steps in the solid-phase synthesis of a polynucleotide are summarized in Figure 25.16.

Scientist operating an automated DNA synthesizer. *(© Hank Morgan, Rainbow)*

After the 3′-terminal nucleoside is anchored to the resin, the DMTr group protecting the 5′-hydroxyl is removed (Step 2). The second nucleoside is added to the growing chain by a phosphite triester bond (Step 3) in a reaction catalyzed by the heterocyclic aromatic amine, tetrazole. A two-electron oxidation of phosphorus by molecular iodine, I_2, converts the phosphite triester to a phosphate triester (Step 4). At this stage, the cycle 2, 3, 4 is repeated, adding a new nucleotide with each repeat. When chain length is complete, the DMTr-protecting group is removed and the molecule treated with ammonia. Ammonolysis removes all amide protecting groups, cleaves the methyl group from the phosphotriester to give a phosphodiester, and cleaves the polynucleotide from the solid support.

SUMMARY

Nucleic acids are composed of three types of monomer units: heterocyclic aromatic amine bases (more commonly referred to simply as bases) derived from purine and pyrimidine, the monosaccharides D-ribose and 2-deoxy-D-ribose, and phosphate (Section 25.1). A **nucleoside** is a compound containing D-ribose or 2-deoxy-D-ribose bonded to a heterocyclic aromatic amine base by a *β*-*N*-glycoside bond. A **nucleotide** is a nucleoside in which a molecule of phosphoric acid is esterified with an —OH of the monosaccharide, most commonly either the 3′-OH or the 5′-OH. Nucleoside monophosphate esters are strong diprotic acids and at pH 7.0, have a charge of −2. Nucleoside diphosphates and triphosphates are also strong polyprotic acids and are extensively ionized at pH 7.0. At pH 7.0, adenosine triphosphate is a 50:50 mixture of ATP^{3-} and ATP^{4-}.

The **primary structure of deoxyribonucleic acids (DNA)** consists of units of 2-deoxyribose bonded by 3′,5′-phosphodiester bonds (Section 25.2A). A heterocyclic aromatic amine base is attached to each deoxyribose by a *β*-*N*-glycoside bond. The sequence of bases is read from the 5′-end of the polynucleotide strand to the 3′-end.

There are two important differences between the primary structure of **ribonucleic acids (RNA)** and DNA. (1) The monosaccharide unit in RNA is D-ribose. (2) Both RNA and DNA contain the purine bases adenine (A) and

guanine (G), and the pyrimidine base cytosine (C). As the fourth base, however, RNA contains uracil (U), whereas DNA contains thymine (T).

The **Watson-Crick model** of the **DNA double helix** was based on chemical analyses of DNA base composition and on mathematical analyses of x-ray diffraction patterns of crystals of DNA. The heart of the Watson-Crick model is the postulate that a molecule of DNA consists of two antiparallel polynucleotide strands coiled in a right-handed manner about the same axis to form a double helix (Section 25.2B). Purine and pyrimidine bases point inward toward the axis of the helix and are always paired G-C and A-T. In **B-DNA,** base pairs are stacked one on top of another with a spacing of 0.34 nm and 10 base pairs per 3.4-nm helical repeat. In **A-DNA,** bases are stacked with a spacing of 0.256 nm between base pairs and 11 base pairs per 2.8-nm helical repeat. In B-DNA, deoxyribose is in the (C)2′-endo conformation, whereas in A-DNA it is in the (C)3′-endo conformation.

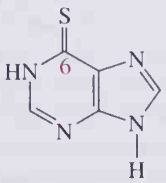
Tertiary structure of DNA is commonly referred to as **supercoiling** (Section 25.2C). **Circular DNA** is a type of double-stranded DNA in which the ends of each strand are joined by phosphodiester bonds. Opening of one strand followed by partial unwinding and rejoining the ends introduces strain in the nonhelical gap. This strain can be spread over the entire molecule of circular DNA by introduction of **superhelical twists.** Interconversion of supercoiled and relaxed DNA is catalyzed by tropoisomerases and gyrases. Supercoiling in double-stranded DNA in plants and animals is the result of complex formation between negatively charged DNA and positively charged proteins called histones. **Histones** are particularly rich in lysine and arginine and, therefore, have an abundance of positive charges. The association of nuclear DNA and histones produces a pigment called **chromatin.**

Polynucleotides can be synthesized in the laboratory (Section 25.3) by automated **solid-phase synthesis** using the same strategies we discussed for the synthesis of polypeptides: protection of reactive groups, anchoring the growing chain to a solid support, activation, coupling, deprotection, and cleavage of the completed chain from the solid support.

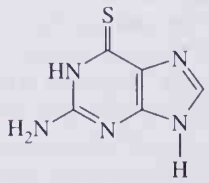
ADDITIONAL PROBLEMS

Nucleosides and Nucleotides

25.1 Two important drugs in the treatment of acute leukemia are 6-mercaptopurine and 6-thioguanine. In each of these drugs, the oxygen at carbon 6 of the parent molecule is replaced by divalent sulfur. Draw structural formulas for the enol forms of 6-mercaptopurine and 6-thioguanine.

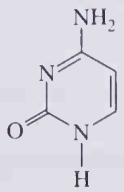


6-Mercaptopurine

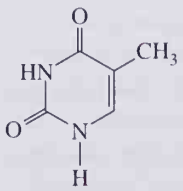


6-Thioguanine

25.2 Following are structural formulas for cytosine and thymine. Draw two additional tautomeric forms for cytosine and three additional tautomeric forms for thymine.



Cytosine (C)



Thymine (T)

25.3 Draw structural formulas for a nucleoside composed of

(a) β-D-Ribose and adenine **(b)** β-D-Deoxyribose and cytosine

25.4 Nucleosides are stable in water and in dilute base. In dilute acid, however, the glycoside bond of a nucleoside undergoes rapid hydrolysis to give a pentose and a heterocyclic base. Propose a mechanism for this acid-catalyzed hydrolysis.

25.5 Estimate the net charge on the following nucleotides at pH 7.4, the pH of blood plasma:

(a) ATP **(b)** GMP **(c)** dGMP

The Structure of DNA

25.6 Draw the structural formula of the DNA tetranucleotide 5′-A-G-C-T-3′. Estimate the net charge on this tetranucleotide at pH 7.0. What is the complementary tetranucleotide to this sequence?

25.7 Discuss the role of the hydrophobic effect in stabilizing

(a) Soap micelles **(b)** Lipid bilayers **(c)** Double-stranded DNA

25.8 At elevated temperatures, nucleic acids become denatured, that is they unwind into disordered single-stranded DNA. Account for the observation that the higher the G-C content of a nucleic acid, the higher the temperature required for thermal denaturation.

25.9 The Watson-Crick pattern of hydrogen bonding is not the only type of interaction possible for nucleic acids. Draw the structure of an A-T base pair in which the purine uses N-7 instead of N-1 as a hydrogen bond acceptor.

25.10 Reading J. D. Watson's account of the discovery of the structure of DNA, *The Double Helix,* you will find that for a time in their model-building studies, he and Crick were using alternative (and incorrect, at least in terms of their final model of the double helix) tautomeric structures for some of the heterocyclic bases.

(a) Write at least one alternative tautomeric structure for adenine.

(b) Would this structure still base-pair with thymine, or would it now base-pair more efficiently with a different base and if so, with what base?

25.11 Different functional groups are exposed in the DNA major groove and the DNA minor groove. Given the way the base pairs are normally written (Figure 25.7), the groups at the top of the diagram (for an A-T base pair, purine N-7, purine NH_2-6, and pyrimidine O-4) are exposed in the DNA major groove. The groups at the bottom of the diagram (for a G-C base pair, purine N-3, purine NH_2-2, pyrimidine O-2) are exposed in the DNA minor groove.

(a) What is the pattern of hydrogen bond-donating and accepting groups for an A-T, T-A, G-C, and C-G base pair in the major and the minor groove?

(b) Can a protein, using the disposition of hydrogen bond-donating and accepting groups, unambiguously recognize the four possible base pairs by binding in the major groove?

(c) Can it do so in the minor groove?

25.12 The following questions deal with the chemistry and physical properties of the sulfur and nitrogen mustard compounds discussed in the box Chemistry in Action: Mustard Gases and the Treatment of Neoplastic Diseases.

(a) Account for the fact that sulfur mustards undergo more rapid reaction with nucleophiles than do nitrogen mustards.

(b) Account for the fact that substitution of phenyl for methyl in a nitrogen mustard decreases the nucleophilicity of nitrogen.

(c) Account for the fact that substitution of carboxyl in the para position of the aromatic ring further decreases the nucleophilicity of nitrogen.

(d) Account for the fact that N-7 of guanine is more nucleophilic than $—NH_2$ at C-2; than N-1; than N-9.

(e) Draw the structural formula for the product of reaction of two molecules of guanine, each at N-7, with one molecule of nitrogen mustard, that is, show how a nitrogen mustard cross-links DNA.

(f) Consider a guanine alkylated at N-7 by a nitrogen mustard. Draw the enol form of this guanine.

(g) Account for the fact that the enol form of guanine hydrogen bonds with thymine rather than with cytosine.

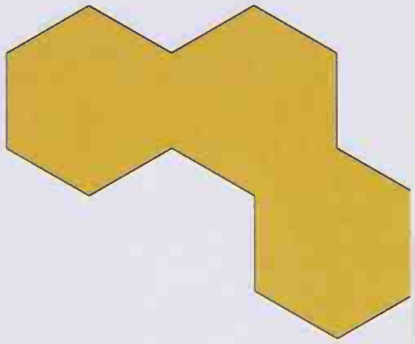
Solid-Phase Synthesis of DNA

25.13 The chemical synthesis of RNA is much more difficult than the chemical synthesis of DNA. Why is this the case?

25.14 In chemical synthesis of DNA, the triphosphate ester is attached to three different alkyl groups. One alkyl group is the sugar 3′-carbon, a second is the 5′-sugar carbon, and the third is a $—CH_3$ group. Why is the $—CH_3$ group preferentially removed by treatment with NH_3? What is the result if one of the other alkyl groups is removed?

25.15 The function of the tetrazolium ion in chemical synthesis of DNA is to act as a weak acid in the chain extension step. What functional group is protonated by the tetrazolium ion?

APPENDIX 1



Bond Dissociation Energies

Bond dissociation energy (BDE) is defined as the amount of energy required to break a bond homolytically into two radicals in the gas phase at 25°C.

$$A\overset{\curvearrowleft}{-}B \longrightarrow A\cdot + \cdot B \qquad \Delta H^\circ \text{ (kcal/mol)}$$

Bond	ΔH°	Bond	ΔH°	Bond	ΔH°
H—H bonds		**C—C multiple bonds**		**C—Br bonds**	
H—H	104	$CH_2{=}CH_2$	≈165	CH_3—Br	70
D—D	106	HC≡CH	≈230	C_2H_5—Br	68
X—X bonds		**C—H bonds**		$(CH_3)_2CH$—Br	68
F—F	38	CH_3—H	105	$(CH_3)_3C$—Br	68
Cl—Cl	58	C_2H_5—H	100	$CH_2{=}CHCH_2$—Br	55
Br—Br	46	$(CH_3)_2CH$—H	96	C_6H_5—Br	81
I—I	36	$(CH_3)_3C$—H	93	$C_6H_5CH_2$—Br	55
H—X bonds		$CH_2{=}CH$—H	106	**C—I bonds**	
H—F	136	$CH_2{=}CHCH_2$—H	86	CH_3—I	57
H—Cl	103	C_6H_5—H	111	C_2H_5—I	53
H—Br	88	$C_6H_5CH_2$—H	88	$(CH_3)_2CH$—I	54
H—I	71	HC≡C—H	132	$(CH_3)_3C$—I	51
O—H bonds		**C—F bonds**		$CH_2{=}CHCH_2$—I	41
HO—H	119	CH_3—F	108	C_6H_5—I	65
CH_3O—H	104	C_2H_5—F	106	$C_6H_5CH_2$—I	45
O—O bonds		$(CH_3)_2CH$—F	107	**C—N bonds**	
HO—OH	51	**C—Cl bonds**		CH_3—NH_2	79
CH_3O—OCH_3	36	CH_3—Cl	85	C_6H_5—NH_2	91
$(CH_3)_3CO$—$OC(CH_3)_3$	35	C_2H_5—Cl	80	**C—O bonds**	
C—C single bonds		$(CH_3)_2CH$—Cl	81	CH_3—OH	92
CH_3—CH_3	90	$(CH_3)_3C$—Cl	82	C_6H_5—OH	103
C_2H_5—CH_3	89	$CH_2{=}CHCH_2$—Cl	69		
$CH_2{=}CH$—CH_3	102	C_6H_5—Cl	96		
$CH_2{=}CHCH_2$—CH_3	72	$C_6H_5CH_2$—Cl	72		
C_6H_5—CH_3	101				
$C_6H_5CH_2$—CH_3	75				

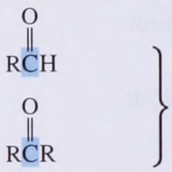
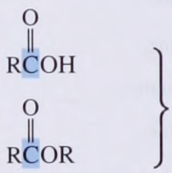
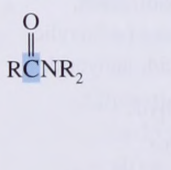
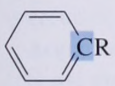
APPENDIX 2

Characteristic ^{1}H-NMR Chemical Shifts

Type of Hydrogen (R = alkyl, Ar = aryl)	Chemical Shift (δ)	Type of Hydrogen (R = alkyl, Ar = aryl)	Chemical Shift (δ)
$(CH_3)_4Si$	0 (by definition)	$RCOCH_3$	3.4–3.8
ROH	0.5–6.0	$RCOCH_2R$	3.9–4.3
RNH_2	0.6–3.0	RCH_2I	3.1–3.3
RCH_3	0.8–1.0	RCH_2Br	3.4–3.6
RCH_2R	1.2–1.4	RCH_2Cl	3.6–3.8
R_3CH	1.4–1.7	RCH_2F	4.4–4.5
$R_2C{=}CRCHR_2$	1.6–1.9	ArOH	4.5–7.7
$RC{\equiv}CH$	2.5–3.1	$R_2C{=}CH_2$	4.6–5.0
$ArCH_3$	2.2–2.5	$R_2C{=}CHR$	5.2–5.7
$ArCH_2R$	2.3–2.8	ArH	6.5–8.5
RCH_2OH	3.3–4.0	RCH	9.4–9.8
RCH_2OR	3.3–3.9	RCOH	10–13
$RCCH_3$	2.0–2.5		
$RCCH_2R$	2.1–2.6		

APPENDIX 3

Characteristic ^{13}C-NMR Chemical Shifts

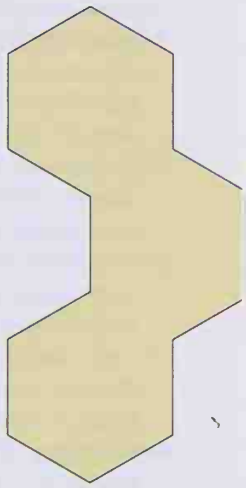
Type of Carbon	Chemical Shift (δ)	Type of Carbon	Chemical Shift (δ)
RCH_3	0–40		190–210
RCH_2R	15–55		
R_3CH	20–60		
$R_2C{=}CR_2$	100–150		160–190
$RC{\equiv}CR$	65–85		
RCH_2Cl	35–80		
RCH_2Br	25–65		150–185
RCH_2I	0–40		
R_3COH	40–80		
R_3COR	40–80		
	110–160		

APPENDIX 4

Characteristic Infrared Absorption Frequencies

Bond		Frequency (cm^{-1})	Intensity	Type of Vibration (stretching unless noted)
C—H	alkane	2850–3000	s	
	$-CH_3$	1375 and 1450	m	out-of-plane bending
	$-CH_2-$	1450	m	out-of-plane bending
	alkene	3000–3100	m	
		650–1000	s	out-of-plane bending
	alkyne	≈3300	s	
	aromatic	3030–3150	s	
		690–900	s	out-of-plane bending
	aldehyde	2700–2800	w	
		2800–2900	w	
C—C	alkane	(not interpretatively useful)		
C=C	alkene	1600–1680	w-m	
	aromatic	1475 and 1600	w-m	
C≡C	alkyne	2100–2250	w-m	
C—O	alcohol, ether, ester carboxylic acid, anhydride	1000–1300	s	
C=O	aldehyde	1705–1740	s	
	ketone	1680–1750	s	
	carboxylic acid	1700–1725	s	
	ester	1735–1750	s	
	amide	1630–1680	s	
	anhydride	1760 and 1810	s	
	acid chloride	1800	s	
O—H	alcohol, phenol free	3600–3650	m	
	hydrogen bonded	3200–3500	m	
	carboxylic acid	2400–3300	m	
N—H	amine and amide	3100–3500	m-s	
C≡N	nitrile	2240–2260	m	

GLOSSARY



Acetal A functional group consisting of a carbon bearing a combination of two —OR or —OAr groups. Acetals are stable to nucleophilic reagents and aqueous base but undergo hydrolysis in aqueous acid to form the carbonyl group of an aldehyde or ketone and two —OH groups. Acetals are often used as a protecting group for the carbonyl groups of aldehydes and ketones or the —OH groups of a glycol.

Achiral An object that lacks chirality.

Activating group A group on a benzene ring that causes the rate of an electrophilic aromatic substitution to be faster than that for benzene.

Acyl group The characteristic feature of an acyl group is RCO— or ArCO—.

Acylation A reaction involving substitution of an acyl group (RCO— or ArCO—) for a hydrogen atom. Examples of acylation reactions are Friedel-Crafts acylation to form an aryl ketone, conversion of an alcohol to an ester, and conversion of an amine to an amide.

Addition polymerization A type of polymerization in which monomer units are joined together without loss of atoms.

Aliphatic compound A term used to refer to nonaromatic hydrocarbons (alkanes, alkenes, alkynes) and their derivatives.

Alkylation A reaction involving substitution of an alkyl group for a hydrogen atom. Examples of alkylation reactions are Friedel-Crafts alkylation of aromatic rings, alkylation of enolate anions, and Williamson ether synthesis.

Allylic A term used to refer to a position next to a carbon-carbon double bond. The carbon atom next to a carbon-carbon double bond is an allylic carbon, and a substituent on an allylic carbon is an allylic substituent. 3-Bromocyclohexene, for example, is an allylic bromide.

Angle strain Strain in a molecule or ion arising from the creation of either abnormally large or abnormally small bond angles.

Angstrom, Å A unit of length. 1 Å = 10^{-10} m.

Annulene A cyclic hydrocarbon with continuous alternation of single and double bonds. Examples of aromatic annulenes are [14]annulene and [18]annulene.

Anomeric carbon The new stereocenter formed in a monosaccharide as a result of cyclic hemiacetal formation. The resulting diastereomers are given the special name anomers.

Anti addition Addition of atoms or groups of atoms from opposite sides or faces of a pi bond. In cyclic systems, anti addition is equivalent to *trans* coplanar addition.

Antiaromatic compound According to Hückel's criteria, a compound that is cyclic, planar, has continuous overlap of $2p$ orbitals, and contains $4n$ pi electrons. An antiaromatic compound is less stable than its acyclic analog of the same number of pi electrons. Cyclobutadiene, for example, is antiaromatic.

Antibonding MO A molecular orbital where the electron density is concentrated outside the region between the two nuclei and consequently there is little or no electron density between nuclei to offset nuclear repulsion. An antibonding MO is higher in energy than the atomic orbitals from which it is formed.

Aprotic solvent A solvent that cannot serve as a hydrogen bond donor; nowhere in the molecule is there a hydrogen bonded to an atom of high electronegativity so as to provide a dipole with hydrogen bearing the partial positive charge.

Arene An aromatic hydrocarbon. Benzene is the simplest arene.

Aromaticity (*see* Hückel's criteria for aromaticity)

Asymmetric carbon A term used, when chirality in organic molecules was first recognized, for a tetrahedral carbon atom with four different groups attached to it.

Aufbau principle A rule stating that orbitals in atoms and molecules fill in order of increasing energy from lowest to highest.

Axial bonds Bonds parallel to the axis of the imaginary sphere in which a chair conformation of a cyclohexane ring is centered. Three axial bonds (those on carbons slightly above the equator) point upward; the other three axial bonds (those on carbons slightly below the equator) point downward.

Base peak The most abundant ion current recorded in the detector of a mass spectrometer; the tallest peak in the mass spectrum. The relative abundances of all other peaks in a mass spectrum are reported as percentages of abundance of the base peak.

Basicity An equilibrium property measured by the position of equilibrium in an acid-base reaction.

Benzylic A term referring to a carbon atom bonded to a benzene ring. An anion, radical, or cation derived from a benzylic carbon is referred to as a benzylic anion, radical, or cation.

Betaine A neutral substance with nonadjacent negative and positive charges. Examples are the first intermediate in a Wittig reaction and the zwitterion form of an α-amino acid.

Bimolecular reaction A reaction in which two reactants undergo a chemical change in the transition state of the rate-determining step.

Bond dissociation energy The energy required to break a chemical bond in such a way that one electron from each bonding pair remains with each atom; that is, the bond is broken homolytically.

Bond order One-half the difference of the number of electrons in bonding molecular orbitals minus the number in antibonding molecular orbitals.

Bonding MO A molecular orbital where the electron density is concentrated in the region between the two positively charged nuclei and serves to offset the repulsive interaction between them. A bonding MO is lower in energy than the atomic orbitals from which it is formed.

Brønsted acid A proton donor.

Brønsted base A proton acceptor.

Chain initiation A step in polymerization. The characteristic feature of a chain initiation step is formation of a reactive intermediate (a radical, an anion, or a cation) from less reactive compounds.

Chain length The number of times that a cycle of chain propagation steps repeats in polymerization.

Chain propagation A step in polymerization. The characteristic feature of a chain propagation step is reaction of a reactive intermediate (a radical, an anion, or a cation) and a molecule to give a new reactive intermediate or two compounds, one a new molecule and the other a new reactive intermediate.

Chain reaction A reaction that, once initiated, continues by repetition of a set of chain propagation steps. Chain propagation steps are the product-forming steps of a chain reaction.

Chain termination A step in polymerization. The characteristic feature of a chain termination step is destruction of reactive intermediates.

Chair conformation A puckered conformation of a cyclo-

hexane ring in which all C—C—C bond angles are 109.5°, and groups on adjacent carbons are staggered (gauche or anti) with respect to one another.

Chemical shift, δ The frequency shift, expressed in ppm, of an NMR signal from tetramethylsilane (TMS) divided by the operating radio frequency of the spectrometer.

Chiral (Greek: *cheir*, hand) Having handedness. Objects that are not superposable on their mirror images have handedness; they are chiral.

Cis (Latin: on the same side) A prefix indicating that substituents are on the same side of a ring or carbon-carbon double bond.

Conformation Those forms of a molecule which differ only by rotation about one or more single bonds.

Conjugate acid The product that results when a Brønsted base accepts a proton.

Conjugate addition Addition to atoms 1 and 4 of a conjugated system. Examples are 1,4-addition to conjugated dienes and Michael reactions.

Conjugate base The product that results when a Brønsted acid loses a proton.

Conjugated diene A diene in which the double bonds are between adjacent pairs of atoms. The simplest conjugated diene is 1,3-butadiene.

Constitutional isomers Compounds that have the same molecular formula but different structural formulas (different orders of attachment of atoms).

Coupling constant, J A measure of the spin-spin interaction between nuclei whose spins are coupled.

Covalent bond A chemical bond formed by sharing electrons.

Cumulated diene A diene in which two double bonds share a carbon atom. The simplest cumulated diene is 1,2-propadiene (allene).

Cyanohydrin A molecule containing —OH and —CN groups bonded to the same carbon atom.

Cycloaddition A reaction in which two reactants add together without loss of atoms to give a cyclic product. An example is the Diels-Alder reaction.

Deactivating group A group on a benzene ring that causes the rate of an electrophilic aromatic substitution to be slower than that for benzene.

Decarboxylation The loss of CO_2 from the carboxyl group. Two combinations of functional groups that undergo nonoxidative decarboxylation upon mild heating are β-ketoacids, and malonic and substituted malonic acids.

Dehydration A reaction in which one or more molecules of water are removed from a starting material. The term is most commonly used to refer to removal of a molecule of water from adjacent carbon atoms of an alcohol (a β-elimination) to form an alkene.

Dehydrohalogenation Removal of HCl, HBr, or HI from an alkyl halide.

Deshielding Any effect that causes a nucleus to come into resonance at a weaker applied magnetic field. Deshielding shifts an NMR signal downfield (to the left on the chart paper) to a larger chemical shift value. Two common factors resulting in deshielding are the electron-withdrawing effect of adjacent atoms of greater electronegativity and local magnetic fields resulting from induced circulation of electrons in pi bonds.

Dextrorotatory (Latin: *dexter*, on the right side) A term indicating that a compound, when placed in a polarimeter, rotates the plane of polarized light to the right, that is, in a clockwise direction.

Diamagnetic substance A substance that is not attracted to a magnetic field. Substances with all electrons paired are diamagnetic.

Diastereomers Stereoisomers that are not mirror images of each other.

Dielectric constant A measure of the ability of a substance to act as an insulator between two charges of opposite sign. Dielectric constant is the most common measure of solvent polarity; the greater the value of the dielectric constant for a solvent, the smaller the interaction between ions of opposite charge dissolved in that solvent.

Dienophile Literally, a diene-loving compound. The special name given to an alkene, alkyne, or other pi bond-containing molecule participating in a Diels-Alder reaction.

Dihedral angle, θ The angle created by two intersecting planes.

Dipole-dipole interaction A force resulting when the end of one dipole interacts with the end of another dipole. When the interaction is between the positive end of one dipole and the negative end of another, the dipole-dipole force is one of attraction. When the interaction is between dipole ends of like charge, the force is one of repulsion. Hydrogen bonding is one example of attractive dipole-dipole interaction.

Dispersion forces Weak electrostatic attractive interactions that occur between temporary induced dipoles of adjacent atoms or molecules.

Disulfide A molecule containing adjacent divalent sulfur atoms, each of which is also bonded to an alkyl or aryl group, as for example, R—S—S—R.

Downfield A term meaning that a signal in an NMR spectrum is shifted to the left on the chart paper, that is, to a larger chemical shift value.

Eclipsed conformation A conformation in which an atom or group of atoms on one carbon is lined up, or eclipsed, with an atom or group of atoms on an adjacent carbon.

Electronegativity A measure of the force of an atom's attraction for electrons that it shares in a chemical bond with another atom. The most widely used scale of electronegativities was devised by Linus Pauling and is based on bond energies.

Electrophile Any atom, molecule, or ion that can accept a pair of electrons from a nucleophile to form a new covalent bond. By definition, an electrophile is also a Lewis acid.

Electrophoresis The process of separating compounds on the basis of their electric charges.

β-Elimination Removal of atoms or groups of atoms from adjacent carbon atoms to form a carbon-carbon double or triple bond. Examples of common types of β-elimination reactions are formation of alkenes by acid-catalyzed dehydration of alcohols and base-promoted dehydrohalogenation of alkyl halides.

Enantiomeric excess, ee The difference in number of moles of each enantiomer in a mixture compared with the total number of moles of both. Thus, ee is numerically equal to the percent optical purity.

Enantiomers (Greek: *enantios* + *meros*, opposite parts) Stereoisomers that are mirror images of each other.

Energy of activation The difference in potential energy between reactants and the transition state for their conversion to products.

Enol A compound containing a hydroxyl group attached to a carbon-carbon double bond. Such compounds are also referred to as vinylic alcohols.

***Entgegen*, E** The German word meaning "opposite." A term used to designate the configuration of groups on a carbon-carbon double bond. To use the E-Z system, first assign priority to the two atoms or groups of atoms on one carbon of the double bond, and then repeat the process for the two atoms or groups of atoms on the other carbon. If the groups of higher priority are on opposite sides of the double bond, the configuration of the alkene is designated **E**. If the groups of higher priority are on the same side of the double bond, the configuration is designated **Z** (from the German word *zusammen*, together).

Equatorial bonds Bonds directed more nearly along the equator of the sphere in which a chair conformation of cyclohexane is centered. Three equatorial bonds (those on carbons slightly above the equator) point downward; the other equatorial bonds (those on carbons slightly below the equator) point upward.

Equivalent atoms Atoms within a molecule having the same chemical environment. The term is most often used to refer to hydrogen or carbon atoms. A direct way to determine which hydrogens in a molecule are equivalent is to replace each in turn by a "test atom." If replacement of two different hydrogens by a test atom gives the same compound, the hydrogens are equivalent. If replacement gives a different compound, the hydrogens are nonequivalent.

Fats Triacylglycerols that are semisolid or solid at room temperature. Fats are generally rich in palmitic acid, stearic acid, and other saturated fatty acids.

Fatty acids Long-chain carboxylic acids derived from the hydrolysis of fats, oils, and the phospholipids of biological membranes. Nearly all fatty acids have an even number of carbon atoms, most between 12 and 20, in an unbranched chain.

First-order reaction A reaction whose rate-determining step is unimolecular, and whose kinetics, therefore, are dependent on the concentration of one reactant only. In a first-order nucleophilic substitution reaction of an alkyl halide, for example, the rate of reaction is dependent on the concentration of the alkyl halide and independent of the concentration of the nucleophile.

Fischer projection A convention for representing the configuration at tetrahedral stereocenters in two dimensions. In a Fischer projection, vertical bonds to the stereocenter are directed away from you and the horizontal bonds from the stereocenter are directed toward you.

Fishhook arrow A barbed arrow used to show the change in position of a single electron.

Formal charge A bookkeeping method for determining the charge on an atom in a molecule or polyatomic ion.

Frequency The number of full cycles of a wave that pass a given point in a fixed period of time. Frequency is given the symbol ν (nu) and is reported in Hz (hertz).

Frosti circle A diagram showing relative energies of bonding, nonbonding, and antibonding pi molecular orbitals for cyclic, planar, fully conjugated compounds. To

construct such a diagram, draw a circle and then inscribe a polygon with the same number of atoms as the ring. Inscribe the polygon in such a way that one point of the polygon is at the bottom of the circle. The relative energies of the pi MOs in the compound are then given by the points where the polygon touches the circle. Those MOs below the horizontal line through the center of the circle are bonding MOs. Those on the horizontal line are nonbonding MOs, and those above the line are antibonding MOs.

Gauche A term used to describe the orientation in space of groups on adjacent carbon atoms that lie at a dihedral angle of 60° to each other.

Geometric isomers Stereoisomers that differ in the arrangement of substituent groups, either in a cyclic structure or on a double bond. These isomers are more commonly called *cis-trans* isomers.

Glycol A compound with hydroxyl groups on adjacent carbon atoms.

Glycoside A cyclic acetal derived from a monosaccharide.

Glycoside bond The bond from the anomeric carbon of a monosaccharide to the —OR group in a glycoside.

Ground-state electron configuration The electron configuration of lowest energy.

Halohydrin A compound containing a halogen atom and a hydroxyl group on adjacent carbon atoms; those containing —Br and —OH are called bromohydrins, those containing —Cl and —OH are called chlorohydrins.

Hammond's postulate A postulate stating that the higher the energy of activation for a process, the later in the course of the reaction the transition state is reached. The transition state for an exothermic reaction is reached earlier in the course of a reaction and resembles the starting material(s). The transition state for an endothermic reaction is reached later in the course of a reaction and resembles the product(s).

Haworth projection A graphic representation for five-member and six-member monosaccharide cyclic hemiacetals and acetals. Rings are represented as planar pentagons and hexagons lying perpendicular to the plane of the paper with the anomeric carbon at the right and the hemiacetal oxygen to the right rear. Groups attached to carbons of the ring are shown either above or below the plane of the ring and parallel to the plane of the paper.

Hemiacetal A functional group consisting of a carbon bearing either —OH and —OR or —OH and —OAr groups. Hemiacetals are formed by addition of one molecule of alcohol to the carbonyl group of an aldehyde or ketone.

Heterocycle A molecule containing a ring of atoms in which there is more than one kind of atom in the ring. The heterocycles most commonly encountered in organic chemistry contain one or more atoms of nitrogen, oxygen, or sulfur in the ring.

Hückel's criteria for aromaticity A rule stating that for a compound to be aromatic, it must (1) be cyclic, (2) have one *p* orbital on each atom of the ring, (3) be planar or nearly planar so that there is continuous or nearly continuous overlap of all *p* orbitals of the ring, and (4) have $4n + 2$ pi electrons in the cyclic arrangement of *p* orbitals.

Hydroboration The regioselective and syn-stereoselective addition of borane, BH_3, or an alkylborane to an alkene to form a new alkylborane.

Hydrogen bonding A weak attractive force resulting from interaction between a partially positive hydrogen atom of one dipole and the negative end of another dipole. A dipole with a hydrogen atom bearing the partial positive charge results when a hydrogen atom is covalently bonded to an atom of high electronegativity (most commonly F, O, or N).

Hydrolysis Literally, breaking apart by reaction with water. Examples of hydrolysis are reaction of an ester group with water to give a carboxyl group and a hydroxyl group, and reaction of an anhydride group with water to give two carboxyl groups.

Hydrophilic Loving water; having an affinity for water; capable of dissolving in water.

Hydrophobic Fearing water; tending not to combine with water; incapable of dissolving in water.

Imide The characteristic structural feature of an imide is two acyl groups bonded to nitrogen.

Index of hydrogen deficiency The number of rings and pi bonds in a molecule. The formula for calculation of the index of hydrogen deficiency is: one-half the difference in the number of hydrogens in the molecular formula of a reference compound compared with a compound of unknown structure. The reference compound is one with the same number of carbon atoms as the unknown compound and with no rings or pi bonds.

Inductive effect The attraction of electrons from adjacent bonds by a more electronegative atom.

Ionic bond A chemical bond between a positively charged ion and a negatively charged ion.

Isoelectric point, pI The pH at which molecules of a compound containing both positively and negatively

charged regions undergo no migration in an applied electric field. When pH is greater than pI, molecules of the compound bear a net negative charge and migrate toward the positive electrode; when pH is less than pI, molecules of the compound bear a net positive charge and migrate toward the negative electrode.

Kekulé structure A term used most commonly with reference to the structure of aromatic compounds. In a Kekulé structure, a line between atoms represents a bond.

Keto-enol tautomerism The type of constitutional isomerism that deals with keto and enol tautomers.

Kinetic (rate) control For a reaction under kinetic control, the distribution of products is determined by the relative rates of formation of each.

Lactam A cyclic amide.

Lactone A cyclic ester.

Levorotatory (Latin: *laevus*, on the left side) A term indicating that a compound, when placed in a polarimeter, rotates the plane of polarized light to the left, that is, in a counterclockwise direction.

Lewis acid A species that accepts a pair of electrons to form a new covalent bond.

Lewis base A species that donates a pair of electrons to form a new covalent bond. Note that donating does not mean that the electron pair is removed from the valence shell of the base. Rather, it means that the electron pair becomes shared with another atom to form a covalent bond.

Lipids A heterogeneous class of naturally-occurring organic compounds grouped together on the basis of common solubility properties. Lipids are insoluble in water but are soluble in aprotic-organic solvents, including diethyl ether, methylene chloride, and acetone. Carbohydrates and nucleic acids, as well as amino acids and proteins are largely insoluble in these organic solvents. The major classes of lipids are triacylglycerols, phospholipids, prostaglandins, fat-soluble vitamins, and steroids.

Markovnikov's rule A rule stating that in additions of HX to an alkene, hydrogen adds to the double-bonded carbon that has the greater number of hydrogens already attached to it. According to a more modern formulation of this rule, in electrophilic addition to an alkene, the electrophile adds to the double bond to give the more stable carbocation.

Mass spectrum A plot of relative ion abundance versus mass-to-charge ratio.

McLafferty rearrangement A molecular rearrangement observed in mass spectrometry. In a McLafferty rearrangement, an atom with an unpaired electron, most commonly oxygen or nitrogen, abstracts a hydrogen five atoms away. Reaction occurs through a six-member ring transition state.

Meso compound A compound whose molecules are achiral even though they contain two or more tetrahedral stereocenters.

Meta A locator used to show that substituent groups on a benzene ring are 1,3- to each other.

Meta directing group A group on a benzene ring that directs an incoming group preferentially to the meta position during the course of electrophilic aromatic substitution.

Micelle A cluster of molecules assembled in such a way that nonpolar hydrophobic groups are buried within a region where water is excluded, and polar hydrophilic groups are on the surface and in contact with surrounding water molecules. Soap molecules placed in water spontaneously cluster into micelles in which the carboxylate groups form a negatively charged surface and the nonpolar hydrocarbon chains are buried within the interior.

Mirror image The reflection of an object in a mirror.

Molecular spectroscopy The experimental process of measuring which frequencies of radiation are absorbed or emitted by a particular molecule and then attempting to correlate patterns of energy absorptions or emissions with details of molecular structure.

Mutarotation The change in specific rotation that accompanies interconversion of α- and β-anomers of a monosaccharide, oligosaccharide, or polysaccharide. As an example, a freshly prepared solution of α-D-glucopyranose shows an initial rotation of $+112°$, which gradually decreases to an equilibrium value of $+52.7°$ as α-D-glucopyranose reaches an equilibrium with β-D-glucopyranose.

$n + 1$ rule If a hydrogen atom has a set of n nonequivalent hydrogens on the same or adjacent atom(s), its NMR signal is split into $n + 1$ peaks. Coupling between equivalent hydrogens, whether they are on the same or adjacent atoms, does not result in signal splitting.

Nanometer, nm A unit of length. 1 nm = 10^{-9} m.

Node Any point where the value of a wave equation is zero.

Nonbonded interaction strain Strain that arises in a molecule or ion because nonbonded atoms are forced into

close proximity. Nonbonded interaction strain gives rise to the greater stability of *trans* compared with *cis* alkenes, and of equatorial-substituted cyclohexanes compared with axial-substituted cyclohexanes.

Nucleophile Literally, nucleus-seeking. Any reagent that donates an unshared pair of electrons to form a new covalent bond.

Nucleophilic substitution Any reaction in which one nucleophile is substituted for another nucleophile.

Nucleophilicity A kinetic property measured by the rate at which a nucleophile attacks a reference compound under a standardized set of experimental conditions.

Nucleoside A compound containing D-ribose or 2-deoxy-D-ribose bonded to a heterocyclic aromatic amine base by a β-*N*-glycoside bond. The glycoside bond is between C-1′ (the anomeric carbon) of ribose or deoxyribose and N-1 of a pyrimidine base or N-9 of a purine base.

Nucleotide A nucleoside in which a molecule of phosphoric acid is esterified with a free hydroxyl of the monosaccharide, most commonly either the 3′-hydroxyl or the 5′-hydroxyl.

Oils Triacylglycerols that are liquid at room temperature. Oils are generally rich in oleic acid, linoleic acid, and other unsaturated fatty acids.

Optical activity A term referring to the fact that a compound, when placed in a polarimeter, rotates the plane of polarized light.

Optical purity The observed specific rotation of a sample compared with the specific rotation of the pure enantiomer.

Ortho A locator used to show that substituent groups on a benzene ring are 1,2- to each other.

Ortho-para directing group A group on a benzene ring that directs an incoming group preferentially to the ortho and para positions during the course of electrophilic aromatic substitution.

Oxidation The loss of electrons. If electrons appear on the right side of a balanced half-reaction, the reactant has given up electrons and has been oxidized.

Oxymercuration The regiospecific and anti-stereoselective addition of mercury(II) to one carbon of a carbon-carbon double bond and oxygen to the other.

Para A locator used to show that substituent groups on a benzene ring are 1,4- to each other.

Paramagnetic substance A substance that is weakly attracted to a magnetic field. All substances that have one or more unpaired electrons are paramagnetic.

Pauli exclusion principle A rule stating that no more than two electrons may be present in an orbital, one with spin quantum number $+\frac{1}{2}$, the other with spin quantum number $-\frac{1}{2}$.

Penultimate carbon The next to the last carbon on the Fischer projection of a monosaccharide. The configuration of this stereocenter in glyceraldehyde is the reference for assignment of relative configuration to all other monosaccharides. A monosaccharide that has the same configuration as D-glyceraldehyde at its penultimate carbon is classified as a D-monosaccharide. A monosaccharide that has the same configuration as L-glyceraldehyde at its penultimate carbon is classified as an L-monosaccharide.

Peptide bond The special name given to the amide group in polypeptides and proteins.

Peracid A shortened form of peroxycarboxylic acid. The characteristic structural feature of a peroxycarboxylic acid is the $-CO_3H$ group.

Phase-transfer catalyst A substance that transports anions, inorganic as well as organic, from an aqueous phase into an organic phase and vice versa.

Phospholipids A group of lipids derived from phosphatidic acid, a molecule containing glycerol esterified with two molecules of fatty acids and one molecule of phosphoric acid. The fatty acids most common in phosphatidic acids are palmitic and stearic acids (both fully saturated) and oleic acid (one double bond in the hydrocarbon chain). Further esterification of phosphatidic acid with a low-molecular-weight alcohol, most commonly ethanolamine, choline, serine, or inositol, gives a phospholipid.

Pi (π) bond A covalent bond formed by overlap of parallel *p* orbitals.

Plane of symmetry An imaginary plane passing through an object, dividing it such that one half is the reflection of the other half. Also called a mirror plane.

Plane-polarized light Electromagnetic radiation vibrating in only one plane.

Point of symmetry A point so situated that identical components of the object are located equidistant from the point along any axis passing through the point.

Polarizability A property of electrons in molecules which depends on how tightly they are held to the nucleus. The higher the principal quantum number of electrons, the greater their polarizability. In addition, unshared electron pairs have a higher polarizability than electrons shared in a covalent bond. The strength of dispersion forces, the

weakest of all intermolecular forces, depends on the polarizability of electrons.

Polymerization The building together of many small monomers (Greek: *mono* + *meros*, single part) into very large, high-molecular-weight polymers (Greek: *poly* + *meros*; many parts).

Primary, secondary, tertiary, and quaternary structure of proteins Terms used to describe levels of structural complexity in proteins.

Primary (1°) structure	The sequence of amino acids in a polypeptide chain.
Secondary (2°) structure	The ordered conformations of amino acids in localized regions of a polypeptide or protein molecule. Two of the most common ordered conformations are α-helices and β-pleated sheets.
Tertiary (3°) structure	The arrangements in space of all atoms in a single polypeptide chain.
Quaternary (4°) structure	The arrangement of protein monomers into an aggregation.

Primary, secondary, tertiary, and quaternary Terms used to classify carbon atoms, hydrogen atoms, alcohols, and amines as shown in the following table. The R group may be aliphatic or aromatic. The group R_4N^+ is called a quaternary ammonium ion because of the positive charge on the nitrogen atom.

	Carbon	Hydrogen	Alcohol	Amine
Primary	RCH_3	RCH_3	RCH_2OH	RNH_2
Secondary	R_2CH_2	R_2CH_2	R_2CHOH	R_2NH
Tertiary	R_3CH	R_3CH	R_3COH	R_3N
Quaternary	R_4C	—	—	R_4N^+

Principle of microscopic reversibility The sequence of transition states and reactive intermediates for any equilibrium reaction must be the same but in reverse order for the backward reaction as for the forward reaction.

Prostaglandins A group of lipids having the 20-carbon skeleton of prostanoic acid.

Prostanoic acid

Protic solvents Solvents that are hydrogen bond donors; the most common protic solvents contain —OH groups and for this reason are often called hydroxylic solvents.

Quantum mechanics, or wave mechanics The branch of science that describes the motion of particles and their associated waves.

Quaternary structure (*see* Primary structure of proteins)

R-S convention A convention, known alternatively as the Cahn-Ingold-Prelog convention, for designating the configuration of a tetrahedral stereocenter. The orientation of groups about the stereocenter is specified using the set of priority rules. Each group at the stereocenter is assigned a priority (1, 2, 3, 4) and the molecule is oriented in space such that the group of lowest priority (4) is directed away from you. The three groups projecting toward you are read in order from highest priority (1) to lowest priority (3). If reading the groups proceeds in a clockwise direction, the configuration is designated as **R** (Latin: *rectus*, right hand); if reading proceeds in a counterclockwise direction, the configuration is **S** (Latin: *sinister*, left hand).

Racemic mixture An equimolar mixture of two enantiomers. The term is derived from the name "racemic acid" (Latin: *racemus*, a cluster of grapes), the name given to the equimolar mixture of the enantiomers of tartaric acid derived from grapes.

Radical A molecule or ion that contains one or more unpaired electrons. Although most radicals are highly reactive species, a few are stable, an example of which is molecular oxygen, O_2.

Rate-determining step The slowest step in a multi-step reaction.

Reaction coordinate The motion of atoms associated with the change in potential energy in going from reactants to products.

Reactive intermediate A potential energy minimum between two transition states. Reactive intermediates are never present in appreciable concentration because the energy of activation for their conversion to either reactants or to products is so small.

Reducing sugar A carbohydrate that reduces copper(II) ion to Cu_2O or silver(I) ion to metallic silver. Any carbohydrate that contains an aldehyde group or is converted to one that contains an aldehyde group under the conditions of the test is a reducing sugar. A carbohydrate that does not reduce these reagents is classified as a nonreducing sugar.

Reduction The gain of electrons. If electrons appear on the left side of a balanced half-reaction, the reactant has gained electrons and has been reduced.

Regioselective reaction A reaction in which one direction of bond making and bond breaking occurs preferentially over all other possible directions. Examples include radical bromination of propane to give 2-bromopropane and electrophilic addition of HCl to propene to give 2-chloropropane.

Resolution The process of separating a racemic mixture into its pure enantiomers.

Resonance energy The difference in energy between a resonance hybrid and the most stable contributing structure in which electron density is localized on particular atoms and in particular covalent bonds.

Saponification Hydrolysis of an ester group in aqueous base to give a carboxylate anion group and an hydroxyl group. The term is derived from use of this reaction in the manufacture of soaps (Latin: *saponem,* soap).

Saturated A term used to indicate that the structural formula of a compound contains only carbon-carbon single bonds. Hexane, for example, is a saturated hydrocarbon and cyclohexanol is a saturated alcohol.

Second-order reaction A reaction whose rate-determining step is bimolecular, and whose kinetics, therefore, are dependent on the concentration of two reactants. In a second-order nucleophilic substitution reaction of an alkyl halide, for example, the rate of reaction is dependent on the concentration of the alkyl halide and on the concentration of the nucleophile.

Secondary structure (*see* Primary structure of proteins)

Shielding Any effect which causes a nucleus to come into resonance at a stronger external magnetic field. Shielding shifts an NMR signal upfield (to the right on the chart paper) to a smaller chemical shift value.

1,2-Shift A molecular rearrangement in which an atom or group of atoms with its bonding electrons moves from one atom to an electron-deficient adjacent atom.

Sigma (σ) bond A covalent bond in which orbital overlap is concentrated along the axis joining the two nuclei.

Solvolysis A nucleophilic substitution reaction in which the nucleophile is a molecule of the solvent.

***sp* Hybrid orbitals** Equivalent hybrid orbitals produced by combination of one 2*s* orbital and one 2*p* orbital. The axes of the unhybridized 2*p* orbitals are perpendicular to each other and to the axes of the two *sp* hybrid orbitals; *sp* hybridization results in bond angles of approximately 180°.

***sp*^{2} Hybrid orbitals** Equivalent hybrid orbitals formed by combination of one 2*s* orbital and two 2*p* orbitals. The axes of the three *sp*^{2} hybrid orbitals lie in a plane and are directed toward the corners of an equilateral triangle; *sp*^{2} hybridization results in bond angles of approximately 120°.

***sp*^{3} Hybrid orbitals** Equivalent hybrid orbitals formed by the combination of one 2*s* orbital and three 2*p* orbitals. The axes of the four *sp*^{3} hybrid orbitals are directed toward the corners of a regular tetrahedron; *sp*^{3} hybridization results in bond angles of approximately 109.5°.

Specific rotation, [α] The observed rotation at a specific cell length and sample concentration. The standard cell length is 1.0 decimeter. For a pure liquid sample, the concentration is expressed in g/mL (density). The concentration of a sample dissolved in a solvent is also expressed in g/mL.

Step-growth polymerization A type of polymerization involving reaction between difunctional molecules, with each new bond created in a separate step. No reactive intermediate, such as a carbocation or radical, is involved in this type of polymerization; rather, new covalent bonds are generally formed by polar reactions, as for example, nucleophilic acyl substitution. The four common types of polymers formed by this means are polyesters, polyamides, polycarbonates, and polyurethanes.

Stereocenter Alternatively, a stereogenic center. An atom in a molecule at which interchange of two atoms or groups of atoms bonded to that atom produces a different stereoisomer. The type of stereocenter encountered most often in organic chemistry is a carbon atom with four different groups attached to it; namely a tetrahedral carbon stereocenter.

Stereoisomers Molecules that have the same molecular formula and the same order of attachment of atoms but a different arrangement of atoms in space that cannot be interconverted by rotation about single bonds. Stereoisomers include *cis-trans* isomers, enantiomers, and diastereomers.

Stereoselective reaction A reaction in which one stereoisomer or an enantiomeric pair of stereoisomers is formed or destroyed preferentially over all others that may be formed or destroyed. Examples are anti addition of bromine to an alkene and syn addition of borane to an alkene.

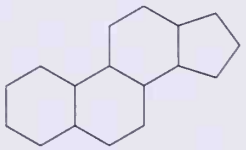
Stereospecific reaction A reaction in which different stereoisomeric starting materials give different stereoisomeric products. Examples of stereospecific reactions are addition of bromine to *cis*-2-butene to give the enan-

tiomers of 2,3-dibromobutane and to *trans*-2-butene to give meso-2,3-dibromobutane.

Steric hindrance The ability of groups, because of their size, to hinder access to a reaction site within a molecule.

Steric strain The term steric strain includes both angle strain and nonbonded interaction strain.

Steroids A group of lipids having in common the tetracyclic ring system known as the steroid nucleus.



Steroid nucleus

Sulfide A molecule containing a divalent sulfur atom bonded to two alkyl or aryl groups, as for example, R—S—R.

Syn addition Addition of atoms or groups of atoms to the same side or face of a pi bond.

Synthesis gas A mixture of carbon monoxide and hydrogen formed from the reaction of water with methane, coal, and various petroleum products. Synthesis gas is now the major source of both methanol and acetic acid, and it is likely that in the decades ahead it will be a major feedstock for the production of other organics.

Tautomers Constitutional isomers in equilibrium with each other which differ in location of a hydrogen atom and a double bond. The most common are keto-enol tautomers.

Terpene A molecule whose carbon skeleton can be divided into two or more units all of which are identical with the carbon skeleton of isoprene.

Tertiary structure (*see* Primary structure of proteins)

Thermodynamic (equilibrium) control For a reaction under thermodynamic control, the distribution of products is determined by the relative stabilities of each.

Trans (Latin: across) A prefix indicating that substituents are on opposites side of a ring or carbon-carbon double bond.

Transition state The point on a reaction coordinate at which the potential energy is a maximum. A transition state has a definite geometry and a definite distribution of electron density and charge. Because a transition state is an energy maximum on the reaction coordinate and for all practical purposes has zero lifetime, it cannot be isolated and its structure cannot be determined experimentally. However, we can often infer a great deal about its probable structure from other experimental observations.

Transition state aromaticity A reaction that proceeds by a planar transition state involving cyclic redistribution of $4n + 2$ pi electrons is said to have transition state aromaticity. Such reactions have especially low energies of activation and take place readily. Examples are Diels-Alder reactions and decarboxylation of β-ketoacids.

Unimolecular reaction A reaction in which only one reactant undergoes a chemical change in the transition state of the rate-determining step.

Unsaturated A term used to indicate that the structural formula of a compound contains one or more carbon-carbon double or triple bonds. 2-Butene, for example is an unsaturated hydrocarbon, and 3-buten-2-one (methyl vinyl ketone) is an α,β-unsaturated ketone.

Upfield A term meaning that a signal in an NMR spectrum is shifted to the right on the chart paper, that is, to a smaller chemical shift value.

Vinylic A term used to refer to a substituent on a carbon-carbon double bond of an alkene. An enol, for example, is a vinylic alcohol, and 2-bromopropene is a vinylic bromide.

Wave equation The mathematical equation that describes a wave. The numerical value of a wave equation may be positive (corresponding to a wave crest), negative (corresponding to a wave trough), or zero.

Wave function, ψ Solution of the Schrödinger equation gives a set of wave functions, each associated with a unique set of quantum numbers and with a particular atomic orbital. The value of ψ^2 is proportional to the probability of finding an electron at a given point in space; or looked at in another way, the value of ψ^2 at any point in space is proportional to the electron density at that point.

Wavenumber, $\bar{\nu}$ Wavenumber is equal to 1/(wavelength in cm) and has units of cm^{-1}. Radiation in the infrared region of the electromagnetic spectrum is commonly referred to by its wavenumber.

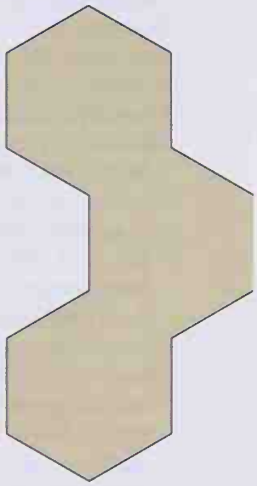
Ylide A molecule that, when written in a Lewis structure showing all atoms with complete octets, has positive and negative charges on adjacent atoms. Phosphonium ylides, which are involved in Wittig reactions, are derived by removal of a hydrogen from alkyl triphenylphosphonium salts.

Zaitsev's rule A rule stating that when isomeric alkenes are obtained in a β-elimination reaction, the alkene having the greater number of substituents on the double bond generally predominates.

***Zusammen*, Z** The German word meaning "together." A term used to designate the configuration of groups on a carbon-carbon double bond. If the groups of higher priority are on the same side of the double bond, the alkene is designated **Z**. (See also *Entgegen*, E)

Zwitterion The special name given to the internal salt of an α-amino acid. A zwitterion has no net charge; it contains one positive charge and one negative charge. Zwitterions belong to the more general class of compounds called betaines.

INDEX



B

C

D

E

F

G

H

I

J

K

L

M

N

O

P

Q

R

S

T

U

V

W

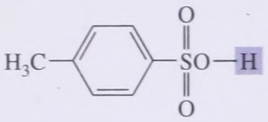
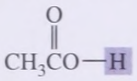
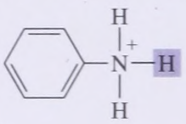
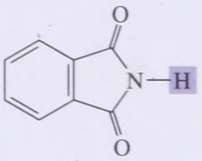
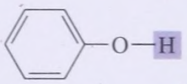
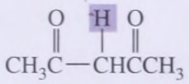
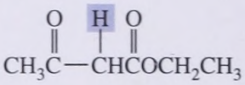
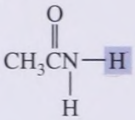
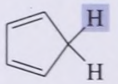
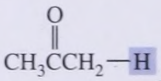
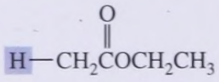
X

Y

Z

Acid Ionization Constants for the Major Classes of Organic Acids

Increasing acid strength

Name and Example	Typical pK_a
Sulfonic acid 	0–2
Carboxylic acid 	3–5
Aromatic ammonium ion 	4–5
Imide 	8–9
Thiol $CH_3CH_2S—H$	8–12
Phenol 	9–10
Ammonium ion $\overset{+}{N}H_3—H$	9.24
β-Diketone 	10
Nitroalkane $H—CH_2NO_2$	10
Aliphatic ammonium ion $(CH_3CH_2)_3\overset{+}{N}—H$	10–12
β-Ketoester 	11
Water $HO—H$	15.7
Alcohol $CH_3CH_2O—H$	15–19
Amide 	15–19
Cyclopentadiene 	16
Aldehyde, ketone 	18–20
Ester 	23–25
Alkyne $HC\equiv C—H$	25
Ammonia $NH_2—H$	35
Amine $[(CH_3)_2CH]N—H$	40

SAUNDERS GOLDEN SUNBURST SERIES

ISBN 0-03-009618-9

90094

9 780030 096181